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EFFICACY AND SAFETY OF ORAL CYCLOSPORIN IN TREATMENT OF PYODERMA GANGRENOSUM

Dermatology

Dr Priya kariya third year resident, department of dermatology venerology and leprology, GMERS medical college and civil hospital, sola, Ahmedabad.

Dr Sneha patel third year resident, department of dermatology venerology and leprology, GMERS medical college and civil hospital, sola, Ahmedabad.

Dr Krina patel* professor and head, department of dermatology, venerology and leprology, GMERS medical college and civil hospital, sola, Ahmedabad. *Corresponding Author

ABSTRACT

INTRODUCTION: Pyoderma gangrenosum (PG) is an idiopathic, non-infectious ulcerating disorder predominantly involving skin, with primarily neutrophilic inflammatory infiltrate. The mainstay of therapy for PG has been high-dose corticosteroids but systemic agents such as cyclophosphamide, cyclosporine or azathioprine can be used.

AIMS: To evaluate efficacy and safety of oral cyclosporine in patients with pyoderma gangrenosum.

MATERIALS AND METHOD: A retrospective study of patients presenting with pyoderma gangrenosum from February 2014 to February 2018 was carried out. All patients were given oral cyclosporine 3 mg/kg/day for minimum 6 weeks to maximum 12 weeks as per requirement. At the end of therapy patients were classified according to response and reduction ulcer area score.

RESULTS: Ulcer area in each patient reduced above 60% with minimal side effects after giving cyclosporine for 12 weeks. Out of 27 patients, 12 had excellent response (>90%). While 10 patients had good response (70-90 %) and 5 had good response (50-70%).

CONCLUSION: This study shows that systemic low dose cyclosporine is an effective and safe treatment option available for pyoderma gangrenosum.

KEYWORDS

Cyclosporin, Pyoderma gangrenosum, IgA gammopathy.

INTRODUCTION

Pyoderma gangrenosum(PG) is a chronic, recurrent, idiopathic, sterile ulcerating disorder predominantly involving skin, with primarily neutrophilic inflammatory infiltrate. PG was first described and named by Brunsting, Goeckerman and O'Leary in 1930 and initially believed to be due to streptococcal infection, producing secondary cutaneous gangrene hence named 'pyoderma gangrenosum'[1]. It is characterized by rapidly, progressing ulceration of the skin with an ill-defined border. The diagnosis of PG depends mainly on recognition of the evolving clinical features as the histopathological changes are not specific. It commonly affects the lower extremities, in particular the pretibial area 2.It is often associated with systemic diseases including inflammatory bowel disease, rheumatoid arthritis; monoclonal gammopathy etc.[3]

The mainstay of therapy for PG has been high-dose corticosteroids but not all patients have a favorable outcome and corticosteroids lead to several side-effects. Other systemic agents have also been used as steroid sparing agents with variable success such as cyclosporine, azathioprine, cyclophosphamide. Cyclosporine is found to be most effect agent with least side-effects among all in various studies.

AIMS AND OBJECTIVES: to analyze the efficacy and safety of oral cyclosporine in pyoderma gangrenosum.

MATERIALS AND METHOD

After permission of institutional ethics committee, all confirm cases of pyoderma gangrenosum attending the dermatology outpatient department, tertiary care unit during the 5 year study period from February 2014 to February 2018 were enrolled in the study.

A full evaluation including history, physical examination, duration, onset and evolution of the disease and co-existing systemic diseases was carried out in all patients. Data regarding age, gender and evolution of the ulcer site, size, number, morphology and clinical characteristics of lesions were documented. Data on past history of similar lesions and as well as details of investigations done were collected. The treatment received by the patient in past as well as the response were recorded.

A complete hemogram, renal and liver function test, random blood sugar, urine microscopy, peripheral smear for atypical cells and blast forms, fasting lipid profile, serum electrolytes, serology for antinuclear antibody, rheumatoid factor, human immunodeficiency virus and hepatitis B and C viruses, Mountoux test and thyroid function tests were performed in each patient. X-ray chest and abdominal sonography were done in all patients. Oher investigations were done as an when indicated. All patients presenting with leg ulcers were examined to identify any clinical features suggestive of arterial or venous insufficiency and Doppler studies of the arterial and venous systems were also carried out.

Patients with renal insufficiency, pregency, severe infection, uncontrolled hypertension, immunodeficiency and those receiving concomitant nephrotoxic drug were excluded from the study.. A diagnosis of pyoderma gangrenosum was made based on clinical presentation, histopathology and exclusion of other diseases that may have a similar clinical presentation.After confirmation of diagnosis and pre treatment evaluation and informed consent form sign, all patients were given oral cyclosporin 3 mg/kg/day for minimum 6 weeks to maximum 12 weeks as per requirement; besides local wound care and topical medication. Regular monitoring was done as per standard protocol for CyA. Before and after giving cyclosporin the area of ulcer was calculated by using the formula (length *width *0.7854) and percentage reduction in area of ulcer was calculated by using the formula (final area-initial area*100/ initial area).[5][6].

Response was also evaluated by decrease in pain severity, evaluation of clinical photographs and clinical healing. Adverse effects if any were recorded. Patients were classified according to response at the end of therapy in 4 groups.

RESULTS :

Total 27 patients were included in the study 13 male and 14 female.(M:F = 0.92:1). Age varied from 18-60 years. Most common cause of PG in our study was idiopathic in 19 (70.37%) patients , 4 (14.8%) patients had post- traumatic PG,2(7.4%) had post surgical PG and 1 (3.7%) patient had post tubal ligation PG. One 60 years old male had IgA gammopathy associated recurrent PG.

Table :1: Etiology of PG

Cause of pyoderma gangrenosum		Male	Female
1)	Idiopathic		
a)	Post-traumatic	3	1
b)	Appendicitis surgery wound	1	1
c)	Post tubal ligation wound	0	1
d)	Unknown	8	11
2)	IgA gammopathy	1	0

Most common site of PG in our study was lower leg in 14 (51.8%) of patients followed by thigh 5(18.5%), 3(11.11%) abdomen 3 (11.11%), 2(7.4 %) buttock and perineum.

Duration of PG varied from 4 months to 2 years with an average duration of 9.7 months. Number of lesions in our study were single in 18 (66.6%), three lesion in 2(7.4%) patients, two lesion in 5(18.5%). While one patient with IgA gammopathy had 6 lesions of vegitative and ulcerative type, which were recurrent in nature. Out of 27 patients, 3(11.11 %) patients had associated diabetes mellitus and 1 patient had IgA gammopathy plus DM, HTN and IHD. Rest had no associated comorbidity.

According to formula mentioned above the average initial area of ulcer (before starting cyclosporin) is 45.58 cm2, while at the end of 12 week average area is 7 cm2.The difference in ulcer area before and after treatment was statistically significant. (p value <0.0001).

Patients were divided in 4 groups according to % reduction in ulcer area at the end of 12 weeks of treatment. Excellent response that is 90 to 100% reduction in ulcer area was seen in 12(44%) of patients, good response (70 to 89% reduction in ulcer area) was seen in 10(37%) of patients. Moderate response (50 to 69%) was seen in 5(18.5%).

Image 1,2: Pyoderma gangrenosum over endoscopy scars for appendicectomy; excellent healing with cribiform scarring at the end of 10 week of oral cyclosporin.

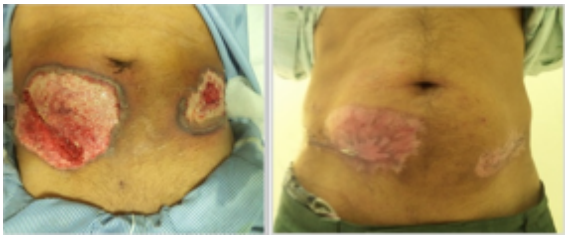
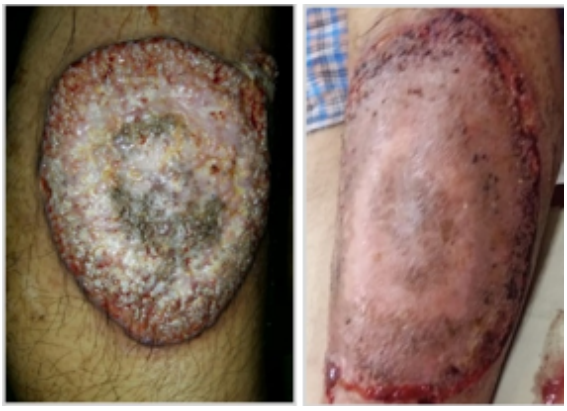
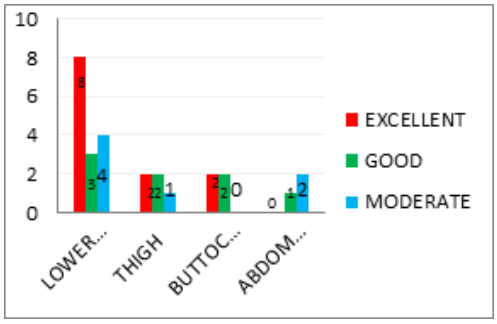


Figure 3,4: A 60 year old male with vegitative PG associated with IgA GAMOPATHY showed central clearing of vegitative lesion at the end of 12 week .



None of our patients had poor response (less than 50% reduction in ulcer area).

CHART 1: Site wise response



In all patients pain was significantly reduced after 3 weeks of starting treatment. During treatment blood pressure and renal function (RFT) of all patients remained within normal limit .

None of our patients required to stop treatment due to adverse effect as no major adverse effect was noted in any patient.

Table 2: Adverse effects in our study

Side effects	No of patients
Not significant	15
Gi disturbance	4
Headache	6

All patients are under remission with no recurrence in 1 year of follow up, except in one patient with multiple leg ulcer recurrence was seen within 3 months of stopping cyclosporin so cyclosporin was restarted and within 1 month of starting cyclosporin; patient developed renal function impairment in form of raised creatinine and nephropathy; on further investigating patient was diagnosed to have IgA gammopathy. so, cyclosporine was stopped.

DISCUSSION:

Pyoderma gangrenosum is an inflammatory disease characterized by neutrophil infiltration involving the skin and other organs. Management of PG has always been a therapeutic challenge. Exclusion of other diagnoses such as bacterial pyoderma, deep fungal infection, and factitial ulcer is mandatory. Management of underlying diseases, correction of anemia, relief of pain, treating secondary infections and bed rest are also important.[7][8] Cyclosporine acts by inhibition of intracellular enzyme calcineurin by complex formed between cyclosporine and cyclophilin which leads to reduced activity of transcription factor, nuclear factor of activated T cells(NFAT-1), leading to suppression of IL-2.The dose required to achieve remission is between 5 and 10 mg/kg daily[4] Potential side effects may be significant and include hypertension, hirsutism, tremor, hepatotoxicity, abnormalities of the central nervous system, nephrotoxicity and a potential for lymphoma development.

In comparision with study by Najeeba Riyaz et al[9], slight female predilection noted in our study. While mean age of our study population was similar to their observations. The most common sites of involvement was lower leg (51%) which is lower than their observation(78%). Whether pyoderma gangrenosum affecting areas other than the legs is at high risk for developing multiple ulcers (as observed by us) needs further evaluation. We found systemic associations in 8% of total patients with diabetes being the most commom entity. In Comparison to Anthony D et al [10]in which 28 (47%) out of 59 patients showed healing of ulcer in 6 months on cyclosporine 4 mg / kg and adverse effects like headache in 5(8%) and GI disturbances in 17(64%) while we found excellent response in 12 (44%) patients out of 27 patients with oral cyclosporine 3mg /kg at the end of 12 weeks and mild adverse events like headache (22%, n=6) and gastrointestinal disturbances (14.8%, n=4).

Matis WL and Ellis CN [11]presented a series of 11 patients with pyoderma gangrenosum, with a wide range of underlying diseases, whose ulcers were refractory to usual therapy and who were treated with low-dose cyclosporine. 10 of the 11 patients cleared rapidly and completely.

Zumdick M treated 6 patients with pyoderma gangraenosum with oral cyclosporine at daily doses of 3 mg/kg[12] Marked improvement of the skin lesions and complete healing occurred in all patients over a period of 3-6 months.The results show that low-dose cyclosporine treatment can be considered a first-line treatment of pyoderma gangraenosum.

Cyclosporine given in 3mg/kg in our study proved to be an effective management option in treatment resistant pyoderma gangrenosum patients with excellent response in 44% of the cases.None of our patients had inflammatory bowel disease, though we found IgA paraproteinemia in one patient with treatment resistant multiple lesions of PG who showed excellent response to CyA.

CONCLUSION:

Pyoderma gangrenosum is a devastating condition which affects quality of life and to add on to this treatment of it which mainly includes systemic high dose corticosteroids poses great challenges as these also comes with their added side effects.

Low dose Cyclosporin therapy in our patients of pyoderma gangrenosum showed rapid clinical improvement with comparatively tolerable adverse effects. We recommend further studies with

cyclosporine in low dose (3mg/kg/day) in PG.

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