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CASE AND RESEARCH LETTER

Four-case Report of Upadacitinib as an Alternative Treatment for Patients With Recalcitrant Pyoderma Gangrenosum

Upadacitinib como alternativa terapéutica en pacientes con pioderma gangrenoso recalcitrante: reporte de cuatro casos

To the Editor,

Pyoderma gangrenosum (PG) is an uncommon inflammatory skin disorder characterized by chronic and recurrent blistered or necrotic ulcers, and a predominantly neutrophilic infiltrate on histopathology.¹ Several subtypes of PG exist such as ulcerative, bullous, pustular, peristomal and superficial granulomatous, yet the ulcerative variant represents about 85% of cases.^{1,2} The etiology of this debilitating disease is not fully understood. PG can be idiopathic, or be associated with drug consumption (cocaine/levamisole),³ inflammatory bowel disease (IBD), rheumatoid arthritis (RA), hematologic disorders, or be part of an inherited inflammatory syndrome.² The pathogenesis of PG has not yet been completely defined and currently no drugs have been approved for the management of this disease. In most cases, management is based on off-label classical immunosuppressors and biological agents.⁴ Recent studies have demonstrate that the Janus kinase (JAK) pathway may be involved in the progression of PG.^{4,5} Off-label treatment with JAK inhibitors has been proposed by some authors⁶⁻¹⁰ as an optimal therapeutic strategy for the management of refractory PG in patients in whom other systemic therapies have failed. Experience with tofacitinib⁵⁻⁹ has been the most widely reported to this date; however, the use of more-selective JAK inhibitors such as upadacitinib could be also effective with a better safety profile and, indeed, a few cases have already been published.¹⁰

We conducted a retrospective bi-centric case-series evaluating short-term safety and efficacy profile of upadacitinib

15 mg/daily or 30 mg/daily for the management of refractory PG. Clinical response was assessed by Physician Global Assessment (PGA) during the evaluated period. An optimal response was considered when reaching a PGA ≤ 2 . Four cases of recalcitrant PG were included. Two patients were women and two were men, ranging from 26 up to 62 years. The mean baseline PGA was 4 (ranging from 0 to 4). The mean course of PG prior to upadacitinib treatment was 4.3 years (range, 1-10). A well-known trigger or comorbidity were identified in all patients. One patient had poorly-controlled inflammatory bowel disease and a different participant, well-controlled rheumatoid arthritis. In the last two patients the PG onset was associated with the use of levamisole-adulterated-cocaine in one case and breast surgery in the other one. Two patients had ulcerative PG limited to the lower legs, one patient had generalized pustular PG and the other one, the generalized vegetative subtype. Prior to upadacitinib treatment, a mean 5 (range, 4-6) systemic therapies had failed in all patients. Three patients were on concomitant systemic treatments during upadacitinib initiation; however, they had been on these additional drugs for a significant amount of time without improvement, prior to starting upadacitinib. Systemic corticosteroids could be down titrated or completely removed after upadacitinib introduction in the entire cohort. All patients reached a PGA ≤ 2 after a mean follow-up of 17.5 weeks (range, 12-26), controlling pain and without developing drug-related severe adverse events or miss-controlling PG-related comorbidities. Baseline characteristics, comorbidities, prior and concomitant therapies are illustrated in [Table 1](#). Clinical response to upadacitinib in patients #2 and #3 can be seen in [Fig. 1](#).

While this is a small case-series with a short follow-up based on our own observations, and according to Kooybaran et al.,¹⁰ upadacitinib seems to be a promising therapeutic alternative and possible corticosteroid sparing option for patients with either pustular, vegetative or classic PG with failed multiple systemic therapies (combined or in monotherapy) as previously reported for tofacitinib. Nonetheless, the drug safety profile could be better.¹⁰ Currently, no therapies have been approved by the EMA or the FDA for the management of PG; therefore upadacitinib

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Table 1 Summary of our cases of PG treated with upadacitinib (including treatment regimens).

	Age (years) and gender	Age of the PG ^a	Cardiovascular risk factors	Smoker	PG associated comorbidities or trigger factors	Prior systemic treatments	Upadacitinib dose	Concomitant therapies	Basal PGA ^b (0–4)	Weeks of follow-up (number)	Final PGA (0–4)
Case 1 Vegetative	45, male	1 year	No	No	Inflammatory bowel disease	Scs ^c Methotrexate Cyclosporin Adalimumab	15 mg daily	Adalimumab 40 mg/weekly Scs 20 mg/daily	4	26	1
Case 2 Pustular	26, female	1 year	No	No	Mammoplasty	Scs Methotrexate Cyclosporin Adalimumab	15 mg daily first month, and then 30 mg/daily	Adalimumab 40 mg/weekly Scs 20 mg/daily	4	16	2
Case 3 Ulcerative	62, female	5 years	Dyslipidemia, diabetes	Yes	Rheumatoid arthritis	Scs Methotrexate Cyclosporin Adalimumab Golimumab	30 mg/daily	Scs 75 mg/daily	4	16	2
Case 4 Ulcerative	50, male	10 years	Arterial hypertension	Yes	Cocaine abuse	Scs Methotrexate Azathioprine Cyclosporin Adalimumab Certolizumab Infliximab	30 mg/daily	No	4	12	1

^a Pyoderma gangrenosum.^b Physician Global Assessment.^c Systemic corticosteroids.

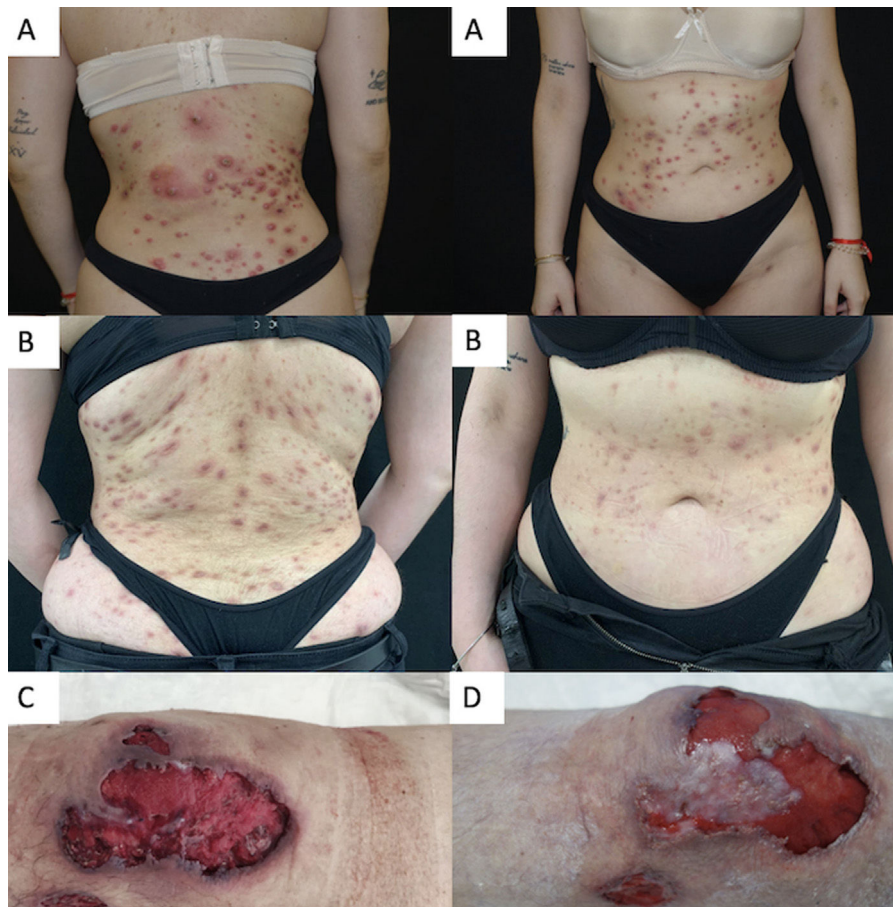


Figure 1 Pyoderma gangrenosum treated with upadacitinib: (a) case #2 prior to upadacitinib therapy; (b) case #2, 10 weeks after starting upadacitinib; (c) case #3 prior to upadacitinib; (d) case #3, 4 weeks after starting upadacitinib.

and other JAK-inhibitors^{5–10} could be considered a reasonable alternative (combined or in monotherapy) especially for patients with inflammatory bowel disease or rheumatoid arthritis. However, future clinical trials and long-term real-world series will be needed to evaluate the efficacy profile of upadacitinib and other JAK inhibitors in the management of refractory PG.

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Informed consent

All informed consents are available.

Conflicts of interest

Pedro Mercader-García declared having received speaker fees and compensation for being a member of advisory boards from Sanofi, Leo Pharma, Lilly and Abbvie, outside the submitted work. The remaining authors declared no conflicts of interest whatsoever.

Data availability

All data are available on request from the authors.

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References

1. George C, Deroide F, Rustin M. Pyoderma gangrenosum – a guide to diagnosis and management. *Clin Med (Lond)*. 2019;19:224–8.
2. Ahn C, Negus D, Huang W. Pyoderma gangrenosum: a review of pathogenesis and treatment. *Expert Rev Clin Immunol*. 2018;14:225–33.
3. Martínez-Gómez M, Ramírez-Ospina JA, Ruiz-Restrepo JD, Velásquez-Lopera MM. Pyoderma gangrenosum associated to the use of cocaine/levamisole. Series of three cases and literature review. *An Bras Dermatol*. 2021;96:188–95.
4. Maronese CA, Pimentel MA, Li MM, Genovese G, Ortega-Loayza AG, Marzano AV. Pyoderma gangrenosum: an updated literature review on established and emerging pharmacological treatments. *Am J Clin Dermatol*. 2022;23:615–34.

5. Orfaly VE, Kovalenko I, Tolkachjov SN, Ortega-Loayza AG, Nunley JR. Tofacitinib for the treatment of refractory pyoderma gangrenosum. *Clin Exp Dermatol.* 2021;46:1082–5.
6. Scheinberg M, Machado LAM, Castro LG, Ferreira SB, Michalany N. Successful treatment of ulcerated pyoderma gangrenosum with baricitinib, a novel JAK inhibitor. *J Transl Autoimmun.* 2021;4:100099.
7. Gregory MH, Ciorba MA, Deepak P, Christophi GP. Successful treatment of pyoderma gangrenosum with concomitant tofacitinib and infliximab. *Inflamm Bowel Dis.* 2019;25:e87–8.
8. Choi AW, Abuav R, Rabizadeh SM, Ansari R, Marsch AF. Recalcitrant and severe pyoderma gangrenosum attributable to levamisole-adulterated cocaine and treated successfully with oral tofacitinib. *JAAD Case Rep.* 2020;6:939–41.
9. Lee SD, Singla A, Harper J, Barahimi M, Jacobs J, Kamp KJ, et al. Safety and efficacy of tofacitinib in combination with biologic therapy for refractory Crohn's disease. *Inflamm Bowel Dis.* 2022;28:309–13.
10. Kooybaran NR, Korsten P, Schön MP, Mössner R. Response of rheumatoid arthritis-associated pyoderma gangrenosum to the JAK1 inhibitor upadacitinib. *J Dtsch Dermatol Ges.* 2022;20:522–4.

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