Rapid resolution of pyoderma gangrenosum with brodalumab therapy

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INTRODUCTION

Pyoderma gangrenosum (PG) is a burdensome ulcerative dermatosis, which presents in isolation or in association with other inflammatory conditions (eg, inflammatory bowel disease).[1] PG can be therapeutically challenging, especially when first-line treatments (such as oral corticosteroids and cyclosporine) fail to resolve the condition.[1,2] Although interleukin (IL)-17 and IL-23 antagonism may ameliorate disease activity, only case reports of secukinumab therapy currently exist.[2] We report 2 cases of PG that showed rapid resolution in response to brodalumab, 210 mg/1.5 mg, for co-existing hidradenitis suppurativa (HS).

Abbreviations used:

EOW: every other week
HS: hidradenitis suppurativa
IL: interleukin
PG: pyoderma gangrenosum

CASE REPORTS

Patient 1, a 23-year old man with PASH syndrome (pyoderma gangrenosum, acne conglobata and suppurative hidradenitis) presented with a 24-month history of painful superficial PG on the anterior and posterior surfaces of the lower limbs (Fig 1, *A* and *B*). Previous therapy with oral corticosteroids (up to 1 mg/kg/d), adalimumab (40 mg/wk), and adjuvant methotrexate (7.5 mg/wk) (Fig 2, *A* and *B*) failed to resolve the ulceration (Fig 1, *A* and *B*) and pain (7/10). He enrolled in a clinical trial of brodalumab, 210 mg/1.5 mg subcutaneous weekly, for treatment of HS (NCT04249713).[3] Within 4 weeks, he experienced a rapid reduction in swelling, pain, and re-epithelialization of PG (Fig 1, *A* and *B*). Follow-up 6 months after starting brodalumab indicated no recurrence of his PG (Fig 2, *B*).

Patient 2, a 52-year-old woman with a 10-year history of recurrent PG of the left anterolateral lower limb (Fig 1, *C*), was previously treated with intermittent use of oral and intralesional corticosteroids and adalimumab for both PG and coexistent HS (Fig 2, *A* and *B*). She started brodalumab, 210 mg/1.5 mL every other week (EOW) as part of a clinical trial for HS (NCT03960268).[4] No PG was apparent during the course of the clinical trial. After exiting the trial, brodalumab was withheld for 6 weeks when unwell with presumed coronavirus disease 2019, resulting in the development of a rapidly expanding, painful ulceration on the left anterolateral lower limb (Fig 1, *C*). Recommencement of brodalumab EOW resulted in slow improvement with cyclical increase in pain the week before brodalumab administration. An increase in the frequency of administration of brodalumab was unavailable. Within 12 weeks, the PG had re-epithelialized with minimal residual pain and edema (Fig 1, *C*). Follow-up 4 months after recommencement of brodalumab indicated no recurrence of PG (Fig 2, *B*).

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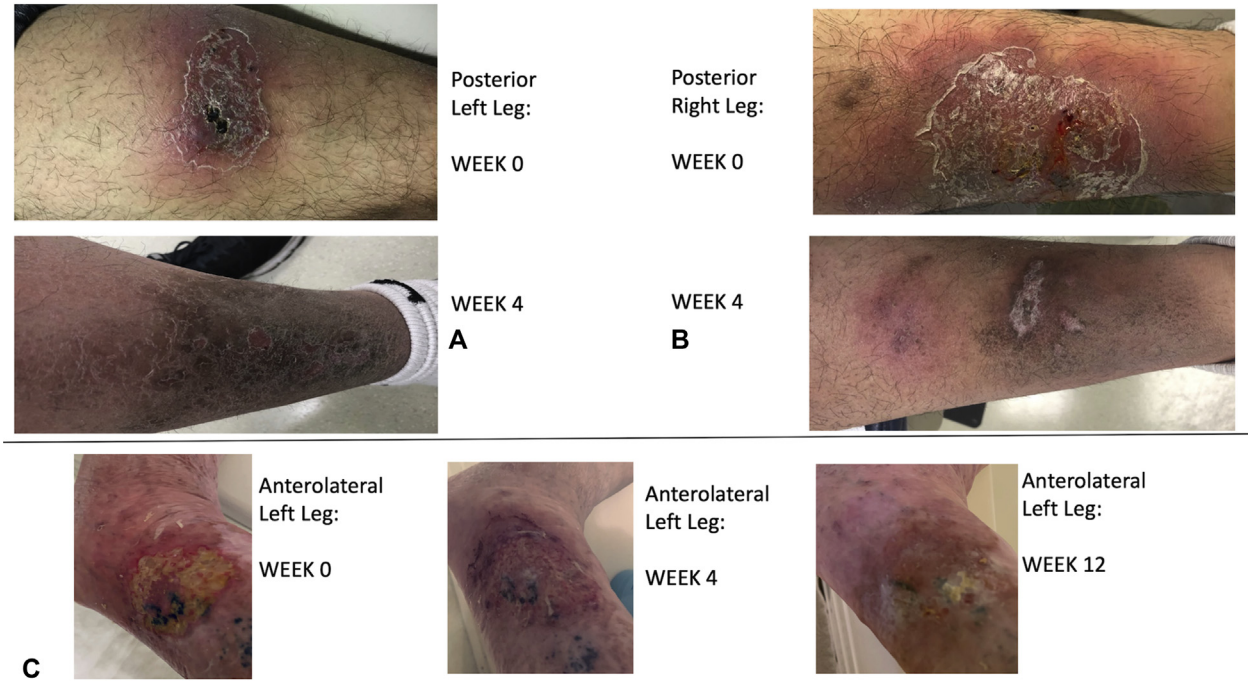

Fig 1. Clinical pictures of patient 1 (**A** and **B**) and patient 2 (**C**) with active PG at week 0 of brodalumab therapy and after 4 weeks of therapy (patient 1) and week 0 of re-commencement of brodalumab therapy and at 4 and 12 weeks of therapy (patient 2). Findings in both patients demonstrate cutaneous ulceration with violaceous undermined borders surrounded by peripheral inflammation. Hemorrhagic (patient 1) and purulent (patient 2) discharge can be seen. After treatment with brodalumab there is re-epithelialization of the previous ulceration with marked reduction in inflammation and edema. Residual scarring is noted in both cases.

A

Patient	Gender	Age	Smoker	BMI	Site(s)	Subtype	Comorbidities	Prev Treatments
Patient 1	M	23	N	37.4	Lower Limbs	Ulcerative	HS	ILCS, Oral CS,MTX, Ada
Patient 2	F	52	Y	29.5	Lower Limbs	Ulcerative	Arthritis, HS	ILCS, Oral CS, Ada

B

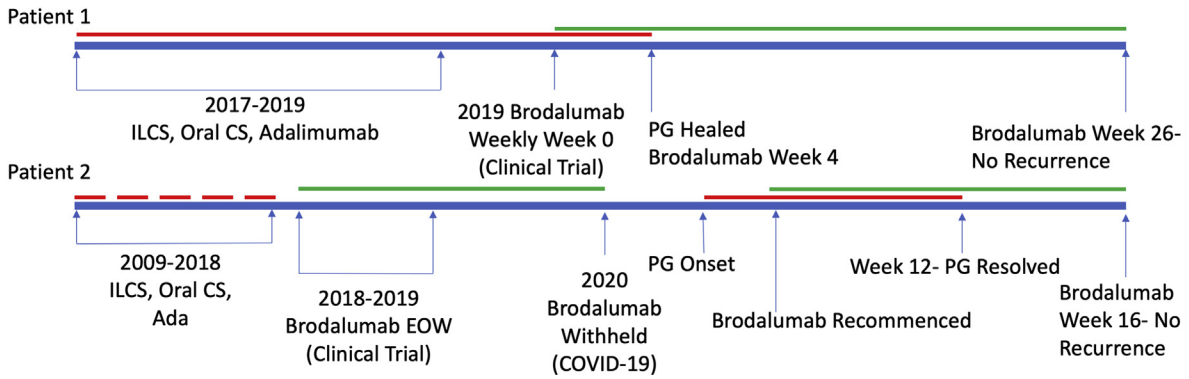

Fig 2. Demographic and disease characteristics of both patients (**A**) as well as a schematic time course of the disease, previous treatments, and brodalumab therapy (**B**). Blue lines indicate time and red lines indicate time periods when PG was active. Green lines indicate when brodalumab was actively being administered.

DISCUSSION

The pathophysiology of PG is not completely understood. Dysregulated helper T cell 17/regulatory T cell ratios are observed in lesional tissue[1,5]; however, both improvement and exacerbation with secukinumab (IL-17a antagonist) are reported.[2] Brodalumab (IL-17 receptor-A antagonist) is unique in blocking multiple IL-17 isoforms (IL-17A, IL-17C, IL-17F),[2] which are upstream regulators of CXCL1 and CXCL8 (IL-8). CXCL1 and CXCL8 (IL-8) are known chemotactic mediators of neutrophils and highly upregulated in PG tissue.[1] This blockade of multiple IL-17 isoforms may contribute to the rapid resolution of PG observed in these cases. Additionally, the high recapture rate of the drug[6] suggests that it is much less likely to result in decreased efficacy if withheld as demonstrated by patient 2. Neither patient had depression or thoughts of self-harm or suicidal ideation and reported their mood was improved due to the rapid decrease in pain from brodalumab therapy. Both patients also showed acceptable control of their HS achieving greater than 75% reduction in the number of inflammatory abscesses and nodules.[3,4]

The slower improvement in patient 2 concurs with findings in HS that weekly brodalumab dosing provides more rapid disease control than EOW dosing.[3] This finding may be a result of receptor-mediated clearance by neutrophils (brodalumab binding to neutrophils and removal in the form of pus) in a mechanism similar to that proposed in HS.[4] Alternatively, brodalumab therapy may be more effective in small lesions or more superficial variants of PG (patient 1) rather than larger ulcerative lesions (patient 2).

Although larger placebo-controlled studies and studies in idiopathic PG (without co-existent HS) are needed, these case reports suggest that brodalumab, 210 mg/wk, results in rapid resolution of PG. EOW dosing may also aid resolution of PG; however, resolution is likely to be significantly slower than with weekly dosing.

REFERENCES

1. Ahn C, Negus D, Huang W. Pyoderma gangrenosum: a review of pathogenesis and treatment. *Exp Rev Clin Immunol*. 2018; 14(3):225-233.
2. McKenzie F, Cash D, Gupta D, Gupta A, Cummings LW, Ortega-Loayza AG. Biologic and small-molecule medications in the management of pyoderma gangrenosum. *J Dermatol Treat*. 2019;30(3):264-276.
3. Frew JW, Navrazhina K, Sullivan-Whalen M, Gilleaudeau P, Garcet S, Krueger JG. Weekly administration of brodalumab in hidradenitis suppurativa: an open label cohort study. *J Eur Acad Dermatol Venereol*. 2020 (In Press).
4. Frew JW, Navrazhina K, Grand D, et al. The effect of subcutaneous brodalumab upon clinical disease activity in hidradenitis suppurativa: an open label cohort study. *J Am Acad Dermatol*. 2020;83(5):1341-1348.
5. Caprioni M, Antiga E, Volpi W, et al. The Treg/Th17 cell ratio is reduced in the skin lesions of patients with pyoderma gangrenosum. *Br J Dermatol*. 2015;173(1):275-276.
6. Lebwohl M, Cather J, Armstrong A, Van Voorhees A, Jacobson A. Recapture rate of brodalumab in patients with a lapse in treatment. *J Drugs Dermatol*. 2020;19(4): 384-387.