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Tumor necrosis factor- α inhibitors for the treatment of pyoderma gangrenosum not associated with inflammatory bowel diseases: A multicenter retrospective study



To the Editor: Pyoderma gangrenosum (PG) is a rare neutrophilic dermatosis characterized by chronic neutrophilic skin ulceration in the absence of infection.¹ An underlying systemic disease is identified in more than 50% of patients, with inflammatory bowel diseases (IBDs) being the most frequent.² Systemic steroids and cyclosporine are the first-line treatments. Recently, tumor necrosis factor- α (TNF- α) inhibitors have been used for refractory PG. The efficacy of TNF- α antagonists has been well demonstrated in PG associated with IBD.³ One study⁴ has already investigated the efficacy of TNF- α antagonists in some British patients with IBD (n = 7) and without IBD (n = 6). The aim of this study was to evaluate the efficacy of TNF- α antagonists in non-IBD-associated PG.

This retrospective and multicenter study included adult patients in whom PG was diagnosed from 1995 to 2018, with confirmation of the diagnosis by clinical examination, histology, and sterile microbiologic examination. Patients with PG

associated with IBD were excluded. Complete remission (CR) was defined as complete healing of ulceration(s), partial remission was defined as healing of 50% to 100% of ulceration(s), and failure was as healing of less than 50%.

A total of 10 patients with PG without IBD that was treated with a TNF- α antagonist were included (Table 1). PG was idiopathic in 2 patients and associated with an underlying disease or predisposing factor in 8 patients (with ankylosing spondylitis in 3 patients; relapsing polychondritis in 1; hidradenitis suppurativa in 1; synovitis, acne, pustulosis, hyperostosis, and osteitis in 1; IgA monoclonal gammopathy in 1; levamisole consumption in 1; and surgery in 1). Infliximab was used in 8 cases and adalimumab, etanercept, and golimumab were used in 1 case each. CR was obtained in 7 of 10 cases. The median complete healing time was 3 months (range, 0.5-7). Partial remission was obtained in 2 of 10 cases. Failure was observed for 1 patient treated first with infliximab and then with etanercept for idiopathic PG. A TNF- α antagonist was generally used as a third line of treatment (range, 1-7). Among the 6 patients receiving concomitant steroid treatment, steroid weaning was obtained in 4. The median follow-up time was 33.5 months (range, 4-89). No serious infectious adverse events were observed. One limitation of our study was the use of concomitant therapy in association with TNF- α antagonists, which may not truly reflect their efficacy when used as a single agent.

A total of 58 cases of PG without IBD treated with TNF- α antagonists have been reported in the literature. Of those cases, 24 (41%) were idiopathic PG, 10 (17%) were associated with rheumatoid arthritis, 6 (10%) were postoperative or posttraumatic, 4 (7%) were associated with hidradenitis suppurativa, 2 (4%) were associated with monoclonal gammopathy, and 2 (3.5%) were associated with cocaine (levamisole) abuse. CR was achieved in 76% (31 of 41), 64% (9 of 14), 47% (9 of 19), and 100% (1 of 1) of patients treated with infliximab, adalimumab, etanercept, and certolizumab pegol, respectively. The median complete healing time was 4 months (range, 0.75-48). TNF- α antagonists were used after failure of multiple lines of treatments (range, 1-10). The response rate was similar when TNF- α antagonists were used after cyclosporine failure. The treatment was well tolerated in most cases.

The efficacy of TNF- α antagonists in idiopathic PG and in PG with an underlying disease in which TNF- α does not have a formerly demonstrated role (relapsing polychondritis and cocaine abuse) suggests a broader role of this cytokine in the

Table I. Patients' characteristics and clinical response to TNF- α antagonists

Patient No.	Sex, age	PG characteristic, duration	Associated disease	Prior treatment	TNF- α antagonist: molecule, dosage	Clinical response/time to response	Concomitant treatment	Steroid withdrawal
1	F, 21 y	Disseminated, 5 mo	Levamisole consumption	Steroids Dapsone Colchicine	Infliximab, 7.5 mg/kg/6 wk	CR/7 mo	Oral steroids	Yes
2	F, 54 y	Multilesional, 8 mo	Postoperative	Steroids	Infliximab, 5 mg/kg 1 infusion (serum sickness)	CR/2 mo	Oral steroids Topical tacrolimus	Yes
3	F, 26 y	Localized, 16 y	Relapsing polychondritis	Steroids Dapsone Minocycline Cyclosporine Colchicine Methotrexate	Infliximab, 7.5 mg/kg/6 wk	CR/3 mo	Oral steroids	Yes
4	M, 37 y	Multilesional, 5 mo	Ankylosing spondylitis	Steroids	Adalimumab, 40 mg/2 wk	CR/2 mo	Oral steroids	Yes
5	F, 51 y	Localized, 3 y	SAPHO	Steroids Methotrexate	Infliximab, 5 mg/kg/8 wk	CR/a few mo	Methotrexate	NR
6	M, 28 y	Multilesional, 5 mo	Ankylosing spondylitis	Steroids	Infliximab, 5 mg/kg/6 wk	CR/4 mo	None	NR
7	M, 46 y	Multilesional, 6 y	MGUS IgA λ	Steroids Methotrexate Minocycline	Infliximab, 7.5 mg/kg/4 wk	PR/2 wk	Oral steroids Topical tacrolimus	No Prednisone 10 mg/d
8	M, 50 y	Multilesional, 5 y	Idiopathic	Steroids Dapsone Colchicine	Infliximab, 5 mg/kg/8 wk	PR/3 mo	Oral steroids Dapsone	No Prednisone 6 mg/d
9	M, 53 y	Multilesional, 2 mo	Ankylosing spondylitis Hidradenitis suppurativa	None	Golimumab, 50 mg/4 wk	CR/3 mo	Topical steroids	NR
10	M, 57 y	Multilesional, 6 y	Idiopathic	Steroids Methotrexate	Infliximab, 5 mg/kg/8 wk Etanercept, 50 mg \times 2/wk	Failure	Topical steroids	NR

CR, Complete remission; F, female; M, male; MGUS, monoclonal gammopathy of undetermined significance; NR, not relevant; PR, partial remission; SAPHO, synovitis, acne, pustulosis, hyperostosis, and osteitis; TNF- α , tumor necrosis factor- α .

pathophysiology of PG. TNF- α antagonists may represent an alternative to cyclosporine in steroid-refractory PG.

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Recent dermatology visit is associated with thinner Breslow depth nodular melanomas



To the Editor: Nodular melanomas (NMs) account for 10% of melanomas, but account for >50% of deep melanomas (>2 mm).¹ The goal of this study is to characterize health care use patterns of individuals with NM compared with other types of melanomas in a US population. We evaluated melanomas diagnosed between September 1996 and December 2015 in the Veterans Affairs Miami Health Care System.

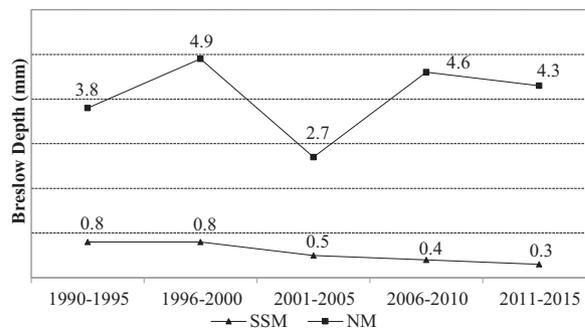


Fig 1. Average Breslow thickness of nodular melanoma (NM) and superficial spreading melanoma (SSM) over time. NM had an average Breslow thickness of 3.8 mm at diagnosis in 1996 compared with 4.3 mm in 2015 ($P = .84$). SSM had an average Breslow thickness of 0.8 mm at diagnosis in 1996 compared with 0.3 mm in 2015 ($P = .01$).

We found no significant change in average Breslow thickness of NM over time (3.8 mm in 1996 vs 4.3 mm in 2015, P trend = .84) while the detection for superficial spreading melanomas had improved significantly (0.8 mm in 1996 vs 0.3 mm in 2015, P trend = .01; Fig 1).

The percentage of patients with NM who had seen a primary care physician or a dermatologist in the 6 months preceding the diagnosis was significantly lower than for those with other types of melanomas (primary care physician, $P = .05$; dermatologist, $P = .03$, χ^2); patients who had seen a dermatologist in the 6 months preceding their diagnosis had significantly thinner NMs than those that had not been seen (1.81 mm vs 3.85 mm, $P = .006$). Individuals with NM were significantly less likely to have had age-appropriate colonoscopy screening compared with those with other types of melanomas (47.0% for NM vs 73.7% for melanoma—other, $P < .01$, χ^2 ; Table I).

This study revealed several important findings. First, the detection of NM has not improved over time in this group of predominantly older, white men. Second, patients who develop NM are more likely to be lacking in skin-specific and general preventative care. Third, routine dermatology contact resulted in significantly thinner NMs at diagnosis.

In this population of US veterans with standardized health care, institutional factors such as differential access to Veterans Affairs care is less likely a significant contributor in accounting for the difference between individuals with NM versus other types of melanomas. Personal factors, such as a general low perceived need for preventive care and a lack of preventive habits (eg, sunscreen use, self-examinations) may play a greater role accounting for overrepresentation of health care underusers in the NM group. Future study should