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<LRH>Research Letters

<DOC>Research Letter

**<AT>Ustekinumab treatment for neutrophilic dermatoses associated with Crohn's disease:
A multicenter retrospective study**

<BEGIN ARTICLE>

To the Editor: Systemic corticosteroids and tumor necrosis factor- α (TNF- α) antagonists are first-line therapies for neutrophilic dermatoses (NDs) associated with Crohn's disease (CD), the most frequent being pyoderma gangrenosum (PG).¹ Ustekinumab, a monoclonal antibody directed against the interleukin 12/interleukin 23 p40 subunit, was recently approved for use in CD.² This multicenter retrospective study conducted in 9 French hospitals between January 2013 and July 2017 assessed the efficacy of ustekinumab in CD-associated ND. Consecutive patients referred for active CD-associated ND and treated with ustekinumab following ND onset were included. Diagnosis of ND was based on previously published diagnostic criteria for NDs³ and confirmed by skin biopsy. The efficacy of ustekinumab was assessed at week 16 after initiation: efficacy in relation to ND was evaluated by determining whether it resulted in a complete, partial (a >50% reduction in symptoms), or no response, and efficacy in relation to CD was evaluated by using the Harvey-Bradshaw index.

The study included 7 patients from among the 320 of 8298 patients with CD who received ustekinumab; the 7 patients included 5 women, 4 patients with PG, 2 with pustulosis of the folds (APF), and 1 with chronic recurring Sweet syndrome (Table I). The result of microbiologic skin sampling was negative except in the case of patient 6, who had staphylococcal superinfection, as is frequently reported in APF.³ The median ages at onset of ND and CD were 28 years (range, 6-43] and 22 years (range, 13-38), respectively. The median

durations of ND and CD at initiation of ustekinumab therapy were 4 and 8 years, respectively. Of the 7 patients studied, 4 had active CD at initiation of ustekinumab therapy; 6 of the 7 patients had previously received TNF- α antagonists that were discontinued because of side effects or inefficacy. A history of lupus erythematosus contra was indicated in patient 5. Patients received ustekinumab, 90 mg every 8 weeks subcutaneously, with slightly varying induction protocols for both CD and ND treatment (Table I).

At week 16, although most NDs were refractory to multiple therapies and ustekinumab was used as the third to eighth line of treatment, ustekinumab induced remission of ND in 6 of 7 cases (86%) (Table I): complete response in 4 of 7 cases (57%), partial response in 2 of 7 cases (29%), and no response in 1 case (patient 7 with refractory recurring Sweet syndrome). At week 16, the CD of 4 patients who had active CD on day 0 was in complete remission, 2 patients had stable CD with prolonged remission, and 1 patient had a worsening of CD activity that had previously be controlled by adalimumab. No serious side effects were reported. The median follow-up time was 36 months. One patient with ND eventually relapsed (patient 2). A literature review yielded 12 additional cases of ND that had been successfully treated with ustekinumab; of the total of 13 patients (11 with PG and 2 with APF), 9 (69%) were complete responders^{4,5} and 3 (23%) were partial responders (Table II). The limitations of our study are linked to its retrospective nature. Open labeled or randomized studies are needed to confirm these results. Associated immunosuppressants were sometimes required because of the severity of the ND (in patients 3 and 5); however, ustekinumab allowed tapering and/or discontinuation of the associated therapies.

Ustekinumab may control both ND and CD. It should therefore be considered as alternative therapy for refractory ND in cases of resistance, intolerance, or contraindication to corticosteroids or TNF- α antagonists.

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Table I. UST treatment modalities, response to treatment, adverse events, and follow-up

ND	Previous Tx before occurrence of ND	Previous Tx after occurrence of ND	ND/CD duration before UST, y	UST						Associated Tx	Adverse events	Follow-up, mo
				Dose, mg	Frequency	Duration, mo/reason for interruption	Efficacy					
							ND	CD (HBI at d 0/wk 16)				
PG	AZA, IFX, MTX, mesalazine	dCS	1/22	90	8 wk	>42 (ongoing)	CR	CR [†] (3/2)	dCS,	0	42	
PG	CST, mesalazine, AZA, mercaptopurine, IFX, MTX	IFX, topical tacrolimus	2.5/0.8	90	8 wk	8	PR	CR (NA) [‡]	Topical tacrolimus, mercaptopurine	0	47 Relapse of CD; switch to golimumab; CD and ND	
PG	5-ASA, AZA, IFX, ADA, CST, mercaptopurine,	dCS, DAPS, cyclosporine, tacrolimus, MTX, certolizumab anakinra, vedolizumab	4.5/18	90	wk 0-wk 4-wk 8, and every 8 wk	>12 (ongoing)	CR	CR (11/3)	CS, anakinra (discontinued within 3 mo)	0	12	
PG	CST, IFX, ADA	CST, MTX	4/11	90	wk 0-wk 2-wk 4 and every 8 wk	11 (CD relapse)	CR	CR (NA) [‡]		Arm erysipelas [§]	31 Relapse of CD treated with surgery; CR of CD and ND since	
AP F	—	dCS, CS, DAPS, isotretinoin, colchicine, cyclosporine, anakinra	16/1.5	90	8 wk	27 (pregnancy desire)	PR	CR (7/1)	MTX, cyclosporine	0	36 Switch to AZA Good control of CD ND, CR of CD	
AP F	—	Antibiotics, dCS, ADA, CS	3/3	90	wk 0-wk 2 and every 8 wk	>14 (ongoing)	CR	CR (3/2)	dCS	0	14	
SS	AZA, 5-ASA	Colchicine, MTX, CS, ADA, DAPS	7/8	90	8w	6 (inefficacy)	NR	NR (1/5)	CS (intermittent)	0	41 CR of ND + CD IFX	

ADA, Adalimumab; APF, amicrobial pustulosis of the folds; 5-ASA, 5-aminosalicylic acid; AZA, azathioprine; CD, Crohn's disease; CR, complete response; CS, systemic corticosteroid; DAPS, dapsone; dCS, dermocorticosteroid; F, female; HBI, Harvey-Bradshaw index; IFX, infliximab; M, male; MTX, methotrexate; NA, not assessed; ND, neutrophilic dermatosis; NR, no response; PG, pyoderma gangrenosum; PR, partial response; Tx, treatment, UST, ustekinumab.

*Case report previously published: Al-Raddadi R, et al. *Acta Derm Venereol.* 2016.

†Complete response of CD to UST defined by an HBI less than 4 or complete remission of CD-related symptoms.

‡The HBI could not be assessed for patients 2 and 4 (permanent stoma), but complete remission of digestive symptoms was observed at week 16.

§ND in the context of HIV infection.

Table II. Reported cases of neutrophilic dermatoses treated with UST (based on a search of the MEDLINE, EMBASE, CENTRAL databases)

Article	Sex, age, y	ND	Associated disorder	Previous Tx	UST		Associated Tx	Response of ND to UST and delay, wk
					Dose, mg	Frequency		
Guenova et al, 2011	F, 37	PG	No	CS	90	wk 0-wk 4-wk 8 and every 8 wk	Topical tacrolimus	PR: 8 CR: 14
Fahmy et al, 2012	F, 34	PG	CD	Intralesional CS, tacrolimus, AZA	90	wk 0-wk 2 and every 8 wk	No	PR: 4 CR: 10
Goldminz et al, 2012 Greb et al, 2016	M, 47	PG	No	CS, cyclosporine, DAPS, AZA, MTX, ADA, IFX, golimumab	90	wk 0-wk 4, and every 8 wk	CS + DAPS	PR: 4 CR: 22 Relapse after 2 years, controlled by increased doses of UST (135 mg/6 wk)
Cosgarea et al, 2014	F, 71	PG	Renal cell carcinoma	CS, cyclosporine, excision of renal cell carcinoma	NI	NI	No	PR: few days CR: 12 only after excision of renal cell carcinoma
Marzano et al, 2015	F, 35	APF	CD	CS, ADA	NI	NI	NI	CR
Acquitter et al, 2015	F, 46	PG	Psoriasis (cutaneous + arthritis)	CS, MTX, DAPS, etanercept	NI	NI	NI	NR Switch to anakinra after 6 months: PR
Barbosa et al, 2016 ⁴								
Case 1	NI	Peristomal PG	NI	NI	NI	NI	Cyclosporine	PR
Case 2	NI	Peristomal PG	NI	NI	NI	NI	CS + DAPS + 6MP	CR
Benzaquen et al, ⁵ 2017	F, 56	PG	Psoriasis (cutaneous + arthritis)	ADA	45	NI	No	CR: 3 injections

Zirwas et al, 2017	F, 27	APF	CD, PPP	ADA, certolizumab pegol for CD (APF and PPP occurring with certolizumab), CS, MTX, colchicine	90	wk 0-wk 4 and every 3 months	CS	PR: 4 CR: 2 injections
Low et al, 2017 ⁵								
Case 1	F, 42	PG	No	Several immunosuppressants	90	wk 0-wk 4 and every 6 wk	CST, MMF, IVIg, DAPS	PR: 12
Case 2	F, 57	PG	No	Several immunosuppressants	90	wk 0-wk 4 and every 8 wk	CST, MMF, DAPS	PR: 24
Case 3	F, 36	PG	No	Several medications	90	wk 0-wk 4 and every 8 wk	CST, MMF, IVIg	PR:20 CR: 56

ADA, adalimumab; *APF*, amicrobial pustulosis of the folds; *AZA*, azathioprine; *CD*, Crohn's disease; *CR*, complete response; *CS*, corticosteroids; *DAPS*, dapsone; *F*, female; *IFX*, infliximab; *IVIg*, intravenous immunoglobulin; *M*, male; *MMF*, mycophenolate mofetil; *6MP*, 6-mercaptopurine; *MTX*, methotrexate; *ND*, neutrophilic dermatosis; *NI*, not indicated; *NR*, no response; *PG*, pyoderma gangrenosum; *PPP*; palmoplantar pustulosis; *PR*, partial response; *Tx*, treatment; *UST*, ustekinumab.