



Thalidomide in Severe Hidradenitis Suppurativa: A Therapeutic Option

Claire HOTZ¹, Emilie SBIDIAN¹⁻³, Saskia INGEN-HOUSZ-ORO^{1,3}, Olivier CHOSIDOW^{1-3#} and Pierre WOLKENSTEIN^{1,3#}

¹Department of Dermatology, Assistance Publique-Hôpitaux de Paris, Henri-Mondor Hospital, Créteil, ²Institut National de la Santé et de la Recherche Médicale, Centre d'Investigation Clinique 1430, and ³EA EpiDermE Université Paris-Est Créteil-Val de Marne, Créteil, France

#These authors contributed equally to the study.

Accepted Jul 17, 2019; E-published Jul 17, 2019

Hidradenitis suppurativa (HS) or acne inversa (AI) is a debilitating chronic inflammatory skin disease (1). Treatment of HS is challenging because of its persistence and poor response to treatment. Although only surgery leads to complete remission, antibiotics or biologics may be helpful. The potential efficacy of anti-tumor necrosis factor (anti-TNF) α agents to treat HS was demonstrated in a patient who received 5 mg/kg/day intravenous infliximab for Crohn's disease (CD): HS lesions substantially improved after two doses (2). The use of anti-TNF α agents (infliximab and adalimumab) to treat HS has since been evaluated (3, 4). European guidelines were recently published (5).

CASE REPORTS

We report retrospectively the cases of 6 HS patients who received thalidomide after failure to respond to multiple broad-spectrum antibiotics and anti-TNF α agents. Three of the 6 patients showed good response to the treatment.

All patients (4 men, 2 women; age range 17–38 years) presented severe Hurley stage III HS and had a very severe hidradenitis suppurativa-physicians global assessment (HS-PGA) score (**Table I**). All had chronic, disabling disease (duration from 6 to 20 years) with a major impact on quality of life and all requested analgesic treatment. For the two women, the body mass index was >30 kg.m⁻², and two of the men were smokers. The phenotype, as described by

Canoui-Poitaine et al. (6), was axillary-mammary in two patients, follicular in one patient and gluteal in 3 patients. No patient had inflammatory bowel disease or inflammatory arthritis, acne or diabetes mellitus.

Most patients received multiple antibiotics, such as rifampicin-clindamycin, doxycycline, or amoxicillin-clavulanic acid, and anti-TNF α therapy. All treatments failed to control the disease. Only patient 1 had limited surgery. Only patient 6, with a gluteal phenotype, and associated verrucous genital lesions, did not receive anti-TNF α therapy. Squamous cell carcinomas on HS lesions were previously reported; most cases were in men with a gluteal phenotype, and the role of human papillomavirus was suggested (7). Previously, we had a male patient with the gluteal phenotype and associated verrucous genital lesions who had received anti-TNF α agents; cutaneous squamous cell carcinoma developed secondary to the treatment. Because of this unfortunate event and after a collegial discussion, we decided not to reintroduce anti-TNF α agents in this patient.

For all 6 patients, we introduced thalidomide 50 mg, taken daily. We increased the daily dose to 100 mg after 2 months of treatment because of no meaningful improvement. The use of thalidomide in severe cases HS cases was established in our department based on a collegial decision. An informative leaflet regarding thalidomide is given to the patients, and informed consent and signature was required. After 4 months of daily treatment with 100 mg thalidomide, 3 patients showed improvement, with less inflammation and purulent discharge (**Fig. 1**). The visual analog scale score decreased and the patients no longer used analgesics. The improved condition led us to consider axillary and perineal surgery in patient 1

Table I. Characteristics of hidradenitis suppurativa patients receiving thalidomide

Pat. No	Sex/age, years	BMI, kg.m ⁻²	Tobacco	Duration of disease, years	Skin involvement/phenotype	Hurley stage/HS-PGA score/VAS	CRP level (mg/l)	Past treatment
1	M/30	19	Yes	10	Armpits, groin, perineal areas, back and face/follicular phenotype	III/very severe/9/10	55	-Broad-spectrum antibiotics (rifampicin-clindamycin doxycycline, sulfamethoxazole-trimethoprim, amoxicillin-clavulanic acid, azithromycin, rifampicin-clindamycin-metronidazole, ceftriaxon, rifampicin-metronidazole-moxifloxacin, ertapenem) -Zinc gluconate, steroids, retinoids, dapsone, pentasa -Axillary and perineal surgeries -Anti-TNF α therapy (infliximab 6 months, etanercept 3 months, adalimumab 5 months)
2	F/20	31	No	7	Armpits, breast, groin/axillary-mammary phenotype	III/very severe/5/10	46	-Broad-spectrum antibiotics (rifampicin-clindamycin, doxycycline, amoxicillin-clavulanic acid, azithromycin) -Anti-TNF α therapy (infliximab 3 months, adalimumab 7 months)
3	M/38	ND	Yes	20	Groin, perineal areas/gluteal phenotype	III/very severe/8/10	170	-Broad-spectrum antibiotics (rifampicin-clindamycin, doxycycline, amoxicillin-clavulanic acid, pristinamycin, oxacillin) -Retinoids -Anti-TNF α therapy (infliximab 3 months), methotrexate
4	F/17	32	No	6	Armpits, breast, groin, perineum areas/axillary-mammary phenotype	III/very severe/9/10	ND	-Broad-spectrum antibiotics (rifampicin-clindamycin, doxycycline, amoxicillin-clavulanic acid, azithromycin, rifampicin-metronidazole-moxifloxacin) -Anti-TNF α therapy (infliximab 4 months, adalimumab 4 months)
5	M/17	27	No	5	Perineum areas/gluteal phenotype	III/very severe/6/10	18	-Broad-spectrum antibiotics (rifampicin-clindamycin, doxycycline, amoxicillin-clavulanic acid, azithromycin, rifampicin-metronidazole-moxifloxacin, ceftriaxon, sulfamethoxazole-trimethoprim) -Anti-TNF α therapy (infliximab 2 months)
6	M/24	19	No	6	Perineum areas/gluteal phenotype	III/very severe/na	ND	-Broad-spectrum antibiotics (rifampicin-clindamycin, doxycycline, amoxicillin-clavulanic acid, azithromycin)

BMI: body mass index; HS-PGA scale: Hidradenitis Suppurativa-Physicians Global Assessment; VAS: visual analog scale; CRP: C-reactive protein (before start of thalidomide), ND: not done; NA: not applicable; TNF: tumor necrosis factor.

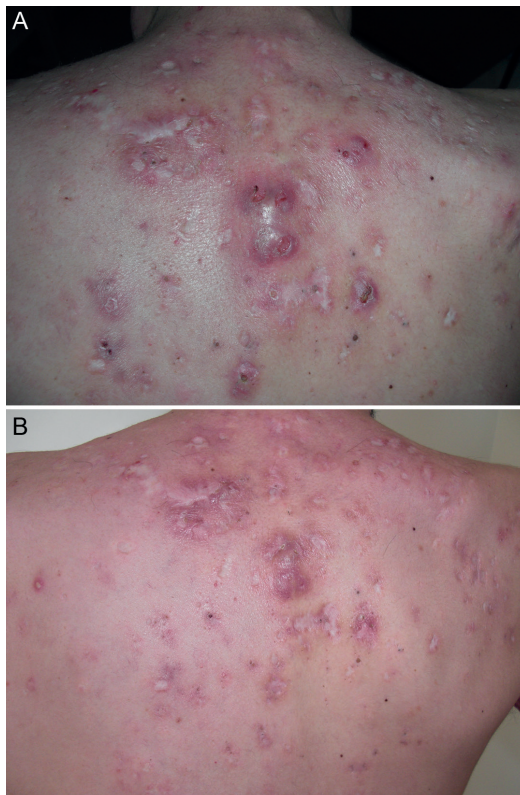


Fig. 1. Patient 1. Back involvement (A) before thalidomide and (B) after 4 months of thalidomide.

at 9 months after starting thalidomide treatment and at 4 months in patient 2. Patient 3 refused surgery.

Clinical changes in the cutaneous lesions occurred in patients 4, 5 and 6 after 3 months of thalidomide treatment, with a decrease in degree of inflammation but an increase in purulent discharge. Thus, the drug was stopped because of lack of substantial improvement.

Paresthesia of the lower limbs occurred 6 months after patient 1 started treatment and 10 months later in patient 2, requiring withdrawal of the drug. We confirmed sensitive neuropathy by electromyography. Painful inflamed lesions recurred 1 month after patient 1 stopped treatment, but the alleviation in paresthesia allowed us to reintroduce 50 mg thalidomide, daily. Because efficacy was observed in patient 1 with 100 mg per day, we proposed to continue with the 50-mg dosage.

Patient 1 was followed 14 months after the introduction of thalidomide. He then moved and was lost to follow-up. Thalidomide was discontinued after extensive surgery in patient 2. She did not consult for 3 years because of no inflammatory flares, and this without treatment. Genital recurrence occurred after 3 years. Patient 3 stopped thalidomide because of significant improvement. He consulted 5 months after the discontinuation because of recurrence; however, thalidomide was not reintroduced in a context of schizophrénia.

DISCUSSION

We report the potential efficacy of daily treatment with 100 mg thalidomide for 4 months in patients with severe inflammatory HS showing failure of conventional treatments based on recent published guidelines (5). A meaningful improvement was obtained, allowing us to consider surgery. Starting with 50 mg/day for 2 months was sub-therapeutic

and an unnecessary step. CD and HS share common physiological elements and an association between these two diseases has been reported (8). We decided to initiate thalidomide treatment as previously suggested for CD because of a therapeutic impasse in our 6 patients (9).

Thalidomide has anticancer and anti-inflammatory properties. The underlying mechanism of action of this drug remains unclear but involves modulation of the production of inflammatory cytokines such as TNF- α and interferon (IFN)- γ . Elevated TNF- α levels in HS blood and skin has been reported (10). In addition, keratinocytes isolated from hair follicles of HS patients exhibit an inflammatory IFN- γ production profile (11). Targeting TNF- α and IFN- γ could be effective in HS.

The benefits of thalidomide treatment had to be balanced against potential adverse effects. Two patients showed sensitive neuropathy, which was confirmed on electromyography of the lower limbs 6 months after the start of daily treatment with 100 mg, requiring the daily dose to be decreased. Women must have contraception because of the teratogenicity of thalidomide.

Thalidomide may be considered for treating severe inflammatory forms of HS, regardless of phenotype, after failure of all conventional treatments. Cohorts or randomized clinical trials will be necessary before including thalidomide in HS therapeutic strategies.

REFERENCES

1. Jemec GBE. Clinical practice. Hidradenitis suppurativa. *N Engl J Med* 2012; 366: 158–164.
2. Martínez F, Nos P, Benloch S, Ponce J. Hidradenitis suppurativa and Crohn's disease: response to treatment with infliximab. *Inflamm Bowel Dis* 2001; 7: 323–326.
3. Kimball AB, Okun MM, Williams DA, Gottlieb AB, Papp KA, Zouboulis CC, et al. Two Phase 3 Trials of Adalimumab for Hidradenitis Suppurativa. *N Engl J Med* 2016; 375: 422–434.
4. Ingram JR. Interventions for hidradenitis suppurativa: updated summary of an original Cochrane review. *JAMA Dermatol* 2017; 153: 458–459.
5. Zouboulis CC, Desai N, Emtestam L, Hunger RE, Ioannides D, Juhász I, et al. European S1 guideline for the treatment of hidradenitis suppurativa/acne inversa. *J Eur Acad Dermatol Venereol* 2015; 29: 619–644.
6. Canoui-Poitrine F, Le Thuaut A, Revuz JE, Viallette C, Gabison G, Poli F, et al. Identification of three hidradenitis suppurativa phenotypes: latent class analysis of a cross-sectional study. *J Invest Dermatol* 2013; 133: 1506–1511.
7. Lavogiez C, Delaporte E, Darras-Vercambre S, Martin De Lassalle E, Castillo C, Mirabel X, et al. Clinicopathological study of 13 cases of squamous cell carcinoma complicating hidradenitis suppurativa. *Dermatology* 2010; 220: 147–153.
8. Kamal N, Cohen BL, Buche S, Delaporte E, Colombel J-F. Features of patients with Crohn's disease and hidradenitis suppurativa. *Clin Gastroenterol Hepatol Off Clin Pract J Am Gastroenterol Assoc* 2016; 14: 71–79.
9. Franks ME, Macpherson GR, Figg WD. Thalidomide. *Lancet* 2004; 363: 1802–1811.
10. Mozeika E, Pilmane M, Nürnberg BM, Jemec GBE. Tumour necrosis factor- α and matrix metalloproteinase-2 are expressed strongly in hidradenitis suppurativa. *Acta Derm Venereol* 2013; 93: 301–304.
11. Hotz C, Boniotto M, Guguin A, Surenaud M, Jean-Louis F, Tisserand P, et al. Intrinsic Defect in Keratinocyte Function Leads to Inflammation in Hidradenitis Suppurativa. *J Invest Dermatol* 2016; 136: 1768–1780.