Antitumour necrosis factor-α therapy for hidradenitis suppurativa: results from a national cohort study between 2000 and 2013

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To the editor

Hidradenitis suppurativa (HS) is a frequent chronic inflammatory skin disease typically characterized by recurrent painful, deep inflammatory nodules of the axillary, breast, groin and gluteal areas.[1,2] European recommendations are mainly based on expert opinion [3]. Drug treatments are heterogenous (e.g., antibiotics, corticosteroids, retinoids) and lack consensus among expert centres.[3] The most severe disease forms or those failing to respond to conventional drugs may be associated with worsened functional prognosis. Anti-tumor necrosis factor α (anti-TNFα) drugs have been prescribed in these cases. The results of randomized controlled trials (RCTs) are discordant. Three RCTs concluded to the efficacy of adalimumab (ADA),[4-6] and two others did not detect any difference between infliximab (IFX) or etanercept (ETA) and placebo.[7,8] Finally, data from the literature and reported experiences do not conclude on the efficacy of anti-TNFα drugs for HS.

The aim of this study was to assess the efficacy of anti-TNFα drugs in patients with HS seen in routine care.

We conducted a national retrospective cohort. Patients who presented HS and who received at least one anti-TNFα drug during the evolution of the disease were eligible. We contacted 25 centres,

including mainly teaching hospitals (n=22) but also general hospitals (n=3). Eleven had eligible patients, 7 had no eligible patients and the 7 other centres did not respond to our requests.
For each centre with eligible patients, patients were selected by a cross-examination of data from January 1, 2000 to December 31, 2013 in 3 databases (the dermatology department databases, the national database in France PMSI, Programme de Médicalisation des Systèmes d'Information and the hospital pharmacy databases). Duplicates were excluded.

A standardized form was used to record sociodemographic characteristics. Associated inflammatory diseases were also recorded, as was personal history of HS. Anatomic zones involved at least once in the history of the patient were classified as breast and armpit, follicular and gluteal involvement.[9] Disease severity was evaluated at the time of clinical examination by the Hurley grade. Details of the anti-TNFα therapy recorded included the molecule, dosage, treatment duration, and adverse effects.

Patients were classified into 3 groups of response after first-line anti-TNFα treatment: (1) complete response (resolution of all skin lesions or at least 90% improvement), (2) partial response (at least 50% improvement), and (3) no response. Event-free survival was measured from the date of the beginning of anti-TNFα treatment to the date of the first relapse or lost to follow-up. The factors that could influence progression-free survival times were tested with Cox's proportional hazards model.

Among 18 centres, we identified 67 patients with HS (37 [55.2%] women; median age 38.0 years (range 10.9–71.8 years) who received an anti-TNFα drug during this 13-year period. Characteristics of the study population are in Table 1. The most frequent anti-TNFα drug prescribed as first-line treatment was IFX, 5 mg/kg (n=57/66, 86.4%), then ADA, 40 mg every 2 weeks (n=7/66, 10.6%) and ETA, 50 mg twice a week (n=2/66, 3.0 %). The median follow-up was 6.8 months [interquartile range (IQR) 3.6–19.1]. Eight cases (11.9%) achieved complete response, 31 (46.2%) partial response and 25 (37.3%) no response, 3 (4.6%) had just been treated by anti- TNFα drugs and

monitoring data were not available. The median follow-up for the 3 groups was 22.8 [10.4–44.2], 13.2 [4.7–22.9] and 4.6 [1.4–7.9] months, respectively. Twelve patients (17.9%) received 2 anti- TNFα drugs and 5 (7.4%), 3.

Factors associated with a complete or at least a partial response to first line anti-TNFα therapy in univariate and multivariate analysis are summarized Table 2. On multivariate analysis, complete response to first line anti-TNFα therapy was independently associated with currently smoking (hazard ratio [HR] 8.4, 95% confidence interval 1.3–56.0; p=0.03) and associated inflammatory bowel or arthritis diseases (HR 6.8, 1.2–40.0; p=0.03). Only one patient with an inflammatory arthritis disease who achieved complete response had received another immunosuppressive treatment (methotrexate). Partial response to first line anti-TNFα therapy was associated with only ADA treatment (HR 6.6, 2.2–19.7), p=0.001). In total, 5/7 patients (71.4%) receiving ADA achieved a partial response and none receiving ADA had a complete response. Four patients had to stop anti-TNFα treatment because of severe side effects (1 case each of hepatitis, lupus, repeated urinary tract infection, and pulmonary embolism).

Our results suggest modest and inconsistent efficacy of anti-TNFα therapy for moderate to severe HS. Complete and persistent clinical responses were rarely obtained (11.9%) and partial response was achieved in 46.2% of patients. These results are consistent with a retrospective Spanish cohort study of 19 patients.[10] Anti-TNFα therapy could be efficient in this subset of patients presenting an associated inflammatory disorder.

Currently smoking was an independent factor associated with a complete response to anti-TNFα therapy. These results are contrary to data provided by registers dealing with inflammatory arthritis.[11] However, previous reports had suggested that smokers, particularly those who smoked before the HS, had a less severe form of HS than never-smokers.[12] In addition, current smoking is a protective factor in other inflammatory diseases such as ulcerative colitis.[13] Larger studies are needed to better determine the protective effect of tobacco use in patients with HS.

Finally, partial response to anti-TNFα therapy was about 7 times higher for patients who received ADA as compared with ETA or IFX. This result highlights a possible class effect of ADA and agrees with results of other RCTs and the recent approval of ADA (40 mg weekly after initial doses of 160 mg at week 0 and 80 mg at week 2) as a possible treatment for patients with active moderate to severe HS by the European Medicines Agency (EMA).[4-6,14] Higher dosages of ADA as mentioned above might be associated with higher response rates as compared with a standard dosage (40 mg every 2 weeks).[5] All patients of our cohort received the standard dosage which could have undermined the overall response rate.

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To conclude, anti-TNFα therapy in patients with moderate to severe HS seems more efficient in a subset of patients with associated arthritis or inflammatory bowel disorder. Complete and persistent clinical response, with anti-TNFα drugs used as a single agent, was rarely obtained. ADA seems to be more efficient than IFX and ETA. Other therapeutic strategies, such as anti-TNFα drugs especially higher dosages of ADA used before surgery or low dose methotrexate in combination, have yet to be assessed.

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Table 1. Initial characteristics of patients with hidradenitis suppurativa (HS) who received an anti-tumor necrosis factor α (anti-TNFα) drug (n=67)

Characteristics (n=missing data)	**N (%)**
Women	37 (55.2)
Age, years, median (range)	38.0 (10.9–71.8)
Smoking status (n=5)	
Non-smoker	19 (30.7)
Current smoker	34 (54.8)
Ex-smoker	9 (14.5)
Body mass index, kg/m^2, median (range)	28.0 (16.7–53)
>25	48 (71.6)
>30	29 (43.4)
History of severe acne	13 (19.4)
HS phenotype *	
Classical	32 (47.8)
Follicular	14 (20.9)
Gluteal	21 (31.3)
Highest Hurley grade (n=5)	
II	16 (25.8)
III	46 (74.2)
Associated inflammatory disorder	
Inflammatory bowel disease	2 (3)
Inflammatory arthritis	11 (16.4)
Inflammatory bowel diseases or arthritis	12 (17.9)

Neutrophilic skin disease	8 (12)
Fist line anti-TNFα treatment (n=1)	
Adalumimab	7 (10.6)
Infliximab	57 (86.4)
Etanercept	2 (3)
Second line anti- TNFα treatment	12 (17.9)
Adalumimab	9/12 (52.9)
Infliximab	5/12 (29.4)
Etanercept	3/12 (17.7)
Third line anti- TNFα treatment	5 (13.4)
Adalumimab	1/5 (20)
Infliximab	1/5 (20)
Etanercept	3/5 (60)

Data are no. (%) unless indicated

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Table 2. Factors associated with a complete or a partial response to anti-TNFα therapy (univariate analysis, n=67)

Initial characteristics (n=missing data)	**Complete response (n=8)**				**At least a partial response(n=39)**			
	Univariate analyses		**Multivariate analyses**		**Univariate analyses**		**Multivariate analyses**	
	HR (95% CI) †	**P value‡**	**HR (95% CI) †**	**P value‡**	**HR (95% CI) †**	**P value‡**	**HR (95% CI)†**	**P value‡**
Women	0.8 (0.2–3.4)	0.75			0.7 (0.3–1.4)	0.32		
Age, years	1.0 (0.9–1.1)	0.42			1.0 (0.9–1.0)	0.92		
Current smoker	**5.1 (0.9–28.3)**	**0.06**	**8.4 (1.3 – 56)**	**0.03**	1.4 (0.7–3.1)	0.36		
Body mass index, kg/m^2								
>25	0.4 (0.08–2.1)	0.28			1.1 (0.5–2.4)	0.88		
>30	0.9 (0.2–3.9)	0.92			1.0 (0.5–2.0)	0.89		
History of severe acne	1.1 (0.1–9.5)	0.96			1.4 (0.5–3.4)	0.52		
HS phenotype (n=2)*								
Classical	1.2 (0.3–5.1)	0.81			0.8 (0.4–1.6)	0.51		
Follicular	0.4 (0.4–3.4)	0.29			1.0 (0.4–2.4)	0.95		
Gluteal	2.7 (0.4–19.4)	0.34			1.3 (0.6–3.0)	0.50		
Highest Hurley score (n=5)								
II (vs III)	1.3 (0.3–7.1)	0.72			0.70 (0.3–1.6)	0.40		
Associated inflammatory disorder								
Inflammatory bowel	**8.4 (0.7–102.0)**	**0.09**			1.1 (0.2–8.6)	0.90		

disease	**4.0 (0.8–20.3)**	**0.10**			1.3 (0.4–3.8)	0.64		
Inflammatory arthritis								
Inflammatory bowel	**3.7 (0.7–18.7)**	**0.12**	**6.8 (1.2 – 40)**	**0.03**	1.3 (0.5–3.4)	0.64		
diseases or arthritis	0.5 (0.05–4.0)	0.49			0.7 (0.2–1.8)	0.41		
Neutrophilic skin disease								
Anti-TNFα treatment with adalumimab as compared with etanercept or infliximab	-	-			**6.6 (2.2–19.7)**	**0.001**	**6.6 (2.2–19.7)**	**0.001**

*Canoui-Poitrine et al, J Invest Dermatol 2013; 133:1506-11

† Hazard ratios (HR) and two-sided 95% confidence intervals (CIs) were estimated by Cox's model

‡*p* value from Cox's model