ORIGINAL ARTICLE

# Efficacy and Safety of Tumour Necrosis Factor-α Antagonists for Folliculitis Decalvans: A Retrospective Case-series Pilot Study

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**Folliculitis decalvans is a chronic inflammatory skin disease leading to scarring alopecia. Management of this disabling disease is difficult and no treatment is currently approved. Current knowledge regarding the pathogenesis of folliculitis decalvans suggests the benefit of using anti-tumour necrosis factor-α. This pilot study aimed to evaluate the clinical efficacy of anti-tumour necrosis factor-α for management of folliculitis decalvans. A single-centre retrospective pilot study included patients with refractory folliculitis decalvans treated by tumour necrosis factor-α inhibitors. An Investigator's Global Assessment (IGA) score was designed and validated to assess the efficacy of the therapy. Response to treatment was considered good to excellent when an IGA ≤ 2 was obtained at month 12. Eleven patients were included, with a mean time from diagnosis of folliculitis decalvans to the introduction of infliximab ($n = 9$) or adalimumab ($n = 2$) of 8.55 ± 1.26 years. Nine patients had failed on at least 2 lines of systemic therapies before starting anti-tumour necrosis factor-α. The median IGA score at baseline was 3. At the end of follow-up, 5 patients were considered responders. Overall, the safety profile of anti-tumour necrosis factor-α was good. The results suggest that the clinical benefit of anti-tumour necrosis factor-α is obtained after at least 6 months of treatment. However, further prospective studies are needed to confirm these results.**

*Key words:* folliculitis decalvans; infliximab; adalimumab; TNFα inhibitors; cicatricial alopecia.

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## SIGNIFICANCE

Folliculitis decalvans is a rare chronic inflammatory disease of the scalp leading to primary cicatricial alopecia. Management of folliculitis decalvans is difficult and no treatment is currently approved for this disabling disease. The aim of this pilot study was to evaluate retrospectively the clinical efficacy of anti-tumour necrosis factor-α for refractory folliculitis decalvans. An Investigator's Global Assessment score was designed and validated to assess this outcome. Eleven patients were included and 5 patients were considered good responders at month 12. The safety profile of anti-tumour necrosis factor-α was good. In addition, good results were obtained after at least 6 months.

Folliculitis decalvans (FD) is a rare chronic inflammatory disease of the scalp leading to primary cicatricial alopecia (1). FD has a long-standing evolution of flare-ups of pustules and crusts with the growth of scleroatrophic alopecic patches that may be associated with pruritus or pain (1). Histological findings at the initial stage of the disease include a dense perifollicular neutrophilic infiltrate evolving into a lympho-plasmocytic infiltrate located close to the dermis part of the hair follicle (2). However, the pathogenesis of FD is unknown. FD and hidradenitis suppurativa (HS) share some pathogenic similarities, as they are both chronic follicular and neutrophilic diseases (3). Changes in the normal follicular microbiota were recently suggested in patients with FD. This follicular dysbiosis could result from a break in the epidermal barrier, leading to subepidermal colonization by *Staphylococcus aureus* (4). Recently, we found involvement of the innate immune response in FD through the inflammasome and interleukin (IL)-1β signalling pathway (5). Other studies suggest that the Th17 immune response is involved in FD (3), associated with local expression of pro-inflammatory mediators, such as TNFα (6).

FD has a major impact on patients' quality of life (7) and there is limited effective therapy. Currently, antibiotics are the most commonly used treatment (8), particularly tetracyclines and the combination of clindamycin and rifampicin, which has shown clinical efficacy in some cases. However, relapses are often observed after discontinuation of treatment (8–10). TNFα inhibitors have showed promise for the management of HS, and anti-TNFα has been used successfully in some cases of refractory FD (11–14). Nevertheless, the clinical efficacy of this strategy needs to be evaluated. Moreover, as-

sessment of the benefit of therapeutic strategies in FD is limited by the lack of validated clinical scores.

In this context, we conducted a single-centre retrospective pilot study to evaluate the clinical efficacy and safety of anti-TNFα for the management of FD. To assess response, an Investigator's Global Assessment (IGA) score was designed and validated.

## PATIENTS AND METHODS

*Patients*

This was a retrospective single-centre study conducted between January 2010 and December 2020 in the Department of Dermatology, University of Bordeaux, France, including patients aged more than 18 years with refractory FD who were treated by TNFα inhibitors for at least 6 months. Diagnosis of FD was based on clinical features (history of recurrent pustules and/or crusts, erythema and/or follicular hyperkeratosis, tufted follicles, and scarring alopecia on the scalp) and/or histological criteria (perifollicular neutrophilic to lympho-plasmocytic infiltrate, fibrosis and polytrichia). Clinical data were obtained from the patients' records, including demographic information (age, sex, age of onset, comorbidities and personal medical history), clinical presentation (number and location of alopecic areas, intensity of symptoms) and therapeutic details (previous therapies, treatment regimen, concurrent therapies, response to treatment, time to discontinuation of anti-TNFα and adverse events). Refractory FD was defined as failure of previous topical and/or systemic antibiotics. Clinical photographs of the lesions were analysed. The severity of pruritus was self-evaluated by patients using a numerical rating scale (NRS). When necessary, they were contacted by phone to collect missing data. The study was approved by the local ethics committee of the University of Bordeaux.

*Construction of scoring system*

To assess the severity of inflammation in FD, an IGA of FD activity (FD-IGA) was designed. The clinical relevance of items included in the FD-IGA was supported by the opinion of expert dermatologists (Bordeaux, Paris). The selection of items was based on a discussion by videoconference. The selected items were: erythema and/or hyperkeratosis regarding their localization strictly perifollicular or beyond hair follicles, and the presence of pustules and/or crusts (**Fig. 1**). Tufted follicles were not considered as associated with FD activity. Scoring was introduced during a training session (by AD and JS) of approximately 10–15 min, which was supported by several clinical photographs and definitions that served as a reference for the scoring. Five experienced dermatologists (SB, MB-B, EC, A-SD, M-SD) scored a set of clinical pictures independently on a separate sheet. Inter-rater reliability was assessed by comparing the severity grading score between the raters. To evaluate intra-rater reliability, measurements were repeated on the same series of photographs at least 2 weeks between rating sessions (test–retest).

*Assessment of response and tolerance to tumour necrosis factor-α inhibitors*

All patients were evaluated for treatment efficacy at baseline 6 and 12 months of treatment using FD-IGA performed on clinical photographs. Responders were defined by an IGA score 0–2 and non-responders by a score 3–4. Secondary endpoints were the evaluation of pruritus intensity using NRS (0–10) and the tolerance of TNFα blocker.

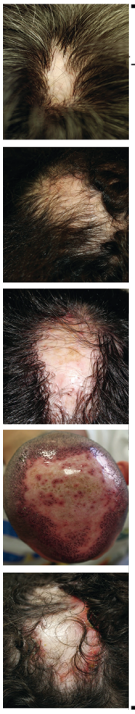
*Statistical analysis*

Descriptive statistics were expressed as median and range or mean ± standard error of the mean (SEM), and performed using GraphPad Prism 9.0 (GraphPad Software, CA, USA). Inter- and intra-rater reliabilities were evaluated by comparing the scores between the groups and at 2 separate time points (test–retest) respectively, using the 2-way random for inter-rater (or 2-way mixed for intra-rater), absolute agreement, single measures intra-class correlation coefficient (ICC). The following guidelines were used for ICC interpretation: $<0.4$ was considered poor, 0.4–0.59 fair, 0.6–0.74 good and $\geq 0.75$ excellent (15).

## RESULTS

*Demographic and clinical characteristics of patients*

The characteristics of the patients are shown in **Table I**. Eleven patients with FD were included (6 women and 5 men). Mean age at inclusion was 36.82 ± 3.98 years and mean body mass index (BMI) was 23.77 ± 1.39 kg/m$^2$. Mean age at FD onset was 28.27 ± 4.07 years. None of the patients were active smokers or had cardiovascular risk factors. No past medical history of follicular occlusion diseases, such as severe acne and/or HS, was



| Stage | |
|---|---|
| 0 *Clear* | No perifollicular erythema or hyperkeratosis<br>No pustule or crust |
| 1 *Almost clear* | Slight perifollicular erythema without hyperkeratosis<br>No pustule or crust |
| 2 *Mild* | Strictly perifollicular erythema and/or hyperkeratosis<br>No pustule or crust |
| 3 *Moderate* | Interfollicular erythema and/or hyperkeratosis beyond hair follicles<br>Possible presence of few pustules and/or thin crusts |
| 4 *Severe* | Interfollicular erythema and/or hyperkeratosis beyond hair follicles<br>Many pustules and/or thick crusts |

**Fig. 1. Stages of Investigator's Global Assessment for folliculitis decalvans (FD-IGA).**

**Table I. Demographic and clinical characteristics of patients with folliculitis decalvans (FD)**

| Characteristics | |
|---|---|
| Age, years, mean±SEM | 36.82±3.98 |
| Median (range) | 37 (19–63) |
| Sex, *n* | |
| Female | 6/11 |
| Male | 5/11 |
| Disease duration, years, mean±SEM | 8.55±1.26 |
| Median (range) | 8 (3–15) |
| Previous treatments, *n* | |
| Topical treatments | |
| Topical steroids | 7/11 |
| Topical antibiotics | 5/11 |
| Topical retinoids | 2/11 |
| Systemic treatments, *n* | |
| Clindamycin + rifampicin | 9/11 |
| Tetracyclines | 9/11 |
| Other antibiotics | 2/11 |
| Isotretinoin | 3/11 |
| Other immunomodulating agents | 1/11 |
| Prior line(s) of systemic therapy before anti-TNFα, *n* | |
| 1–2 | 7/11 |
| ≥3 | 4/11 |
| Symptoms, *n* | |
| Pruritus | 9/11 |
| Pain | 0/11 |

SEM: standard error of mean; TNF: tumour necrosis factor.

noted. Almost all patients ($n=10/11$) had only 1 scalp lesion of FD and the other patient had 2 lesions. Their history of FD was a mean of 8.55±1.26 years prior to the introduction of TNFα blocker. All patients had previously received topical therapies consisting of topical steroid ($n=7/11$), topical antibiotics ($n=5/11$) or topical retinoids ($n=2/11$). Nine/11 had failed on at least 2 lines of systemic therapies prior to starting TNFα blocker. Systemic therapies consisted of antibiotics (combination of rifampicin + clindamycin or tetracycline) for most of the patients (9/11). Other systemic therapies tested were dapsone, isotretinoin and/or immunomodulating agents, such as hydroxychloroquine, methotrexate and cyclosporine.

### *Reliability of folliculitis decalvans-Investigator's Global Assessment*

The FD-IGA score was composed of 5 items (0: clear; 1: almost clear; 2: mild; 3: moderate; 4: severe). The presence of the lesional site of interfollicular erythema and/or hyperkeratosis beyond hair follicles with the association of pustules and/or crusts defined the moderate and/or the severe stages (Fig. 1). Results of FD-IGA grading by the 5 dermatologists are shown in Table SI. Overall, inter- and intra-rater reliabilities showed ICCs of 0.62 (95% confidence interval (95% CI) 0.51–0.78) and 0.62 (95% CI 0.46–0.76), respectively. This corresponds to substantial good agreement according to the nomenclature proposed by Cicchetti et al. (15). Intra-rater concordance was excellent (ICC >0.9) for raters 3 and 5, who are considered expert on scalp diseases (data not shown). However, inter-rater concordance varied widely when comparing raters with each other. Weighted kappa statistic values between dermatologists are shown in Table SII.

### *Efficacy and tolerance of tumour necrosis factor-α inhibitors*

Treatment regimens and results regarding efficacy and tolerance are shown in **Table II**. Nine patients received infliximab (5 mg/kg) every 4–8 weeks, while the other 2 received adalimumab (40 mg every 2 weeks). One patient first received infliximab and then adalimumab 6 months later. Concomitant therapies included mainly topical therapies (9/11), mostly used during the first months after the initiation of anti-TNFα. One patient received methotrexate (10–20 mg/week) and a second had systemic clindamycin (600 mg/day) after 6 months of follow-up.

The median IGA score at baseline was 3. Patients were considered as responders when an IGA score ≤2 was obtained at month 12. At month 6, 4/9 patients reached this score, and 5/10 patients were considered as responders at month 12 (**Fig. 2**). One patient was lost to follow-up and stopped anti-TNFα at month 6 for personal convenience, while another patient was not evaluated at

**Table II. Treatments and clinical responses at months 6 and 12**

| | Mean±SEM; median (range) | *n* |
|---|---|---|
| Infliximab (5 mg/kg) | | 9/11 |
| Every 6 weeks | | 6/9 |
| Every 8 weeks | | 2/9 |
| Every 4 weeks | | 1/9 |
| Adalimumab 40 mg every 2 weeks | | 2/11 |
| Treatment duration (months) | 25.18±8.7; 12 (6–93) | |
| FD-IGA at baseline | 3±0.23 | |
| Observed response (FD-IGA ≤2) | | |
| Month 6 | | 4/9 |
| Month 12 | | 5/10 |
| NRS pruritus at baseline | 4.14±1.41; 5 (0–8) | |
| NRS pruritus ≤1 at month 12 | | 6/7 |
| Concurrent treatments | | |
| Topical treatments | | *9/11* |
| Topical steroids | | 4/11 |
| Topical antibiotics | | 4/11 |
| Topical retinoids | | 2/11 |
| Systemic treatments | | 2/11 |
| Methotrexate | | 1/11 |
| Clindamycin | | 1/11 |
| Concurrent treatments | | |
| Topical treatments | | 9/11 |
| Topical steroids | | 4/11 |
| Topical antibiotics | | 4/11 |
| Topical retinoids | | 2/11 |
| Systemic treatments | | 2/11 |
| Methotrexate | | 1/11 |
| Clindamycin | | 1/11 |
| Reasons for discontinuation of TNFα inhibitor from month 0 to month 12 | | |
| Personal convenience | | 1/11 |
| Adverse events | | 2/11 |
| Insufficient efficacy | | 2/11 |
| Switch to: | | |
| Topical treatment only | | 2/11 |
| Another systemic treatment only | | 1/11 |
| Combination of topical and systemic treatment | | 2/11 |
| Follow-up (months) | 36.64±9.1; 21 (9–93) | |

SEM: standard error of the mean; FD-IGA: Investigator's Global Assessment for folliculitis decalvans; TNF: tumour necrosis factor; NRS: numerical rating scale.

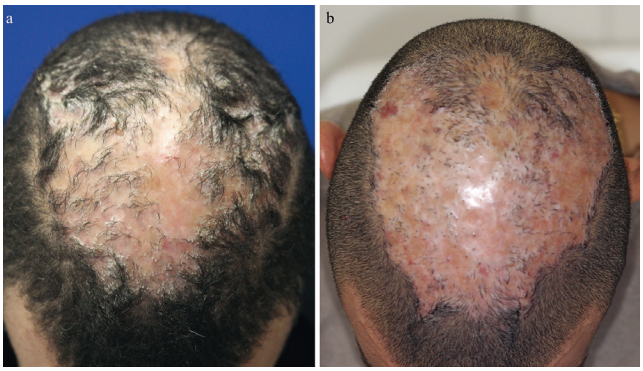



**Fig. 2. Clinical evolution of patient 1 treated by infliximab 5 mg/kg every 6 weeks.** (a) Before treatment, many pustules and crusts at edge of alopecic patch (Investigator's Global Assessment for folliculitis decalvans; FD-IGA 4); (b) at month 12, follicular hyperkeratosis at edge of alopecic patch without any pustules (FD-IGA 2).

month 6 due to the COVID-19 pandemic. At baseline, the median NRS pruritus score was 5. At month 12, 6/7 patients had reached an NRS pruritus score of 0 or 1. Overall, the safety profile of anti-TNFα was good during the short-term period of treatment: 1 patient reported lower-limb vasculitis that resolved after a short course of systemic steroids, and another had moderately elevated liver enzymes (grade 2).

## DISCUSSION

This is one of the largest studies to date evaluating the efficacy and safety of anti-TNFα in patients with FD refractory to conventional therapies. To assess the response to anti-TNFα, an FD-IGA score was designed and validated. The clinical response was considered good to excellent when an FD-IGA score ≤2 was obtained. This cut-off corresponds to the absence of pustules and/or crusts, which are considered the classical signs of disease activity (5, 9, 10).

In the current study, treatment with anti-TNFα resulted in improvement of the disease in half of the patients. Most of the remaining patients had achieved a good response at 12 months of follow-up. Interestingly, anti-TNFα therapies seemed to be particularly efficient on symptoms such as pruritus in our patients. This suggests that the clinical efficacy of anti-TNFα is observable after at least 6 months of treatment. This delayed response could be because only patients with a severe form of FD were treated with anti-TNFα. Although few patients had concomitant treatment, the addition of methotrexate or clindamycin in 2 patients after 6 months of follow-up did not change the clinical response to anti-TNFα. More importantly, 6 patients continued anti-TNFα therapy after 12 months, with maintenance of a good therapeutic response. Indeed, 1 patient is still on the treatment after 7.5 years of follow-up. Few studies have reported the use of anti-TNFα patients with refractory FD (11–14). Recently, adalimumab showed good efficacy and safety in a case series of 23 patients with refractory FD (16). In contrast to the current study results, significant improvement was rapidly observed from 2–3 months after initiation of anti-TNFα (11–14, 16). However, it is important to note that the dose of adalimumab used in Iorizzo et al.'s study (16) was comparable to the dose indicated to treat hidradenitis suppurativa (subcutaneous injections of 160 mg at week 0, 80 mg at week 2, and 80 mg every other week) that higher than the dose used in the current study. In addition, when treatment duration was limited to 3–4 months, patients relapsed rapidly, suggesting that disease control is obtained only with longer treatment (12, 14). Anti-TNFα showed, in addition, good result in a case of chronic non-scarring folliculitis (17).

### *Study limitations*

This study has some limitations. First, as a single-centre study, it may not reflect the general population of patients with FD. Secondly, although this study comprises one of the largest cohorts of patients with severe FD treated with anti-TNFα, the number of patients is too small to confirm the observed response. In addition, the score designed to assess the clinical response should be better validated in prospective studies. Trichoscopy was not used to assess the disease activity in the current study.

### *Conclusion*

Anti-TNFα therapies could be a reliable treatment for refractory FD. However, the best response is obtained only after at least 1 year of treatment. Given the good safety profile of anti-TNFα, these therapies could be offered to patients with severe FD, a quasi-orphan disease that has no approved therapies to date.

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*Conflicts of interest:* MB-B and JS declare accommodation and speaker honoraria for Abbvie.

*The authors have no conflicts of interest to declare.*

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