BJD
British Journal of Dermatology

Frontal fibrosing alopecia: a clinical review of 36 patients

A. Samrao, A-L. Chew* and V. Price

Department of Dermatology, University of California San Francisco, San Francisco, CA 94115, U.S.A.
**Department of Dermatology, Orpington Hospital, Orpington BR6 9JU and St John's Institute of Dermatology, Guy's and St Thomas' NHS Foundation Trust, London SE1 7EH, U.K.*

Correspondence
Vera H. Price.
E-mail: pricev@derm.ucsf.edu

Accepted for publication
27 April 2010

Key words
doxycycline, frontal fibrosing alopecia, hydroxychloroquine, Lichen Planopilaris Activity Index, mycophenolate mofetil, retrospective review

Conflicts of interest
None declared.

DOI 10.1111/j.1365-2133.2010.09965.x

Summary

Background Frontal fibrosing alopecia (FFA) is a primary lymphocytic cicatricial alopecia with a distinctive clinical pattern of progressive frontotemporal hairline recession. Currently, there are no evidence-based studies to guide treatment for patients with FFA; thus, treatment options vary among clinicians.

Objectives We report clinical findings and treatment outcomes of 36 patients with FFA, the largest cohort to date. Further, we report the first evidence-based study of the efficacy of hydroxychloroquine in FFA using a quantitative clinical score, the Lichen Planopilaris Activity Index (LPPAI).

Methods A retrospective case note review was performed of 36 adult patients with FFA. Data were collected on demographics and clinical findings. Treatment responses to hydroxychloroquine, doxycycline and mycophenolate mofetil were assessed using the LPPAI. Adverse events were monitored.

Results Most patients in our cohort were female (97%), white (92%) and postmenopausal (83%). Apart from hairline recession, 75% also reported eyebrow loss. Scalp pruritus (67%) and perifollicular erythema (86%) were the most common presenting symptom and sign, respectively. A statistically significant reduction in signs and symptoms in subjects treated with hydroxychloroquine ($P < 0{\cdot}05$) was found at both 6- and 12-month follow up.

Conclusions In FFA, hairline recession, scalp pruritus, perifollicular erythema and eyebrow loss are common at presentation. Despite the limitations of a retrospective review, our data reveal that hydroxychloroquine is significantly effective in reducing signs and symptoms of FFA after both 6 and 12 months of treatment. However, the lack of a significant reduction in signs and symptoms between 6 and 12 months indicates that the maximal benefits of hydroxychloroquine are evident within the first 6 months of use.

Frontal fibrosing alopecia (FFA), first described by Kossard in 1994,[1] is scarring hair loss characterized by progressive recession of the frontotemporal hairline, with or without progressive loss of eyebrows. At the time of Kossard's original description of FFA, it was thought that the disease occurred primarily in postmenopausal women.[1] However, since then there have been multiple case reports of FFA in premenopausal women.[2–5] A few cases of FFA in men have also been reported.[6,7]

Histologically, FFA is characterized by a variably dense lymphocytic infiltrate around the infundibulum, isthmus and bulge regions of the affected hair follicles.[2] Inflammation eventually results in loss of sebaceous glands, permanent destruction of the follicle, and replacement with fibrotic scar tissue. This is manifest clinically as loss of follicular markings. The histological findings seen in FFA are indistinguishable from those in lichen planopilaris (LPP)[8] and the other lymphocyte-mediated cicatricial alopecias (with the exception of chronic cutaneous lupus erythematosus). Currently, FFA is considered a variant of LPP[2,9] because of the presence of concurrent or prior cutaneous and/or mucous membrane lichen planus (LP) in patients with FFA. Treatment options for FFA are similar to those used in LPP.

The Lichen Planopilaris Activity Index (LPPAI) was recently introduced to allow statistical comparison of pre- and post-treatment response to oral immunosuppressives in LPP.[10,11] As no evidence-based clinical trials currently exist for therapy of FFA, we assessed treatment responses in our cohort of patients with FFA, using the LPPAI.

Materials and methods

A retrospective review of the medical records and histopathology reports of 36 patients with FFA seen at the University of

California San Francisco (UCSF) Hair Center between October 2003 and May 2009 was performed. Ethical approval was obtained from the Committee of Human Research at the UCSF.

Inclusion criteria were adult patients over 18 years of age presenting with scarring alopecia in a band-like frontal or frontotemporal distribution. Whenever consent was obtained, histopathological evidence of scarring alopecia and a lymphocytic infiltrate was sought to confirm the diagnosis. Exclusion criteria were patients presenting outside the time period specified and patients who had been followed for < 3 months.

Medical records were examined for data on demographics (age, sex, ethnicity and menopausal status), duration and extent of the disease, clinical findings (symptoms and signs of the disease), anagen pull test results, concurrent scalp diagnoses, concurrent or prior diagnosis of cutaneous and/or mucous membrane LP, scalp biopsy results, laboratory studies, prior and/or concurrent treatments, and duration of follow up. Laboratory studies including a full blood count, ferritin level and thyroid function tests were performed on all patients to evaluate other factors contributing to hair loss.

Pre- and post-treatment responses to three oral medications, namely hydroxychloroquine, doxycycline and mycophenolate mofetil, were analysed using the LPPAI.[10,11] The LPPAI has previously been validated to correlate with clinical responses in LPP[10] and ranges from 0 (no evidence of clinically active disease) to 10 (most severe activity). The index comprises eight subjective and objective surrogate markers of disease activity: pruritus, pain, burning, erythema, perifollicular erythema, perifollicular scale, anagen pull test, and spreading. The index was created by weighting each criterion according to reproducibility and objectivity. For example, the anagen pull test is the most reproducible and objective of all the criteria so it received the greatest weight. The other criteria, such as spreading, received a lower weighting because they were either subjective or less reproducible. Therefore, surrogate markers were measured on the following scale: 0, absent; 1, mild; 2, moderate; 3, severe. The anagen pull test was scored as: 0, negative or 1, positive. Assessment of disease spread was measured with the following scale: 0, no spreading; 1, indeterminate; 2, spreading.[10,11] LPPAI values were calculated using the following equation:

$$\begin{aligned}\text{LPPAI} = {} & (\text{itch} + \text{pain} + \text{burning})/3 + (\text{scalp erythema} \\ & + \text{perifollicular erythema} + \text{perifollicular scale})/3 \\ & + 2.5\,(\text{pull test}) + 1.5\,(\text{spreading}/2).\end{aligned}$$

LPPAI scores were calculated separately for hydroxychloroquine, doxycycline and mycophenolate mofetil at baseline (pretreatment), 6 months and 12 months following commencement of treatment. For purposes of statistical comparison, patients seen between 3 and 9 months were grouped into the '6 month' time period, while those seen between 9 and 15 months were grouped into the '12 month' time period. For hydroxychloroquine, pre- and post-treatment scores were compared using a Friedman test based on Cochran–Mantel–Haenszel statistics to determine if there was a statistically significant difference between LPPAIs across all time periods. Pairwise Friedman tests were then used for comparisons between the various time points. Statistical significance was assumed for $P < 0{\cdot}05$. In patients who had received multiple courses of hydroxychloroquine, only the first course was included in the statistical analysis. For doxycycline and mycophenolate mofetil, the number of subjects was deemed too small for statistical analysis.

To stratify the clinical effectiveness of the treatments, the changes in LPPAI scores were arbitrarily used to divide patients into responders (> 85% reduction in LPPAI), partial responders (25–85% reduction in LPPAI) or treatment failures (< 25% reduction in LPPAI).[10,11]

Results

Patient demographics and clinical findings are reported in Tables 1 and 2, respectively. Thirty-four of the 36 (94%) patients included in the study had a scalp biopsy confirming a primary cicatricial lymphocytic alopecia. One patient did not consent to a biopsy and one patient was lost to follow up. Of the 34 biopsies performed, all showed a diminished number of terminal follicles, a lymphocyte-predominant infiltrate, concentric perifollicular fibrosis, scarred fibrous tracts, and loss of sebaceous glands.

Treatment response

At the UCSF Hair Center, systemic treatment with hydroxychloroquine or mycophenolate mofetil is initiated in patients with FFA when biopsy specimens show a moderate to dense inflammatory infiltrate. Doxycycline is considered when the

Table 1 Patient demographics

Category	No. (%)	Median (range)
Total no. of patients		
Age at presentation (years)	36 (100)	60 (31–83)
Age at onset (years)		59 (30–79)
Delay before presentation (years)		2 (0–10)
Women		
Age at presentation (years)	35 (97)	60 (31–83)
Age at onset (years)		59 (30–79)
Delay before presentation (years)		1 (0–10)
Men		
Age at presentation (years)	1 (3)	52
Age at onset (years)		47
Delay before presentation (years)		5
Ethnicity		
Caucasian	33 (92)	
African-American	2 (6)	
Asian (Oriental)	1 (3)	
Menopausal status of women		
Premenopausal	6 (17)	
Postmenopausal	29 (83)	

Table 2 Clinical findings

Findings	No. (%)
Site of alopecia	
Frontal or frontotemporal scalp	36 (100)
Eyebrows	27 (75)
Eyelashes	3 (8)
Upper limbs	7 (19)
Lower limbs	6 (17)
Axilla	1 (3)
Pubic area	0
Concurrent scalp diagnoses	
Lichen planopilaris	5 (14)
Central centrifugal cicatricial alopecia	1 (3)
Androgenetic or senescent alopecia	5 (14)
Alopecia areata	2 (6)
Chronic telogen effluvium	1 (3)
Concurrent or prior lichen planus	
Oral[a]	1 (3)
Vulval[b]	1 (3)
Cutaneous[b]	1 (3)
Symptoms at onset	
Pruritus	24 (67)
Pain	6 (17)
Burning	3 (8)
Signs at onset	
Absence of follicular ostia	36 (100)
Scalp erythema	8 (22)
Perifollicular erythema	31 (86)
Perifollicular scale	14 (39)
Tufting	12 (33)
Anagen pull test	
Positive	17 (47)

[a]Concurrent; [b]prior.

infiltrate is sparse. In one of our 36 patients (patient 28), ciclosporin was used following nonresponse to mycophenolate mofetil.

Of the 36 patients included in our study, 21 (58%) met criteria for calculation of the LPPAI, of whom four met criteria for calculation of the LPPAI following treatment with two different agents. Sixteen of the 25 evaluable treatment courses (64%) were with hydroxychloroquine, four (16%) with doxycycline, and five (20%) with mycophenolate mofetil. Fifteen patients were excluded from LPPAI calculations. Exclusion criteria were not receiving systemic treatment and not being followed up within the 6- and/or 12-month time periods.

Hydroxychloroquine

The 16 patients included in LPPAI calculations for hydroxychloroquine were treated for a median of 12 months (Fig. 1). One patient (patient 8) did not attend follow up at 6 months and seven patients had no follow up at 12 months. Eleven of the 15 patients (73%) showed reduction in signs and symptoms at 6-month follow up. Of these, four (36%) were considered responders and seven (64%) were partial responders. Four of the 15 (27%) showed no response. At 12-month

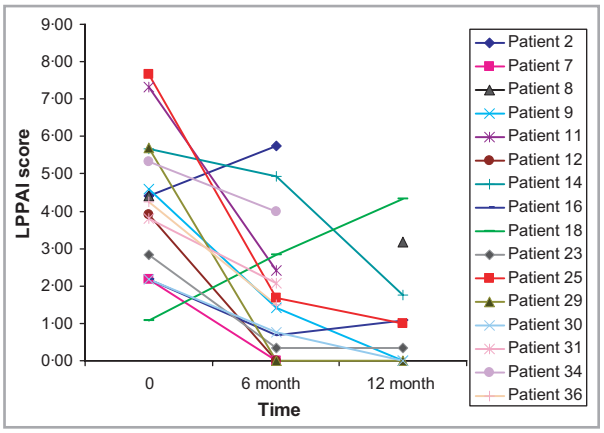

Fig 1. Lichen Planopilaris Activity Index (LPPAI) scores in patients treated with hydroxychloroquine at baseline, 6 months and 12 months following commencement of treatment.

follow up, eight of the nine patients (89%) had reduction in signs and symptoms. Of these, five (62%) were responders and three (38%) were partial responders. One of nine patients (11%) had not responded to treatment at 12-month follow up. The difference between LPPAIs across all time periods was statistically significant ($P = 0{\cdot}003$). The difference between LPPAI at 0 and 6 months and between LPPAI at 0 and 12 months was also significant ($P = 0{\cdot}0045$ and $0{\cdot}0196$, respectively). However, the difference between LPPAI at 6 and 12 months was not significant.

Doxycycline

The four patients included in LPPAI calculation of doxycycline were treated for a median of 18 months (Fig. 2). At 6-month follow up, two (50%) had a reduction in signs and symptoms. One was a responder and one was a partial responder. Two of four (50%) were nonresponders. Only three patients returned for 12-month follow up. One of the three was a responder, one was a partial responder, and one remained a nonresponder (patient 32).

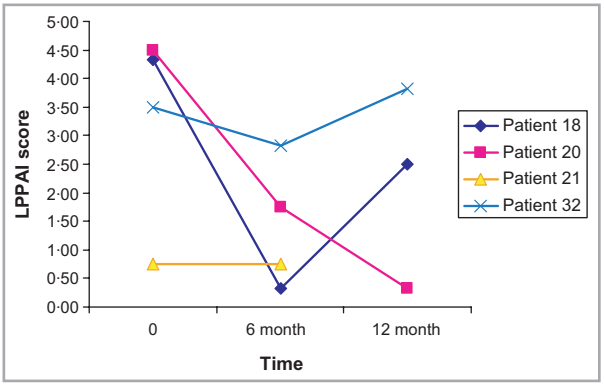

Fig 2. Lichen Planopilaris Activity Index (LPPAI) scores in patients treated with doxycycline at baseline, 6 months and 12 months following commencement of treatment.

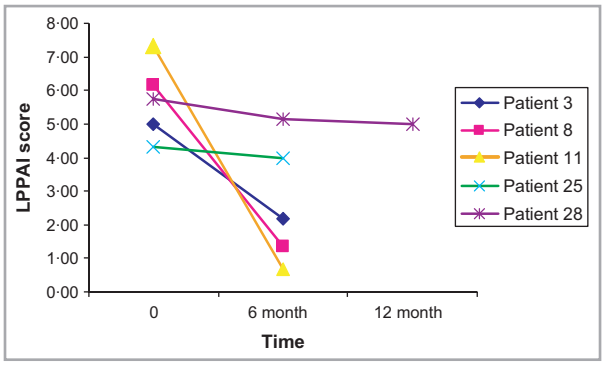

Fig 3. Lichen Planopilaris Activity Index (LPPAI) scores in patients treated with mycophenolate mofetil at baseline, 6 months and 12 months following commencement of treatment.

Mycophenolate mofetil

Five patients were treated with mycophenolate mofetil for a median of 6 months and all were included in LPPAI calculations (Fig. 3). At 6-month follow up, three (60%) patients had responded to treatment. Of these, one (33%) was a responder and two (67%) were partial responders. Only one patient remained on mycophenolate mofetil long enough to calculate the 12-month LPPAI (patient 28) and was a nonresponder at that visit.

Adverse events

None of the patients on hydroxychloroquine experienced any adverse event, including no retinopathy. Three of our 36 patients experienced an adverse event with the use of doxycycline. Two of these patients had a photosensitive reaction (patients 19 and 29) while patient 3 experienced gastrointestinal symptoms. All three patients stopped the medication prior to the 3-month cut-off point required for calculation of the LPPAI. None of the patients reported an adverse reaction to mycophenolate mofetil. Patient 28 reported perioral numbness and tingling with ciclosporin.

Discussion

FFA is a primary lymphocytic cicatricial alopecia that occurs predominantly in postmenopausal women.[2–5] The patient demographics of our cohort showed that 29 (83%) were postmenopausal and six (17%) were premenopausal, which reflects the general trend in the literature. Only isolated case reports of male patients exist.[6,7]

In most cases, FFA is easily recognized by its distinctive clinical presentation of a band-like recession of the frontal or frontotemporal hairline. This appearance, being one of our inclusion criteria, was universally present in our cohort. Kossard[1] describes the band of alopecia as 'uniformly pale… contrast(ing) with the mottled, sun-damaged skin of the forehead'. However, the contrast between scalp and forehead skin may be subtle, as severe sun damage is not always present. An invariable sign is the absence of follicular ostia within the band of hair loss. In our cohort, perifollicular erythema and loss of eyebrows were frequently seen at initial presentation (86% and 75%, respectively) (Table 2). Seven of 36 patients (19%) also reported hair loss on their upper and/or lower limbs (Table 2). No associated laboratory or hormonal abnormalities[4,12,13] have been consistently identified in FFA and none was identified in our patients.

Five of our 36 patients (14%) also had LPP, and associated lesions of either cutaneous or mucous membrane LP were identified in three (8%) patients (Table 2). This is in contrast to LPP, where the incidence of cutaneous or mucous membrane LP is 17–50%. As FFA is currently considered a variant of LPP it follows that therapeutic options used for LPP should be effective in FFA. At the UCSF Hair Center, systemic treatments are initiated as early as possible in both FFA and LPP in order to alleviate signs and symptoms and potentially arrest disease progression. In addition, local treatments, such as potent topical or intralesional corticosteroids, topical immune modulators (e.g. pimecrolimus, tacrolimus) or topical minoxidil are generally used in conjunction with systemic treatment. Ultimately, patients who respond well may be maintained on topical treatment alone.

In 2010 Chiang *et al.*[10] introduced the LPPAI to analyse pre- and post-treatment response with hydroxychloroquine in 40 patients with LPP, including 11 with FFA. The data showed a statistically significant reduction in LPPAI scores at 6 months with continued significant reduction in LPPAI scores at 12 months. Our data indicate that hydroxychloroquine significantly reduces signs and symptoms in patients with FFA after both 6 and 12 months of treatment ($P < 0{\cdot}05$). However, in contrast to LPP, in FFA the maximal benefits of hydroxychloroquine are seen within the first 6 months of therapy. Due to the inherent biases of a retrospective case note review, larger, prospective studies with controls will be helpful.

In conclusion, this retrospective study is the first evidence-based study on the efficacy of a therapeutic agent, hydroxychloroquine, in FFA. Hydroxychloroquine is significantly effective in reducing signs and symptoms in patients with FFA and has its maximal benefit within the first 6 months of treatment.

What's already known about this topic?

- Frontal fibrosing alopecia (FFA) is a primary cicatricial lymphocytic alopecia, currently thought to be a variant of lichen planopilaris.

What does this study add?

- We utilize a numerical clinical score, the Lichen Planopilaris Activity Index (LPPAI), to assess the efficacy of hydroxychloroquine in patients with FFA.
- Hydroxychloroquine is effective in reducing signs and symptoms of FFA and has its maximal benefit within the first 6 months of treatment.

References

1 Kossard S. Postmenopausal frontal fibrosing alopecia. *Arch Dermatol* 1994; **130**:770–4.

2 Kossard S, Lee MS, Wilkinson B. Postmenopausal frontal fibrosing alopecia: a frontal variant of lichen planopilaris. *J Am Acad Dermatol* 1997; **36**:59–66.

3 Faulkner CF, Wilson NJ, Jones SK. Frontal fibrosing alopecia associated with cutaneous lichen planus in a premenopausal woman. *Australas J Dermatol* 2002; **43**:65–7.

4 Moreno-Ramírez D, Camacho Martínez F. Frontal fibrosing alopecia: a survey in 16 patients. *J Eur Acad Dermatol Venereol* 2005; **19**:700–5.

5 Tan KT, Messenger AG. Frontal fibrosing alopecia: clinical presentations and prognosis. *Br J Dermatol* 2009; **160**:75–9.

6 Kossard S, Shiell RC. Frontal fibrosing alopecia developing after hair transplantation for androgenetic alopecia. *Int J Dermatol* 2005; **44**:321–3.

7 Stockmeier M, Kunte C, Sander CA, Wolff H. Frontale fibrosierende Alopezie Kossard bei einem Mann. *Hautarzt* 2002; **53**:409–11.

8 Mirmirani P, Willey A, Headington JT *et al.* Primary cicatricial alopecia: histopathologic findings do not distinguish clinical variants. *J Am Acad Dermatol* 2005; **52**:637–43.

9 Olsen EA, Bergfeld WF, Cotsarelis G *et al.* Summary of North American Hair Research Society (NAHRS)-sponsored Workshop on Cicatricial Alopecia, Duke University Medical Center, February 10 and 11, 2001. *J Am Acad Dermatol* 2003; **48**:103–10.

10 Chiang C, Sah D, Cho B *et al.* Hydroxychloroquine and lichen planopilaris: efficacy and introduction of Lichen Planopilaris Activity Index scoring system. *J Am Acad Dermatol* 2010; **62**:387–92.

11 Cho B, Sah D, Chwalek J *et al.* Efficacy and safety of mycophenolate mofetil for lichen planopilaris. *J Am Acad Dermatol* 2010; **62**:393–7.

12 Tosti A, Piraccini BM, Iorizzo M, Misciali C. Frontal fibrosing alopecia in postmenopausal women. *J Am Acad Dermatol* 2005; **52**:55–60.

13 Moreno-Ramirez D, Ferrandiz L, Camacho FM. Diagnostic and therapeutic assessment of frontal fibrosing alopecia. *Actas Dermosifiliogr* 2007; **98**:594–602.