INTRODUCTION

Frontal fibrosing alopecia (FFA) is a form of primary cicatricial alopecia characterized by progressive recession of frontal, and often temporoparietal, hairline mainly in postmenopausal women. Currently, there are no guidelines or proposed evidence-based treatment for FFA. Aims: The aim of this study was to retrospectively evaluate the effect and safety of intralesional triamcinolone acetonide injections (ITAI) either as monotherapy or as concomitant treatment in the management of hairline recession in FFA. Subjects and Methods: All patients with FFA, who visited our specialist hair clinic from July 2012 to October 2016 and were treated with ITAI either as monotherapy or as concomitant treatment, were enrolled in our study. Measurements were performed from five different points on the scalp. The analysis of data included demographics, associated symptoms, clinical and dermoscopic findings, comorbidities, family history of FFA, concomitant medication, treatment outcome, and recording of adverse events. Statistical Analysis: Statistical analysis was performed using the Statistical Package for the Social Sciences, version 22.0. Results: A total of 40 patients, all females were enrolled in our study. The mean age of the patients was 65.88 ± 8.18 whereas the mean age of the diagnosis was 61.24 ± 7.4. A total of 39 patients were treated with a combination of treatments, including ITAI, and only one with ITAI as monotherapy. There was a halting of the progress of the disease, and no significant adverse events were noted, apart from mild pain. Conclusions: A halting in the progression of FFA was achieved, with unremarkable adverse events. ITAI could serve as an effective and safe option for the treatment of FFA, although difficult to assess it as monotherapy. Further randomized controlled trials are needed to evaluate its efficacy and safety as the sole treatment in the management of FFA. Key words: Alopecia, frontal fibrosing alopecia, hair disorders, intralesional triamcinolone injections, treatment
the affected areas may be present. Complete or partial eyebrow loss is recorded in 50%–83% of cases, and in many cases, it may precede hairline recession. Occasionally, FFA may be associated with loss of body hair and eyelash volume loss. Keratosis pilaris-like papules over the forehead and cheeks and mucocutaneous lichen planus have been also reported as rare FFA manifestations. The disease is slowly progressive over the years, although spontaneous stabilization has been described.

FFA is considered to be a variation of lichen planopilaris (LPP) by some researchers. Both entities histologically are characterized by lichenoid lymphocytic inflammatory infiltrate, perifollicular fibrosis in the infundibulum, and isthmus of the hair follicle, and interface dermatitis involving the upper follicle and loss of sebaceous glands. Others consider it as a separate entity with different clinical picture, prognosis, and management.

The pathogenesis of FFA remains unclear. Key role in FFA appears to play the involvement of bulge area of hair follicles. The bulge area is characterized by the presence of ectodermal stem cells which give rise to epithelial hair follicle cells and sebaceous glands. These type of cells interact with mesenchymal cells found at the dermal papilla, giving rise to the future follicular unit. In FFA, due to the inflammatory process, triggered by proinflammatory cytokines (interferon-gamma and transforming growth factor-β), the bulge area is destroyed, leading to loss of regenerative potential, and permanent hair loss. Other potent pathogenetic factors include loss of hair follicles, bulge immune privilege, loss of CD 200 expression, increased apoptosis, sebaceous glands dysfunction, deficiency in peroxisome proliferator-activated receptor-γ-mediated signaling, programmed cell death (apoptosis), and environmental triggers such as infection or trauma. The role of androgens has been also proposed as supported by the observations that 5-alpha-reductase inhibitors can stabilize or even improve FFA. Finally, during the last years, familial cases of FFA have been reported, suggesting a potent genetic predisposition.

Currently, there are no guidelines or proposed evidence-based treatment for FFA. In 2013, a systematic review on the treatment of FFA and lichen planopilaris was published, trying to shed light on the optimum and safest treatment options. For FFA, the improvement was most often seen when treated with oral finasteride or dutasteride that possibly affected the accompanying androgenetic alopecia. However, according to Harries commentary, intralesional steroids were the most effective treatment strategy in FFA, showing the greatest proportion of “good” or “partial” treatment effects (89%) compared with 62% for the finasteride/dutasteride group.

Systemic medication, such as antimalarials (hydroxychloroquine) or 5α-reductase inhibitors (finasteride and dutasteride), appears to be among the popular treatment options, although there is a continuous need for monitoring and a risk of potent severe adverse events. Treating with antimalarials entails a significant risk of ophthalmological adverse effects whereas treatment with 5α-reductase may be related to a theoretical increased risk of breast cancer. All treatments are aimed at reducing symptoms and signs of disease and slowing disease progression but rarely stimulate hair regrowth.

The purpose of this study was to retrospectively evaluate the effect and safety of intralesional triamcinolone acetonide injections either as monotherapy or as concomitant treatment in the management of hairline recession in patients with FFA.

**SUBJECTS AND METHODS**

The present study was approved by the local Institutional Review Board/Clinical Effectiveness Unit and adhered to the principles of the Declaration of Helsinki.

Initially, all patients, who visited our specialist hair clinic and were diagnosed with FFA from July 2012 to October 2016, were identified. The diagnosis of FFA was made in most cases, clinically, based on the typical clinical presentation (irregular recession of the frontotemporal and preauricular hairline with eyebrow and/or eyelash loss), and dermoscopically. In cases, where there were differential diagnostic issues, a diagnostic biopsy was performed to confirm the histological diagnosis of FFA.

Of 52 patients with FFA, 40 patients, who were treated with intralesional injections of triamcinolone acetonide 10%, were selected and were enrolled in our study. We retrospectively reviewed their medical records. The analysis of data included demographics (sex, age, ethnicity, presence, and/or onset of menopause), family history of FFA, associated symptoms (pruritus and trichodynia), clinical and dermoscopic findings (staging of baseline disease severity, lonely hairs, facial papules, occipital involvement, eyebrow and/or eyelash loss, body hair involvement, perifollicular scale, and follicular hyperkeratosis), comorbidities, concomitant medication, objective treatment outcome (response to treatment, measurements, and adverse events), and a follow-up ranging from 6 months to 4 years. Macroscopic and
dermoscopic photographs were taken from the patients who provided consent.

Macroscopic photographs were taken at the medical photography department and trichoscopy was performed using the Dermatoscope Heine Delta 20 T®.

For each patient, at their visit, we had five different measurements from five different points from face to scalp, using a tape-line. Measurements were taken on each visit from lateral orbital margins to hairline, midglabellar point to hairline and midbrow points to hairline [Figure 1].

Response to treatment was assessed based on the results of measurements at each visit. We reported either stabilization or improvement or worsening of FFA at each of the five points on the head. For each patient, at each visit, we gave a median assessment of response to treatment from the five different points. Subjective symptoms, such as pruritus or trichodynia, were assessed separately.

Diagnosis, treatment, and evaluation were undertaken by one clinician dermatologist. Therefore, in statistical analysis, intrapersonal variability was considered in the interpretation of our results.

Regarding the injection technique, it was performed in all cases, according to our clinic protocol. This includes triamcinolone injections at a concentration of 10 mg/ml deep in the dermis, to avoid atrophy. On the scalp, 0.1 ml was injected with an 1-ml BD insulin syringe 31G every cm² whereas on eyebrows 0.125 ml every cm² of 5% mg/ml concentration. The interval between sessions was 3 months.

Finally, the statistical analysis was performed using the Statistical Package for the Social Sciences, version 22.0 (IBM®).

Age of the patient, age of the diagnosis as well as number of follow-ups were expressed as the mean ± standard deviation. Measurements from the five different points were expressed as median in cm pre and posttreatment. Definite variation was also evaluated. The paired sample t-test was performed between measurements pre and posttreatment from each point, to assess any significant differences in measurements. Cohen's d test was used for the calculation of effect size, evaluating the strength of the analysis. Coefficient of variation was also calculated using the mean ± standard deviation (SD) of the measurements at each of the five points. Finally, intraclass correlation was used to determine the consistency of the data for all points.

RESULTS

All patients (100%) were women. Mean age of patients was 65.88 ± 8.18, while the mean age of the diagnosis of FFA was 61.4 ± 9.25. Most of the patients (87.5%) were postmenopausal. Almost all patients (97.5%) were Caucasian, and only one (2.5%) was of Indian-Pakistani origin. Two of them had a family history of FFA and 15 had also concomitant female pattern hair loss [Tables 1 and 2]. Out of 40 patients, four (10%) complained about pruritus, and six (15%) about trichodynia at their baseline visit.

Three patients (7.5%) had concurrent eyebrow loss, and two (5%) had also eyelash loss. None of the patients had hair loss in other parts of the body, apart from face and scalp. Out of all patients, only one had facial papular lesions [Table 1].

Regarding concomitant disorders, three patients (7.5%) had LPP. Furthermore, four patients (10%) had concomitant lichen planus. Other concomitant conditions included keratosis-such as papules (2.5%), Hashimoto’s disease (2.5%), psoriasis (2.5%), eczema (2.5%), fatty liver disease (2.5%), angular cheilitis (2.5%), perioral dermatitis (2.5%), seborrheic dermatitis (2.5%), breast cancer (2.5%) and hypertrichosis (2.5%) [Table 2].

One patient (2.5%) had been receiving letrozole for breast cancer, and one patient (2.5%) had been on hormonal replacement treatment for 4 years.

All 15 patients with concomitant androgenetic alopecia were on lotion or foam minoxidil 2% or 5%. One of them was also on ethinyloestradiol 2 mg. One patient was treated with spironolactone 200 mg and one with cyproterone acetate 50 mg during the first 10 days of the menstrual cycle monthly, as she was premenopausal.
Diagnosis of FFA was performed in most cases clinically and dermoscopically. All patients had recession of frontal and/or parietal hairline along with loss of follicular ostia, and 95% of them had lonely hairs. 30% of patients had perifollicular erythema, and only 10% had peripilar sign [Table 1].

A diagnostic 4-mm punch biopsy was performed in only five of the patients for confirmation of the diagnosis. The perifollicular lichenoid inflammatory infiltrates involving the isthmus and infundibulum was present. Apoptotic cells were present in the external root sheath. Perifollicular fibrosis was also seen in some areas along with follicular scars replacing the pilosebaceous unit, all findings consistent with FFA.

After measurements from the five different points, as described above, the median values in cm were assessed pretreatment (6 – 8 – 9 – 8 – 5, respectively) [Table 3]. Median absolute deviation (MAD) from each point in cm was also evaluated [Table 4], to assess the spreading of the data.

Treatment combinations provided included monotherapy with intralesional injections (one patient, 2.5%), intralesional injections + steroid lotions ± calcineurin inhibitors ± doxycycline (22 patients, 55%), intralesional injections + dutasteride ± steroid lotions  ± calcineurin inhibitors  ± doxycycline (15 patients, 37.5%), and intralesional injections + hydroxychloroquine ± steroid lotions ± calcineurin inhibitors ± doxycycline (two patients, 5%), as shown in Table 5. Main medications included intralesional triamcinolone injections and/or topical treatment (steroid lotions and calcineurin inhibitor ointments) and/or doxycycline and/or dutasteride and/or hydroxychloroquine. All patients with eyelash loss (5%) were treated with bimatoprost 0.03% eye drops.

Posttreatment median measurements from each point were respectively 6 – 8 – 8 – 8 – 5, showing that patients mainly remained stable regarding their frontotemporal recession [Table 3]. MADs were also similar for baseline and posttreatment for all points except for point 1 [Table 4].

Paired sample t-test was also performed for each point pre- and post-treatment [Table 6]. No significant differences in the mean scores for each point were noted. The effect size was very low, showing that treatment did not alter measurements, which means halting the progress of the disease.

Coefficient of variations was also calculated. In Figure 2, we can see the dispersion of the coefficient of variations (CVs) for all patients. The figure shows that there were CVs that were similar pre- and post-treatment, confirming once more that there were no changes in the measurements when applying the ITAI.
Intraclass correlation at baseline and posttreatment showed fair consistency for one single point, compared to a very high consistency for the overall average of all points, revealing a reliability in our results [Table 7].

The number of follow-up appointments ranged from 1 to 7 within a period of 48 months, with the mean number of follow-up appointments being 3.05 ± 1.3. We see that all patients came for a follow-up appointment and 10 patients, after two follow-up appointments, and treatment which halted the progress of their disease did not come back.

The interval between ITAI sessions was 3 months although 25% of the patients had their ITAI every 6 months. No significant adverse effects were noted. No atrophy was seen due to the injections as our technique includes injecting ITAI deeply in the dermis in a concentration of 10 mg/ml. For the eyebrows, the concentration was 5% mg/ml. Furthermore, no infection, no granuloma formation, and no cyst formation were noted. All patients reported mild pain and discomfort, with a mean severity score of 2 in a linear analog scale ranging from 1 to 10 (1 = no pain, 10 = unbearable pain). The low intensity of pain was attributed to the use of a vibrating machine, to distract the patient. One patient (2.5%) mentioned headache after the procedure, which resolved with paracetamol, while six (15%) mentioned slight discomfort on the scalp during the first 24 h after the injections. All of them, apart from one, reported that they would repeat the procedure if needed. Even this one repeated the injections, despite her comments.

**DISCUSSION**

FFA is a form of primary cicatricial alopecia sharing clinical and histological features with LPP. Kossard in 1994 was the first to describe FFA as a condition characterized by frontotemporal recession of hairline,
mainly affecting postmenopausal Caucasian women.\cite{1,4}
Our present data confirm these observations, as most of our patients were postmenopausal and only one patient was of Indian-Pakistani origin. It can be also seen in premenopausal women and very rarely in men. Of note, our youngest patient was 42 years old. More studies show that the increasing prevalence of FFA in younger women.\cite{10‑12} Two of our patients had a history of familial FFA, suggesting that there may be a genetic background predisposing to the disease.\cite{6,8}

Regarding the associated symptoms, we found that patients mainly complained about the hair loss, as in other studies,\cite{10‑12} although in our study other symptoms, such as pruritus, etc., were not reported as frequently, which is not in favor with findings from other case series.\cite{10‑12} The presence of symptoms is characteristic of the inflammation process. Nevertheless, from our clinical experience, it is not always representative of the severity of inflammation. Recently, more physicians report that the presence of keratosis-like papules in FFA, suggesting and underlining the potent systemic nature of the disease.\cite{13,14} From our case-series, we reported the presence of facial papules only in one patient (2.5%), in accordance with other colleagues.\cite{11‑12} The latter finding contradicts the observation made in two recent studies, in which researchers reported a much higher incidence of the presence of facial lesions in 12 out of 55 cases and a percentage of 37%, respectively.\cite{14,15}

Interestingly, the percentage of patients with eyebrow loss in our cohort was almost 5%, slightly lower compared to most-case series published till now.\cite{3,10‑12,15‑18} Furthermore, there were six patients (15%) with body hair loss, lower percentage compared to other researchers.\cite{3,10‑12,15‑18} One potential explanation could be missing data during documentation, as our study was retrospective. All patients had recession of the frontal and some of them of the temporal hairline. Almost all of them (95%) had the presence of lonely hairs, which is indicative of the FFA diagnosis, reducing the need for diagnostic biopsies. The percentage of lonely hairs reported is much higher compared to other studies,\cite{11} however, confirms the findings reported by Banka et al.\cite{19} Furthermore, along with clinical features, the use of trichoscopy and the characteristic trichoscopic features, such as loss of follicular openings, peripilar sign, and perifollicular erythema,\cite{19} have opened new horizon in diagnostics of hair diseases. Biopsy is required for few indeterminate cases.

The most common concomitant disorders were LPP (7.5%), lichen planus (10%), and female pattern hair loss (37.5%), which was in accordance with other researchers.\cite{16,18} Only one of our patients had autoimmune disorders, percentage quiet low compared to other researchers, who reported a percentage of 16.5%–30%.\cite{3,16}

Regarding efficacy, we see that the combinations of treatments with ITAP proved to be effective in halting the disease progress. Median measurements and median absolute deviations showed that the values for baseline and posttreatment for all points were almost similar, thus showing no significant change [Tables 3 and 4]. Reason for using median and MAD is that both are less affected by outliers; therefore, they constitute a better approximate than the mean and SD. Intracelosal injections ± steroid lotions ± calcineurin inhibitors ± doxycycline was the most common treatment provided, due to the anti-inflammatory properties of the latter. The second most common was the combination including dutasteride, as many patients had concomitant androgenetic alopecia and dutasteride can be an option for both conditions. There was fair agreement in the ratings of the conditions for the patients at all points, showing a reliability in our measurements and results. There were no differences in the mean scores for each point pre- and post-treatment, further proving that the treatment halted the progression, although the result was not statistically significant. Paired sample t-tests and Cohen’s tests were also in support of the stabilization of the condition. Most coefficients of variations were similar to each other for most patients, showing no changes in the results when applying ITAI. Finally, individual measurements were not that consistent compared to average measurements, when evaluating the improvement, worsening, or stabilization.

Our study had some limitations. It was a retrospective study, and it was not clear whether the effect of the treatment was due to the ITAI or due to other topical and/or systemic agents, as the majority of the patients were treated with combination treatments [Table 5]. However, according to the international bibliography, efficacy with treatments such as dutasteride or hydroxychloroquine is variable.\cite{13} According to Racz et al., oral 5-alpha-reductase inhibitors resulted in good clinical response in 45% of patients, while hydroxychloroquine resulted in good clinical response in 30% of treated patients.

In our case series, we saw a stabilization (good clinical response) in almost all of the patients, irrespective of the concomitant treatment. Common denominator in the different therapeutic combinations was the ITAI. The result was the stabilization of the disease, thus suggesting that ITAI could potentially serve as a safe and effective treatment for FFA, although this conclusion is with reservation taking into account that ITAI were
not assessed as monotherapy. Their safety profile was excellent. The advantage of ITAI is that there is no need for monitoring, as with most systemic agents, such as dutasteride and hydroxychloroquine. Some more recent data have shown achievement of halting the progress of hair loss in FFA with ITAI, which is in favor of our indirect findings.\(^\text{[5,6]}\) Nevertheless, further randomized controlled trials are needed to evaluate objectively the efficacy and safety profile of ITAI as monotherapy in the management of FFA, a new “epidemics” in the alopecia chapter.

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Conflicts of interest
There are no conflicts of interest.

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