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Adalimumab (Humira) for the Treatment of Hidradenitis Suppurativa

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Conflicts of interest: Aditya Gupta has been a clinical trials investigator for Valeant Canada, Nuvolase, Bristol Meyers Squibb, Eli Lilly, Merck, Novartis, Janssen and Allergan; and has served as a speaker or consultant for Valeant Canada, Janssen, Novartis, Sandoz, Moberg Pharma, and Bayer. Catherine Studholme is an employee of Mediprobe Research Inc. which conducts clinical trials under the supervision of Aditya Gupta.

ABSTRACT

Adalimumab (Humira®) is a novel therapy approved by the US Food and Drug Administration, Health Canada, and the European Commission for the treatment of hidradenitis suppurativa (HS). Results of two Phase III trials of adalimumab demonstrate significantly higher efficacies compared to placebo. Primary efficacy outcome of 50% reduction in abscess and inflammatory nodule count was seen in 41.8% and 58.9% of participants receiving adalimumab in PIONEER I and PIONEER II studies, respectively, showing substantial improvement compared with placebo groups in both trials (26.0% and 27.6%, respectively). Although the significance of secondary efficacy measures of adalimumab every week treatment (EW) was not consistent between PIONEER I and PIONEER II studies, participants achieving abscess and inflammatory nodule counts of 0, 1, or 2 were significant (EW 51.8%) compared to placebo (32.2%) in the PIONEER II trial. Participants also demonstrated a marked decrease in skin pain measurements from baseline between EW patients (45.7%) and placebo (20.7%) in the PIONEER II trial. Modified Sartorius scores were decreased from baseline in both PIONEER I (-24.4) and PIONEER II (-28.9) trials versus placebo (-15.7 and -9.5, respectively). Adverse events were mild to moderate and comparable between all treatment groups including placebo. Taken together, these data conclude that treatment of HS with adalimumab is a safe and effective therapy resulting in a significant decrease in abscess and inflammatory nodule counts within the first 12 weeks of treatment.

Key words: adalimumab, hidradenitis suppurativa, immune modulators, tumor necrosis factor-alpha inhibitor

Introduction

Hidradenitis suppurativa (HS), also known as acne inversa, is a severe and chronic inflammatory disease resulting from occlusion and rupture of hair follicles followed by an overreaction of the immune response.[1,2] This results in painful inflammation and abscess formation, which can lead to sinus tract development and scarring, as seen in the later stages of HS.[1,2] This affliction is generally located in areas where skin-skin contact occurs, but has been observed on atypical areas such as the ears, back, and chest.[3] Although the exact etiology of HS remains unknown, prevalence is reported to range from 1%-4%.[4–7] There is a lack of regulatory body-approved drugs for the treatment of HS, leaving surgery as the established treatment option for severe disease; however, surgery is associated with a high risk of HS recurrence.[8,9] Therefore, there is an unmet need to find safe and effective therapeutic options for the treatment of HS.

Adalimumab (Humira®) is a human monoclonal antibody that binds to and neutralizes tumor necrosis factor-alpha (TNF-α).[10] It has been shown to be effective at treating inflammatory conditions, including rheumatoid arthritis, Crohn's disease, psoriatic arthritis, and psoriasis.[11,12] Since these diseases all involve overreaction of the immune system resulting in inflammation, adalimumab has been used off-label for the treatment of HS for several years.[13] Adalimumab is now the first and only approved drug for the treatment of HS by the US Food and Drug Administration (FDA), Health Canada, and the EU's European Commission. A Phase II clinical trial was initially completed to analyze the safety and efficacy of adalimumab for the treatment of HS, which showed promising results.[14] The findings from further analysis through two Phase III trials have recently been released, and are summarized herein.

Clinical Efficacy

Phase II Trial (NCT00918255)

A parallel, randomized, double-blind, Phase II clinical trial to assess the safety and efficacy of adalimumab in the treatment of HS was completed.[15] One hundred and fifty-four participants (110 female and 44 male) were measured at baseline. Participants were randomized into three treatment arms: placebo (N = 51), adalimumab every week (EW; subcutaneous [SC] dose

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of 160 mg week 0, 80 mg week 2, 40 mg weekly from weeks 4-15; N = 51), or adalimumab every other week (EOW; SC 80 mg week 0, 40 mg every other week from weeks 1-15; N = 51). Average age of participants was 36.3 years and all efficacy measures were completed at week 16. Participants in the EW treatment group achieved statistically higher clinical response (17.6%), compared to EOW (9.6%) and placebo (3.9%) groups (P = 0.022; Cochran-Mantel-Haenszel method). Clinical response was defined as a 2 point reduction or score of 0, 1, or 2 using the Physician's Global Assessment. The EW treatment group also had significant improvement in secondary efficacies of decreased inflammatory nodules and plaques (P = 0.019; analysis of covariance [ANCOVA] method), clinical response at week 12 (P = 0.020; Cochran-Mantel-Haenszel method), and Modified Sartorius Scale (P = 0.014; van Elteren test) compared to placebo. The EOW treatment group did not exhibit a significant increase in efficacy compared to placebo. Adverse events were comparable between treatment groups; reported in 71% of EW, 64% of EOW, and 59% of placebo participants.

Phase III Trials

Two Phase III randomized, double-blind clinical trials to assess the safety and efficacy of adalimumab in the treatment of patients with moderate-severe HS were recently completed.[16,17] The severity of HS was defined using Hurley Staging: Stage I characterized by single or multiple abscess formations without sinus tracts or scarring; Stage II characterized by one or more recurrent abscesses with tract formation and scars; and Stage III characterized by abscesses covering an extended area with numerous interconnected tracts and diffuse or near diffuse involvement. Inclusion criteria included adults 18-99 years of age with a diagnosis of HS for at least one year and the presence of at least two areas exhibiting HS lesions with at least one categorized as Hurley Stage II or Stage III, stable HS for at least 60 days prior to screening and baseline visits, previous inadequate response to other HS treatments, and total abscess and inflammatory nodule (AN) count of ≥3 at baseline.

The primary outcome measure was the Hidradenitis Suppurativa Clinical Response (HiSCR), defined as a 50% reduction in AN count at week 12. Secondary outcome measures were percentage of baseline Hurley Stage II participants with AN counts of 0, 1, or 2 at 12 weeks, percentage of participants with ≥30% reduction and at least one unit reduction in Patient's Global Assessment of Skin Pain Numeric Rating Scale (NRS30) at 12 weeks, and change in Modified Sartorius Score from baseline to week 12. The Sartorius scoring system is based on the type and number of lesions, location of lesions, and presence of healthy skin.[18] There were six treatment arms for each study, as shown in Table 1.

PIONEER I Trial (NCT01468207)

Three hundred and seven participants (196 female and 111 male) were measured at baseline. The participants were randomized into the placebo or adalimumab EW (SC 160 mg week 0, 80 mg week 2, and 40 mg weeks 4-12) treatment group for weeks 0-12. The average age of placebo (N = 154) and EW (N = 153) participants was 37.8, and 36.2 years, respectively. All efficacy measures were completed at the end of week 12, and results of primary efficacy measures are summarized in Figure 1. Clinical response was significantly increased in the EW treatment group compared to placebo (P = 0.003). Moreover, the clinical response was significantly greater in participants with Hurley Stage II (P = 0.048) and Hurley Stage III (P = 0.027) compared to placebo. However, secondary efficacy measures were not significant between EW and placebo groups, as less than one-third of all participants experienced a reduction in their AN count to 0, 1, or 2 (P = 0.961; chi-squared method) and NRS30 (P = 0.628; Cochran-Mantel-Haenszel method) by week 12. Finally, there was a reduction in Modified Sartorius Score of -15.7 and -24.4 in the placebo and EW treatment groups (P = 0.124; ANCOVA method).

PIONEER II Trial (NCT01468233)

Three hundred and twenty-six participants (221 female and 105 male) were measured at baseline. As in PIONEER I, the participants were randomized between the placebo and EW treatment groups for weeks 0-12, where efficacy measures were completed at the end of week 12. Both groups had a similar mean participant age of 36.1 and 34.9 years for placebo and EW groups, respectively. Primary efficacy results are summarized in Figure 2, which show a significant increase in clinical response in all adalimumab treatment groups compared to the placebo group (P < 0.001). In contrast to PIONEER I secondary efficacy studies, a decrease in AN count of 0, 1, or 2 (P = 0.01) and decrease in NRS30 (P < 0.001) was found in a significant proportion of adalimumab EW group participants compared to the placebo group (Figure 3). Finally, the Modified Sartorius Score for the EW group (-28.9) was notably improved compared to placebo (-9.5; P < 0.001; ANCOVA method).

	PIONEER I				PIONEER II			
Period 1 treatment arms (12 weeks)	Placebo N = 152	EW N = 153			Placebo N = 151	EW N = 155		
Period 2 treatment arms (weeks 12-35)	EW** N = 145	EW* N = 48	Placebo N = 49	EOW N = 48	Placebo N = 151	EW* N = 51	Placebo N = 51	EOW N = 53

Table 1. Treatment arms for PIONEER I and PIONEER II Phase III clinical trials.

EW = treatment every week with adalimumab SC 160 mg at week 0, 80 mg at week 2, and 40 mg for weeks 4-12

EW* = treatment every week with adalimumab SC 40 mg for weeks 12-35

EW** = treatment every week with adalimumab SC 160 mg at week 12, 80 mg at week 14, and 40 mg for weeks 16-35

EOW = treatment every other week with adalimumab SC 40 mg for weeks 12-35

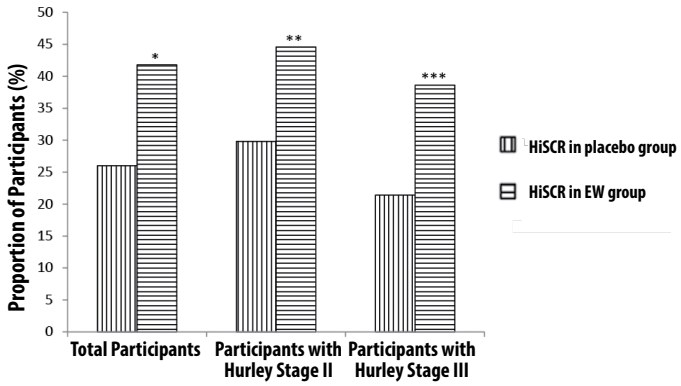

Figure 1. PIONEER I primary efficacy measure of HiSCR for patients in the placebo and adalimumab every week treatment groups at week 12.
HiSCR = ≥50% abscess and inflammatory nodule count reduction
EW group = patients receiving treatment every week with adalimumab SC 160 mg at week 0, 80 mg at week 2, and 40 mg weeks for 4-12
* P = 0.003 compared to placebo; Cochran-Mantel-Haenszel method
** P = 0.048 compared to placebo; chi-squared method
*** P = 0.027 compared to placebo; chi-squared method

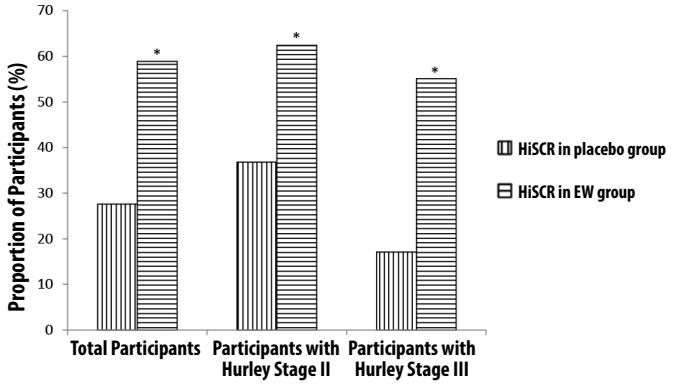

Figure 2. PIONEER II primary efficacy measure of HiSCR for patients in the placebo and adalimumab every week treatment groups at week 12.
* P < 0.001 compared to placebo; Cochran-Mantel-Haenszel method

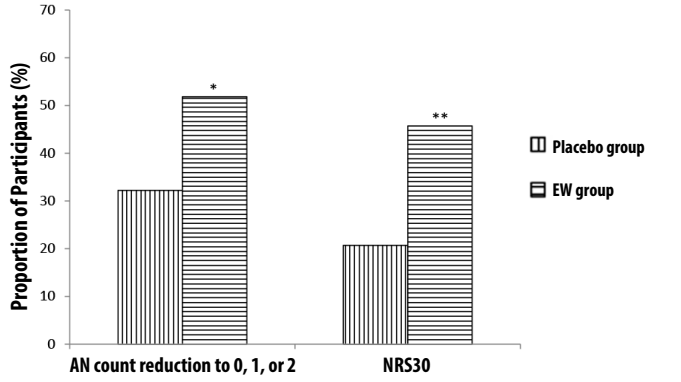

Figure 3. PIONEER II secondary efficacy measures of AN count and NRS30 reduction for patients in the placebo or adalimumab every week treatment groups at week 12.
AN = abscess and inflammatory nodule count reduction to 0, 1, or 2
NRS30 = ≥30% and 1 unit reduction in the patient's global assessment of skin pain numeric rating scale
* P = 0.01 compared to placebo; Cochran-Mantel-Haenszel method
** P < 0.001 compared to placebo; Cochran-Mantel-Haenszel method

Safety and Adverse Events

In the Phase II study, a low percentage of participants from each treatment arm reported serious adverse events (SAEs), whereas less serious adverse events (AEs) were reported in 70.59%, 63.46%, and 58.82% of EW, EOW, and placebo treatment groups, respectively. The most common AEs were nasopharyngitis (N = 19), headache (N = 17), and hidradenitis (N = 16).

PIONEER I SAE rates were low in every treatment arm, seen in only 3.29% of placebo, 1.96% of EW, 3.45% of placebo/EW (SC placebo weeks 0-12, and SC 40 mg adalimumab weeks 12-35), 4.08% of EW/placebo (adalimumab SC 160 mg week 0, 80 mg week 2, and 40 mg weeks 4-12, and SC placebo weeks 12-35), 6.25% of EW/EOW (adalimumab SC 160 mg week 0, 80 mg week 2, and 40 mg for weeks 4-12, and 40 mg adalimumab every other week for weeks 12-35), and 2.08% of EW/EW (adalimumab SC 160 mg week 0, 80 mg week 2, and 40 mg weeks 4-35) patients. The most common SAE was hidradenitis, which was experienced in 5 of the 6 treatment arms (N = 9). Other less serious AEs were seen in 53.29% for placebo, 41.83% for EW, 46.90% for placebo/EW, 61.22% for EW/placebo, 50% for EW/EOW, and 58.33% for EW/EW groups. Common side effects were hidradenitis (N = 61), headache (N = 47), urinary tract infection (N = 17), upper respiratory tract infection (N = 23), and nasopharyngitis (N = 49).

PIONEER II SAEs were also low in each treatment arm, with occurrences of 3.68% for placebo, 1.84% for EW, 4.64% for placebo/placebo (placebo for weeks 0-35), 0% for EW/placebo, 3.77% for EW/EOW, and 3.92% for EW/EW groups. The most common SAE was hidradenitis seen in three treatment arms (N = 4). Other AEs were reported in 47.24% of placebo, 40.49% of EW, 37.19% of placebo/placebo, 52.94% of EW/placebo, 47.17% of EW/EOW, and 41.18% of EW/EW groups. Common side effects were nasopharyngitis (N = 31), upper respiratory tract infection (N = 40), headache (N = 58), and hidradenitis (N = 60).

Conclusion

The data reported from two Phase III clinical trials on the efficacy of adalimumab for the treatment of moderate to severe HS has been promising. In both trials, patients receiving adalimumab every week had a significant reduction in abscess and inflammatory nodule count at week 12 compared to placebo. Furthermore, adverse events in each treatment arm were comparable to placebo, with no new adverse events recorded. This indicates that adalimumab is a safe and effective therapy for the treatment of HS by demonstrating the potential to achieve disease control within the first 12 weeks of treatment.

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Frontal Fibrosing Alopecia

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ABSTRACT

Frontal fibrosing alopecia, described just over 20 years ago, has become one of the most frequently seen causes of scarring alopecia at many specialist hair clinics. Considered a clinical variant of lichen planopilaris (LPP), it has distinctive features and associations which distinguish it from LPP. Although largely affecting postmenopausal women, a small but increasing number of men and premenopausal women are affected. The spectrum of the disease has expanded from involvement of the frontal hairline and eyebrows, to potentially affecting the entire hairline, facial and body hair. Genetic and environmental factors have been implicated but the aetiology remains uncertain. A range of treatments have been used in management of the condition, but clinical trials are required to establish effectiveness.

Key words: cicatricial alopecia, frontal fibrosing alopecia, hair loss, lichen planopilaris, scarring alopecia

Introduction

Frontal fibrosing alopecia (FFA) was first described in 1994 by Kossard as a new type of scarring alopecia.[1] Clinically, the follicular features appeared identical to lichen planopilaris (LPP) however, the pattern of the disease was distinct from typical LPP in several ways.[2] Firstly, those affected were exclusively postmenopausal women. Secondly, the condition resulted in a distinctive pattern of alopecia affecting the frontal hairline, associated with loss of eyebrows. Histologically, the findings were indistinguishable from LPP, with reduction in hair follicle numbers, perifollicular fibrosis, perifollicular lymphoid infiltrate and follicular interface dermatitis.[2] Since this first description, FFA has been the subject of more than 80 papers. The clinical spectrum of the disease has also expanded. As well as eyebrows, eyelashes may be lost[2,3] and involvement of facial vellus hairs can sometimes result in small flesh coloured facial papules[4-6]. Limb and flexural hair are also frequently affected, usually with no associated symptoms or rash.[7,8] The condition no longer exclusively affects postmenopausal women as a small but increasing number of cases have been reported in premenopausal women and in men.[9] There may be differing ethnic susceptibility: FFA is most frequently recorded in Caucasian women, being reported less frequently in black women[10,11] and rarely in Asians[12,13]. However, it has been suggested that in black patients, FFA is under-recognized as it frequently co-presents with traction alopecia.[10,11]

The clinical and histological similarities between FFA and LPP suggest that FFA is a clinical variant of LPP.[2] Like LPP,[14] an increased association between FFA and autoimmune disease, particularly thyroid, has been noted[3,15]. However, there are several areas in which FFA appears to differ from classical LPP. Firstly, FFA affects predominantly women: in two large cases series, male to female (M:F) ratio ranged from 1:289 to 1:31, whereas in LPP, M:F has been estimated at between 1:1.8 to 1:4.9.[16] Lichen planus affecting other sites (cutaneous, nail, mucosal) is seen more frequently in association with LPP (28-50%)[17,18] than with FFA (1.6-9.9%)[3,9,15]. Loss of facial and body hair concomitant with LPP is reported in 7-10%.[16,18] In FFA, loss of eyebrows has been reported in around 80% of cases[2,4,9,15] and may occasionally precede loss of hairline[3,15]. Loss of eyelashes is uncommon[2,3,9] and has been associated with more severe disease[9]. Loss of body hair also occurs, affecting both limb and flexural hair. Loss of hair from limbs has been documented in around 20-25% of patients in large case series[3,9,15] but affected 77% of patients in a smaller case series and was confirmed histologically. Unlike typical LPP, loss of hair from eyebrows and body in FFA is clinically largely non-inflammatory.[7] Classical diffuse LPP elsewhere on the scalp has been reported in association with FFA in <1-16%.[2,3,9,15] While scalp LPP is primarily a disorder of terminal pigmented hairs, it has been suggested that in FFA, vellus and intermediate hairs are affected preferentially,[8,19] although this has not been confirmed in another study[7]. Paradoxically, most terminal pigmented hairs on the scalp are unaffected in FFA, with only those at the hairline involved. Symptoms may also be less frequent in FFA[3,9,19] (3-55%) than in LPP (60-70%)[18] but this has not been confirmed in all case series[15,20].

Currently, there are no epidemiological data on the incidence or prevalence of FFA in the general population. However, most papers published over recent years suggest that the incidence of FFA may be increasing.[3,4,9,15,21] Figures from my own hair clinic in Glasgow, UK demonstrate that the numbers of new cases of FFA have increased significantly over the last 16 years, both in terms of absolute number and as a percentage of the total number of new cases seen annually (Table 1).

It should be borne in mind that there are potential sources of bias inherent in this type of data: for instance, when a new condition is described, it is likely that the number of recorded cases will increase as awareness of the condition increases amongst medical practitioners. However, as FFA progresses slowly and may be asymptomatic, the identified cases may represent only the "tip of the iceberg". Certainly, in a proportion of cases, hair loss is unrecognized by patients and the diagnosis is made when patients attend with another dermatological condition.[3,22] Given these observations, there is considerable interest in the aetiology(ies) of FFA and how this might explain why we are apparently seeing increasing numbers of cases.

Year	Number of New FFA Cases	FFA as % of Total New Cases
2015	67	28
2014	41	22.5
2013	42	23
2012	31	16
2011	20	17
2010	24	11
2009	13	6.0
2008	11	6.8
2007	6	3.4
2006	3	2.2
2005	4	5.6
2004	3	3.4
2003	5	6.0
2002	1	2.3
2001	1	1.7
2000	1	1.6
1999	0	0

Table 1. New FFA cases seen annually at the author's hair clinic

Since the first case reports of FFA affecting siblings,[23-25] there have been an increasing number of reports of familial cases,[26,27] suggesting a possible genetic predisposition and studies are underway to try to identify genes which may be associated with FFA. However, genetic susceptibility alone would not explain the apparent increase in FFA incidence. It has been proposed that clusters of affected cases within families may indicate not only genetic susceptibility but possible environmental triggers.[26] Karnik et al[28] published experimental evidence which demonstrated a possible role for peroxisome proliferator-activated receptor-gamma (PPAR-gamma) in pathogenesis of LPP. They established that PPAR-gamma, a transcription factor that belongs to the nuclear receptor super-gene family, is required for maintenance of follicular stem cells and demonstrated that mice with PPAR-gamma deleted from follicular stem cells developed a scarring alopecia. In scalp biopsies from patients with LPP, it was found that PPAR-gamma was down-regulated in hair follicles. The authors postulated a possible role for xenobiotic metabolism as an environmental trigger for LPP, through the aryl hydrocarbon receptor (AhR). Environmental toxins such as dioxin-like substances, activate AhR which is known to suppress PPAR-gamma.[28] The role of PPAR-gamma and AhR in FFA remain to be elucidated.[26]

The possible role of environmental factors in FFA is supported by other observations. In our cohort of FFA patients, we observed a statistically significant association ($p < 0.001$) between FFA and affluence, as measured by the Carstairs Index, when compared with age and gender matched patients attending the hair clinic with other causes of alopecia, and with age and gender matched women in the general population. This finding was supported by the observation that the same cohort were significantly less likely to be smokers ($p = 0.01$), compared with the general population.[3] A review of 355 Spanish patients[9] showed 87% were non-smokers however, this was not significantly different from the general population. While it seems unlikely that affluence per se is relevant in the pathogenesis of FFA, this may be a surrogate marker for an as yet unidentified risk factor associated with affluence. Interestingly, in a cohort of US patients with FFA, affected women were significantly more likely to have attained the highest educational level (US cooperative FFA study group, Elise Olsen chairman, unpublished data).

The development of FFA/LPP following hair transplant or cosmetic surgery[29] further supports the role of environmental triggers in the pathogenesis of FFA/LPP. One possible explanation that has been proposed to explain this finding suggests that the immunosuppressive milieu which normally surrounds hair follicles ("immune privilege") is disturbed by inflammatory mediators stimulated as a result of cutaneous surgery, leading to loss of follicle immune privilege and increasing hair follicle susceptibility to inflammatory attack.[29] Further studies examining the role of environmental agents in FFA are currently being undertaken.

As FFA was first described exclusively affecting postmenopausal women, it has been postulated that FFA may be due to hormonal changes at the time of the menopause.[9,19] However, no hormonal abnormalities have been identified in FFA patients[2,19] and hormonal changes alone would not explain the apparent increasing incidence of the condition, nor the cases of FFA arising in premenopausal women and in men. The observation of FFA affecting transplanted occipital hairs in a man with FFA concomitant with androgenetic alopecia,[30] suggests that hair follicle androgen susceptibility may not be required for pathogenesis of FFA. However, the possible role of hormones in the pathogenesis of FFA has been supported by the observations that 5-alpha-reductase inhibitors (5ARIs) can stabilize[9,19,21] and improve FFA[9,31,32]. Hair regrowth in a scarring alopecia in which destruction of hair follicles is a cardinal histopathological feature[2,7] is a puzzling phenomenon. However, personal experience and documented cases have demonstrated improvement in eyebrow growth in some FFA patients treated with topical calcineurin inhibitors.[33] Similarly, regrowth of hair in apparently scarred areas of scalp in chronic discoid lupus erythematosus (CDLE) and other scarring alopecias is occasionally observed.[34,35] There have been several sporadic case reports of improvement in FFA with 5ARIs, which have included photographic images.[31,32] The largest published review of FFA cases suggested that of 111 patients treated with 5ARIs, 47% stabilized and 53% improved.[9] Further clarification of these results however, indicated that clinical improvement at the hairline was minimal and response to antiandrogens was more frequent if concomitant androgenetic alopecia was present, although not exclusively so.[36] Where stabilization of FFA with treatment is reported, it is important to be aware that spontaneous stabilization of FFA can occur.[4] Given the often slow progress of FFA, prolonged periods of observation would be required to confirm true stabilization. Clearly, randomized controlled trials, using objective measurements of disease, are required to assess the role of treatments for FFA.

Conclusion

In summary, the incidence of FFA, first described only 20 years ago, appears to be increasing. Clinically and histologically, it appears to be a variant of LPP. The identification of familial cases suggests a genetic susceptibility but also raises the possibility of environmental triggers. Randomized controlled trials are required to confirm the effect of treatments and epidemiological studies should be considered to confirm the incidence and prevalence of FFA within the population.

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Erratum to Blakely K, Gooderham M, Papp K. Dupilumab, a monoclonal antibody for atopic dermatitis: a review of current literature. *Skin Therapy Lett.* 2016 Mar-Apr;21(2):1-5. On page 2, section entitled Immune Dysfunction in AD, the word "induce" has been changed to "regulate" in the following sentence: Additionally, IL-4 and IL-13 have also been demonstrated to regulate expression of genes, such as β-defensins and cathelicidin, involved in susceptibility to skin pathogens including *Staphylococcus aureus* and herpes simplex virus, potentially accounting for the fact that AD patients have an increased propensity for infection by these pathogens.[36-38] This correction is reflected in the web version.

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Update on Drugs

Name/Company	Approval Dates/Comments
Bilastine tablet *Blexten*™ Aralez Pharmaceuticals	Health Canada approved bilastine 20 mg oral tablet in April 2016 for treating the symptoms of seasonal allergic rhinitis and chronic spontaneous urticaria (such as itchiness and hives). This is the first new antihistamine introduced in Canada in over 15 years.
Ixekizumab SC injection *Talz*® Eli Lilly and Company	In April 2016, the European Commission (EC) granted marketing authorization for ixekizumab for the treatment of moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy. Ixekizumab is an antibody specifically designed to target the cytokine interleukin IL-17A, a protein that plays a role in driving underlying inflammation in psoriasis. The approved dosing regimen for ixekizumab is a 160 mg SC injection, followed by an 80 mg injection every 2 weeks for 12 weeks and then a maintenance monthly dose of 80 mg.
Wound care gel *Lasercyn™ gel* Oculus Innovative Sciences	US FDA 510(k) clearance was granted to Microcyn®-based Lasercyn™ gel in April 2016. Under the supervision of a healthcare professional, Lasercyn™ gel is intended for the management of post-nonablative laser therapy procedures, post-microdermabrasion therapy and following superficial chemical peels. Lasercyn™ may also be used to relieve itch and pain from minor skin irritations, lacerations, abrasions and minor burns. CE Marks in Europe were gained in March 2016.
Ceftaroline fosamil *Teflaro*® Allergan plc	The FDA approved a supplemental New Drug Application in May 2016 for ceftaroline fosamil, an IV antibiotic, which grants new indications for pediatric patients 2 months of age to less than 18 years of age with acute bacterial skin and skin structure infections (ABSSSI), including infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA), and community-acquired bacterial pneumonia (CABP) caused by *Streptococcus pneumoniae* and other designated susceptible bacteria.
Nivolumab + ipilimumab *Opdivo*® + *Yervoy*® Bristol-Myers Squibb Company	In May 2016, the EC approved nivolumab (Opdivo®, anti-PD-1 monoclonal antibody) in combination with ipilimumab (Yervoy®, anti-CTLA-4 monoclonal antibody) for the treatment of advanced (unresectable or metastatic) melanoma in adults. This approval allows for the marketing of the combination IV regimen in all 28 EU Member States.
PDT for actinic keratosis *Ameluz® gel + BF-RhodoLED®* Biofrontera AG	In May 2016, the FDA approved the topical prescription drug Ameluz® (aminolevulinic acid, a porphyrin precursor) for use in combination with the BF-RhodoLED® lamp for photodynamic therapy (PDT) treatment of mild to moderate actinic keratoses on the face and scalp. This approval covers lesion-directed as well as field-directed treatment.

Drug News

In May 2016, the FDA issued an update to its Drug Safety Communication from 2013 limiting the usage of ketoconazole (Nizoral®) oral tablets due to potentially fatal liver injury and risk of drug interactions and adrenal gland problems. Healthcare professionals are warned to avoid prescribing the antifungal medicine ketoconazole oral tablets to treat skin and nail fungal infections. Label changes for oral ketoconazole tablets in 2013 reflected these serious risks and removed the indications for treatment of skin and nail fungal infections. However, an FDA safety review found that oral ketoconazole continues to be prescribed for these types of conditions. Since the 2013 labeling change, one death has been reported to the FDA due to liver failure associated with oral ketoconazole prescribed to treat a fungal infection of the nails. For more information: http://www.fda.gov/Drugs/DrugSafety/ucm500597.htm