EFFECTIVENESS AND SAFETY OF ORAL TOFACITINIB IN PATIENTS WITH RECALCITRANT FRONTAL FIBROSING ALOPECIA: A PILOT STUDY

BY

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Abstract

Frontal fibrosing alopecia (FFA) predominantly affects women aged 50–60 and is characterized by symmetrical hairline recession with redness and scaling. Treatments including hydroxychloroquine, corticosteroids and Janus kinase (JAK) inhibitors show promising results, although no standard guidelines exist. Studies indicate that tofacitinib, a JAK1/3 inhibitor, is effective in treating FFA, with reported symptom improvement ranging from 30% to 94% compared to baseline. However, large-scale studies demonstrating optimal outcomes are lacking and there might be financial constraints and logistical issues for patients. Assessing the effectiveness and safety of tofacitinib could provide valuable insights into its potential benefits against FFA, addressing a significant unmet medical need. The pilot single-arm study aimed to evaluate effectiveness and safety of tofacitinib in Thai patients with recalcitrant FFA, addressing treatment effectiveness and safety concerns in this population. This study involved 11 eligible participants who underwent a 12-week treatment regimen of oral tofacitinib at a daily dose of 10 mg for FFA. Assessments included the Frontal Fibrosing Alopecia Severity Index (FFASI), the Frontal Fibrosing Alopecia Severity Score (FFASS), the Lichen Planopilaris Activity Index (LPPAI), and photographic and dermoscopic evaluations. Descriptive statistics and statistical tests, including the Wilcoxon rank test, were used for data analysis. The qualitative clinical outcome was evaluated by dermatoscopy examination. There are statistically significant improvements in FFASI (47.5 to 44.0, $p = 0.045$) and FFASS (16.3 to 15.9, $p = 0.016$) at week 16, while LPPAI did not show significant changes (median 1.83 vs. 1.33, $p = 0.13$). Safety monitoring included surveillance for adverse events and laboratory assessments. By week 16, four out of eleven (36.4%) of participants experienced mild acne vulgaris, while five out of them (45.5%) had a slight increase in cholesterol. Three in five (60%) of those with dyslipidemia sought treatment from specialists, and two out of three (66.7%) were able to normalize their cholesterol levels with medication.

These results offer preliminary support for effectiveness of tofacitinib as a treatment for FFA. However, additional studies with extended follow-up periods and larger participant groups are required to substantiate its effectiveness and safety.

(Total 44 Pages)

Keywords**:** Frontal fibrosing alopecia, oral Tofacitinib therapy, Effectiveness, Safety

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Chapter 1

Introduction

1.1 Background and Significance of the Problem

Frontal fibrosing alopecia (FFA) was first described in 1994 (Kossard, 1994). FFA is most common in 50-60-year-old females. This condition can be found in up to 13 percent of women of reproductive age and 4 percent in men of color. When comparing the incidence of FFA among women of reproductive age, the number was higher in the black ethnic than in white women (Kerkemeyer, Eisman, Bhoyrul, Pinczewski& Sinclair, 2021). Patients with FFA usually present with symmetrical bandlike hairline recession in the frontotemporal region with scaling and redness in the perifollicular region of the lesion (Kossard, 1994). FFA has three patterns: linear, diffuse, and pseudo “fringe signs”. The progression of hairline recession can spread to the posterior ear hairline and occipital area. It could be noticed that the skin in the hairline recession area was lighter and glossier after long exposure to the sun when compared to the normal skin area. The “lonely hairs sign” is a clinical clue to the diagnosis. Terminal scalp hairs in the original 3-7 cm hairline were found in more than 50% of FFA patients (Kerkemeyer et al., 2021). Currently, there is no standard guideline for treating FFA (To & Beecker, 2018). The FFA treatments include 5-alpha reductase inhibitors, corticosteroids (oral and oral), hydroxychloroquine, isotretinoin, antibiotics and Pioglitazone (Autrup, Thurlow &Warwick, 1975; Rakowska, Gradzińska, Olszewska & Rudnicka, 2017; Tan & Messenger, 2009). Those treatments showed different outcomes and no definitive information regarding the effectiveness of individual drugs. Systemic therapies may only slow down the progression of the disease (Autrup et.al., 1975; Tan & Messenger, 2009). In recent years, JAK inhibitors such as tofacitinib have been reported to treat Lichen planopilaris and FFA. Tofacitinib improved symptoms ranged 30-94% compared to baseline (Yang, Khanna, Sallee,

Christiano, Bordone, 2018). JAK inhibitors are believed to decrease interferon-gamma and interleukin 15, resulting in reducing white blood cells and inhibiting hair follicle growth (Xing et al., 2014). The treatment with tofacitinib in FFA has not been studied in Thailand before. Due to its high cost, patients may not have financial support to receive treatment, including travel expenses and time constraints. Therefore, if the effectiveness and safety of this drug can be studied to assess the effectiveness and safety of tofacitinib, this may indicate a benefit of tofacitinib against FFA.

1.2 Research Objectives

1.2.1 To study the effectiveness of tofacitinib therapy in Thai patients with recalcitrant frontal fibrosing alopecia.

1.2.2 To study the safety of tofacitinib therapy in Thai patients with recalcitrant frontal fibrosing alopecia.

1.3 Research Questions/ Assumptions

1.3.1 Is tofacitinib significantly reduce Frontal Fibrosing Alopecia Severity Index (FFASI), Frontal Fibrosing Alopecia Severity Score (FFASS), Lichen Planopilaris Activity Index (LPPAI) comparing to baseline and after 16 weeks?

1.3.2 Is tofacitinib significantly different for adverse effect comparing to baseline and after 16 weeks?

1.4 Research Framework

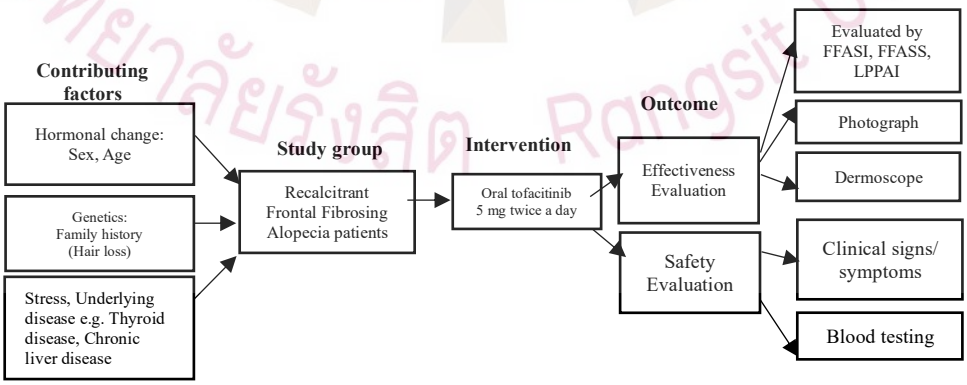

Figure 1.1 Research Framework

1.5 Definition of Terms

Frontal Fibrosing Alopecia (FFA)

Frontal Fibrosing Alopecia (FFA) is a dermatological condition diagnosed by dermatologists based on criteria proposed by Vañó-Galván et al. These criteria encompass specific features, including a biopsy or recession of the frontotemporal and preauricular hairline, eyebrow loss, and distinctive trichoscopy findings (Vañó-Galván et al., 2019).

Frontal Fibrosing Alopecia Severity Index (FFASI)

The Frontal Fibrosing Alopecia Severity Index (FFASI) is a scoring system employed to evaluate the severity of FFA. It assigns most of its points (80 out of 100) to assess the recession of the frontal and temporal hairlines. Subsequently, it takes into account factors such as inflammation, eyebrow loss, the presence of facial papules, cutaneous lichen planus (LP), oral or genital LP lesions, and nail involvement, which significantly contribute to the overall score (Saceda-Corralo et al., 2018).

Frontal Fibrosing Alopecia Severity Score (FFASS)

The Frontal Fibrosing Alopecia Severity Score (FFASS) involved assessing its criterion validity through the Investigator Global Assessment and evaluating construct validity by examining the convergence with other severity measures such as the Patient Global Assessment, clinical features, the Lichen Planopilaris Activity Index, and quality of life assessments like the Dermatology Life Quality Index and Hospital Anxiety Depression Scale. Additionally, intraobserver and interobserver reliability were assessed (Saceda-Corralo et al., 2018) .

Lichen Planopilaris Activity Index (LPPAI)

The Lichen Planopilaris Activity Index (LPPAI) is a numerical scoring system designed to quantify the signs and symptoms of LPP and frontal fibrosing alopecia (FFA) for statistical comparison. It encompasses symptoms such as pruritus, pain, and burning, along with signs like erythema, perifollicular erythema, and scale, and includes measures of disease activity such as the anagen pull test and extension of the disease. The equation for calculating the LPPAI (ranging from 0 to 10) involves assigning weights to these subjective and objective measures. Symptoms and signs are assessed on a 4-point scale ranging from absent to severe. The anagen pull test, indicative of local disease activity, involves grasping hair shafts and pulling firmly to evaluate the presence of anagen hairs, recorded both as a binary value and as the ratio of anagen hairs to total hairs pulled (Saceda-Corralo et al., 2018).

Janus Kinase Inhibitors (Tofacitinib) Treatment

Janus Kinase Inhibitors (specifically tofacitinib) treatment involves prescribing oral tofacitinib at a dosage of 5 mg twice daily continuously for 12 weeks. Tofacitinib belongs to a class of medications known as Janus kinase (JAK) inhibitors. This drug functions by inhibiting specific enzymes called JAKs, which are involved in the immune system's inflammatory response. It is primarily utilized to manage autoimmune diseases such as psoriatic arthritis, rheumatoid arthritis, ulcerative colitis etc (Saceda-Corralo et al., 2018).

Chapter 2

Literature Review

2.1 Frontal Fibrosing Alopecia

Frontal fibrosing alopecia (FFA) was originally identified by Kossard in 1994 as a progressive scarring alopecia affecting the frontal and temporoparietal hairlines in postmenopausal women. Initially referred to as postmenopausal frontal fibrosing alopecia, Kossard later described FFA as a rare frontal variation of LPP in 1997. However, there remains significant debate among writers as to whether FFA and LPP are distinct conditions (Vañó-Galván et al., 2019)

2.1.1 Pathogenesis

While the exact cause of FFA remains unclear, it is thought to involve hormonal factors, autoimmunity, genetic predisposition, and external influences. The initial step in developing scarring alopecias, such as FFA, appears to be the loss of the hair follicle's immune protection. This immune privilege breakdown is potentially induced by IFN-γ, according to Harries et al. (2013). Furthermore, a Th1-biased cytotoxic T-cell autoimmune response primarily targeting hair follicles in the infundibular and isthmic regions seems to play a significant role in FFA (Katoulis et al.,2021) .This autoimmune response ultimately destroys the hair follicle, affecting the bulge region where vital stem cells are situated.

In LPP, studies have reported decreased expression of the proliferative marker Ki-67 and the hair follicle epithelial progenitor cell marker keratin 15 in the bulge area (Harries & Paus, 2009; Mobini, Tam & Kamino, 2005). Additionally, FFA patients exhibit a reduced melanocyte count in the upper follicle of lesional skin, suggesting that melanocytes in the hair follicle may be an antigenic target unique to FFA (Katoulis

et al., 2018; Lin et al., 2017). A novel theory proposes that FFA may result from excessive facial photoprotection, disrupting immune balance and leading to immune privilege collapse at the hair bulge via the aryl hydrocarbon receptor-kynurenine pathway axis (AhR/KP) (Noakes, 2020). Recent research has revealed increased AhR expression in the epidermis of both unaffected and affected scalp regions in both FFA and LPP(Doche et al., 2020). The CYP1A1 gene, regulated by AhR signaling for xenobiotic metabolism, is upregulated in affected and unaffected skin in LPP (Karnik et al., 2009). Chemical substances can indirectly activate AhR by inhibiting CYP enzymes. AhR also suppresses PPAR-γ (Doche et al., 2020). In LPP, increased expression of IFN-inducible chemokines in the hair follicle bulge suggests a significant role of IFN signaling, which may attract cytotoxic CD8+ cells. Additionally, signs of immune privilege collapse are evident in LPP bulge epithelial cells, characterized by heightened class I and II major histocompatibility complex (MHC) expression and reduced transforming growth factor (TGF) β and cluster of differentiation (CD) 200 expression.

Laboratory experiments have demonstrated that IFNγ can induce immune privilege breakdown in hair follicles, suggesting the potential for therapeutic approaches targeting IFN signaling to restore immune privilege in LPP (Harries et al., 2013). Another study found up-regulation of JAK1 and JAK3 in dermal inflammatory cells in patients with inflammatory skin conditions, including LPP (Alves de Medeiros et al., 2016). This implies that JAK inhibition could potentially mitigate IFN-mediated inflammation, halt hair follicle destruction, and yield positive patient outcomes. These promising results in case series call for further investigation of JAK inhibitors in LPP through randomized, placebo-controlled clinical trials, with the potential to extend these findings to the treatment of FFA, which is considered a subtype of LPP

2.1.2 Clinical Features

Frontal Fibrosing Alopecia (FFA) is a type of scarring hair loss condition characterized by the recession of hairlines in the frontal and temporoparietal regions, forming a scar-like band. This band often contrasts with the sun-damaged skin on the

upper forehead. FFA can also affect the occipital area in approximately 15% to 30.4% of cases (Imhof, Claudhry, Larkin, Torgenson & Tolkachjov, 2018; MacDonald, Clark & Holmes, 2012; Vañó-Galván et al, 2019). In males, FFA may manifest solely as the loss of sideburn hair (Ramaswamy, Mendese & Goldberg, 2012). The affected region typically appears shiny, atrophic, and pale with incomplete hair loss(Ross, Tan & Shapiro, 2005). The recession of the hairline in FFA typically occurs bilaterally and symmetrically (Moreno-Ramirez & Camacho Martinez, 2005). Although there have been instances of asymmetric presentations. In advanced cases, FFA can lead to a distinctive "clown alopecic pattern," characterized by complete hair loss in the frontoparietal region (Moreno-Ramírez, Ferrándiz & Camacho, 2007).

2.1.3 Diagnosis and Severity determination

The diagnostic criteria for Frontal Fibrosing Alopecia (FFA) have shown significant variability across different publications and presentations. The United States FFA Cooperative Group (USFCG) employed a point-scoring system that considered clinical observations and biopsy results as criteria for inclusion in their registry. Vañó-Galván diagnosed patients based on either biopsy results or hairline recession in the frontotemporal and preauricular regions, along with eyebrow loss and distinctive trichoscopy findings. Tolkachjov utilized a diagnostic algorithm that considered a range of factors, including scalp and eyebrow characteristics, as well as common FFA features such as noninflammatory facial papules and the presence of pain or itching in the affected areas, either preceding or concurrent with the condition (Olsen et al., 2021).

2.1.4 Risk factors of FFA

1) Hormonal Influence

FFA predominantly affects postmenopausal women, accounting for approximately 70-80% of cases (Tosti, Piraccini, Iorizzo, & Misciali, 2005).

Nevertheless, there has been an increasing number of documented cases in premenopausal women (Faulkner, Wilson, & Jones, 2002) and even in males (Moreno-Ramirez & Camacho Martinez, 2005). A study involving 168 patients with lichen planopilaris (LPP) revealed a noteworthy presence of endocrine or hormonal dysfunction, particularly in the FFA subtype with lower androgen levels. This underscores the importance of considering hormonal imbalances in LPP patients and the potential role of androgens in the progression of the disease. Further research is necessary to comprehensively understand the relationship between LPP and hormonal irregularities and establish normal androgen levels for postmenopausal women. Notably, obesity and diabetes were prevalent among the LPP population, but no significant association was observed with androgen excess (Ranasinghe, Piliang, & Bergfeld 2017).

2) Genetic Factors

As evidenced by its occurrence within families, FFA is likely involve a genetic component, Investigation into the molecular genetics linked to FFA susceptibility has identified common alleles at four genomic loci: 2p22.2, 6p21.1, 8q24.22, and 15q2.1 contributing to the risk of developing the condition. These genetic loci are associated with the function of MHC Class I molecule-mediated antigen processing, T-cell, and homeostasis (Tziotzios et al., 2019).

3) Chronic Stress and Underlying Conditions

FFA shows associations with hormonal exposures like pregnancy, hormone replacement therapy (HRT), and raloxifene. It is also linked to specific comorbidities, including hypothyroidism, rosacea, and other autoimmune diseases. Interestingly, individuals with FFA are less likely to have diabetes compared to the general population (Fertig et al., 2018).

4) Environmental Factors

The increasing reports of frontal fibrosing alopecia (FFA) suggest potential links to environmental factors in its pathogenesis. Recent studies have reported a potential link between the use of facial care products like sunscreen and anti-wrinkle creams with FFA. Researchers are also exploring the impact of occupational exposure to alkylphenolic compounds and dietary habits. While a pilot study has hinted at a potential connection between regular consumption of buckwheat and millet groats and FFA, further research is necessary to confirm their roles as causative factors. Additionally, smoking has been proposed as a potential protective factor against FFA, although this observation requires validation from other studies (Moreno-Ramirez & Camacho Martinez, 2005).

2.1.5 Treatments for FFA

1) Topical treatment

1.1) Topical corticoids: It is the most common treatment for the initial stages of inflammation, but when they are stopped, recurrence develops (Moreno-Ramirez & Camacho Martinez, 2005). Potent topical steroids and calcineurin inhibitors reduce inflammation, but delaying alopecia is no significant benefit (MacDonald, Clark, & Holmes, 2012; Moreno-Ramirez & Camacho Martinez, 2005). Though disease stabilization with a combination of both treatments has been published (Heppt et al., 2018).

1.2) Topical minoxidil: The topical minoxidil monotherapy is not recommended for patients with Frontal Fibrosing Alopecia (FFA) as it is unlikely beneficial. It should be considered as an adjuvant with other treatments to enhance hair volume. Tosti and colleagues achieved positive outcomes when combining topical minoxidil 2% BID with oral finasteride 2.5 mg per day to treat FFA patients, successfully halting disease progression in 50% of cases after 12–18 months of treatment (Tosti et al., 2005).

2) Systemic Treatment

2.1) Hydroxychloroquine: This antimalarial medication is considered a primary systemic treatment for FFA due to its anti-inflammatory properties and minimal side effects. Hydroxychloroquine benefits FFA patients by reducing the upregulation of T-cells. Studies have shown that hydroxychloroquine leads to overall improvement or stabilization in a significant proportion of FFA patients when used alone or in combination with other medications. However, it typically takes up to a year to reach peak effectiveness, and individuals on long-term hydroxychloroquine therapy should undergo regular eye exams to monitor for the rare side effects of retinopathy (Ho & Shapiro, 2019).

2.2) Oral Immunosuppressants: Medications like methotrexate, mycophenolate mofetil, and cyclosporine are examples of oral immunosuppressive drugs that may be prescribed to suppress the immune response and reduce inflammation associated with FFA (Ho & Shapiro, 2019).

2.3) 5-α-Reductase Inhibitors (5α-RI): Finasteride and Dutasteride are potent antiandrogens used to treat both androgenetic alopecia and Frontal Fibrosing Alopecia (FFA). Studies have demonstrated their effectiveness in stabilizing hair loss and improving symptoms in FFA patients. They are considered among the most effective treatment options for FFA. However, caution should be exercised when using 5α-RI during pregnancy due to potential adverse effects on male fetuses. Combination therapies involving 5α-RI and other treatments like topical medications have also shown positive outcomes in halting disease progression and achieving disease stability in FFA patients (Ho & Shapiro, 2019).

2.4) Tetracyclines: Drugs like minocycline and doxycycline have been explored as treatment options for FFA owing to their anti-inflammatory properties. Some studies have reported positive results, including disease stabilization or improvement; however, responses have been somewhat unpredictable. It is important to note that tetracyclines may be associated with side effects such as nausea, photosensitivity, and gastrointestinal discomfort, which may limit their use (Ho & Shapiro, 2019).

2.5) Mycophenolate Mofetil: This prodrug of mycophenolic acid (MPA), an inhibitor of inosine monophosphate dehydrogenase (IMPDH), has been proposed as a treatment for Lichen Planopilaris (LPP) with some degree of effectiveness, although a high recurrence rate has been reported. There is limited literature regarding its use in FFA cases to draw conclusive findings (Litaiem & Idoudi, 2023).

2.6) Pioglitazone Hydrochloride: An oral PPAR-γ agonist, pioglitazone hydrochloride, has demonstrated improvement in itching and a reduction in inflammatory infiltrate in some LPP patients; however, it has not resulted in remission. In studies involving larger patient populations, mostly negative outcomes have been observed, and no successful results have been reported in FFA patients (Mobini, Tam & Kamino, 2005).

2.2 Tofacitinib

Tofacitinib, categorized as an immunomodulator within the Janus kinase inhibitor family, functions by inhibiting the tyrosine kinases associated with the Janus kinase family (Shreberk-Hassidim, Ramot & Zlotogorski, 2017). The intracellular Janus kinase-signal transducer and activator of transcription (JAK/STAT) system orchestrates a range of pro-inflammatory processes. Given the well-established effectiveness of Janus kinase inhibitors in managing inflammatory conditions, notably rheumatoid arthritis (RA) and ulcerative colitis (UC), it becomes plausible to explore their potential benefits in various inflammatory dermatoses as well (Samadi, Ahmad Nasrollahi, Hashemi, Nassiri Kashani & Firooz, 2017).

2.2.1 Mechanism of Action

JAKs are intracellular enzymes that interact with the cytoplasmic domains of various cytokine receptors. Numerous inflammatory skin disorders are associated with the JAK/STAT signaling pathway (Figure 2.1), particularly those induced by cytokine linked to type I/II cytokine receptors (Samadi et al., 2017).

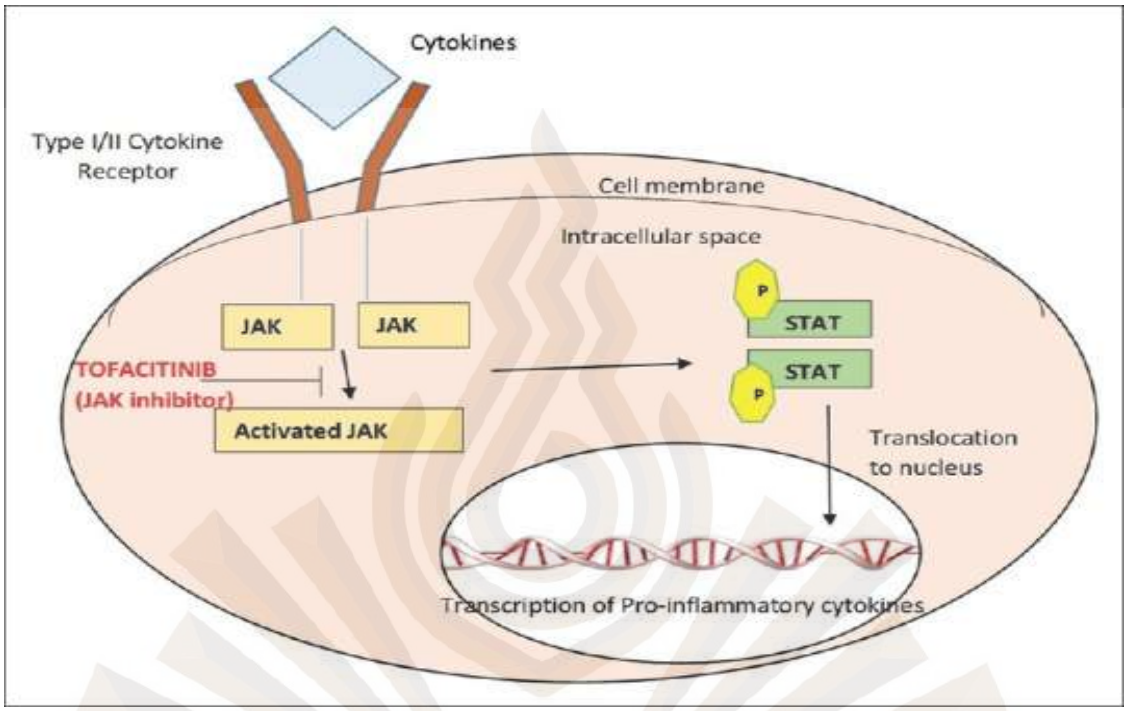

Figure 2.1 Mechanism of action of Tofacitinib (The JAK/STAT pathway)

Source: Samadi et al., 2017

2.2.2 JAK Isoforms

There are four identified isoforms of Janus kinase (JAK): JAK1, JAK2, JAK3, and TYK2. JAK1, JAK2, and TYK2 interact with multiple cytokine receptors, while JAK3 specifically binds to the common gamma chain, a receptor subunit. This shared receptor subunit is utilized by a select group of cytokines, including interleukin (IL)-2, IL-4, IL-7, IL-9, IL-15, and IL-21. First-generation Jakinibs like tofacitinib, ruxolitinib, and baricitinib inhibit multiple JAKs, while second-generation Jakinibs like decernotinib and experimental agents such as VX-509 and GLPG0634 target specific JAK isoforms (Mahajan et al.,2015).

2.2.3 Clinical Use of Oral Tofacitinib in Skin Disorders

Given the well-established effectiveness of Jakinibs in managing inflammatory diseases, notably rheumatoid arthritis (RA) and ulcerative colitis (UC), it is reasonable to consider their potential benefits in various inflammatory skin conditions (Samadi et

al., 2017). These skin conditions include psoriasis, atopic dermatitis, morphea, and eosinophilic fasciitis. Tofacitinib has been found to lower IL-17 levels, resulting in promising clinical outcomes in clinical trials (Welsch, Holstein, Laurence & Ghoreschi. 2017). Research indicates that oral tofacitinib, administered at doses of 5 or 10 mg twice daily, yields significantly better results compared to placebo and demonstrates comparable or superior effectiveness to etanercept in the treatment of inflammatory skin disorders like psoriasis (Bachelez et al., 2015). Additionally, in specific cases, oral tofacitinib at doses of 5-10 mg twice daily has been employed for the treatment of Crohn's disease (primarily associated with severe inflammatory arthritis), atopic dermatitis, and pyoderma gangrenosum that did not respond to biologics, leading to the resolution of pyoderma gangrenosum lesions within 12 weeks (Kim et al., 2018; Kochar et al., 2019). Furthermore, when used in conjunction with other immunomodulatory therapies like low-dose methotrexate, oral tofacitinib at a dosage of 5 mg two to three times daily has demonstrated significant improvement in patients with generalized deep morphea and eosinophilic fasciitis that were unresponsive to corticosteroids (Kochar et al., 2019). These encouraging findings warrant further investigation and open new possibilities for treating various inflammatory skin disorders using Jakinibs. In terms of alopecia treatment, there is evidence to suggest that tofacitinib can significantly improve the severity of Alopecia Areata, with more than 50% improvement measured in the Severity of Alopecia Tool (SALT) score in 32–66% of patients receiving tofacitinib treatment, alongside adjuvant therapies. Better outcomes were reported for patchy Alopecia Areata compared to totalis or universalis forms, with higher dosages of 10 mg twice daily being more effective than 5 mg twice daily. Concomitant oral steroids also enhanced results (Jabbari et al., 2018; Liu & King, 2018).

2.2.4 Evidence of Oral tofacitinib in FFA

Growing evidence supports the use of oral tofacitinib in the treatment of frontal fibrosing alopecia (FFA). Tofacitinib, a Janus kinase (JAK) inhibitor, targets the inflammatory pathways involved in FFA. Several case reports and small studies have reported promising results with tofacitinib in FFA patients, leading to improved hair regrowth and disease stabilization. In one case series involving six FFA patients treated

with tofacitinib, all experienced significant hair regrowth and symptom reduction after six months. Another case report detailed a patient with FFA who achieved complete hair regrowth after six months of tofacitinib therapy (Yang et al., 2018). A larger study by (Vañó-Galván et al., 2021) assessed the effectiveness and safety of tofacitinib in 28 FFA patients. After 12 months of treatment, 75% of patients showed stabilization or improvement in their condition (Vañó-Galván et al., 2019). These findings suggest that oral tofacitinib may be a promising treatment option for FFA. However, larger controlled trials are needed to establish its effectiveness and safety in this condition. As with any medication, it is important for patients to undergo close monitoring by their healthcare provider while on tofacitinib therapy.

Chapter 3

Research Methodology

3.1 Population and Samples

3.1.1 Target population

Recalcitrant Frontal Fibrosing Alopecia patients who were confirmed diagnosed. Participants were out-patients treated at The Hair and Nails Center, Institute of Dermatology from November 2023 to March 2024 and qualified for inclusion criteria.

3.1.2 Sample size

Since this study has never been conducted in Thailand, many case series and case reports have been identified in the department in worldwide research; researchers intend to conduct a pilot study to determine its effectiveness and safety. In this study, there were a total of eleven volunteers.

3.1.3 Inclusion criteria

1) Thai males or females who were at least 18 years old

2) Participants who were diagnosed with Frontal Fibrosing Alopecia

The criteria for the diagnosis of Frontal Fibrosing Alopecia are 2 major criteria or 1 major criterion plus 2 minor criteria. as demonstrated in Table 3.1(Vañó-Galván et al., 2019).

Participants who were diagnosed with recalcitrant Frontal Fibrosing Alopecia

1) The patient who fails treatment at least one drugs such as hydroxychloroquine and/or receives others such as immunosuppressive drugs, Pioglitazone, Retinoids. However, the symptoms of FFA still appear such as perifollicular erythematous and/or scale after taking treatment more than 3 months

1) The patient continued taking the medicine as prescribed and coming to follow-up

2) The patient still had the medical record, such as a picture and dermoscopy.

3) The patient did not need a washout time from the current medicine.

Table 3.1 The diagnostic criteria for Frontal Fibrosing Alopecia

Major Criteria	**Minor Criteria**
1. Cicatricial alopecia of the frontal, temporal, or frontotemporal scalp in the absence of follicular keratotic papules on the body.	1. Typical trichoscopic features (perifollicular erythema and/or follicular hyperkeratosis, lonely hair sign).
2. Diffuse bilateral eyebrow alopecia.	2. Histopathological features of FFA and LPP.
	3. Involvement (hair loss or perifollicular erythema) of additional FFA sites (occipital area, facial hair, sideburns, or body hair).
	4. Non-inflammatory facial papules.
	5. Preceding or concurrent symptoms (pruritus or pain) at the areas of involvement.

Source: Vañó-Galván et al., 2019

3.1.4 Exclusion criteria

1) Patients who were diagnosed with a disease that may relate to hair growth within six months, such as thyroid disease, iron deficiency anemia, liver disease, heart disease, neurological system disease, gastroenteritis disease, sexual disease, cancer, and psychologic disease

2) Pregnancy

3) Patients who have contraindication to take oral tofacitinib such severe infection, allergy to tofacitinib, venous thromboembolism, leukopenia, severe liver disease, severe kidney failure, pneumonia, cancer.

4) Patients who received strong or moderate to strong CYP3A4 agents

5) Patients who had positive on HBsAg and/or HCV

6) If abnormal blood test results are found during each follow-up visit, such as a 3-fold increase in liver enzymes (AST and/or ALT) from the baseline, consideration should be given to immediately stop taking tofacitinib.

3.2 Research Instruments

3.2.1 Research design

A pilot single-arm before and after clinical trial

3.2.2 Research Procedures

1) A total of 11 patients with recalcitrant FFA were eligible for the study if they were 18 or older, met the diagnosis criteria of FFA, and had been on systemic medication for at least 6 months. Patients were excluded if they had any other hair loss that could interfere with treatment outcomes.

2) Patient demographic data were collected, including disease duration, medical and medication history, symptoms, diagnoses, FFA type, comorbidities, and family history, as well as baseline laboratory testing including Complete Blood Count (CBC), liver function tests, lipid profile, fasting blood sugar, renal function tests, hepatitis B and C screening, chest X-ray, and urine pregnancy test for reproductive-age women.

3) The researchers collected data on the disease symptoms of the patients using photograph taken with a Nikon D850 DSLR Full Frame Digital Camera, Nikon Lens AF-S Micro NIKKOR 105 mm f/2.8G IF-ED VR, and Dermoscope model APBM body studio (Bad Bimbach, Germany) on the scalp, forehead, eyelashes, patches on the face, flexures, arms, legs, nails, mouth and dark spots (if any).

4) Eleven volunteers would be prescribed tofacitinib 5 mg 2 times per day in morning evening for 12 weeks. Participants would be to follow up every 4 weeks throughout the 12-week treatment period and for 4 weeks after discontinuing the medication. The total duration of the research would be 16 weeks in order to evaluate the effectiveness and safety after treatment as follows

a. Assess the disease sign/symptoms as follows:

b. Evaluate effectiveness by Frontal Fibrosing Alopecia Severity Index (FFASI) Show in Figure 3.2.2.4.1

c. Evaluate effectiveness by Frontal Fibrosing Alopecia Severity Score (FFASS) Show in Figure 3.2.2.4.2

d. Evaluate effectiveness by Lichen Planopilaris Activity Index (LPPAI) Show in Figure 3.2.2.4.3

e. Photograph by Nikon D850 DSLR Full Frame Digital Camera Body Nikon Lens AF-S Micro NIKKOR 105mm f/2.8G IF-ED VR at scalp hairline, eyebrows, eyelashes, facial papules, flexures, limbs, oral mucosa, and nails. Two medical specialists will evaluate the photograph separately, and a total of 11 patients' images will be assessed to ensure consistency among the doctor before examining the actual patients. The evaluation will determine whether the patients' condition have improved, stabilized and worsening.

f. Dermoscope by APBM body studio (Bad Bimbach, Germany) at scalp hairline, eyebrows, eyelashes, facial papules, flexures, limbs, and nails

g. Patients were evaluated abnormal symptoms of patients after taking the medication such as respiratory tract infection, abnormal skin conditions like acne, rashes, abnormal gastrointestinal symptoms such as loss of appetite, nausea, vomit, diarrhea, bloating, Urinary tract infection and others such as headache, muscle soreness, athralgia, fever, swelling of arms/legs, numbness and insomnia.

h. Laboratory tests was collected include blood tests to evaluate safety of the medication including Complete blood count (CBC), SGOT, SGPT, cholesterol, triglyceride, fasting blood sugar (FBS), Blood Urea Nitrogen (BUN), Creatinine (Cr) at week 4,12 and 16.

i. The researchers collected the data and statistically analyzed the collected data.

Scalp margin	**cm.**	**score**	**Note**
Frontal			Grade 1-5 No loss : score 0 Grade 1(<1cm) : score 4 Grade 2(1-2.9cm.) : score 8 Grade 3(3-4.9cm) : score 12 Grade 4(5-7.9cm.) : score 16 Grade 5(>8cm.) : score 20
Right Lateral			
Left Lateral			
Posterior			
Frontal Band			score 0 : not inflamed, normal density score 2 : inflame or reduce density score 4 : inflame and reduce density
Total (/84)			

Other Hair loss (No loss = 0, Partial loss = 1, Complete loss = 2)	
Eyebrow	
Eyelash	
Flexural (Axillary/pubic)	
Upper limb	
Lower limb	
Total	
Additional Features (Absent =0, Present = 1)	
Typical scalp LPP	
Facial papules	
Cutaneous LP/LP variants	
Oral mucosal LP	
Genital mucosal LP	
Nail LP	
Total	

Figure 3.1 Record form of Frontal Fibrosing Alopecia Severity Index (FFASI)

Clinical Signs			
Hairline recession	cm.	score	Note
Frontal (x2)			Grade 1-5 No loss: score 0 Grade 1(<1cm): score 1 Grade 2(1-2.99cm.): score 2 Grade 3(3-4.99cm): score 3 Grade 4(5-6.99cm.): score 4 Grade 5(>7cm.): score 5
Temporal (Lt)			
Temporal (Rt)			
Loss of eyebrows			No = 0, Partial = 0.5, Total = 1
Perifollicular Inflammation			
A. Severity			
Erythema			No = 0, Mild = 0.1, Severe = 0.2
Hyperkeratosis			No = 0, Mild = 0.5, Severe = 1
B. Extent (Along the frontotemporal hairline)			
Erythema			<25% = 0, 25%-75% = 0.1, >75% = 0.2
Hyperkeratosis			<25% = 0, 25%-75% = 0.5, >75% = 1
Total			

Associated symptoms		
	Score	
Pruritus		No = 0, Mild /Occasion= 0.1, Severe/ Daily = 0.2
Severity		
Frequency		
Pain		No = 0, Mild /Occasion= 0.3, Severe/ Daily = 0.6
Severity		
Frequency		
Total (Grade of Inflammation score)		

Figure 3.2 Record form of Frontal Fibrosing Alopecia Severity Score (FFASS)

	score	
A: Pruritus		Note: Absent = 0 Mild = 1 Moderate = 2 Severe = 3
B: Pain		
C: Burning		
D: Erythema		
E: Perifollicular Edema		
F: Perifollicular Scale		
Pull Test (neg =0, Pos=1)		
Spreading		Note: No spreading = 0 Indeterminate = 1 Spreading = 2

Figure 3.3 Record form of Lichen Planopilaris Activity Index (LPPAI)

3.3 Data Collection

In this research investigation, each section contains discrete data entries presented in a specific format, and these records are subject to restricted access. The primary objective is to safeguard the anonymity and personal details of the research participants, guaranteeing that their information remains confidential and is not disclosed to unauthorized individuals. The data collection process utilized a case record form (depicted in Figure 3.1), which deliberately omitted patient-specific information. This data is restricted solely to authorized personnel, including research physicians, research teams, and the Human Research Ethics Committee of the Institute of Dermatology. After the research is published, all data will be securely deleted to uphold participant confidentiality and privacy further.

3.4 Data Analysis

1) Demographic information

Analyze the demographic information including age, gender, weight, height, body mass index, waist circumference, personal medical history, history of medication uses in the past 3 months (menstruation history for female subjects), as well as records of symptoms such as hair loss history and diagnosis, pattern of hair loss on the scalp or other areas, comorbidities, family history, and other accompanying symptoms. Descriptive statistics such as number (n) and percentages are used for qualitative data, while median and interquartile range (IQR) are used for quantitative data.

1) Comparison of Frontal Fibrosing Alopecia Severity Index (FFASI), Frontal Fibrosing Alopecia Severity Score (FFASS) and Lichen Planopilaris Activity Index (LPPAI) assessment scores before taking 5 mg of oral tofacitinib and after 16 weeks after taking oral tofacitinib, analayzed using Wilcoxon signed rank test for quantitative data. We applied the Friedman test for data that did not follow a normal distribution. Statistical significance was determined with a p-value equal to or less than 0.05.

2) Evaluate safety after taking oral tofacitinib including sign, symptoms, side effects and laboratory results. Qualitative data was reported in number (n) and percentages

Chapter 4

Research Results & Discussion

4.1 Results

4.1.1 Demographic data

All volunteers were female, with an average age of 56 years, an average BMI of 24.58, an average waist circumference of 78 cm, an average age at onset of 44.9 years, and an average age of diagnosis of 50 years. None of the patients had diagnosed any associated underlying diseases (such as thyroid disease, anemia, liver disease and hypercholesterolemia) or family history (Table 4.1). All eleven patients diagnosed with FFA received hydroxychloroquine treatment, while ten of them (90.91%) also underwent topical steroid treatment. Further details are available in Table 4.2 Among the FFA patterns observed, five participants (45.5%) exhibited a linear pattern, five (45.5%) displayed a diffuse pattern, and only one (9.1%) presented with a double-line pattern as shown in Table 4.3.

Table 4.1 Baseline characteristic of the eleven volunteers

Baseline Characteristic	**Total**
Gender (n (%))	
Male	0 (0.0%)
Female	11 (100.0%)
Age	
≥ 60	4 (36.3%)
< 60	7 (63.7%)
Mean±SD.	56.1 ± 9.6
Median	55 (42 - 71)

Table 4.1 Baseline characteristic of the eleven volunteers (cont.)

Baseline Characteristic	Total
Body weight (kg)	
Mean±SD.	58.9 ± 9.9
Median	58 (46 – 75)
Height (cm)	
Mean±SD.	155 ± 0.05
Median	155 (146 – 162)
BMI	
Mean±SD.	24.6 ± 3.7
Median	24.2 (19.4 - 30.6)
Waist circumference (cm)	
Mean±SD.	78.0 ± 10.2
Median	75 (62.5 – 95.0)
Age at the onset (years old)	
Mean±SD.	44.9 ± 9.4
Median	46 (29 – 63)
Age at the diagnosis (years old)	
Mean±SD.	50 ± 6.8
Median	49 (40 – 61)
The delay from onset to diagnosis (years)	
Mean±SD.	5.1 ± 6.9
Median	2 (2-20)

Table 4.2 The treatment history of FFA of the eleven volunteers

Medications	n	% of Cases
Hydroxychloroquine	11	100%
Topical steroids	10	90.9%

Table 4.2 The treatment history of FFA of the eleven volunteers (cont.)

Medications	n	% of Cases
Tacrolimus	7	63.6%
Pioglitazones	4	36.4%
Mycophenolate Mofetil	3	27.3%
Doxycycline	3	27.3%
Minoxidil	1	9.1%
Neoglitasone	0	0%

Table 4.3 The pattern of FFA of the eleven volunteers

Pattern of FFA	n	% of Cases
Linear	5	45.5%
Diffuse	5	45.5%
Double line	1	9.1%

4.1.2 The effectiveness of tofacitinib

The effectiveness of tofacitinib for FFA was assessed by comparing the Frontal Fibrosing Alopecia Severity Index (FFASI) (ranging from 0 to 100), Frontal Fibrosing Alopecia Severity Score (FFASS) (ranging from 0 to 25), and Lichen Planopilaris Activity Index (LPPAI) (ranging from 0 to 10) between baseline (week 0) and week 16. Lower scores across these indices indicated greater treatment effectiveness. Additionally, two independent dermatologists reviewed patient photographs to determine improvements, stability, or deterioration in the patient's condition regarding FFASI, FFASS, LPPAI

1) Comparison of FFASI between baseline and after 16 weeks

A median FFASI showed statistically significant improvement comparing between baseline and week 16, decreasing from 47.5 to 44.0, according to a Wilcoxon test (W= 10.5, p = 0.04). The effect size (r = 0.60) indicated a medium effect**,** as shown in Table 4.4. Figure 4.1 illustrates the change in FFASI from baseline to week 16, with measurements taken at weeks 4, 8, 12, and 16.

Table 4.4 The FFASI between baseline and at week 16

	Mean	**Median**	**Standard deviation**
FFASI at the baseline (week 0)	52.14	47.5	13.25
FFASI after follow up (week 16)	48.40	44.0	13.50
	z	**p**	**r**
Change in week 16 from baseline	-2.0	.045	0.60

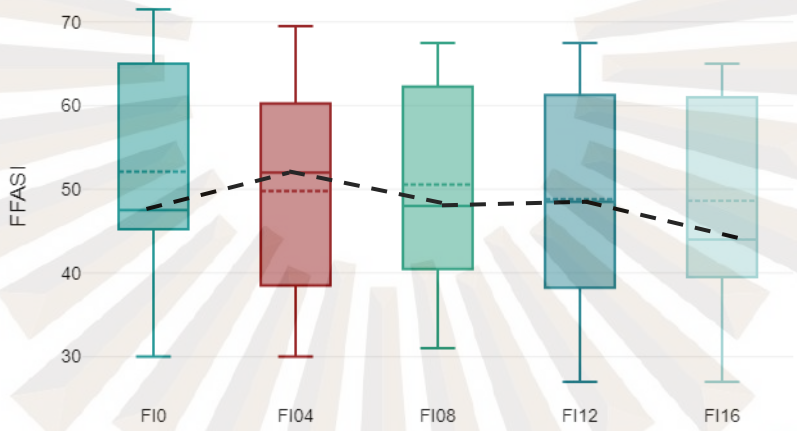

Figure 4.1: Box plot shows the change in the FFASI between baseline (FI0), week4 (FI04), week 8 (FI08), week 12 (FI12), and week 16 (FI16)

2) Comparison of FFASS between baseline and after 16 weeks

A median FFASS decreased significantly from 16.3 at baseline to 15.9 at week 16, as per a Wilcoxon test (W = 6, p = 0.016). The effect size (r = 0.72) suggested a

substantial impact, as illustrated in Table 4.5. Figure 4.2 depicts the change in FFASS from baseline to weeks 4, 8, 12, and 16.

Table 4.5 The FFASS between baseline and at week 16

	Mean	**Median**	**Standard deviation**
FFASS at the baseline (week 0)	17.12	16.3	4.07
FFASS after follow-up (week 16)	15.60	15.9	4.62
	z	p	r
Change in week 16 from baseline	-2.40	.016	0.72

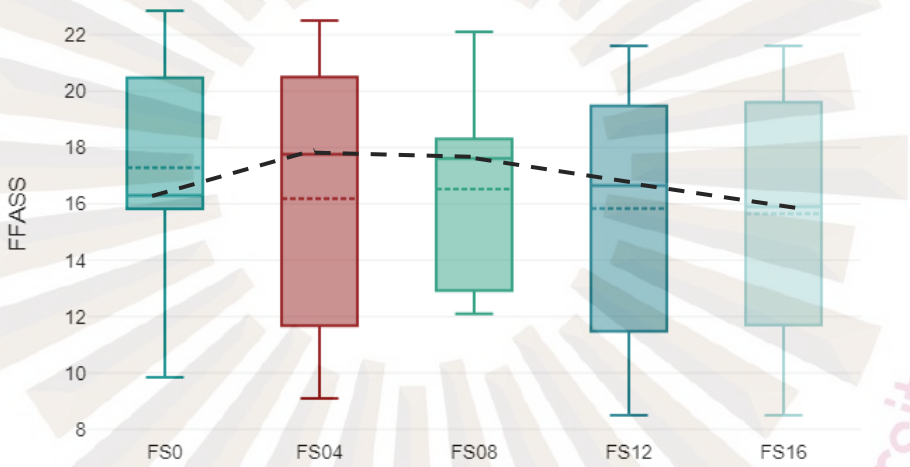

Figure 4.2: Box plot show the change of The FFASI between baseline (FS0) week 4 (FS04), week 8 (FS08), week 12 (FS12) and at week 16 (FS16)

3) Comparison of LPPAI between baseline and after 16 weeks

There was no statistically significant difference in LPPAI between baseline (1.83) and week 16 (1.33), according to a Wilcoxon test (W = 16, $p = 0.13$) (Table 4.6). Figure 4.3 showed the change in LPPAI from baseline to weeks 4, 8, 12, and 16.

Table 4.6 The LPPAI between baseline and at week 16

	Mean	Median	Standard deviation
LPPAI at the baseline (week 0)	1.87	1.83	1.01
LPPAI after follow up (week 16)	1.27	1.33	0.49
	z	**p**	**r**
Change in week 16 from baseline	-1.51	0.13	0.45

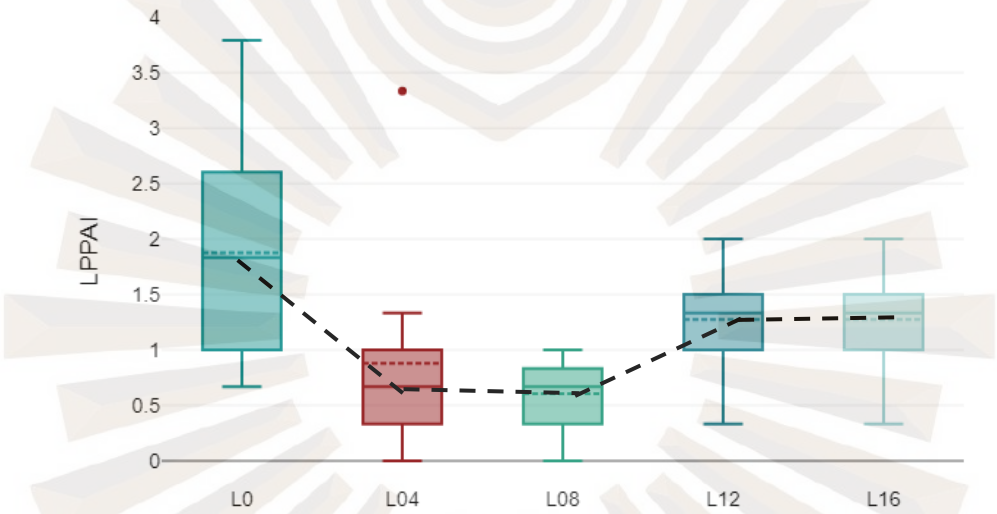

Figure 4.3: Box plot shows the change in LPPAI between baseline (L0), week 4 (L04), week 8 (L08), week 12 (L12), and week 16 (L16).

1) Clinical and Physician Evaluation

The physician evaluation was done by two evaluators. It was divided in two parts: scalp margin and other parts of hair loss. Each of them was seen as having improved their clinical signs at least partially. In the scalp margin evaluation, after treatment, All (100%) patient have improvement on frontal area of scalp. Moreover ten (90.9%) of them have problem on the right and left lateral part five (50%) showed the improvement, the remaining five (50%) showed stability. Whereas on their first visit, three (27.3%) of

them had a posterior section problem, following treatment, all (100%) of them remained showing clinical symptoms. Additionally, seeing in eyebrow area; nine (81.8%) showed the problem of this and three (33.3%) of them show positive results, the remaining six (66.7%) show the same clinical findings. Furthermore, there is no evidence that the patient's condition has gotten worse overall. Further details are available in Table 4.7

Table 4.7 The physician evaluation of the volunteers

Physician Evaluation	no. of patient		improvement		stability	
	n	% of cases	n	% of case*	n	% of case*
Scalp margins						
Frontal	11	100%	11	100%	0	0%
Right lateral	10	90.9%	5	50%	5	50%
Left lateral	10	90.9%	5	50%	5	50%
Posterior	3	27.3%	0	0%	3	100%
Other parts						
Eyebrows	9	81.8%	3	33.3%	6	66.7%
Eyelashes	1	9.1%	0	0%	1	100%
Flexural area	1	9.1%	0	0%	1	100%

*Note: The percentage of cases of improvement and stability was calculated from patients who had that clinical before treatment.

Clinical evaluation showed notable improvement observed in dermoscopy examinations across various areas of the scalp and eyebrows. providing visual evidence of the effects of treatment over 16 weeks. In Figure 4.4, we see a comparison between two images of the eyebrows. Image A represented the baseline, capturing the initial state of the eyebrows before any treatment. Image B was the follow-up taken 16 weeks later. When comparing these two images, there was a noticeable increase in eyebrow volume. The eyebrows in the follow-up image appeared fuller, denser, and more defined, suggesting a positive response to the treatment. In figure 4.1.2.4.2 and 4.1.2.4.3 present the set of dermoscopic images focused on the scalp hair from a frontal view. Image A of figure 4.1.2.4.2 show the condition at the start of the study, with visible signs of hyperkeratosis, perifollicular erythema, and scaling. The follow-up image (image B) was taken after 16 weeks later and revealed significant changes.

There was an almost clear reduction in hyperkeratosis, with less thickening of the skin around the hair follicles. The perifollicular erythema, characterized by redness and inflammation, had also decreased. Additionally, the level of scaling, which often indicates a dry or flaky scalp, was notably diminished. Figure 4.1.2.4.4 provides a comparison of hair and scalp images to demonstrate changes over time. Image A, the baseline, showed the presence of hyperkeratotic papules—small, raised, and thickened patches of skin (blue arrow). In Image B, taken 16 weeks later, there was a significant reduction in these papules. The decrease in hyperkeratotic growths indicates a positive response to treatment, suggesting improved skin health and a more even texture on the scalp. Additionally, figure 4.1.2.4.5 differs from the previous figures as it used stereo-camera technology to capture images of the hair from a frontal perspective. Image A shows the initial state of the hair at the front, which appears relatively thin or sparse. In the follow-up image (B), taken 16 weeks later, there was a clear thickening of the frontal hair. This increase in hair density suggested a positive outcome from the treatment, providing visual evidence of hair growth and improved scalp health.

Overall, these figures collectively demonstrated significant improvements in eyebrow volume and hair and scalp health following 16 weeks of treatment or intervention. The changes observed through dermoscopy and stereo-camera imaging indicated reduced hyperkeratosis, perifollicular erythema, scaling, and thickening of hair volume.

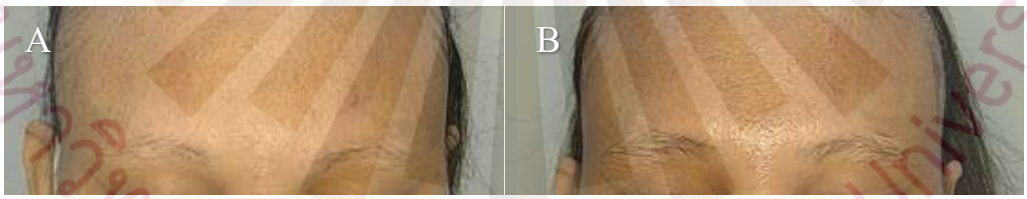

Figure 4.4 The baseline image of eyebrows(A) alongside the follow-up after 16 weeks (B)

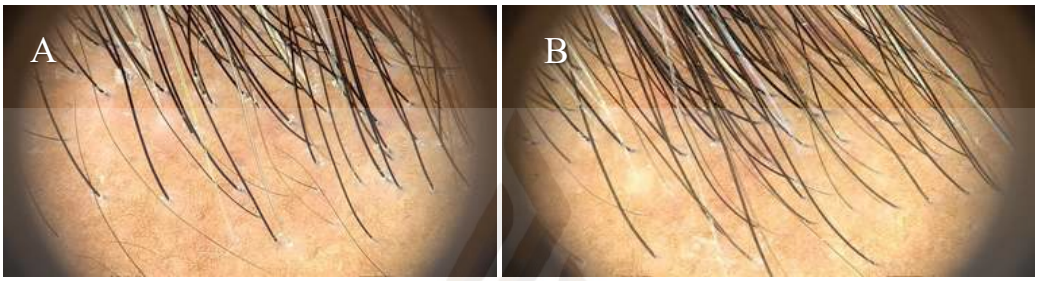

Figure 4.5 The dermoscopic view of the hair image of two patients compares with the follow-up at 16 weeks. A shows dermoscopic pictures from before (week 0), showing that after the treatment, the same patient in image B had less hyperkeratosis, perifollicular erythema, and scaling.

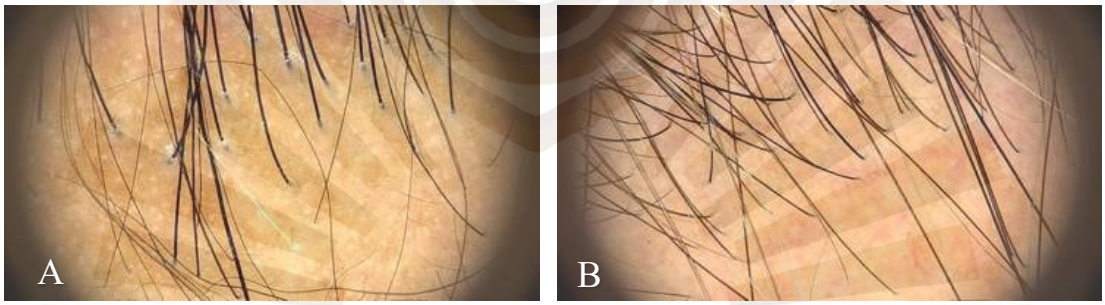

Figure 4.6 in image A, the dermoscopic view of another patient shows a positive response (hyperkeratosis, perifollicular erythema, and scaling) after receiving treatment in image B

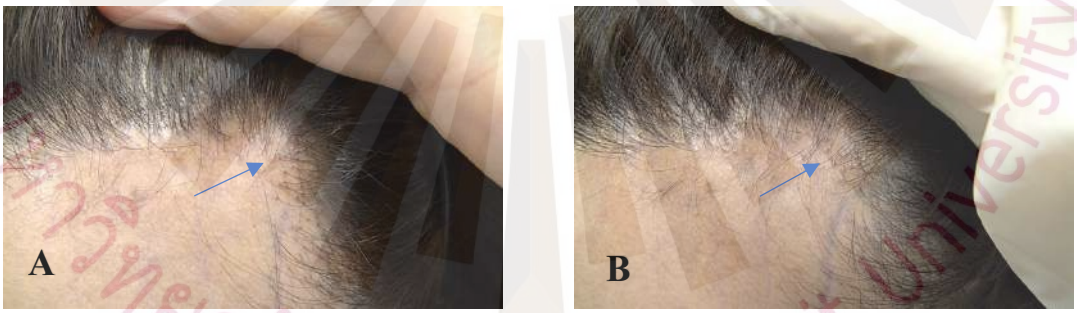

Figure 4.7: The dersmoscopic pictures show the hyperkeratotic papules (blue arrows) at the baseline week (A) contrasted with the 16-week follow-up.

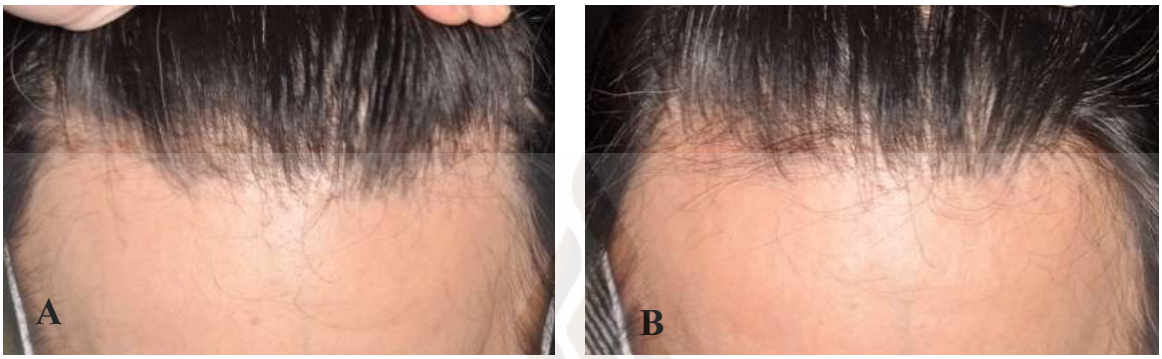

Figure 4.8 The stereo-camera shows density of hair image on baseline week (A) compared follow-up (B)

4.1.3 Safety in Clinical and Laboratory Investigation

Safety monitoring included the symptoms such as respiratory tract infections, skin irregularities, gastrointestinal disturbances, urinary tract infections, or any other adverse events. There were no serious clinical adverse events reported. Moreover, mild acne vulgaris (new or worsening disease) occurred in 4 (36.4%) of them. Additionally, the other adverse events reported included headache, myalgia, athralgia, nausea, vomiting, dizziness, insomnia and disorientation was not reported.

Furthermore, laboratory results were evaluated at weeks 4, 12, and 16. After taking oral tofacitinib, five of them (45.5%) had a slight increase in cholesterol. In five patients, three (60%) sought therapy from specialists for their dyslipidemia, and two of the three had normalized their cholesterol levels following cholesterol-lowering medication.

In addition, other laboratory investigations, such as complete blood count (CBC), fasting blood sugar (FBS), blood urea nitrogen (BUN), and creatinine (Cr) were not seen the abnormal report

4.2 Discussion

Frontal fibrosing alopecia is a cicatricial alopecia that follows destruction of hair follicles by an inflammatory lymphocytic infiltrate that is localized around the upper portion of the hair follicle (Tosti et al., 2005). The disease was mainly found in postmenopausal females aged between 50 and 60 years, and in our study, all

participants were women, and the average age is 56 years. In recent years, JAK inhibitors such as tofacitinib have been reported to treat Lichen planopilaris and FFA (Yang et al., 2018). JAK inhibitors are believed to reduced interleukin 15 and interferon-gamma, which inhibits white blood cells and limits the growth of hair follicles (Xing et al., 2014). In the previous research assessed the effectiveness and safety of tofacitinib in 28 FFA patients, with 75% of patients showing stabilization or improvement in their condition after 12 months of treatment (Vañó-Galván et al., 2019). Our study's dosage regimen mirrors successful outcomes reported in specific cases where oral tofacitinib, ranging from 5 to 10 mg twice daily in a previous study assessed the effectiveness and safety of tofacitinib in 28 FFA patients, with 75% of patients showing stabilization or improvement in their condition after 12 months of treatment (Vañó-Galván et al., 2019).

The effectiveness of oral tofacitinib was assessed using various indices, including the Frontal Fibrosing Alopecia Severity Index (FFASI), Frontal Fibrosing Alopecia Severity Score (FFASS), and Lichen Planopilaris Activity Index (LPPAI). At week 16, we observed improvements in FFASI (47.5, 44.0; $p = 0.045$) and FFASS (16.3, 15.9; $p = 0.016$), but not in LPPAI (median 1.83 vs. 1.33; $p = 0.13$).

Several factors explain why LPPAI did not show significant improvement, unlike FFASI and FFASS. Additionally, there is no correlation between these three scores – from our study “The feasibility and consistency of frontal fibrosing alopecia scores for evaluating the effectiveness of oral tofacitinib in patients with recalcitrant frontal fibrosing alopecia: A pilot study”. LPPAI is specifically designed to assess the activity of Lichen Planopilaris, which, while related, may not be the primary focus of improvement for treatments aimed at Frontal Fibrosing Alopecia (FFA). The indices FFASI and FFASS are more tailored to measure the severity and progression of FFA, making them more sensitive to changes in this condition. Therefore, a larger sample size and/or longer duration of treatment may be needed to observe changes in LPPAI. This lack of significance is intuitive, given the specific design and focus of LPPAI on Lichen Planopilaris rather than FFA.

Upper respiratory infections were found to be the most frequent adverse event among 11 patients treated for an average of 1.7 years, according to preliminary data.

Additional adverse events included other infections, anemia, and avascular necrosis; there were no reported malignancies (Montealegre et al.,2015). No clinical adverse effects were reported, in this study, but dyslipidemia was observed on initial study. By week 16, and four out of seven patients with elevated cholesterol levels demonstrated improvement after consulting specialists for treatment and the others did not need to take the medication due to high HDL.

The effectiveness of oral tofacitinib should be interpreted with caution, as confounding factors impacting the response to treatment of frontal fibrosing alopecia are not adjusted. Factors found in previous studies include the duration and severity of the condition, patient adherence to the treatment regimen, and individual variations in response to medications. Duration and Severity of the Condition: Early-stage FFA tends to respond better to treatment compared to advanced stages where significant scarring has already occurred (Dlova et al., 2013). Adherence to long-term treatment protocols is necessary to achieve and maintain positive results (Misirlioglu et al., 2016). Genetic factors, immune system variations, and overall health can influence how patients respond to treatments (Samrao et al., 2010). The presence of other medical conditions can affect treatment outcomes. Patients with autoimmune diseases, for example, may experience different responses due to their underlying immune dysfunctions (Tziotzios et al., 2015). Diet, stress levels, and overall lifestyle choices can impact the effectiveness of FFA treatments (Rogers and Bergfeld, 2010). This study has limitations in analyzing confounding factors due to the very small sample size. Further research with a larger sample size is warrant.

Chapter 5

Conclusion and Recommendations

5.1 Conclusion

This study possesses several notable strengths, notably in providing initial evidence regarding the effectiveness of oral tofacitinib treatment in recalcitrant Frontal Fibrosing Alopecia (FFA) among Thai patients. This innovative treatment approach holds promise for individuals with FFA, a condition for which effective therapies are currently limited. The study's methodology encompasses a comprehensive evaluation of treatment effectiveness, incorporating various clinical indices such as the Frontal Fibrosing Alopecia Severity Index (FFASI), Frontal Fibrosing Alopecia Severity Score (FFASS), and Lichen Planopilaris Activity Index (LPPAI). These indices offer objective measures to assess treatment outcomes accurately.

Moreover, the study employs dermoscopy examination, providing invaluable insights into changes in scalp morphology and hair follicle health. This multi-dimensional approach, utilizing both objective clinical indices and subjective expert evaluations, ensures a holistic assessment of treatment effectiveness. The investigation also explores the feasibility and correlation of each score, enhancing the robustness of the findings.Furthermore, the utilization of dermoscopy images offers visual evidence of treatment effects, bolstering the credibility of the study outcomes. This visual aid facilitates clearer communication of results to clinicians and patients alike, promoting better understanding and informed decision-making regarding treatment options.

While this pilot study provides valuable insights into the effectiveness and safety of oral tofacitinib in treating recalcitrant frontal fibrosing alopecia (FFA), it is essential to consider its limitations – small sample size, lack of control group, relatively short duration of follow up and assessment bias. The study included only 11 female volunteers, which limits the generalizability of the findings. A larger sample size is

needed to validate the results and ensure their applicability to a broader population. The absence of a control group makes it challenging to attribute the observed improvements solely to the treatment with tofacitinib. Without a comparison to a placebo or alternative treatment, it is difficult to determine the true effectiveness of tofacitinib. However, those subjects had never been improved from previous medication, but tofacitinib. The study's follow-up period was limited to 16 weeks. Longer-term follow-up is necessary to assess the sustainability of the treatment effects and to monitor for any potential long-term adverse effects. The study's reliance on subjective assessments, such as expert physician evaluations of patient photographs, introduces the possibility of bias. Blinding procedures could help mitigate this bias, but it's unclear if such procedures were implemented. Addressing these limitations in future research would strengthen the evidence base for the use of oral tofacitinib in the treatment of recalcitrant FFA and provide more strong guidance for clinicians and patients.

5.2 Recommendations

The findings of this study have several clinical implications that could guide the management of Frontal Fibrosing Alopecia (FFA) and potentially improve patient outcomes. tofacitinib shows promise as a novel treatment option for FFA. Clinicians can consider incorporating tofacitinib into their therapeutic armamentarium, particularly for patients who have not responded adequately to conventional treatments like topical steroids. The study highlights the heterogeneity in FFA presentation, including different patterns and disease severity. Clinicians should adopt a tailored treatment approach, considering individual patient characteristics, disease phenotype, and treatment history when selecting therapeutic interventions. Regular monitoring of patients undergoing tofacitinib therapy is essential to assess treatment response and monitor for adverse effects. Clinicians should schedule frequent follow-up visits to evaluate clinical indices, dermoscopy findings, and any potential side effects. Clinicians should engage patients in shared decision-making, considering their preferences, values, and treatment goals. Some patients may prioritize cosmetic outcomes, while others may prioritize safety or convenience of treatment.

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