EFFECTIVENESS AND SAFETY OF TOFACITINIB IN PATIENTS WITH EXTENSIVE AND RECALCITRANT ALOPECIA AREATA

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Part I: Type of research study

⊘ New research study

◯ Ongoing research project

Part II: Components in the preparation of the study

1. Investigators

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2) Pantip Yimwadsana, RN	Research assistant
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4) Penny Pimonrat	Research assistant
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2. Main agency and supporting unit

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3. Type of research

Clinical trial

4. Academic disciplines and research subjects

Medical Sciences (Dermatology)

5. Keywords

Alopecia areata, Alopecia totalis, Alopecia universalis, Tofacitinib, JAK inhibitor

6. The importance of the research problem and its origin

Alopecia areata (AA) is a condition that causes sudden hair loss, primarily affecting the scalp and beard but can be on any part of the body. This condition affects 0.2% of the population and can occur in all age groups and both genders. From outpatient statistical data at the Institute of Dermatology, a total of 2,406 patients with patchy AA were treated in 2012, 3,079 patients in 2013, 2,814 patients in 2014, and 1,887 patients in 2015. Three hundred forty-nine extensive AA cases were treated in 2012, 654 in 2013, 691 in 2014, and 455 in 2015. The cause of the disease remains unknown. It is believed to be an autoimmune disorder caused by an abnormal immune response to hair follicle correlated antigens. Interferon-gamma (IFN-γ) is an important cytokine inducing and tampering normal immune privilege of the anagen hair bulb to collapse, therefore triggering the hair follicle destruction.

AA presents in the shape of oval or round, well-circumscribed, bald patches anywhere all over the scalp. Hair loss can extend to the entire scalp, called alopecia totalis, and alopecia universalis is the loss of all scalp hair and body hair. It can cause embarrassment and affects the quality of life.

There are a few efficacy data for robust treatment of AA. An expert consensus seems to treat localized AA with intralesional and topical corticosteroids. In extensive AA, alopecia totalis, and alopecia universalis, diphenycyclopropenone or Janus kinase (JAK) inhibitors are good treatment options. Other options include the combination of short contact anthralin and topical minoxidil or high potency topical corticosteroids with topical minoxidil. Clinical improvement after applying short contact anthralin and topical minoxidil is approximately 75% in the case of patchy AA and 25% in the case of extensive AA, similar to that of topical corticosteroids with minoxidil. There is a 25% chance of hair growth. Systemic corticosteroids may be used to treat severe AA with methotrexate, cyclosporine, or azathioprine but should not be used as a routine long-term treatment because of the risk of side effects. However, those treatments may not be effective for recalcitrant cases. Recently, Janus kinase (JAK) inhibitors such as tofacitinib and ruxolitinib have been used to treat patients with extensive AA. Many studies found that patients with AA had more significant hair growth (>50%) by 54-81.9% after taking tofacitinib. JAK inhibitors are expected to reduce interferon-ɣ and interleukin-15, causing fewer white blood cells to destroy hair follicles.

The effectiveness of tofacitinib for AA treatment has not been studied in Thailand, and only a few studies reported it in Asians. Although tofacitinib may be a choice in AA standard guidelines, the price of this medication may not be affordable. It is essential to prove the effectiveness to generate concrete evidence for the debates and stakeholders' consideration in the cost-effectiveness of tofacitinib for extensive AA.

7. The objective of this study

7.1 Primary objective

To study the effectiveness and safety of tofacitinib in Thai patients with recalcitrant and extensive AA at 24 weeks

7.2 Secondary objectives

To measure the quality of life in economic evaluation in Thai patients with recalcitrant and extensive AA treated with tofacitinib

8. The scope of this study

8.1 Study population

8.1.1 Specific disease or condition(s): Subjects with extensive and recalcitrant AA coming to the hair and nail clinic and outpatient department at the Institute of Dermatology

8.1.2 Gender: Male and Female

8.1.3 Age: Subjects aged 18 years or older

8.1.4 Number of subjects: calculated from the formula

$$n = \frac{Z^2_{\alpha/2} P(1-P)}{d^2}$$

$Z_{\alpha/2}$ = 1.96

P = Proportion of the population who had improvement = 0.87

d = A maximum tolerated error determined by an investigator = 0.2

$$n = \frac{(1.96)^2(0.8)\,(1-0.8)}{(0.2)^2} = 16$$

Therefore, the number of subjects should be approximately 16. Given approximately 20% of the number of patients who may have missed follow-up treatments, a total of 19 subjects are planned to be collected.

8.2 Selection criteria

8.2.1 Inclusion criteria

8.2.1.1 Thai subjects aged 18 years or over

8.2.1.2 Subjects with extensive AA greater than 50% of the scalp

8.2.1.3 Subjects who can come for follow-ups during the first 6 months of treatment

8.2.1.4 Subjects who are unresponsive to diphenylcyclopropenone, anthralin, clobetasol cream, and topical minoxidil for at least 6 months.

8.2.2 Exclusion criteria

8.2.2.1 Subjects with hair loss from other causes, e.g., Telogen effluvium, Trichotillomania, onychomycosis (Tinea capitis)

8.2.2.2 Subjects with chronic or severe disease with unstable symptoms that may affect hair condition during the 6 months prior to screening, such as thyroid diseases, iron deficiency anemia, liver diseases (subjects with chronic hepatitis but with stable symptoms can participate in the study), heart diseases, neurological diseases, digestive disorders, reproductive diseases, cancer, and psychiatric diseases

8.2.2.3 Subjects who had been treated for AA with topical corticosteroids or topical anthralin or diphenylcyclopropenone within 1 month prior to screening, or subjects who had been treated for AA with systemic corticosteroids or any other oral medication during 3 months before screening

8.2.2.4 Subjects who are pregnant

8.3 Research site and study period

8.3.1 Study site: Hair and Nail Clinic, Institute of Dermatology Department of Medicine Ministry of Public Health, Bangkok

8.3.2 Research period: January 2019 - January 2021

9. Theories, hypotheses and conceptual frameworks of this study

Alopecia areata (AA) is a condition in which the body's immune system is sensitive to itself. The in vitro studies showed this natural killer gene 2D-expression CD8+ T cell is the leading cause of an increase in interleukin-15 in the hair follicle, increasing interferon-ɣ and leading to hair follicle destruction.

The standard guideline for extensive AA includes diphenylcyclopropenone, short contact anthralin, high potency topical corticosteroids. A recent study found that the combination therapy between diphenylcyclopropenone and anthralin was more effective than diphenylcyclopropenone monotherapy (55% vs. 88). However, the chance of treatment response is approximately 25-50%, upon the severity and duration of the disease. The diphenylcyclopropenone powder is expensive and must be mixed with acetone or alcohol solution before use in different concentrations. The high cost of diphenylcyclopropenone and the difficulty of mixing in different concentrations are why diphenylcyclopropenone solutions are unavailable in most hospitals. Most of the patients, especially those in the provincial areas, could not access such services. Inaccessible diphenylcyclopropenone treatment leads to inappropriate use of systemic corticosteroids. The successful rate of using systemic corticosteroids is only 43%, with a 17% chance of relapse. Nevertheless, many patients have poor clinical improvement after receiving various therapies. Those patients have reduced their quality of life, lost their self-confidence, and could develop stress, anxiety, and depression.

Tofacitinib is a potent, selective inhibitor of the Janus Kinase (JAK) family of kinases and was approved by US Food and Drug Administration to treat adults with moderate to severe rheumatoid arthritis. This medication can inhibit signaling by receptors associated with JAK3 and/or JAK1. The inhibition of JAK3 and/or JAK1 disrupts the signals of interferon-ɣ and interleukin-15 between white blood cells (WBC) and the nucleus of hair follicle cells, slowing down the production of WBC type CD8+NKG2D+ T cell, one of the causes of hair loss.

The safety and effectiveness of tofacitinib for AA treatment have been demonstrated in adults. In the three studies, subjects with extensive AA had clinical improvement of about 54-81.9% during the six months, and the Severity of Alopecia Tool (SALT) score was improved by 50-90% approximately.

The side effects of the treatment were mild. Subjects may develop headaches, hyperlipidemia, upper respiratory tract infection, and a slight increase in hepatic enzyme activity. Those side effects usually return to normal even after the patient did not stop taking the drug, and in very few cases, erythema, leg swelling, paleness, bone ischemia have been reported. However, no cancer was found in patients taking the drug yet, though, the company has a warning about this in the drug leaflet.

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11. Beneficial impact

The researchers anticipate that the research project results will bring new knowledge as a basis for better treatment of hair and scalp conditions and diseases. Clinical outcome data can be used as information for patients to make informed decisions about AA treatments. It is also used in healthcare policy to make decisions and find the most suitable service for patients with recalcitrant AA.

12. Plans for transferring technology or results to target groups

12.1. To be published in international medical journals to provide information to the public

12.2. To be presented at academic conferences both in Thailand and abroad

13. Methods of conducting research and place for conducting study/data storage

13.1 Study design

This is a prospective cohort study conducted at the Institute of Dermatology. Nineteen male and female Thai volunteers with extensive hair loss of more than 50% of the head area were recruited.

13.2 Conducting research procedures

13.2.1 The principal investigator selects the volunteers according to the inclusion and exclusion criteria.

13.2.2 The principal investigator takes a personal history of the volunteers, such as date of birth, age, ethnicity, age of onset, stage of disease progression, past medical history, weight, and height.

13.2.3 The principal investigator will ask the volunteers about their health, pre-existing disease conditions such as allergies, asthma, thyroid disease, psoriasis, vitiligo, autoimmune diseases, rheumatoid arthritis, diabetes, irritable bowel syndrome, immunodeficiency states, current medications, or medications taken or treated prior to the administration for 1month, severe illness and severe stress.

13.2.4 The principal investigator examines the condition of the scalp, hair, and body by measuring the area of hair loss on the scalp, including the body hair by recording the SALT score, hair loss on the body, and examining the nail characteristics.

$$\frac{\text{SALT BL} - \text{SALT F/U}}{\text{SALT BL}} \times 100\% = \%\ \text{change from baseline.}$$

13.2.5 All subjects will have photos taken from the side, back, and top of their scalp with a stereotactic device.

13.2.6 All subjects will undergo tests prior to treatment, including complete blood count, lipid profiles, anti-HIV, HBs Ag, Anti HCV, renal function test (BUN, Cr), liver function test (LFT), urine pregnancy test (UPT; female), chest x-ray, stool exam.

13.2.7 All subjects will be asked to take Tofacitinib 5 mg twice a day.

13.2.8 All subjects will be evaluated after the treatment every four weeks during the 24-week duration of the treatments. The SALT score is assessed each time, including the potential side effects. Also, they will have photos taken from the side, back, and top of their scalp with a stereotactic device every visit. The treatment with tofacitinib is successful should subjects have hair regrowth more than 50% compared to the baseline photo.

13.2.9 All subjects are required to have blood tests later for CBC, cholesterol, triglyceride, low-density lipoprotein (LDL), LFT, BUN, and Cr after weeks 4, 12, 24 of treatments.

13.2.10 All female subjects are required to have UPT every four weeks during the 24-week duration of the treatments.

13.2.11 When AA subjects finish treatments either at week 24, or resolved before, or discontinue tofacitinib due to the side effects before the end of the treatments, they are required to have a follow-up after four weeks of discontinuation.

13.3 Consent Process

Before volunteering to participate in this study, subjects are explained by an investigator about the study objective, method, advantages, and disadvantages, including side effects that may be caused by tofacitinib. Subjects have the right to choose to participate or not participate in a voluntary research study without coercion or persuasion and have the right to terminate their participation in the study at any time. The termination will not affect the current and future medical care that the subjects will receive. When subjects decide to participate in the study, they will be asked to sign their first and last name in the informed consent before enrolling.

13.4 Data Collection

In this study, subjects' personal records were separated into a specific form with limited access to the data. The data was recorded using a programmed computer, and the confidentiality of the data was protected. A password is required to access the data of the subjects. Persons who can access the subjects' data are the research physician, research team, research sponsor, and the Institutional Review Board Committee.

13.5 Data Analysis

The research data was then comparatively assessed using the SPSS program.

13.6 Statistics used in data analysis

13.6.1 General data will be calculated by using Univariate analysis as a percentage, standard deviation, range, mean

13.6.2 Treatment efficacy will be evaluated by bivariate analysis calculated for a percentage of hair loss area at 12 and 24 weeks, compared with pre-treatment data using One-way ANOVA.

13.6.3 Side effects from treatment will be presented with event frequency, the number and the percentage of subjects in each event will be compared using Friedman Two-way Analysis.

13.7 The place of conducting study and data collection

Hair and nail clinic, Institute of Dermatology, Department of Medical Services, Ministry of Public Health, Thailand

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14. Research period and operational plans throughout the study

The period will be from January 2019 to January 2021.

15. Factors contributing to research

The budget was granted by the Institute of Dermatology, Department of Medical Services, Thailand.

16. Research study budget

The budget source of money is from National Annual budget of Thailand.

17. Expected results and value of research

The researchers anticipate that the results of this study will bring new knowledge as a basis for better treatment of hair and scalp conditions and diseases. Clinical outcome data can be used as information for patients to make decisions about AA treatment. It is also used as information for doctors and policymakers to make policy decisions and find the most suitable service and treatment for AA patients.