A review on: Ritlecitinib

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Abstract: Alopecia areata (AA) is an autoimmune condition that causes patchy hair loss, affecting up to 147 million people globally. Currently, there are no treatments approved by US Food and Drug Administration (FDA) specific for AA, and there are few effective therapeutic options for widespread and persistent illness. There is an ongoing need for a treatment that demonstrates a good clinical response with a benefit-risk ratio that is suitable for long-term use, especially for patients with chronic, extensive disease. Several clinical trials and case studies that have assessed Janus kinase inhibitors have had encouraging results. Ritlecitinib, a selective JAK3/TEC kinase inhibitor has been demonstrated to inhibit the action of signaling molecules and immune cells that are responsible for hair loss in people with alopecia areata. Furthermore, several clinical trials are investigating the utility of ritlecitinib in patients with vitiligo, rheumatoid arthritis, Crohn's disease, and ulcerative colitis. Advantages of using ritlecitinib when compared with other non-selective JAK inhibitors include avoiding JAK1/JAK2 inhibition's clinical repercussions, which include pharmacodynamic effects such as increased cholesterol and liver enzymes, and those related to JAK2 inhibition (thrombocytopenia, anemia). Treatment with Ritlecitinib 50 mg and 30 mg daily for 24 weeks has been shown to induce hair regrowth with a significant proportion of patients reaching SALT 20 (≤20% scalp hair loss) after six months of therapy compared to placebo. Additional research is needed for long-term effects.

Keywords: Alopecia aerta, ritlecitinib.

Introduction: Alopecia areata (AA) is a chronic autoimmune disorder characterized by the acute onset of smooth, sharply demarcated, nonscarring, and patchy hair loss ranging from small circumscribed patchy areas on the scalp, which sometimes may progress to involve the entire scalp, face, and/or body [1,2,3,4]. AA is a condition with a lifetime risk of approximately 2% in the global population, with an annual incidence rate ranging from 2.53 to 26 per 100,000 [5]. Over the past two decades (1990–2019), the incidence of AA has increased by 49.14% [6]. Despite this significant rise, a slight decrease in age-standardized incidence rates has been observed. However, in some low-income regions and countries, the burden of AA has increased. Furthermore, females have a significantly higher age-standardized incidence rate than males [6]. The global prevalence of AA ranges from 0.02% to 0.21%, with a lifetime prevalence observed between 2.5% and 13.8%. Higher prevalence rates of AA are observed in high-income countries and in adults compared to children [5,7]. Alopecia universalis (AU) (total body hair loss), alopecia totalis (AT) (total scalp hair loss), alopecia in an ophiasis pattern (band-like hair loss on the temporal and occipital scalp), and ophiasis inversus (band-like hair loss in the frontoparietotemporal area) are the variants of AA [8]. Severity of AA is defined as follows based on SALT categories: no hair loss = 0%; mild/limited = 1–20%; moderate = 21–49%; severe = 50–94%; and very severe = 95–100% [9]. AA is commonly associated with psychiatric and medical comorbidities such as depression, anxiety, autoimmune thyroid disease, vitiligo, atopy, lupus erythematosus, psoriasis, and rheumatoid arthritis; specifically, severe and extensive forms of AA, such as alopecia totalis (AT) and alopecia universalis (AU), are often thought to have stronger associations with comorbidities [4,8,10]. Nail abnormalities are also associated with the disease, in which nail pitting is frequently observed . Various internal stressors, encompassing both psychological and physiological factors such as adrenocorticotropic hormone (ACTH), corticosterone, and estradiol, are identified as etiological factors contributing to AA. Additionally,

external environmental stressors, including infections, vaccinations, hormonal fluctuations, and dietary factors, may also play a role in the development of AA [8]. Treatment for AA encompasses a variety of options such as corticosteroids, immunotherapy, and other therapies, in which corticosteroids are widely regarded as the mainstay of treatment and can be administered topically, orally, or through injections. Topical or intralesional corticosteroids are usually regarded as the first-line therapy among them. Topical corticosteroids are preferred in adults and in children due to their ease of application and to avoid the severe discomfort associated with injections. Systemic corticosteroids are beneficial for refractory cases; however, they are used cautiously in children as they impede growth. Immunotherapy, such as squaric acid dibutylester and diphencyclopropenone, serves as a second-line treatment for patients who do not respond to corticosteroids JAK-STAT inhibitors such as tofacitinib (JAK 1 and 3 inhibitors) and oral ruxolitinib are emerging potential treatments that have shown promising results when compared to conventional systemic treatments, but relapse rates have been observed. However, baseline investigations are recommended prior to the initiation of treatment. Other treatments for AA include topical minoxidil, 5% solution or foam for adults and 2% for children, which promotes hair regrowth. Prostaglandin F2 alpha analogues are specifically used for eyebrow and eyelash AA. Steroid-sparing agents are frequently employed alongside systemic steroids or as immunotherapy to prevent relapses of AA . Supplementation with antihistamines such as fexofenadine and ebastine has demonstrated beneficial effects in AA associated with atopic dermatitis [13]. Additionally, topical contact irritants like anthralin followed by topical retinoids, phenol, salicylic acid, azelaic acid, retinoid, and tincture iodine are used in children to induce localized irritation which in turn stimulates the immune response. Psoralen plus ultraviolet A radiation, or exciter laser therapy, and systemic immunomodulators are also utilized in the treatment of AA Early studies have revealed that a new emerging drug, Ritlecitinib, which belongs to the class of kinase inhibitors, is associated with a notably positive outcome in treatment of severe AA.However, there remains a significant need for more extensive data to guide future research and clinical use. Given the lack of meta-analyses on Ritlecitinib, this study aims to conduct a systematic literature review (SLR) and meta-analysis to evaluate its efficacy and safety in patients with AA.

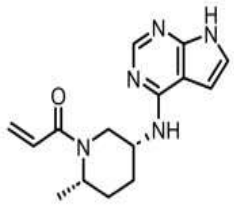
Drug Summary: Pills with ritlecitinib as the generic name Litfulo is the brand name.

Class of Drug: Other, Dermatologic, Antineoplastic Inhibitors of Tyrosine Kinase

LITFULO: WHAT IS IT? Litfulo (ritlecitinib) is. is a kinase inhibitor is used for the treatment of severe alopecia areata in adults and adolescents 12 years of age and older. 4 Ritlecitinib is the first medication in a new class of crosslinking kinase inhibitors with superior selectivity against Janus kinase 3 (JAK3). In vitro experiments, ritlecitinib has been shown to inhibit the immune cells' and signaling molecules' actions, which cause alopecia sufferers to experience persistent hair loss. 2 Figure 4. Structure of Ritlecitinib **PHYSICOCHEMICAL PROPERTIES Solubility:** A test tube: DMSO: 438.07 mM (125 mg/ML; ultrasonic is needed) 6.67 mg/ML (23.38 mM) of water; ultrasonic is needed. In Vivo After adding 0.5% MC and Tween-80 to each solvent, the solubility of 6.67 mg (23.38 m

Drug Profile:

Drug Name	Ritlecitinib

Structure	
Categoery	Dermatologic, Antineoplastic
Solubility	DMSO: 438.07 mM (125 mg/ML; ultrasonic is needed) 6.67 mg/ML (23.38 mM) of water
Brand Name	Litfulo
Melting Point	Melting point: Ritlecitinib has a melting point of 199°C.
BCS Class	itlecitinib belongs to category II drugs, which have high permeability.

Physicochemical Properties

Solubility: A test tube: DMSO: 438.07 mM (125 mg/ML; ultrasonic is needed) 6.67 mg/ML (23.38 mM) of water; ultrasonic is needed. In Vivo After adding 0.5% MC and Tween-80 to each solvent, the solubility of 6.67 mg (23.38 mM)/mL.

Melting point: Ritlecitinib has a melting point of 199°C. Pharmocokinetics properties BCS **Classification**:Ritlecitinib belongs to category II drugs, which have high permeability and poor solubility.

Mechanism Of Action: Litfulo is a kinase inhibitor: Alopecia areata is an autoimmune disease that causes hair loss, mostly on the scalp but also on the face and other areas of the skin. Hair-producing folicles are immune-privileged regions that are often characterized by naturally suppressed natural killer cells. However, interference with this system can lead to immunological privilege loss and alopecia areata. The pathogenesis of alopecia areata has been linked by genome-wide association studies to the amplification of UL16-binding protein 3 (ULBP3), a protein that binds to naturally occurring killer cell receptors.The overexpression of ULBP3 promotes the attack of lethal clusters of differentiated 8-positive NK group 2D-positive. Journal of Foundry [ISSN: 1001-4977] Vol. 26, No. 9, Page No. 53 T-cells attacking hair follicles result in hair follicle dystrophy. CD8+ (NKG2D+) T cells stimulate the allergic response of hair follicles through the interferon alpha and interleukin 15 signaling pathways. This activates the Janus Kinase (JAK)/signal transduction and promoter of transcription (STAT) biochemical pathways. Thus, JAK inhibitors have been proposed as a potential alopecia areata treatment. [7,8]. Ritlecitinib irreversibly suppresses Janus Kinase 3 (JAK3) and the tyrosine kinase family expressed in hepatocellular carcinoma (TEC) kinase by blocking the adenosine triphosphate.

ABSORPTION	DISTRIBUTION	ELIMINATION	METABOLISM	EXCRETION
has an about 64% oral bioavailability overall. Peak plasma concentrations of ritlecitinib	About 14% of the circulating ritlecitinib is bound by plasma proteins.	Ritlecitinib's mean terminal half-life is between 1.3 and 2.3 hours .	The metabolism is mediated by a number of pathways; no single process accounts for more than 25% of the	Feces and urine both eliminate 20% and 66% of the radiolabeled dosage, respectively.

were reached in less thann 1 hour			total metabolism. Glutathione Stransferase is the initial mechanism, The CYP enzymes namely CYP2C9,CYP1A2, CYP3A, CYP28.	Urine contains 4% of the medication that is excreted unchange

| **Methods:** Study Design and ParticipantsALLEGRO-2b/3 was a randomized, double-blind, multicenterclinical trial in which participants were randomized to re-ceive ritlecitinib 30 or 50 mg QD with or without an initial4-week 200-mg QD loading dose, ritlecitinib 10 mg (includedonly for dose–response evaluation), or placebo for 24 weeks[17]. During a subsequent 24-week extension period, ritleci-tinib groups continued on their maintenance dose (50, 30, or10 mg), and those initially randomized to placebo switched toritlecitinib 50 mg QD with or without a 4-week 200-mg QDloading dose.ALLEGRO-LT is an ongoing study that includes rolloverparticipants who received ritlecitinib in the ALLEGRO-2a(NCT02974868) and ALLEGRO-2b/3 clinical trials, as well asde novo participants with ≥ 25% scalp hair loss who had notreceived ritlecitinib treatment in either study. Rollover partic-ipants received ritlecitinib 50 mg QD, and de novo participantsreceived ritlecitinib 200 mg QD for 4 weeks followed by 50 mgQD for up to 60 additional months [20, 21].This subgroup analysis included Asian participants (de-fined as those of Asian descent) from ALLEGRO-2b/3. Aftercompleting ALLEGRO-2b/3, patients could roll over intoALLEGRO-LT (Figure 1). In this analysis, patients in the200/50-mg group received either an initial 4-week loadingdose of ritlecitinib 200 mg QD followed by ritlecitinib 50 mgfor 44 weeks, or placebo for 24 weeks followed by a 4-week ri-tlecitinib 200-mg QD loading dose then ritlecitinib 50 mg QDfor 20 weeks in ALLEGRO-2b/3. Patients who initially receivedplacebo were re-baselined, as discussed below. Patients in the50-mg group in this analysis received either ritlecitinib 50-mgQD dose for 48 weeks, or placebo for 24 weeks followed by ri-tlecitinib 50 mg QD for 24 weeks in ALLEGRO-2b/3. Patientswho initially received placebo were re-baselined, as discuss Participants from ALLEGRO-2b/3 and ALLEGRO-LT included in the Asian subpopulation analysis. *Data from participant's ingroups B, D, and E were not included in this analysis. **Data from participants in groups F and G while on placebo were not included in this analysis;data from participants in groups F and G were re-baselined from the start of treatment with ritlecitinib.

2.Analysis:PopulationsThe key inclusion criteria in ALLEGRO-2b/3 were ageof ≥ 12 years, a diagnosis of AA with ≥ 50% scalp hair loss due toAA (including alopecia totalis and alopecia universalis), no evi-dence of terminal hair regrowth within 6 months at both screen-ing and baseline visits, and a maximum duration of current hairloss episode of ≤ 10 years [17].Participants who rolled over from ALLEGRO-2b/3 intoALLEGRO-LT had to have completed ≥ 34 weeks of study in-tervention in ALLEGRO-2b/3. Adolescents in ALLEGRO-LTwere required to have an improvement in Severity of AlopeciaTool (SALT) score of ≥ 50% from baseline (in ALLEGRO-2b/3)at Month 3 and a SALT score of ≤ 20 by Month 6 to continue inALLEGRO-LT.This subgroup analysis included patients who self-identified asAsian (defined as patients of Asian descent).All analyses were descriptive and exploratory and conductedwithout formal hypothesis testing

3 Re-Baselining:Among the patients who rolled over from ALLEGRO-2b/3 intoALLEGRO-LT, a portion received placebo during the initial 24weeks of the study. In order to allow for analysis of all patientswithin the ALLEGRO-LT study concurrently, patients who initiallyreceived placebo were re-baselined to align the start of ritlecitinibtreatment and time points within and across groups (Figure 1). Alldata are reported in months; 4 weeks in ALLEGRO-2b/3 was con-sidered equivalent to 1 month in ALLEGRO-LT.

4 Efficacy Measures: this subgroup analysis, efficacy data are presented up toMonth 24 for the two groups (i.e., the 200/50-mg and 50-mggroups). The clinician-reported outcomes included the proportion of participants with response through Month 24 based on aSALT score of ≤ 20 and ≤ 10. SALT assesses the amount of scalphair loss and has scores ranging from 0 (no scalp hair loss) to 100(complete scalp hair loss).In participants with abnormal eyebrow assessment (EBA) andeyelash assessment (ELA) scores at baseline, the proportion ofparticipants achieving EBA and ELA responses were analyzedbased on a ≥ 2-grade improvement from baseline or achievinga normal score (3). EBA and ELA are four-point scales rangingfrom 0 (none, or no eyebrows/eyelashes) to 3 (normal eyebrows/eyelashes).The participant-reported outcome endpoints included the pro-portion of participants achieving a Patients' Global Impressionof Change (PGI- C) score of "moderately improved" or "greatlyimproved" from baseline. PGI- C is a self-reported single-itemscale on which participants rate the improvement or worseningof AA symptoms compared with status at the start of the study;the scale has seven responses ranging from "greatly improved"to "greatly worsened."In addition, the proportion of participants with a sustainedSALT ≤ 20 response (participants with a SALT ≤ 20 response atMonths 12 and 24 who did not have a SALT score of > 20 at anyin-between time point) and the proportion with a maintainedSALT ≤ 20 response (participants with a SALT ≤ 20 response atMonths 12 and 24, regardless of SALT scores at in-between timepoints) were assessed.

5 Safety Assessments: Adverse events (AEs), serious AEs (SAEs), and events of interest (i.e., opportunistic infections, cardiovascular and malignancyevents) were monitored throughout the study. The events ofinterest were reviewed by adjudication committees using pre-defined criteria (MedDRA v27.0).TABLE Baseline characteristics of the Asian subpopulation.Ritlecitinib,50 mg (n = 58)Ritlecitinib,200/50 mg(n = 47)AgeMean (SD), years 31.1 (10.9) 30.4 (11.8)12–17 years, n (%) 3 (5.2) 5 (10.6)≥ 18 years, n (%) 55 (94.8) 42 (89.4)Female, n (%) 30 (51.7) 31 (66.0)AT/AU, n (%)* 25 (43.1) 23 (48.9)Baseline SALT score,mean (SD)89.4 (15.2) 92.7 (12.9)Duration of AA sincediagnosis, mean (SD),years7.2 (7.0) 7.5 (5.6)Duration of currentAA episode, mean(SD), years3.5 (2.8) 3.5 (2.9)Abbreviations: AA, alopecia areata; AT, alopecia totalis; AU, alopeciauniversalis; SALT, Severity of Alopecia Tool; SD, standard deviation.*Participants in the AT/AU category had a SALT score of 100 at baseline(regardless of the category in the AA history case report form).

SIDE EFFECT

- Diarrhea
- headache
- eczema
- folliculitis (inflamed hair follicles)
- fever
- disorientation
- mouth sores
- decreased red blood cell count

- mild allergic response The following are examples of serious side effects and their symptoms
- Reduced white blood cell count
- fever

- infection-related symptoms, such as coughing or sore throat
- Lowered platelet count.
- Bleeding, such as nosebleeds or bleeding gums, is one of the possible symptoms.
- scorching or stabbing pain.
- Chills or fever
- A headache
- Elevated liver enzyme values, which could indicate liver injury.

CONCLUSION: The preceding review article delves into the ritlecitinib of litfulo. Litfulo is a JAK3 and the TEC family kinase. Ritlecitinib [litfulo] indicated for the treatment of severe alopecia areata in adults and adolescents 12 years and older. This article disscus about the physicochemical and pharmacokinetic properties in details and mechanism of action. It also includes its medicinal uses, side effect,contraindication and intraction of the drug ritlecitinib. The Conventional and Novel Marketed Formulation which includes dosage, price is shown here. Patents of the drug also studied. In overall the article goes in detail of the drug Ritlecitinib of LITFULO to treat an Alopecia condition.

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