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Litfulo- Ritlecitinib: A Review

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ABSTRACT
Litfulo (ritlecitinib) is an oral, once-daily prescription treatment for severe alopecia areata in adults and adolescents aged 12 and older. Litfulo is a TEC family kinase and JAK3 inhibitor. Alopecia areata pathogenesis may be impeded by Litfulo's inhibition of JAK3 and TEC kinase family members, which may prevent cytokine signaling and T cell cytolytic activity. An autoimmune condition called alopecia areata causes patchy hair loss, primarily on the scalp but sporadically also on the face (beard, brows, and eyelashes). It is brought on by the immune system of the body attacking healthy hair follicles, which results in hair loss. Litfulo works by selectively and irreversibly inhibiting Janus kinase 3 (JAK3), and other tyrosine kinases, and inhibiting cytokine-induced STAT phosphorylation mediated by JAK3-dependent receptors. In addition, it inhibits the signalling of immune receptors dependent on TEC kinase family members. Litfulo was approved on June 23, 2023, and was the first treatment to be approved for adolescents as well as adults with alopecia areata. It belongs to the class of medicines known as covalent kinase inhibitors. The review of Litfulo has been documented in this article.

Keywords:Litfulo, Alopecia, Physicochemical Properties,Pharmacokinetic.

I. INTRODUCTION

Alopecia Areata (AA) is a persistent, autoimmune, non-scarring alopecia that results in hair follicle loss..byautoreactive CD8+ T lymphocytes that destroy hair follicles (HF). Interferon gamma (IFN γ) and interleukin (IL) 15 are JAK STAT dependent cytokines that contribute to the main signaling cascade that, through JAK1 and JAK3, causes autoreactive CD8+ T cell proliferation.

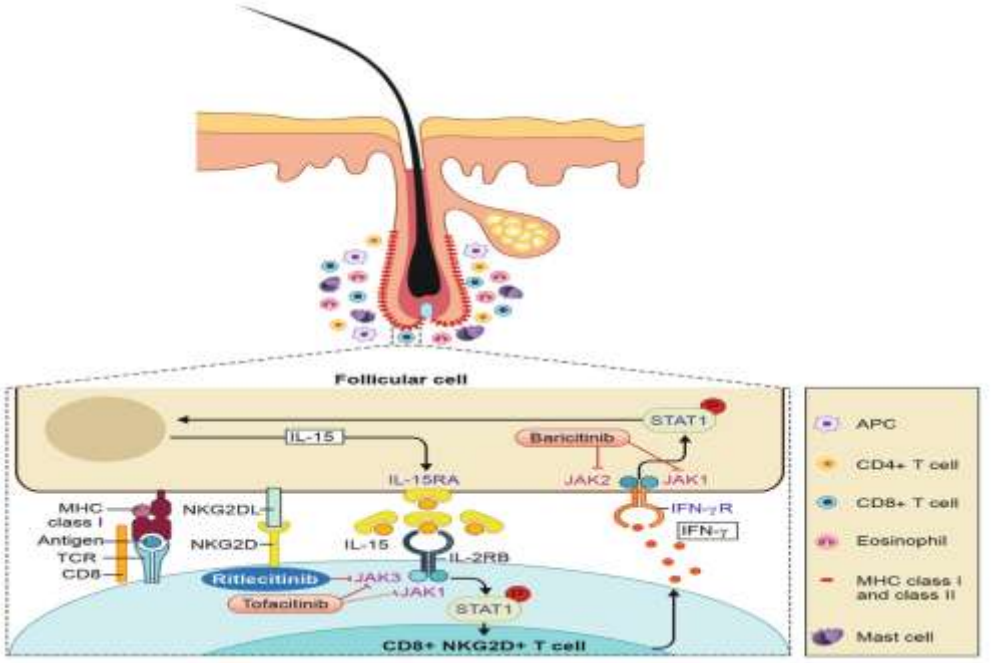

Figure 1. A Depiction of role of JAK-STAT pathway in Alopecia Areata

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Patchy hair loss, mainly on the scalp but also on the face and other body parts on occasion, is the outcome of an autoimmune disease known as alopecia areata.While children and teenagers of older adults may also be affected, the average age of onset is between 25 and 35 years old. [2]

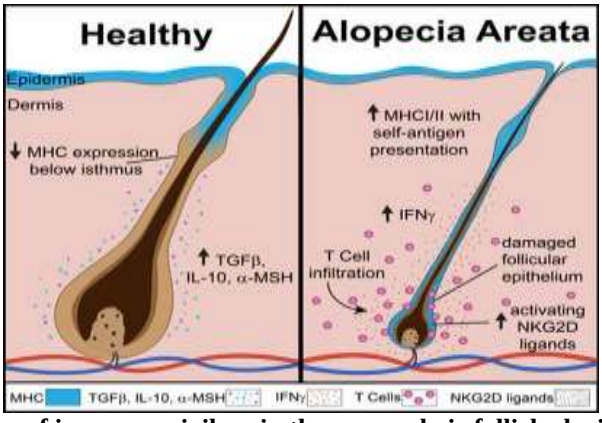

Figure 2. The collapse of immune privilege in the anagen hair follicle during alopecia areata. [3]

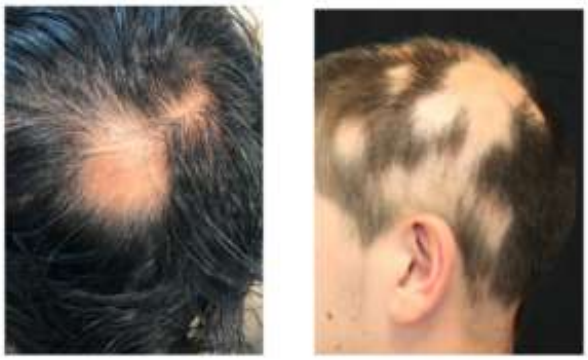

Figure 3. Alopecia condition

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 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]

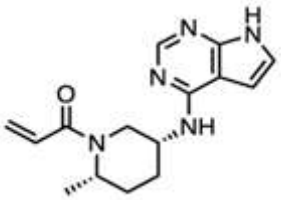

Figure 4. Structure of Ritlecitinib

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 mM)/mL

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necessitates the use of an ultrasonic for suspended solution.

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.

Table 1. Pharmacokinetic Properties

Tmax	Cmax	T-half
The AUC0-tau of ritlecitinib rises approximately dose-proportionately up to 200 mg. When a 100mg Ritlecitinib tablet and a high-fat meal were given concurrently, the AUCinf increased by 11%.	The Cmax of ritlecitinib increases to 200 mg in an approximately dose-proportional manner. When taken in combination with a high-fat meal, the Cmax was reduced by 32%.	The formula for calculating the half-life of ritlecitinib is t1/2=0.693*(vd/CL) where vd=1.3 L/kg2 and CL=5.6 mL/min/kg2.

ABSORPTION	DISTRIBUTION	ELIMINATION	METABOLISM	EXCRETION
It has an about 64% oral bioavailability overall. Peak plasma concentrations of ritlecitinib were reached in less than an hour.	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 total metabolism. Glutathione Stransferase is the initial mechanism, The CYP enzymes namely CYP2C9,CYP1A2, CYP3A, CYP28.	Feces and urine both eliminate 20% and 66% of the radiolabeled dosage, respectively. Urine contains 4% of the medication that is excreted unchanged.

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

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(ATP) binding site. In cellular contexts, ritlecitinib inhibits the phosphorylation of STAT triggered by cytokines, which is mediated via JAK3-dependent receptors. Additionally, ritlecitinib stops immune receptors from signaling when they are dependent on TEC kinase family members. It is yet uncertain whether blocking a specific TEC family or JAK enzyme could impact how well a treatment works.[2]

How does Litfulo work?

Litfulo is used to treat alopecia areata, an autoimmune disease that results in hair loss. Your immune system, which is your body's defensive mechanism, wrongly targets your hair follicles when you have this illness. This results in inflammation, which harms the hair follicle and triggers hair loss.One class of medication known as a kinase inhibitor is litfulo. It functions by reducing immune system activity. Litfulo specifically inhibits the function of two proteins known as TEC kinases and Janus kinase 3 (JAK3). These proteins transmit signals that trigger the production of cytokines (inflammatory proteins) by immune cells.Litfulo inhibits the production of cytokines by your immune cells by suppressing the JAK3 and TEC kinases. This promotes hair growth by lowering the inflammation that harms your hair follicles.[5]

INTERACTION WITH MEDICATIONS, FOOD, AND VACCINE

Medications that can interact with Litfulo

1. Abatacept: When paired with ritlecitinib, the probability or severity of side events may increase.
2. Abemaciclib - When combined with ritlecitinib, abemaciclib's serum levels can rise.
3. Abiraterone: When paired with ritlecitinib, abiraterone's serum levels can rise.
4. Acyclovir: When paired with ritlecitinib, acyclovir's serum levels can rise.

5. Ritlecitinib's AUC and Cmax may be lowered by rifampicin, which could lead to a decrease in clinical response.
6. Rifampin inhibits the hepatic/intestinal enzyme CYP3A4 metabolism, which lowers the dosage or impact of ritlecitinib.[4]

Foods that can interact with Litfulo :caffeine from beverages including energy drinks, cola, coffee, and tea

Lab tests or vaccines that can interact with Litfulo ;Live vaccines, such as chickenpox vaccine (Varivax) or measles, mumps, and rubella (MMR).[5]

Clinical Indications

Ritlecitinib is being studied in Phase II and Phase III clinical trials

- Ritlecitinib is in Phase III clinical trial for the treatment of alopecia areata
- In Phase II clinical trial for the treatment of Crohn's disease, Rheumatoid arthritis, Ulcerative colitis and Vitiligo. [6]

SIDE EFFECT

The following are examples of mild Litfulo side effects

- 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.
- Elevated creatinine phosphokinase values[5]

CONTRAINDICATION AND PRECAUTION

Ritlecitinib affects liver enzymes, complete blood count, and increases the risk of infections. For these reasons, patients with an infection that requires hospitalization for IV antimicrobials within six months, or those with an active or latent infection (i.e., not well treated hepatitis or tuberculosis), recurrent or disseminated herpes zoster, or those taking concurrent medications linked to peripheral neurologic or hearing loss, occupational or recreational noise exposure, or HbA1c >7.5% at screening should not use this medication.[6]

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CONVENTIONAL MARKETED FORMULATION[2]

Table 2. Marketed Formultion of Litfulo

TYPES	BRAND NAME	COMPANY NAME	DOSE	PRIZE
Capsule	LITFULO	Pfizer	5mg 10mg 25mg 50mg	6,5636 10,255.25 20,510.50 31,996.38

Figure 5. Capsule of Ritlecitinib[7]

PATENT

Lauren E. Ingram is the inventor of LITFULO (Ritlecitinib) capsules; Reference ID: 5196496; NDA 215830 has approved the starting process; Federal Food Drug and Cosmetic Act (FDCA) has approved.

The inventors of the following patents are listed: BROWN, Mathew Frank, Massachusetts; CHE, Ye; COE-Jotham Wadsworth; FLANGAN, Mark Edward; GILBERT, Adam Matthew; HAYWARD, Matthew Merrill; LANGILLE, Jonathan David; MONTGOMERY, Justin Ian; TELLIEZ, Jean-Baptiste; THORARENSEN, Atli; UNWALLA, RayomandJal. The international application number is PCT/IB2014/066202. The international filling date is November 20, 2014. The filling and publication language is English.[2]

II. 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.

REFERENCE

[1]. KabirSardana, SavithaBathula, AnantaKhurana .Which is the Ideal JAK Inhibitor for Alopecia Areata – Baricitinib, Tofacitinib, Ritlecitinib or Ifidancitinib - Revisiting the Immunomechanisms of the JAK Pathway. Indian Dermatol Online J .2023;14:465-74. DOI: 10.4103/idoj.idoj_452_22

[2]. PeriyasamyParthiban, ArthanariSaravanakumar , ChellamuthuKavinkumar , SangeethaSaravanan , AbinayashreeSekar , ArumugamGowtham, SomasundharamSabari,NandhiyaVenkatachalam.A Revolutionary Drug:Ritlecitinib. Foundary Journal. 2023; 26(9):52.DOI:10.29014/FJ-1001-4977.89.1815

[3]. Maddison Lensing,Ali Jabbari.An overview of JAK/STAT pathways and JAK inhibition in alopecia areata. Drug Design, Development and Therapy. 2022;16: 363—374. DOI: https://doi.org/10.3389/fimmu.2022.955035

[4]. S. R. Agrawal, M. P. Narode, P. R. Thombare, N. R. Kuhile, O. M. Kadam. Litfulo : Is An Innovative Medication. Int. J. in Pharm. Sci. 2023;1(12):919-925. DOI:10.5281/zenodo.10442173

[5]. Elizabeth Scheffel,By Helen Marshall,editors.Litfulo (ritlecitinib)[Internet]. January 9, 2024.Available from:https://www.medicalnewstoday.com/articles/drugs-litfulo#_noHeaderPrefixedContent.

[6]. Hassiel Aurelio Ramírez-Marín, AntonellaTosti. Evaluating the Therapeutic Potential of Ritlecitinib for the Treatment of Alopecia Areata.Drug Design, Development and Therapy. 2022;16:363-374.DOI:https://doi.org/10.2147/DDDT.S334727

[7]. Diana Ernst.Litfulo Approved for Severe Alopecia Areata in Adults,Adolescents [Internet].Medical Professional Reference;2023.Available from: https://www.empr.com/home/news/litfulo-approved-for-severe-alopecia-areata-in-adults-adolescents.