International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 2 Mar–Apr 2025, pp: 1081-1089 www.ijprajournal.com ISSN: 2456-4494

A Concise Review on Novel Drugs Applied in Treatment of Alopecia

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Date of Submission: 01-04-2025 Date of Acceptance: 10-04-2025

ABSTRACT:
Alopecia, characterized by hair loss, significantly impacts the quality of life due to its aesthetic and psychological effects. Traditional treatments, such as topical minoxidil and oral finasteride, often show limited efficacy and carry potential side effects. In recent years, novel targeted therapies have emerged, offering promising alternatives. These include Janus kinase (JAK) inhibitors like tofacitinib and ruxolitinib, which modulate immune responses in autoimmune-related alopecia areata. Additionally, therapies targeting the Wnt signaling pathway, such as the small molecule CB-103, aim to stimulate hair follicle regeneration. The development of platelet-rich plasma (PRP) therapy and stem cell-based interventions also represents innovative approaches, focusing on enhancing follicular microenvironments. This review explores the mechanisms, clinical efficacy, and safety profiles of these targeted therapies, highlighting their potential to revolutionize alopecia management. Future research should focus on optimizing treatment protocols, understanding long-term outcomes, and addressing individual patient variability.

I. INTRODUCTION :

Alopecia is a condition, which results in loss of hair from one's head or other body parts where hair is naturally supposed to be found. There are diverse categories of alopecia but the commonest are androgenic alopecia (common baldness), alopecia areata and chemotherapy induced alopecia. Although the FDA sanctioned only two serendipitous drugs (finasteride and minoxidil) for the management of alopecia, there are many unapproved medications which are claimed to reverse the condition.

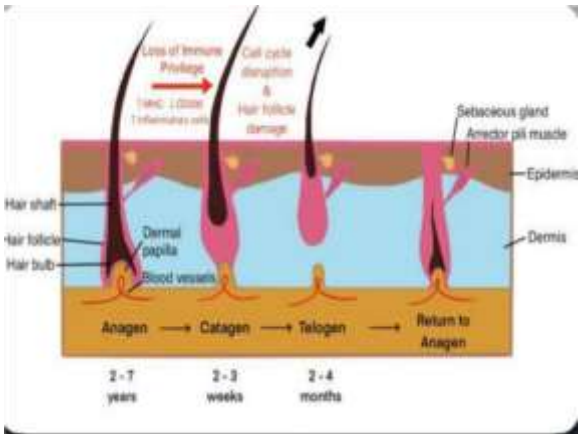

Figure: Immunogenesis of Alopecia areata

Types of Alopecia:

1. Androgenic alopecia

It is the famous cause of baldness in male and female, which is a hereditary determined, aging symptom, intensifying hair loss condition with sex specific contestation in prevalence and intensity.

Two drugs have been approved in the past by the medical organizations: Oral finasteride (for male) and topical minoxidil (for male and female), due to poor efficacy of these therapeutic agents and adverse effects which can decrease the patient adherence and lead to discontinuing of the treatment (e.g., occasionally gynecomastia with finasteride, and frequently hirsutism in the case of minoxidil.

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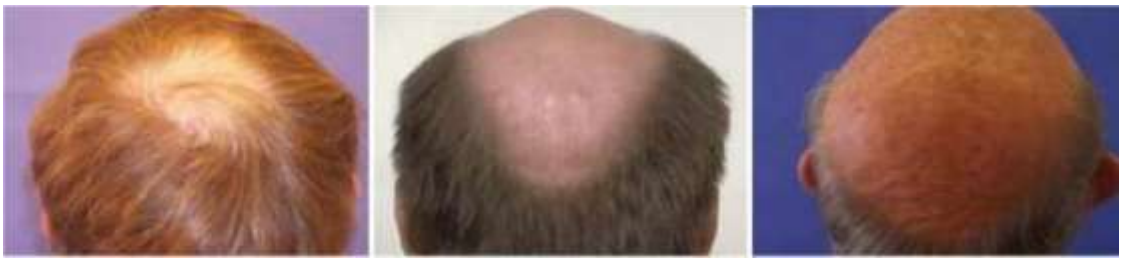

Figure: Alopecia androgeniticaMicroscopical examination of the dermis showed 20% heterogeneity in the diameter of the hair

2.Alopeciaareata

Alopecia areata is a non- scarring autoimmune condition, which results in loss of hair in one's scalp or any other body parts. The condition affected both male and female equally but most popular in infants. Alopecia areata can also result in loss of hair on the whole body, a condition known as alopecia universalis. Alopecia areata may not ordinarily lead to death of hair follicle cells as hair often grows after recovery when proper body signals are assumed.

Plenty products have been purported to reverse alopecia areata but none stood the test of time because of ineffectiveness and side effects. Interventions with products such as zinc, cortocosteroids, systematic cortisone, minoxidil and immuno suppressive remedies have been widely used with limited success to combat alopecia areata. There is still need to find reliable cure for alopecia areata.

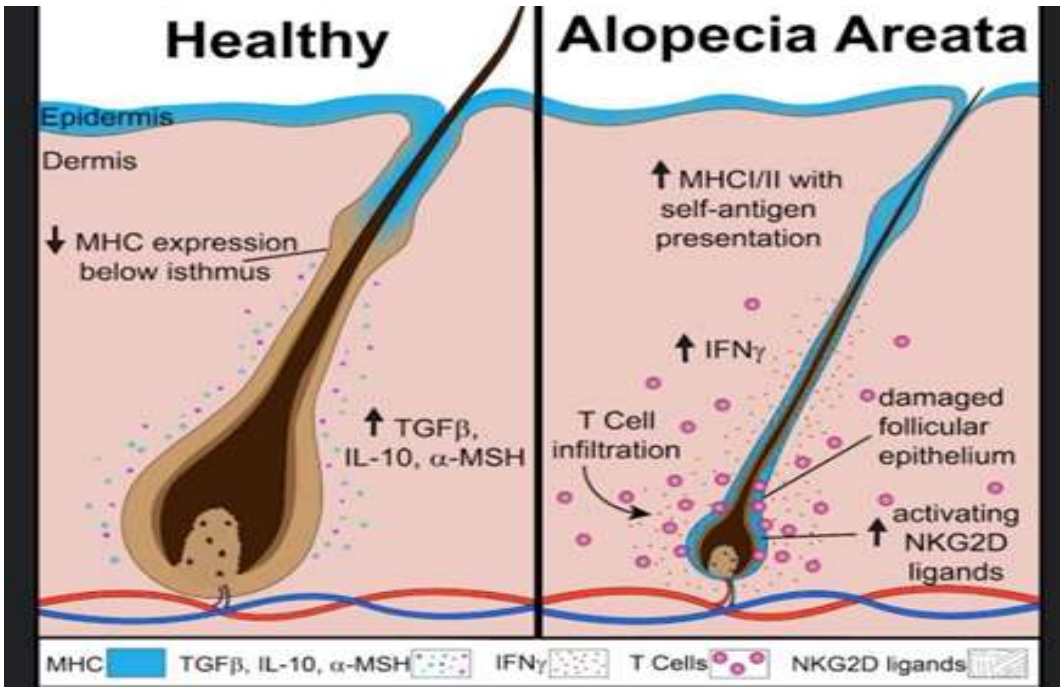

Figure: The collapse of immune privilege in the anagen hair follicle during alopecia areata

3.Chemotherapy induced alopecia

Loss of scalp hair is one of the dreaded adverse effects of chemotherapy causing some patients to deny or omit treatment. Chemotherapy treatments attack fast growing cell types and not only neoplastic cancer cells. This leads to the attack of fast-growing hair fiber keratinocytes in the active growth phase leading to loss of hair. Hair matrix keratinocytes at the anagen stage are the absolute quickest multiplying cells in the body, about 60% of them stay in the synthesis (S) stage. Regrettably at present there are no apoptosis obstructive agents or telogen arresting remedies to give to patients. It is desirous to come up with

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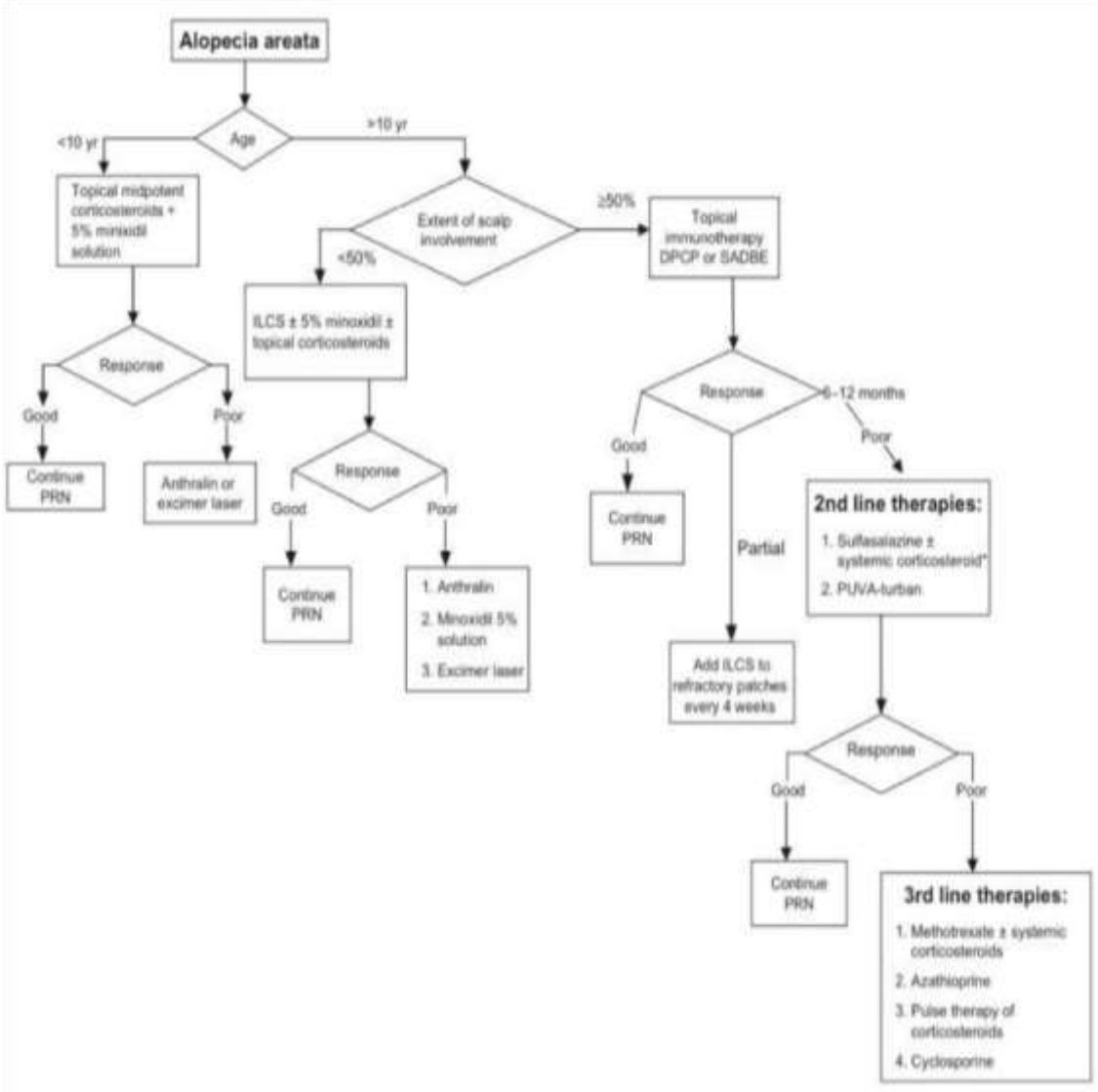
treatments for fortifying hair healthy during chemotherapy.

Symptoms of Alopecia

The symptoms of alopecia vary depending on the type, but some common signs include:

- Gradual thinning of hair on scalp, often noticeable in the crown or temples.
- Sudden patches of hair loss, appearing as round or oval-shaped areas.
- Increased hair shedding in the shower or on the pillow, changes in hair texture, such as becoming thinner or brittle Scalp itching, pain, or tenderness.

NOVEL TARGETED THERAPIES



Treatment

First-line therapies:

1) **Minoxidil:** In a placebo-controlled, double-blind study, hair regrowth was observed in 63.6% and 35.7% of the minoxidil-treated and placebo groups, respectively.However, only 27% of the minoxidil- treated patients showed cosmetically acceptable hair regrowth. In another study, hair regrowth was achieved in 38% and 81% of patients treated with 1% and 5% topical minoxidil, respectively. Most studies have shown no beneficial effect of topical minoxidil in alopecia totalis and

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alopecia universalisMinoxidil 5% solution or foam is frequently used with other therapeutic agents as an adjuvant therapy. The adverse effects of topical minoxidil include contact dermatitis and facial hypertrichosis.

2) **Anthralin:** A few controlled trials have assessed the efficacy of topical anthralin in the treatment of alopecia areata. In an open study, a cosmetic response was seen in 25% of patients with severe alopecia areata treated using 0.5%–1.0% anthralin cream. In ano acceptable hair regrowth. Anthralin needs to be applied in a high enough concentration (0.5%–1%) and sufficiently frequently (daily) to produce a mild irritant reaction in order to be effective Severe irritation and staining of skin and clothes are some of the possible adverse events with anthralin the trial, combination therapy of 5% minoxidil and 0.5% anthralin was used to treat 51 patients with severe alopecia areata; only 11% of patients achieved.

Second-line therapies:

1) Sulfasalazine:

Sulfasalazine is a combination of sulfapyridine and 5- aminosalicylic acid linked by a diazo bond. Sulfasalazine has both immunomodulatory and immunosuppressive actions that include suppression of T cell proliferation and reducing the synthesis of cytokines, including interleukin (IL) 6, 1, and 12, tumor necrosis factor alpha, and antibody production. Sulfasalazine has been used safely as a long-term treatment of various inflammatory and autoimmune diseases, including inflammatory bowel disease and rheumatoid arthritis. Several case reports and case series showed good hair regrowth with sulfasalazine in the treatment of alopecia areata.

2) Ritlecitinib:

Ritlecitinib is a medication that is being studied for its potential use in treating autoimmune diseases, particularly alopecia areata. It works as a Janus kinase (JAK) inhibitor, which helps to modulate the immune response. Ritlecitinib is a selective JAK inhibitor that targets specific pathways involved in the immune system. It's primarily being investigated for conditions like alopecia areata, a type of hair loss caused by an autoimmune response. Clinical trials have shown promising results in promoting hair regrowth in affected individuals. Ritlecitinib is part of a class of medications known as JAK inhibitors, which block specific enzymes involved in the inflammatory process. By inhibiting these pathways, ritlecitinib aims to reduce inflammation and restore normal immune function, particularly in autoimmune conditions.

Third-line therapies:

1. Cyclosporine:

The success rate with oral cyclosporine is 25%–76.6%. A recent study showed that a good response to oral cyclosporine can be predicted if the serum level of IL is elevated and the level of soluble IL 2 receptor is low. The use of oral cyclosporine in patients with alopecia areata is not generally favored due to its adverse event profile (nephrotoxicity, immune suppression, and hypertension) and a high relapse rate (up to 100%). Also, alopecia areata incidence has been reported in several organ transplant patients receiving cyclosporine. Although hypertrichosis is a documented side effect of oral cyclosporine, a good response has not been achieved by using topical cyclosporine in humans.

2. Deuruxolitinib

Deuruxolitinib is an investigational drug primarily being studied for the treatment of autoimmune diseases, particularly atopic dermatitis. It is also a selective Janus kinase (JAK) inhibitor, similar to ritlecitinib, targeting the JAK1 enzyme to modulate inflammatory pathways. Deuruxolitinib is a deuterated form of ruxolitinib that selectively inhibits Janus kinases (JAK) JAK1 and JAK2. Deuteration allows the drug to circumvent extensive oxidative metabolism around the cyclopentyl ring, which increases the duration of the pharmacological activity of deuruxolitinib.

Prevention and Management of Alopecia:

- Treatment options should be selected according to patient age and extent of disease.
- For patients younger than 10 years, a combination of 5% minoxidil solution twice daily with midpotent corticosteroids should be tried first.
- If there is no good improvement after 6 months, short-contact anthralin is considered as second-line therapy.
- For patients older than 10 years of age with alopecia areata involving less than 50% of the scalp, intralesional triamcinolone acetonide injection (5 mg/cc) is the recommended option for treatment.

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- If there is no good response after 6 months, other options can be tried, including potent topical corticosteroids under occlusion at night, 5% topical minoxidil twice a day, short-contact anthralin, and excimer laser.
- If alopecia areata involves more than 50% of the scalp, topical immunotherapy with diphenylcyclopropenone is the first therapeutic option recommended by many experts in hair diseases.
- For patients who respond poorly to diphenylcyclopropenone and those who cannot use it, second-line therapies can be used.

1) Properties of Minoxidil

- Name of drug- Minoxidil
- Approved by FDA- on sep 1 2022
- Brand name- Rogaine
- Generic name - minoxidilSulphate
- Dosage Form- oral (tablets) 2.5mg, 5 mg,10 mg
- Class of Drug- Vasodilator

No.	Description	Details
1	Color	White or Pale Yellow
2	Odor	Mild Alcoholic
3	Taste	Bitter
4	Molecular Weight	209.25 g/mol
5	Solubility	**Water:** Slightly Soluble **Ethanol:** Soluble
6	pH	4.5 - 6.5
7	Melting Point Range	248 - 250°C
8	Density	0.95 - 1.03 g/mL
9	Molecular Formula	C9H15N5O
10	Route of Administration	**Topical:** Scalp **Oral:** Tablets for Hypertension

Mechanism of Action:

Step 1: Absorption

Topical application Absorption through skin. Peak plasma levels within 1-2 hours**.**

Step 2: Vasodilation

Relaxes smooth muscle cells Increases blood vessel diameteropens potassium channels (ATP-sensitive).

Step 3: Hair Growth Stimulation

Increased blood flow to hair follicles Enhanced oxygenation and nutrient delivery Stimulation of hair growth factors (VEGF, FGF-5)

Step 4: Hair Follicle Enlargement

Increased hair follicle size Enhanced hair shaft thickness Prolonged anagen phase

Step 5: Hair Growth Maintenance

Sustained blood flow and vasodilation Continued stimulation of hair growth factors Maintenance of hair follicle health

Pharmacokinetic parameter:

No.	Parameter	Topical
1	**Absorption**	2-5%
2	**Distribution**	Primarily localized to scalp
3	**Metabolism**	Hepatic metabolism
4	**Elimination Half-life**	4-5 hours
5	**Clearance**	N/A
6	**Dosage Form**	N/A

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Prescribing information:

1) Dosage Form and Strength

- **Topical:** Apply 1/2ml twice daily morning and night
- **Oral:** varies depending on hypertension treatment regimen.

2) Dosage and administration

- **Topical:** 1ml twice daily apply to dry scalp using dropper or spray. Massage into scalp, avoid applying to broken skin.
- **Oral:** for mild to normal 2.5mg-5mg tablet once daily swallow the tablets once with water.

3) Contraindications

- **Topical:**

-Children under 18 years.

- **Oral:**

- Pregnant or breastfeeding women.
- Pheochromocytoma.
-Cardiac failure.

4) Warnings and Precautions

- **Topical Warning:** Allergic reactions

-Systemic absorption
-Scalp irritation
-Unwanted facial hair

- **Oral Warning:** Severe hypotension

-Reflex tachycardia
-Pericardial effusion
-Cardiac failure

Precautions:

- Children under 18 are not recommended
- Avoid applying on broken skin
- Avoid contact with eyes
- Start with lower concentration
- Seek medical attention if accidental ingestion occurs

5) Adverse Reactions:

- Myocardial infarction
- Cerebrovascular accident
- Hypersensitivity reactions
- Psychiatric disorders

2) Properties of Ritlecitinib

Name of drug- Ritlecitinib
Approved by FDA- on 23 June 2023
Brand name-Litfulo
Generic name - ritlecitinib succinct
Dosage Form-Oral Capsules:200mg,300mg
Class of Drug- Immunomodulators

No.	Parameter	Description
1	Colour	White or Off White
2	Odour	Odourless
3	Taste	Tasteless
4	Molecular Weight	415.53 g/mol (free base)
5	Solubility (Water)	Slightly Soluble
6	Solubility (Ethanol)	Soluble
7	pH	5.5 - 7.5
8	Melting Point Range	192-196°C
9	Density	1.37 g/cm³
10	Molecular Formula	C23H27N7O2
11	Route of Administration	Oral

Mechanism of Action:

Step 1: Targeting Kinases

Retlecinib inhibits certain receptor tyrosinekinase (RTKs) involved in tumor growth and progression

Step 2: Blocking Signal Transduction

By inhibiting these kinases, retlecinib disrupts the downstream signaling pathways thatpromote cell proliferation and survival

Step 3 :Inducing Apoptosis

The drug may induce apoptosis (programmed cell death) in cancer cells by altering the balance of pro- and anti-apoptotic factors.

Step 4: Inhibiting Tumor Angiogenesis:

Retlecinib can prevent the formation of new blood vessels (angiogenesis) that tumors need to grow.

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Step 5:Potential Resistance Overcoming
It targets specific mutations associated with resistance to other therapies, making it useful for patients with refractory tumors

Step 6:Tissue Specificity
The drug's action may vary depending on the tissue type and the specific molecular characteristics of the tumor

Pharmacokinetic parameter:

No.	Parameter	Details
1	**Absorption**	Oral bioavailability 45-55%
2	**Peak Plasma Concentration (Tmax)**	2-4 hours
3	**Distribution**	Volume of distribution: 200-300 L
4	**Plasma Protein Binding**	95-98% (primarily to albumin)
5	**Metabolism**	Glucuronidation metabolism
6	**Elimination Half-life**	12-15 hours
7	**Clearance**	Total clearance (CL): 10-15 L/h

1)Dosage Form and Strength
- **Oral Capsules**: 200 mg to 300 mg are given as per treatment to the patient.
- **Alopecia Areata**: 200 mg twice daily.
- **Alopecia Totalis**: 300 mg twice daily. **Alopecia Universalis**: 300 mg twice daily.

2)Dosage and Administration
- **Alopecia Areata**: Orally 200 mg twice daily taken with or without food.
- **Capsules/Tablets**: Swallow whole without chewing or crushing.
- **Timing**: Take at approximately the same time daily, morning or night.

3)Contraindications
- History of renal disease or renal injury
- History of liver disease or liver injury
- Immunocompromised patients (HIV/AIDS, cancer)

4) Warning and Precautions
- Potential for liver injury
- Potential for renal impairment
- Increased risk of allergic reactions

5) Adverse Reactions:
Renal Failure
Hepatic failure
Aplastic anaemia

3)Properties of Deuruxolitinib
Name of drug-Deruxolitinib
Approved by FDA- on 26 July 2024
Brand name-leqselvi
Generic name -leqselvi
Dosage Form-oral tablet:10 mg ,20 mg,30mg(as per treatment)
Oral capsule:10ng,20mg,30mg
Class of Drug-Janus Kinase(JAK) Inhibitors

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No.	Parameter	Description
1	Colour	White to off-white
2	Odour	Slightly sweet
3	Taste	Slightly bitter, slightly sweet
4	Molecular Weight	632.5 gm/mol
5	Solubility	Water: slightly soluble; Ethanol: soluble
6	pH	5.5 - 7.0
7	Melting Point Range	175-185°C
8	Density	1.2-1.4 gm/cm³
9	Molecular Formula	C33H41N7O5S
10	Route of Administration	Oral

Mechanism of Action:

Step 1: JAK Inhibition
Selectively inhibits Janus kinase (JAK) enzymes, particularly JAK1 and JAK3

Step 2: Cytokine Signaling Modulation
Disrupts cytokine signaling pathways, including interleukins.

Step 3: Anti-inflammatory Effects:
Reduces inflammation by limiting immune cell activity in autoimmune responses.

Step 4: Immune Response Regulation:
Modulates the immune system, potentially beneficial for conditions like atopic dermatitis and other autoimmune disorders.

Step 5: Cellular Proliferation Control:
Inhibits JAK signaling, affecting the proliferation and survival of certain immune cells.

Pharmacokinetics parameters:

No.	Parameter	Details
1	**Absorption**	Moderate to slow, taking 2-4 hours
2	**Distribution**	Volume of distribution is 200-400 L
3	**Plasma Protein Binding**	98-99%, primarily to albumin
4	**Metabolism**	Undergoes hydroxylation and glucuronidation metabolism
5	**Elimination Half-life**	12-24 hours, with an effective half-life of 6-12 hours
6	**Clearance**	Total clearance (CL): 10-15 L/h

1)Dosage Form and Strength:
•Available in 10 mg, 20 mg, and 30 mg dosages, depending on treatment requirements.
•10 mg is given once daily in mild to moderate conditions.

2)Dosage and Administration: 20 to 30 mg is administered orally once daily, with or without food.

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Swallow tablets or capsules whole; do not crush, chew, or split the tablets.

3)Contraindications:
•Pregnancy or lactation.
•Severe renal impairment.
•Severe hepatic impairment
4)Warnings and Precautions:
•Increased risk of serious infections (e.g., pneumonia).
•Increased risk of malignancies (e.g., lymphoma, skin cancer).

5)Adverse Reactions:
•Hypertension.
•Increased heart rate.

II. CONCLUSION:

Here's a potential conclusion for a review on Deuruxolitinib, Ritlecitinib, and Minoxidil for the treatment of Alopecia: The advent of Deuruxolitinib and Ritlecitinib, novel Janus kinase (JAK) inhibitors, combined with the established efficacy of Minoxidil, hassignificantly expanded treatment options for Alopecia patients. These therapies have demonstrated impressive clinical efficacy in promoting hair growth, improving quality of life, and addressing unmet medical needs.

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