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Baricitinib: First Systemic Oral Drug for Alopecia Therapy

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ABSTRACT

Baricitinib, a Janus kinase inhibitor, was originally approved as anti-rheumatic drug in 2017. In 2020, it was approved for the treatment of COVID-19 in selected hospitalized adults. Baricitinib received priority review designation for treatment of adult patients with severe alopecia areata and got USFDA approval on June 23, 2022 based on the results of 02 phase III trial: BRAVE-AA1 and BRAVE-AA2. In this review, we aim to summarize the different pharmacokinetic and pharmacodynamics aspects including drug interactions, adverse effects/black box warnings and their clinical relevance. We reiterate that oral JAK inhibitors are expensive, may carry significant risks, and are not yet recommended for routine treatment of alopecia areata. There is ongoing research on other topical and oral JAK inhibitors (tofacitinib and ruxolitinib), giving hope that better treatments for alopecia areata will become available in future.

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Introduction

Alopecia areata (AA) is an immune-mediated inflammatory disorder affecting hair follicles leading to no scarring hair loss, ranging from small patches of alopecia on any hair-bearing area to the complete loss of scalp, eyebrow, eyelash, and body hair (alopecia totalis to alopecia universalis); few may develop associated fingernail or toenail abnormalities (1-6). Approximately 1 person in 50 will suffer from AA at some point in their life (7). It occurs in men and women of all races equally (8). It has been seen that up to 50% of patients with patchy AA may have spontaneous hair regrowth within one year, but generally will relapse months or years after remission (9-11). The management of AA involves educating patients, treating patients with available therapies, informing realistic expectations from treatment, along with addressing the psychologic needs of the patient (12,13). A number of topical, intralesional, and systemic agents, as well as cosmetic devices, have been used for AA with varied inter-individual and intra-individual variation in response to treatment (14). Intralesional corticosteroids for isolated patches of hair loss, or oral corticosteroids for patients who are experiencing rapid, extensive hair loss are one of the mainstay therapies. Topical minoxidil, anthralin for localized lesions and topical immunotherapy and immunosuppressive drugs for extensive AA are also successful in certain cases (15-18). The above available therapies can have significant risks and side effects and are to be used judiciously (9)

However, new therapies for alopecia areata are now emerging (19). Baricitinib, a Janus kinase (JAK) inhibitor, is the first oral systemic drug, recently approved for treatment of adult patients with severe AA (20,21). Baricitinib was originally approved as anti-rheumatic drug (in 2017) and later approved for the treatment of COVID-19 in selected hospitalized adults in 2020. Tofacitinib and ruxolitinib, previously discovered JAK inhibitor have also looked promising in initial studies for alopecia areata though the use continues to be off label presently and may become available in future for AA (22-25). Platelet-rich plasma, lipid-lowering medications, changing the gut microbiome are other options studied, but evidence from robust clinical trials are lacking (26-30). In this review, we aim to summarize the different pharmacokinetic and pharmacodynamic aspects of baricitinib including drug-drug interactions, adverse effects/black box warnings and their clinical relevance.

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Regulatory approval of Baricitinib for Alopecia areata: A glimpse

In February 2022, the United States Food and Drug Administration (USFDA) granted priority review for baricitinib in adults with severe AA to Eli Lilly and Incyte Corporation and gave final approval on 23 June 2022 based on the results of the phase 3 BRAVE-AA1 and BRAVE-AA2 trials (31). The summary of the clinical trials is given in Table 1. The regulatory approval by European Medicines Agency (EMA) and in Japan is in pipeline.

Table 1. Summary of clinical trials leading to approval of Baricitinib (31).

The efficacy and safety of baricitinib in alopecia areata was studied in two randomized, double blind, placebo-controlled trials with patients who had at least 50% scalp hair loss as measured by the Severity of Alopecia Tool for more than six months. Patients in these trials received either a placebo, 2 milligrams of baricitinib, or 4 milligrams of baricitinib every day. The primary measurement of efficacy for both trials was the proportion of patients who achieved at least 80% scalp hair coverage at week 36.	
BRAVE-AA1 Trial	22% of the 184 patients who received 2 milligrams of baricitinib and 35% of the 281 patients who received 4 milligrams of baricitinib achieved adequate scalp hair coverage, compared to 5% of the 189 patients who received a placebo.
BRAVE-AA2 Trial	17% of the 156 patients who received 2 milligrams of baricitinib and 32% of the 234 patients who received 4 milligrams of baricitinib achieved adequate scalp hair coverage, compared to 3% of the 156 patients who received a placebo.
As per safety data, few patients discontinued treatment because of adverse events (2.6% or less across both studies), and most treatment-emergent adverse events were mild or moderate in severity.	
Trial details available at: Trial AA1 (https://clinicaltrials.gov/ct2/show/NCT03570749) Trial AA2 (https://www.clinicaltrials.gov/ct2/show/NCT03899259)	

Mechanism of Action

Baricitinib inhibits Janus kinase (JAK) enzymes, an intracellular tyrosine kinases involved in hematopoiesis and immune cell function through a signaling pathway. JAKs phosphorylate and activate signal transducers and activators of transcription (STATs) in response to extracellular cytokine or growth factor signaling and modulate intracellular activity including gene expression. Inhibition of JAKs prevents the phosphorylation and activation of STATs and reduces inflammatory markers, serum IgG, IgM, IgA, and C-reactive protein (32,33). In AA, baricitinib modulates the signaling pathway at the point of JAKs, preventing activation of STATs thereby interfering with the pathway that leads to inflammation (34). The mechanism of action is illustrated in Figure 1.

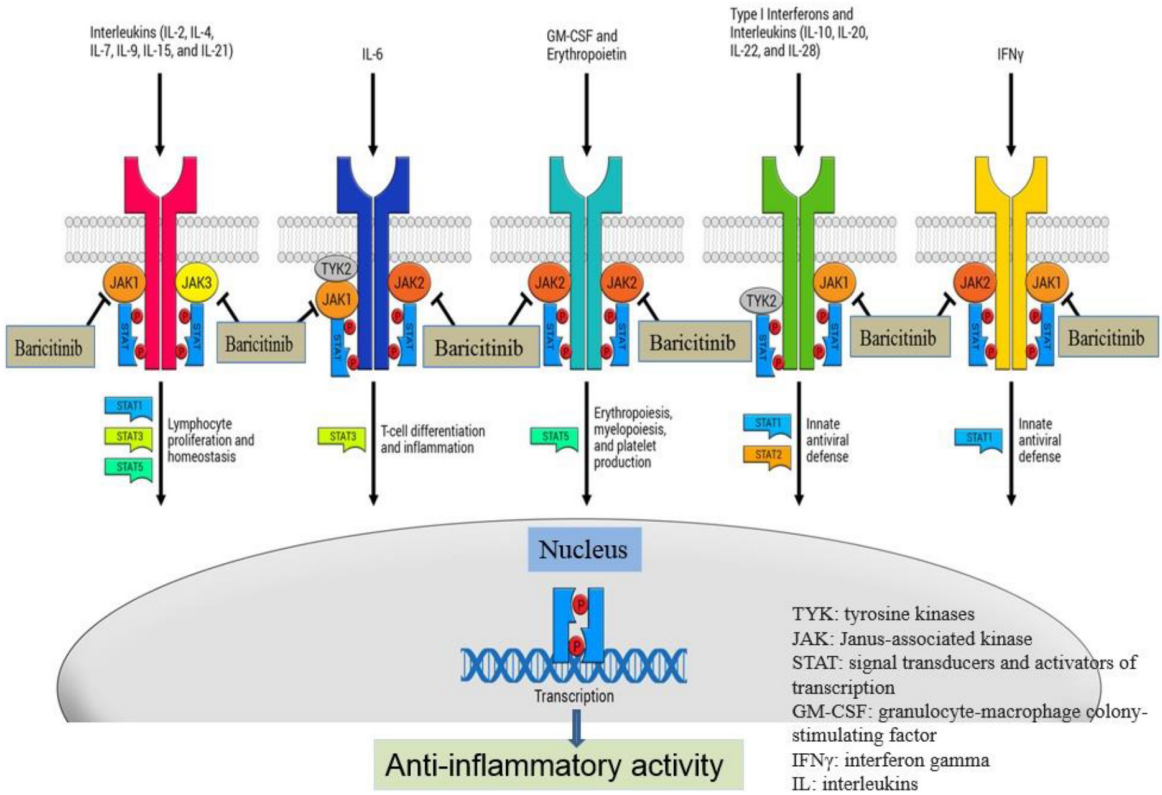

Figure 1. Mechanism of action of baricitinib.

Pharmacokinetics

The pharmacokinetic parameters of baricitinib are mentioned in Table 2. In renal function impairment: area under curve (AUC) increases by 1.41-, 2.22-, 4.05- and 2.41-fold for mild, moderate, and severe renal impairment, and end stage renal disease (with hemodialysis), respectively. In moderate hepatic impairment: AUC and Cmax increases by 1.19- and 1.08-fold, respectively. Hence, modification of dose is required in case of renal and hepatic impairment.

Table 2. Pharmacokinetic parameters of Baricitinib (35).

Process	Parameters
Absorption	Absolute bioavailability: ~80%
Distribution	Volume of distribution (V_d): 76 L; Protein binding: ~50% (plasma proteins); 45% (serum proteins); Substrate of the P-gp, BCRP, OAT3 and MATE2-K transporters, which play roles in drug distribution.
Metabolism	Hepatic, primarily via CYP3A4, Half-life elimination: ~12 hours, Time to peak: ~1 hour, Steady-state achieved: 2-3 days; ~6% of the orally administered baricitinib dose is identified as metabolites (3 from urine and 1 from feces), No metabolites of baricitinib were quantifiable in plasma
Excretion	Urine: ~75% (69% as unchanged drug); feces: ~20% (15% as unchanged drug); Total body clearance: 8.9 L/hr.

[Abbreviations: P-gp: P-glycoprotein; BCRP: Breast Cancer Resistance Protein; OAT3: Organic anion transporter 3; MATE2-K: Multi-drug and toxin extrusion transporter; CYP3A4: Cytochrome P450 3A4.]

Approved Indications

Baricitinib have been approved for: (i) Rheumatoid arthritis: Originally approved in 2017 for treatment of adult patients with moderately to severely active rheumatoid arthritis having inadequate response to one or more tumor necrosis factor blockers (36). (ii) COVID-19, hospitalized patients: In year 2020, it got emergency use authorization (EUA) for use in combination with remdesivir for treatment of COVID-19 in hospitalized adults requiring supplemental oxygen, noninvasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation. The FDA has updated the EUA in July 2021 where baricitinib can be used alone for the treatment of COVID-19 in hospitalized adults and pediatric patients 2 years and older, other conditions remains same (37-38) (iii) Alopecia areata: On June 13, 2022, US-FDA approved baricitinib oral tablets to treat adult patients with severe alopecia areata (31).

Dosage forms and storage conditions (35,39)

Baricitinib is available as oral tablet with a strength of 1 mg, 2 mg and 4 mg (contains soybean lecithin), with a common brand name of Olumiant. The tablets should be stored at 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F). Can be stored at room temperature in a dry and safe place, out of the reach of children and pets. The dispersed tablet in water is stable up to 4 hr. The cost per tablet can vary between Rs 5000 to 7000 ($90 to 100 approx.). An FDA-approved patient medication guide, which is available with the product information must be dispensed along with this medication.

Dose & administration in Alopecia areata (35,39)

Before initiating baricitinib, evaluations as mentioned in Table 3 should be considered. The dose indicated for adults with severe alopecia areata is 2 mg PO once a day (qDay); increase to 4 mg qDay if inadequate response. With nearly complete or complete scalp hair loss, with or without substantial eyelash or eyebrow hair loss, 4 mg qDay may be considered. Once adequate response achieved with 4 mg/day, dose may be decreased to 2 mg/day. If a dose is missed, it is advisable to take missed dose as soon as one remembers. However, if it is close to time of next dose, missed dose to be skipped and next dose taken. The dosage may need to be modified in certain situations as given in Table 4. The tablet may be taken with or without food. For patients unable to swallow whole tablets, tablets may be dispersed in water. The required number of tablets to achieve desired dose is placed in a container with ~10 mL (minimum: 5 mL) of room temperature water; gently swirl the tablet(s) to disperse. After ensuring tablets are sufficiently dispersed, it has to be consumed immediately. Rinse container with an additional 5 to 10 mL of room temperature water and swallow. Tablets may be crushed to facilitate dispersion. According to the manufacturer, since it is not known if powder from the crushed tablets may pose a reproductive hazard to the preparer, if tablets are crushed, proper control measures (eg. ventilated closure) or personal protective equipment (ie N95 respirator) has to be followed by the preparer.

Table 3. Evaluations before initiating baricitinib therapy (35,39)

1	Active and latent tuberculosis (TB) infection: Do not give to patients with active TB; if latent infection positive, consider prophylaxis treatment for TB before initiating.
2	Screen for viral hepatitis in accordance with clinical guidelines.
3	Baseline hepatic and renal function: Assess baseline values and monitor for laboratory changes; modify dosage based on hepatic and renal impairment
4	Assess baseline complete blood cell count (CBC) to determine whether treatment can be initiated. Monitor CBC during treatment and modify dosage as recommended.
5	Avoid in patients with active, serious infection, including localized infections; if serious infection occurs, withhold treatment.
6	Update immunizations in agreement with current immunization guidelines before initiating.
7	Check drug history: Not recommended for use in combination with other Janus kinase (JAK) inhibitors, biologic DMARDs, or with potent immunosuppressants (eg, azathioprine, cyclosporine).

Monitoring parameters: Lymphocyte, neutrophil, platelet counts, and hemoglobin, LFTs, and renal function (baseline and periodically thereafter); lipids (12 weeks after therapy initiation and periodically thereafter); viral hepatitis (prior to initiating therapy in accordance with clinical guidelines); signs/symptoms of infections (including tuberculosis) during and after therapy; abdominal symptoms; skin examination (periodically, in patients at increased risk for skin cancer).

Table 4. Dosage modifications of baricitinib (35,39).

Parameters	Values	Remarks
Absolute lymphocyte count (ALC)	ALC ≥500 cells/mm3	Maintain dose
	ALC <500 cells/mm3	Avoid initiation or interrupt dosing until ALC ≥500 cells/mm3
Absolute neutrophil count (ANC)	ANC ≥1000 cells/mm3	Maintain dose
	ANC <1000 cells/mm3	Avoid initiation or interrupt dosing until ANC ≥1000 cells/mm3
Anemia	Hgb ≥8 g/dL	Maintain dose
	Hgb <8 g/dL	Avoid initiation or interrupt dosing until Hgb ≥8 g/dL
Renal impairment Mild (eGFR 60 to <90 mL/min/1.73 m2)		No dose adjustment required
	Moderate (eGFR 30 to <60 mL/min/1.73 m2)	Reduce dose by 50%
	Severe (eGFR <30 mL/min/1.73 m2)	Not recommended
Hepatic impairment (Interrupt if ALT/AST increased and drug-induced liver injury (DILI) suspected, until DILI diagnosis excluded)	Mild or moderate	No dose adjustment required
	Severe	Not recommended
Coadministration with strong organic anion transporter 3 (OAT3) inhibitors (e.g., probenecid)	If recommended dose is 4 mg/day, reduce to 2 mg/day If recommended dose is 2 mg/day, reduce to 1 mg/day If recommended dose is 1 mg/day, consider discontinuing probenecid	

eGFR:estimated glomerular filtration rate

Reproductive, Pregnancy and Lactation Considerations

Due to paucity of data on safety of use in reproductive age groups, recommendations for use of baricitinib in patients planning to become pregnant or who are planning to father a child are not available (40). It is better to discontinue use one month prior to conception (41). In animal embryo-fetal development studies, oral baricitinib administration to pregnant rats and rabbits at exposures equal to and greater than ~20 and 84 times the maximum recommended human dose (MRHD), respectively, resulted in reduced fetal body weights, increased embryo lethality (rabbits only), and dose-related increases in skeletal malformations. Recommendations for use of baricitinib in pregnant patients are also not available due to lack of human data (40). Baricitinib is present in the milk of lactating rats, however whether it is distributed in human breast milk is not known. Transfer into breast milk may be expected based on molecular weight (40). Owing to species-specific differences in lactation physiology, the clinical relevance of these data is not known. Because of the potential for serious adverse reactions in nursing infants, it is advisable not to breastfeed while taking baricitinib.

Drug-drug Interactions

The baricitinib can have a number of drug-drug interactions. Some potential and clinically relevant interactions are enumerated in Table 5. (35,39)

Table 5. Drug-drug interaction of baricitinib.

Agent	Effect	Remarks
5-Aminosalicylic Acid Derivatives Olaparib	May enhance the myelosuppressive effect of Myelosuppressive Agents	*Monitor therapy*
Abrocitinib Anifrolumab Belimumab Natalizumab	May enhance the immunosuppressive effect	*Avoid combination*
BCG (Intravesical)	May diminish the therapeutic effect of BCG (Intravesical).	*Avoid combination*
Clozapine	May enhance the adverse/toxic effect of Clozapine (risk for neutropenia).	*Monitor therapy*
Corticosteroids (Systemic)	May enhance the immunosuppressive effect of Baricitinib.	Consider therapy modification: The use of baricitinib in combination with potent immunosuppressants is not recommended. Doses equivalent to more than 2 mg/kg or 20 mg/day of prednisone (for persons over 10 kg) administered for 2 or more weeks are considered immunosuppressive
Denosumab	May enhance the immunosuppressive effect of Denosumab.	*Consider therapy modification:* Consider the risk of serious infections versus the potential benefits of coadministration of denosumab and immunosuppressants. If combined, monitor for signs/symptoms of serious infections.
Immunosuppressants (Cytotoxic Chemotherapy)	May enhance the immunosuppressive effect of Baricitinib	*Avoid combination*
Methotrexate	May enhance the immunosuppressive effect of Baricitinib.	Consider therapy modification: Concomitant use of baricitinib with high-dose or IV methotrexate is not recommended. Use with antirheumatic doses of methotrexate is permitted, and if combined, patients should be monitored for infection.
Pretomanid	May increase the serum concentration of OAT1/3 substrates.	*Monitor therapy*
Probenecid	May increase the serum concentration of Baricitinib.	*Consider therapy modification: as per Table-4.*
Sipuleucel-T	May diminish the therapeutic effect of Sipuleucel-T.	*Consider therapy modification:* Consider reducing the dose or discontinuing the use of immunosuppressants prior to initiating sipuleucel-T therapy.
Talimogene Laherparepvec	May enhance the adverse/toxic effect of Talimogene Laherparepvec. Specifically, the risk of infection from the live, attenuated herpes simplex virus contained in talimogene laherparepvec may be increased.	*Avoid combination*
Teriflunomide	May increase the serum concentration of OAT1/3 Substrates	*Monitor therapy*
COVID-19 Vaccines	Baricitinib may diminish the therapeutic effect of COVID-19 Vaccines.	Consider therapy modification: Guidelines recommend holding baricitinib for 1 to 2 weeks after vaccine administration as permitted by the underlying disease.
Influenza Virus Vaccines	May diminish the therapeutic effect of Influenza Virus Vaccines	Consider therapy modification: Administer influenza vaccines at least 2 weeks prior to initiating immunosuppressants if possible. If vaccination occurs less than 2 weeks prior to or during therapy, revaccinate 2 to 3 months after therapy discontinued if immune competence restored.
Pneumococcal Vaccines	May diminish the therapeutic effect of Pneumococcal Vaccines.	*Monitor therapy*
Poliovirus Vaccine (Live/Trivalent/Oral)	May enhance the adverse/toxic effect of Poliovirus Vaccine (Live/Trivalent/Oral). Specifically, the risk of vaccine-associated infection may be increased. May diminish the therapeutic effect of Poliovirus Vaccine also.	*Avoid combination*
Rabies Vaccine	May diminish the therapeutic effect of Rabies Vaccine.	*Consider* therapy *modification:* Complete rabies vaccination at least 2 weeks before initiation of immunosuppressant therapy if possible. If post-exposure rabies vaccination is required during immunosuppressant therapy, administer a 5th dose of vaccine and check for rabies antibodies.
Typhoid Vaccine	May enhance the adverse/toxic effect of Typhoid Vaccine. Specifically, the risk of vaccine-associated infection may be increased. Immunosuppressants (Therapeutic Immunosuppressant Agents) may diminish the therapeutic effect of Typhoid Vaccine.	*Avoid combination*
Vaccines (Inactivated)	May diminish the therapeutic effect of Vaccines (Inactivated).	*Consider therapy modification:* Give inactivated vaccines at least 2 weeks prior to initiation of immunosuppressants when possible. Patients vaccinated less than 14 days before initiating or during therapy should be revaccinated at least 2 to 3 months after therapy is complete.
Vaccines (Live)	May enhance the adverse/toxic effect of Immunosuppressants. Specifically, the risk of vaccine-associated infection may be increased. Vaccines (Live) may diminish the therapeutic effect of Immunosuppressants	*Avoid combination*

Adverse Reactions (42-44)

The following adverse drug reactions and incidences are derived from product labeling unless otherwise specified. Reported adverse reactions are for adults only. The most common side effects associated with baricitinib include: Hepatic dysfunction (>10%); Cardiovascular: Deep vein thrombosis (2%), pulmonary embolism (2%), septic shock (2%); Genitourinary: Urinary tract infection (2%); Hematologic & oncologic: Thrombocythemia (8%) malignant neoplasm, neutropenia; Respiratory: Upper respiratory tract infection (16%), Pneumonia (3%), Tuberculosis; Infection: Infection (29%; serious infection: 1% , Herpes zoster infection (1%)); Gastrointestinal: Nausea (3%); Dermatologic: Acne vulgaris; Endocrine & metabolic: Increased HDL cholesterol, increased LDL cholesterol, increased serum cholesterol, increased serum triglycerides; Neuromuscular & skeletal: Increased creatine phosphokinase in blood.

Post-marketing safety alerts (45)

Some post marketing safety alerts related to use of baricitinib have been issued: Cardiovascular: Acute myocardial infarction (FDA Safety Alert September 1, 2021), cerebrovascular accident (FDA Safety Alert September 1, 2021), thrombosis (FDA Safety Alert September 1, 2021); Gastrointestinal: Gastrointestinal perforation; Hematologic & oncologic: Lung carcinoma (FDA Safety Alert September 1, 2021), skin carcinoma (nonmelanoma); Hypersensitivity: Angioedema, hypersensitivity reaction.

Conclusion

Alopecia areata is a chronic, immune mediated relapsing disorder causing nonscarring hair loss. Various treatment modalities, mostly topical applications are available for management of alopecia areata with inter-individual and intra- individual variations in response to treatment. Baricitinib is the first systemic oral therapy approved for alopecia areata. Patients with extensive alopecia areata, including alopecia totalis, as well as patients with more limited disease who do not respond to the above therapies can be treated with oral baricitinib. However, while prescribing baricitinib, patient should be evaluated and close monitoring is recommended due to potential drug-drug interactions and adverse effects. It is not recommended for use in combination with other JAK inhibitors, biologic immunomodulators, cyclosporine or other potent immunosuppressant. Baricitinib comes with a boxed warning for serious infections, malignancy, major adverse cardiovascular events and thrombosis. Other JAK inhibitors look promising in initial studies for alopecia areata and may become available in future.

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