Baricitinib (OLUMIANT) in Alopecia Areata
National Drug Monograph Addendum
August 2023

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA Approval Information

Description / Mechanism of Action

- Baricitinib is a Janus kinase inhibitor (JAKI) with greater potency at JAK1, JAK2 and TYK2 receptors than JAK3.[1]
- JAK1/2 and JAK1/3 signaling are involved in the autoimmune mechanism and perifollicular inflammatory response in alopecia areata (AA).[2,3]
- Previously approved for rheumatoid arthritis and COVID-19, baricitinib was granted priority review and breakthrough therapy designations by the FDA for AA and is the first agent approved for this disease.

Indication Under Review in This Document

- Treatment of adults with severe AA.
- *Limitations of Use*: Not recommended for use in combination with other JAKIs, biologic immunomodulators, cyclosporine or other potent immunosuppressants.

Dosage Regimen and Dosage Forms Under Review

- *Recommended Dose*: 2 mg orally once daily with or without food. If response is inadequate, increase to 4 mg once daily.
- For patients with nearly complete or complete scalp hair loss, with or without substantial eyelash or eyebrow hair loss: Consider treating with 4 mg once daily.
- After an adequate response is obtained with 4 mg once daily: Decrease to 2 mg once daily.
- *Dosage Forms*: 1 mg, 2 mg, and 4 mg tablets

Dosage Modifications and Interruptions in Patients with AA

- *Hematocytopenias.* Dosage interruptions are recommended in patients who have absolute lymphocyte counts < 500 cells/µL, absolute neutrophil count < 1000 cells/µL, or hemoglobin < 8 g/dL.
- *Renal Impairment.* Dosage modification is recommended for moderate renal impairment (eGFR 30 to ≤ 60 mL/min/1.73 m^2. Use of baricitinib is not recommended in severe renal impairment (eGFR < 30 mL/min/1.73 m^2.
- *Hepatic Impairment*. Dosage interruption is recommended if increases in ALT or AST occur and drug-induced liver disease is suspected. Baricitinib is not recommended for use in patients with severe hepatic impairment.

- *Strong OAT3 Inhibitors* (e.g., probenecid). Dosage reduction is recommended if the recommended daily dosage is 2 mg or 4 mg. If the recommended dose is 1 mg daily, discontinuation of probenecid should be considered.

Efficacy Considerations

- No active-controlled trials have been performed.
- A phase 2 / 3 placebo-controlled randomized clinical trial (RCT), BRAVE-AA1, and a phase 3 placebo-controlled RCT, BRAVE-AA2, showed the efficacy of baricitinib in achieving mild AA (Severity of Alopecia Tool [SALT] score of ≤ 20) in patients with severe AA (SALT score ≥ 50) at Week 36[4] and Week 52.[5]
- The phase 2 RCT BRAVE-AA1 evaluated baricitinib 1 mg, 2 mg, and 4 mg vs placebo in a separate study population and provided supportive evidence of dose-related efficacy.[5]

Phase 3 Randomized Clinical Trials

- Table 1 and Table 2 summarize the methods of the phase 3 RCTs and the baseline patient characteristics, respectively. The phase 2 results of BRAVE-AA1 were excluded from the published report.

Table 1 Methods of Phase 3 RCTs

Topic	AA1 and AA2	Long-term extension
Study Design	36-week adaptive phase 2/3 MN DB DD PC RCT with 3:2:2 randomization stratified by geographic region and duration of current episode (< 4 / ≥ 4 years) Did not analyze differences between dose groups.	Up to 200-week DB RCT Results reported for up to 52 weeks. Week-36 placebo nonresponders were rescued to baricitinib. Placebo responders remained on placebo through Week 52 (but results were not reported for placebo). Patients continued the baricitinib dose to which they were originally randomized in the 36-wk phases regardless of their Week-36 response.
Major Entry Criteria	Males 18–60 years old, females 18–70 years old, SALT score of ≥ 50, current episode of alopecia > 6 months to < 8 years without spontaneous improvement (≤ 10-point reduction in SALT score) in previous 6 months, or episodes lasting ≥ 8 years if episodes of hair regrowth were observed on the affected areas of the scalp in the previous 8 years Excluded "diffuse" pattern of AA or other forms of alopecia; inadequate response to oral JAKIs after ≥ 12 weeks of treatment; co-use of probenecid (increases exposure to baricitinib)	
Interventions	For 36 weeks: • Baricitinib 4 mg QD • Baricitinib 2 mg QD • Placebo The 4-mg dose was adjusted to 2 mg for renal impairment (eGFR ≥ 40 to < 60 mL/min/1.73 m^2) in a blinded fashion. *Allowed co-therapies*: TCS or TCNIs except on scalp, eyebrows, and eyelids; stable doses of finasteride, other 5-alpha-reductase inhibitors, oral or topical minoxidil for previous 12 mos and during study; stable doses of bimatoprost ophthalmic solution for ≥ 8 wks prior for treatment of eyelids.	For additional 16 weeks: • Baricitinib 4 mg QD • Baricitinib 2 mg QD • Placebo / Baricitinib • Placebo
Primary Efficacy Measure(s)	SALT score of ≤ 20 at Wk 36	SALT score of ≤ 20 at Wk 52

DB, Double-blind; **DD**, Double-dummy; **MN**, Multinational; PC, Placebo-controlled; **SALT**, Severity of Alopecia Tool (SALT score ranges from 0 / No scalp hair loss to 100 / Complete scalp hair loss); **TCNI**, Topical calcineurin inhibitor; **TCS**, Topical corticosteroid.

Table 2 Baseline Patient Characteristics

Characteristics	AA1 N = 654	AA2 N = 546
Age, mean, y	37.2	38.0
Male, %	41.5	36.6
White, %	46.3	58.3
Asian, %	41.2	30.9
North American, %	54.8	34.7
Time since onset, y	12.2	12.3
Duration of current episode, mean, y	3.6	4.3
Duration of current episode < 4 y, %	69.1	62.0
Duration of current episode ≥ 4 y, %	30.9	38.0
Alopecia universalis, %	43.2	44.9
Atopic background,† %	36.5	40.2
SALT score, mean	85.6	85.1
Very severe AA,‡ %	54.1	52.8
Therapy-naïve, %	10.7	7.3
Prior systemic IMM therapy, %	49.4	57.4
Corticosteroid, %	33.5	47.5
JAKI, %	5.1	4.6
Other, %	30.5	25.8
Prior systemic non-IMM therapy, %	10.0	9.2
Intralesional therapy, %	52.5	51.1
Topical non-immunotherapy, %	58.0	62.7
Topical immunotherapy, %	28.2	24.4
Phototherapy, %	16.6	16.4

IMM, Immunomodulator / immunosuppressive; **SALT**, Severity of Alopecia Tool (score range0 / No scalp hair loss to 100 / Complete scalp hair loss)

† Atopic background was defined as history of or current atopic dermatitis, allergic rhinitis, allergic conjunctivitis, or allergic asthma

‡ Very severe alopecia areata was defined as SALT score of 95–100

- Primary efficacy data are summarized in Table 3.

Table 3 SALT ≤ 20 Response at Week 36

Trial	BARI 4 mg, n/N (%)	BARI 2 mg, n/N (%)	PBO, n/N (%)	RR 4 mg (95% CI)	RR 2 mg (95% CI)	AAE 4 mg (95% CI)	AAE 2 mg (95% CI)	NNT 4 mg (95% CI)	NNT 2 mg (95% CI)	Q
AA1	109/281 (38.8)	42/184 (22.8)	12/189 (6.2)	6.1 (3.5, 10.8)	3.6 (2.0, 6.6)	326 (256, 395)	166 (95, 238)	4 (3, 4)	7 (5, 11)	L[α B]
AA2	84/234 (35.9)	30/156 (19.4)	5/156 (3.3)	11.2 (4.6, 27.0)	6.0 (2.4, 15.1)	326 (256, 396)	161 (91, 232)	4 (3, 4)	7 (5, 11)	L[α B]

AAE, Anticipated absolute effect for achieving the outcome per 1000 patients; **CFB**, Change from baseline; **NNT**, Number needed to treat for one additional patient to benefit; **Q**, GRADE quality of evidence (H = High, M = Moderate, L = Low, VL = Very low); **RR**, Relative risk

[α] Downgraded for imprecision (optimal information size not met and wide CIs).

[B] Downgraded for indirectness (not a clinical outcome).

- Secondary efficacy results

BRAVE-AA1

  - Baricitinib 4 mg was significantly better than placebo for all 10 secondary outcomes in the graphical testing (multiplicity-adjusted) testing procedure.
  - Baricitinib 2 mg failed the graphical testing procedure for SALT score of ≤ 20 at Week 16; therefore, this dose did not pass statistical testing for the Clinician Reported Outcome (ClinRO)

Measure for Eyelash Hair Loss score of 0 or 1 with a decrease from baseline to Week 36 of at least 2 points.

BRAVE-AA2

- Baricitinib 4 mg was significantly better than placebo for the first seven secondary outcomes but failed for SALT score ≤ 10 at Week 24 and the subsequent three outcomes (SALT ≤ 10 at Week 24, SALT-50 at Week 12, and SALT ≤ 20 at Week 16).
- Baricitinib 2 mg was significantly better than placebo for the first two secondary outcomes but failed for ClinRO Measure for Eyebrow Hair Loss score of 0 or 1 at Week 36 and the subsequent eight outcomes.

- Subgroup Analyses
  - Not reported.
- 52-Week Results of the Long-term Extension[5]
  - SALT ≤ 20 response rates increased from Week 36 to Week 52. In BRAVE-AA1, Week-52 responses were 40.9% of 281 patients and 21.2% of 184 patients on baricitinib 4 mg and 2 mg, respectively. The corresponding rates in BRAVE-AA2 were 36.8% of 234 patients and 24.4% of 156 patients, respectively.
  - SALT ≤ 20 response rates in patients with very severe disease (SALT 95–100) at baseline were achieved by 27.7% and 10.3% of the baricitinib 4 mg and 2 mg groups, respectively, in BRAVE-AA1, and 27.7% and 15.1%, respectively, in BRAVE-AA2.

Onset of Treatment Benefit and Duration of an Adequate Therapeutic Trial

- Onset of effects (earliest significant treatment difference) in SALT ≤ 20 response occurred at Week 16 in BRAVE-AA1 and at Week 24 in BRAVE-AA2.
- The duration of an adequate therapeutic trial (time to peak response rate) was 52 weeks on baricitinib 4 mg; however, the peak response may not have been reached in the two phase 3 trials.[5] On baricitinib 2 mg, a peak response was reached at Week 36 in BRAVE-AA1 but may not have been reached by Week 52 in BRAVE-AA2.[5]

Durability of Response

- Results not reported.

Safety Considerations

Safety Profile from US Prescribing Information

- **Boxed Warnings, Contraindications, Other Warnings and Precautions**: Same as for rheumatoid arthritis.
- **Common Adverse Events**: Overall, the adverse event profile of baricitinib in AA was similar to that seen in rheumatoid arthritis.

Safety Results from Clinical Trials

- An integrated safety analysis of the long-term extensions of the pivotal RCTs showed that overall the safety of baricitinib in AA was consistent with its previously described safety profile.[6]
- After 36 weeks of therapy, rates for discontinuations due to adverse events and serious adverse events were similar between the 4-mg and 2-mg doses of baricitinib and somewhat higher or similar between each baricitinib group and the placebo group.
- After 52 weeks of therapy in the extension phase, the rates of serious adverse events (overall range, 2.2% to 4.3%) and discontinuations due to adverse events (overall range, 2.6% to 5.6%) were higher in the

baricitinib 4-mg than the 2-mg group in both BRAVE-AA1 and BRAVE-AA2.[5] Serious infections occurred in 1.7% (4/233) and 1.3% (2/155) of patients in the baricitinib 4 mg and 2 mg groups, respectively, in BRAVE-AA2, and in no patients in BRAVE-AA1. No patients developed opportunistic infections or tuberculosis.

- An analysis of data from the RCTs showed a low incidence of adverse events of special interest (serious infections, mortality, malignancies, MACE, and venous thromboembolism) in populations with AA (1.05, 0.00, 0.31, and 0.10 per person-year of exposure, respectively).[7]

Evidence Gaps

- Health-related quality of life
- Functional ability / Disability
- Patient satisfaction

Network Meta-analyses

- No network meta-analyses that included baricitinib in AA were found.

Other Therapeutic Options

The Alopecia Areata Scale and Potential Treatments as per the National Alopecia Areata Foundation

- According to the National Alopecia Areata Foundation (Alopecia Areata - National Alopecia Areata Foundation | NAAF), the selection of treatment is partly based on the type and severity of hair loss. In clinical practice the severity of AA can be determined using the expert consensus–developed comprehensive Alopecia Areata Scale, which is initially based on the extent of scalp hair loss.[8] Mild, moderate, and severe scalp hair loss are defined as ≤ 20%, 21%–49%, and ≥ 50% scalp hair loss, respectively. Mild or moderate severity ratings are increased by one level if one or more of the following modifiers are present: negative impact on the patient's psychosocial functioning, noticeable eyebrow or eyelash hair loss, inadequate response after ≥ 6 months of treatment (selected as the definition of an adequate therapeutic trial), and diffuse or multifocal positive hair pull test (consistent with rapidly progressing hair loss). Treatments used for AA according to disease severity are as follows:
    - *Mild or Limited AA*. Intralesional glucocorticoids may be used as primary treatment for patchy hair loss or adjunctive localized treatment of more extensive hair loss. Topical glucocorticoids may be used when local injections cannot be used or are not tolerated. Topical minoxidil may be used off-label to treat hair loss often in combination with topical glucocorticoids (minoxidil monotherapy is often ineffective). Low-dose oral minoxidil has also been used off label.
    - *Moderate AA*. Topical glucocorticoids, oral minoxidil, and pulse oral or intravenous glucocorticoids may be used. Dermatologist-applied topical or contact immunotherapy with squaric acid dibutyl ester (SADBE) or diphencyprone (DPCP), which cause an allergic contact dermatitis, can alter the immune attack on hair follicles and allow hair regrowth. Oral **JAKIs** such as tofacitinib have been used for moderate AA. Dupilumab may be used as primary treatment for AA in patients with comorbid atopic dermatitis or a family history of atopic dermatitis. (However, a phase 2 placebo-controlled trial showed a nonsignificantly better Week-24 SALT-30 response rate with dupilumab 300 mg once weekly.[9] Longer open-label observational treatment with dupilumab to Week 48 improved SALT-30 response rates, suggesting that longer controlled trials may be needed to adequately assess efficacy of dupilumab.)

- *Severe AA*. A **JAKI** is considered first-line treatment for extensive AA including alopecia totalis (total loss of scalp hair) and alopecia universalis (total loss of body hair). Oral minoxidil and intralesional glucocorticoids may be used as adjunctive therapy.

Treatments Based on Society Recommendations

- The 2012 British guidelines recommended contact immunotherapy (strength of recommendation C) or a wig (strength of recommendation D) for alopecia totalis / universalis.[10] The expected hair regrowth with topical / contact immunotherapy is less than 50% of patients with severe AA. The British guideline could not recommend systemic corticosteroids and PUVA because of the potential for serious adverse effects and inadequate evidence of efficacy.
- Current evidence-based guidelines and American guidelines for the management of AA are not available. In the absence of current evidence-based guidelines, society recommendations are reviewed in this section.
- Table 4 and Table 5 summarize the recommended place in therapy of systemic treatments and the alternative systemic treatments for AA, respectively, based on the 2020 Alopecia Areata Consensus of Experts international statement,[11] 2019 Australian expert consensus statement,[12] and 2019 Italian guidelines,[13] all of which preceded the approval of baricitinib in the US.

Table 4 Potential Place in Therapy of Systemic Treatments for AA in Adults

Reference	Indication	First-line Treatment	Second-line Treatment	Third-line Treatment
2020 Alopecia Areata Consensus of Experts[11]	SALT 31%–50%, Acute AA	ILC Oral CS Oral CS + ILC		
	SALT > 50%, Acute AA	TCS Oral CS Oral CS + TCS	**JAKIs (preferred†)** Cyclosporine Methotrexate Each agent above ± systemic CS	
	SALT > 50%, Chronic AA	TCS Oral CS	**JAKIs (preferred†)** Cyclosporine Methotrexate Each agent above ± systemic CS	
2019 Australian Expert Consensus[12]	Rapid progressive hair loss, diffuse AA, or extensive AA (≥ 50% hair loss), AT, or AU	Systemic CS (oral preferred)	**Non-CS systemic treatment‡**	
		Monotherapy with TCS, topical minoxidil, or topical immunotherapy	Combination of 2 or 3 of TCS, topical minoxidil, or topical immunotherapy	**Non-CS systemic treatment‡**
	Multiple patches	ILC	**Non-CS systemic treatment‡** Topical immunotherapy	
	Solitary stable patch of > 12 months' duration	ILC	**Non-CS systemic treatment‡** Topical immunotherapy	
2019 Italian Guidelines[13]	Patchy, Active Phase	ILC and/or TCS Add short course of systemic CS only if needed to halt progression of AA		
	Severe (> 50% scalp hair loss), Active Phase	Short course of systemic CS plus TCS	Methotrexate or azathioprine if there is an inadequate response to systemic CS	

Bold blue text indicates potential place in therapy of systemic JAKIs.
AA, Alopecia areata; **AT**, Alopecia totalis; **AU**, Alopecia universalis; **CS**, Corticosteroid; **ILC**, Intralesional corticosteroid; **TCS**, Topical corticosteroid
† JAKIs would be the preferred second-line treatment if all treatments were equally reimbursed.
‡ Non-CS systemic treatments included "steroid-sparing" agents (azathioprine, cyclosporine, methotrexate) and other systemic therapies (e.g., **JAKIs**), which only had case series or retrospective studies to support potential use at the time the report was published.

Table 5 Potential Alternative Systemic Treatments for AA

Treatment†	On VANF	CFU Place in Therapy	FDA Place in Therapy	Guideline Place in Therapy	Safety Considerations	Other Considerations
JAKIs						
Tofacitinib 5–10 mg BID	No	NA in AA CFU in AS, PsA, RA, UC	Off label	"Other systemic therapy" Active or chronic patchy AA, AT, or AU JAKIs would be the preferred second-line agent if all treatments were equally reimbursed.[12]	Limited safety data in patients with AA. Safety profile is similar to that of baricitinib. Involvement of a dermatologist experienced with prescribing JAKIs is recommended	Supported by case series,[14,15,16] a small, retrospective study,[17] a small OL OS,[18] and a small OL ACT, which used a dosage of 5 mg BID.[19] Experts agree that JAKIs can be used as monotherapy or with systemic corticosteroids.[11]
Ruxolitinib	Yes, PA-F	NA in AA CFU in myelofibrosis and polycythemia vera	Off label	"Other systemic therapy" Active or chronic AA	Limited safety data in patients with AA. Thrombocytopenia, anemia, neutropenia, infections, NMSC, HLD, MACE, thrombosis, malignancies, DDIs. Involvement of a dermatologist experienced with prescribing JAKIs is recommended	Supported by small studies: an NIH OL OS[20] and an OL ACT, which used a dosage of 20 mg BID for 3–6 mos.[19] Produced shorter duration of initial hair growth than tofacitinib (4.2 vs 7.1 wks, respectively).[19] Topical ruxolitinib cream 1.5% was ineffective in a PCT.[21]
Glucocorticoids						
Prednisone / Prednisolone 50 mg QD or equivalent tapered over 4–6 wks Triamcinolone acetonide 40 mg IM every 15 days, tapered over 6–12 wks	Yes	NA	Off-label	First-line, short-term therapy for patients with trichoscopically active severe AA to temporarily stop progression, especially in rapidly progressing disease.[12,13] Active patchy AA.[13]	Treatment is limited by risks of known GC-related harms and disease recurrence upon cessation of therapy.	No consensus on dosage regimen and duration of therapy.[12] Treatment may need to be tapered off over ≥ 12 wks to achieve durable remission.[11] A small PCT in 43 patients with severe AA (≥ 40% scalp hair loss or > 10 scalp and body patches) showed efficacy in hair regrowth response rates with pulse prednisolone 200 mg PO QW for 3 mos.[22]

Treatment†	On VANF	CFU Place in Therapy	FDA Place in Therapy	Guideline Place in Therapy	Safety Considerations	Other Considerations
				First-line for acute, severe AA with SALT score ≥ 50. (Topical corticosteroids are also first-line options.)[11]		
Conventional Immunomodulators						
Azathioprine	Yes	NA	Off label	2nd-line alone or with glucocorticoids Active severe AA	Malignancy, cytopenias, serious infections, diarrhea, elevated ALT/AST, pancreatitis, TPMT-based dosage adjustments	No consensus on appropriate use.[11] An OL RCT of 50 patients with AA involving > 10% scalp hair loss showed that pulse azathioprine therapy (300 mg weekly) was similar to pulse betamethasone (5 mg 2 consecutive days per week) in hair regrowth and was associated with fewer adverse events.[23]
Cyclosporine 3–5 mg/kg/d for maximum of 6–12 months	Yes	NA	Off label	2nd-line alone or with glucocorticoids	Avoided because long-term use is limited by potential for serious adverse events such as nephrotoxicity and HTN. Multiple DDIs	A small (32-patient) PCT evaluating cyclosporine 4 mg/kg/d for 3 mos in moderate–severe AA showed nonsignificantly better SALT-50 response.[24]
Methotrexate 10–25 mg weekly or target dose of 15–20 mg weekly	Yes	NA	Off label	2nd-line alone or with corticosteroids. Active severe AA	Hematologic, renal, liver, and pulmonary toxicity Methotrexate toxicity from DDIs Evaluation for liver toxicity may require liver biopsy	A small, two-step PC RCT in France suggested that MTX was similar to placebo in achieving complete / near complete hair regrowth (SALT ≤ 10%) in patients with AT or AU.§[25] An SRMA of 14 ROSs and 1 POS of methotrexate in children and adults with AA showed good response in 63% of patients and complete response in 36%.[26]

Sources: 11,12,13

AA, Alopecia areata; **ACT**, Active-controlled (randomized) trial; **AT**, Alopecia totalis; **AU**, Alopecia universalis; **BW**, Boxed warning; **CFB**, Change from baseline; **CFU**, Criteria for Use; **DDI**, Drug-drug interactions; **HI**, Hepatic impairment; **HLD**, Hyperlipidemia; **IST**, Immunosuppressive therapy; **MTX**, Methotrexate; **NA**, Not applicable; **NIH**, National Institutes of Health; **OL**, Open-label; **OS**, Observational study; **PBO**, Placebo; **PCT**, Placebo-controlled (randomized) trial; **POS**, Prospective observational study; **QE**, Quality of evidence; **RI**, Renal impairment; **ROS**, Retrospective observational study; **SRMA**, Systematic review / meta-analysis; **WP**, Warnings and precautions

† Dose is shown if it was mentioned in guidelines.

§ This was a multicenter, double-blind RCT with rerandomization of inadequate responders (<25% hair regrowth at Month 6) to methotrexate + prednisone or methotrexate + PBO. Methotrexate alone was NSD from PBO in complete/near complete hair regrowth (cHR; SALT ≤ 10) at Month 12 (primary outcome): 2.2% (1/45) vs 0% (0/44), respectively. Pooled results showed global hair regrowth of > 10% (SALT ≤ 90), including cHR, at Month 12 in 20% (7/35; 95% CI 8.4, 37.0) on methotrexate alone (methotrexate or methotrexate + placebo), 60% (21/35; 95% CI 42.1, 76.1) on methotrexate x 6 or 12 months + prednisone from Months 6–12, and 11.1% (1/9) on PBO. cHR was achieved in 31.2% (5/16; 95% CI 11.0, 58.7) on methotrexate x 12 months + prednisone from Months 6–12. Total SKINDEX and total SCALPDEX quality-of-life measures showed significantly better improvements in responders vs nonresponders. There was no significant responder-vs-nonresponder difference in Dermatology Life Quality Index. No quality of life data were given by treatment group. A total of 30 patients (33.7%) dropped out mostly because of inefficacy, 10 and 7 patients on methotrexate in the first and second 6 months of treatment, respectively (6 and 2 patients, respectively, on PBO). All were counted as nonresponders for the primary outcome. However, 1 patient who achieved cHR at Month 9 and could not be evaluated at Month 12 was included in the pooled global hair regrowth counts rather than being counted as a nonresponder for the Month-12 endpoint. GRADE quality of evidence was very low (risks of selection and reporting biases, indirectness, imprecision). The RCT did not evaluate whether methotrexate + prednisone is better than prednisone alone, and whether methotrexate could maintain responses achieved with initial tapering of prednisone therapy (from Months 0–6), the more likely real-world scenario.

- According to the 2019 Australian expert consensus statement,[12] there is no standard indication for initiation of systemic therapy for AA. However, disease affecting more than 15% to 20% of the scalp (95–130 cm^2) generally requires systemic therapy.[12] Other potential indications for systemic therapy include
    - rapid hair loss likely to lead to ≥ 50% hair loss;
    - diffuse AA;
    - extensive AA (≥ 50% scalp hair loss), alopecia totalis, or alopecia universalis;
    - chronic disease;
    - severe distress;
    - failure of multiple hair-loss patches to respond to a 6-month trial of topical or serial intralesional glucocorticoids given every 4–6 weeks (where *failure* refers to medically unfeasible, inadequate response or intolerance); or
    - failure of solitary, stable hair-loss patches of > 12 months' duration to respond to intralesional glucocorticoid injections every 4–6 weeks.
- The AA Consensus of Experts advise discontinuing systemic treatment for reasons that include (1) when complete regrowth has been achieved and maintained for 6 months; (2) when regrowth can be managed with topical agents; or (3) after 6 months if vellus hair regrows without conversion to terminal hair.[11]

Projected Place in Therapy

- **Epidemiology and Prevalence of AA**. AA is a common chronic relapsing inflammatory disorder that affects hair follicles and less often the nails. In a US population, it has an estimated lifetime risk of 2.1% and a prevalence of 0.1% to 0.2% in the general population.[27,28] AA is considered to be an autoimmune disease etiologically related to loss of the immunologic privilege of hair follicles that normally protects against T-cell immune surveillance. It is commonly associated with other immune-mediated diseases such as atopic dermatitis.[10] The immunologic T-cell attack on hair follicles results in nonscarring hair loss that is often acute in onset and varies in extent from small patches to complete loss of scalp and/or body hair. AA can cause significant physical disability (e.g., due to loss of eyelashes or severe nail disease), psychosocial effects such as depression and anxiety, and decreased quality of life.[29]
- **Potential Place in Therapy Based on the Evidence**. No active-controlled trials with baricitinib were available to inform place in therapy and there were no network meta-analyses to inform its comparative balance of

efficacy, safety, and tolerability. Evidence from two placebo-controlled trials supports the use of baricitinib in patients aged 18–60 years for males or 18–70 years for females with severe AA (≥ 50% scalp hair loss) and a current episode of alopecia > 6 months to < 8 years without spontaneous improvement (≤ 10-point reduction in SALT score) in the previous 6 months, or episodes lasting ≥ 8 years if episodes of hair regrowth were observed on the affected areas of the scalp in the previous 8 years. Patients were primarily prior treatment-exposed and did not necessarily experience an inadequate response or intolerance to previous therapy. About 50% had prior exposure to systemic corticosteroid or nonsteroidal immunomodulators, and more than 50% of patients had received intralesional therapy. Overall, 36-week SALT ≤ 20 response benefits with baricitinib relative to placebo were small to moderate, and treatment effects were greater and more consistent on baricitinib 4 mg than 2 mg. Remarkably, about 28% of patients with very severe disease (SALT score of 95–100) achieved SALT ≤ 20 with baricitinib. Although responses increased from 36 weeks to 52 weeks with continued therapy especially with the 4-mg dose, the ability of baricitinib to maintain response and durability of response were not evaluated. Longer term safety beyond 52 weeks is also uncertain. The clinical relevance (e.g., patient health-related quality of life or physical or psychosocial functioning) of the achieved hair regrowth is uncertain, and measures of anxiety and depression have not been reported to date. Without these quality of life and functional ability data, there is low certainty of clinical benefits. The effects of baricitinib are uncertain in patients with moderate scalp hair loss who can be classified as severe based on the presence of modifying factors using the Alopecia Areata Scale. The main advantage of baricitinib over other systemic treatments is the availability of evidence of efficacy and acceptable safety from two large, well-designed RCTs and a dose-comparative phase 2 RCT. The hair regrowth effect size and appropriate dosage with baricitinib are known, whereas the benefits, harms, and optimal dosages of other systemic treatments are uncertain because of inadequate evidence. Although systemic corticosteroids are suggested as first-line therapy for severe AA especially for rapidly progressing disease, their efficacy has not been adequately evaluated and they are unsuitable for long-term therapy. In contrast, the FDA labeling for baricitinib allows first-line use for severe AA and places no restrictions on the duration of therapy. A disadvantage of baricitinib is its cost, which greatly exceeds those of systemic steroidal and nonsteroidal immunomodulatory drugs.

- **Potential Place in Therapy in VHA**. Baricitinib may be used in patients with severe AA (≥ 50% scalp hair loss). Patients should have tried and had intolerance or an inadequate response to a **systemic corticosteroid** unless it is medically inadvisable. Based on limited available data, baricitinib should not be used in patients with severe AA who had no hair regrowth with previous systemic JAKI therapy since it is likely to be ineffective.[30]

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