# Characterizing Lipid Changes and Use of Lipid-Lowering Medications in Patients With Alopecia Areata Treated With Baricitinib: Integrated Results From the BRAVE-AA1 and -AA2 Clinical Trials

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## OBJECTIVE

- To characterize changes in lipid levels and use of lipid-lowering medication among patients with severe AA treated with baricitinib to a maximum exposure of 4 years using pooled data from BRAVE-AA1 and BRAVE-AA2

## CONCLUSIONS

- Lipid levels can be elevated for a variety of reasons in patients with AA independent of JAK inhibitor therapy as illustrated by the prevalence of elevated baseline lipids
- The majority of patients with baseline hypercholesterolemia or elevated lipids during the trial were not on lipid-lowering medications, suggesting undertreatment
- Elevation of lipids during baricitinib treatment is consistent with a class effect for JAK inhibitors and is largely characterized by elevated LDL-C and HDL-C, and not triglycerides[2-4]
- The mean magnitude of lipid elevation observed with baricitinib is modest (eg, 10-12 mg/dL for LDL-C)
- There were no discontinuations due to lipid elevations
- Lipid monitoring, as indicated by product labeling for JAK inhibitors, may help identify patients requiring management per lipid guidelines prior to or associated with JAK inhibitor therapy


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## BACKGROUND

- The chronic nature of AA underscores the importance of understanding the long-term safety of indicated treatments
- The efficacy and safety profile of baricitinib in patients with severe AA has been reported through at least 104 weeks of follow-up in the BRAVE-AA1 (NCT03570749) and BRAVE-AA2 (NCT03899259) randomized, double-blind, placebo-controlled trials[1]
  - Elevations in total cholesterol, LDL-C, and HDL-C, but not triglycerides, were observed[1]
- Increases in lipid parameters are considered a class effect of JAK inhibitors[2-4]

## KEY RESULTS

### Incidence of Shifts to Higher Lipid-Level Categories Was Low With Baricitinib Treatment

- The IR for category shift to ≥"borderline high" LDL-C (≥130 mg/dL) in baricitinib-treated patients was consistent with that reported in the previous safety update[1]
- The IR for patients who experienced a category increase to "very high" triglycerides (≥500 mg/dL) remained low and was the same across groups

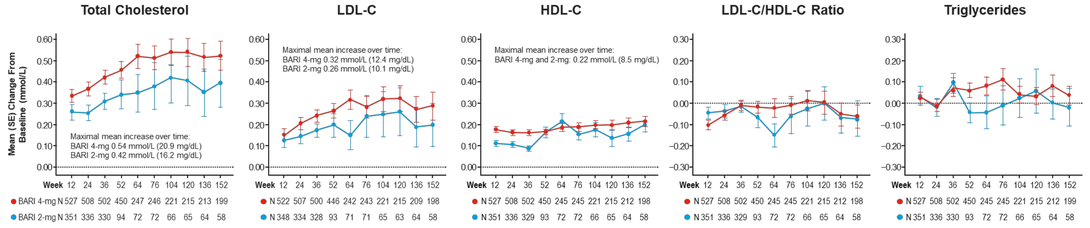
### IRs of Treatment-Emergent Increases in Lipid Parameters (Observed)[5]

| Category Shift, n (IR) | Extended BARI AA | | All-BARI AA |
|---|---|---|---|
| | BARI 2-mg (N=383) | BARI 4-mg (N=565) | All BARI Doses (N=1303) |
| **Total cholesterol ≥240 mg/dL (≥6.21 mmol/L)[a] (high NCEP criteria)** | 63 (12.0) | 153 (13.8) | 329 (11.8) |
| **LDL-C ≥130 mg/dL (≥3.36 mmol/L)[a] (≥borderline high NCEP criteria)** | 80 (15.3) | 170 (15.4) | 372 (13.3) |
| **HDL-C ≥60 mg/dL (≥1.55 mmol/L)[a] (high NCEP criteria)** | 90 (17.2) | 168 (15.2) | 360 (12.9) |
| **Triglycerides ≥500 mg/dL (≥5.65 mmol/L)[a] (very high NCEP criteria)** | 3 (0.6) | 7 (0.6) | 16 (0.6) |

[a]To convert mmol/L to mg/dL, total cholesterol, LDL-C, and HDL-C were multiplied by 38.67 and triglycerides by 88.57.
Notes: IRs were calculated per 100 patient-years. Lipid laboratory parameters include patients that shifted from baseline to the new category, the criterion for inclusion was having a single time point change to the new grade/range post baseline.

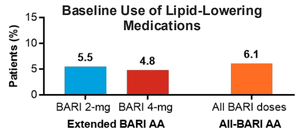
### Extended BARI AA: Mean Changes From Baseline in Lipid Levels Were Low and Stabilized Over Time

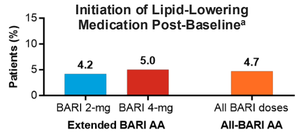
- No patients discontinued baricitinib therapy due to TEAEs related to hyperlipidemia




### Use of Lipid-Lowering Medications Was Low at Baseline and Remained Low During the Study

- 79 patients (6.1%) in All-BARI AA reported use of lipid-lowering medications at baseline, and of these, 65% discontinued these medications post-baseline (n=51 [3.9%; IR=2.1])
- 61 patients (4.7%; IR=2.2) in All-BARI AA initiated lipid-lowering medication post- baseline




[a]Among patients not on lipid-lowering medications prior to first dose of study treatment.
Notes: Use of statins for the treatment of AA within 4 weeks of randomization or during the study was an exclusion criterion. Percentage is calculated based on subject and treatment reported in safety population; Based on Cardiovascular System ATC2 code C10 Lipid Modifying Agents: atorvastatin, atorvastatin + amlodipine, colestipol, colesevelam, cholestyramine, evolocumab, ezetimibe, ezetimibe + rosuvastatin, lovastatin, pravastatin, rosuvastatin, rosuvastatin + amlodipine + telmisartan, and simvastatin.

## Methods

### Study Design

**Phase 2/3 BRAVE-AA1 and Phase 3 BRAVE-AA2 trials:**

- **36-Week, Double-Blind, Placebo-Controlled Period** (completed)
  - Randomization to placebo, baricitinib 1-mg (Phase 2 cohort only), 2-mg, and 4-mg
- **68-Week Long-Term Extension Period** (Week 36 to Week 104; completed)
  - Included a randomized withdrawal (BRAVE-AA1) or randomized down-titration (BRAVE-AA2) of baricitinib
- **Bridging Extension Period** (began at Week 104; ongoing)
  - Up to 96 additional weeks of treatment

### Eligibility Criteria

**Key Inclusion Criteria**

- Males (18-60 years) and females (18-70 years)[a]
- Severe AA as defined by a SALT score ≥50 (≥50% scalp hair loss)
- Current AA episode lasting >6 months to <8 years[b] without spontaneous improvement (≤10-point reduction in SALT score) in the 6 months before screening

**Key Exclusion Criteria**

- Use of HMG-CoA reductase inhibitors (statins) for the treatment of AA within 4 weeks before randomization or during the study[c]

[a]Different upper age limits included for male and female patients based on the difference in prevalence of concomitant androgenetic alopecia; [b]Patients who had AA for ≥8 years could be enrolled if episodes of regrowth (spontaneous or under treatment) had been observed on the affected areas over the past 8 years; [c]Use of HMG-CoA reductase inhibitors for the treatment of hypercholesteremia and the prevention of cardiovascular disease was permitted during the study.


**References**

1. Senna M, et al. *J Eur Acad Dermatol Venereol.* 2024;38:583-593. 2. Olumiant (baricitinib) [US Package Insert]. Indianapolis, IN: Eli Lilly and Company, 2022. 3. Xeljanz (tofacitinib) [US Package Insert]. New York, NY: Pfizer, 2018. 4. Rinvoq (upadacitinib) [US Package Insert]. North Chicago, IL: AbbVie, 2022. 5. Expert Panel on Detection Evaluation and Treatment of High Blood Cholesterol in Adults. *JAMA.* 2001;285:2486-2497.


**Abbreviations**

*AA=alopecia areata; ASCVD=arteriosclerotic cardiovascular disease; BARI=baricitinib; BMI=body mass index; HDL-C=high-density lipoprotein-cholesterol; HMG-CoA reductase=3-hydroxy-3-methyl-glutaryl-coenzyme A reductase; IR=incidence rate; JAK=Janus kinase; LDL-C=low-density lipoprotein cholesterol; N=number of patients in the analysis population; n=number of patients in the specified category; NCEP=National Cholesterol Education Program; NEC=not elsewhere classified; PYE=patient-years of exposure; SALT=Severity of Alopecia Tool; SD=standard deviation; SE=standard error; TEAE=treatment-emergent adverse event; vLDL=very low-density lipoprotein; VTE=venous thromboembolism*

### Lipid Assessments and Analyses

**Laboratory Evaluations**

- Assessment of lipids was performed at baseline and every 12 to 28 weeks
  - Patients were instructed not to eat or drink anything except water for 8 hours before sample collection
  - If patients attended the visit in a non-fasting state, samples were nonetheless collected for evaluation
- Clinical laboratory tests were performed for total cholesterol, LDL-C, HDL-C, and triglycerides
- Permanent or temporary discontinuation of study drug was not required for patients with laboratory changes in lipids

**Lipid-Lowering Medication Use**

- Use of lipid-lowering agents was identified from "prior therapy" (ie, baseline use) and "concomitant therapy" (ie, post-baseline use) in the BRAVE-AA1 and -AA2 clinical trial database
- All terms were reviewed by an Eli Lilly lipidologist blinded to study treatment

### Statistical Analysis

**Treatment-Emergent Changes in Lipid Parameters**

- Two integrated datasets from BRAVE-AA1 (data cutoff: May 22, 2023) and BRAVE-AA2 (data cutoff: May 08, 2023) were analyzed:
  - **Extended BARI AA:** Patients treated with continuous baricitinib 2-mg or 4-mg from baseline to the data cutoff in the long-term extension and bridging extension periods, with data censored at dose or treatment change
  - **All-BARI AA:** All available data during baricitinib exposure for all patients who received ≥1 dose of baricitinib (1-mg, 2-mg, or 4-mg) at any time from randomization or switch from placebo, up to 30 days after the last dose of baricitinib
- Mean change from baseline in lipid parameters is based on observed data
- IRs per 100 patient-years calculated based on time at risk for patients experiencing an event

## Results

### Baseline Demographics and Disease Characteristics

- In All-BARI AA, 1303 patients received ≥1 dose of baricitinib, reflecting 2789.7 PYE (median 2.3 years, maximum 4 years)
- Approximately 43% of patients had hypercholesterolemia at baseline

| | Extended BARI AA | | All-BARI AA |
|---|---|---|---|
| | BARI 2-mg (N=383) | BARI 4-mg (N=565) | All BARI Doses (N=1303) |
| **Age, years** | 38.4 (13.0) | 37.0 (13.0) | 37.5 (12.9) |
| **<40** | 210 (54.8) | 339 (60.0) | 757 (58.1) |
| **≥40** | 173 (45.2) | 226 (40.0) | 546 (41.9) |
| **≥65** | 13 (3.4) | 11 (1.9) | 30 (2.3) |
| **Female, n (%)** | 241 (62.9) | 350 (61.9) | 804 (61.7) |
| **Duration since AA onset, years** | 12.5 (10.9) | 11.7 (10.9) | 12.2 (10.9) |
| **Duration of current AA episode, years** | 4.1 (5.3) | 3.7 (3.3) | 3.9 (4.3) |
| **SALT score** | 86.1 (18.2) | 85.1 (18.0) | 85.8 (17.8) |
| **SALT score, median** | 99.0 | 95.0 | 97.0 |
| **Atopic background,[a] n (%)** | 147 (38.4) | 198 (35.0) | 494 (37.9) |
| **BMI, kg/m²** | 25.9 (5.3) | 26.2 (5.3) | 26.2 (5.5) |
| **BMI ≥30 kg/m², n (%)** | 71 (18.5) | 115 (20.4) | 265 (20.4) |
| **Current smoker, n (%)** | 70 (18.3) | 96 (17.0) | 222 (17.0) |
| **Hypercholesterolemia,[b] n (%)** | 162 (42.3) | 233 (41.2) | 556 (42.7) |
| **Hypertension, n (%)** | 41 (10.7) | 59 (10.4) | 145 (11.1) |
| **Diabetes mellitus, n (%)** | 11 (2.9) | 16 (2.8) | 40 (3.1) |
| **Having ≥1 of 5 VTE risk factors,[c] n (%)** | 135 (35.2) | 178 (31.5) | 436 (33.5) |

[a]Defined as medical history of or ongoing atopic dermatitis, or allergic rhinitis, or allergic conjunctivitis, or allergic asthma; [b]Defined as baseline total cholesterol ≥200 mg/dL or LDL-C ≥130 mg/dL, or preferred terms of "blood cholesterol abnormal, blood cholesterol increased, LDL abnormal, LDL increased, vLDL abnormal, vLDL increased, LDL-C/HDL-C ratio increased, total cholesterol/HDL-C ratio increase, total cholesterol/HDL-C ratio abnormal, lipids abnormal"; high-level terms of "elevated cholesterol, hyperlipidemias NEC"; [c]Current smoker, hypertension, HDL-C <40 mg/dL, diabetes mellitus, ASCVD (defined by medical history of myocardial infarction, coronary artery bypass, stroke, transient ischemic attack, or peripheral vascular disease). Note: Data are presented as mean (SD) unless stated otherwise.


**Disclosures**

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