

Effect of Upadacitinib on Biomarkers of Systemic Inflammation in Patients with Moderate-to-Severe Atopic Dermatitis

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OBJECTIVE

To evaluate changes in biomarkers of systemic inflammation, including high-sensitivity C-reactive protein (Hs-CRP), absolute eosinophil count (AEC), and selected protein mediators from the Olink cardiovascular panel, in patients with moderate-to-severe atopic dermatitis (AD) treated with upadacitinib (UPA)

CONCLUSIONS

Treatment with UPA in moderate-to-severe AD was associated with reductions in Hs-CRP, AEC and decreases across multiple proteins on the Olink cardiovascular panel

Reductions in markers of systemic inflammation were rapid and sustained

Further research may be warranted to assess the long-term impact and clinical relevance of UPA's effects on systemic inflammation

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SYNOPSIS

- Moderate-to-severe AD is a chronic inflammatory skin disease associated with systemic inflammation¹
- High-sensitivity C-reactive protein (Hs-CRP) is a blood biomarker for systemic inflammation and is sensitive to low-grade inflammation; Hs-CRP is frequently elevated in moderate-to-severe AD and correlates with disease severity^{2,3}
- Absolute eosinophil count (AEC), which is often elevated in AD, is associated with increased inflammatory markers and cytokine activation^{4,5}
- The Janus kinase (JAK)/signal transducer and activator of transcription (STAT) signaling pathway involves multiple cytokines and is a key mediator of immune and inflammatory responses⁶
- UPA is a selective JAK-1 inhibitor approved for use in multiple chronic immune-mediated systemic inflammatory disorders, including rheumatoid arthritis, atopic dermatitis, psoriatic arthritis, ankylosing spondylitis, inflammatory bowel disease, and giant cell arteritis⁷
- Limited data exist on how UPA impacts markers of systemic inflammation in patients with moderate-to-severe AD

METHODS

- Biomarker data were analyzed from the Heads Up study (NCT03738397), in which UPA 30mg was compared to dupilumab (DUPI) 300mg, as well as from the monotherapy Phase 3 trials Measure Up 1 (NCT03569293) and Measure Up 2 (NCT03607422)
- In Heads Up, 672 patients were assessed, with an optional biomarker cohort consisting of 116 patients in the UPA 30mg group and 118 patients in the DUPI 300mg group who provided serum samples for Olink analysis
- Select serum biomarkers, Hs-CRP and AEC, were measured at baseline and weeks 2, 4, 8, 12, and 16
 - A certified immunochemiluminometric assay was used to measure Hs-CRP; AEC was assessed from blood samples

RESULTS

- In the integrated Measure Up studies and the Heads Up study, UPA-treated patients demonstrated significant reduction of Hs-CRP from baseline to week 16 (Figure 1)
- In the integrated Measure Up studies, UPA 15mg and UPA 30mg groups showed statistically significant reductions in mean Hs-CRP (Figure 2) and AEC (Figure 3) versus placebo as early as week 2 and sustained through week 16
- In Heads Up, UPA 30mg showed greater reductions in mean Hs-CRP (Figure 4) and AEC (Figure 5) than DUPI; these differences were statistically significant at most visits, including week 16
- In the Heads-Up study, serum proteins measured with the Olink cardiovascular panel were significantly decreased from baseline in patients treated with UPA 30mg (Figure 6)
- Limitations: exploratory, observed-case analyses with short follow-up and a smaller biomarker subgroup; nominal p-values (no multiplicity adjustment); findings were descriptive and hypothesis-generating

Figure 1. Hs-CRP Reduction from Baseline at Week 16 with UPA

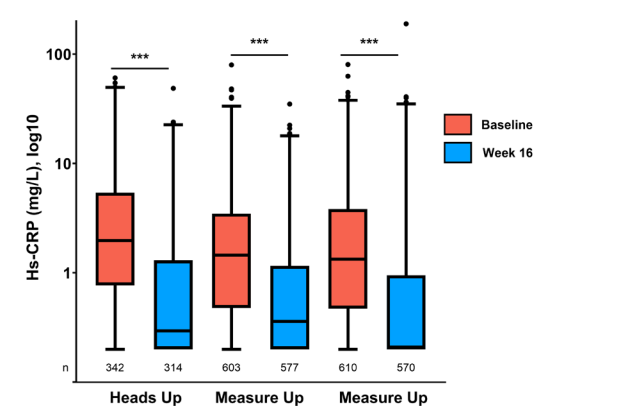
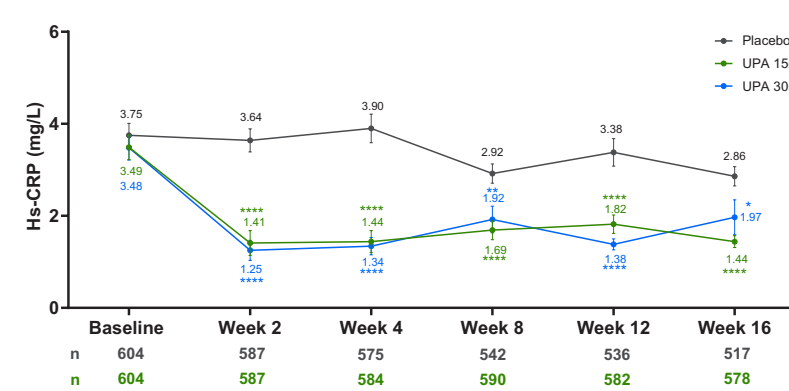
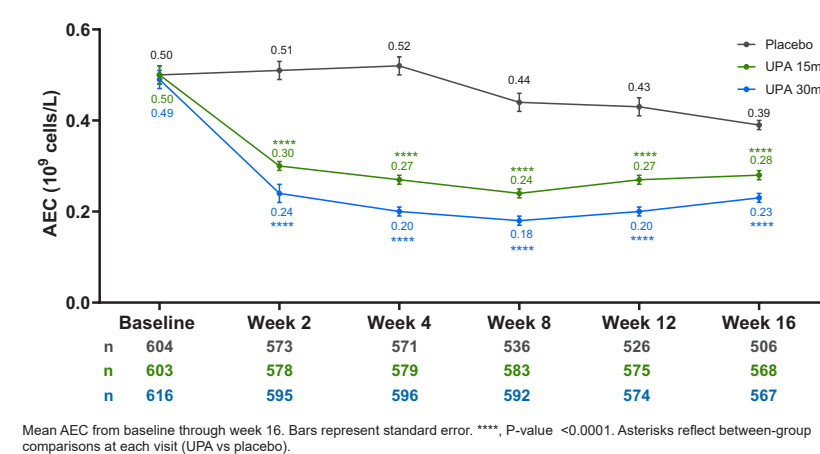


Figure 2. Hs-CRP is Reduced in UPA-Treated Patients in Measure Up



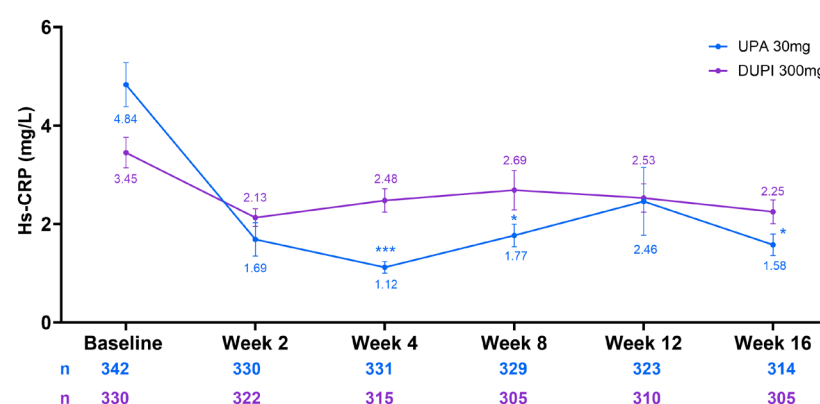
Mean Hs-CRP from baseline through week 16. Bars represent standard error. *, P-value <0.05; **, P-value <0.01; ***, P-value <0.0001. Asterisks reflect between-group comparisons at each visit (UPA vs placebo).

Figure 3. AECs are Reduced in UPA-Treated Patients in Measure Up



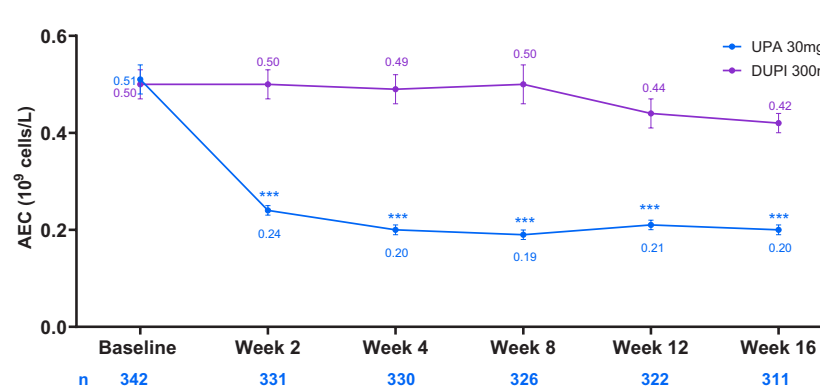
Mean AEC from baseline through week 16. Bars represent standard error. ***, P-value <0.0001. Asterisks reflect between-group comparisons at each visit (UPA vs placebo).

Figure 4. Hs-CRP is Reduced in UPA-Treated Patients in Heads Up



Mean Hs-CRP from baseline through week 16. Bars represent standard error. *, P-value <0.05; **, P-value <0.001. Asterisks reflect between-group comparisons at each visit (UPA 30mg vs DUPI 300mg).

Figure 5. AECs are Reduced in UPA-Treated Patients in Heads Up



Mean AEC from baseline through week 16. Bars represent standard error. ***, P-value <0.001. Asterisks reflect between-group comparisons at each visit (UPA 30mg vs DUPI 300mg).

METHODS CONT.

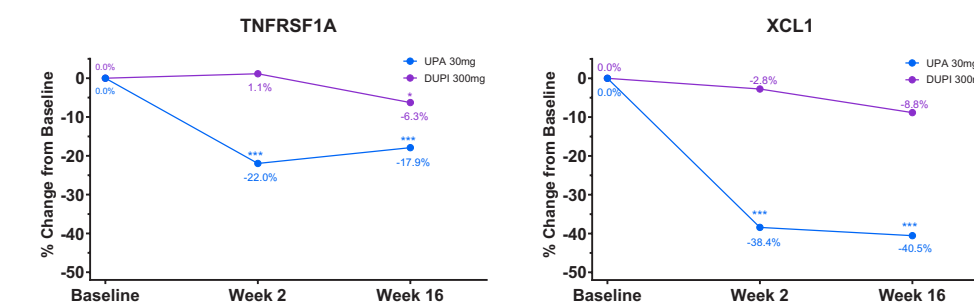
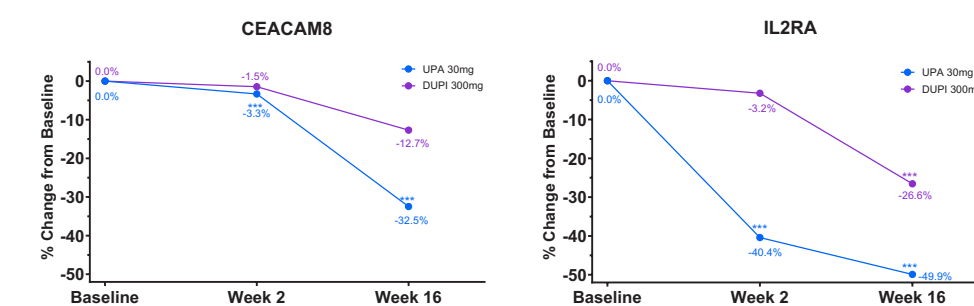
- Select proteins associated with cardiovascular inflammation were profiled from the Olink Cardiovascular II/III panels, including CEACAM8, IL2RA, LGALS3, MMP3, TNFRSF1A, and XCL1 (Table 1)
- Between-group, visit-wise comparisons of Hs-CRP and AEC used Analysis of Covariance (ANCOVA) with baseline as a covariate
- Within-group Hs-CRP change from baseline used paired t-tests
- Olink percent changes were analyzed via paired Normalized Protein eXpression (log2) analyses with false discovery rate (FDR)-adjusted q-values

Table 1. Biomarkers Included in Olink Serum Protein Analysis

Biomarker	Gene Name	Description
CEACAM8	Carcinoembryonic antigen-related cell adhesion molecule 8	Cell surface glycoprotein that plays a role in cell adhesion in a calcium-independent manner
IL2RA	Interleukin-2 receptor subunit alpha	Involved in regulation of immune tolerance by controlling regulatory T cells
LGALS3	Galectin-3	Galactose-specific lectin which binds Immunoglobulin E
MMP3	Stromelysin-1	Can degrade fibronectin; laminin; gelatins of type I, III, IV, and V; collagens III, IV, X, and IX; and cartilage proteoglycans
TNFRSF1A	Tumor necrosis factor receptor superfamily member 1A	Receptor for TNFSF2/TNF-alpha and homotrimeric TNFSF1/lymphotoxin-alpha
XCL1	Lymphotactin	Chemotactic activity for lymphocytes but not for monocytes or neutrophils

Descriptions provided from Olink cardiovascular II/III panel biomarker list. Abbreviations: TNF, tumor necrosis factor; TNFSF, tumor necrosis factor superfamily.

Figure 6. Proteins from the Olink Cardiovascular Panel were Decreased from Baseline in UPA-Treated Patients in Heads Up



Percent change from baseline in proteins associated with inflammation and cardiovascular risk from the Olink cardiovascular II/III panel. *, Adjusted P-value <0.05; **, Adjusted P-value <0.01; ***, Adjusted P-value <0.001. Asterisks reflect within-group percent change from baseline.