Vitiligo biomarker CXCL10 correlates with clinical response in the phase 2 randomized, double-blind, vehicle-controlled TRuE-V mechanism of action study

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Introduction/Background: Ruxolitinib cream is a topical formulation of the selective Janus kinase (JAK) 1/JAK2 inhibitor ruxolitinib and is the first and only repigmentation treatment approved by the US Food and Drug Administration and European Commission for nonsegmental vitiligo in patients ≥12 years old.

Objectives: To evaluate treatment-associated changes in biomarkers among patients with vitiligo, correlate changes in key biomarkers with efficacy, and assess the safety and tolerability of ruxolitinib cream.
**Methods:** The phase 2, randomized, double-blind, vehicle-controlled TRuE-V mechanism of action study (NCT04896385) was conducted in adult patients (≥18 years) with vitiligo ≤50% of total body surface area. Patients were randomized 2:1 to twice-daily 1.5% ruxolitinib cream or vehicle cream for 24 weeks, after which all patients could apply 1.5% ruxolitinib cream through Week 52. Changes from baseline in local and systemic immune biomarkers, including C-X-C motif chemokine ligand 10 (CXCL10), were evaluated at Weeks 4, 12, and 24. The relative expression of >3000 serum protein analytes was assessed using the Olink Explore platform, and a validated Meso Scale Discovery (MSD) assay was used to confirm absolute levels of serum CXCL10. Relative CXCL10 expression was determined by quantitative polymerase chain reaction (qPCR) from isolated biopsy samples. Punch biopsies (2.5 mm) were taken from lesional and nonlesional skin at baseline and lesional skin (even if the lesion had cleared) at Weeks 12, 24, and 40. Treatment efficacy was determined by the percentage change from baseline in facial and total Vitiligo Area Scoring Index (F-VASI and T-VASI, respectively). Safety was evaluated by the frequency and severity of adverse events.

**Results:** The study enrolled 60 patients (ruxolitinib cream, n=41; vehicle, n=19). Patients’ mean (SD) age was 44.7 (12.8) years, 56.7% were male, and 53.3% had lighter skin (Fitzpatrick skin types I–III). At baseline, patients had a median (range) disease duration of 12.0 (0.1–52.9) years and mean (SD) F-VASI and T-VASI scores of 1.1 (0.6) and 12.1 (9.4), respectively. Olink Explore identified few differentially expressed proteins in patient sera (adjusted \( P<0.05 \) and log2 fold change >1.25), including CXCL10, SH2D1A, and granzyme B. As early as Week 12, serum CXCL10 levels (in MSD assay) were significantly reduced in ruxolitinib cream–treated patients compared with baseline. Skin CXCL10 levels were similar in lesional and nonlesional skin at baseline but were significantly lowered in lesional skin at Week 12 with ruxolitinib cream. In
ruxolitinib cream–treated patients, significant mean [SD] percentage reductions from baseline were seen in F-VASI scores at Week 12 (−32.9 [33.6]) and in T-VASI scores at Week 24 (−21.2 [18.5]). Further, T-VASI scores significantly correlated with a change in serum CXCL10 levels between baseline and Week 24. Most systemic proteins did not correlate or only weakly correlated with F-VASI and T-VASI scores. Through Week 24, 46.3% of 41 patients who applied ruxolitinib cream reported treatment-emergent adverse events (none serious), the most common being COVID-19 (9.8%), application site acne (4.9%), and application site rash (4.9%).

**Conclusions:** Taken together, these data are consistent with the role of the interferon-gamma:CXCL10 axis as a central mediator of vitiligo pathogenesis. Serum CXCL10 levels decreased significantly in patients who applied ruxolitinib cream, which correlated with improvement in T-VASI scores. Additionally, skin CXCL10 levels were significantly reduced after 12 weeks of ruxolitinib cream treatment.

**Keywords:** ruxolitinib cream, vitiligo, mechanism of action, CXCL10, Vitiligo Area Scoring Index (VASI)

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