Brepocitinib, a Selective TYK2/JAK1 Inhibitor Under Evaluation for the Treatment of Dermatomyositis, Reduces Inflammatory Cytokine Signaling and Interferon-induced Apoptosis in Primary Human Epidermal Keratinocytes

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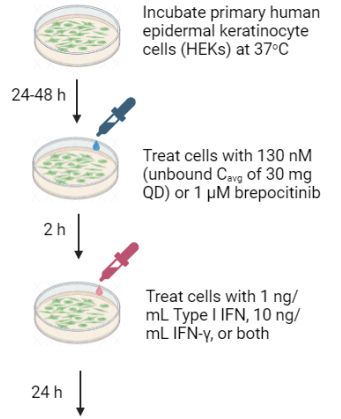
Background

- Dermatomyositis (DM) is characterized by inflammatory and degenerative changes of skin and muscle.[1]
- Type I IFN and other pro-inflammatory cytokines relevant to DM signal through the JAK-STAT pathway.[2]
- Cutaneous disease activity poses a significant unmet need for many patients, which is characterized by exaggerated keratinocyte apoptosis[3] and correlated with serum levels of IFN-β, IL-6, and IL-10[4]
- Brepocitinib (15 mg and 30 mg QD) is being evaluated in a double-blind, randomized, placebo-controlled Phase 3 study in patients with active DM (NCT05437263; VALOR Study).

Objective

To evaluate the efficacy of brepocitinib in preventing Type I IFN-induced apoptosis and pro-inflammatory cytokine signaling in primary human epidermal keratinocytes.

Methods

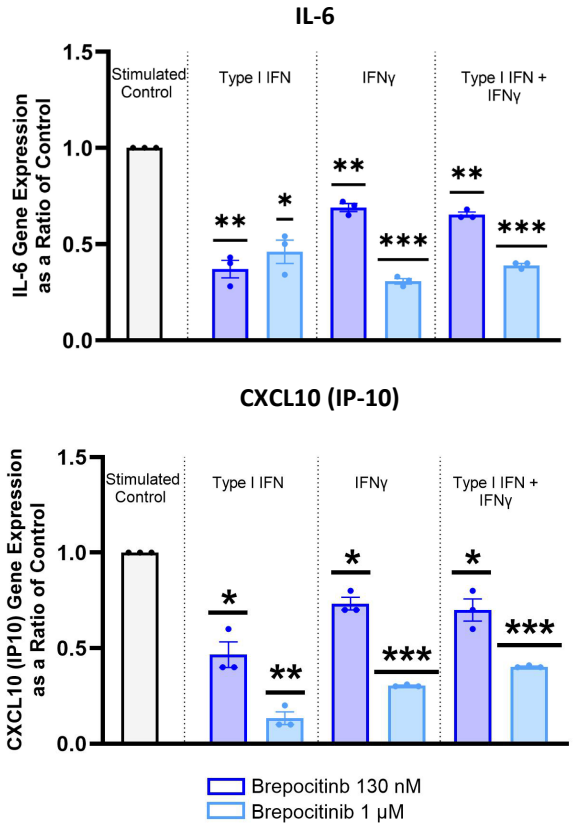


1. **Gene expression (IL-6, IL-12, ICAM-1, IP-10, MCP-1):** qPCR
2. **STAT phosphorylation:** western blotting
3. **Apoptosis:** flow cytometry via Annexin V staining

Full abstract available at the Priovant Therapeutics booth in the exhibit hall.

Results

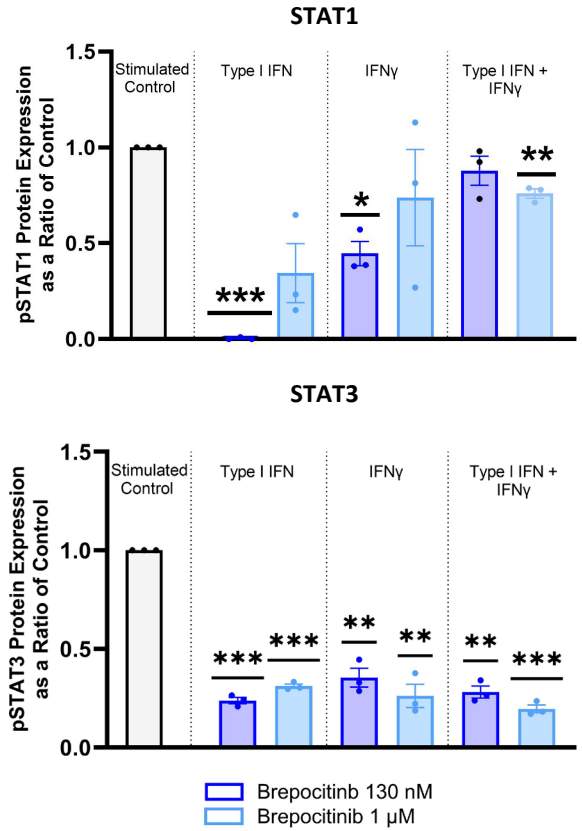
Brepocitinib Reduces IFN-induced Inflammatory Gene Expression



N=3 replicates per condition. Control bar represents the matched stimulation alone. * = p < 0.05, ** = p < 0.01, *** = p <0.001 using a one-sample T-test, relative to the matched stimulated control condition.

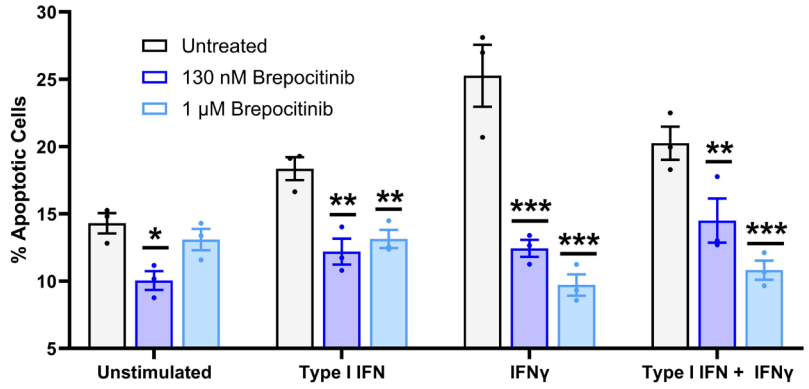
- CCL2 (MCP1) demonstrated similar dose dependent and significant reductions
- ICAM-1 and IL-12 demonstrated similar dose dependent but not consistently significant reductions

Brepocitinib Decreases STAT1 and STAT3 Phosphorylation



N=3 replicates per condition. Control bar represents the matched stimulation alone. * = p <0.05, ** = p < 0.01, *** = p <0.001 using a one-sample T-test, relative to the matched stimulated control condition.

Brepocitinib Reduces IFN-induced Apoptosis



N=3 replicates per condition. * = p < 0.05, ** = p < 0.01, *** = p < 0.001 using a two-way ANOVA with Dunnett's multiple comparisons test. Comparisons made to untreated control for each condition.

Conclusions

1. Brepocitinib's unique mechanism of action, inhibiting both TYK2 and JAK1, may be uniquely suited to improving skin manifestations in DM, as IL-6 signals via JAK1 and IFN-β and IL-10 signal via TYK2/JAK1.
2. Brepocitinib demonstrated significant inhibition of Type I IFN signaling, a central driver in the pathogenesis of DM, and IFNγ signaling, a more recently appreciated driver in dysregulated cytokine signaling in DM.
3. Brepocitinib significantly reduced STAT1 and STAT3 phosphorylation, led to concentration-dependent reductions in pro-inflammatory gene expression levels, including IL-6, and normalized apoptosis to basal levels in IFN-stimulated HEKa.
4. These data provide further support for the potential of once-daily oral brepocitinib to be effective for the treatment of active DM, a hypothesis currently being tested in the ongoing Phase 3 VALOR study.

References

1. Dalakas MC et al., *N. Engl. J. Med.* 1991 Nov 21;325(21):1487-98
2. Greenberg S et al., *Genes Immun.* 2012 Apr;13(3):207-13.
3. Pablos JL et al., *J Pathol.* 1999 May;188(1):63-8.
4. Chen M et al., *Br J Dermatol.* 2018 Dec;179(6):1334-1341.

Disclosures

Jiří Vencovský Speakers bureau: Abbvie, Biogen, Boehringer, Eli Lilly, Gilead, MSD, Novartis, Pfizer, Roche, Sanofi, UCB, Werfen, Consultant of: Abbvie, Argenx, Boehringer, EliLilly, Gilead, Octapharma, Pfizer, UCB, Grant/research support from: Abbvie. **Alexandra Goriounova, Lisa McConnachie, Brendan Johnson** Employees of: Priovant Therapeutics