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JAK3/TEC Inhibition is Safe and Effective in Cicatricial Alopecias: Evidence from a Prospective Trial

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Introduction

Cicatricial alopecias (CAs) such as frontal fibrosing alopecia (FFA), lichen planopilaris (LPP), and central centrifugal alopecia (CCCA) are chronic, progressive, scarring hair loss conditions impacting quality of life. Th1/JAK3 activation in CAs provides rationale for investigating ritlecitinib, a selective JAK3/TEC kinase inhibitor in CAs (NCT05549934).

Materials and Methods

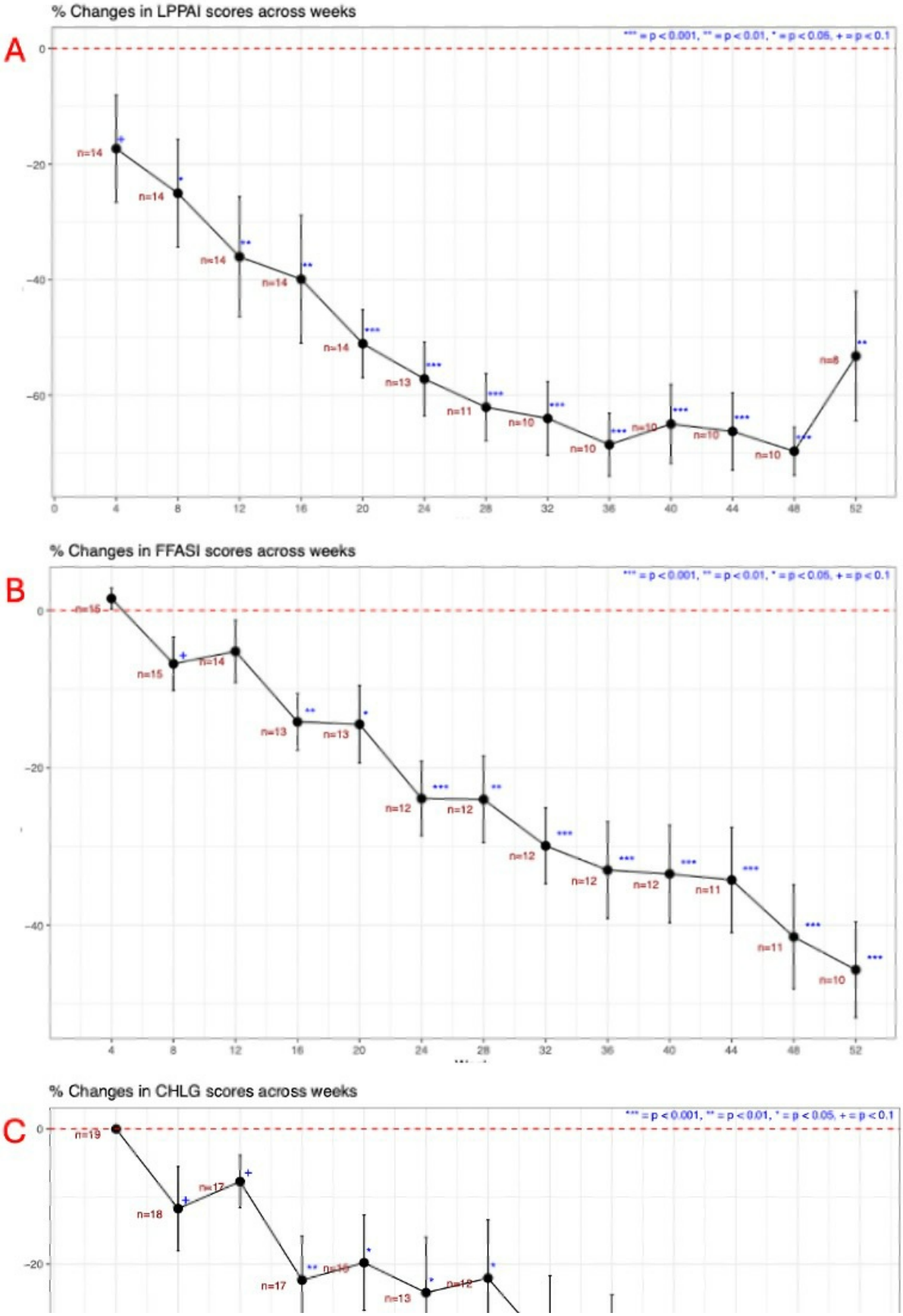
In this single-arm, open-label trial, 50 patients with FFA (N=15), LPP (N=15), and CCCA (N=20) were treated with ritlecitinib for 48 weeks (200 mg daily x 8 weeks, then 100 mg daily). Safety and changes in Th1 biomarkers (CCL5) and fibrosis biomarkers (e.g., TGFB1/2, vimentin) at week 24 were defined as primary endpoints. Secondary endpoints included changes in clinical activity scores (LPP activity/LPPAI, FFA severity index/FFASI, change in hair loss grade/CHLG), Dermatology Life Quality Index (DLQI), and Physician Global Assessment of Improvement (PGA-I). Scalp biopsies were collected from lesional/non-lesional skin at baseline and weeks 8, and 24 and analyzed for molecular changes by RT-PCR.

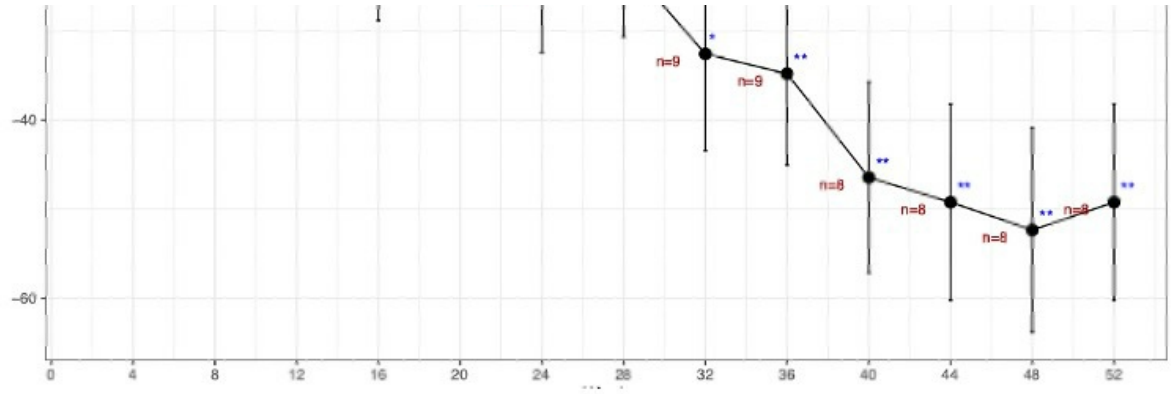
Results

Ritlecitinib (a JAK3/Tec inhibitor) showed improvements from baseline in LPPAI, FFASI, and CHLG scores of 57% ($p<0.001$), 24% ($p<0.01$), and 24% ($p<0.05$) at week 24 (N=38; Figure 1), and 70% ($p<0.001$), 41% ($p<0.001$), and 52% ($p<0.01$) at week 48 (N=29; Figure 1), respectively. No new safety signals were observed over the 48-week period. The majority (92%) of adverse events were mild/moderate with only 9.6% considered likely drug related. Molecular analysis showed significant downregulation of the primary endpoint biomarker CCL5, across all subtypes ($p<0.05$) at Week 24. All groups demonstrated downregulation of key inflammatory genes (already evident at week 8) including significant reductions in markers related to general inflammation (*PDE4B*), Th1 (*CCL5*, *CXCL9*, *CXCL10*), and cytotoxic/NK-T cell markers (*IL2RA*, *GZMB*) in FFA and/or LPP ($p<0.05$). CCCA showed the most significant and robust immune downregulation across multiple axes, including T cell activation (*IL2RA*, *IL2RB*), Th1 (*CCL5, CXCL9, CXCL10, IL12RB1*), Th2 (*CCL13*, *CCL22*), Th17/Th22 signaling (*IL23R*, S100A12), and JAK-STAT and NK/T cell–associated signaling pathways (*IL2RA*, *IL2RB*, *IL15RA*, *IL16*, *JAK1*, *JAK3*, *GZMB*) ($p<0.05$). While COL1A1 showed trends of downregulation across subtypes, no significant downregulation was seen in other fibrosis markers. Upregulation of hair keratins (*KRT85*, *KRT35*, *KRT83*, *KRT75*, *KRT86*, *KRTAP1; p<0.05*) were observed in FFA. While more robust changes were seen during the initial 8-week 200mg treatment, similar

trends were obtained throughout the 24 weeks, with the most pronounced changes seen in CCCA.

Figure 1. Mean (±SE) percentage change from baseline in (A) LPPAI, (B) FFASI, and (C) CHLG scores over 52 weeks of ritlecitinib treatment. Red numbers indicate the number of evaluable patients at each timepoint. Statistical significance versus baseline: ***p<0.001, **p<0.01, *p<0.05, +p<0.1. At week 24, mean improvements were 57%, 24%, and 24% in LPPAI, FFASI, and CHLG scores, respectively (N=38); at week 48, mean improvements were 70%, 41%, and 52%, respectively (N=29).





Conclusion

Ritlecitinib was associated with a favorable safety profile and rapid improvements in clinical scores and molecular biomarkers supporting JAK3/TEC inhibition as a potential therapeutic approach in treatment of CAs.