Noninvasive Genomic Characterization of Patients with Nonsclerotic and Superficially Sclerotic Chronic Cutaneous Graft-Versus-Host Disease Identified a Novel Gene Signature in Responders to Ruxolitinib Cream.

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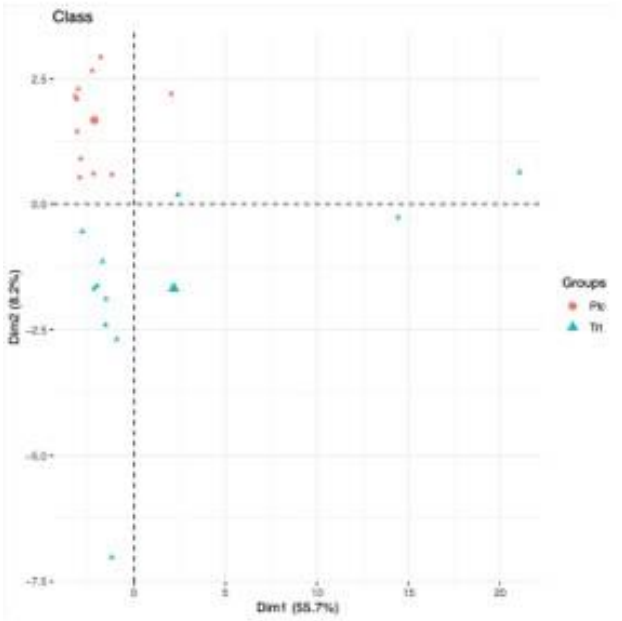
Abstract Text:

Chronic GVHD (cGvHD) negatively impacts QoL and late outcomes after allogeneic HCT. Over half of cGvHD patients have skin involvement. Oral ruxolitinib, a JAK1/2 inhibitor, has been FDA approved for the treatment of acute and chronic GvHD. Further, ruxolitinib cream has been effective in clinical trials for vitiligo, atopic dermatitis, and psoriasis. In this study, we evaluated topical ruxolitinib cream for cutaneous non-sclerotic (lichen-planus like, poikilodermatous) and superficially sclerotic (lichen sclerosus, morphea-like) cGvHD in a 28-day, prospective, randomized, double-blind, vehicle-controlled, phase 2, proof-of-concept study (NCT03954236). Patients were eligible to enroll if systemic therapy, when applicable, was stable for ≥4 weeks and concurrent topical therapy (including phototherapy) was not used. Patients were randomly assigned (1:1) to receive ruxolitinib 1.5% cream to left side or right side of face/body with vehicle cream to contralateral side of face/body twice daily for 28 days. The primary endpoint was efficacy as measured by cutaneous GvHD BSA on the side of face/body treated with ruxolitinib cream vs contralateral side treated with vehicle cream at Day 28. Secondary endpoints were Physician's Global Assessment of clinical condition (PGA) of the ruxolitinib cream-treated side vs vehicle cream-treated side at Day 14 and 28.

Interim analyses were performed to evaluate secondary and exploratory endpoints once 10 patients were evaluable of the planned 24 patients. Skin treated with ruxolitinib cream had significantly improved PGA scores compared to skin treated with vehicle cream (2.5 vs 4.0; p= 0.026) at Day 28. Skin samples were noninvasively collected using the SmartSticker™ to investigate 1) the gene expression in cutaneous non-sclerotic and superficially sclerotic cGVHD, 2) differences between treatment with ruxolitinib cream and vehicle cream, and 3) differences between responders (PGA 0-4) and non-responders (PGA 5-6) at Day 28. RNA sequencing from 11 right and left patient pairs at day 28 identified 310 differentially expressed genes (DEGs, fold change > 2 and p< 0.01) between ruxolitinib (n = 11) and vehicle (n = 11) treatments with primary pathway differences in immune modulation and cell-signaling (Figure 1).

Additionally, 383 DEGs (fold change > 2 and p< 0.01) were identified between responders (n = 8) and non- responders (n = 3) at Day 28 (Figure 2). Principal component analysis and hierarchical clustering separated the responders and non-responders using 383 DEGs (figure 1). This is the first study to characterize the effect of topical JAK1/2 blockade with ruxolitinib cream on cutaneous cGVHD and differentiate the genomic signatures between responders and non-responders. This data supports the need for deeper interrogation to understand the clinical significance for patients with cutaneous nonsclerotic and superficially sclerotic cGvHD.

1A



1B

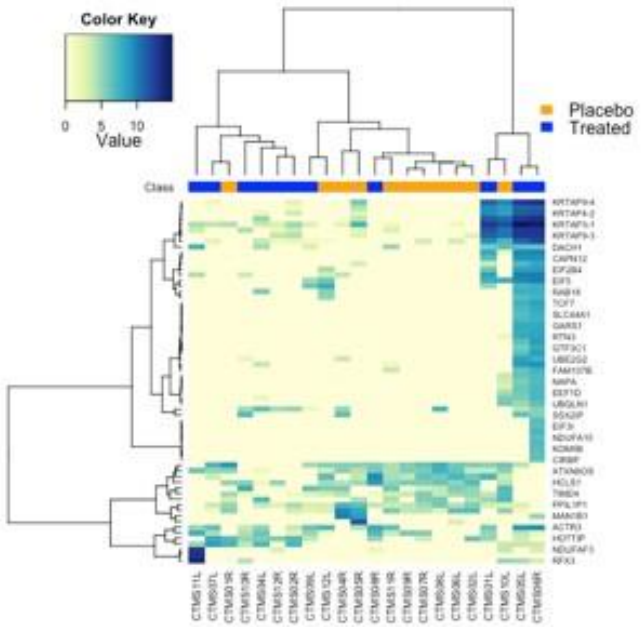
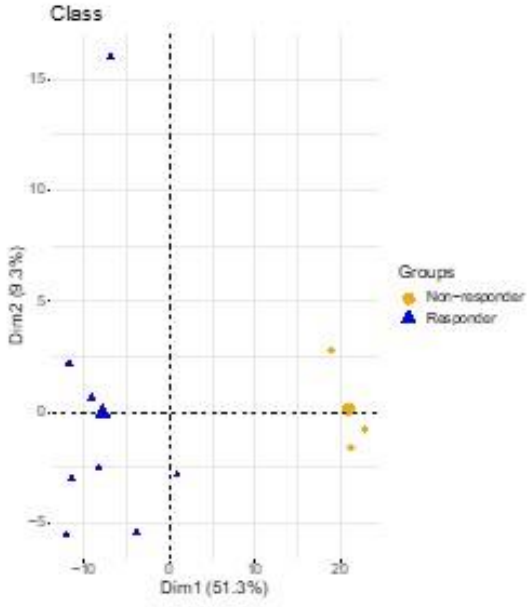


Figure 1. Genomic differences in the skin of cutaneous cGVHD lesions treated with ruxolitinib cream or vehicle (placebo). **(A)** Principal component analysis and **(B)** hierarchical clustering separate vehicle cream (placebo) and ruxolitinib cream (treated) using 310 DEGs.

2A



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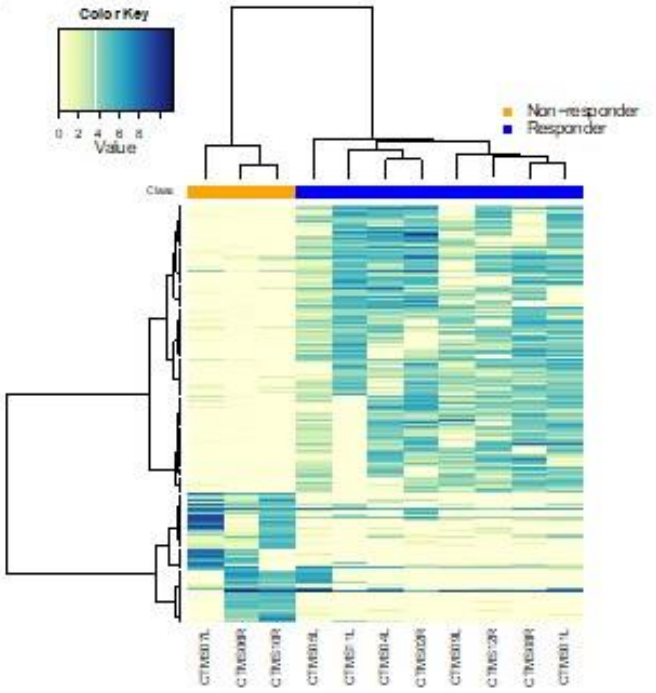

Figure 2. Differentiation between responders and non-responders in the skin of cutaneous cGVHD lesions following treatment with ruxolitinib cream **(A)** Principal component analysis and **(B)** hierarchical clustering separate responders and non-responders using by 383 DEGs.