RPT193, A CCR4 Antagonist, Improves the Inflammatory Skin Transcriptomic Profile in Patients with Atopic Dermatitis

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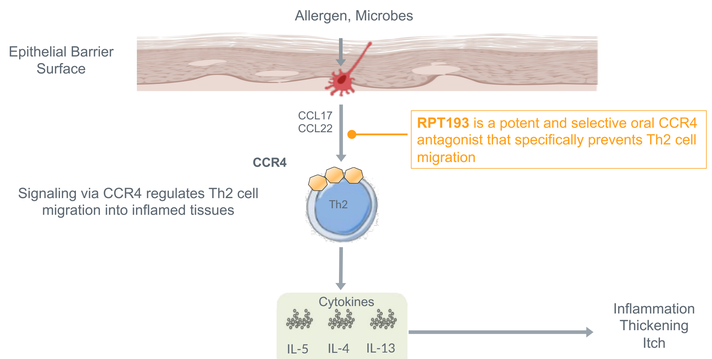
Abstract

The chemokine receptor CCR4 mediates CCL17- and CCL22-driven chemotaxis of Th2 cells into the skin of patients with atopic dermatitis (AD). RPT193 is an oral CCR4 antagonist that has been developed to treat AD and other allergic inflammatory diseases. The safety and efficacy of RPT193 as monotherapy for moderate-to-severe AD was previously described in a placebo-controlled, double-blinded Phase 1 study. Here, we present the skin and peripheral biomarker analysis from this Phase 1 trial. Following 28 days of 400 mg daily RPT193 treatment, RNA-seq and/or RT-PCR demonstrated significant downregulation of general inflammation- (MMP12; p<0.01), innate immunity- (IL8; p<0.01), T-cell/T-cell activation- (IL2, CCL19, CCR7, ICOS; p<0.05), Th1- (CCL2; p<0.05), Th2- (CCL22, CCR4; p<0.05), and Th17/Th22-related markers (IL22, CCL20, CCR6, S100A8, S100A9, S100A12, PI3/Elafin; p<0.05) compared to baseline in RPT193-treated, but not placebo-treated, subjects. Significant modulation was also seen compared to placebo in genes related to general inflammation, T-cell activation, and T helper subsets (MMP12, IL-2, ICOS, CCR6, DEFB4, IL-22, and S100A8, p<0.05). We also observed decreased CCR4 surface expression on circulating Th2 cells but no major changes in proportion of T-cell subsets. In conclusion, these data suggest that RPT193 treatment improves the AD skin transcriptome, consistent with the observed clinical efficacy, as well as decreases CCR4 expression in the skin and on circulating Th2 cells in the periphery. A Phase 2 study is planned to investigate the safety and efficacy of RPT193 in patients with moderate to severe AD.

Introduction

Figure 1.



- Atopic dermatitis (AD), also known as atopic eczema, is a chronic inflammatory skin disease that causes dry skin, intense pruritus (itching), and a red, raised rash
- The Th2 cytokines IL-4, IL-5 and IL-13 are critical in driving AD pathology
- The chemokine ligands CCL17 and CCL22, which are elevated in the inflamed skin and serum of AD patients, recruit Th2 cells to lesions via CCR4 expression on Th2 cells
- We hypothesize that RPT193-mediated antagonism of CCR4 will limit Th2 migration, ultimately ameliorating human AD severity

Phase 1B Study Design and RPT193 Efficacy

Figure 2.

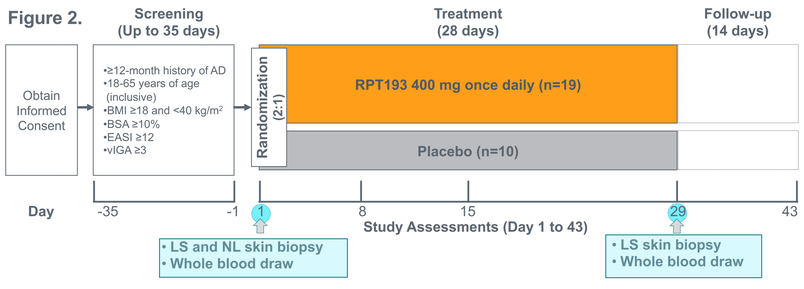


Figure 2. *Phase 1B Study Design.* Consented adult patients with at least 1 year of AD history were screened for AD disease severity (BSA, IGA, EASI) and BMI prior to randomization. Randomized patients received placebo (PBO) or a 400mg RPT193 tablet daily for 28 days. Study assessments were conducted from screening through two weeks-post treatment cessation. Whole blood for immunophenotyping, and skin biopsies (lesional [LS] and non-lesional [NL]) for transcriptional profiling, were collected at Day 1 and Day 29.

Figure 3.

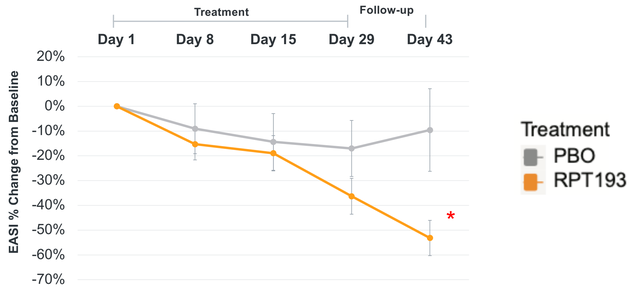


Figure 3. *RPT193 Clinical Efficacy.* Eczema Area and Severity Index (EASI) was assessed for placebo (PBO) and RPT193-treated subjects at Day 1 (predose), Day 8, Day 15, Day 29 (treatment-cessation), and Day 43 (follow-up). Post-hoc analysis demonstrated a statistically significant difference between placebo and RPT193 (p<0.05) at Day 43. Data points show the mean +/- standard error of the mean.

RPT193 Decreases CCR4 Cell Surface Expression (MFI) on Circulating T Helper Subsets

Figure 4.

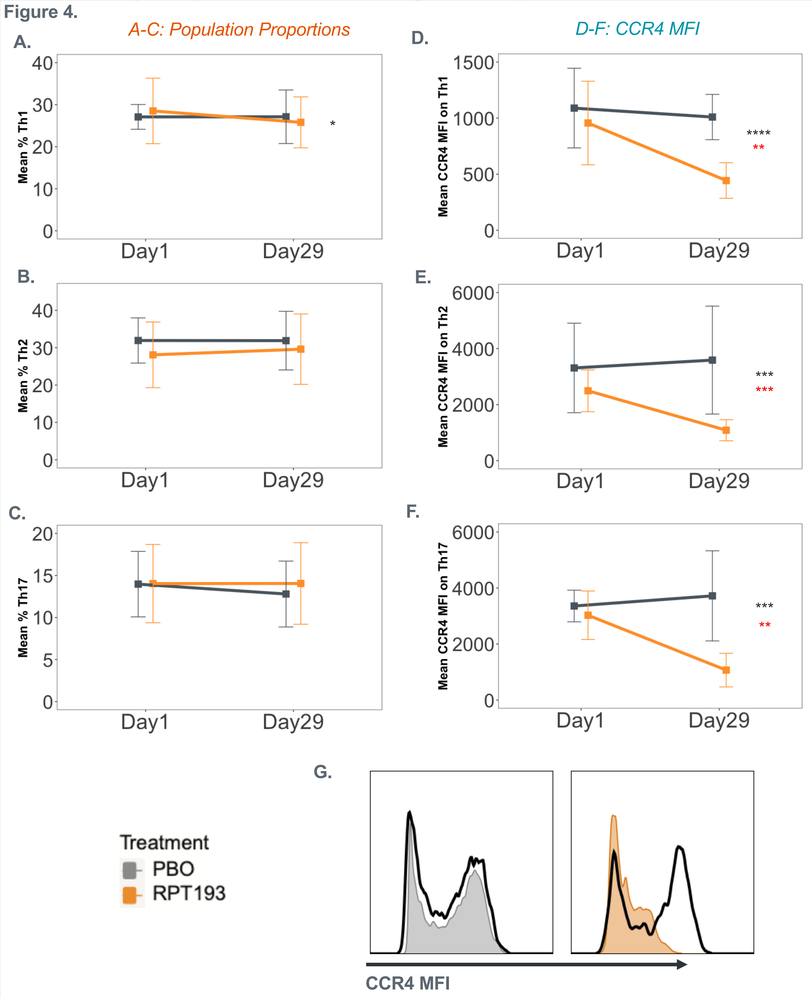


Figure 4. *Whole Blood Immunophenotyping.* Percentage (A) Th1, (B) Th2 and (C) Th17 of CD4⁺ T cell populations were quantified at Day 1 (baseline) and Day 29 (24 hours after treatment cessation) by flow cytometry. CCR4 Mean Fluorescent Intensity (MFI) was assessed on (D) Th1, (E) Th2, and (F) Th17 cells by flow cytometry. Data points show the mean +/- standard deviation. A Wilcoxon paired test was used to determine the p values within treatment groups between Day 1 and Day 29 (black symbols). An unpaired Wilcoxon test was used to assess differences between treatment groups (red symbols). ***(p<0.001), **(p<0.01), *(p<0.05), +(p<0.1). (G) Representative histograms showing CCR4 MFI on Th2 cells at baseline (black line) or Day 29 (shaded) for placebo- and RPT193-treated subjects.

RPT193 Modulates the Skin Transcriptomic Profile

Figure 5.

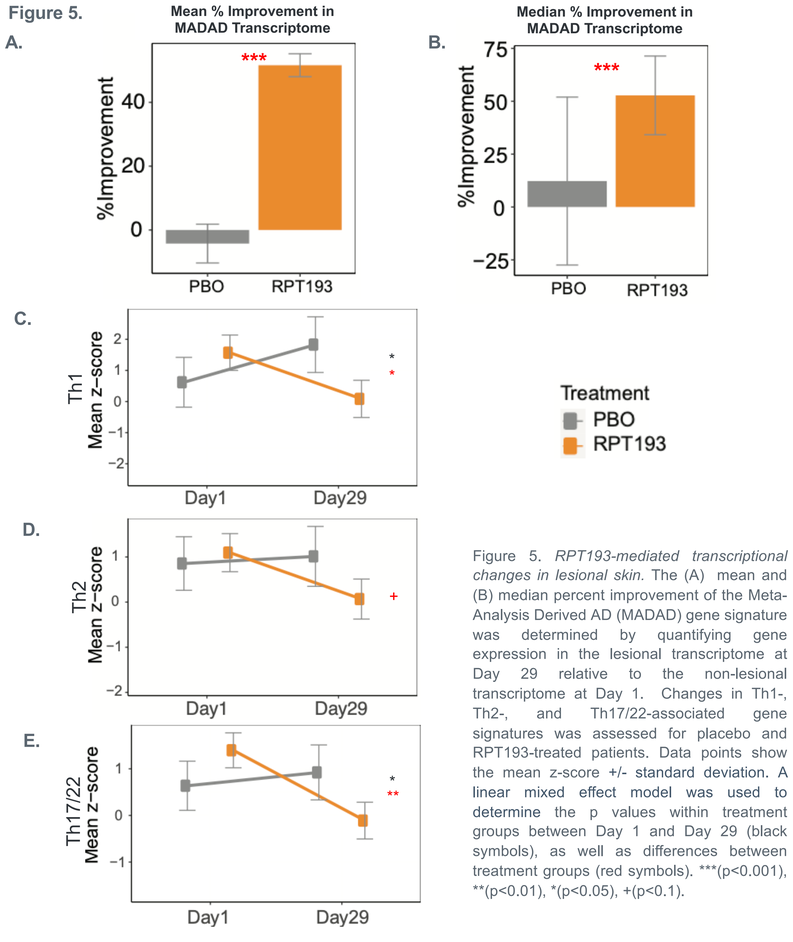


Figure 5. *RPT193-mediated transcriptional changes in lesional skin.* The (A) mean and (B) median percent improvement of the Meta-Analysis Derived AD (MADAD) gene signature was determined by quantifying gene expression in the lesional transcriptome at Day 29 relative to the non-lesional transcriptome at Day 1. Changes in Th1-, Th2-, and Th17/22-associated gene signatures was assessed for placebo and RPT193-treated patients. Data points show the mean z-score +/- standard deviation. A linear mixed effect model was used to determine the p values within treatment groups between Day 1 and Day 29 (black symbols), as well as differences between treatment groups (red symbols). ***(p<0.001), **(p<0.01), *(p<0.05), +(p<0.1).

RPT193 Normalizes Key AD Skin Transcriptomic Signatures

Figure 6.

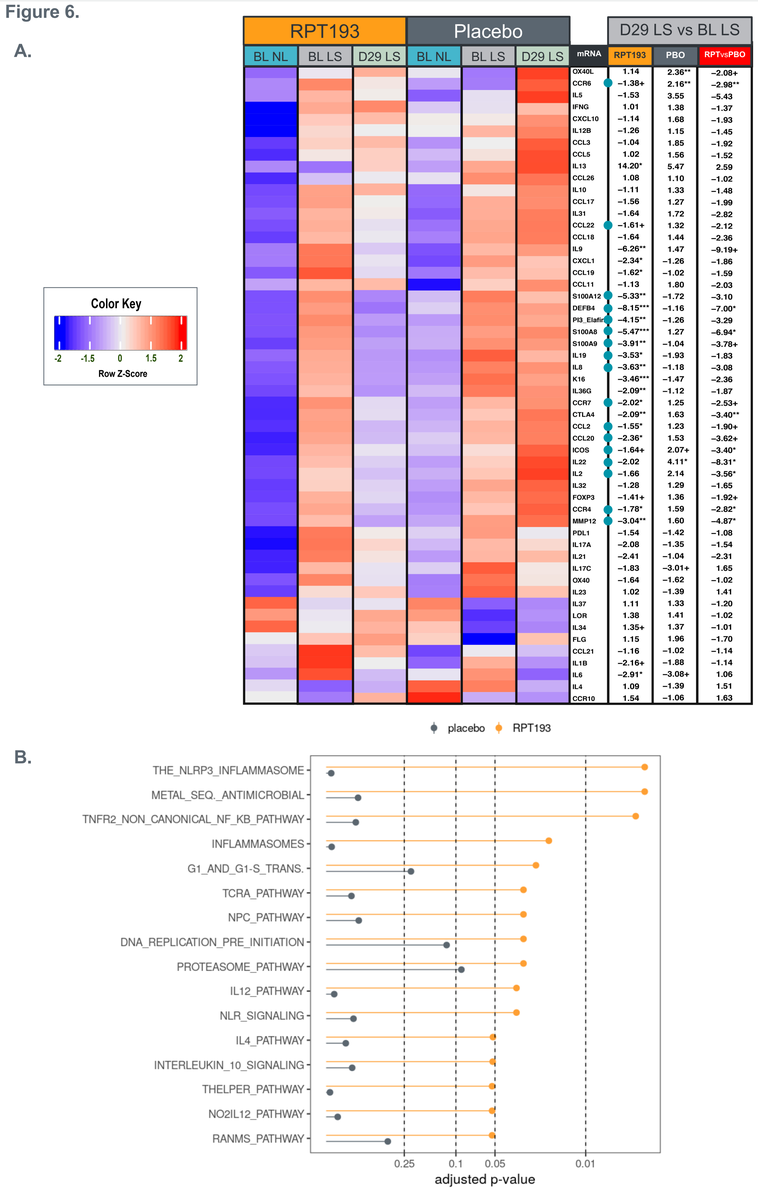


Figure 6. *Pathway analysis of RPT93-mediated transcriptional changes.* (A) TaqMan low-density array (TLDA) or RT-PCR was performed on skin biopsies to assess low-abundance genes associated with Th2-driven AD biology. Heatmap depicts Z-score of transcripts (mRNA) assessed in non-lesional (NL) skin biopsy at baseline (BL), as well as lesional skin (LS) biopsy at BL and at Day 29. Turquoise dots highlight pathway- or cell-related gene sets discussed in the abstract. A linear mixed effect model was used to determine the p-values within treatment groups between Day 1 and Day 29, as well as differences between treatment groups. ***(p<0.001), **(p<0.01), *(p<0.05), +(p<0.1). (B) Gene set enrichment analysis (GSEA) of lesional biopsy RNAseq data. Lollipop plot depicts pathways with the lowest adjusted p-values for placebo- or RPT193-treated groups relative to lesional baseline gene sets. Biocarta and Reactome gene sets taken from MsigDB.

Conclusions

- This is the first study conducted with a chemokine receptor antagonist that showed positive efficacy and biomarker signals in patients with AD
- In this Phase 1b study, RPT193 improved EASI score at the end of treatment (Day 29) with further decrease at Day 43 (vs. placebo)
- RPT193-treated subjects show a decrease in CCR4 MFI on Th1, Th2 and Th17 cells at Day 29 relative to placebo-treated subjects. This is consistent with data from our Healthy Volunteer study
- Significant decreases in the AD gene signature (MADAD) were seen in RPT193-treated compared to placebo-treated subjects at Day 29
- RPT193-treated subjects exhibited decreases in gene signatures associated with Th2, Th17/Th22 and Th1 immune pathways at Day 29
- Skin transcriptional profiling revealed that RPT193 treatment resulted in significant downregulation of genes associated with general inflammation, innate immunity, T cell activation, and Th17/Th22 cells at Day 29
- Pathway analysis of skin transcriptional profiling demonstrates that RPT193 significantly alters anti-microbial peptides, inflammasome activation, and T cell biology at Day 29
- Future clinical investigations include a dose-ranging, Phase 2b trial to further assess efficacy and safety of RPT193 in AD subjects and a Phase 2a trial in asthma