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Dimethyl Fumarate in Psoriasis

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Introduction & Objectives:

Analysis of patients receiving dimethyl fumarate (DMF) therapy to determine differential gene regulation in response to treatment.

Materials & Methods:

As part of a phase 3b clinical study assessing the efficacy and safety of DMF a sub-cohort of participants had additional blood (n=48) and skin (lesional, n=28 and non-lesional, n=15) biopsies (3mm) from photo-protected back or buttock skin taken for a multiomic analysis. Here we present the blood RNA gene expression from baseline, week 4 and 24 week correlating with the clinical outcomes of PASI (Psoriasis Area and Severity Index) and physicians global assessment. Whole blood RNA was extracted using PAXgene blood RNA System and gene regulation was assessed using RNA-seq GEN27012 by Novogene.

Results:

In the full 48 samples blood RNA sequence analysis demonstrated statistically significant differences in gene regulation when baseline samples were compared with samples both at 4 weeks and at 24 weeks post treatment irrespective of response (fig.1). Expression of IDO1 and TFF3 increased over time whilst CD2 and KIF5C decreased. CD2 is reported to stimulate Naïve T cells via keratinocytes (Orlik et al., 2020) and is a target for a biologic (Alefacept), which reduces infiltrating T cells while activating dendritic cells and inflammatory genes (Chamian et al., 2005). TFF3 is associated with cell migration by activating STAT3, MAPK and PI3K. CLC, STAC, and CCL23 gene expression significantly increased at week 4 compared to that of baseline. CLC is reported to be involved in imune surveillance for inflammatiuon and tumours and has recently been reported to play vital role in immune sipression function of the regulatoiry T cells (Swaminathan et al., 1999; Liu et al., 2005; and Kubach 2007). In the preliminary analysis 33 patients were assessed for PASI and response was categorised into PASI75, PASI50-75, PASI<50 or a final absolute PASI (<3). In this cohort KIF5C, CXCR3, and GZMK all decreased in expression over time (fig.2), with CXCR3 showing evidence of a more prominent effect in responders (blue dots) at week24. CXCR3 is present in infiltrating T cells in psoriasis lesion. GZMK gene expression was significantly reduced at week 24.

Figure 1

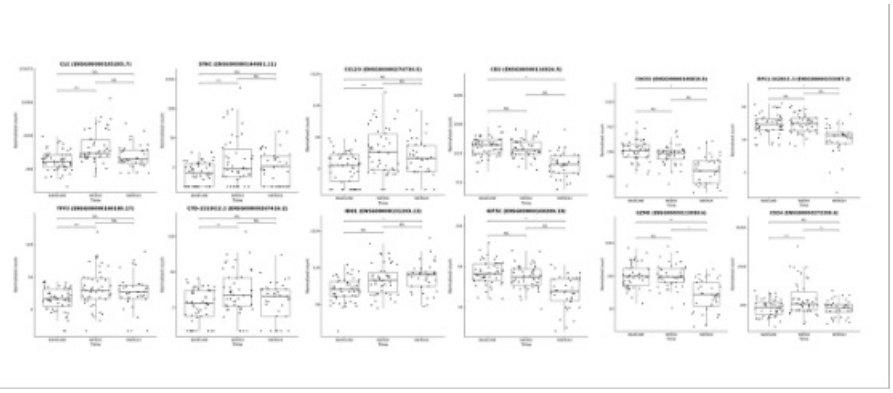
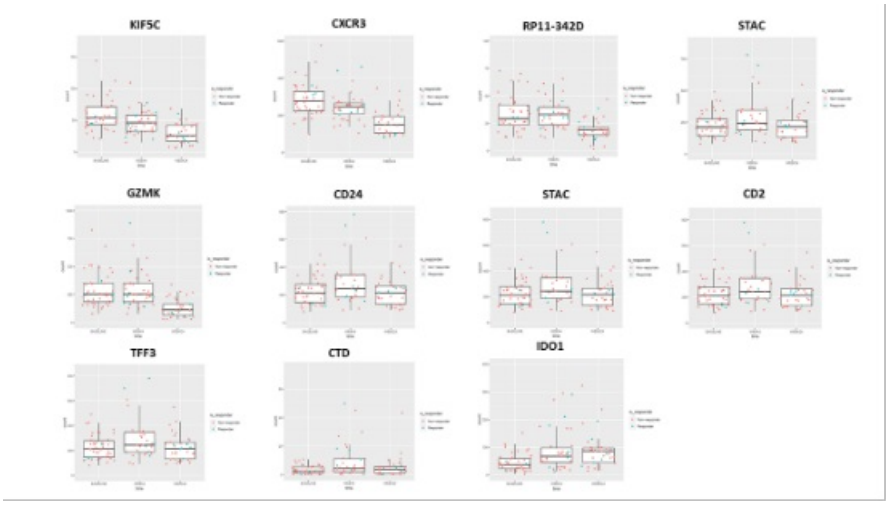


Figure 2



Conclusion:

Gene expression changes significantly from baseline by week 4 in patients taking DMF, with pathways relevant to the pathogenesis of psoriasis being dis-regulated. Preliminary data also indicate patients who achieve a higher level of response may have reduced CXCR3 at week 24 although this will require validation. Future analysis will be able to compare these signals in skin and blood and perform a multiomic assessment of response layering in analyses of DNA and the proteome.

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