## 32 COLON-TARGETED CYCLOSPORINE IN THE IL10 KNOCK OUT MODEL OF CROHN'S COLITIS

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10.1136/gutjnl-2013-305143.32

**Introduction** Cyclosporine A (CyA) is a powerful immunosuppressive agent and has been used off label for steroid-dependent or steroid-refractory ulcerative colitis. However, systemic exposure results in a number of side effects. A novel advanced oral drug delivery system, SmPill®, has been developed to permit targeted release of CyA directly into the colon tissue with limited systemic exposure.

**Aims/Background** The objective was to compare SmPill®-CyA activity in the IL10 knock-out mouse model of Crohn's colitis against the marketed Neoral® (po) and Sandimmun® (ip).

**Method** Mice were treated for 42 days, received the equivalent of 15 mg/kg/day CyA as well as untreated and SmPill® placebo. A secondary objective was to measure systemic pro-inflammatory cytokine activity in isolated spleen cells.

**Results** General Mouse Health:

The SmPill®-CyA group were significantly heavier than mice in all other groups on Day 42.

The SmPill®-CyA group had the lowest Disease Activity Index scores relative to the other groups.

Colon Tissue Inflammatory Biomarkers:

The untreated mice had the highest Serum Amyloid A levels (SAA), with the lowest levels seen with those treated with SmPill®-CyA ($p<0.001$) followed by Sandimmun® (i.p) ($p<0.01$) treated mice.

Sandimmun (i.p) and SmPill®-CyA groups had significantly lower ($P<0.01$) histology scores relative to Neoral®. Neoral® (po) had the greatest relative score.

The highest levels of Myeloperoxidase (MPO) activity were seen in the untreated and placebo mice. There was statistically lower MPO activity in both the SmPill®-CyA and Sandimmune® (i.p.) groups relative to untreated mice ($p<0.05$).

Similarly to a reduction in MPO activity, the SmPill®-CyA groups also had reduced IL-1α, IL-17 and TNFα pro-inflammatory cytokine levels ($p<0.05$) in colon tissue at Day 42.

Systemic Tissue Inflammatory Biomarkers:

In a measure of systemic CyA activity, the activity of a number of pro-inflammatory cytokines in activated isolated spleen cells was measured. The Sandimmune® (i.p) treated mice had significantly reduced production of TNF-α ($p<0.01$) and IL-17 ($p<0.05$) relative to cells from the untreated and placebo treated mice. In mice treated with SmPill®-CyA the reduction in TNF-α and IL-17 release by cells was non-significant. The pro-inflammatory cytokine expression levels for Neoral® was between that of Sandimmune® and SmPill®-CyA.

**Conclusion** The above study demonstrated that SmPill®-CyA conferred preferential local colonic efficacy with limited systemic activity, in effect, harnessing the local efficacy of CyA and reducing systemic side effect risks. A SmPill®-CyA formulation, CyCol®, has progressed through human Phase I (PK) study in Canada and Phase IIb study in Ireland and the UK. A multicentre Phase IIb study is being planned.