

V565, a Novel Oral Anti-TNF Domain Antibody, Binds to Mucosal Macrophages and T Cells and Reduces Colonic Mucosal Inflammation after 6 Days Oral Dosing to Ulcerative Colitis Patients

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Introduction

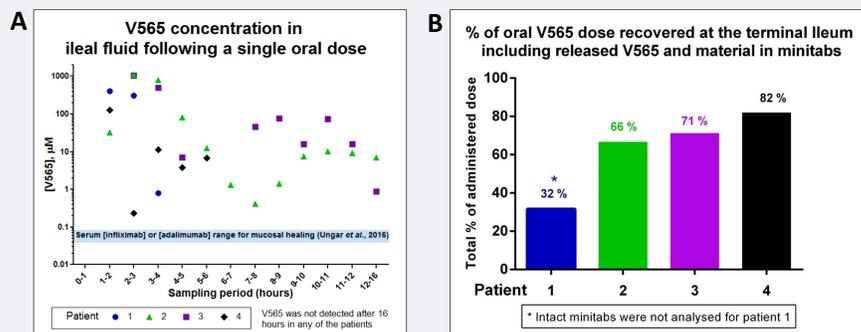
Anti-TNF α monoclonal antibodies have transformed treatment options for patients with Inflammatory Bowel Disease (IBD).

V565 is a novel oral anti-TNF α domain antibody (Vorabody) engineered to be resistant to intestinal proteases. It is in development as a potential oral treatment for IBD.

In vitro it suppressed phosphorylation of tyrosine kinases and signalling proteins and inhibited the release of inflammatory cytokines following culture with biopsies taken from patients with UC and CD¹.

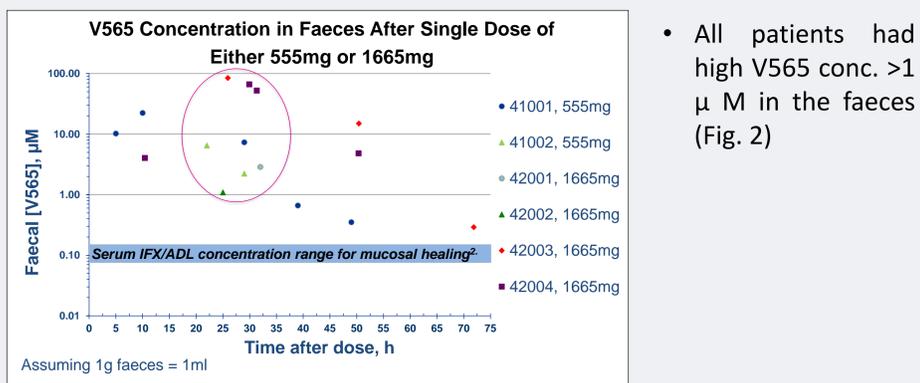
It was safe and well tolerated after high single and multiple doses in healthy volunteers and patient volunteers with CD and resulted in high concentrations of active drug in ileal fluid and faeces (Figure 1, 2).

Figure 1: Four healthy subjects with terminal ileostomies received a single oral dose of 1665mg V565 in encapsulated minitablets. Ileal fluid was collected over 24 hours.



V565 recovered from ileostomies after a single 1665 mg dose, measured by competitive ELISA. A) soluble [V565] in the lumen; B) % of dose recovered, comprising the dissolved V565 in Graph A plus that in partially dissolved mini-tablets.

Figure 2: V565 concentration in faecal samples measured by competitive ELISA. 6 subjects with CD received a single oral V565 dose (2 with 555mg; 4 with 1665mg).



Aims and Methods

This open label study was designed to demonstrate that orally delivered V565 enters intestinal mucosa at sites of disease and exerts a beneficial effect on inflammatory processes following dosing for 7 days to patients with Ulcerative Colitis.

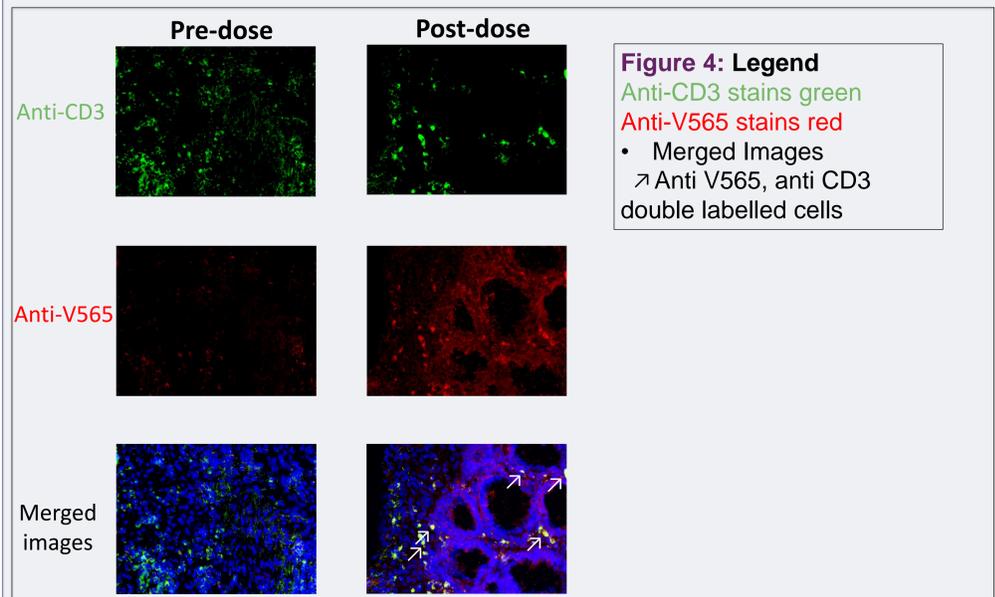
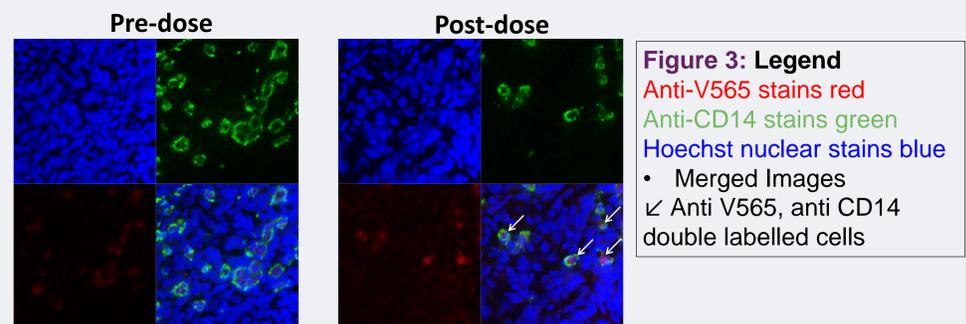
Patients with a Mayo score of 3-10 including an endoscopy score of ≥ 1 had up to 7 days of oral dosing with 555mg tid V565. Sigmoidoscopy with biopsies was performed before and after the dosing period.

The primary outcomes of interest were presence of V565 in the mucosa and reduction from baseline in phosphorylation of a panel of tyrosine kinases and signalling proteins. Detection of V565 was determined by immunohistochemistry. Phosphorylation was determined using PathScan RTK signalling arrays².

Results

- 5 patient volunteers with UC (Mayo score: 3-7) were treated with oral V565 at a dose of 555 mg tid. Due to visit scheduling most received 6 days treatment.
- Presence of V565 was confirmed in the inflamed lamina propria and co-localised with CD14+ macrophages and CD3+ T cells in post-treatment biopsies (Figure 3, 4).

Immunohistochemistry demonstrating co-localisation of V565 and CD14+ / CD3+ cells in colon tissue biopsies after 6 days oral dosing with V565 555mg tid



- Overall phosphorylation of the panel of kinases and signalling proteins was reduced by approximately 50% from baseline in four of the five patients (Figure 5)

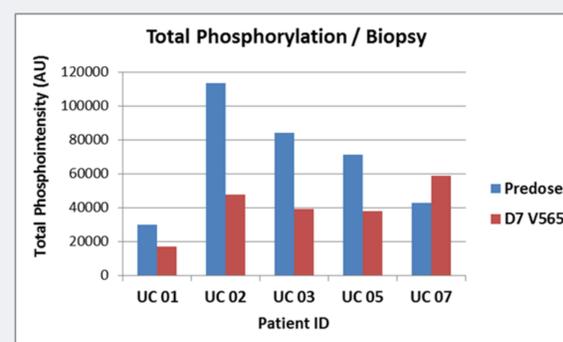


Figure 5: Overall phosphoprotein levels in pre- and post-dose inflamed mucosal biopsy samples after 6-7 days treatment

Conclusions

V565, an oral anti-TNF domain antibody engineered to be resistant to intestinal proteases, was demonstrated bound to membrane TNF on CD14+ macrophages and CD3+ T cells in the lamina propria of UC patients and resulted in inhibition of mucosal inflammatory processes after 6-7 days oral dosing.

The reduction of 50% in overall phosphorylation is similar to that seen in an earlier study of UC biopsy cultures with infliximab at a concentration of 67nM (10 $\mu\text{g}/\text{ml}$)¹ a serum concentration associated with mucosal healing in IBD patients³.

These results provide encouragement that oral dosing with V565 will be a beneficial oral treatment option for patients with IBD.

References

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