Pilot study to assess pharmacokinetic and pharmacodynamic markers following enema-dosing with adalimumab in patients with active ulcerative colitis (UC)

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INTRODUCTION

Active ulcerative colitis (UC) is associated with significant morbidity and impairment to quality of life. Tumor necrosis factor alpha (TNF-α) is a key pathogenic pro inflammatory cytokine elevated in the serum and intestinal mucosa of ulcerative colitis (UC) patients.[1] The development of anti-TNF-α therapies, such as adalimumab, has revolutionized the treatment of IBD. However, the efficacy of adalimumab for UC at the currently approved dosages is suboptimal, possibly due to inadequate local drug concentrations in diseased tissue of patients with active UC and/or lack of adequate suppression of the high TNF-α burden.[2,3]

Previously, we have demonstrated a sustained and improved pharmacodynamics response, reducing both histological scores and tissue inflammatory cytokines, in animals receiving targeted intracecal (IC) anti TNF-α antibody when compared with vehicle controls in a chronic T-cell transfer colitis mouse model.[4] Targeted IC delivery was also shown to be more efficacious when compared to systemic administration via intra-peritoneal (IP) dosing to reduce the total histologic score and lymphocyte count from the inner lumen to the submucosa of the proximal colon.[4] We believe these preliminary findings provide proof of efficacy for targeted delivery of anti TNF-α to treat UC at the disease site.[4]

Topical administration has the potential to provide higher exposures of adalimumab in the target tissue, in comparison to plasma exposures, with less systemic risk. Topical administration of adalimumab also results in pharmacologically relevant tissue levels, as suggested by the pharmacodynamic response shown in the preclinical disease model.[4] These analyses provide further support for the hypothesis that targeted topical delivery of adalimumab might provide an advantage over systemic delivery by substantially reducing TNF-α burden within the tissue.

In this study, we assessed pharmacokinetic (PK) and pharmacodynamic (PD) parameters following dosing with an adalimumab enema in patients with active UC. Data obtained from this study will provide further understanding of the extent of absorption, relative bioavailability, and the early safety data of adalimumab following topical administration in patients with active UC in local tissues as well as systemically.

METHODS

- This was a pilot study to evaluate safety and PK/PD responses of local administration of adalimumab via enema in tissue and blood.
- Four eligible patients with active UC (fecal calprotectin ≥ 250 µg/g or serum C-reactive protein ≥ 2) participated in the study **(Table 1)**.
- Patients received a single dose of adalimumab enema (160mg/50mL or 80mg/50mL) on days 1, 2, and 3. Adalimumab dose was adjusted based on initial PK and PD data for previous subjects **(Figure 1 and Table 1)**.
- Patients underwent sigmoidoscopy with biopsy on days 0, 4, 5, and 8. Serum samples were collected on days 1, 2, 3, 4, 5, 8 and 30. Tissue PK analysis was perfomed in real time and serum PK/PD was analyzed after each patient had completed dosing, on the indicated days **(Figure 1)**.
- Available stool samples for fecal calprotectin, adalimumab drug concentration, and exploratory PD biomarkers were collected at screening, prior to each adalimumab administration via enema, and prior to each sigmoidoscopy **(Figure 1)**.

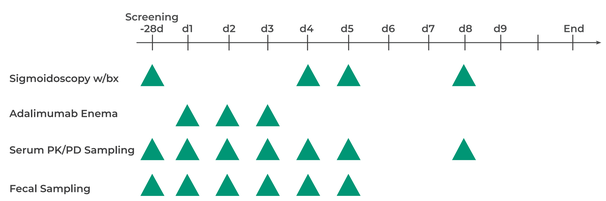

FIGURE 1. Study design and schedule of assessments.

TABLE 1. Patient demographics and treatment dose (mg) of adalimumab enema.

	Age	Sex	Treatment Dose (mg)
Patient 1	26	F	160
Patient 2	28	F	160
Patient 3	29	M	160
Patient 4	67	F	80

RESULTS

- Tissue cytokine profiles (TNF-α, IL-6, Oncostatin M [OSM]), fecal calprotectin levels (fCAL), and Mayo endoscopy scores are presented in **Table 2**.
- Subject 1 and subject 2 were considered responders based on decrease in total Mayo score. The tissue biomarkers (TNF-α, IL-6 and OSM) and fecal calprotectin decreased, demonstrating agreement with endoscopic outcomes.
- Subject 3 showed minimal reduction in TNF-α, OSM, and Mayo score. However, IL-6 and fCAL were increased suggesting activation of alternative pathway. This subject was considered a clinical non-responder on day 8, although target engagement was observed.
- Subject 4 showed decrease in TNF-α and fCAL but increase in IL-6 and OSM. Clinically, this subject is a non-responder on day 8. Interestingly, topical adalimumab did demonstrate target engagement along with reduction in tissue target levels (TNF-α) as observed with subject 3.

TABLE 2. Study results summary. Cytokine profiles of colon biopsy samples, fecal calprotectin, and Mayo histology index are presented. Patients were assigned Responder or Non-responder according to clinical outcome; changes in tissue-based biomarkers can be correlated with Mayo scores.

	Day	Tissue TNF-α (ng/g)	Tissue OSM (ng/g)	Tissue IL-6 (ng/g)	fCAL (µg/g)	Mayo Score	Responder/Non-Responder at Final Visit
Patient 1	0	14.9	40.5	24.6	1643	10	Responder
	4	8.1	10.8	4.6		3	
	8	4.49	3.4	4.8	358	1	
	120				25		
Patient 2	0				2760	4	Responder
	4	6.68	35.3	32.2		2	
	8	5.08	18.5	10.2	235	3	
Patient 3	0	29.8	9.7	43	681	7	Non-Responder
	4	42.1	31.6	24	3143	5	
	8	29.2	13.2	36.9	754		
Patient 4	0	174.4	60.7	13.7	2432	9	Non-Responder
	4	121	89.6	19	258		
	8	141	346	228	1834		

CONCLUSION

- Topical treatment with adalimumab may be beneficial in patients with active UC. Target engagement and modulation was demonstrated.
- Monitoring tissue TNF-α, IL-6, and OSM might be useful in understanding pathway redundancy or feedback loops.

References

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