Development of targeted therapeutic antibodies for the treatment of inflammatory bowel disease: A proof of concept

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Introduction

There is an urgent need to achieve higher rates of clinical response, remission and mucosal healing in inflammatory bowel disease (IBD). Several therapeutic monoclonal antibodies have revolutionized the treatment of Crohn's disease (CD) and ulcerative colitis (UC). Despite the potency of these agents towards well accepted targets of disease, they have afforded limited long-term efficacy in patients resulting in loss of response and chronic complication. Here we hypothesize that improved efficacy can be achieved using resistant and highly absorbable formulations of existing monoclonal anti-body drugs that can be delivered in a targeted fashion to the site of disease at concentrations sufficient to drive improved efficacy while avoiding the systemic toxicity normally associated with these agents. Furthermore, we believe a targeted approach affords the opportunity to deliver combination therapies targeting multiple known drivers of disease which has largely been avoided due to the potential for heightened systemic toxicity.

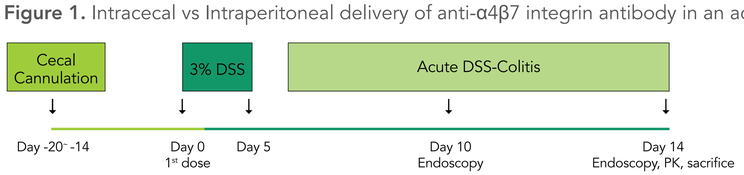
Methods

As a proof of concept, we conducted several studies evaluating whether intracecally (IC) delivered monoclonal antibodies might penetrate disrupted mucosa and confer improved efficacy when compared with systemic administration.

INTRACECAL VS INTRAPERITONEAL DELIVERY OF ANTI-α4β7 INTEGRIN ANTIBODY IN AN ACUTE DSS-COLITIS MODEL

In this first experiment, we evaluated the Pharmacokinetic (PK) and Pharmacodynamic (PD) effects of targeted intracecal (IC) versus systemic intraperitoneal (IP) delivery of an anti-α4β7 integrin antibody (DATK32) in a mouse model of acute colitis (Figure 1). Prior to the experiment, animals in IC treatment groups underwent implantation of a cecal cannula for bolus delivery to the cecum. Mice were treated with anti-mouse α4β7 integrin antibody (DATK32) during the acute phase of colitis. DATK32 was administered IP (25 mg/kg) every 3 days (Q3D), and IC (25 mg/kg) Q3D or every day (QD). A lower dose (5 mg/kg) was also given IC QD. At termination, blood, colon content and tissue were collected for bioanalysis. Peyer's Patches (PP), mesenteric Lymph Nodes (mLN), and whole blood were collected from all animals and processed pharmacodynamic analysis of T cell count by FACS analysis.

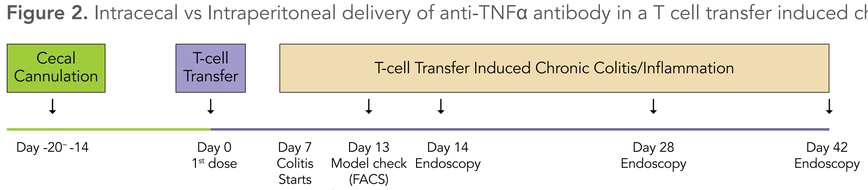
Figure 1. Intracecal vs Intraperitoneal delivery of anti-α4β7 integrin antibody in an acute DSS-colitis study design.



INTRACECAL VS INTRAPERITONEAL DELIVERY OF ANTI-TNFA ANTIBODY IN A T CELL TRANSFER INDUCED CHRONIC COLITIS MODEL

In a second experiment, we evaluated the efficacy of targeted intracecal (IC) anti-mouse-TNFα antibody (a surrogate for human anti-TNFα antibodies) when compared with systemic intraperitoneal (IP) injection in an adaptive T-cell transfer induced chronic colitis mouse model. All animals underwent surgical implantation of a cecal cannula prior to the experiment for bolus topical delivery to the cecum. Colitis was induced by intraperitoneal (IP) injection of $0.5x10^6$ CD44-/CD62L+ T-cells isolated and purified from C57Bl/6 donor to the male RAG2-/- recipient mice on Day 0. To minizine variation due to different routes of administration, animals were treated with both IP every third day (Q3D) and IC once daily (QD) of either the anti-TNFα antibody or the control (Vehicle solution or IgG controls) from Day 0 to 42 (Figure 2).

Figure 2. Intracecal vs Intraperitoneal delivery of anti-TNFα antibody in a T cell transfer induced chronic colitis study design.



Results

PHARMACOKINETICS

- IC administration of DATK32 resulted in a significantly lower mean drug concentration in plasma, higher concentrations in both colon contents and colon tissues as compared to IP administration (Figure 3 & Figure 4).
- Drug levels remained elevated, above levels observed in the systemic circulation, in colon contents and tissues for up to 48h after dosing where values were significantly elevated for up to 8h and 24h respectively (Figure 5).

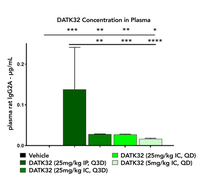


Figure 3. Mean concentration of DATK32 (µg/mL) in plasma of IP (25mg/kg, Q3D) and IC (25 & 5 mg/kg, QD).

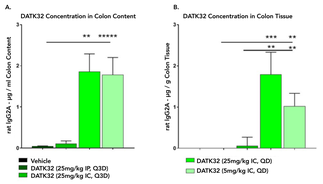


Figure 4. Mean concentrations of DATK32 (µg/mL) in colon contents (a) and colon tissues (b) of IP (25mg/kg, Q3D) and IC (25 & 5 mg/kg, QD) where IP is compared to IC.

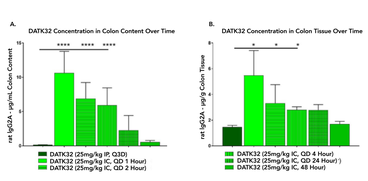


Figure 5. Mean Concentration of DATK32 (µg/mL) in colon contents (a) and colon tissue (b) of IP (25mg/kg, Q3D) and IC (25 mg/kg, QD) over time (1, 2 ,4, 24, and 48 hours) where IP is compared to IC.

Note: Pair-wise comparisons by two-tailed Mann-Whitney U-Test for treatment effects; $p<0.05$*, $p<0.01$** and $p<0.001$***.

PHARMACODYNAMICS

- Mean number of α4β7 memory T-cells were significantly increased in blood of groups receiving IC delivery over both vehicle control and systemically treated animals
- Mean number of α4β7 memory T-cells were significantly reduced in mesenteric lymph nodes (MLN) and Payer's Patches (PP) groups receiving IC QD anti-α4β7 integrin antibody over vehicle control and animals treated with the drug systemically (Figure 6B & C).

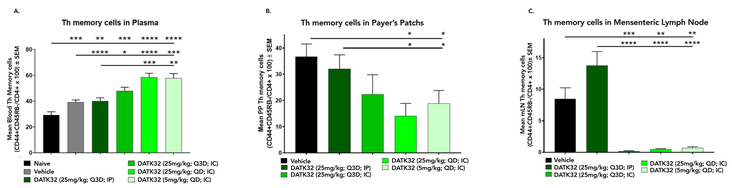


Figure 6. Mean number of Th memory cells (mean ± SEM) measured by FACS analysis, for IP (25mg/kg, Q3D) and IC (25 & 5 mg/kg, QD) in plasma (A), Payer's Patches (B), and mesenteric lymph node (C) when compared to vehicle control (Vehicle) and when IP is compared to IC. Pair-wise comparisons by two-tailed Mann-Whitney U-Test for treatment effects; $p<0.05$*, $p<0.01$**, $p<0.001$***, and $p<0.0001$****.

EFFICACY

- Significant decrease of Disease Activity Index (DAI), a combination of colitis score and stool score via video endoscopy plus body weight loss score was when compared to the Vehicle control (IP/IC) group on Day 28 and Day 42 (Figure 7).
- Significant reduction in the mean concentration of inflammatory cytokines was found in groups treated with anti-TNFα by IC or IP route when compared with Vehicle (IP/IC) control and the IgG1 controls (IC or IP) in colon tissue (Figure 8).
- Targeted IC anti-TNFα treatment showed a significant improvement in the mean histopathologic score when compared with the Vehicle controls (IP and IC) groups in proximal and distal colon tissues indicating that anti-TNFα treatment was generally more effective in this group (Figure 9).
- This study demonstrated targeted IC administration of anti-TNα antibody was superior at reducing histopathological damage of colon tissue compared to systemic IP administration in this chronic colitis model.

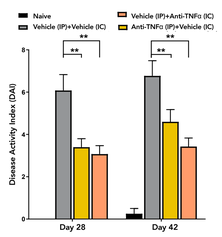


Figure 7. Shows Disease Activity Index (DAI) (mean ± SEM) in Naïve group and groups receiving CD44-/CD62L+ T-Cell transfer and administration of anti-mouse TNFα antibody (IP and IC) or Vehicle control.

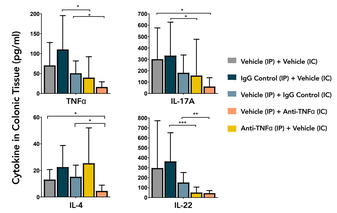


Figure 8. Shows inflammatory cytokines (pg/mL) (mean ± SEM) in the Naïve group and groups receiving CD44-/CD62L+ T-Cell transfer and administration of anti-mouse TNFα antibody (IP and IC) or Vehicle control.

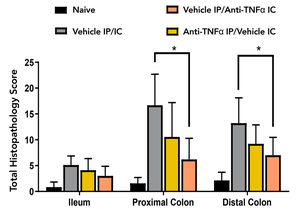


Figure 9. Comparison of total histopathology score (mean ± SD) in ileum, proximal colon and distal colon tissues.

Note: Pair-wise comparisons by two-tailed Mann-Whitney U-Test for treatment effects; $p<0.05$*, $p<0.01$** and $p<0.001$***.

Conclusion

- Targeted IC DATK32 treatment lead to significantly higher drug exposure in colon contents and tissues with limited blood exposure when compared with IP in an acute colitis model.
- Targeted IC DATK32 treatment showed a significantly reduced number of α4β7 memory T-cells in PP and mLN each representing populations within inflamed jejunal and colon tissues in an acute colitis model.
- Targeted IC anti-TNFα antibody led to a significant reduction of disease activity index (DAI), key inflammatory cytokines, including TNFα, and total histology score when compared to vehicle control (IP/IC) in a chronic colitis model.
- Results of these two studies point to the potential for increased pharmacodynamic effects and efficacy with high concentrations of anti-α4β7 integrin antibody and anti-TNFα antibody in local inflamed tissues.
- Together, these findings provide a proof of concept for targeted and topical delivery of therapeutic antibodies and suggest the potential for improved efficacy in the treatment of IBD.

References

Wang C, Hanly EK, Wheeler LW, Kaur M, McDonald KG, Newberry RD. Effect of α4β7 blockade on intestinal lymphocyte subsets and lymphoid tissue development. Inflamm Bowel Dis. 2010 Oct;16(10):1751-62.

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