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 antibody 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-α7 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-α7 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 α7 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) QOD for every 24h (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.

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 & 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).

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 6 & C).

Conclusions

- 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-α7 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


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