A comparison of systemic versus targeted anti-TNFα antibody treatment in colitis induced by adoptive transfer of CD44-/CD62L+ T-cells into RAG2−/− mice recipients

Shayong Nikki Lee PhD1, Sharat Singh PhD1, Allison Luo MD, William J Sandborn MD, Chris Wahl MD, Emil Chuang MD, and Mitchell Jones MD PhD

Progeny, Inc. Ami Arbor, Michigan, United States; 2Gastroenterology, University of California San Diego, San Diego, CA, United States.

Introduction

Inflammatory bowel disease (IBD) is characterized by a disproportionate inflammatory response in gastrointestinal tissues leading to damage and clinical symptoms. TNFa is a potent proinflammatory cytokine exerting pleiotropic effects and is generated in a precursor form called transmembrane TNFα expressed on activated macrophages and lymphocytes. A soluble form of TNFα can be released at the cell surface by TNFα converting enzyme (TACE). Soluble TNFα binds to soluble TNFα receptors type I and type II (TNFR1 and TNFR2). The development of therapies targeting TNFα such as infliximab, adalimumab and others has revolutionized the treatment of IBD. These antibodies bind soluble TNFα, thereby blocking receptor binding and subsequent cytokine-driven inflammatory processes. In addition, when these anti-TNFα antibodies bind transmembrane TNFα many are capable of targeted cell death through antibody-dependent cell-mediated cytotoxicity (ADCC). Recent publications have established that there may be inadequate anti-TNFα antibody drug reaching diseased tissue in patients with active IBD and that the high TNFα burden is not adequately suppressed.1 In the present study 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.

Methods

All animals underwent surgical implantation of a cecal cannula 2 weeks prior to the experiment for the ease of bolus topical delivery to the cecum. Colitis was induced by intraperitoneal (IP) injection of 0.5x10^9 CD44+CD62L+ T-cells isolated and purified from C57Bl/6 donor to the male RAG2−/− recipient mice on Day 0. To minimize variation due to different routes of administration, animals were treated with both IP every third day (QD) and intracecal (IC) once daily (QD) of either the anti-TNFα or the control (Vehicle solution or IgG1 controls) from Day 0 to 42 (Figure 1).

Results

• Significant body weight loss was observed in groups treated with Vehicle or IgG control (IP/IC) starting at Day 7 to 14 after T-cell transfer. The 98% T-cell engraftment rate found on Day 13 indicating successful development of colitis (Figure 1).
• Treatment with either IP or IC anti-TNFα antibody led to a significant reduction of body weight loss (%) AUC from Day 0 to Day 42 (Figure 2) and DAI at Day 28 and Day 42 (Figure 3).
• Significant reduction in 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 respective IgG controls (IP or IC) in colon tissue (Figure 4).
• Targeted IC anti-TNFα treatment showed a significant improvement in 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 5).
• Targeted IC anti-TNFα treatment showed the greatest magnitude of lymphocyte reductions in all counted field from inner lumen to submucosa when compared with vehicle control groups (Figure 6). Similar trend of lymphocyte count reduction was found in distal colon but with less lymphocyte count in general.

Conclusion

• Human studies have shown there is inadequate anti-TNFα antibody reaching the diseased tissue resulting in persistent inflammation. Thus, we hypothesized that targeted and topical administration of anti-TNFα antibody would result in improved efficacy when compared to systemic (IP) distribution in an adaptive T-cell transfer mouse model of colitis.
• Significantly reduced weight loss (%), decreased Disease Activity Index, improved histological score and reduced tissue inflammatory cytokines was found in animals receiving targeted (IC) anti-TNFα antibody when compared with vehicle controls.
• Targeted IC delivery was significantly more efficacious when compared to systemic (IP) anti-TNFα in inflammatory cytokines and tissues were fixed for histopathologic analysis.

References


CONTACT INFO
Mitchell Jones
Progeny, Inc.
4330 La Jolla Village Drive Suite 200
San Diego, CA 92121
Email: Mitch.Jones@progeny.com

4260 S. State Road, Ann Arbor, MI 48108
© 2019 Progeny, Inc. All rights reserved. Progeny® is a registered service mark of Progeny, Inc.