COMBINATION OF FXR AGONIST MET642 WITH TOFACITINIB EXHIBITS SYNERGISTIC EFFECTS IN IMPROVING COLITIS IN ADOPTIVE T-CELL TRANSFER IBD MODEL

Xueqing Liu[1], Angelica Milik[1], Robert O'Connell[2], Julie White[2], Brent Palmer[3], Sharon Sen[3], Brandee Wagner[1]

1. Metacrine, San Diego, CA; 2. Bolder BioPath, Inc., Boulder, CO; 3. ClinImmune, Aurora, CO

3985 Sorrento Valley Blvd., Suite C
San Diego, CA 92121
www.metacrine.com

INTRODUCTION

Farnesoid X receptor (FXR) is a ligand-activated nuclear hormone receptor that is highly expressed in the liver and gastrointestinal tract. FXR agonists are in development for the treatment of nonalcoholic steatohepatitis (NASH) and other hepatobiliary diseases. We have previously shown that FXR agonists with sustained activity demonstrated efficacy in multiple chronic IBD models (adoptive transfer (AT) colitis, Mdr1a$^{-/-}$ colitis, and SAMP1/YitFc ileitis) with efficacy similar to that of anti-IL-12/23. Our previous RNAseq analysis has identified a direct effect of FXR in promoting expression of genes in gut transporter/barrier function, gut healing and anti-microbial function. To further understand the therapeutic potential of FXR in IBD, we tested the combination of our clinical candidate FXR agonist MET642 with tofacitinib, a JAK inhibitor that inhibits inflammation.

MATERIAL & METHODS

Colitis was induced by transferring CD4+CD45RB^{hi} T-cells to recipient C.B-17 SCID mice. All treatments were started 21 days post transfer and lasted for 4 weeks: FXR agonist MET642 (0.03mg/kg or 0.3mg/kg, QD), tofacitinib (5mg/kg or 50mg/kg, BID), a combo of MET642 0.03 mg/kg + tofacitinib 5mg/kg, n=10 for each treatment. Anti-IL-12p40 (0.5mg/mouse) was dosed intraperitoneally weekly (n=5). Efficacy was assessed by terminal colon weight to length ratio (W/L) and colon histopathology. Histopathology scores were determined for inflammation, erosion, gland loss and hyperplasia, each with a score of 0-5, and cumulative sum score of 0-20. Immunophenotyping was performed by flow cytometry analysis on cells isolated from mesenteric lymph node (MLN) and colon.

CONCLUSIONS

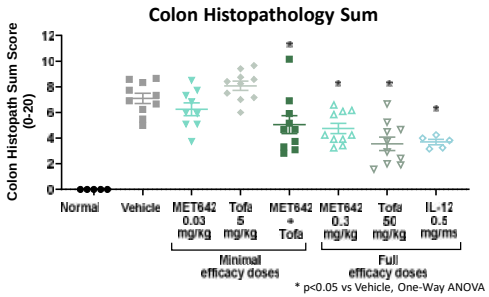
FXR agonist MET642 exhibited efficacy similar to tofacitinib or anti-IL-12. A combination of sub-efficacious doses of MET642 and tofacitinib synergistically improved colitis, similar to each agent when dosed at maximally efficacious dose levels.

MET642 reduces innate immune cell population but not T-cell population in MLN.

These findings support further development of MET642 as a potential oral therapy for IBD - either as monotherapy or in combination with JAK inhibition.

RESULTS

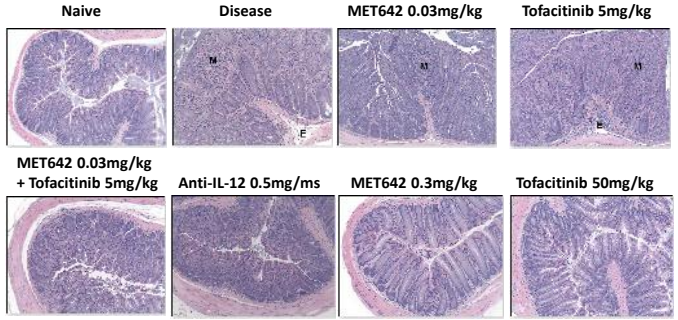
MET642 alone and in combination with tofacitinib improves colon histopathology



* p<0.05 vs Vehicle, One-Way ANOVA

Treatments	Inflammation Score (0-5)	Hyperplasia Score (0-5)	Gland loss Score (0-5)	Histopathology Sum (0-20)
Naïve	0.0	0.0	0.0	0.0
Vehicle	2.9[a]	3.4[a]	0.7[a]	7.1[a]
MET642, 0.03mg/kg	2.6[b]	3	0.5	6.3
Tofacitinib, 5mg/kg	3.0	3.7	1.1[b]	8.1
MET642 0.03mg/kg + Tofacitinib 5mg/kg	2.5[b]	2.0[b]	0.7	5.3[b]
MET642 0.3mg/kg	2.5[b]	2.1[b]	0.2[b]	4.8[b]
Tofacitinib, 50mg/kg	1.9[b]	1.2[b]	0.5	3.6[b]
Anti-IL-12p40	2.2[b]	1.1[b]	0.5	3.7[b]

Data shown is mean; a, p<0.05, vs Naïve, b, p<0.05, vs Vehicle, One-Way ANOVA



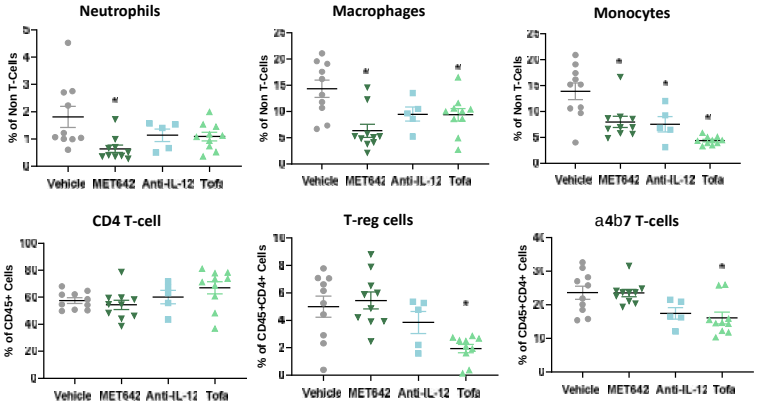
- Maximally efficacious dose of MET642 (0.3 mg/kg) improves colon histopathology similar to tofacitinib (50 mg/kg) and anti-IL-12
- Sub-efficacious doses of MET642 and tofacitinib alone have no effect, but in combination significantly improves colon histopathology

Profiles of immune cells in mesenteric lymph node (MLN) post treatment

- Both innate and adaptive immune cells are crucial in IBD pathology, inflammation of macrophages and neutrophils drives the down-stream activation of effector T-cells
- Our previous work showed similar changes induced by MET642 in immune cell profile in MLN and colon in the adoptive T-Cell transfer model
- In this study, we examined the effects of MET642 on various immune cells in MLN, and compared that with anti-IL-12 and tofacitinib at fully efficacious doses

Single cell suspension from MLN → Flow cytometry analysis of different cell types

Gating	Cell types
CD45+CD4+CD3+	T cells
CD45+CD4-CD3-CD11b+	Monocytes
CD45+CD4-CD3-CD11c+F4/80+	Macrophages
CD45+CD4-CD3-Ly6G+	Neutrophils
CD45+CD4+CD25+FoxP3+	T-regs



All treatments are at full dose level, *p<0.05, vs Vehicle, One-Way ANOVA

- MET642 significantly reduces population of innate immune cells (neutrophils, macrophages and monocytes) in MLN, with no significant effect on T cells
- Tofacitinib significantly reduces macrophage, monocytes, T-reg and α4β7 T-cells and similar trends were observed with anti-IL-12
- FXR mediated improvement in barrier function and anti-microbial activity likely decreases the activation of innate immune cells, leading to reduced colitis.

DISCLOSURES

B.W., A.M., X.L. are employees and equity holders in Metacrine, Inc.