PRECLINICAL CHARACTERIZATION OF PTG-100, AN ORAL α4β7 INTEGRIN PEPTIDE ANTAGONIST FOR TREATMENT OF ULCERATIVE COLITIS

Larry Mattheakis, Ashok Bhandari, Lu Bai, Genet Zemedes, Vinh Tran, Natalie Spencer, Herodion Celino, Brian Frederick, Jennifer Dias, Li Zhao, Thamli Annamalai, Dinesh Patel, David Liu

Protagonist Therapeutics, Milpitas, CA USA

ABSTRACT

PTG-100 is a selective oral α4β7 integrin antagonist with low exposure in blood and high exposure in GI tissues. PTG-100 and the clinically validated anti-α4β7 antibody vedolizumab have comparable potency and selectivity in a variety of assays including blocking adhesion of human CD4+ T cells to MAdCAM-1, and binding to primary leukocytes in human blood. Pharmacokinetic studies in cynomolgus monkey show that exposure of PTG-100 in GI tissues is >100-fold compared to that in blood. In murine DSS acute colitis studies, PTG-100 showed a dose dependent reduction of CD4+CD45RO+CD45RBlow α4β7+ T cells in the MLN and Peyer’s Patches, and a concomitant increase in the spleen and blood. There was also a dose-dependent reduction in body weight loss and mucosal injury as assessed by endoscopy. A close analogy of PTG-100 reduced disease severity as assessed by histopathology, and it reduced the infiltration of α7+ cells into the lamina propria and isolated lymphoid follicles of the distal colon in a murine chronic DSS model. In cynomolgus monkeys, PTG-100 saturated the receptor occupancy of α4β7−memory CD4+ T cells and increased the percentage of circulating α4β7+CD4+ T cells in blood after seven days dosing. Together, these results suggest that PTG-100 may be acting locally within the gut lymphoid compartment to block memory T cell pathology and support its clinical advancement.

BACKGROUND

Figure 1. Lymphocyte trafficking. Oral PTG-100 crosses the epithelial barrier from the lumen to block lymphocyte trafficking in gut lymphoid tissues and blood

RESULTS

IN VITRO STUDIES

Table 1. PTG-100 is selective for human circulating α4β7+ memory T cells.

PHARMACOKINETICS STUDIES CYNOMOLGUS MONKEY

Table 2. PTG-100 exposure in cynomolgus monkey is much greater in intestinal tissues compared to plasma.

PHARMACODYNAMICS/EFFICACY ACUTE DSS COLITIS MICE

Figure 3. PTG-100 reduces α4β7+ T cells in gut lymphoid tissues and redirects them to blood.

Figure 4. The tool Peptide X reduces colon macroscopic and histopathology scores comparable to antibodies in a murine 15 day chronic DSS model.

Figure 5. The tool Peptide X reduces infiltration of β7+ cells into the lamina propria of the distal colon.

PHARMACODYNAMICS STUDIES CYNOMOLGUS MONKEY

Figure 6. PTG-100 increases blood receptor occupancy of α4β7+ memory CD4+ T cells in cynomolgus monkey.

CONCLUSIONS

• PTG-100 is the first oral antagonist selective for α4β7 integrin.
• In murine colitis models, PTG-100 and similar analogs block T cell trafficking and reduce histopathology to levels similar to that of pathway specific Abs.
• In the blood of cynomolgus monkeys, PTG-100 saturates blood receptor occupancy and increases circulating levels of α4β7+ CD4+ T cells.
• PTG-100’s low blood exposure and high GI exposure suggests it may be acting locally within the gut lymphoid compartment to block memory T cell pathology.

CORRESPONDENCE

Larry Mattheakis, Ph.D.
Protagonist Therapeutics
521 Cottonwood Drive
Milpitas, CA 95035 USA
Email: l.mattheakis@protagonist-inc.com
www.protagonist-inc.com