Guanylyl Cyclase-C Agonists, a New Class of Drug Candidates for Treatment of Inflammatory Bowel Disease

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ABSTRACT

Uroguanylin (UG) is an endogenous peptide secreted into the GI lumen, where it binds to guanylyl cyclase-C (GC-C) and stimulates intracellular production of cyclic guanosine monophosphates (cGMP). The resultant stimulation in cGMP synthesis leads to activation of cyclic-B, Novel tissue transmembrane conductance regulator (CPT), resulting in enhancement of the transepithelial efflux of sodium, potassium, chloride and influrof calcium. We previously reported that the expression of UG is dramatically reduced in human colonic polyps and in cancerous tissues. Importantly, oral treatment with UG also inhibited poly formation in Amin mice. Recently, we discovered that UG agonists develop as a safe and an effective oral drug for treatment of ulcerative colitis and inflammatory bowel disease. We previously reported that the anti-inflammatory activity of UG agonists in murine models of colitis. We previously administered orally may enhance the production of cGMP, which in turn activates cystic fibrosis transmembrane conductance regulator (CFTR), resulting in downregulation of certain pro-inflammatory cytokines. Thus, we reasoned that GC-C agonists, when administered orally may produce anti-inflammatory effects in murine models of colitis. We previously reported that oral treatment with plecanatide (SP-334), a superior analog of UG, ameliorated DSS-induced IBN in mice. Recently, we discovered SP-333, a highly potent and a protectin-resistant peptide analog of UG. In this study, we report for the first time that oral treatment with SP-333 ameliorated IBN inflammation through downregulation of pro-inflammatory cytokines such as IL-1, IL-5, IL-17, IL-23 and TNF-a. Thus, SP-333 has potential to be developed as a safe and an oral drug for treatment of ulcerative colitis and Crohn’s Disease in humans.