Letter to the Editor: Naltrexone Therapy for Crohn's Disease and Ulcerative Colitis

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To the Editor:

In the April edition of Journal of Clinical Gastroenterology, Dr. Smith and colleagues published a randomized, placebo controlled study of low dose naltrexone therapy for Crohn's disease (1). Naltrexone was used as sole therapy in children with moderate to severe Crohn's disease. Therapy was safe and clinical improvement was demonstrated as evidenced by statistically significant reduction in CDAI and improvement in quality of life scores. Two prior publications from this group focused on adults with Crohn's disease and LDN was used as adjunctive therapy (2,3). The double blind study showed statistically significant clinical and endoscopic healing (3). A fourth study in the literature was a case report showing success in a child with duodenal Crohn's disease (4).

Neuropeptides (e.g., enkephalins and endorphins) are present in the gastrointestinal tract and modulate immune responses (5,6). Up-regulation of met-enkephelin (opioid growth factor) and opioid receptors can be induced by a rebound effect from administration of short-acting, low dose naltrexone (7). Higher levels of endogenous opioids and receptors inhibit cell proliferation which suppress B and T lymphocyte responses (8,9). Naltrexone acts to reverse a mouse colitis model by decreasing pro-inflammatory interleukins 6 and 12 (10).

In light of the Crohn's disease naltrexone literature and similar clinical experience, LDN was prescribed as adjunctive therapy to adults with moderate to severe ulcerative

colitis who failed or had partial response to mercaptopurine and/or infliximab in a clinician's practice. Questionnaires were administered as part of routine follow up. Adverse events were evaluated. Preliminary evidence for clinical efficacy was determined by self-assessed questionnaires. Positive responses included "markedly or moderately improved". Failed responses were "mild help", "temporary help", "not helped" or "withdrew due to side effects". A retrospective chart review was performed. Twelve patients received naltrexone 4.5 mg/day. Duration (mean ±SD) of naltrexone treatment was 46 ±75 weeks (maximum 270 weeks). One patient withdrew after 8 weeks owing to insomnia. Positive clinical responses were reported in 6 of 12 patients. Two clinical responders had colonoscopy before and after naltrexone and each had complete mucosal healing. Adjunctive low dose naltrexone is appears to be effective in some ulcerative colitis patients who are failing conventional therapy. A double blind study is required owing to a high placebo rate in ulcerative colitis (11).

References

1. Smith JP, Field D, Bingaman SI, Evans R, Mauger DT. Safety and tolerability of low-dose naltrexone therapy in children with moderate to severe Crohn's disease: a pilot study. J Clin Gastroenterol 2013;47:339-345.
2. Smith JP, Stock H, Bingaman S, et al. Low-dose naltrexone therapy improves active Crohn's disease. Am J Gastroenterol 2007;102:820-828.
3. Smith JP, Bingaman SI, Ruggiero F, et al. Therapy with the opioid antagonist naltrexone promotes mucosal healing in active Crohn's disease: a randomized placebo-controlled trial. Dig Dis Sci 2011;56:2088-2097.

4. Shannon A, Alkhouri N, Mayacy S, Kaplan B, Mahajan L. Low-dose naltrexone for treatment of duodenal Crohn's disease in a pediatric patient. Inflamm Bowel Dis 2010;16:1457.
5. Gross K, Pothoulakis C. The role of neuropeptides in inflammatory bowel disease. Inflamm Bowel Dis 2007;13:918-932.
6. Holzer P. Opioid receptors in the gastrointestinal tract. Regul Pept 2009;155:11-17.
7. Zagon IS, McLaughlin PJ. Targeting opioid signaling in Crohn's disease: new therapeutic pathways. Expert Rev Gastroenterol Hepatol 2011;5:555-558.
8. Zagon IS, Donahue RN, Bonneau RH, McLaughlin PJ. B lymphocyte proliferation is suppressed by the opioid growth factor-opioid growth factor receptor axis: Implication for the treatment of autoimmune diseases. Immunobiology 2011;216:173-183.
9. Zagon IS, Donahue RN, Bonneau RH, McLaughlin PJ. T lymphocyte proliferation is suppressed by the opioid growth factor ([Met(5)]-enkephalin)-opioid growth factor receptor axis: implication for the treatment of autoimmune diseases. Immunobiology 2011;216:579-590.
10. Matters GL, Harms JF, McGovern C, Fitzpatrick L, Parikh A, Nilo N, Smith JP. The opioid antagonist naltrexone improves murine inflammatory bowel disease. J Immunotoxicol 2008;5:179-187.
11. Garud S, Brown A, Cheifetz A, Levitan EB, Kelly CP. Meta-analysis of the placebo response in ulcerative colitis. Dig Dis Sci 2008;53:875-891.