Octreotide and its effects on Steroid resistant Crohn's Disease

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A. Introduction

The treatment of Crohn's disease continues to be a challenge as its pathogenesis remains obscure. Compounded by the increased incidence of Crohn's disease in the past twenty years incidence of 5/100,000, prevalence of 50/100,000), we are faced with an ever increasing number of treatment failures.

The pathogenesis of inflammatory bowel disease stems from a dysregulation of the immune system, with persistent amplification of inflammatory cytokines, ultimately leading to tissue destruction and disease. Conventional treatment continues to be sulphasalazine or 5-ASA and glucocorticoids. For early disease and maintenance therapy, these medications have proven to be satisfactory and widely tolerated. Yet by the nature of this disease, patients relapse. They require increasing doses of medications thereby becoming resistant and simultaneously developing side effects. Sulphasalazine was shown to be more effective than placebo in controlling active disease, but was not as efficacious as steroids (2,3). In addition, not all patients can tolerate 5-ASA secondary to mild side effects including diarrhea, dizziness, nausea, and headache. Glucocorticoids are still considered to be very effective and are the most popular prescribed medications for acute active disease. The National Cooperative Crohn's Disease Study showed that 47% of patients achieved remission and 60% improvement under therapy with varying doses of prednisilone. (2) Despite it effectiveness, glucocorticoids have a wide and significant side effect profile, and are considered unsafe to be used with frequent exacerbations and moreover as maintenance therapy.(1)

Most recently, immunosuppressive agents such as azathioprine (Imuran) and Purinethanol (6-mercaptopurine.) have been introduced as potential therapies for patients who have chronic active disease or who are steroid dependent. The above medications work similarly in that they inhibit the synthesis of protein, RNA, and DNA.(4) In an important study by Present et al., they showed that 6-MP was effective in active disease, but that its clinical effect was delayed by 3-6 months.(5) Side effects of 6-MP and AZT include allergic type reactions as well as leukopenia, thrombocytopenia, hepatitis, and malignancy.(4) As a result of the increasing number of patients with steroid resistant disease and the long delay of action of 6-MP and azathioprine, researchers have been looking to directly target those cytokines which are deficient or overproduced in inflammatory bowel disease to control this chaotic inflammatory process.(1)

Of these proinflammatory cytokines, TNF (has been the most explored to date. TNF alpha has been shown to be overproduced by the T cells in patients with IBD. Two pivotal studies have shown that cA2, a TNF (chimeric monoclonal antibody, resulted in either a significant decrease in the Crohn's Disease Activity Index (a decrease in the CDAI to > 70) or remission (CDAI <150).(7,8) The antibody was FDA approved and has been used at our institution. The initial response is remarkable however it is transient. In addition, when the cA2 is able to effect a response, most patients form an antibody to the mouse portion of the TNF antibody and are not further able to tolerate the medication on another occasion. To resolve this complication, Stack et all demonstrated in a double blind placebo controlled trial of patients with mild to moderate Crohn's disease, that CDP571, a genetically engineered human antibody to TNF (had a significant reduction in the Crohn's Disease Activity Index in patients from a score of 263 to 167 with 6 remissions out of twenty.(6)

IL –10 has also been studied as a potential anti-inflammatory agent in IBD. IL-10 suppresses inflammation by reducing monocyte HLA class II expression, decreasing T cell secretion of IL-2, interferon gamma and other inflammatory cytokines produced by monocytes (9). A study by Sander et al. showed a mean decrease in the CDAI from 280-179 in steroid resistant patients treated with placebo vs. IL-10.(9) However a further study by Schreiber et al. did not show a difference.(10)

Immunomodulation therefore, remains at the forefront of Crohn's disease therapy research. Somatostatin has been used widely for other gastoenterological diseases and has most recently been studied for its effects in inflammatory bowel disease. Somatostatin has been shown to have an immunoregulatory effect in vitro and in vivo colitis. In a laboratory at Mount Sinai Hospital, it was demonstrated that somatostatin inhibits TNF (mRNA expression in IEC-6 rat intestinal epithelial cells and also in isolated human intestinal mucosal cells from IBD patients. In addition, rat models with induced colonic mucosal damage from acetic acid, showed that somatostatin was preferentially produced indicating its protective function of the normal bowel.(11) As hypothesized, somatostatin gene expression was significantly decreased in patients with inflammatory bowel disease from OR samples. Currently work is in progress at Mount Sinai hospital by Dr. Mark Babyatsky, who is comparing local mRNA somatostatin production in patients with IBD versus patients with other forms of inflammation and showing that the former is deficient in somatostatin synthesis.

As a continuation to the above research, patients are currently being recruited at the Mount Sinai Medical Center for the use of subcutaneous octeotride, a long acting analog of somatostatin, in patients with active Ulcerative colitis on an outpatient basis.

In this study, we are looking to see the effects of somatostatin by using its long acting analog, octeotride, in patients with active steroid resistant Crohn's disease, over a two week treatment period.

B. Study design and Methods

Prospective double blind placebo controlled trial of approximately 80 patients to assess the efficacy of octeotride in patients with two weeks of steroid resistant Crohn's disease. The primary endpoint is a reduction in the Crohn's Disease Activity Index to $\geq$ 70 at at the end of a two week evaluation. Secondary endpoints include a decrease in the CRP (C-reactive protein) and or the ESR and remission as identified as a CDAI of less than 150.

Patients who are eligible should have two weeks of steroid resistant active disease. After consent is obtained, they will be screened one week prior to treatment to establish baseline scores on the CDAI. In addition baseline CRP and ESR's are drawn at that time. Patients will then be admitted to the hospital and randomly assigned to treatment or placebo. Treatment will consist of 500 mcg of octreotide subcutaneously TID and the placebo is normal saline. Patients will continue their current dose of steroids and cannot change the dosage thoughout the treatment period. Patients who are already taking 5-ASA may also continue, however it should be noted that all patients may not be using a mesalamine at the time of analysis and this dosage should remain stable throughout the study. While in the hospital, potential confounders such as diet, attentiveness to patient care, adherence to the protocol can be accounted for. At two weeks, The CDAI questionnaire will be readministered as well as an ESR and CRP drawn.

Approximately 10 patients per attending physician at CPMC are admitted with Crohn's disease per year. This amounts to approximately 100 patients and is sufficient for this study. The expected time needed for this study is one year.

The Crohn's Disease Activity Index was developed in 1976 by Best et al. to standardize overall Crohn's disease activity in response to the need to evaluate the clinical response of patients to new therapies. The Crohn's Disease Activity Index incorporates eight variables of disease including the number of liquid or soft stools, the severity of abdominal pain or cramping, general well being, the presence of extraintestinal manifestations, abdominal mass, the use of antidiarrheal drugs, the hematocrit and body weight.(13) In total, the score can range from 0 –600, with higher scores implying worse disease. The CRP and ESR are surrogate markers of disease activity.

The use of endoscopy in Crohn's disease as a measure of activity of disease has been largely abandoned since it was reviewed at the Los Angeles world conference in 1994 and found not to be consistent.(1)

C. Study Subjects: Inclusion and Exclusion Criteria

Patients eligible for the study are to be between the ages of 18-65 with active steroid resistant Crohn's disease of the colon or both the ileum and the colon. A firm diagnosis of Crohn's disease is required by either radiologic or histologic evidence, or a combination of the two. Active steroid resistant Crohn's disease is defined as a CDAI score of >250 and <400 despite treatment with a minimum of 20 mg of prednisone over a two week period. Patients on 5-ASA are not excluded nor are patients on azathioprine or 6-mercaptopurine as long as the dose has been stable over a six month period.

Exclusion criteria include patients who have been on any immunomodulating therapies including IL-10, cyclosporin, TNF alpha antibody, methotrexate, or any other experimental therapies in the last six months as this may have unknown lasting effects on the inflammatory cytokine cascade. In addition patients will also be excluded with short bowel syndrome, profuse rectal bleeding, pregnancy, immediate need for surgery, severe obstruction, h/o known drug abuse, cigarette use, and positive Hepatitis B or C or HIV serologies.

D. Study Drug

Octeotride is a widely used and well-known drug used in a variety of medical conditions. Somatostatin was first described in 1968 by Krulich and coworkers when they discovered that a rat hypothalamic extract inhibited the release of growth hormone from the rat pituitary in vitro. In 1983, a long acting analog of somatostatin had already been synthesized and was available for investigational use. Somatostatin has its effects in numerous locations thoughout the body from the nervous system to the kidney, thyroid, and salivary glands. Most of all somatostatin has its effect on the GI tract where its secretory cells are ubiquitous. Its functions vary according to the receptor and the location in the body, from neurotransmitter to an endocrine, paracrine and autocrine substance.(12)

Native somatostatin occurs in two biologically active forms, a tetradecapeptide and a 28 residue peptide. Exogenous somatostatin has a very short half-life of 2-3 minutes which is the reasoning behind the long acting synthetic analog. Octeotride is a synthetic cyclic octapeptide with a 4 amino acid sequence identical to the active tetradecapeptide, responsible for its biological activity. Octeotride can be administered IV or SC with an elimination half-life of 90 minutes and 100% bioavailability when given SC. (12)

Current gastroenterological uses of octeotride include diarrhea secondary to carcinoid syndrome, VIP secreting tumors, and AIDS. Other therapies include its use for dumping syndrome, acute variceal bleeds, and enterocutaneous fistulas.(12)

To date, the side effect profile has been generally mild. Approximately 10% of patients complain of pain at the injection site, which can be decreased by slowing the infusion or warming the solution prior to injection. Patients also complain of nausea, bloating, diarrhea, and constipation. Steatorrhea can be seen at high doses of the medication. Octeotride can also suppress insulin release and rarely causes glucose intolerance in normal subjects. Patients with or without diabetes should be monitored for glucose control. Also well described in the literature is the development of gallstones while on long term octeotride. The incidence is rare, however and careful physical exams with routine labs should be sufficient to screen for gall bladder disease. Ultrasound should be done as needed.(12)

E. Statistical Analysis

The calculation of sample size was based upon published data giving a standard deviation between patients for activity index of patients with Crohn's disease of approximately 100. This formulation derives a total sample size of 80, with 40 patients in each arm. The study plans to have 80% power to detect a fall in the CDAI of $\geq$70, using a t test at p=.05. The patients in the placebo group are not expected to have a significant change in their mean CDAI during the two week treatment period.

F. Risks and Benefits

There is no anticipated long or short term risks. Patients who are unable to tolerate the study drug will stop and continue on conventional therapy. The potential benefits include the possibility of a new acute therapy for Crohn's disease, a new maintenance therapy, and to possibly decrease steroid dependence and/or an earlier taper of steroids during an acute flare.

G. Limitations

Intolerance to the medication.

H. Compensation

Patients will not incur any extra costs by participating in this study. The pharmaceutical company will provide the medication, octeotride. All other lab work, hospital admission etc. should be paid for by the insurance company.

I. References

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