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An Observational Chart Review on the Efficacy of Subcutaneous Methotrexate in Mild to Moderate Ulcerative Colitis and the Description of Occurrence of Adenomatous Polyps in Afflicted Patients

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ABSTRACT

Ulcerative Colitis (UC) is a type of Inflammatory Bowel Disease (IBD) that affects the large intestine and produces mainly symptoms of abdominal pain and bloody stools. Chart reviews of patients from July 2011 to July 2012 with mild to moderate UC enrolled in a community-based NIH trial on the efficacy of 8 weeks of 12.5 mg once daily subcutaneous methotrexate demonstrated no significant improvement of abdominal pain and bloody stools. In their patient diaries and IBD Questionnaire, all 9 patients reported a sense of heaviness or abdominal fullness, bloating or cramps. The patients experienced decreased energy levels and depressed feelings with anxiety and decreased sleep at night. Overall, the majority of them reported a decreased quality of life despite the 8 week trial of MTX. We also noted in the chart review the incidental finding of histopathologically-confirmed distal adenomatous polyps in all 9 patients for which we postulate the following: 1) that distal adenomatous polyps may be a risk factor in UC, 2) that surgical removal or polypectomy for these polyps, if diagnosed earlier especially in those younger than 40 years of age, may delay progression or prevent development of UC, 3) the presence of polyps in all 9 patients could have prevented the desired therapeutic response from methotrexate, and 4) that the presence of the polyps may indicate that low dose methotrexate is not an effective treatment for UC. The presence of intestinal polyps realigns the structural integrity and dynamics of the movement of the intestinal walls and valves, causing affected patients to frequently report feelings of discomfort and lethargy. It is important to understand that further diagnosis and therapies for UC and IBD are accompanied with ethical questions, such as treating affected patients with cytotoxic medications and performing colonoscopies under the standard age care of 50 years. Further research needs to address combination therapies and other risk factors such diets and preservatives to determine the full extent of this potential ground-breaking science.

KEYWORDS AND ABBREVIATIONS: Ulcerative Colitis (UC); Inflammatory Bowel Disease (IBD); Methotrexate (MTX); Subcutaneous (SC); Mayo Disease Activity Index (Mayo DAI); Inflammatory Bowel Disease Questionnaire (IBDQ).

INTRODUCTION

Inflammatory Bowel Disease (IBD) is a chronic inflammatory disease primarily of the large intestine. It is a disease that affects mostly Caucasians in western countries and those

of Jewish ancestry.[1,2] IBD consists of two major subsets of unknown etiology: Crohn's Disease and Ulcerative Colitis (UC). In both diseases, the inflammation of the large intestine, or colon, is a result of the complex interaction of genetic predisposition, immune dysfunction and environmental triggers.[1,3] The environmental trigger (food, bacteria, or any intestinal material) may directly cause the inflammation or stimulate the immune system to go unregulated e.g. "turned on" for chronic periods of time. This cascade of events damages the intestines and inflicts severe, adverse biological consequences on the human body.

In Ulcerative Colitis, the mucosal lining of the colon has marked erythema, edema, granularity, abnormal vascular patterns with varying depth and severity of ulcerations. Major gastrointestinal symptoms include crampy abdominal pain, persistent diarrhea and bloody stools. There are also associated extraintestinal symptoms. These symptoms can go for long periods of times and can be unpredictable, so-called flare-ups. In a Norwegian Study,[4] it was found that there is an incidence of 32% of rectal involvement (proctitis), 33% left-sided colitis, and 35% extensive or pancolitis. It is believed that 90% of cases will experience a relapsing course of which approximately 10% may require surgery.[4-6] However the American Society of Colon and Rectal Surgeons estimates that 38% will require surgery within 13 years of diagnosis.[7] The majority of patients will be on lifetime medical treatment.

The severity (mild, severe, or fulminant) of disease in afflicted UC patients can be assessed by the Mayo Score and the Disease Activity Index[8] which is based on the following parameters: stool frequency, rectal bleeding, mucosal appearance at colonoscopy and physician rating of disease activity. The extent of the disease determines mode of therapy with distal disease requiring topical therapy and more extensive disease requiring a combination of oral and topical medications. It is the goal of medical treatment to induce and maintain remission in mild to moderate disease and prevent surgery in severe cases. Surgery can be curative in severe cases when complications are life-threatening (massive bleeding, perforation, and infection) with increased risk of developing colon cancer.[9]

The standard medical treatment of UC consists of a combination of oral and rectal (enema, suppositories) aminosalicylates and corticosteroids (oral, intravenous, rectal).[1,2,8,10-16] Immunosuppressants (6-mercaptopurine, azathioprine, methotrexate, cyclosporine, tacrolimus, and infliximab) have been used in steroid-dependent or steroid-refractory cases.[1,17-19]

Methotrexate (MTX) is an antimetabolite used in the treatment of certain neoplastic diseases, severe psoriasis, and adult rheumatoid arthritis.[20-23] It is classified as antineoplastic and anti-metabolite. As an anti-metabolite it inhibits folic acid reductase which is responsible for the conversion of folic acid to tetrahydrofolic acid which is important in DNA synthesis. It selectively affects the most rapidly dividing cells.[22-25] Both mechanisms of action lead to cell death. Side effects of low-dose MTX therapy include: anorexia, nausea, stomatitis or diarrhea. Adverse events include bone marrow suppression, liver toxicity, and on rare occasions, opportunistic infections.[2,14,26,27]

Chemically methotrexate is N-[4-[[(2,4-diamino-6-pteridinyl)methyl]-methylamino]benzoyl]-Glutamic acid. The structural formula is:

Molecular weight: 454.45 $C_{20}H_{22}N_8O_5$

MTX has been found to induce and maintain remission in Crohn's disease.[26,28,29] However there have been limited studies of its application in UC. The oral dose of 20 mg/week has been found to be well-tolerated and moderately effective.[30] In uncontrolled studies, the parenteral intramuscular dose of 12.5 mg has been found to be effective.[27,28,31] It has been described that the Subcutaneous (SC) and intramuscular administration produces similar bioavailability of the drug but the SC is better tolerated.[10,29,32-34] In a prospective double-blind controlled trial using SC methotrexate in rheumatoid arthritis a higher response rate is produced.[24,35] There are limited studies comparing oral *versus* parenteral efficacy of MTX in IBD. However it has been established that in Rheumatoid Arthritis (RA) and IBD, there is limited value in monitoring drug levels as they do not correlate with efficacy.[35-39] Currently, there is an on-going MERIT-UC NIH funded multi-center prospective placebo controlled study investigating the safety and efficacy of 25 mg MTX applied subcutaneously once weekly in patients with active UC, who are either steroid dependent or are intolerant or not responding to aminosalysilate therapy or have not responded or lost response to infliximab.[20] Preliminary data show 46% clinical response after 4 weeks of subcutaneous MTX following failure of a 12 week course of steroids.[20]

METHODOLOGY

Purpose of Study

A multi-center, community-based, double blind,[40] NIH trial on the efficacy and safety of 12.5 mg subcutaneous Methotrexate (MTX) in mild to moderate ulcerative colitis or proctitis from July 2011 to July 2012.

The aims of the trial were: 1) To evaluate the safety and tolerability of 12.5 mg MTX applied SC once weekly over a time period of 8 weeks, 2) To objectively evaluate the relapse-free survival of MTX maintenance therapy after 8 weeks of therapy through colonoscopy or proctosigmoidoscopy, and 3) To evaluate the efficacy of MTX over a time period after 8 weeks of therapy through patient diary of presence or absence of abdominal pain and bloody stools, and response to quality of life issues in the 32-question Inflammatory Bowel Disease Questionnaire.

Materials and Methods

A review of clinic notes of patients included in the phase IIIa study trial of open-label use of 12.5 mg of subcutaneous methotrexate in mild to moderate ulcerative colitis as assessed by the Mayo Disease Activity Index (Mayo DAI) (Table 1).[8] Table 2 and Table 3 lists the parameters used in patient selection. A protocol guideline for allowed medications and procedures and prohibited chemotherapeutic agents was followed (Table 4).

Methotrexate 12.5 mg was administered subcutaneously for 8 weeks. At the end of the study period, the patients were administered the Inflammatory Bowel Disease Questionnaire (IBDQ; Mc Master University, Hamilton, ON, Canada 2010). This 32-item questionnaire is a reliable and validated tool widely used to assess the general well-being of patients in the recent 2 weeks. It is scored in four domains: bowel symptoms, emotional health, systemic systems, and social function.

Stool Frequency 0= normal no. of stools for this patient 1= 1-2 stools/day more than normal 2= 3-4 stools/day more than normal 3= >=5 stools/day more than normal
Rectal bleeding* 0 = None 1 = Streaks of blood with stool less than half the time 2 = Obvious blood with stool half of the time or more 3 = Passing blood alone
Mucosal appearance at endoscopy 0 = Normal or inactive disease 1 = Mild disease (erythema, decreased vascular pattern, mild friability) 2 = Moderate disease (marked erythema, absent vascular pattern, friability, erosions) 3 = Severe disease (spontaneous bleeding, ulceration)
Physician rating of disease activity: takes into consideration the patient's abdominal discomfort, general sense of well-being, and functional status 0 = Normal 1 = Mild 2 = Moderate 3 = Severe

Table 1: Mayo Disease Activity Index (DAI).

RESULTS

Of the 9 subjects reviewed in this observational chart review, 5 were under 40 years of age. After 8 weeks of subcutaneous therapy of 12.5 mg of MTX, bloody stools were evident in 9 of the 9 patients (100%). Many instances of abdominal pain were also noted by the patients as well. Some of them mentioned having suffered leg cramping, especially during the middle of the night. Individually, many of them complained of being unable to get a good night's rest, and as a result, demonstrating a lack of energy throughout the day. However, even if the former was not the case, some of these individuals indicated in their diaries that they experienced lethargy, perhaps due to the pressure of the colonic disease affecting their ability to properly perform the tasks that they would normally do. Another prominent symptom common among these patients is the negativity of their emotional and psychological state. Subjects were given a set of standardized questionnaire, called the IBDQ that characterized and assessed their emotional state and well being. In their responses, these subjects often noted feelings of depressed mood and or uneasiness indicating that the abdominal condition may have inflicted a heavy toll on their mental and physical state.

An interesting finding during colonoscopy was the presence of histopathologically-confirmed distal adenomatous polyps in all 9 patients. Adenomatous colonic polyps are rare in ulcerative colitis.[41] In this 2004 study reviewing 150 patients, only 6 (4%) had adenomatous polyps. The authors postulate that the decreased prevalence of adenomatous polyps in UC may be possibly due to drug treatments undergone by the patients. Dixon et al. in 2006 reviewed 80 ulcerative colitis patients and found distal adenomatous polyps in only 3 patients ages 55-64 years.[42] Neither did they document polyps in those with Crohn's disease or indeterminate colitis. Our findings of distal polyps in 9 out of 9 patients (100%) do not support these prior 2 studies.

1- male or non-pregnant females, 18 years old and older with the diagnosis of mild to moderate ulcerative colitis confirmed by colonoscopy. 2-Mild to Moderate UC as graded as a Mayo DAI total score between 5 and 10. 3- score of 2 or more for the rectal bleeding subscore of the Mayo DAI 4- score of 2 or more for the findings of the flexible sigmoidoscopy or colonoscopy 3- failure of prior therapies for ulcerative colitis 4- absence of other malignancy or cancer 5- absence of intestinal infections and prior surgeries such as intestinal resections and partial intestinal removal procedures 6-Any clinically significant condition or disease that in the opinion of the investigator would interfere in patient safety 7- signed informed consent to participate in this study	1- presence of other digestive diseases and malignancies 2- chronic use of aminosalicylates 3- significant use of corticosteroids, immunosuppressants or biologic agents prior to the study 4- known contraindications to analgesia, flexible proctosigmidoscopy or colonoscopy 5- abnormal screening laboratory values (complete blood count or CBC and serum chemistry with liver profile) 6- presence of other clinical significant medical and or psychological illnesses precluding participation 7-participation in other observational studies 8- unable or unwilling to complete the follow-up evaluation required in this study

Table 2: Inclusion Criteria and Exclusion Criteria.

Subject	Pt 1	Pt 2	Pt 3*	Pt 4	Pt 5	Pt 6	Pt 7	Pt 8	Pt 9
Bloody stool	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Abdominal Pain	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Colonoscopy Distal Polyps	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Age < 40 yrs	No	Yes	No	Yes	Yes	No	No	Yes	Yes
Prior Therapies	No	No	No	No	No	No	No	No	No
Mayo DAI score	8	8	1	5	9	8	9	8	10

*These were the only enrolled patients in the 12-month study from July 2011 to July 2012.
*Patient 3 did not complete 8 week course because of low Mayo score but had a mild UC classification per colonoscopy.

Table 3: Patient Characteristics and Findings after 8 week administration of SC MTX.*

1. Allowed Concomitant Medications:

Medications taken 90 days prior to and during the study were documented such as intravenous fluids, herbal products, vitamins and any over the counter medications

2. Prohibited Medications:

Aminosalycilates, corticosteroids, immunosuppressants, biologic response modifiers, change in use of nicotine products, probiotic supplements

3. Allowed Adjunctive Therapy or Procedures:

Procedures such as psychotherapy, surgery, dental work, acupuncture, physiotherapy, chiropracty, osteopathy or massage therapy for other illnesses were documented in the chart including diagnostic tests done (such as chest x-rays or electrocardiogram) for other diseases outside the study.

Table 4: Protocol Guideline on Use of Other Medications, Therapies and Procedures.

CONCLUSION

Although methotrexate is a specific drug considered to be effective in Inflammatory Bowel Disease specifically in Crohn's disease, its effectiveness given as a low dose (12.5 mg) subcutaneously for 8 weeks in mild to moderate Ulcerative Colitis may be limited. However, its therapeutic effect may be altered by the dosage, mode of administration and length of treatment. In particular, if required to be administered through the SC method may require a higher dosage. For this particular study and experiment, the sample size was chosen from a predominantly hispanic community with low prevalence of IBD. This could hypothesize that individuals of this ethnic heritage do exhibit immunity to IBD/UC. Therefore, it would remain to be seen whether or not this would legitimately result in a valid conclusion, since it has yet to be tested from a larger sample size representative of a Hispanic population.

DISCUSSION

Methotrexate plays an important role in the blockage of lymphocytes, proliferation of inflammatory precursors, reduction of neutrophil chemotaxis and adherence, and decrease of serum immunoglobulins.[24,25] These biological phenomena serve as the basis of its usage as an immunomodulator in inflammatory bowel disease. Methotrexate bioavailability is affected adversely if high doses are absorbed all at once, thus affecting the rate of response by the patient receiving the drug.[27] This drug must be utilized by controlled entry in order to efficiently ensure the clinical benefits for patients with IBD or UC.[27]

The administration of low dose Methotrexate has been effectively used in the treatment of inflammatory diseases such as Crohn's and more recently has been administered in ulcerative colitis. Roughly 12 observational trials were reviewed and data was analyzed.[27] Results showed that at a 12.5 mg oral dose no results were observed; however in an uncontrolled analysis and at a dose between 20-25 mg a clinical response was observed in 30%-80% of patients.[27]

In this observational chart review of patients with mild to moderate UC given low dose subcutaneous methotrexate (12.5 mg) there was no significant improvement of abdominal pain and bloody stools. Moreover, in the review of all the patient diaries, all 9 of them experienced a sense of heaviness or abdominal fullness, bloating or cramps. The patients also reported with decreased energy levels and depressed feelings with anxiety and decreased sleep at night. Overall, the majority of them reported a decreased quality of life despite the 8 week trial of MTX.

Although distal adenomatous polyps are rare in ulcerative colitis, it has been described that ulcerative colitis is a risk factor for the development of polyps.[43] In this observational chart review of 9 patients, the incidental finding of distal adenomatous polyps in all 9 patients leads us to postulate the following: 1) that distal adenomatous polyps may be a risk factor in UC, 2) that surgical removal or polypectomy for these polyps, if diagnosed earlier especially in those younger than 40 years of age, may delay progression or prevent development of UC, 3) the presence of polyps in all 9 patients could have prevented the desired therapeutic response from methotrexate. However another pos-

sible explanation would be that the polyps are a manifestation of the ineffectivity of low dose SC MTX in UC. As Kitiyakara suggested in 2004, the decreased prevalence of adenomatous polyps in UC may be due to the therapeutic response.[41]

However, the presence of these polyps in these younger patients described may be a cause for concern as the standard care for colorectal cancer screening as presented by the U. S. Preventive Services Task Force (USPSTF) is age 50.[9] Although only a small percentage of adenomatous polyps become cancerous, almost all malignant polyps are adenomatous.[43] As such, the possibility of development of malignant tumors in these patients increases.

Although there is no data or evidence regarding whether or not patient diet was a factor in terms of the biological abnormalities, it could possibly be that artificially added preservatives could be a factor in disease activity. There are not enough studies regarding foreign substances and unconventional body chemicals affecting UC response to medical treatment. Dietary recall should have been included in the questionnaire or patient diaries.

The extent of distribution of the inflammation in UC determines treatment. In most cases of UC, approximately 25-75% suffer inflammation within the proctosigmoid region, proctosigmoiditis.[1,27] Other types of inflammation, such as left-sided colitis, backwash ileitis, and extensive colitis, are relatively less severe compared to proctosigmoiditis. Treatment of the latter three types of inflammations would generally require therapy with oral or intravenous aminosalicylates, which would suffice for the abatement of the effects of the inflammation around the lower intestinal area.[44]

Overall, the use of low dose subcutaneous methotrexate in mild to moderate ulcerative colitis has been found to have limited therapeutic value in inducing remission in the 9 patients reviewed. The findings support previous recommendations that further research is needed incorporating higher dosages of MTX given parenterally.[27]

FURTHER RESEARCH

The use of MTX subsequent to or in conjunction with other immunosuppressants and or biologic therapies may be worth investigating. Also, in order to fully understand and formulate a procedure to investigate the true nature of the IBD UC with regards to the particular presence of intestinal polyps, it may be necessary to determine the primary cause of the appearance of polyps. Specifically, data must be accounted regarding the biochemical content of the food intake during the time spanning the initial mention of the symptoms to the time of the colonoscopy. This will allow conclusions to be made based on any relationships observed between the amount of preservatives, type of food consumed, and the frequency of the symptoms. Also, the idea in which very young patients, the majority of them under the age of 50, experience signs of IBD UC, warrants the need to implement clinical studies that would investigate the pros and cons of performing earlier colonoscopy screening than the recommended age of 50. In particular, a comparative study, consisting of a control group that represents the standard care age group of 50-yr. old patients, and a younger group with several risk factors may provide more information on the incidence of polyps, UC and colorectal cancer. First and foremost, investigation of adenomatous polyps in UC involving a larger sample size in a community where IBD, specifically UC, is of high prevalence would be an interesting study. This will ultimately determine if it is a beneficial, short term approach to the prevention of ulcerative colitis and or colorectal cancer. It remains to be seen if the premature treatment either subsidizes the effects of polyp growth, or causes chronic adverse events that are essentially unrelated to IBD UC inflammation. The financial costs and code of ethics would also be a major factor in this potential approach, especially if it were to yield positive results.

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