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Combined azithromycin and metronidazole therapy is effective in inducing remission in pediatric Crohn's disease

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Abstract

Background: Crohn's disease (CD) is characterized by an aberrant response to the gut microbiota. We aimed to assess whether azithromycin based therapy is effective in inducing remission in CD, due to its effect in inducing apoptosis and efficacy against biofilms and intracellular bacteria.
Methods: Retrospective analysis of patients treated with an 8 week course of combined azithromycin and metronidazole. Patients were included if they had active CD defined as pediatric CD activity index (PCDAI) $\geq$10, and were not receiving any other medication for inducing remission in active disease. PCDAI score and CRP were recorded at baseline and 8 weeks thereafter.
Results: Thirty two patients (mean age 13.1 $\pm$ 3.9, mean duration of disease 0.65 years) were included, of whom 21 (66%) entered clinical remission (PCDAI $<$ 10) after 8 weeks of treatment. The mean age at treatment and duration of disease did not differ between patients entering remission and those unresponsive to therapy. CRP, normalized in 54% of patients with elevated CRP at baseline. Factors associated with lack of response were a more severe disease (reflected by higher PCDAI and CRP values at baseline), presence of arthritis and extensive disease (ileocolonic, or prominent upper intestinal disease).
Conclusions: An 8 week course of azithromycin and metronidazole therapy may be effective in inducing clinical remission in mild-moderate luminal CD in children and young adults.

1. Introduction

Growing evidence suggests that Crohn's disease (CD) results from a defective or inappropriate response to the gut microbiota. Bacteria have been shown to reside on and invade epithelial cells of inflamed mucosa and granulomas and to

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replicate inside macrophage phagolysosomes.[1–8] Patients with CD often have circulating antibodies against bacterial antigens.[4,8] Several disease susceptibility genes in CD are associated with innate immunity, recognition of bacterial pathogens, and handling of intracellular bacteria.[9–15] A second derangement that may be seen in association with CD is defective apoptosis of activated T cells, possibly via defective NOD2/CARD15 that may prevent apoptosis of dendritic cells.[12,16]

These data might suggest that constant bacterial triggering of the immune system combined with the inability to eradicate bacteria and down regulate T cell activation may be the underlying reason for disease activity. The major flaw in this proposed pathogenesis to date has been the relative lack of efficacy of antibiotics. Multiple previous studies failed to show a benefit of antibiotic therapy for inducing remission in CD,[18,19] with the exception of one small study.[17] Subsequently, recent reviews and guidelines did not recommend antibiotic therapy for induction of remission.[19,20] These studies focused primarily on the azole family of antibiotics (mainly metronidazole) and quinolones. Azithromycin has never been studied to date despite its several intriguing properties that make it an attractive candidate for inducing remission. It has excellent intracellular penetration and with its high luminal concentrations, it may be ideal for acting against the persistent intracellular bacteria in CD that, in turn, may trigger the on-going inflammation. It also acts on biofilms which may be resistant to many types of antibiotics,[7] and is a potent activator of apoptosis of T cells.[21–23] Combined with metronidazole, it covers a wide variety of bacteria that colonize the small and large intestine. Several years ago one of the authors (AL) encountered several patients with Crohn's colitis refractory to medical therapy who responded to azithromycin based therapy. The index case was a 7 year old girl with CD colitis from age 1 year, who had required a hemicolectomy at age 3. She had not responded previously to antibiotics. A colonoscopy at the time of treatment displayed active colitis. She received azithromycin based therapy for 8 weeks, with complete remission and mucosal healing, the remission lasted 1 year, and two subsequent relapses over the second year responded to a repeat course of azithromycin and metronidazole. This led us to use of azithromycin based therapy, using the same protocol, as the preferred antibiotic therapy in our practice.

The aim of this study was to review our experience with a combination treatment of azithromycin and metronidazole for induction of remission in active CD, following a standardized protocol.

2. Methods

This is a retrospective report of our experience with azithromycin based antibiotic therapy for active CD in children and young adults, over a five year period. This study was approved by the hospital's ethical committee. All underwent an ileocolonoscopy and small bowel imaging at diagnosis, and all except three underwent gastroscopy. CD was confirmed by established criteria based on clinical, radiological, endoscopic and histopathological findings.[24] Location of disease was defined by macroscopic involvement using the Montreal classification.[25]

Children and young adults $\leq$21 years with active CD, defined as a PCDAI$\geq$10,[26] were included. Patients were excluded if they received any other medication for inducing remission (i.e. corticosteroids, biologics and nutritional therapy above 50% of their daily requirements) or had perianal or fistulizing disease. Concurrent maintenance therapy with immunomodulators was allowed, as they were not expected to induce remission in active disease before the time of our endpoint at 8 weeks. All patients had negative results on stool culture and parasites prior to therapy.

All patients received azithromycin 7.5–10 mg/kg day up to a maximal dose of 500 mg, once daily, for five consecutive days per week for 4 weeks, and three times a week for the following 4 weeks. This was used in conjunction with metronidazole 15–20 mg/kg/day in two divided doses, given daily for 8 weeks. Patients intolerant to either medication (e.g. nausea or abdominal pain) had the dose reduced by 25%.

Our primary endpoint was remission rate after 8 weeks of therapy (defined as PCDAI<10 or <7.5 without the height item)[25] and secondary endpoints were normalization of CRP (defined as $\leq$0.5 mg/dL), improvement rate (defined as a drop in the PCDAI of at least 12.5 points[25]), change in standard blood tests from baseline and side effects.

2.1. Statistical analysis

Data are presented as means (±standard deviation), or medians (interquartile range (IQR)), as appropriate for the distribution normality. Unpaired categorical data were compared using X^2 or Fisher's exact test as appropriate. Unpaired Student's *t*-test, or Wilcoxon rank sum test was used to compare unpaired continuous data, and paired Student's *t*-test for paired data, such as PCDAI score before and after treatment. Following a modified intention to treat (ITT) principle, all patients receiving at least one week of antibiotic therapy were included in the analysis. All comparisons were made using two sided significance levels of $p<0.05$. Statistical analyses were performed using SPSS V15.0.

3. Results

A total of 32 eligible children were treated with the antibiotic protocol, of whom 15 (47%) had mild disease (PCDAI 10–27.5 points), 12 (37%) had moderate disease (30–37.5 points) and 5 (16%) had severe disease (>37.5 points) (Table 1).These children and young adults comprise all patients treated that met inclusion and exclusion criteria. The mean PCDAI score dropped from 28±10 before starting therapy to 8.6±8.3, 8 weeks later ($P<0.001$). Twenty one patients (66%) entered remission and 11 (34%) did not. Of the 11 children who did not enter remission, one discontinued treatment due to severe *C. difficile* infection (regarded as failure by the ITT principal), and all others were with mild disease (mean PCDAI score 20±5); 7/11 (64%) improved. Thus, only 4 (13%) of the total 32 children, including the one with the *C. difficile*, did not improve at all.

All blood tests improved from baseline to week 8 (CRP declined from 3.2±2.7 to 1.2±2.6 mg/dL ($P=0.04$), ESR from 44±19 to 26±12 ($P<0.001$), albumin increased from 3.8±0.6