Pilot study of the Effect of Conjugated Linoleic Acid (CLA) on the Modulation of Immune Responses in Patiets with Mild to Moderately Active Crohn's Disease

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Background

Dietary conjugated linoleic acid (CLA) has demonstrated efficacy as an immune modulator and anti-inflammatory compound in mouse and pig models of colitis. Conjugated linoleic acid (CLA) is a mixture of positional and geometric isomers of octadecadienoic acid. Several CLA isomers, including cis-9, trans-11 CLA, are naturally found in milk, cheese and ruminant products. CLA exerts numerous anti-inflammatory and anti-oxidant properties that have been characterized in animal models including arthritis , type I hypersensitivity and intestinal inflammation.

The anti-inflammatory effects of CLA in mice are mediated through a mechanism dependent on activation of peroxisome proliferator-activated receptor gamma. The effect of oral CLA treatment in human inflammatory bowel disease is unknown.

Objectives

A pilot study was designed to investigate the effects of oral CLA treatment on the modulation of the inflammatory response in patients with mild to moderate Crohn's disease.

Methods

Thirteen patients with mild to moderately active Crohn's disease (CDAI (Crohn's disease activity index) (200 - < 450) were enrolled in an open-label study of CLA (6 g/d orally) for 12 wk. Peripheral blood was collected at baseline, and 6 and 12 weeks after treatment initiation for isolation of peripheral blood mononuclear cells for functional analyses of lymphoproliferation and cytokine production. As a secondary endpoint, disease activity was calculated at baseline, week 6 and week 12 using the Crohn's Disease Activity Index (CDAI). A quality of life measurement (Inflammatory Bowel Disease Questionnaire IBDQ) was calculated for the baseline and week 12 visits. Study approved by IRB at Virginia Tech and UNC Chapel Hill.

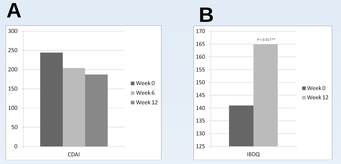
Results

CLA significantly suppressed the ability of peripheral blood CD4+ and CD8+ T cell subsets to produce IFN-g, TNF-a and IL-17 at week 12. In addition, CLA treatment suppressed the lymphoproliferative ability of CD4+ T cells to anti-CD3/CD28 and PMA stimulation at week 12, although it increased overall PBMC proliferation at week 6. Overall, at 6 weeks there was non-significant drop in the CDAI from 245 to 212 (p = 0.23). The mean CDAI decreased by 58 between week 0 and week 12 (p = .0136). Three patients had a > 100 pt drop in the CDAI and three patients had a > 75 pt drop in the CDAI.

Patient Characteristics

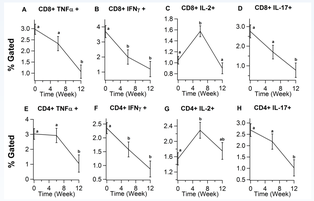
Patient Profile	
Age Range	25-61 (mean 40)
M/F	2/11
Smoking Status	
Former	4
Never	9
Prior Surgery	
Yes	10
No	3
Disease Distribution	
Small Bowel (SB)	6
Colon	2
SB + Colon	5
Disease duration	2-24 years (mean 12.1)
Concomitant Medications	
Mesalamine	6
Sulfasalazine	1
Adalimumab	1
Methotrexate	2
Cerolizumab	2
No medications	1

Clinical Endpoints



A. Mean CDAI at baseline, week 6 and week 12 n= 13 for week 0 and week 6 n=12 for week 12 due to missing diary information from one subject B. Mean quality of life score at baseline and week 12 (p= 0.017)

Immunologic Assays



Effect of oral conjugated linoleic acid (CLA) treatment on cytokine production by peripheral blood T cell subsets. Blood was collected from each subject on weeks 0, 6, and 12 for isolation of peripheral blood mononuclear cells. Flow cytometry was performed on cells derived from whole blood to assess immune cell subsets affected by CLA. Figures represent % Gated cells of each subset population. Values are means ± SEM, n = 13. Statistically significant differences (P<0.05) between treatments are indicated with different letter superscripts.

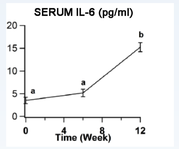
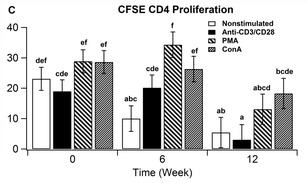


Figure 2. Effect of oral conjugated linoleic acid (CLA) treatment on serum cytokine concentrations. Cytometric bead array was performed on serum samples to assess the ability of CLA to modulate cytokine production. Graph shows IL-6 levels in serum on weeks 0, 6, and 12. Values are means ± SEM, n=13. Statistically significant differences (P<0.05) between treatments are indicated with different letter superscripts.



Effect of oral conjugated linoleic acid (CLA) treatment on proliferation of CD4 following *ex vivo* stimulation with anti-CD3/CD28, Concanavalin A (ConA) and phorbol myristate acetate (PMA). Peripheral blood mononuclear cells (PBMC) were isolated from all subjects at weeks 0, 6, and 12, stained with CFSE and stimulated with anti-CD3/CD28, PMA, or ConA and cultured for 5 days. Percentages of proliferating CD4+ T cells. Values are means ± SEM, n=13. Statistically significant differences (P<0.05) between treatments are indicated with different letter superscripts.

Conclusion

Oral CLA administration at 6 grams per day was well tolerated by patients with mild to moderate Crohn's disease. Oral CLA did have effects on the pro-inflammatory activity of peripheral blood CD4+ and CD8+ T cell subsets, decreasing peripheral pro-inflammatory markers. At 12 weeks there was a statistically significant drop in the CDAI from 245 to 187 (p= 0.013). There was also a significant change in the IBDQ with an increase from 141 to 165 (p= 0.017) These data suggests that CLA may have promise as a potential therapy in patients with mildly active Crohn's disease and further study is warranted.

References

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Funding:

This work was funded by a grant from Cognis/BASF to JBR.