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Original article

Conjugated linoleic acid modulates immune responses in patients with mild to moderately active Crohn's disease

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SUMMARY

Background & aims: Conjugated linoleic acid (CLA) has demonstrated efficacy as an immune modulator and anti-inflammatory compound in mouse and pig models of colitis. We investigated the immunoregulatory efficacy of CLA in patients with mild to moderate Crohn's disease (CD).
Methods: Thirteen patients with mild to moderately active CD were enrolled in an open-label study of CLA (6 g/d orally) for 12 weeks. Peripheral blood was collected at baseline, 6 and 12 weeks after treatment initiation for isolation of peripheral blood mononuclear cells for functional analyses of lymphoproliferation and cytokine production. Disease activity was calculated using the CD activity index (CDAI) and quality of life was assessed using the Inflammatory Bowel Disease Questionnaire (IBDQ).
Results: CLA significantly suppressed the ability of peripheral blood CD4+ and CD8+ T cell subsets to produce IFN-γ, TNF-α and IL-17 and lymphoproliferation at week 12. There was a statistically significant drop in CDAI from 245 to 187 ($P = 0.013$) and increase in IBDQ from 141 to 165 ($P = 0.017$) on week 12.
Conclusion: Oral CLA administration was well tolerated and suppressed the ability of peripheral blood T cells to produce pro-inflammatory cytokines, decreased disease activity and increased the quality of life of patients with CD.
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1. Introduction

Inflammatory bowel disease (IBD) is a chronic relapsing immune-mediated inflammatory disease of the gastrointestinal tract characterized by two clinical and histopathologic manifestations: Crohn's disease (CD) and ulcerative colitis (UC). CD results in transmural lesions that can affect the entire gastrointestinal tract, whereas in UC lesions are continuous, reside within the mucosal layer and are localized in the colon. The etiology of IBD is unknown although there is increasing evidence of an interplay between genetic susceptibility factors, environmental triggers and immune dysregulation.[1] Dietary supplementation with anti-inflammatory agents provides a unique and potentially safer way of treating mucosal disease and has lead to the evolution of the field of nutritional immunology.[2,3]

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. In addition to the well characterized benefit of CLA on body composition, CLA exerts numerous anti-inflammatory and anti-oxidant properties that have been characterized in animal models including arthritis,[4] type I hypersensitivity[5] and intestinal inflammation.[6–8]

Dietary CLA-supplementation suppresses colonic inflammation and up-regulates colonic PPAR γ expression in pigs with bacterial-induced colitis.[6] In addition, activation of colonic peroxisome proliferator-activated receptor (PPAR) γ by CLA mediates protection from experimental IBD in mice[7] and n-3 PUFA antagonizes the effects of CLA on PPAR γ in a pig model of DSS colitis.[8] Dietary CLA has been shown to ameliorate inflammation-driven colorectal cancer by activating immune and epithelial cell PPAR γ in a mouse model.[9] There have been reports documenting increases of PPAR γ expression and activity in adipocytes,[10] skeletal muscle,[11] colonic

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mucosa[12] and macrophages[13,14] with CLA treatment or CLA-rich diets. However, a reduction in PPAR γ expression in adipocytes by CLA has also been reported.[15,16] This may be due to cell-type specificity of the response to CLA or isomer specificity since the t10, c12 reduced PPAR γ expression in adipocytes but the c9, t11 failed to show the same suppressive effect on PPAR γ activity.[17] Interestingly, some probiotic bacteria produce c9, t11 CLA and other anti-inflammatory metabolites locally in the gut that targets PPAR γ in colonic lamina propria macrophages to suppress colitis.[18]

Modulation of gut inflammation through PPAR γ-dependent mechanisms has a precedent in IBD therapy, the intestinal anti-inflammatory effect of 5-aminosalycylate, a broadly used IBD therapy, is mediated by PPAR γ[19] and rosiglitazone, a PPAR γ ligand used in diabetes has been shown to be effective in the treatment of ulcerative colitis.[20] However, the universal application of rosiglitazone or other (thiazolidinediones) TZDs to IBD treatment is unlikely due to reports of increased cardiovascular effects including myocardial infarction and heart failure and the restrictions on rosiglitazone (Avandia) use set by the U.S. Food and Drug Administration (FDA).[21]

CLA has also demonstrated efficacy in modulating immune responses to vaccination and challenge in pig models, which have the advantage of closely resembling the human immune system. Specifically, dietary CLA-supplementation enhanced cellular immunity by modulating phenotype and effector functions of CD8+ T cells[22] and enhanced anti-viral responses in pig models.[23,24] These results were in line with the findings of a human study suggesting modulation of immune responses to hepatitis B virus vaccination.[25]

Together the previous findings highlight the importance of CLA as a unique compound that can suppress inflammatory lesions in the gut while stimulating adaptive cellular immune responses to viral and bacterial pathogens. This is in contrast with current IBD therapies that have potent immune suppressive effects that can increase the risk of patients to infections. The objective of the present study was to characterize the systemic immune modulatory activity of CLA in patients with active CD and as a secondary endpoint to explore its effects on ameliorating disease activity and quality of life.

2. Research design and methods

2.1. Patients

A total of 24 patients with mild to moderately active CD (estimated CDAI $>$ 150 - $<$ 450) were screened for enrollment into the study between August 2009 and February 2011. Patients were required to be on stable medications 2 months prior to entry and could not be on prednisone at the time of screening. There were 11 screening failures. Thirteen patients completed the study and 1 patient withdrew prior to the six-week evaluation due to side effects related to joint pain. Clinical and demographic characteristics of the patients are included in Table 1. All patients had well-documented CD on the basis of prior colonoscopy, surgery, and/or small bowel imaging. Patients were allowed to continue their baseline CD medications with the exception of oral prednisone and oral dietary supplements.

2.2. Study design

This was an open label pilot study. Patients were screened for inclusion criteria for the study which included well-documented mild to moderate CD. Patients underwent a screening visit which included a complete history and physical and blood work. If all the admission criteria were met a diary was dispensed to capture 1 week of symptom data for CDAI calculation. The baseline visit was carried after 7 days with blood work, clinical assessment and calculation of the CDAI,[26] completion of a quality of life index, IBDQ[27] and CLA was dispensed.

Table 1
Clinical and demographic characteristics of patients.

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
Certolizumab	2
No medications	1

2.3. Oral administration of CLA

CLA was self-administered on a daily basis by the subject. The subject was required to take the prescribed dose (6 capsules) one time daily. On study day one the subject received a 6 week supply of CLA (50% cis9, trans-11, 50% trans10, cis12–C18:2) as softgel capsules (6 g/d). The purity of the CLA in the capsules was 77.7% (39% cis9, trans-11, 38.7% trans10, cis12—CLA). The oil was also comprised of 13% oleic acid, 2.7% palmitic acid, 2.6% stearic acid and 0.2% linoleic acid. CLA is an isomeric fatty acid mixture of same length as linoleic acid which is one of the essential fatty acids required for normal human growth and development. At the 6-week study visit all unused capsules were collected and counted to assess compliance and the remaining 6 weeks of CLA was dispensed.

2.4. Physical assessment

A complete physical assessment was performed during the following visits: screening, baseline, week 6 and week 12 and for unscheduled visits or early withdrawal. At each visit, blood was collected via venipuncture for clinical laboratory assessments. Subjects maintained a diary of liquid stools, abdominal pain, and general well-being for the entire course of the study. The CDAI was calculated at baseline, week 6 and week 12 based on subject diary responses, laboratory data, and physical assessment. At the baseline, week 6 and week 12 visits, a 24-h dietary recall questionnaire was obtained. Patients completed a quality of life questionnaire (IBDQ) at the baseline visit and at the week 12 visit.

2.5. Isolation of peripheral blood mononuclear cells

Peripheral blood mononuclear cells (PBMCs) were isolated by using a gradient centrifugation procedure.[22] Briefly, PBMCs were isolated by overlaying lymphoprep (Mediatech, Herndon, VA) with whole blood diluted 1:4 in phosphate-buffered saline (PBS). Mononuclear cells located in the interface between the diluted plasma and the lymphoprep were recovered by using a sterile Pasteur pipette. PBMCs were washed twice with PBS and re-suspended in complete medium.[22] Complete medium was prepared by supplementing RPMI-1640 with 25 mmol HEPES

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