A special carnitine, PLC, is renowned for its prosexual activities and now …

PROPIONYL L-CARNITINE DISPATCHES ULCERATIVE COLITIS

PLC may be sequestered from circulating in ulcerative colitis to serve as a source of L-carnitine and propionyl-coenzyme-A in the colon

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Inflammatory bowel disease is thought to be caused by the chronic or recurring immune response and inflammation of the gastrointestinal tract. The most common inflammatory bowel diseases are Crohn's disease and *ulcerative colitis (UC)*.

Colitis is inflammation of the colon. It is also called colonitis. No matter what you call it, it's a miserable condition, and it's likely to hang on unless you do something about it. Colitis should not be confused with *irritable bowel syndrome* (spastic colon), a different and much less serious condition that is aggravating and a disorder that affects the motility (muscle contractions) of the colon. But it does not entail inflammation. In colitis, furthermore, inflammation is typically accompanied by ulceration, which damages or destroys patches of the mucosal lining of the colon or rectum. UC—the standard term for the most common form of the disease—causes bloody diarrhea, and stools may contain mucus and pus. There may also be fever and abdominal pain. One thing more—patients with UC are at increased risk of colon cancer.

Prevalence and Toll

Inflammatory bowel disease is one of the five most prevalent gastrointestinal disease burdens in the United States, with an overall health care cost exceeding $1.7 billion. Currently, there is no medical cure. Thus care is commonly a life-long endeavor. Every year in the United States, inflammatory bowel disease accounts for more than 700,000 physician visits, 100,000 hospitalizations, and disability in 119,000 patients.[1] Up to 75% of patients with Crohn's disease and 25% of those with UC will require surgery.

Patients with ulcerative colitis are at increased risk of colon cancer.

Ulcerative colitis is regarded as an impaired fatty-acid oxidation disease.

The Many Adversities of Drugs

So what can you do about all this? Well, there are the drugs of course, and they can be quite effective, although you may have to pay a price beyond mere money to obtain their benefits (see the sidebar "Drug Side Effects—A Cascade of Adversities"). If the condition affects just the rectum and lower part of the colon, the drugs of choice are aminosalicylates or corticosteroids, administered rectally. But if the condition goes farther up the pipeline, so to speak, oral medication is indicated, and the drug of first choice is usually a thiopurine (both drugs are in the sidebar).

A Disease of Fatty Acid Oxidation

UC is regarded as an impaired fatty-acid oxidation disease. *Short-chain fatty acids* are produced in the lumen of the colon by *bacterial fermentation of consumed complex carbohydrates*. These fatty acids—and butyrate in particular—are the primary metabolic fuel of *colonocytes* (epithelial cells of the colon). As well, short-chain fatty acids affect colonic blood flow, motility, and mucus secretion. And while the pathogenesis (cause) of UC is

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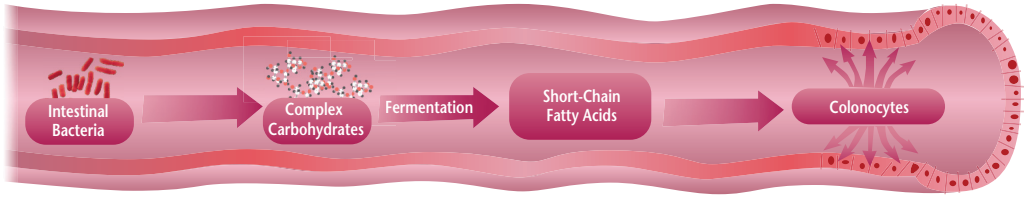
not yet fully understood, there is a growing amount of evidence suggesting that a deficiency of these short-chain fatty acids in the colon lining's colonocytes may provide an answer.



In fact, several studies suggest that impaired beta-oxidation of short-chain fatty acids may lead to colonic mucosal damage due to an energy deficiency that can only partly be compensated for by the oxidation of other substrates.[2–4] Unfortunately, treatment of UC with fatty acid enemas has not produced definitive results.

Carnitine Helps Feed Mitochondria

L-Carnitine is needed for the transport of activated fatty acids into the mitochondria for beta-oxidation in order to generate Acetyl-CoA, the entry molecule for the citric acid cycle. As at least one study has shown, while plasma levels of free L-carnitine are similar in patients with UC and matched healthy controls, plasma levels of the ester **propionyl L-carnitine** (PLC) are lower in patients with UC.[5] This suggests that PLC may be sequestered from circulating in UC patients, thus inhibiting its service as a source of L-carnitine and propionyl-coenzyme-A in the colon.

Higher L-carnitine levels, in turn, facilitate energy release through beta-oxidation of fatty acids, while propionyl-coenzyme-A—an efficient energy source—enters the citric acid cycle as succinate.[6] PLC supplementation has the potential to improve cellular energy levels, and is able to stimulate energy production in ischemic skeletal muscles, and increases maximum walking distance in patients with peripheral arterial obstructive disease.[7]

New Study Finds PLC Can Co-Treat Mild UC

Taking the above into consideration, a team of multinational researchers set out to evaluate efficacy and safety of PLC in patients with mild-to-moderate UC who were employing oral aminosalicylate or thiopurine therapy.[8] In a multicenter study, straddling five European nations, the study was double-blinded, placebo-controlled, and randomized. Each of three different groups of 40, 41, and 40 patients respectively received PLC at 1 g/day, PLC at 2 g/day, or placebo.

In the PLC 1 g/day group, 30 of 40 (75%) patients had a clinical/endoscopic response and 27 of 39 (69%) in the PLC 2 g/day group.

All of the patients were between the ages of 18–75 with *disease activity index* (DAI) scores of 3–10 (mild UC is 3–6 and moderate UC is 6–10). Of the 121 patients who were randomized, 57 of 79 (72%) receiving PLC (combined 1 g and 2 g cohort) had a *clinical/endoscopic response* vs. 20 of 40 (50%) compared to a clinical/endoscopic response for those receiving placebo. Clinical/endoscopic response was defined as a decrease in DAI score ≥ 3 points or as remission, defined as a DAI score ≤ 2. Clinical/endoscopic response findings for the stratum of patients in the combined PLC cohort who had *mild disease* were also significantly different from placebo. Due to the small number of patients with *moderate disease,* no statistical conclusions can be made for this stratum.

The patients were not permitted to change their stable oral concomitant aminosalicylate or thiopurine therapy during the trial. Very few patients (n = 4) received stable oral thiopurine therapy; and thus stratification was limited to disease severity only (rather than for the drug used). Furthermore, the use of systemic or topical corticosteroids, rectal therapies, NSAIDs, probiotics or antibiotics was not allowed.

In the PLC 1 g/day group, 30 of 40 (75%) patients had a clinical/endoscopic response and in the PLC 2 g/day group the response was 27 of 39 (69%). PLC 1 g/ day treatment was significantly superior compared with placebo. Results for the stratum of patients in the PLC 1 g/day arm with mild disease were similarly significant compared to placebo. Results for the PLC 2 g/day arm were not statistically significantly different to the placebo arm.

Remission Analysis

Rates of disease absence (remission) were 22/40 (55%), 19/39 (49%), 14/40 (35%) in the PLC 1 g, PLC 2 g, and placebo groups, respectively [41/79 (52%) patients in the combined PLC cohort]. However, none of the remission rates for patients receiving PLC were significantly greater than that for patients receiving placebo. When considering data stratified by disease severity, only PLC 1 g/day in patients with mild disease significantly increased the probability of remission compared to corresponding placebo.

When the response rates for each of the four items (rectal bleeding, stool frequency, mucosal appearance and physician global assessment) of the DAI was analyzed—for each item, response was defined as a lowering of at least 1 point of the score over baseline—the group receiving PLC 1 g/day had a rate of response for rectal bleeding that was significantly improved compared to the group receiving placebo.

PLC, as a group, had a similar safety profile to placebo; the most common adverse events were gastrointestinal. This phase II trial confirmed that PLC is a potential treatment for the management of mild-to-moderate UC. Patients receiving PLC were more likely to have a clinical/endoscopic response than those receiving placebo.

As there is no statistically significant clinical difference between the two PLC doses investigated, the lower dose

of PLC 1 g/day should be used in future studies. When separated into layers for disease severity, clinical/endoscopic response rates for the combined PLC cohort and the PLC 1 g/ day arm were statistically significant vs. placebo in patients with mild UC.

Patients with mild disease receiving PLC 1 g /day were more likely to achieve remission than those taking placebo. Because there were a relatively small number of patients with moderate UC, no conclusions could be drawn. Further studies are therefore needed to confirm the effectiveness of PLC in patients with moderate and severe UC.

When considering data stratified by disease severity, only PLC 1 g/day in patients with mild disease significantly increased the probability of remission compared to corresponding placebo.

Maximizing Colonocyte Uptake Through PLC

PLC was administered in an oral colon-release formulation that allows the active ingredient to be released directly into the colon lumen, facilitating maximum uptake by colonocytes. This may explain why a low 1 g /day dose is effective and that the lack of additional benefit with a 2 g/day dose may be due to saturation at the site of uptake.

As there is no statistically significant clinical difference between the two PLC doses investigated, the lower dose of PLC 1 g/day should be used in future studies.

Assessment of remission induction did not yield significant data. But future studies with more patients or of longer duration may further clarify the positive remission trends shown for PLC treatment in this trial and even evaluate the role of PLC in maintaining remission.

PLC could provide an alternative treatment for patients with aminosalicylate or thiopurine intolerance, or for those wanting to avoid their adverse effects (see sidebar) and corticosteroids. Certainly, data from this trial, where patients were already receiving stable oral treatment, suggest a role for PLC as an adjunctive therapy for the induction of remission.

As PLC was well tolerated, long-term therapy for remis-

DRUG SIDE EFFECTS—A CASCADE OF ADVERSITIES

Aminosalicylate and thiopurine are two of the drugs used to treat the inflammatory bowel disease ulcerative colitis. Aminosalicylate belongs to the family of medicines called anti-infectives. Thiopurine is an immune system suppressant.

The common side effects of aminosalicylate include gastrointestinal problems (nausea, vomiting, diarrhea, abdominal pain) Then, by category: Cardiovascular; Central Nervous System [including headache (35%), dizziness (8%), asthenia (7%), weakness (6%); hypertonia (5%)]; Dermatologic; Eye-Ear-Nose-Throat; GI [including abdominal pain (18%); eructation (16%); nausea (13%); abdominal cramps/discomfort (8%); diarrhea (7%); dyspepsia, flatulence (6%); vomiting (5%)]; Genitourinary; Hematologic-Lymphatic; Hepatic; Lab Tests; Local; Metabolic-Nutritional; Musculoskeletal; Respiratory; Dyspnea; Miscellaneous [Pain (14%); fever (6%); flu syndrome (5%)]. In each category, only those adverse effects greater than 5% are listed. There are a great many more, and some are quite serious.

Thiopurine drugs can also cause side effects. The most common side effects are stomach related problems (such as nausea, vomiting, diarrhea, abdominal pain) and bone marrow problems. Also there may be severe allergic reactions (rash; itching; hives; difficulty breathing; tightness in the chest; swelling of the mouth, face, lips, or tongue); chest pain or tightness; dizziness; fatty stools; fever, chills, or persistent sore throat; increased or painful urination; muscle pain or aches; painful, red bumps or blisters on the arms, face, neck, or back; severe or persistent nausea, vomiting, or diarrhea; shortness of breath; stomach pain; symptoms of liver problems (e.g., dark urine, loss of appetite, pale stools, right-sided stomach pain, yellowing of the eyes or skin); unusual bleeding or bruising; unusual growths or lumps; unusual weakness or tiredness. And this is not a complete list. Either way, this is one rough road to travel, so any new prospects of treatment should be welcome, especially when there is virtually no adversity.

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sion maintenance is plausible, and might reduce the risk of colon cancer, which is the case with regular aminosalicylate treatment. In conclusion, this trial has provided proof of concept for the use of PLC in the treatment of mild-to-moderate UC. PLC 1 g/day appears to be well tolerated with a favorable safety profile and should be further investigated as a treatment for mild-to-moderate UC.

Carnitines for Energy, Muscle Strength, and Sex

Recent findings have shown that acetyl-L-carnitine (ALC) and PLC are beneficial in other ways. ALC is thought to proffer benefits for memory and for various neurological disorders: such as Alzheimer's dementia, depression in the elderly, chronic fatigue syndrome, peripheral neuropathies, ischemia and reperfusion of the brain, and cognitive impairment associated with various conditions.

PLC has also been shown to replenish the intermediates of the citric acid cycle via propionyl-CoA moiety (boosting energy levels), strengthen muscle cells, and assist peripheral vasodilator activity, including the enhancement of sexual prowess. As well, PLC has been found to help prevent and treat ischemic heart disease, congestive heart failure, hypertrophic heart disease, and peripheral arterial disease. It might be a good idea to add this supplement to your program, if you are not already taking it.

Possible Parkinson's Neuroprotection

Lastly, there is new evidence to indicate that ALC, along with **α-lipoic acid,** may inhibit bradykinesia (slowed ability to start and continue movement) and motor impairment in rats when given at a human dose equivalent of 1215 mg/day of ALC and 608 mg/day of α-lipoic acid.[9] In this study, ALC also enhanced ATP production. According to the researchers, "Taken together, our study reinforces the view that acetyl-L-carnitine and α-lipoic acid are promising candidates for neuroprotection in Parkinson's disease." ✳

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