

The Efficacy and Tolerability of AST-120 (Spherical Carbon Adsorbent) in Active Pouchitis

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Background

- Pouchitis is the most common long-term complication in ulcerative colitis patients with ileal pouches
- Bacterial overload and associated bacterial toxins, as well as increased production of deconjugated bile acids are speculated to play an important role in the pathogenesis
- While the majority of patients with pouchitis respond favorably to antibiotic therapy, many relapse frequently.
- Non-absorbable and non-antibiotic-based agents are desirable to reduce bacterial resistance and systemic adverse effects associated with long-term antibiotic exposure.
- AST-120 (spherical carbon adsorbent) is comprised of highly adsorptive, porous, carbon microspheres with the ability to adsorb small molecular weight toxins, inflammatory mediators, and harmful bile acids.

Aim

The aim of this pilot trial was to evaluate efficacy and tolerability of AST-120 in the treatment of active pouchitis.

Methods

IRB approved, FDA registered

Patients Recruitment:

From the Pouchitis Clinic, the Digestive Disease Institute, Cleveland Clinic, Cleveland, Ohio and IBD Clinic, Mayo Clinic, Rochester, MN

Inclusion Criteria:

- Patients with active pouchitis (Pouchitis Disease Activity Index [PDAI] score >7 points) after IPAA for ulcerative colitis;
- Active symptoms;
- 18-75 years of age

Exclusion Criteria:

- Patients previously treated with infliximab or any investigational immunomodulators;
- Antibiotic use within 2 weeks prior to the entry of the trial;
- Crohn's disease of the pouch;
- Active specific infection of the pouch: cytomegalovirus infection and Clostridium difficile infection;
- History of non-inflammatory disease of the pouch: decreased pouch compliance, irritable pouch syndrome, afferent or efferent limb obstruction;
- Isolated cuffitis;
- Ileal pouch patients with familial adenomatous polyposis;
- Known celiac disease;
- Primary sclerosing cholangitis (PSC) with or without liver transplant; PSC with or without ursodeoxycholic Acid therapy

Trial Design

- This was an open-label pilot trial in which all patients received AST-120 in 2g sachets (oral) three times a day for 4 weeks
- All antibiotics, probiotics, and nutritional agents must have been discontinued for at least 2 weeks prior to trial entry
- Pouch endoscopy before and after trial

The primary efficacy endpoint:

Induction of remission as defined by a PDAI score < 7 points

The secondary efficacy endpoints:

Response defined as a ≥ 3 point reduction in the 18-point PDAI scoring system; reduction in the PDAI symptom, endoscopy, and histology subscores

The primary safety endpoint:

Any adverse event deemed possibly, probably, or definitely related to treatment with investigational product during 4 weeks of treatment

The secondary safety endpoints:

Abnormalities in clinical laboratory tests, worsening GI symptoms or new GI and ex-intestinal systemic symptoms.

Statistical analyses

Wilcoxon rank sum tests were conducted to assess differences in the pre- and post- treatment PDAI scores after 4 weeks of treatment.

Results

- All 19 eligible patients completed the trial
- 11 patients (57.9%) had a clinical response. All of them had endoscopic response
- 10 patients (52.6%) entered remission
- The agent was well tolerated
- One patient developed transient mild elevation of alkaline phosphatase
- One non-responder was found to have developed Clostridium difficile infection at the 4-week follow-up visit, and was treated with vancomycin at the end of the trial

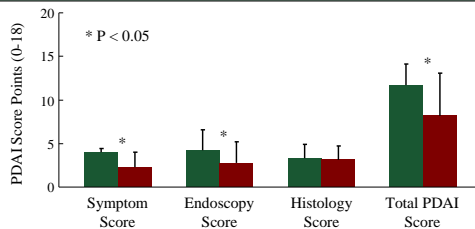


Table 1. Demographic and Clinical Data (N = 19)

Variable	Count	Percentage
Age, years	44.26	± 11.39
Male gender	13	(68.4%)
Caucasian race	19	(100%)
Family history of Crohn's disease	1	(5.3%)
Family history of ulcerative colitis	2	(10.5%)
Family history of celiac disease	1	(5.3%)
Current smoker	2	(10.5%)
Ex-smoker	6	(31.6%)
Regular alcohol drinker	1	(5.3%)
Osteoporosis	2	(10.5%)
Renal stones	4	(21.1%)
Pre-op diagnosis of ulcerative colitis	16	(84.2%)
Pre-op diagnosis of Indeterminate colitis	3	(15.8%)
Duration of UC, yrs	15.00	± 7.86
Pancolitis	17	(94.4%)
Colectomy for refractory colitis	15	(78.9%)
Colectomy for dysplasia	4	(21.1%)
Duration of pouch, yrs	6.05	± 4.12
J pouch configuration	18	(94.7%)
2-stage of pouch surgery	10	(55.6%)
History of Pouchitis		
- None	1	(5.3%)
- Antibiotic-responsive pouchitis	2	(10.5%)
- Antibiotic-dependent pouchitis	13	(68.4%)
-Antibiotic-refractory pouchitis	3	(15.8%)
Extra-intestinal Manifestations		
- Arthralgia	9	(47.4%)
- Thromboembolic events	1	(5.3%)
Concurrent Meds at the entry		
- Anti-diarrheal	7	(36.8%)
- Topical narcotics	3	(15.8%)
- Topical or oral 5-ASAs	1	(5.3%)
- Antidepressants	3	(15.8%)
- Antianxiety	2	(10.5%)
- Topical corticosteroid	1	(5.3%)
- Oral budesonide	1	(5.3%)
- Aspirin	2	(10.5%)
- Statins	2	(10.5%)
- Estrogens	1	(5.3%)

Table 2. Treatment Outcome (N = 19 analyzable patients)

	Pre-Treatment	Post-Treatment	Reduction in Scores	P value
PDAI Symptom Score (range 0-6)	4 (4, 4)	2 (0, 4)	-2 (-4, 0)	0.002
PDAI Endoscopy Score (range 0-6)	3 (4, 5)	3 (0, 5)	-2 (-4, 0)	0.003
PDAI Histology Score (range 0-6)	3 (2, 5)	2 (2, 3.5)	0 (-1.5, 0.5)	0.32
Total PDAI Score (range 0-18)	11 (9.5, 12.5)	7 (3.5, 11)	-4 (-7, -0.5)	0.001

Conclusion

- AST-120 appeared to be safe, well-tolerated, and efficacious in induction of remission or response in patients with active pouchitis
- AST-120 may be a promising treatment option for pouchitis
- A randomized, placebo-controlled trial is warranted