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Combined restitutive therapy for treatment of immunosuppressive refractory Crohn's Disease

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Introduction

Crohn's Disease (CD) is believed to be the result of dys-regulated interactions between a genetically susceptible host and their commensal gut microbiota (1). CD affects over 600,000 Americans and treatment still faces many challenges (2). Pharmacotherapy centers on the use of anti-inflammatories and immunosuppressants (3). However, a sub-set of patients with CD are refractory to immunosuppressive therapy. Recent studies have implicated defects in autophagy and bacterial killing as a possible etiology leading to host-microbe dysregulation (4). This could explain the lack of response to immunosuppression seen in these CD patients. A recent study in adults with CD showed the potential for granulocyte-macrophage colony stimulating factor (GM-CSF) to enhance bacterial killing and restore intestinal homeostasis (5), but very little data exists in pediatric patients (6).

Another study reports a role for low-dose naltrexone (LDN, a mu opioid antagonist) in helping restore the epithelial barrier in active CD (7). The mechanism of action of LDN is

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thought to be through activation of endogenous opioid signaling (8). Recent murine studies have shown that direct mu opioid receptor (MOR) activation can enhance intestinal epithelial healing and prevent epithelial apoptosis (9).

Here, we report a combined intestinal-restitutive approach using GM-CSF and loperamide (a peripheral MOR agonist) to induce and maintain remission in a 17-year-old CD patient.

Case Report

The patient was a 17-year-old female with a history of colonic CD, first diagnosed in 2009. In the past, she had responded well to steroids during flares, but this approach ceased to work. She had previously failed 5-ASA, azathioprine, and infliximab. She was receiving adalimumab up until two weeks prior to presentation at a dose of 40 mg s.c. weekly (double-dose) for the prior 4 months; she had paused due to an upper respiratory infection. Methotrexate was avoided due to sexual activity in a female of child-bearing age. The patient's other medical history was significant for depression. At the time of admission, she had progressively worsening symptoms for the past month despite recent adalimumab and the completion of a 60 mg prednisone taper one week prior to admission.

Her symptoms were primarily crampy, dull, aching abdominal pain and diarrhea, with the diarrhea in particular worsening. At presentation, she had approximately 20 bowel movements per day, with 8–10 night-time wakings. She described her stools as semi-formed to loose, usually with mucus, and occasionally streaked with blood. There was no frank blood in her stools or melena. She noted tenesmus as being a cause of her urgency, often at night. Her pain was mostly with defecation, but also intermittently in her LLQ. The patient also noted post-prandial abdominal pain associated with nausea. During the last month, she had only one episode emesis. The patient denied any fever, rashes, or arthralgias with her disease. She had no urinary symptoms and her LMP was 4 weeks ago. The patient's last esophagogastroduodenoscopy and colonoscopy ~2 months prior to admission showed no disease in the stomach and duodenum, and inflammation throughout the colon, worst at the splenic flexure with sparing of the cecum and terminal ileum (Figure 1A&B).

Physical exam at the time of admission was largely unremarkable, except for quiet bowel sounds and diffuse abdominal tenderness, worse in the left half. She was anicteric, with no signs of aphthous ulcers, skin lesions, or perianal skin tags concerning for fistulizing disease. Laboratory tests (Table 1) revealed normal blood counts and electrolytes, and elevated CRP and ESR (Figure 2A&B).

Upon admission, the patient was placed on methylprednisolone 25 mg IV bid. However, this failed to improve her symptoms after two days of therapy. Given her history failing all immunosuppressive regimes, we decided to try a restitution-therapy-based approach. Steroids were discontinued (with a taper), and the patient was started on GM-CSF at 6 mcg/kg/day s.c., as well as 2 mg loperamide qhs. To decrease rectal inflammation and urgency, we added a nightly mesalamine enema. The patient reported decreases in bowel movements and abdominal pain within 24 hours. After two days, the patient's bowel movements were down to approximately 10/day, with ~4 night-time wakings. We added a morning mesalamine suppository, and the patient continued to improve.

10-days after admission, the patient was discharged home on GM-CSF therapy, 2 mg loperamide nightly, and a nightly mesalamine suppository. At discharge, she had ~5 bowel movements daily with occasional blood and no night-time urgency. Her Crohn's Disease Activity Index improved from 568 on admission to 205 on discharge (Figure 2C). Metronidazole 250 mg bid was added at the time of discharge for additional treatment of rectal urgency. WBCs and ANCs were monitored serially, per the described protocol (5) (Table 1).

At her one-week follow-up, the patient reported onset of headaches 2 days after discharge, which caused her to stop taking her loperamide and flagyl. She reported increased lethargy, and increased bowel movements to 7/day. Her ESR and CRP were also elevated from discharge (Figure 2A&B). The patient was successfully encouraged to restart her medications and at her 2 and 3 week follow-ups, the patient reported a return to 5 BM/day with intermittent blood, improved appetite, and slowly decreasing lethargy. At her 1, 2 and 3 month check-ups, she reported continued stable symptoms and increasing energy levels, which correlated with improved inflammatory markers and decreased CDAI to below the remission threshold of 150 (Figure 2). At each of these follow-ups, she reported taking her GM-CSF and mesalamine suppository regularly, with occasional gaps in her loperamide and frequent, extended gaps in her metronidazole.

Discussion

In recent years, genetic studies have suggested that multiple routes exist leading to the dys-regulated host-microbiome interactions seen in CD (4). While immunosuppressive therapy has been the mainstay, some patients grow resistant to or outright fail immunosuppressive regimes. This case report demonstrates how in such a patient population, a restitutive approach could be employed to induce remission of CD. Currently, restitutive therapies are limited and experimental; GM-CSF for immune enhancement and now MOR activation for epithelial healing being the only options with any amount of clinical and/or translational evidence. Here, we combined both therapies. In our patient, this induced remission within 7 days, with sustained remission at 3 months. This case report is in line with the small GM-CSF trials (5, 6), and provides clinical evidence supporting the recently discovered effect of enterocyte MOR activation leading to intestinal healing (9).

One difficulty in interpreting the results of this case report was the use of other therapies in addition to GM-CSF and loperamide, namely metronidazole and mesalamine. Given that metronidazole was started at discharge, after induction of remission had already been observed, we are confident that metronidazole did not play a role in the induction of remission. Additionally, the patient had poor adherence to metronidazole as an outpatient, but maintained remission. In contrast, rectal mesalamine was started alongside the restitutive therapies, and could have played a role in inducing remission. However, the mesalamine therapy targeted only the rectum and sigmoid colon which on its own would likely have been insufficient to induce the level of remission observed given this patient's history of active, pan-colonic disease (Figure 1). Thus, we feel that GM-CSF and loperamide both had to play a significant role in inducing remission in the patient.

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Figure 1.

Colonoscopy and histology of a 17-year old with Crohn's Disease, two months prior to admission. A) Sample colonoscopy image from the splenic flexure demonstrates severe inflammatory disease, with granulation, erosions, active bleeding, erythema, severe friability, mucus, pus, and edema. At the time of the colonoscopy, disease was found to be present in a continuous and circumferential manner from the rectum to the ascending colon, with sparing of the cecum, and showed worsening of disease compared to a colonoscopy from 6 months earlier. B) Histological specimen taken from the same procedure as in A. Sample is of rectal mucosa, showing moderate to severe chronic active colitis, with cryptitis, crypt abscesses, crypt architectural distortion, and diffuse plasmacytosis.

Figure 2.

Longitudinal clinical outcomes for a 17-year old with Crohn's Disease, using day 0 as day of admission. Day 10 is day of discharge from the hospital. A) ESR, erythrocyte sedimentation rate B) CRP, C-reactive protein. C) CDAI, Crohn's Disease Activity Index.

Table 1

Longitudinal clinical laboratory data in a 17-year old with immunosuppressive-refractory colonic Crohn's Disease

	Normal	Admission	Discharge	2 Month Follow-Up
<u>Chemistries</u>				
Na+ (mmol/L)	135–145	138	139	141
K+ (mmol/L)	3.5–5.0	3.9	4.5	4.3
Cl- (mmol/L)	98–107	103	101	102
CO ₂ (mmol/L)	22–30	23	26	23
BUN (mg/dL)	7–21	5	6	6
Creatine (mg/dL)	0.30–0.90	0.68	0.53	0.54
<u>LFTS</u>				
Albumin (g/dL)	3.5–5.0	3.2	3	3.8
AST	5–30	38	5.6	17
ALT	5–35	54	--	28
Alk Phos	50–130	134	--	121
GGT	11–48	36	--	43
<u>Heme/Immuno</u>				
CRP	0.0–1.0	7.6	5.6	1.4
WBC (10 ⁹ /L)	4.5–11.0	6.5	20.4	14
ANC (10 ⁹ /L)	1.5–5.0	4.9	17.5	8.6
HGB (g/dL)	12.0–16.0	12.7	11.9	12.2
Platelets (10 ⁹ /L)	150–440	555	474	449
ESR (mm/hr)	0–20	62	28	16