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Novel Combination Therapy Induced Histological Remission in Patients with Refractory Ulcerative Colitis

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Abstract

Objectives: In many patients, Ulcerative Colitis (UC) is poorly controlled; patients frequently fail to achieve remission or relapse on current therapies. Multiple disease mechanisms have been postulated but resulting therapies fail to deliver complete histological and clinical remission in a majority of patients. This case series reports clinical experience treating patients with active UC, not responding to conventional therapies, with a combination enema and oral therapy, to test whether it could induce remission in refractory, moderate to severe disease.

Methods: A four-component enema consisting of approved medications and generally regarded as safe ingredients, and oral dihydrolipoic acid, was administered daily for up to eight weeks. Thirty-six patients with UC experiencing a current flare not responding to other UC medications were treated. Patients were assessed at the initiation of treatment and two follow-up visits, visit 1 (average 26 days) and visit 2 (average 54 days), for symptoms and by endoscopic and histologic examination.

Results: Thirty-five (of 36) patients had moderate to severe disease at the initial pre-treatment assessment. At visit 1, 71% of patients achieved histological remission, 65% were in complete mucosal remission, 94% patients had a clinical response and 71% of patients achieved clinical remission. By visit 2, 85% of patients achieved histological remission, 85% were in complete mucosal remission, 97% of patients had a clinical response and 87% of patients achieved clinical remission. The regimen was well tolerated.

Conclusion: A combination oral/enema regimen was effective at inducing clinical, endoscopic and histological remission in moderate to severe UC patients experiencing a flare that was not controlled by their existing UC medications.

Keywords: Ulcerative colitis; Histology; Endoscopy; Redox; Remission; Refractory; Combination therapy; Enema

Introduction

Ulcerative Colitis (UC) is an Inflammatory Bowel Disease (IBD) characterized by relapsing episodes of colonic inflammation separated by varying periods of lesser disease activity. In most cases, the inflammation begins in the distal colon and is confined to the colonic epithelium, and patients present with disease of mild-to-moderate severity. However, 10% of patients present with severe disease and approximately 15% of mild-to-moderate patients will develop a severe exacerbation or flare during the course of their lifetime [1]. Prolonged and severe UC carries a risk of colorectal cancer which cumulatively rises to 18% by 30 years since diagnosis [2], and the lifetime colectomy risk may be 10-40% [1]. Ultimately, about 1 in 3 individuals with ulcerative colitis will need surgery to remove their large intestine (total colectomy) during their lifetime due to medical treatment failure [3].

The ultimate goal of any treatment should be, whenever possible, to correct the biology driving the disease. For UC, a treatment should achieve biological remission as measured by tissue and cellular recovery, not just symptom reduction or resolution. Therapy should then maintain that remission, and thereby avoid the elevated risk of colorectal cancer and/or the need for surgical correction. In the case of UC, several mechanisms have been postulated as the cause of the characteristic inflammation and symptomatology including an abnormal or a dysregulated immune response, microbiome derangement, [4] or an oxidative irritant [5]. These have yet to demonstrate an understanding of the driver biology sufficient to produce a durable remission.

Therapeutic benefit of UC therapies is often reported as clinical response based on a reduction in symptoms or in severity of UC upon endoscopic or histologic disease. This is distinct from various definitions of clinical, endoscopic, and histologic remission. The reported rates of patients on therapy achieving more stringent measures of improvement such as endoscopic or histologic remission are typically much lower than those achieving clinical response. There is interest in adding histological remission as a target for measuring therapeutic efficacy; the absence of validated scoring systems may inhibit expanded use [6].

The aim of the present case series was to treat patients with UC of any severity, not responding to conventional therapies, with a novel combination enema and oral therapy for UC and observe whether they had any improvement in their clinical, endoscopic and histologic status.

Materials and Methods

Treatment and assessment was conducted at a large, single outpatient IBD clinic, at Gastro One (Memphis TN). An enema treatment consisted of mesalamine (2.67 g), budesonide (5 mg), cromolyn sodium (100 mg) and sodium butyrate (1.67 g), in 61 mL, prepared in a compounding pharmacy (People's Custom Rx, Memphis, TN) using mesalamine enema (60 mL) as the starting point. Twenty (20) mL of mesalamine was discarded and solutions of the remaining ingredients were added to the 40 mL remaining mesalamine to bring the volume to a total of 61 mL. Patients were instructed to self-administer this enema daily at bedtime by retention.

To manage systemic oxidative products, an oral daily dose of 600 mg R-dihydrolipoic Acid (R-DHLA), a nutraceutical with antioxidant properties, provided in 150 mg capsules (Life Extension), was self-administered by the patient twice daily. Patients were also asked to avoid penicillin, estrogen, alcohol, vitamins and iron because these can increase oxidative stress [7-17].

Colonoscopic examination by the treating physician determined the extent of disease. Flexible sigmoidoscopies with biopsies were obtained at the initiation of therapy (baseline) and at visit 1 and/or visit 2 and were evaluated by a Board-certified gastrointestinal pathologist. Clinical and patient symptoms were recorded as Mayo scores by referring physicians and the treating physician. Response to therapy was determined by clinical evaluation, endoscopy and histopathology, and comparing results at baseline, visit 1 (average 26 days after initiation of therapy) and visit 2 (average 54 days after initiation of therapy). Twenty nine of 36 patients completed all expected visits including baseline, visit 1 and visit 2. Six patients missed a single visit. Patients were included in the evaluation whenever there were complete data at the time point analyzed and no data were excluded except when no baseline was recorded for that measurement for a patient so that improvements against a baseline could not be determined.

Patients were evaluated using the Mayo score system and by histology sampling and analysis. The Mayo score is a composite endpoint consisting of a score of 0-3 on each of four criteria, diarrhea, bleeding, endoscopic examination and physician assessment of disease severity. Total scores can range from 0 (disease free) to 12 (severe disease) [18].

The primary component of histologic scoring of disease activity is the presence and degree of neutrophils. Colorectal biopsies were collected from the site of most significant inflammation, were histologically graded and scored on a 6-point scale (0=quiescent to 5=severe) [19] for disease activity as follows: Quiescent (score=0), which included histologically normal colonic mucosa, colonic mucosa with structural abnormalities, and colonic mucosa with a mild increase in mononuclear inflammatory cells without a neutrophilic infiltrate. Mild (score=1), which included colonic mucosa with a mild neutrophilic infiltrate within the lamina propria and/or epithelium and a mild increase in mononuclear inflammatory cells within the lamina propria. Moderate (score=3), which included colonic mucosa with a moderate or marked mononuclear inflammatory cell infiltrate expanding the lamina propria and a mild neutrophilic infiltrate within the lamina propria and epithelium, typically with occasional crypt abscesses. Severe or marked (score=5), which included colonic mucosa with a moderate or marked mononuclear inflammatory infiltrate expanding the lamina propria and a moderate neutrophilic infiltrate within the lamina propria and epithelium, often associated with breakdown of the integrity of the epithelium such as ulceration and/or crypt destruction. Scores 2 and 4 were applied for colonic biopsies that ranged between mild-to-moderate and moderate-to-severe/marked, respectively.

Histological remission was defined by a histology score=zero (0) [19]. Complete mucosal remission was a composite endpoint consisting of Mayo score ≤ 2, Mayo endoscopy subscore ≤ 1 and histology score=0. Clinical remission was defined as a Mayo score of less than 2 and Clinical response was defined as a Mayo score decrease of 3 or more.

Treatment was administered to patients with mild to severe distal ulcerative colitis. Initially, cases were selected based on involvement of no more than 50 cm from the anus and Mayo scores from 4 to 9. However, as these patients achieved remission, cases were included whose involvement was greater than 50 cm and/or the Mayo score exceeded 9, based on the failure to achieve remission on other agents despite their extended use. These patients were treated to possibly prevent surgery or delay the use of steroids or biologic agents.

Most patients elected to remain on their current therapy (N=21) while being treated with this test therapy, but 13 ceased current therapy prior to initiation of combination enema therapy. For two patients, current therapy status was not recorded. Status regarding continuation of current therapy did not have an observable effect on clinical outcomes. Only patients with on-going failure of conventional treatment to induce remission were treated, therefore any efficacy signals observed were unlikely to be due to a placebo effect.

Results

Drugs and demographics

Of the 36 patients, 36% were male and 64% female, the mean age was 46, and the mean pre-treatment Mayo score was 8.5 (range 3-12). Patients included in this case series presented with sigmoiditis (n=24) and proctitis (n=6) primarily, with 2 cases of distal colitis and 4 cases of pancolitis (Table 1). At baseline, the 36 patients were being treated for UC with the following therapies: 5-ASA products (oral or rectal) in 82% patents, steroids in 57%, immunomodulators (6-MP, AZA) in 16%, and biologics (Remicade, Humira) 16%.

Disease Location/Diagnosis		
Proctitis	6	17%
Sigmoiditis	24	67%
Distal Colitis	2	6%
Pancolitis	4	11%
Total	36	100%

Table 1: Disease location.

Safety

The combination enema therapy was well-tolerated. Among the 36 patients treated, 9 patients experienced 10 Treatment-Emergent Adverse Events (TEAEs). A TEAE is defined as an untoward medical event experienced by a patient who has been administered a treatment, but the event does not necessarily have a causal relationship with a

treatment. The most common TEAEs were: worsening of UC or hospitalization due to UC, and development of a rash (Table 2).

Event Type	N	Related to drug?
Worsening UC or hospitalized due to UC	2	unlikely
Rash/ pruritic rash	2	likely for 1, possible for 1
C. difficile colitis	1	unlikely
Nausea	1	no
Burns to face and arm	1	no
Rectal burning	1	likely related to enema insertion
Shortness of breath	1	no
Viral infection	1	no

Table 2: TEAEs and the number of occurrences.

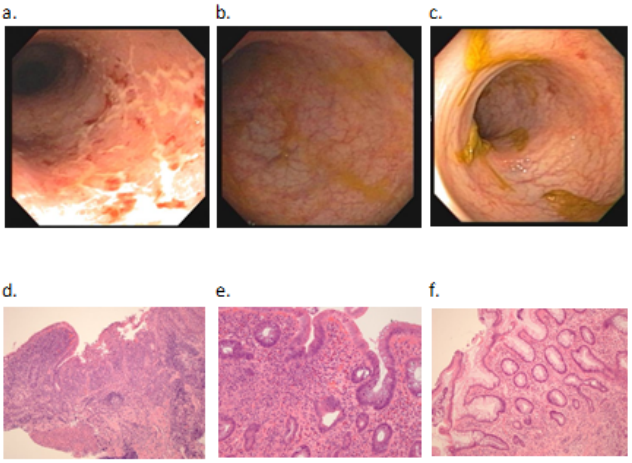
Two TEAE occurrences (rectal burning and rash) were noted to be related to the combination enema therapy. One patient experienced rectal burning and stopped the combination enema therapy and was unable to tolerate when attempting to restart therapy. Another patient experienced severe pruritic rash 14 days after starting the therapy. The therapy was stopped and prednisone was initiated. Biopsies obtained from a dermatologist showed the rash to be consistent with a drug reaction. These adverse events were considered mild and possibly related to therapy, and in each of these cases, therapy was stopped and the TEAE resolved.

Six patients discontinued treatment with the combination enema due to a TEAE: 2 rashes (noted above), 1 *C. difficile*, 1 rectal burning (noted above). One patient who reported a rash had a prior history of rash and shortness of breath in association with rectal 5ASA therapy and developed rash and shortness of breath on the combination enema plus oral R-DHLA. The patient diagnosed with *C. difficile*, discontinued the enema therapy temporarily, was subsequently treated for the infection, and restarted the combination enema therapy with good results. Several other co-workers in the medical office where this patient worked also developed *C. difficile* at the same time so it is unlikely to have been due to therapy.

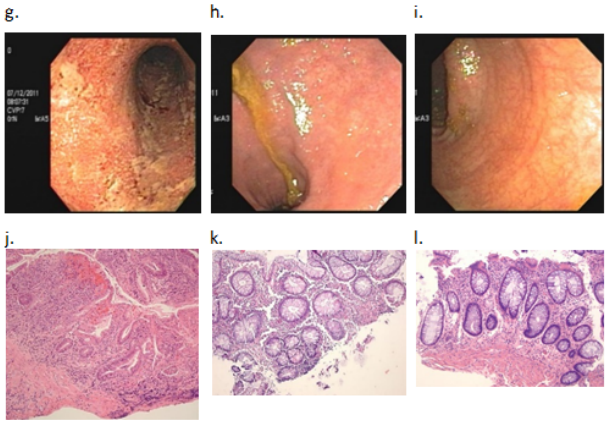
Five patients initially had difficulty retaining the enema overnight. However, all patients remained on the therapy through the follow-up visit 2. In some cases, these patients reduced the amount administered for the first few weeks of the combination enema therapy but eventually were able to retain the full enema.

Endoscopy and histology

Endoscopic and histologic evaluation of patients typically showed rapid normalization of the epithelial mucosa by visit 1, continuing until visit 2. The normalization was also observed at the cellular level in the histopathology examination. Two patient examples are shown in Figures 1a-1l and tables 3 and 4 along with the corresponding components of the Mayo score and the histology score based on the images of tissue biopsies taken during the endoscopy procedure.



Figures 1a-1f: Example patients with endoscopic and histologic images from all three assessment visits.



Figures 1g-1l: Example patients with endoscopic and histologic images from all three assessment visits.

Histology score is not part of the Mayo score. Assessment scores and Endoscopy and Histology images are taken from baseline weeks 0, visit 1 and visit 2 for which representative images are presented in Figures 1a-1l. For patient T42, endoscopy image, Figure 1a shows lesions, ulceration and bleeding characteristic of severe, diffuse colitis in rectum, sigmoid and descending colon, Figure 1b shows healing mucosa which was observed to 60 cm and Figure 1c shows almost completely healed mucosa. Histology image, Figure 1d shows expansion of the lamina propria by marked chronic inflammation and crypt abscess, characteristic of moderate-to-severely active disease. Figures 1e and 1f show normal histology characteristic of quiescent disease. For patient D62, endoscopy image Figure 1g shows lesions, ulceration and bleeding characteristic of moderate disease to 30cm, Figures 1h and 1i show normal mucosa. Histology image Figure 1j shows expansion of the lamina propria by marked chronic inflammation and crypt abscess, characteristic of moderately active disease. Figure 1k shows nearly normal histology characteristic of

minimally active disease and Figure 1l shows normal histology characteristic of quiescent disease.

Patient T42	Baseline (Day 0)	Follow-up Visit 1 (Day 28)	Follow-up Visit 2 (Day 52)
Diarrhea	3	0	0
Bleeding	2	0	0
Physician Global Assessment	3	0	0
Endoscopy	3	1	0
Total (Mayo Score)	11	1	0
Histology score	4	0	0

Table 3: Example patients T42 with corresponding Mayo and histology scores.

Patient D62	Baseline (Day 0)	Follow-up Visit 1 (Day 21)	Follow-up Visit 2 (Day 42)
Diarrhea	2	0	0
Bleeding	2	0	0
Physician Global Assessment	2	0	0
Endoscopy	2	0	0
Total (Mayo Score)	8	0	0
Histology scores	3	0	0

Table 4: Example patients D62 with corresponding Mayo and histology scores.

29 of 36 patients completed all expected visits including baseline, visit 1 and visit 2. Six patients missed a single visit. Endoscopic exams were performed at all visits for all patients, Mayo score data were available at visit 2 for 30 of the 36 patients for which baseline and at least one subsequent Mayo score were determined, and the composite endpoint "complete mucosal remission" which includes Mayo score, endoscopy and histology was available in 26 of 36 total patients at visit 2.

Histology scoring used a 6-point scale (0=quiescent to 5=severe). The average histology score before initiation of therapy (week 0) was 2.9 for all patients. Histological remission was observed in 71% (22 of 31) of evaluable patients at visit 1 as defined by a histology score=zero (0) and the histology scores declined by visit 2 to an average of 0.5 for all patients and histological remission was observed in 85% (23 of 27) of patients. The patients for which histological samples were collected and evaluated are summarized in Figure 2.

Mayo scores

At follow-up visit 1, a clinical response, defined as a decrease in Mayo score ≥ 3 from baseline (day 0), was observed in 94% patients with evaluable data at the follow-up visit 1 time point (32 of 34) (Table 5). Clinical remission, defined as a Mayo score ≤ 2 was observed in 71% (24 of 34) patients. The average Mayo score for the 29 evaluable patients decreased from 8.6 to 1.6 at visit 1. In addition, 65% (20 of 31) of evaluable patients were in complete mucosal remission, a composite endpoint consisting of Mayo score ≤ 2, Mayo endoscopy subscore ≤ 1 and histology score=0.

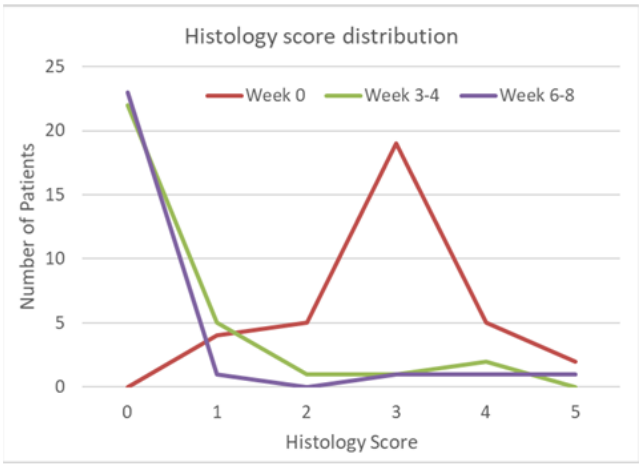


Figure 2: Histology score distribution at baseline (week 0) Follow-up 1 and Follow-up 2.

Variables	Outcomes at Follow-up 1 visit N=35		Outcomes at Follow-up 2 visit N=31	
	N	%	N	%
Histological Remission	31	71%	27	85%
Complete Mucosal Remission	31	65%	26	85%
Clinical Remission Mayo ≤ 2	34	71%	30	87%
Clinical Response Mayo decrease by ≥ 3	34	94%	30	97%

Table 5: Disease outcomes at follow-up visits 1 and 2.

Continued improvement was observed during additional weeks of treatment and at follow-up visit 2, 26 of 30 evaluable patients (87%) were in clinical remission (Mayo score ≤ 2). All but one patient (29 of 30) patients (97%) met the definition of clinical response at visit 2. The average Mayo scores decreased from 8.6 at baseline to 0.8 at visit 2 in the 30 evaluable patients, and 85% (22/26) of evaluable patients were in complete mucosal remission (Mayo score ≤ 2 and Mayo endoscopy subscore ≤ 1 and histology score=0).

The decrease in Mayo score for each patient with a baseline measurement and at least one follow-up visit is plotted in Figure 3.

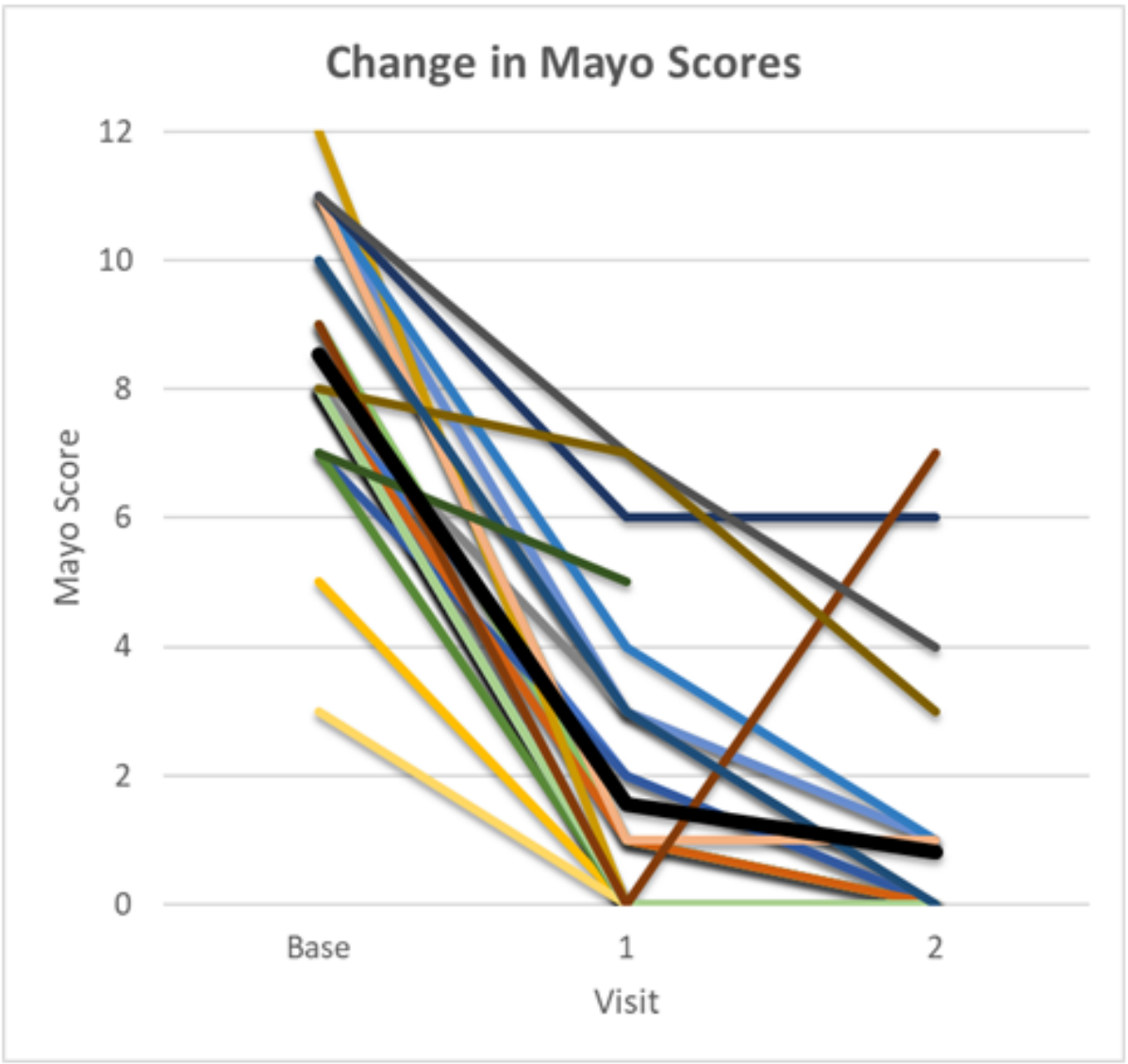


Figure 3: Summary change in Mayo scores for each patient with a baseline and subsequent measurement. Mayo scores are plotted at baseline, follow-up visit 1 and follow-up visit 2. The coloured lines plot data from each individual patient. The average Mayo score is plotted in the heavy black line. Note that multiple patients may overlie a single coloured line, for example 10 patients went from a Mayo score of 8 at baseline to 0 by visit 1.

Nearly all patients showed a precipitous decline in Mayo score at the first follow-up visit. Flexible sigmoidoscopy of the single patient that showed an increase in Mayo score between follow-up visit 1 and 2 (from 0 to 7) showed a completely normal rectum as well as the sigmoid, except for one tiny patch of minimal inflammation, but 3-4 inches of moderate disease was observed near the splenic flexure 70 cm into the intestine. The patient continued on therapy and reported symptom resolution and when examined 7 months later, endoscopic examination to the splenic flexure revealed normal mucosa.

Effect of disease severity and location

Most patients with mild to moderate disease achieved histological, clinical, and mucosal remission including the only mild (Mayo=1-4) patient assessed and in 88-89% of the moderate (Mayo=5-9) patients assessed (Table 6). Most severe patients also responded to treatment, including 75% of severe patients (6 of 8 evaluable patients) achieving histological remission, 78% of severe patients (7 of 9 evaluable patients) with clinical remission, and 63% of severe patients (5 of 8 evaluable) achieving complete mucosal remission (Table 6).

All the severe patients for whom corresponding data were available, regardless of disease location and extent, had a clinical response. Severe patients with more extensive disease included 1 with proctitis, 2 with left-sided colitis, 3 with pancolitis and 4 with proctosigmoiditis (Table 7). All patients diagnosed with proctitis had a complete clinical, histological and mucosal remission by visit 2 (Table 7), as did nearly all proctosigmoiditis patients (89-95%). Left-sided colitis and pancolitis

patients also responded but since there were only two of each at visit 2, an estimate of a population response was not possible.

Outcome at Visit 2 and Disease Severity at Baseline			Clinical Remission			Histological Remission			Mucosal Remission		
			N	%	n	N	%	n	N	%	n
Severity at Baseline	Mayo Score	N=36									
Mild	0-4	1	1	100%	1	1	100%	1	1	100%	1
Moderate	5-9	24	19	89%	17	17	88%	15	17	88%	15
Severe	10-12	10	9	78%	7	8	75%	6	8	63%	5

Table 6: Disease remission outcomes at follow-up visit 2 based on severity of Mayo score at baseline visit.

	Proctitis (6)		Proctosigmoiditis (24)		Left-sided Colitis (2)		Pancolitis (4)	
Outcomes at follow-up visit 1	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Histological Remission	6	50%	19	89%	2	0%	4	50%
Complete Mucosal Remission	6	50%	19	79%	2	0%	4	50%
Clinical Remission	6	67%	21	81%	2	0%	4	50%
Clinical Response Mayo decrease by ≥ 3	6	83%	21	95%	2	100%	4	50%
Outcomes at follow-up visit 2	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Histological Remission	4	100%	19	89%	2	50%	2	50%
Complete Mucosal Remission	4	100%	18	94%	2	100%	2	50%
Clinical Remission	5	100%	20	95%	2	0%	2	100%
Clinical Response Mayo decrease by ≥ 3	5	100%	20	100%	2	100%	2	100%

Table 7: Disease remission outcomes at follow-up visits 1 and 2 based on disease location at baseline visit.

Discussion

This case series describes clinical treatment experience with a novel combination therapy in 36 patients with ulcerative colitis refractory to conventional treatment including patients with severe or pan-ulcerative colitis. Most of the patients treated had UC of moderate severity, but 1 mild patient and 10 severe patients also were treated. In several moderate-to-severe patients, the response to this therapy was sufficient to postpone, in some cases, indefinitely, consideration of a colectomy. A strategy of treatment to salvage serious refractory patients may be the most important contribution of this treatment report.

While 97% of patients (29 of 30 at visit 2) achieved a clinical response defined by a decrease in Mayo score ≥ 3, remission rates for symptomatic, endoscopic, and histological criteria (clinical remission) were 87% (26 of 30), 85% (23 or 27) and 85% (22 of 26) respectively. By contrast, a recent meta-analysis of oral 5-ASA therapy indicates this therapy overall induced a clinical response in 56% of UC patients (versus 45% for placebo) while a clinical remission was achieved in only 29% of UC patients (versus 17% for placebo) [20]. Rectal Amino Salicylates (4-ASA and 5-ASA), produced remission in symptoms, endoscopy, and histology in, respectively, 52%, 41%, and 32% of patients [21]. Most of the studies included in the analysis were done in mild-to-moderate patients not necessarily refractory to treatment.

The experience with moderate-to-severe treatment refractory patients in the cases reported here also contrasts with the pooled remission rates for oral corticosteroids (budesonide, beclomethasone, or prednisolone metasulphobenzoate). For symptomatic, endoscopic, and histological criteria, these rates were: 46%, 31%, and 23%, respectively. Pooled remission rates for patients receiving rectal corticosteroids (hydrocortisone, prednisolone, or betamethasone); by symptomatic, endoscopic, and histological criteria were 45%, 34%, and 29%, respectively. By comparison, placebo remission rates by symptomatic and endoscopic criteria were 9% and 17% [21].

Combinations of 5-ASA and steroids have been tried before in UC patients. One study combined Beclomethasone Dipropionate (BDP; 3 mg/100 ml) with 5-aminosalicylic acid (5-ASA; 2 g/100 ml) in an enema and compared that to either ingredient alone. After 28 days of treatment seven of 19 patients (37%) receiving BDP/5-ASA had healed endoscopically though they do not report whether the patients had healed histologically [22].

A more recent study of patients with mild-to-moderate distal active UC included a group receiving mesalazine tablets 2.4 g/day in combination with a mesalazine (4 g/60 ml) and BDP (3 mg/60 ml) combination enema every day for eight weeks. Complete remission was defined as the simultaneous clinical, endoscopic and histological disease remission at eight weeks. After eight weeks, complete remission rate of the combination enema plus oral mesalazine was at 65%, the highest of any group in the study [23]. With an oral agent and a combination of 5-ASA and steroid, this study comes closest to resembling the case series reported here and also comes closest in obtaining high rates of endoscopic and histologic remission, though it was conducted only in mild-to-moderate patients with 5-ASA pre-treatment.

This treatment administered to these patients was designed based on a model of disease pathogenesis proposing that hydrogen-peroxide generated within colonic epithelial cells is an initiating factor in mucosal inflammation [5,24]. Studies have shown significantly increased H_2O_2 ($P<0.001$) in the inflamed and non-inflamed colonic epithelium of individuals with UC when compared to normal healthy controls [25]. H_2O_2 is highly toxic to tissues and is known to cause ulcerative colitis when introduced into the rectum of humans or laboratory animals [26,27]. Taken together, these results suggest that in UC, the colonic epithelium may have lost the ability to neutralize H_2O_2, which diffuses out of the colonic epithelial cells leading to mucosal inflammation and ulcerative colitis. Once outside the colonic epithelial cells, H_2O_2 may cause oxidative damage to epithelial intercellular tight junctions [28-30] and it may serve as a direct chemo-attractant for neutrophils [31,32].

The enema contains four components, 5-aminosalicylic acid (5-ASA), budesonide, sodium butyrate and sodium cromoglycate, chosen for their potential to inhibit oxidative stress by neutralizing H_2O_2 directly or indirectly, or to upregulate the colonic reductive (antioxidant) capacity to neutralize H_2O_2, and an oral agent, dihydrolipoic acid, a strong anti-oxidant. All four enema ingredients have been used in UC patients individually or in various combinations.

The tetravalent reducing capacity of 5-ASA along with its topical therapeutic action upon the colonic epithelium suggests that it may act as a reducing agent to reduce (neutralize) H_2O_2 within the inflammatory field. Budesonide is a potent locally acting corticosteroid. Its actions prevent neutrophil migration into the inflammatory field located on the surface of the colonic epithelium [33-35]. The once-daily dose of budesonide in this therapy is 25% higher (5 mg) than the daily dose of Uceris (budesonide foam) which is administered twice a day (2 mg each dosing; 4 mg total).

Butyrate is the preferred Short Chain Fatty Acids (SCFA) providing up to 80% of colonic energy requirements [36]. The purpose of adding butyrate is to help restore normal enterocyte bioenergetics. When butyrate replaces glutamine in the Krebs cycle, enterocyte glutathione levels rise, which supports natural neutralization of H_2O_2 and will help patients remain in remission. Thus, butyrate has a sparing effect on cellular glutathione whose cellular concentration is increased after butyrate administration [37]. In a study of 10 patients with distal ulcerative colitis who had been unresponsive to or intolerant of standard therapy for 8 weeks, 2 weeks treatment with sodium butyrate enemas (100 mmol/L) significantly improved endoscopy and histology scores [38]. A combination 5-ASA and butyrate enema was shown to induce remission after 6 weeks of treatment in 25% (6 of 24) of chronically active, refractory mild-to-moderate distal colitis patients while 5-ASA alone induced remission in only 4% (1 of 27) of patients [39].

Sodium cromoglycate is a mast cell degranulation inhibitor. Large numbers of mast cells accumulate at sites of injury in the GI tract [40,41]. Mast cells secrete histamine, a potent vasoactive, bioamine that can contribute to inflammatory persistence in the colonic epithelium. Histamine is highly elevated in the affected colonic mucosa of individuals with ulcerative colitis [42]. A double-blind multicentre study in 70 UC patients comparing sodium cromoglycate (600 mg/100 cc) by enema with prednisolone (20 mg/100 cc) by enema for 8 weeks, showed normal mucosa by sigmoidoscopy in 44% of those receiving the Sodium cromoglycate enema and 52% in those receiving prednisolone. No patients had normal mucosa before dosing commenced. Histology of the rectal biopsies showed 41% normal at study initiation rising to 70 and 75% respectively for sodium cromoglycate and prednisolone respectively [43].

Orally administered R-Dihydro Lipoic acid is a systemic reducing agent that can donate two electrons per molecule to increase the general reductive capacity of the cell. It contributes to an increase in cellular glutathione, which is critical for neutralizing hydrogen peroxide. It has general anti-inflammatory effects and targets mitochondria, which is the largest source of H_2O_2 in the cell [44,45].

While there is a rationale supporting the design of this therapy, and the clinical experience reported here is consistent with it, the patient treatment in this case series did not include a control group, nor was H_2O_2 directly measured in the patients' colonic tissues. However, it is difficult to ignore the improvements seen in severe and refractory patients which are often excluded from clinical investigations. These results suggest a more rigorous, well-controlled, prospective clinical examination of this therapy, or one similar, is warranted.

Conclusion

This case series of 36 patients, 35 with moderate to severe ulcerative colitis, showed that a combination oral/enema regimen was effective at inducing clinical, endoscopic and histological remission in moderate to severe UC patients experiencing a flare that was not controlled by their existing UC medications. The effectiveness of this combination appears to be superior to the 5-ASA plus steroid combinations reported previously. The ability to induce a clinical and histological remission in treatment-resistant patients, including those with severe refractory disease, may allow some to avoid treatment by surgery and the complications and quality of life issues that result.

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Author Contributions

Jay Pravda originated the hypothesis and developed the therapy; Lawrence D Wruble treated patients and performed patient observations, Michael J Weickert analyzed the data and all contributed to the writing of this paper. All authors approved the final version of the article including the authorship list.

Conflict of Interest

Jay Pravda is the inventor on US Patents for Materials and methods for treatment of gastrointestinal disorders and disorders associated with oxidative stress (Patent # 7,312,243; Patent # 9,511,049) and related applications. Michael Weickert has previously served as a consultant for SciDose LLC which holds a license to these patents. Lawrence Wruble does not have any conflicts of interest to report.

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