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Alimentary Tract

Safety and efficacy of sodium hyaluronate (IBD98E) in the induction of clinical and endoscopic remission in subjects with distal ulcerative colitis

Gionata Fiorino, Daniela Gilardi, Patrizia Naccarato, Orsola R. Sociale, Silvio Danese*

IBD Center, Gastroenterology, IRCCS Humanitas, Rozzano, Milan, Italy

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ABSTRACT

Background: Sodium hyaluronate can contribute to the hydration and maintenance of the integrity of the intestinal mucosa. Restoration of the protective layer with sodium hyaluronate may contribute to the induction of remission of active ulcerative colitis.
Methods: We investigated the safety and efficacy of sodium hyaluronate enema (IBD98E) in distal active ulcerative colitis, in a prospective, uncontrolled, open-label pilot trial. Subjects with active distal ulcerative colitis (UCDAI ≥ 4 and sigmoidoscopy score ≥ 1) received IBD98E 60 mL enema once a day. Primary endpoints were safety and clinical response rate at Day 28. Secondary endpoints included clinical remission, endoscopic remission, and tolerability of IBD98E. Paired Student's *t*-test was performed to assess statistically significant differences in subjects between baseline and Day 28.
Results: Twenty-one subjects were enrolled. The overall safety profile was good; no serious adverse events were recorded. At Day 28, 9 subjects (42.9%) were clinical responders, and 10 subjects (47.6%) had an endoscopic response. Eight subjects (38.1%) achieved clinical remission, and 10 subjects (47.6%) achieved endoscopic remission. The mean average UCDAI score decreased from 6.10 to 3.81 at Day 28 ($p = 0.001$), and average endoscopic score decreased from 1.57 to 1.10 ($p = 0.004$).
Conclusion: IBD98E seems to be safe and effective for the induction of clinical and endoscopic remission. Placebo-controlled studies are warranted.

1. Introduction

Ulcerative colitis (UC), one of the two main forms of inflammatory bowel disease (IBD), is a chronic and recurring inflammatory disease of the colonic mucosa, often resulting in abdominal pain, fever, bloody diarrhoea, anaemia and weight loss [1]. The most common presentation is colitis limited to the rectum (ulcerative proctitis) or recto-sigmoid tract (proctosigmoiditis), but it may subsequently spread proximally into any segment of the colon [2].

Sodium hyaluronate is one of the principal components of the extracellular matrix, and contributes significantly to the hydration and maintenance of the integrity of the intestinal mucosa. The intestinal mucosa plays an important role in maintaining the integrity of the intestinal wall, which is constantly challenged by bacteria and antigens. It has been demonstrated that the altered mucosal layer found in UC plays a role in the inflammation by directly interacting with lymphocytes and enhancing phagocytosis [3,4]. In addition, loss of glycosaminoglycan (GAG) from the subepithelial basal lamina in patients suffering from UC leads to alterations of the mucosal layer [5]. Thus, restoration of the protective mucosal layer could contribute to symptom relief and eventually the induction of disease remission.

IBD98E is a medical device, that comprises high molecular weight sodium hyaluronate 1.8×10^6 Da, and low molecular weight sodium hyaluronate 0.35×10^6 Da, together with excipients, including xanthan gum, to ensure that the enema solution adheres to the mucosa of the distal left side colon when administered via the rectum. IBD98E provides a soft barrier to minimize the effects of continuous immune stimulation by triggers from faecal contents, and to provide the ideal environment for the regeneration of the intestinal mucosa.

Standard treatment for the induction and maintenance of remission in mild to moderate distal UC is currently 5-amino salicylic acid drugs [6]. Supplementation of the mucosal lining of the colon with sodium hyaluronate might be a potential alternative treatment.

The aim of this study was to demonstrate the safety and performance of a 28-day treatment course of IBD98E, for the induction of clinical and endoscopic remission in patients with distal UC.

* Corresponding author at: IBD Center, Gastroenterology, IRCCS Humanitas, Via Manzoni 56, 20089 Rozzano, Milan, Italy. Tel.: +39 0282244771; fax: +39 0282242591.
E-mail address: sdanese@hotmail.com (S. Danese).

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2. Methods

This was a single-centre, open-label, prospective study. Eligible subjects were those aged between 18 and 75 years, with a clinically confirmed diagnosis of UC not involving the colon upper than the descending, based on endoscopic and/or histological findings at least 90 days before baseline, with an Ulcerative Colitis Disease Activity Index (UCDAI) ≥4 [7] with sigmoidoscopy score ≥1, who were able to understand and comply with all study procedures. Subjects with confirmed infectious colitis, planned surgical intervention or hospitalization for any indication during the study period, or who received rectal 5-ASA within the 30-day period prior to investigation entry, non-steroidal anti-inflammatory drugs (oral and/or rectal routes) in the 7 days prior to inclusion, steroids (oral and/or rectal routes) within 7 days prior to inclusion, other hyaluronic acid-based products by rectal administration 30 days prior to entry, those hypersensitive to sodium hyaluronate, or those with other medical conditions that could affect their safety during the trial were excluded; pregnant or breastfeeding women were also excluded.

All subjects self-administered IBD98E (60 mL enema) once a day at bed time, for the study period of 28 days. Primary endpoints were the safety of IBD98E, defined as the number and severity of the study device related adverse events, and efficacy of the compound in terms of clinical response at day 28. Secondary endpoints were clinical remission at day 28, mucosal healing at day 28, reduction in the Physician Global Assessment (PGA) score, and increase in the Patients' Global Satisfaction (PGS) score. Tolerability of the product, intended as easiness of use, was also assessed.

Clinical response was defined as a decrease from baseline in UCDAI score of at least 2 points or at least a 30% reduction from baseline, with an accompanying decrease in the sub-score for rectal bleeding of at least 1 point, or absolute sub-score for rectal bleeding of 0 or 1. Clinical remission was defined as UCDAI score of 3 points or lower, with no individual sub-score exceeding 1 point. Mucosal healing was defined as a sub-score for sigmoidoscopy of 0 or 1. The assessments were done at baseline, Day 14, and Day 28, with endoscopic assessment performed only at baseline and Day 28. All subjects were asked to fill in a daily diary at bedtime, recording useful information for efficacy and safety evaluations, such as number of stools, urgency, presence of mucus, presence of blood, abdominal pain, rectal tenesmus, interference with daily life, concomitant medications, etc. Enema retention time was recorded after each administration. The patient was also asked to record symptom-triggering factors, such as intake of any particular food or beverage (i.e. chilli or alcohol), or stress levels during the day. Any adverse event, adverse device effects and device deficiencies were recorded. The patient symptom diary was evaluated by the investigator at the follow-up visits on D14 and D28, together with the PGA and PGS assessments. Drug accountability and assessment of compliance were also performed.

No change in background therapy was allowed during the study period to avoid bias in the primary endpoint evaluation. The shortness of the trial allowed this approach without any harmfulness for patients and, in case of a dramatic worsening of symptoms, an early withdrawal had be considered as the best approach.

Tolerability, intended as easiness of use, was quantified using a quantitative scale, ranging from 1 to 10, where 1 was associated with the lowest ease of use and 10 with the greatest ease of use. We arbitrarily considered a value of 6 as the cut-off for acceptable tolerability. We rated values between 1 and 3 as poor tolerability, 3 and 6 as a moderate tolerability and values >6 as good tolerability. Subjects were asked to score each administration and to record it in the patient's diary.

Since this was an open-label study, and no previous reports on this patient population had been yet performed, we performed a sample size calculation, based on the assumption that 60% of responding subjects could achieve a satisfactory outcome, and considering a statistical power of 0.80 and $\alpha = 0.05$. Twenty subjects were found to be enough to find significant differences in the study population. The data analysis was based on a descriptive evaluation of subjects who responded or achieved remission at D28, based on the criteria defined above.

Statistical analysis was based on the intention-to-treat (ITT) population and the performance-evaluable population. The ITT population is defined as subjects who received at least one administration of the investigation medical device, and the performance-evaluable population is defined as subjects who completed Day 28 of the investigation. Performance and safety variables were analyzed using a paired *t*-test, comparing baseline and Day 28 measures. In case of lack of efficacy data at Day 28, a last observation carried forward evaluation was planned, and the same value of UCDAI and/or endoscopic score reported at the last observation was considered for efficacy evaluation.

The protocol was written according to the ethical guidelines of the 1975 Declaration of Helsinki (6th Revision, 2008), and it was reviewed and approved by our Local Ethical Committee with number 974.

All subjects signed an informed consent form prior to entering the study.

Table 1
Baseline characteristics of enrolled subjects ($n = 21$).

Parameters	Value
Gender	
Female	11
Age	
Mean	40 (21–64)
Height (m)	
Mean	1.7 (1.58–1.85)
Median	1.7
Weight (kg)	
Mean	62.57 (44–87)
Median	62
Months since diagnosis	
Mean	77.9 (3.7–204)
Concomitant UC medications	
5-ASA	15 (71.4%)
Azathioprine	1 (4.7%)
Steroids	0 (0%)
Antibiotics	0 (0%)
None	6 (28.5%)
Disease activity	
Mean UCDAI	6.1 (4–9)
Disease extent	
Left-sided colitis	2 (9.5)
Procto-sigmoiditis	8 (38.1)
Proctitis	11 (52.4)

3. Results

Twenty-two subjects were screened and enrolled from July to December 2012. No patient was found to be a screening failure, but one decided not to begin treatment, and withdrew informed consent. As indicated in the clinical protocol, this patient was excluded from any analysis. Sixteen of the 21 enrolled subjects completed the study and 5 were withdrawn prematurely, four of them for poor compliance ad the last one for intercurrent illness. Two subjects, who completed the study, used only 27 enemas, instead of the 28 required by the protocol, but were included into the final analysis (Fig. 1). Baseline characteristics of the study population are summarized in Table 1. Mean UCDAI was higher in patients with left sided colitis (UCDAI = 8), than in subjects with proctosigmoiditis (UCDAI = 6.9) and proctitis (UCDAI = 5.2).

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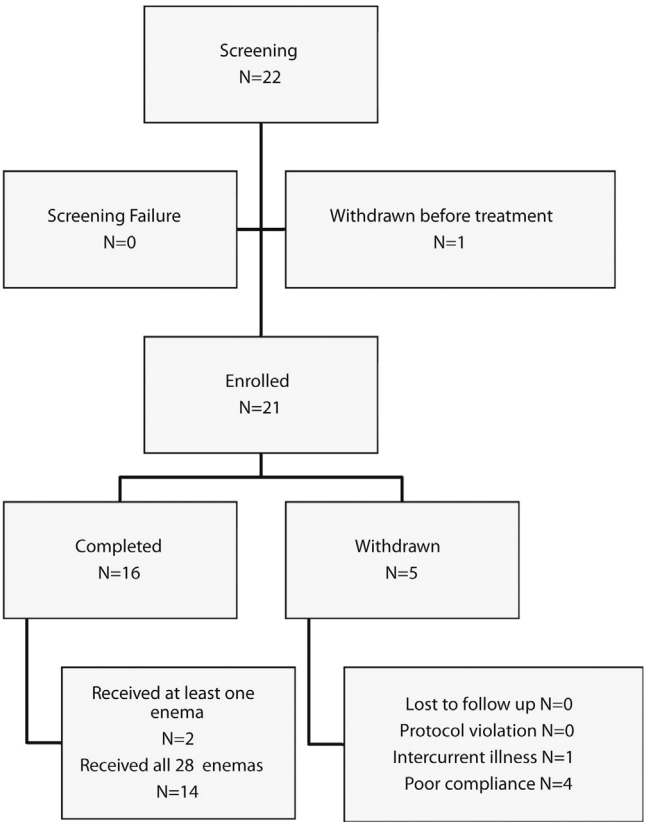

Fig. 1. Study flow diagram.

Table 2
Summary of adverse events reported.

Description	*N*	%
Flatulence and bloating	14	26.92
Pain	8	15.38
Diarrhoea	7	13.46
Nausea	7	13.46
Headache	5	9.62
Worsening of symptoms	4	7.69
Astenia	1	1.92
Burning during insertion	1	1.92
Fever	1	1.92
Generalized malaise	1	1.92
Lack of appetite	1	1.92
Other symptoms	1	1.92
Urgency	1	1.92

Twelve subjects reported at least 1 adverse event, 3 of them reported just one adverse event, while the remaining 9 reported 2 or more adverse events. No serious adverse event was reported, but 3 subjects decided to stop treatment due to the number or intensity of adverse events. No treatment was required for any reported adverse event. All AEs were considered to be mild in severity, with the exception of one report of worsening of symptoms (graded as moderate), and an episode of extreme urgency, reported by the patient as severe (Table 2).

As per study protocol definitions, after 28 days of enema treatment, there were 9 (42.9%) clinical responders in terms of UCDAI score reduction, and 10 subjects achieved endoscopic response (47.6%) at Day 28. Moreover, at the completion of the study, 8 subjects (38.1%) achieved clinical remission (Fig. 2), 10 subjects obtained endoscopic remission (47.6%), out of whom, 5 subjects had complete endoscopic mucosal healing (23.8%, Fig. 3). At the end of trial, the average UCDAI score had significantly decreased from

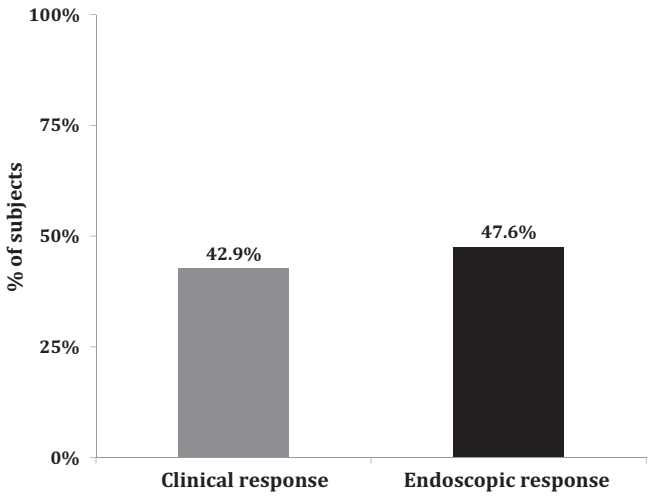

Fig. 2. Clinical and endoscopic response rates to IBD98E at week 4.

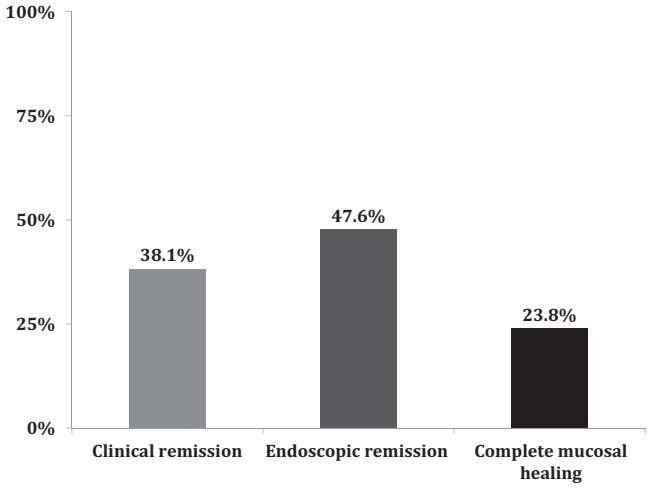

Fig. 3. Clinical and endoscopic remission rates with IBD98E at week 4. The rate of mucosal healing indicates subjects with endoscopic sub-score = 0.

Table 3
Tolerability of IBD98E (10-point scale).[a]

Value[b]	No of IBD98E administrations	%
1	38	7.6
2	26	5.2
3	13	2.6
4	17	3.4
5	41	8.2
6	44	8.8
7	22	4.4
8	23	4.6
9	24	4.8
10	252	50.4

[a] Intended as easiness of use.
[b] A 10-point scale was used from 0 = not tolerated at all to 10 = highly tolerated.

6.10 to 3.81 at D28 ($p = 0.001$). Similarly, the average endoscopic score decreased from 1.57 to 1.10 ($p = 0.004$).

After 28 days of treatment, both mean PGA and PGS significantly improved, from 2.67 to 3.95 ($p = 0.018$) and 3.62 to 4.71 ($p = 0.042$), respectively.

IBD98E administration was well tolerated in the majority of subjects (73% of subjects). Out of all administrations, 64% were well tolerated, and about 50% of administrations were judged to have excellent easiness of use (score 10, Table 3). Some patients reported

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problems related to the hardness of the bottle (with difficulty completely emptying the enemas). In one case, the patient reported problems related to the stiffness of the cannula.

4. Discussion

Ulcerative colitis (UC) is a chronic and recurring inflammation of the intestinal mucosa or sub-mucosa often resulting in intermittent abdominal pain, fever, diarrhoea and weight loss. It is one of the two main forms of inflammatory bowel disease (IBD). The most common presentation is colitis limited to the rectum (ulcerative proctitis), or rectum and sigmoid colon (proctosigmoiditis), but it may subsequently spread proximally into any segment of the colon. Most commonly, UC patients experience remitting and relapsing periods, with acute attacks lasting weeks to months. However, a significant percentage of patients suffer a chronic continuous course. In patients with mild to moderate active UC, treatment aims are usually to rapidly relieve symptoms, or ideally induce remission, so that the patient can return to normal daily life.

For active ulcerative proctitis, an effective approach is the rectal administration of mesalamine, enemas or suppositories, often supplemented with an oral aminosalicylate [8]. Corticosteroid enemas can also be used, but with caution for long-term toxicity. In patients with severe or refractory UC symptoms, oral corticosteroids are indicated. Corticosteroids, while highly efficacious in short-term use, have numerous adverse effects, especially in the elderly, which preclude long-term use.

The 5-aminosalicylic acid preparations are currently available in both oral and rectal formulations. The combination of oral and topical mesalamine is generally considered more effective than either one alone for mild to moderate extensive colitis [9]. The current practice guidelines of the American College of Gastroenterology emphasize the superiority of topical therapy, either alone or in combination with oral 5-ASA agents, for the treatment of distal UC [10]. The rectal products achieve high luminal concentrations of the active component, while minimizing adverse events due to low systemic absorption. The effectiveness of 5-ASA rectal preparations in placebo-controlled trials has been demonstrated by several meta-analyses and critical reviews [11,12].

The mucosal barrier, provided by the mucosal epithelium, plays a key role in protecting the gastrointestinal tract from potential damage. It prevents potential damage from a broad spectrum of harmful substances present within the intestinal lumen including bacterial microorganisms, various dietary factors, gastrointestinal secretory products and drugs. In IBD, this mucosal barrier is disturbed during the course of the condition [13]. It is reported that the loss of glycosaminoglycan from the sub epithelial basal lamina of patients suffering from UC. The hypothesis is that alterations in negative-charged compounds could impair the passage of substances through colonic mucosa, and thus lead to the leakage of proteins, fluid and to the remodelling characteristic of IBD [14]. Sodium hyaluronate is one of the principal components of the extracellular matrix and contributes significantly to the hydration and maintenance of the integrity of the intestinal mucosa. During the initial phase of inflammation, endogenous secretion of sodium hyaluronate is increased to work against oedema formation [15]. Pagnacco et al. reported that, when the mucosal barrier in the ground substance is damaged, topical application of sodium hyaluronate can help reconstruct the barrier due to macro-aggregating effect, which inhibits formation of oedema [16]. By supplementing sodium hyaluronate to the colonic mucosal layer, a soft barrier might be provided to minimize the effects of continuous immune triggers from the contents of the colon on the colonic mucosa. Consequently, it provides an ideal environment for the regeneration of the intestinal mucosa. Enhancement of the mucosal repair mechanisms provides a new potential way of treating UC [17].

From the current study, it was noted that rectal sodium hyaluronate administration might help in restoring mucosal integrity, and promoting mucosal healing in the short term. To the best of our knowledge, this is the first study to investigate the clinical efficacy and safety of rectal sodium hyaluronate in subjects with active distal UC. Of the 21 subjects, about half achieved clinical and endoscopic response, and, one quarter of subjects (23.8%) achieved complete mucosal healing. Data from our study are consistent with recent data on two placebo-controlled studies of topical 5-ASA [18], in which 48.6% and 25% of subjects had clinical remission and endoscopic remission at week 3, respectively. Our study showed more positive results compared to a prospective study on 5-ASA suppositories and hydrocortisone foam at week 4 [19]. Other studies report higher rates of clinical and endoscopic remission with topical conventional treatment, but generally such outcomes are measured at week 6 or 8 [20–23]. It is thus possible that a longer period of treatment with sodium hyaluronate may result in similar remission rates. These results are not enough powered and cannot be used to conclude for a potential efficacy of the product. However there is some evidence of a potential activity that has to be further evaluated.

The device was shown to have a good safety profile. No serious adverse events were reported. Adverse event were reported in less than 22% of subjects, and for the majority of these it was difficult to distinguish them from active UC-linked symptoms, such as diarrhoea, flatulence, asthenia, generalized malaise, fever, or lack of appetite. Only 4/52 (7.7%) reported adverse events were judged to be related to the study device.

Complaints of difficulties with rectal self-administration were reported in 27% of cases, which is in line with the actual rate of tolerability of enema therapy in literature, which ranges from 19% to 33% [24]. It is important to note that active proctitis or proctosigmoiditis can reduce the tolerability of the rectum to enema [25], and may thereby affect the acceptance of any topical treatment.

The main limitation of our study is the lack of a control group. However, IBD98E was shown to be able to induce response and remission (both clinical and endoscopic), and it was also demonstrated to be safe. Second, the treatment period was limited to 4 weeks, whereas a longer study period may be expected to show higher clinical and endoscopic remission rates and to better evaluate safety profile of the product. These encouraging findings support the need for further evaluation in prospective randomized placebo-controlled trials to determine if safety and efficacy are statistically significantly better than those seen with conventional topical treatment for UC.

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Conflict of interest statement

All Authors declare no conflict of interest related to the study.

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