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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

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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.

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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 higher than the descending colon, 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).