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Managing ulcerative colitis in remission phase: usefulness of Casperome®, an innovative lecithin-based delivery system of *Boswellia serrata* extract

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Abstract. – OBJECTIVE: ***Boswellia serrata*** **extracts (BSE) have been traditionally used for the treatment of several inflammatory diseases. The aim of this study was to evaluate the efficacy of a novel delivery form of BSE (Casperome®) in Ulcerative Colitis (UC) during minimally symptomatic remission phase.**

PATIENTS AND METHODS: In this open-label, observational, registry study, informed participants with UC in remission phase (n = 43) freely decided to receive the oral daily Casperome® supplementation (n = 22) or no supplementation (n = 21) for 4 weeks. Several parameters associated with minimally symptomatic UC in remission were evaluated at the inclusion and the end of the study.

RESULTS: A significant beneficial effect of Casperome® was observed for all the parameters evaluated, namely: diffuse intestinal pain, evident and occult blood in stools, bowel movements and cramps, watery stools, malaise, anemia, rectal involvement, number of white blood cells as well as need for concomitant drugs and medical attention. Faecal concentration of calprotectin, a marker of bowel inflammation, resulted ameliorated in Casperome® supplemented patients.

CONCLUSIONS: Our study showed that Casperome® supplementation attenuates symptoms associated with mild UC in remission, reducing the use of drugs and medical consultations. Therefore, our study suggests that Casperome® supplementation could represent a promising alternative approach to manage minimally symptomatic UC and maintain the remission phase.

Key Words:
Ulcerative colitis, Remission phase, *Boswellia serrata* extract, Casperome®.

Introduction

Inflammatory bowel diseases (IBD), namely ulcerative colitis and Crohn's disease are chronic, life-long, and relapsing inflammatory diseases of the gastrointestinal tract. Although it has been shown that genetic/social learning factors, diet, intestinal microbiota, intestinal low-grade inflammation, and abnormal gastrointestinal endocrine cells play a major role, the IBD pathophysiology is not completely known[1].

In particular, ulcerative colitis (UC) is characterized by diffuse mucosal inflammation, limited to the colon, with confluent inflammation extending proximally from the rectum, varying severity and extent[2]. According to the Montreal classification[3], in case of UC, we consider 3 different colon distribution patterns (proctitis, left-sided colitis, pancolitis), 4 degrees of disease activities (remission, mild, moderate, severe), and 4 possible disease courses (asymptomatic after initial flare, increase in severity over time, chronic continuous symptoms, chronic relapsing symptoms)[4]. Therefore, the choice of suitable UC treatment depends on severity, localization and course of the disease.

Topical therapy with 5-aminosalicylic acid (5-ASA) is the treatment of choice in active distal ulcerative colitis (proctitis)[5]. Mild-to-moderate, left-sided active UC should be initially treated with topical and oral aminosalicylates[6]. However, severe left-sided colitis is usually an indication for hospital admission and systemic therapy. In fact, in more extensive UC (pancolitis), 5-ASA compounds administration are usually combined

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with oral steroids treatments[7]. Last, in severe UC, therapy based on calcineurin inhibitors (cyclosporine, tacrolimus) or tumor necrosis factor-antibodies (infliximab) are considered if there is no response to corticosteroids for 3 days[8].

The goal of UC treatment is to induce rapidly and maintain a remission phase, preventing complications related to the disease and to the treatment itself. The first line therapy for the remission maintenance is 5-ASA administered orally or rectally[9]. However, in individuals with established quiescent or mild disease, which has a favorable prognosis even without therapy, the benefits of long-term maintenance treatment are less certain[10]. Herbal remedies could represent an alternative approach for the management of very mild UC or UC during stabilized remission phase[11].

Oleo gum resins from *Boswellia serrata* have been used in traditional medicine in India and African countries as a remedy for the treatment of a variety of inflammatory diseases[12]. Interesting data on the effects of *Boswellia serrata* extracts (BSE) and its active components, boswellic acids, resulted from preclinical studies on animals models[13-15], and clinical studies[16,17] in patients with chronic and ulcerative colitis. However, pharmacokinetics studies revealed low systemic absorption of boswellic acids in animals and human[18]. In order to improve the low bioavailability of BSE, a lecithin-based delivery form of standardized BSE (Casperome®) has been created[19,20].

This study aimed at evaluating the efficacy of a novel delivery form of BSE (Casperome®) in patients with minimally symptomatic UC in remission phase.

Patients and Methods

This was an open-label, observational, registry study conducted in 43 patients with defined UC (clinically evaluated and confirmed by previous biopsies), formally in remission from at least 1 year. Patients presented minimal UC symptoms (namely no major bleeding or major clinical episodes) and were not using any drug at inclusion. Moreover, no other clinical or risk conditions were present.

All participants gave written informed consent before enrolment in this study. All procedures received local Ethics Committee approval, in accordance with the latest version of the Declaration of Helsinki. Informed participants (n = 43) freely decided to receive the oral daily Casperome® supplementation (supplementation group, n = 22) or no supplementation (control group, n = 21).

Supplementation consisted of 250 mg/day of the new standardized BSE, Casperome® (1 tablet of 250 mg, in single administration) for 4 weeks. The dosage scheme was designed based on the pharmacokinetics features of Casperome®.

The following parameters were evaluated before and at the end of the observational period:

1. Diffuse (mild) intestinal pain: episodes were evaluated during the previous week by the patients and classified with an analogue scale of pain ranging from 1 (no pain) to 5 (continuous and severe pain);
2. (Minimal) bloody diarrhea, as episodes/week;
3. Evacuation with blood and mucus, as episodes/week;
4. Bowel movements, as episodes/day;
5. Cramps: episodes were evaluated during the previous week by the patients and classified with an arbitrary scale ranging from 1 (no cramps) to 5 (continuous, severe, requiring analgesic/antispastic drugs cramps);
6. Number of patients with suspected rectal involvement;
7. Watery stools, as number of episodes/week;
8. Malaise: episodes were evaluated by the patients and classified with an arbitrary scale ranging from 1 (no malaise) to 5 (severe episodes requiring medical intervention);
9. Anemia: blood hemoglobin concentration was measured;
10. Body weight;
11. White blood cells (WBC) count: the number of WBC was measured in blood samples;
12. Number of patients who needed specific drugs;
13. Number of patients who needed medical attention or hospital admission.

The fecal immunochemical testing (Second generation FIT® – Pinnacle Biolabs) was used to detect occult blood in stools. Particularly, FIT detects globin levels at 50 ng/mL in spontaneously passed stool. Three stool samples were collected on alternate days. The minimal presence of blood in stools was indicated with an analogue scale (0 = no traces; 1 = occasional minimal traces; 2 = significant traces, not always; 3 = important occult blood, present at all evaluations).

Table I. Details of subjects enrolled in the study.

	Control group	Supplementation (Casperome®) group
Subjects (male)	21 (15)	22 (16)
Dropout	5	3
Age, years (mean ± SD)	51 ± 2.6	52.1 ± 2.2
Follow up (days ± SD)	33.1 ± 2.2	34.3 ± 2.1

SD: standard deviation.

Bowel inflammation was assessed by the fecal concentration of calprotectin (Calprest, Eurospital), an antimicrobial protein found in neutrophils, which is released in the intestinal lumen when inflammatory processes are active in the bowel[21]. Patients with calprotectin concentration exceeding 50 µg/g in stool samples were considered positive and included in this study.

Treatment Formulations

Casperome® (Indena, Milan, Italy) is a delivery form of a highly standardized *Boswellia serrata* extract and soy lecithin in a 1:1 ratio, with about half part of microcrystalline cellulose being also added to improve the physical state and to standardize the product to a content of triterpenoid acids by HPLC of at least 25%.

Statistical Analysis

Numerical data comparisons between groups were performed using unpaired two-sample Student's *t*-test or Mann-Whitney U-test, as appropriate. Categorical data differences between groups were evaluated by Fisher's exact test. *p*-values less than 0.05 were considered significant. According to previous studies on comparable groups, at least 20 subjects were considered adequate to define a difference in target outcomes at 4 weeks.

Results

The two groups showed similar demographics (Table I) and clinical characteristics (Table II) at inclusion. No safety and tolerability issues were observed at inclusion and after the follow-up period. The dropouts were not related to medical problems. As summarized in Table II, we observed a significant beneficial effect of Casperome® supplementation, in all tested parameters. Mild, but almost always present, diffuse intestinal pain and cramps significantly decreased in intensity and frequency with the Casperome® sup-

Table II. Evaluation of several parameters associated with mild UC or UC in remission, observed before and at the end of the study.

	Control group		Supplementation (Casperome®) group	
	0 week	4 week	0 week	4 week
Intestinal pain (range 1-5)	3.0 ± 0.3	2.01 ± 0.7	3.2 ± 0.5	1.1 ± 0.4*,+
Diarrhea with blood (episodes/week)	2.1 ± 1	2 ± 0.7	1.9 ± 1.1	0.4 ± 0.3*,+
Stool with blood and mucus (episodes/week)	2.4 ± 1	2.1 ± 0.5	2.3 ± 1.1	1.2 ± 0.7*,+
Bowel movements (episodes/day)	4.4 ± 0.6	4.3 ± 0.9	4.2 ± 1.1	2.2 ± 0.6*,+
Cramps (range 1-5)	3.3 ± 0.4	3 ± 0.7	3.2 ± 0.3	1.6 ± 0.4*,+
Rectal involvement (n. of patients)	13/21	13/21	12/22*	4/22*,+
Watery stools (episodes/week)	4.1 ± 0.3	3.4 ± 0.4	4 ± 0.4	2.2 ± 0.3*,+
Malaise (range 1-5)	3.7 ± 0.8	3.3 ± 0.3	3.8 ± 0.3	2.1 ± 0.4*,+
Anemia (Hb in g/dl)	11.5 ± 1	11.34 ± 2.1	11.21 ± 1.1	13.2 ± 1.2*,+
Body weight and weight loss/gain (kg)	75.3 ± 4.6	75.5 ± 4.6	73.4 ± 3	73,6 ± 3
WBC (Cell count/µl)	7499 ± 432	6679 ± 1004	7886 ± 317	5339 ± 513*,+
Need for drugs (n. of patients)	–	16/21	–	4/22+
Need for medical attention (n. of patients)	–	9/21*	–	4/22+

Hb = hemoglobin. Data are reported as mean ± standard deviation; *$p < 0.05$ vs. baseline; + *vs*. control.

Table III. Biomarkers evaluation in stool samples.

	Control group		Supplementation (Casperome®) group	
	0 week	4 week	0 week	4 week
Occult blood in stool (range 0-3)	2.0 ± 0.3	2.0 ± 0.1	2.0 ± 0.2	1.0 ± 0.1
Calprotectin > 100 µg/g (n. of patients)	18/21 (85.7%)	16/21 (76.2%)	19/22 (86.4%)	11/22 (50%)*,+

*$p < 0.05$ *vs*. baseline; + *vs*. control.

plementation. Also, the episodes of diarrhea (with some evident blood traces), evacuation with blood/mucus and bowel movements resulted reduced at the end of the study in the Casperome® group, compared with the control group and the values at inclusion. At 4 weeks, a decrease in the number of patients with suspected rectal involvement was observed. Anemia, reported as concentration of hemoglobin, improved following 4-week Casperome® supplementation. This observation represents a further indication of reduced minimal and occult blood traces in stools.

Casperome® supplementation resulted in the reduced occult blood (Table III) and calprotectin levels (Figure 1) in stools. However, more accurate and prolonged evaluation of occult blood is required. Overall calprotectin values, in consideration of the non-active UC phase, were not particularly high. Interestingly, the number of subjects with calprotectin levels in stools > 100 µg/g (86.4% in the supplement group and 85.7% in the controls, at inclusion) significantly decreased after Casperome® supplementation (50%), and in comparison with the control group (76.2%) (Table III).

Need for specific drugs treatment (longer than 3 days) to control UC symptoms or need for new medical consultations were higher in control group compared with supplemented group. However, no hospital admissions were reported during this registry study.

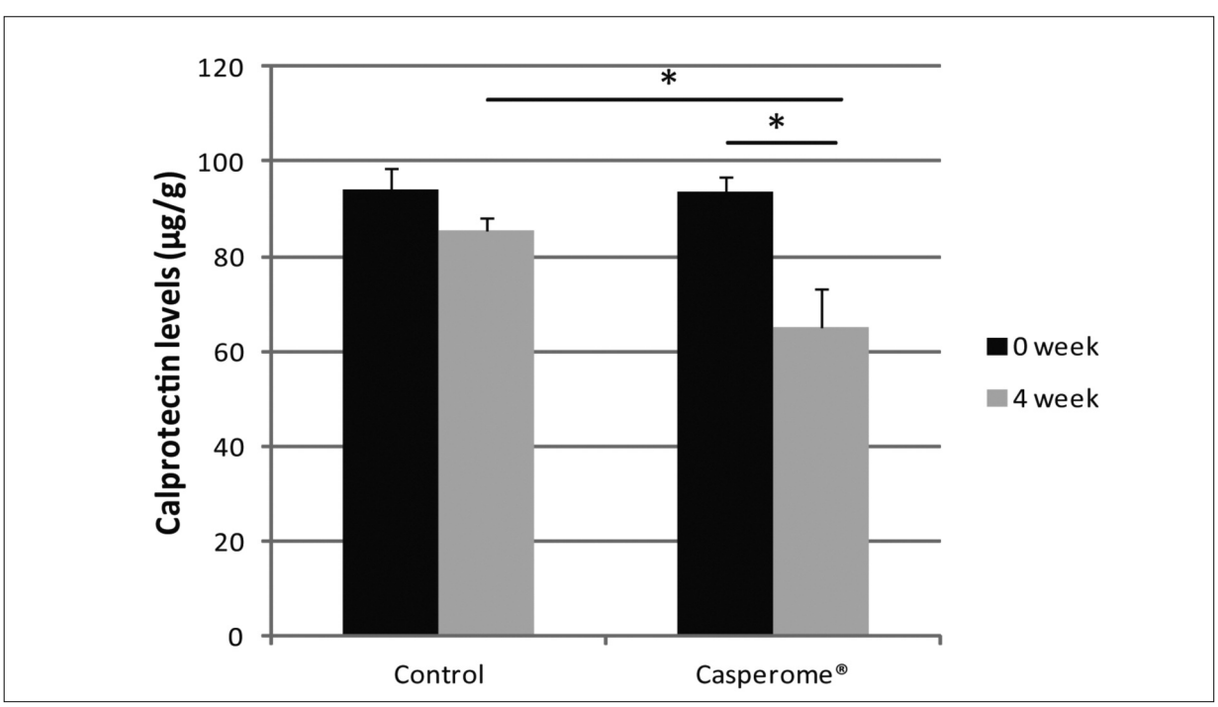

Figure 1. Evaluation of the calprotectin level in stool of patient with minimally symptomatic UC or UC in remission phase. At 4 week, the calprotectin concentration in stool of Casperome®-supplemented patients resulted significantly reduced compared to values of control group and at inclusion. Values are expressed as mean ± SD. Asterisk indicates $p < 0.05$.

Discussion

This registry study provides further evidence on the efficacy of the highly standardized *Boswellia serrata* extracts in the management of inflammatory conditions. In particular, the present study investigated the effects of BSE in alleviating and controlling mild symptoms related to UC in remission phase.

Nowadays, 5-ASA agents represent the main treatment in patients with UC in remission phase. However, the long-term benefits of therapy should be compared with potential clinical risks and social and economical costs. In individuals with mild UC, a prevalent patient population with a favorable long-term prognosis, the absolute risk of colectomy or colorectal cancer (CRC) is low[10]. On the other hand, long-term treatment with 5-ASA drugs could have potential side effects (renal injury, and in some instances, end-stage renal disease), and they are associated with a daily burden and economical cost[10]. At the moment, there are no alternative treatments for the management of mild UC in remission phase, apart from the probiotic strain *Escherichia coli Nissle*[22] and dietary recommendations.

Recently, a novel lecithin-based delivery form of a *Boswellia serrata* extract (Casperome®) has been made available to overcome the known limitations of other *Boswellia serrata* products[19,20]. Casperome® showed an improved systemic bioavailability and an increased penetration across biological membranes, two features which suggest its potential effectiveness in UC[20]. In fact, it has been demonstrated that the effect at the intestinal level of other anti-inflammatory natural products (e.g. curcumin) is only in part due to a topical action, as an important contribution derived from the systemic absorption and the subsequent distribution to the inflamed intestinal segment has been observed[23,24]. In this study, the new delivery form of the standardized *Boswellia serrata* extract (Casperome®) attenuated the symptoms associated with minimally symptomatic UC in remission, reducing the need for other drugs and medical consultations.

The improvements were achieved in a limited period of time, in line with previous studies investigating the effects of BSE in other inflammatory conditions (asthma)[25,26]. Actually, there are no fully validated and internationally recognized guidelines to define and diagnose the remission phase in UC[27,28]. Although potentially useful, in the clinic, endoscopy is rarely applied to confirm remission due to the risks and invasiveness associated with this technique.

Given the limited symptomatology of our patients, we decided not to perform endoscopy, as such an invasive exam could have represented an unneeded burden and risk. Additional studies are currently underway, applying non-invasive endoscopy technique (pill endoscopy) to directly visualize intestinal wall inflammatory changes and to monitor the relapses rate (flare) over a long-term Casperome® supplementation.

Conclusions

Our study suggests that Casperome® supplementation could represent a promising alternative approach to manage minimally symptomatic UC, to maintain the remission phase over a prolonged period of time and, therefore, to improve the quality of life of patients. Despite all the limitations implicit in any observational analysis, our study demonstrated the Casperome® supplementation efficacy in controlling minor symptoms of UC in remission, and in reducing the use of drugs and medical consultation. However, larger scale studies are needed to evaluate further these promising findings.

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Conflict of Interest

The Authors declare that there are no conflicts of interest.

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