

Functional study on *Boswellia phytosome* as complementary intervention in asthmatic patients

T. FERRARA¹, G. DE VINCENTIIS², F. DI PIERRO³

¹ASL 207, Cava dei Tirreni (Salerno), Italy

²IRCS – Ospedale Bambino Gesù, Roma, Italy

³Velleja Research, Milano, Italy

Abstract. – OBJECTIVE: The combination of inhaled corticosteroids (ICS) and long-acting beta-agonists (LABAs) is recommended for the treatment of patients with mild-to-severe persistent asthma. However, given the lack of definite and safe therapies, complementary or alternative medicines are frequently used by asthmatic patients in combination with standard treatments.

PATIENTS AND METHODS: A group of asthmatic subjects have been enrolled in this multicenter study; after having verified the compliance to their current medical therapy (ICS + LABAs), the subjects have been randomized to receive Casperome[®] 500 mg/day or no additional treatment for a period of 4 weeks. They were also asked to keep track of the number of inhalations required per day and any adverse events through a daily form.

RESULTS: A total of 32 subjects were enrolled in the study. Subjects receiving Casperome[®] 500 mg/day in addition to the standard ICS + LABAs treatment showed a decrease in the number of inhalations needed compared to patients who did not receive Casperome[®] therapy. The treatment was well tolerated and only mild-moderate adverse events were registered.

CONCLUSIONS: The use of Casperome[®] 500 mg/day is beneficial for asthmatic patients as it helps reduce the need for inhalation therapy with ICS + LABA.

Key Words:

Asthma, *Boswellia serrata* phytosome, Complementary intervention, Corticosteroids, Long-acting beta-agonists.

symptoms of varying severity such as wheezing, dyspnea, cough, bronchial hyperresponsiveness and mucus hypersecretion¹. In terms of etiology asthma has both an environmental and a genetic component, as the inflammation of the bronchi is triggered by common environmental antigens that generate an inappropriate immune response in genetically predisposed subjects². However, it is now recognized that also neuromuscular and psychological components may play an important role in triggering an asthma attack^{3,4}.

Despite medical advances, the incidence of the disease has continued to increase in the last decades, paralleled by an increase in severity and mortality also caused by a lack of proper and definite cure⁵. Treatment with inhaled corticosteroids (ICS) has substantially changed the therapy for asthmatic patients and is now considered as the cornerstone of maintenance asthma therapy. Indeed current guidelines recommend the combination of ICS and long-acting beta-agonists (LABA) for the treatment of patients with mild-to-severe persistent asthma⁶. However, the combination of ICS and LABAs has raised some concerns over their safety, especially considering the potential for severe asthma exacerbations (SAEs)⁷, and also taking into account the low adherence to ICS therapy⁸.

Given the lack of definite and safe therapies for the chronic treatment of asthma, many patients have turned to integrative medicine to help reduce symptoms burden or avoid dependence to prescription medications. In fact, complementary or alternative medicines (CAM) – such as Chinese herbs, Indian remedies, Japanese herbal medications – are widespread among asthmatic patients and are usually used in combination with standard treatments^{9,10}.

An example of traditional medicine used to treat asthma symptoms is *Boswellia serrata* extract, a preparation extracted from a tropical tree (*Boswellia serrata*) that contains triterpene com-

Introduction

Asthma is a common chronic inflammatory disease characterized by a high heterogeneity both in terms of etiological factors and in symptoms. Although asthma is mainly characterized by reversible airflow obstruction and bronchospasm, patients may present a wide range of inflammatory phenotypes and a combination of

pounds with anti-inflammatory properties used in asthma and other chronic inflammatory diseases^{11,12}. These compounds, called boswellic acids, exert their anti-inflammatory activity through the inhibition of lipoxygenases (responsible for the synthesis of leukotrienes), proteases (cathepsin G)¹³ and nuclear factor kB (activated in many inflammatory chronic diseases)¹⁴. In addition, they reduce the overexpression of alpha tumor necrosis factor (TNF- α)¹⁵ and matrix metallo-proteinases (MMP)¹⁶, which play a role in inflammatory processes.

Boswellia serrata extracts have been used in different chronic inflammatory diseases such as chronic intestinal disorders, asthma and rheumatic diseases, reporting positive results; in particular this remedy is highly tolerable and present a better toxicity profile if compared to other drugs commonly used in inflammatory diseases such as steroids^{11,12,14}.

The aim of this study was to investigate the usefulness of the oral administration of Casperome[®] (Indena SpA), a highly standardized extract of *Boswellia serrata* in a phospholipids based delivery system (known as Phytosome[®], to improve the extract bioavailability) in the reduction of the need for ICS + LABAs therapy in asthmatic patients.

Patients and methods

Study Population

The study population included adult subjects (age between 18 and 80 years old) diagnosed with asthma and currently under treatment with ICS + LABAs; treatment with antihistamines or xanthine derivatives for oral use was also allowed.

The exclusion criteria were:

- Respiratory diseases other than asthma;
- Kidney or renal diseases;
- Tumor diseases;
- Pregnancy, lactation, desire for pregnancy;
- Use of other anti-leukotriene agents (Lukast class of medications);
- Use of supplements other than those prescribed;
- Use of inhalers other than those described in the inclusion criteria;
- Use of any other inhalant method (fumigations, etc.)

All the subjects signed the informed consent form before the enrollment in the study.

Study Design

Subjects enrolled in this monocentric, randomized, parallel-groups study were initially tested for one week to verify the actual use of the anti-asthma therapy: they were asked to continue their treatment with ICS + LABAs, 1 inhalation twice daily (morning and evening), while completing a form with items describing where they reported each day the actual number of inhalations they had used each day.

After the run-in, patients were randomized to receive 1 tablet of a commercial product available on the Italian market (Pharmextracta Srl) and containing Casperome[®] 500 mg/day in the morning (Casperome[®] group) or no additional treatment (control group). All the subjects continued the ICS + LABAs therapy, 1 inhalation twice daily (morning and evening), for a period of 4 weeks. During this period they were allowed to reduce the number of inhalations, based on their perception of their respiratory function, and they were asked to keep track of the number of inhalations they had used each day through a daily form.

Subjects were also asked to keep track of any adverse event (AE) which occurred during the study.

The primary endpoint of the study was the reduction in the number of inhalations used by patients treated with Casperome[®] tablets compared to the control group. The safety of the treatment was also assessed by evaluating the number and type of AEs reported in the form.

Statistical Analysis

Continuous variables were analyzed by descriptive statistics. Continuous outcomes were analyzed through the repeated measures analysis of variance (ANOVA) test, mixed models or the split-plot design. The mixed-design analysis of variance model was used to test for differences both between the Casperome[®] group and the control group and between the baseline data and data observed in the following weeks. A Tukey's range test was performed to evaluate the significance of the differences measured. A *p* value < 0.05 was considered statistically significant. Statistical analysis was performed using SAS and NCSS software for Macintosh.

Results

A group of 32 patients (mean age 45.8 years old, 47% male) was enrolled in the study; 18

subjects received Casperome[®] treatment while 14 were assigned to the control group. The two groups were homogeneous in terms of age (mean age 46.1 years old in the Casperome[®] group vs. 45.4 in the control group; $p = 0.9055$) and gender (50% male in the Casperome[®] group vs. 43% in the control group $p = 0.6879$)

The results of the forms during the run-in phase confirmed that all the patients used the inhalation therapy 2 times a day (14 times a week). The inhalation therapies used by the subjects were: fluticasone + salmeterol, beclomethasone + formoterol or budesonide + formoterol.

Efficacy Data

The analysis of the questionnaire/forms showed that during the 4-week treatment period the frequency of use of the inhalation therapy remained unchanged in the control group. In fact the number of inhalations reported by the subjects were 13.86 in week 1 and 2, 13.64 in week 3 and 13.79 in week 4 (Table I). Conversely, subjects in the Casperome[®] group reported a reduction in the number of inhalations needed each day. As shown in Table I the frequency of use of the inhalers was initially reduced in week 2 (-21% from baseline) and further decreased in week 3 (-29%) and 4 (-43%). The difference in the frequency of use of the inhalers was statistically significant between week 1 and the baseline, between week 1 and 2, week 2 and 4 and between week 3 and 4 ($p < 0.00001$).

In addition the number of inhalations required by subjects in the Casperome[®] group was significantly lower than that of subjects in the control group at week 2 (-26%), week 3 (-28%) and week 4 (-42%) ($p < 0.00001$) (Figure 1).

Last of all according to results of the Tukey's range test if both the components (type and time of treatment) were taken into consideration, there was a statistically significant difference between the control group and the Casperome[®] group ($p = 0.025$).

Safety Data

Overall 19 (59.4%) out of 32 subjects reported an AE during the study; the number and type of AEs registered during the study are summarized in Table II. In detail 8 subjects in the Casperome[®] group suffered from an AE, either headache (5 subjects) or insomnia (3), while 11 subjects in the control group reported headache (5), insomnia (1), nausea (2) or constipation (3). All the AEs were considered as mild and no serious AE was reported.

Two subjects in the Casperome[®] group discontinued from the study as they perceived the treatment was not effective. No patient in the control group discontinued from the study.

Discussion

The results of our study suggest that treatment with a bioavailable delivery form of *Boswellia serrata* extract (Casperome[®]) as complementary therapy can help reduce the need for inhalation therapy with ICS+LABAs in asthmatic patients. Patients receiving 500 mg/day Casperome[®] in addition to the standard ICS+LABAs treatment showed a decrease in the number of inhalations needed in a period of 4 weeks compared to patients who did not receive Casperome[®] therapy. While patients in the control group used around 14 inhalations a week (2 inhalations a day) during the whole treatment period, patients in the treatment group reported a decrease in the number of inhalations needed, from 14 a week at baseline to 13.39 at week 1, 11.0 at week 2, 9.89 at week 3 and 8.00 at week 4. The results of the analysis showed that the reduction during the first week of treatment and during the following weeks was statistically significant ($p < 0.0001$) and that the results obtained in the treatment group were significantly different from those observed in the control group ($p < 0.0001$).

The treatment was well tolerated by all patients with only 8 mild-moderate AEs such as nausea and insomnia. Of note the percentage of

Table I. Mean number of inhalations reported by subjects in the Casperome[®] group and in the control group at the baseline, week 1, 2, 3 and 4.

| | N | Basal | Week 1 | Week 2 | Week 3 | Week 4 |
|------------------------------|----|-------|--------|--------|--------|--------|
| Casperome [®] group | 18 | 14.00 | 13.39 | 11.00 | 9.89 | 8.00 |
| Control group | 14 | 14.00 | 13.86 | 13.86 | 13.64 | 13.79 |

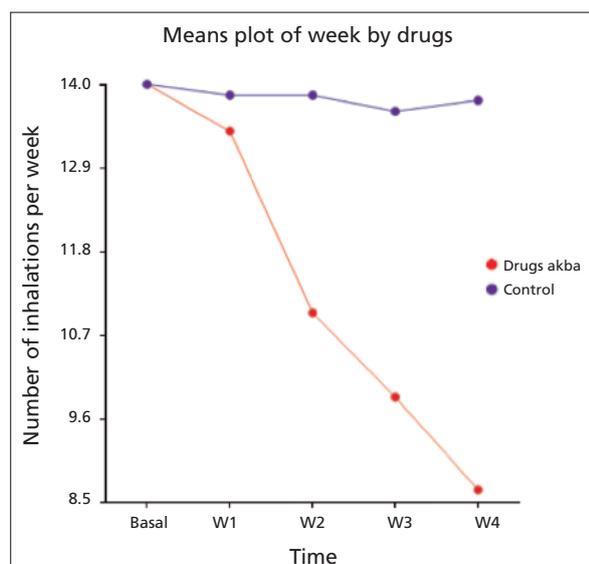


Figure 1. Mean change in the number of inhalations required in the Casperome® group and in the control group during the treatment period.

AEs reported in the control group (78%) was higher than that observed in patients treated with Casperome® (44%).

The beneficial effect of *Boswellia* extract in asthmatic patients has been previously reported in a study by Gupta et al¹⁷ who conducted a double-blind placebo controlled study on 44 patients with persistent bronchial asthma who were treated for 6 weeks with a preparation of *Boswellia* extract 300 mg/tid. The results of this study showed that treatment with *Boswellia* extract was able to improve the condition of patients both in terms of signs and symptoms (decrease in dyspnea, rhonchi and number of asthma attacks) and respiratory function [increase in Forced Expiratory Volume (FEV), Forced Vital Capacity (FVC) and Peak Expiratory Flow Rate (PEFR)]. Moreover the authors reported a decrease in eosinophilic count and in the erythrocyte sedimentation rate (ESR).

Similar results were reported in a study¹⁸ conducted on 63 asthmatic patients who received a combination of different natural extracts with an-

ti-inflammatory properties which are known for inhibiting leukotriene production; namely *Boswellia serrata* extract 150 mg/day, licorice root extract 50 mg/day and curcumin 15 mg/day. The results of the study showed that this treatment combination was effective in reducing asthma symptoms and number of asthma attacks in asthmatic patients. In addition, the authors showed that plasma leukotriene, nitric oxide and malondialdehyde levels were also reduced.

The positive effect exerted by *Boswellia* extract are in fact associated with the anti-inflammatory properties of boswellic acids and in particular with their inhibitory effect on lipoxygenases, the enzymes responsible for the synthesis of leukotrienes. These inflammatory mediators are overexpressed in asthmatic patients and contribute to the pathophysiology of the disease by inducing bronchoconstriction, increasing mucus secretion and edema and promoting the infiltration of inflammatory cells in the airway wall¹⁷. Thanks to the inhibition of lipoxygenases *Boswellia* extract may help reduce the production of leukotrienes, thus decreasing their pro-inflammatory stimulus on the airways.

In addition, *Boswellia* extract exerts other anti-inflammatory activities by inhibiting TH1 and promoting TH2 cytokines production and by regulating vascular responses to inflammation^{16,19}. Taken together these activities may help decrease the inflammation of the airways thus improving the condition of asthmatic patients and reducing their need for corticosteroids and LABAs therapy.

Of note, the pharmacological performance of boswellic acids depends on the chemical structure and functional groups; various pharmacokinetic studies have revealed the low bioavailability of boswellic acids in animals and humans, leading to possible limitations to their pharmacological relevance and use in clinical practice. Casperome® is a particular phospholipidic formulation of boswellic acids characterized by a high bioavailability; this property is achieved thanks to a phospholipidic system that increases the oral absorption of *Boswellia serrata* active compo-

Table II. Adverse Events reported by subjects in the Casperome® group and in the control group.

| | Headache | Insomnia | Nausea | Constipation | Total |
|------------------|----------|----------|--------|--------------|-------|
| Casperome® group | 5 | 3 | | | 8 |
| Control group | 5 | 1 | 2 | 3 | 11 |

nents in terms of peak plasma levels and area under the curve^{20,21}.

The benefits obtained with Casperome® treatment are also important given the good safety profile of this therapy that does not present the negative side effects of corticosteroids or LABAs and could help reduce their use. Although the administration of low doses inhaled corticosteroids is considered safe, their use for long periods of time, as in chronic inflammatory diseases, raises some concern especially when they are administered at higher doses in order to control patient's symptoms²². In addition, the concomitant administration of ICS and LABAs has been associated with an increase in the risk of asthma-related intubation and deaths²³. The use of *Boswellia* extract phytosome as complementary intervention could be beneficial for asthmatic patients as it could reduce the frequency of use of ICS+LABAs, thus exerting a drug sparing effect and improving the quality of life.

Conclusions

Overall, the results of our study suggest that the administration of Casperome® 500 mg/day could help reduce the need of inhalation therapy in asthmatic patients thanks to the anti-inflammatory properties exerted by boswellic acids.

Disclosure

Francesco Di Pierro was the main developer of the study product.

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Conflict of Interest

The Authors declare that there are no conflicts of interest.

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