Original Article

Efficacy of a bacterial immunomodulator (Buccalin®) in the prevention of acute exacerbations in elderly COPD patients: a retrospective study

Summary
Aim of this retrospective study was to evaluate the efficacy of the administration of Buccalin®, a bacterial concentrate made with heat inactivated *Diplococcus pneumoniae*, *Streptococcus haemolitycus, Staphylococcus aureus* and *Haemophilus influenza,* in prevention of exacerbations of elderly COPD (Chronic Obstructive Pulmonary Disease) patients chronically treated in our division. Thirty-three ambulatory patients (16 M, 17 F, mean age 72.6 years) with a diagnosis of Stage 2-4 COPD were prescribed two courses of Buccalin® two months apart (October and December 2009 or November 2009 and January 2010). Additional risk factors (diabetes, CV disease, etc) were present in 20 of these patients (60.1%). During the Winter 2009-2010, the 33 patients had a total of 10 exacerbations, a 61.5% reduction *vs* the 26 episodes recorded in the previous season (2008-2009) in the same group of patients ($p<0.022$). No adverse effects were reported. Even with the limitations of a retrospective analysis, Buccalin® appears to be an effective and well tolerated form of prevention of acute exacerbations in elderly COPD patients.

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Roberto Cogo
Division of Cardiorespiratory Rehabilitation
Zappatoni Hospita
Cassano d'Adda -Mi-
Italy

Acute exacerbations, particularly during the cold season, represent a serious health issue in patients suffering from COPD (Chronic Obstructive Pulmonary Disease). Acute exacerbations, in fact, occur sporadically during the course of COPD and are heralded by increased symptom severity. The specific cause of any exacerbation is almost always impossible to determine, but exacerbations are often attributed to viral upper respiratory infections or acute bacterial bronchitis. As COPD progresses, moreover, acute exacerbations tend to become more frequent, averaging about three episodes/year[1], posing a serious burden on patients, caregivers and the health system.

The search for the effective and safe treatment of those diseases has therefore a great importance.

One of the most widely used strategies in order to reduce the number of exacerbation episodes in these patients is to boost their immune system using bacterial antigens[2,10].

Buccalin® is a bacterial concentrate containing *Streptococcus pneumoniae* I, II, III (formerly classified as *Diplococcus pneumoniae*), *Streptococcus agalactiae* (formerly *Streptococcus haemolyticus*), *Staphylococcus aureus* and *Haemophilus influenzae*, all inactivated by means of heating. The bacterial species contained in Buccalin® are all pathogens that

enter the body mainly via the respiratory mucosa. Therefore, mucosal vaccination (via the oral route) is an attractive alternative to parenteral vaccination against the considered pathogens. This approach is in accordance with the modern approach to vaccination, which states that the most efficient way of preventing infection is at the earliest stage (i.e. at the entry point into the organism).

Oral vaccination in fact triggers mucosal immune response involving both the humoral and the cellular arm of the immune system[3,4].

The presence of a non-specific mechanism and the activation of specific immunity by oral vaccination, in fact, should greatly increase the resistance to infection via the mucosal route[5]. Buccalin® can therefore be considered as an inactivated vaccine for oral use. The constituent bacteria are very often found as pathogens in respiratory tract infections. On contact with the bacterial surface antigens contained in Buccalin®, the differentiation and maturation of immunocompetent lymphocytes is specifically stimulated.

After dissolution in the small intestine, the bacterial antigens undergo phagocytosis by macrophages found in the intestinal wall and then pass with them into the local reticulo-endothelial tissue, where they stimulate the immune system to build up a systemic immunity. One of the most important mechanisms of action for oral vaccines such as Buccalin® is the activation of the immunocompetent cells in the region of the Peyer's patches[3,5]. After contact with the antigen, activated mucosal lymphocytes migrate to local lymph nodes and then return via the lymphatic and blood circulation to all mucosae, where local antibodies are secreted. Secretory IgAs (sIgA) are the predominant antibodies in gastrointestinal and respiratory secretions and exert an important role in the mucosal immune system. Moreover, secretory IgAs are thought to provide mucosal defense by "immune exclusion" which comprises inhibition of: 1) bacterial adherence; 2) colonization and penetration; 3) toxin binding and action; 4) viral attachment and infection. Involved also in the prevention of food allergens and carcinogens penetration, sIgAs are one of the most important defense mechanisms of mucosa. The sIgA immune system has potent immunological memory and is stimulated repeatedly by renewed contact with antigens, which leads to a high level of production of specific IgA[6].

According to the current prescribing information, Buccalin® is administered in adults at the dosage of one tablet the first day, two tablets the second day and four tablets on the third day ("1+2+4 scheme"). In patients particularly prone to exacerbations, the administration of Buccalin® can be repeated every four weeks. In a population of Italian Ministry employees with diagnosed chronic bronchitis, the incidence of acute exacerbations was 8.4% in 649 patients treated with influenza vaccine + 3 cycles of Buccalin® (1+2+4) spaced about one month versus a percentage of 25% in 2.429 untreated controls[7].

These results were confirmed in a later study, where 30 patients with chronic bronchitis were randomized to receive no treatment or Buccalin® 1+2+4 repeated every month for 7 months, plus influenza vaccine. The number of exacerbations was halved in the vaccinated group, while the clinical parameters (FEV1, etc.) remained constant, vs a worsening in the control group[8]. In a parallel group trial, 90 patients with a history of bronchopneumonia or recurrent respiratory infections were randomized to receive no treatment, Buccalin® 1+2+4 repeated after 3 months and Buccalin® plus parenteral IgG[9]. The total number of infective episodes in the control group was 98, *vs* 57 ($p<0.05$) in the Buccalin® alone group and 47 in the Buccalin® + IgG group.

Aim of this retrospective study was to evaluate the efficacy of the administration of Buccalin® in the prevention of exacerbations in elderly COPD patients chronically treated in our ambulatory care center.

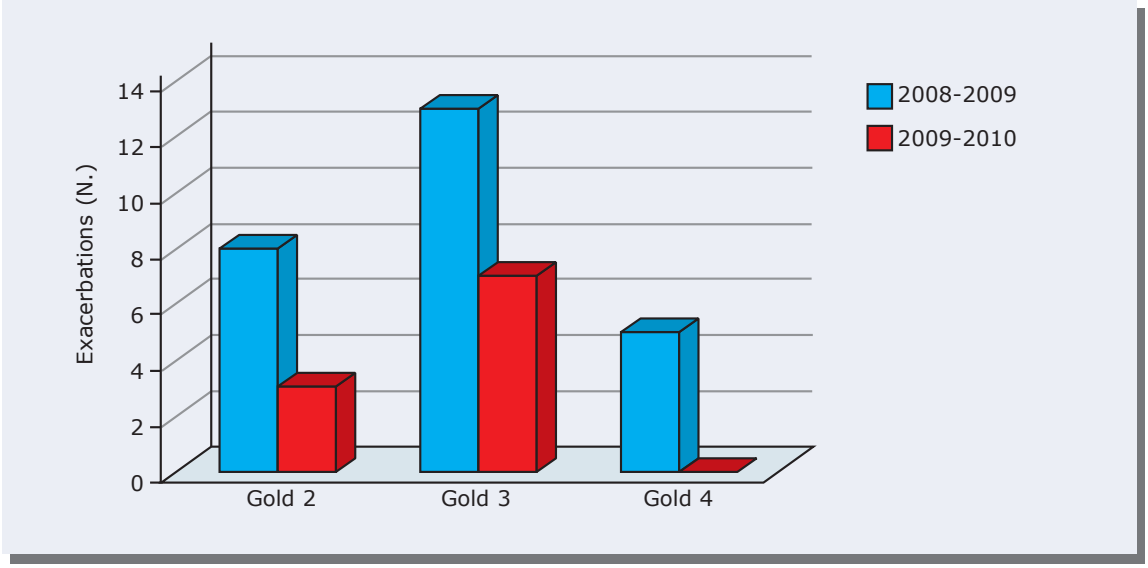
Materials and Methods

The data collection and analysis were performed on the charts of all COPD ambulatory patients followed at the Cardiorespiratory Rehabilitation Division of the "Zappatoni Hospital" in Cassano D'Adda (Milano, Italy). The charts selected (out of a total of about 800 COPD patients followed in the division) were the ones of the patients who, during the cold season 2009-2010 had received two 1+2+4 courses of Buccalin® (either in October and December 2009 or in November 2009 and December 2010). The reasons for prescription of the treatment were:

- medical history of recurrent infections;
- advanced age;
- generally compromised conditions;
- presence of risk factors for cardiovascular disease, diabetes, oxygen therapy.

The information extracted from the charts included the number of exacerbations reported du-

Figure 1. Number of exacerbations in the considered 33 COPD patients (stratified by Gold COPD Stage) in the season 2008-2009 and in the season 2009-2010.



ring the Winter 2009-2010 and the concomitant treatment. The same information was extracted also for the Winter 2008-2009, when no patients had taken Buccalin®. The main endpoint was the total number of exacerbations occurred in the season. This variable was considered as "ordinal" and was therefore analysed with the Wilcoxon non parametric test.

Results

Thirty-three ambulatory patients were prescribed two courses of Buccalin® two months apart (October and December 2009 or November 2009 and January 2010) during the Winter 2009-2010. Sixteen of the patients (48.5%) were male, 17 female (51.5%), their mean age was 72.6 years (SD 9.06), with a range of 45-85. The majority of patient (18/22) in Gold Stage 3 (54.5%), 12 patients were in Stage 2 (36.4%) and 3 in stage 4 (9.1%). Additional risk factors were present in 20 of these patients (60.1%). The number of exacerbations is summarized in figure 1.

During the Winter 2008-2009, the considered group of patients experienced a total of 26 exacerbations, while in the following season the patients experienced a total of 10 exacerbations. The median number of exacerbations in 2008-2009 was 1 (range 0-3), while the median number in the following season was 0 (range 0-1). This 61.5% reduction was statistically significant at the Wilcoxon test ($p<0.022$). As far as concomitant treatment is concerned, there were no relevant differences between the two seasons. It is worth noting that all patients had influenza vaccinations during both seasons and that no antibiotics or mucolytics were given prophylactically. Given the limited sample size, no subgroup or correlation analyses were made. No adverse effects were reported.

Discussion

This preliminary analysis was performed to verify the "on the field" effectiveness and safety of two courses of Buccalin® in the population followed in our Cardiorespiratory Rehabilitation Division, a population characterized by a relatively advanced age and by the presence of additional risk factors.

The endpoint chosen (the simple number of acute exacerbations), even though widely used in other publications, was probably neither the most sensitive one, neither it is distributed normally (whence the use of a non-parametric test, which did sacrifice some sensitivity). The total duration of days of exacerbation in fact, as suggested by other Authors[10], would have probably been a more appropriate and sensitive parameter, since its distribution can be considered as normal. In addition to that, the total number of "sick days" could be more easily translated into measurements of social and pharmacoeconomic impact. Nevertheless, the difference seen between the two seasons

considered, in line with what was reported in previous trials is quite significant, both from the statistical and the clinical point of view.

Conclusions

Even with the limitations of a retrospective analysis based on an "ordinal" endpoint, Buccalin® administered in two cycles two months apart, appears to be an effective and well tolerated form of prevention of acute exacerbations in the COPD patients followed in our centre. A final judgment on the entity of the clinical effect of Buccalin® in the prevention of acute exacerbations in COPD patients could probably be given by a trial using duration of illness as a main endpoint, along with other indicators such grade of dyspnoea, cough and other signs and symptoms, and of sufficient size to allow stratification of the patient population. TiM

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