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I. Franco[a,*], R. Reis[b,c], D. Ferreira[a], S. Xará[d], W. Ferreira[e], N. Bettencourt[e], A. Antunes[a]

[a] *Respiratory Department, Centro Hospitalar Vila Nova de Gaia/Espinho, Portugal*

[b] *Sleep Medical Center, CUF Porto Hospital, Portugal*

[c] *Pulmonology Diagnosis Center of Porto, Portugal*

[d] *Nutrition Department, Centro Hospitalar Vila Nova de Gaia/Espinho, Portugal*

[e] *Cardiology Department, Centro Hospitalar Vila Nova de Gaia/Espinho, Portugal*

* Corresponding author.
E-mail address: inesfranco_@hotmail.com (I. Franco).

http://dx.doi.org/10.1016/j.rppnen.2016.01.007

Clinical and functional impact of inhaled antibiotics in a Portuguese Pulmonology Department

To the Editor,

Chronic infection by gram-negative agents is associated with progressive deterioration of lung function and clinical worsening of patients with respiratory disease.[1]

Inhaled antibiotics have been effectively administered with safety and efficacy in these patients, particular in cystic fibrosis, bronchiectasis and in the prevention and treatment of patients with pneumonia, with promising results.[2–4]

Chronic suppressive therapy, the proactive use of an antibiotic regimen rather than the reactive use of antibiotics following patient deterioration, has become the standard of care over the last decade.[5]

Inhaled antimicrobial therapy is frequently used in chronic suppressive regimens, and has the advantage of targeting the site of infection and achieving higher antibiotic sputum concentrations within the airway surface liquid than intravenous antibiotics.[6,7]

Here, the authors evaluate the efficacy and safety of inhaled antibiotics, as continued and support therapy, for patients with respiratory disease chronically colonized with *Pseudomonas aeruginosa*, determine if the administration of antimicrobials in the respiratory tract was associated with clinical and functional improvement in these patients and also verified if the administration of inhaled antibiotics changes the microorganisms' sensitivity profile.

We retrospectively analyzed the demographic and clinical characteristics of patients who inhaled antibiotics during 2013 in the Pulmonology Department of Centro Hospitalar de São João, a hospital in the northern region of Portugal, as well as evaluated the functional differences and the sensitivity profile in the 6 months before and after initiation of inhaled therapy.

A total of 33 patients were on inhaled antibiotics during this period, 54.5% ($n = 18$) were male and 45.5% ($n = 15$) female, with an average age of 35 years (25–54 years). Of these patients, 54.5% ($n = 18$) had cystic fibrosis, 24.2% ($n = 8$) bronchiectasis, 12.1% ($n = 4$) were transplanted lung, 6.1% ($n = 2$) diffuse pulmonary disease and 3% ($n = 1$) had amyotrophic lateral sclerosis. Inhaled colistin was prescribed in 54.5% ($n = 18$) of patients, tobramycin in 42.4% ($n = 14$) and aztreonam in one patient. We found overlapping in the pre-and post-treatment functional assessment (FEV_1: $45.9 \pm 19.6\%$ vs. $47.2 \pm 20.7\%$, $p = 0.43$; FVC: $68.8 \pm 20.4\%$ vs. $69.4 \pm 21.5\%$, $p = 0.75$, IT: $56.1 \pm 15.3\%$ vs. $55.7 \pm 14.9\%$, $p = 0.71$). Nevertheless, considering the different pathologies as cystic fibrosis or non-cystic fibrosis, statistically significant post treatment functional differences were observed (FEV_1: $54.77 \pm 20.61\%$ vs. $39.08 \pm 18.16\%$, $p = 0.038$; FVC: $76.97 \pm 24.25\%$ vs. $61.29 \pm 14.99\%$, $p = 0.046$). Comparing the groups of the two most prescribed antibiotics, there were no clinical and functional significant differences.

Significant clinical improvement was observed, with a reduction in the number of exacerbations and hospitalizations, 6 months after the start of inhaled antibiotic therapy (number of exacerbations: 1.94 ± 0.9 vs. 0.82 ± 0.6, $p < 0.001$, number of hospital admissions: 1.03 ± 1.5 vs. 0.45 ± 0.8, $p = 0.002$). The reduction in the number of exacerbations was more evident in the group non-cystic fibrosis than in the cystic fibrosis patients, and this difference was statistically significant (0.6 ± 0.632 vs. 1.0 ± 0.485, $p = 0.048$, respectively).

About tolerance to the antibiotic prescribed, 84.8% ($n = 28$) of patients did not experience any side effects associated with the drug; however, 5 patients (15.2%) required its suspension due to headache, upper abdominal pain and oral clefts.

All antibiotics prescribed regimens produced a reduction in sputum volume and there was no development of highly resistant strains throughout the study, the inhaled antimicrobial therapy did not change the microorganisms' sensitivity profile.

In the literature several studies showed similar results, clinical improvement, lower risk of acute exacerbations and risk reduction of unscheduled admissions in patients on inhaled antibiotic therapy. In Portugal, epidemiological studies are scarce, with results mainly in ventilator-associated pneumonia.

Although the data collected was only from patients followed in the Pulmonology outpatient clinic, therefore it is not representative of the all population, the results support the benefit of inhaled antibiotics, in maintenance regime, to reduce the number of admissions and exacerbations in patients with colonization by *P. aeruginosa*, without development of resistant strains and, in most patients, without side effects.

The present study showed that inhaled antimicrobial therapy is an attractive alternative to systemic administration because it is associated with main advantages such as ability to achieve high concentrations of antimicrobials in sputum and in the bronchial and pulmonary tissue; and ability to reach minimum inhibitory concentrations at lower dosages compared with intravenous formulations.

Conflicts of interest

The authors have no conflicts of interest to declare.

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V. Santos*, A.V. Cardoso, C. Damas

Pulmonology Department, Centro Hospitalar de São João, EPE, Portugal

*Corresponding author.
E-mail address: vferreirads@gmail.com (V. Santos).

http://dx.doi.org/10.1016/j.rppnen.2015.12.005

Systemic adverse events from inhaled corticosteroids self-reported by asthma patients: A ''real-life'' cross sectional study

Current guidelines recommend the use of inhaled corticosteroids (ICS) for patients with moderate to severe persistent asthma treatment maintenance.[1] However, the use of high doses for long periods potentially increase systemic adverse events.[2,3] A disconnection between clinician estimates of ICS side effects and the prevalence reported by patients has previously been reported.[4] Furthermore, there is evidence that many asthmatic patients prefer not to discuss or spontaneously report their concerns regarding ICS adverse events with their health care professionals.[5,6] The self-reported questionnaires provide an efficient method of accessing information about adverse events.[7,8] We describe systemic adverse events associated with the use of ICS in patients with moderate to severe asthma using this technique.

Subjects included were 18 or older, had moderate or severe persistent asthma,[1] had been regularly using ICS for 6 or more months between June of 2010 and February of 2011 and presented at the Pharmaceutical Assistance Service of the Pneumology Reference Outpatient Clinic of the Federal University of Bahia, in Salvador, Bahia. Patients taking oral, parenteral, ocular or topical corticosteroids within the previous three months were excluded.

A pilot study assessing questionnaire structure, content and clarity generated data for an expert team who reviewed results and suggested changes. The self-report questionnaire, covered the previous 14 days using a 4-point Likert scale (0 = never; 1 = occasionally; 2 = most days; 3 = daily) and captured patient's perceptions regarding the ICS systemic adverse events (dry skin, swollen face, easy bruising, mood swings, night sweating, brittle breaking nails, hair loss and affected vision). The total score ranged from 0 (no perception of events) to 24 (maximum), this score was standardized to score from 0 (no events) to 100 (worst).

The difference in the intensity of systemic adverse events between the two dosage groups in relation to the total score (accumulated) was analyzed using *t*-test. The correlation between duration of ICS use and the number of systemic adverse events was assessed by using the Spearman Rho correlation coefficient.

Of the 65 patients who were evaluated, 54 (83.1%) were female, with an average age of 49.7 [SD = 12.2] years. Of the total, 29 (44.6%) patients were taking high doses of ICS (budesonide > 800 mcg/day), where the median daily dose of ICS was 800 mcg. The average treatment duration was 38.2 [30.7] months. Sixty (92.3%) patients reported at least one systemic adverse event, and 31 (47.7%) patients reported daily symptoms. A total of 213 events were reported with a median of 3.0 per patient (Table 1).

All patients were taking ICS plus long-acting β_2-agonist (87.7% formoterol plus budesonide, 12.3% salmeterol plus fluticasone). Thirty-six (55.4%) patients received treatment consistent with moderate asthma and 29 (44.6%) received high-intensity treatment, consistent with severe asthma. Demographic characteristics were similar between the two groups. The prevalence of vision disturbances and dry skin was greater in the high-intensity treatment group ($p < 0.05$) suggesting a causal relationship. Asthma severity ($r = 0.274$; $p = 0.027$) and ICS use duration ($r = 0.361$; $p = 0.003$) were correlated with the number of systemic adverse events. Furthermore, patients who used ICS for longer periods reported more face swelling ($p = 0.04$) and dry skin ($p = 0.002$).