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CASE REPORT

Resolution of daytime and night-time respiratory symptoms but persistent sleep apnea in severe asthma with the add-on of benralizumab

Pasquale Tondo,[1,2] Francesco Fanfulla[2]

[1]Respiratory Medicine Unit, Department of Medical and Surgical Sciences, University of Foggia
[2]Respiratory Function and Sleep Medicine Unit, ICS Maugeri IRCCS, Pavia, Italy

ABSTRACT

Introduction: The relationship between asthma and obstructive sleep apnea (OSA) is a widely debated topic in the scientific literature with the controversy surrounding the bi-directional nature of the correlation.

Case presentation: We report the case of a 59-year-old male being affected by severe allergic eosinophilic asthma and severe OSA (apnea-hypopnea index [AHI] 32 ev·hr^{-1}). Due to a clinical worsening of asthma (aggravation of dyspnea, chest constriction and night-time respiratory symptoms), despite the optimal therapy for asthma and recurrent administration of systemic corticosteroids, we have added-on treatment with benralizumab (monoclonal anti-interleukin 5 antibody). After eight months, the patient reported an improvement in asthma control (asthma control test [ACT]= 25 points), in pulmonary function and a good control of nocturnal symptoms of both diseases *(i.e.*, wheezing, snoring, etc.). Then, the follow up polysomnography (PSG) was performed resulting in a high reduction of OSA severity (~18% AHI) even if obstructive events persisted and almost resolution of nocturnal hypoxemia. So, a trial with positive airway pressure (PAP) was proposed to the patient, who declined.

Conclusions: In consideration of our experience, we suggest that the nocturnal profile of patients with severe asthma should be always studied by a sleep investigation to prevent the negative effects of interaction with OSA. However, further studies on larger samples are needed to better understand the pathophysiological mechanisms underlying the beneficial effects of benralizumab on obstructive events during sleep.

Key words: asthma; benralizumab; monoclonal antibody; OSA; therapy.

Correspondence: Francesco Fanfulla, Respiratory Function and Sleep Medicine Unit, ICS Maugeri IRCCS, Via S. Maugeri 4, 27100 Pavia, Italy. Tel. +39.0382.592010. E-mail: francesco.fanfulla@icsmaugeri.it

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Introduction

Asthma is a chronic obstructive respiratory disease that seems to be closely associated to obstructive sleep apnea (OSA), characterized by the total or partial collapse of the upper airway during the night. This evidence is also confirmed by a higher prevalence of OSA in patients with asthma than in the general population.

Several studies have suggested a bi-directional relationship between asthma and OSA based on different factors. Of course, shared factors such as gastroesophageal reflux (GER), rhinitis and obesity play a key role in this interaction, but other mechanisms are also described in literature. Pathognomonic features of asthma, such as airway inflammation, may alter the control mechanisms of breathing and the upper airway. Moreover, long-term therapy with inhaled corticosteroids (ICS) causes remodeling of the upper airways (UA) resulting in collapse during sleep. Conversely, OSA through certain characteristics such as chronic intermittent hypoxia causes lung remodeling by reducing the responsiveness of the system to ICS. Accordingly, a vicious circle would be triggered with irreversible airway dysfunction [1]. It is clear how the worsening of one condition is followed by the worsening of the other. Severe asthma decreases lung function and causes worsening of daytime and night-time respiratory symptoms, leading to severe limitations in life, worsening quality of life and forcing recurrent use of systemic corticosteroids, so therapy with biologics is recommended for asthma symptom control [2]. In this context, however, OSA may negatively influence the outcome of patients with asthma, contributing to poor overall asthma control during the day and sleep as shown by several studies [3].

We report a case with overlap syndrome of severe asthma and OSA treated with asthma biologics. Furthermore, in our case we aimed to assess how closely the two diseases are clinically related.

Case presentation

A 59-year-old male subject, overweight (BMI 27,7 kg/m^{-2}), ex-smoker (12 pack/years) reported GER, rhinosinusitis and recurrent nasal polyposis evaluated by nasal endoscopy at ENT investigation. Allergic asthma was diagnosed in 2009. In January 2021, the patient referred to our Institute for dyspnea, chest constriction and cough, night-time respiratory symptoms (noisy snoring, partner-reported apnea) and daytime sleepiness: the Epworth sleepiness scale (ESS) score was 12 points. He was treated with inhalation of salmeterol/fluticasone propionate 50/250 mcg two inhalations b.i.d and salbutamol 400 mcg p.r.n, cycles of oral corticosteroids and injection of triamcinolone acetonide 40 mg/ml once/4-weeks. Thereafter, the therapeutic schedule was modified: beclomethasone dipropionate/formoterol fumarate 100/6 mcg b.i.d., tiotropium 2,5 mcg once/day, montelukast 10 mg once/day, and mometasone furoate 50 mcg nasal spray. The patient performed an overnight polysomnography (PSG, Nox A1 – Nox Medical, Reykjavík Iceland) in our Sleep Laboratory. The sleep investigation was scored by an expert somnologist according to American Academy of Sleep Medicine (AASM) criteria [4]. The results of investigation showed a severe OSA: apnea-hypopnea index (AHI) 32 ev·hr^{-1} of sleep, oxygen desaturation index (ODI) 29,4 ev·hr^{-1} of sleep, 18,8% of total sleep time with SaO_2 <90% (T_{90}), 91% of mean SaO_2 during sleep and 81% of nadir. Accordingly, we have recommended a therapy trial with positive airway pressure ventilator (PAP) during the night, which the patient refused.

In April 2021, the patient referred again for dyspnea, marked impairment of physical exercise and hyposmia assessed by Sinonasal Outcome Test 22 (SNOT-22= 34 points). The biochemistry showed: eosinophilia (1250 cells/microliter —13,4%), the white blood cells were 9,300 per microliter and FeNO value was 54 ppb. The ACT questionnaire proved poor asthma control (score 8). Additionally, the patient underwent pulmonary function tests that showed a FVC of 3,30 L (80% of pred.), a FEV_1 of 2,29 L (70% of pred.), FEV_1/VC of 69,6%, forced expiratory flow at 25 and 75% of the pulmonary volume ($FEF_{25-75\%}$) of 1,70 L (48% of pred.). Therefore, subcutaneous injection of benralizumab 30 mg/ml once/4-weeks at first and desloratadine 5 mg one tablet/day were added-on to the previous therapeutic schedule.

After six months, the patient reported a clinical improvement, with a reduction in hyposmia assessed by SNOT-22 test (score= 16) and dyspnea as well as a great improvement in asthma control (ACT score= 25). The laboratory tests showed: zero eosinophils (0 cells/microliter) and a reduction of FeNO value (51 ppb) even if not clinically relevant. The spirometry showed an improvement in pulmonary function with a +29% increase in FVC (4.26 L — 104% of pred.), +52.4% in FEV_1 (3,49 L — 108% of pred.) and +112.9% in $FEF_{25-75\%}$ (3.62 L — 103% of pred.). Accordingly, the treatment schedule has been simplified to: subcutaneous injection of benralizumab once/8-weeks (benralizumab was administered every 8 weeks after the 3 initial doses given every 4 weeks), montelukast 10 mg one tablet/day, and inhalation of fluticasone/formoterol 250/100 mcg b.i.d.

At the examination, the patient reported no snoring, no apnea-referred and no daytime sleepiness (ESS= 4 points). In addition, no change in body weight was reported. Nonetheless, we performed a new PSG that documented a reduction of -17.8% in AHI (current value= 26.3), -22.8% in ODI (current value= 22.7) and an improvement in gas exchange (T_{90}=1.9%) (Figure 1). A trial of titration of PAP therapy was again suggested to the patient who declined.

Discussion

A real-life study demonstrated the efficacy of benralizumab (humanized monoclonal anti-IL-5a antibody) in reducing eosinophilic inflammation and corticosteroid use, increasing pulmonary function and improving quality of life [5]. Another study evaluated the efficacy of omalizumab, a monoclonal antibody anti-IgE in the treatment of severe asthma, in a patient with an overlap syndrome of asthma and OSA. In that study the authors demonstrated that as asthma symptoms improved, polysomnographic indices also improved [6]. Similar to our case, a reduction in AHI was observed (~56%) even though OSA still persisted.

Our case is the first report assessing the clinical effect of benralizumab in a patient with an overlap syndrome of severe asthma and OSA. We have observed a significant improvement in lung function, asthma control and both diurnal and nocturnal symptoms. In addition, a reduction of respiratory alterations during sleep was also observed at PSG. Another important finding is the marked improvement in nocturnal hypoxemia (a ~90% reduction in T_{90}) with almost complete resolution of gas exchange alterations during sleep. This improvement is also significant in view of the result of the study by Scioscia *et al.*[6]. Indeed, a slight proportion of nocturnal hypoxemia persists after treatment with omalizumab (T_{90} ~12%), whereas benralizumab appears to resolve the profile completely (T_{90} ~2%). However, this finding should be analyzed by further investigations on larger samples. In any case, both biologic medications have a beneficial effect on nocturnal hypoxemia. The intermittent hypoxemia of OSA causes airway inflammation

through several pathways: the bronchial epithelium in response to hypoxemia produces chemokines and matrix metalloproteases by increasing the permeability of airway epithelial cells and causing an increase in proteins in the epithelial junction; it induces the production of several pro-inflammatory interleukins including IL-8 that leads to neutrophil influx; it also increases the production of vascular endothelial growth factor (VEGF) resulting in bronchial vasodilation that accelerates neutrophil influx. These mechanisms lead to an immune response directed towards a Th_1-predominant cell phenotype. Accordingly, OSA-related hypoxia causing neutrophilia contributes to steroid resistant worsening asthma [7].

However, the link between asthma and OSA is multifaceted. It has been observed that OSA worsens respiratory function in patients with asthma. In addition, another finding suggestive of this negative interaction is that the pharynx occluded by obstructive apnea causes a high negative intrathoracic pressure by drawing blood into the chest; hence, this increase in intrathoracic fluid generates an increase in airway resistance and a reduction of airway caliber that worsen the outcome in asthmatics [8].

Help in understanding the link between asthma and OSA could come from studying the chemical profile of neuronal cells related to sleep and wake processes and respiratory changes during sleep. Sleep and wakefulness are not two separate processes but are intrinsically interconnected. A "sleep-active" role is played by the ventrolateral preoptic region (VLPO), which intervenes in both NREM and REM sleep by expressing mainly GABA. This cellular conglomerate is interconnected to the airway vagal preganglionic neurons (AVPN) that regulate cholinergic flow to the tracheobronchial pathways by performing a GABA-mediated inhibitory action. Consequently, sleep alterations may cause a switch from the inhibitory to the excitatory state of the AVPNs resulting in increased cholinergic flow that may predispose to and worsen bronchoconstriction [9]. Moreover, bronchospasm during an asthma exacerbation causes respiratory drive instability, which in turn is a fertile ground for the onset of respiratory events during sleep [10]. Additionally, several studies have shown that inflammation of the airway mucosa in patients with asthma promotes a reduction in airway surface area, including the UA, favoring the development of OSA [11]. This evidence appears to explain the bidirectional relationship of the two diseases. It should also be taken into account that uncontrolled asthma requires the administration of ICS, which cause fat deposition around the UA structures, atrophy of the tongue as well as atrophy of muscle fibers including those of the genioglossus, worsening the overlap syndrome even more [12]. As a consequence, we may understand that the tested effects of benralizumab on asthma control [5] by reducing inflammation, airway remodeling and exacerbations may positively influence the relationship between asthma and OSA.

The limitation of the study is certainly related to the single case and the possibility of inter-night variability that could be a confounding factor to the results of the sleep investigation.

Figure 1. **Graphical representation of the patient's nocturnal profile in the follow up polysomnography.**

Conclusions

The regular use of benralizumab in subject with severe eosinophilic asthma may have a positive effect not only on asthma control but also on both of these factors: resolution of OSA-related nocturnal abnormalities (i.e., symptoms and sleep events) and daytime sleepiness. Indeed, our case showed a significant improvements of sleep apnea and also nocturnal hypoxemia. This finding is particularly important in the management of asthmatic patients, also in light of the possible bi-directional nature of the two respiratory pathologies. Furthermore, simple monitoring of daytime and night-time symptoms can be misleading; therefore, our study suggests that sleep investigation should be permanently introduced in the follow up of these patients. Of course, further studies on larger samples are needed to investigate the mechanisms, including biological ones, underlying the beneficial effects of benralizumab on the interaction of asthma and OSA.

Abbreviations

ACT: asthma control test;
AHI: apnea-hypopnea index;
BMI: body mass index;
ESS: Epworth sleepiness scale;
$FEF_{25-75\%}$: forced expiratory flow at 25 and 75% of the pulmonary volume;
Fe_{NO}: fractional exhaled nitric oxide;
GER: gastroesophageal reflux;
ICS: inhaled corticosteroids;
ODI: oxygen desaturation index;
OSA: obstructive sleep apnea;
PAP: positive airway pressure;
PFT: pulmonary function test;
PSG: polysomnography;
$SNOT_{22}$: sino-nasal outcome test-22;
T_{90}: total sleep time with oxygen saturation below 90%.

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