Omalizumab therapy in a patient with severe asthma and co-existing chronic obstructive pulmonary disease

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Exposure to tobacco smoke in asthmatics is one of the significant causes of severe asthma [1]. It is generally known that passive and active smoke exposure may induce asthma symptoms and bronchoconstriction in asthmatic patients [2]. Moreover, asthmatics who are regular smokers develop more severe asthma symptoms, have a lower quality of life and more often require emergency medical intervention and hospitalization due to exacerbations [3, 4]; their forced expiratory volume in 1 s (FEV_1) decline over time is faster [5] and their response to inhaled corticosteroids (ICSs) [6], even to higher doses [7, 8], is poorer. Apart from an active struggle with addiction, the treatment of an asthmatic smoker requires medications that overcome steroid resistance (long-acting β_2-adrenergic receptor agonists – LABA [9–11]) and have different mechanisms of action to corticosteroids (leukotriene receptor antagonist – LTRA [8, 12] and long-acting muscarinic receptor antagonists – LAMA [13]). Little is known of the efficacy of anti-IgE biologic therapy in these patients.

The problem of smoking in asthmatics is not rare. Epidemiological data from the USA and Western Europe show that 17–35% of asthmatics [14] smoke cigarettes. In Poland, 17.9–19.7% of asthmatic patients are smokers, 16.9% ex-smokers and 31.86% [10, 15] passive smokers.

This article presents the case of a 54-year-old patient, with a long-term history of smoking, who has been suffering from allergic bronchial asthma for about 20 years. She was referred to the clinic in January 2016 due to severe uncontrolled asthma that had occurred for 3 years. She had been treated chronically with high doses of ICSs and LABA, LAMA, LTRA, with theophylline periodically, short-acting β-agonist (SABA) as required and with oral corticosteroids for 3 months chronically. Despite the treatment, disease control was still unsatisfactory, with five acute exacerbations and two hospitalizations (in October and December) in 2015. An attempt was made to treat her with proton pump inhibitors (PPIs) despite the negative history of gastroesophageal reflux disease (GERD), but the therapy was ineffective. In addition, anxiolytic alprazolam treatment was introduced to alleviate mental state of the patient disturbed by recurrent exacerbations and hospitalization. The patient reported not smoking since January 2016, and before then smoking about 10 cigarettes a day for 20 years. Implementation of anti-IgE biologic therapy was considered (skin prick test – SPT) positive for allergens of house mites, cats and dogs, signs observed in dust exposure, cIgE 483 IU/ml).

Knowledge of the efficacy of omalizumab therapy in asthmatic smokers is based on observational studies conducted in countries where omalizumab therapy is not restricted by smoking status. In Spain, 4.1% of patients treated with omalizumab were smokers, 19.2% ex-smokers and 1.1% passive smokers [16]. A similar distribution of percentage rates relating to tobacco smoking was observed in an Italian cohort treated with omalizumab [17]: 3.6% were current smokers, 27.1% ex-smokers and 68.6% had never smoked. On average, the current and ex-smokers reported 10 pack-years (0.5–67.5). However, while a multi-factor analysis of omalizumab efficacy, including smoking status, was conducted in the latter study, no such analysis was performed in the former. Unlike obesity and aspirin hypersensitivity, smoking had no impact on exacerbation occurrence in patients treated with omalizumab or asthma control measured with the Asthma Control Test (ACT).

In Poland, however, as in the UK, active smokers cannot receive publically funded anti-IgE therapy. A common definition of a non-smoker applied in epidemiologic research includes those who have never smoked and those who used to smoke in the past but no longer do, whereas an ex-smoker has smoked more than 100 cigarettes in

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their lifetime but currently does not smoke [18]. In clinical trials a person who has not smoked for at least 6 months is considered "an ex-smoker". It is, however, an academic criterion not supported by any clinical trials, and the benefit of quitting smoking is observable even within 24 h following cessation.

Our patient was placed under observation to evaluate her determination not to smoke and the influence of cessation on disease control. Studies show that an improvement in pulmonary function parameters [19] may be observed 1 month following smoking cessation, and decreased bronchial hypersensitivity and improved asthma control after 6 weeks [20]. Nevertheless, in December 2016 the patient's asthma was still uncontrolled and severe exacerbations occurred (4 in the observation period, including 1 hospitalization). It was not possible to withdraw oral corticosteroids although the patient had not smoked. The patient was qualified for anti-IgE therapy. The first dose was administered in January 2017 (450 mg *s.c.* every 2 weeks, for cIgE 893 IU/ml and 60 kg body weight). In weeks 16 and 46 of the therapy improvements in current asthma control (ΔACQ = 0.8 and ΔACQ = 0.5 respectively) and quality of life (ΔAQLQ = 1.4 and ΔAQLQ = 1.3 respectively) were observed and complete corticosteroid withdrawal was successful. In that period the patient had two exacerbations, in the 1st and 8th month of therapy, related to a respiratory tract infection, but hospitalization was not required. Therapy efficacy was evaluated as good on the Global Evaluation of Treatment Effectiveness (GETE) scale. No improvement in pulmonary function or pulmonary exercise capacity was achieved.

The patient fulfils the spirometry chronic obstructive pulmonary disease (COPD) diagnosis criteria. Tobacco smoke exposure is a known significant etiologic factor in COPD. Epidemiological studies show that clinically active asthma itself is a factor increasing the risk of COPD development, even more significantly than smoking (HR = 12.5 for asthma and 2.9 for tobacco smoking) [21]. Global Initiative for Asthma (GINA) and Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines suggest that therapy relevant to asthma severity should be applied in patients with asthma-COPD overlap, as signs of uncontrolled asthma are more dangerous than severe COPD. Experts do not express any opinion on use of biological medications in such cases.

Few case reports are available for asthmatics with coexisting COPD receiving omalizumab (1 from Japan [22], 3 from Turkey [23]), with different observation periods (from 36 days up to 1 year). These show improved disease control and fewer severe exacerbations.

A clinical improvement in asthma-COPD overlap in 10 patients was found to be accompanied by a decrease in fractional exhaled nitric oxide (FENO) as well as eosinophils, neutrophils, macrophages, eosinophil cationic protein (ECP) and sIL-4 levels in the systemic blood 1 year following therapy [24].

In 2017, the results of data analyses of 177 asthmatic patients, including 17 with diagnosed COPD, from the Australian register of patients treated with omalizumab were published. The therapy efficacy was evaluated after 6 months. Omalizumab therapy significantly improved asthma control and quality of life; however, it did not improve the pulmonary function (FEV_1, forced vital capacity (FVC), FEV_1/FVC) in those with diagnosed COPD or FEV_1 < 80% and smoking history.

To conclude, omalizumab appears to improve control of severe allergic asthma with coexisting COPD and this is the first Polish scientific report in this field as far as we know. Currently in Poland COPD co-occurrence is not a contraindication that prevents one from obtaining public funds [25] for biologic therapy, unlike active tobacco smoking [26].

Conflict of interest

I. Kuprys-Lipinska received personal fees for lectures from Novartis, P. Kuna received personal fees for lectures and advisory board activities from Novartis, J. Molinska and C. Palczynski declare no conflict of interest.

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