



## LETTERS TO THE EDITOR

### Does omalizumab impair glucose homeostasis in a patient with severe persistent asthma and type 2 diabetes mellitus?



To the Editor:

Severe persistent asthma is characterized by difficulty in achieving disease control despite high-dose inhaled glucocorticoids and long-acting  $\beta_2$ -agonists or oral corticosteroids (OCSs). For patients with uncontrolled severe persistent asthma, the Global Initiative for Asthma recommends adding OCSs or anti-IgE treatment with omalizumab.<sup>1,2</sup> We here describe a severe persistent asthma case with type 2 diabetes mellitus (DM) whose glycemic control deteriorated but asthma control improved after the administration of omalizumab.

A 62-year-old female ex-smoker was diagnosed with childhood-onset asthma and type 2 DM at the age of 50. We treated the asthma with four puffs of budesonide, 160  $\mu\text{g}$ /formoterol, 4.5  $\mu\text{g}$ , twice daily; montelukast, 10 mg, once daily; and theophylline, 200 mg, once daily. We treated DM with gliclazide, 40 mg, once daily; sitagliptin, 50 mg, once daily; and metformin, 500 mg, twice daily. Her hemoglobin A1c (HbA1c) was maintained at approximately 7.0%. However, her asthma control test (ACT) score was less than 20, which is categorized as uncontrolled, and she took OCSs for approximately 7 days per month. Therefore, her glycemic control deteriorated; HbA1c increased from 7.9% in May 2016 to 10.5% in July 2016. Her body weight was 57.7 kg, and her height was 150.0 cm. The forced volume capacity (%predicted) and forced expiratory volume in 1s (%predicted) were 105.5% and 79.5%, respectively. Fractional exhaled nitric oxide level (NIOX VERO<sup>®</sup>, Aerocrine Solna, Sweden) was 42 ppb. The peripheral blood eosinophil count was 3.4% (333/ $\mu\text{L}$ ), with a total IgE level of 340 IU/mL. In August 2016, we administered omalizumab (Xolair<sup>®</sup>; Genentech, San Francisco, CA, USA), 450 mg, once monthly, without any changes in medications for asthma. She did not experience omalizumab-associated anaphylaxis. In September 2016, her ACT score improved to 24, which is categorized as well controlled, and she did not take any OCSs. Therefore, we continued administration of omalizumab. However, in the same month, her HbA1c level increased to 13.5%. Fasting insulin and plasma glucose concentrations were 4.8  $\mu\text{U/mL}$  and 238 mg/dL, respectively. Homeostasis model assessment (HOMA)-B, which was calculated by the following equation:  $(360 \times \text{fasting insulin concentration})/(\text{fasting$

glucose concentration – 63),<sup>3</sup> was 10.3. Her anti-glutamic acid decarboxylase was negative. We started insulin therapy with glargine, 22 U, once daily. Thereafter, her glycemic control improved; HbA1c level decreased from 13.5% in September 2016 to 10.3% in October 2016 to 8.8% in November 2016. In October 2016, we discontinued administration of omalizumab because we were concerned about the possibility of omalizumab-induced exacerbation of glycemic control. However, her asthmatic control deteriorated again. In December 2016, we started mepolizumab (Nucala<sup>®</sup>; GlaxoSmithKline, Isleworth, London, UK), 100 mg, once monthly, without any changes in medications for asthma, which improved her asthmatic control. In March 2017, HbA1c level was 6.9%.

Common adverse effects of omalizumab include headache, injection site reaction, and arthralgia.<sup>4</sup> Yalcin et al. reported two severe asthma cases with DM whose blood glucose level increased during the first 6 h of omalizumab injection; however, the blood glucose level was stable until the next round of omalizumab therapy.<sup>5</sup> They concluded that this was because each vial of omalizumab (150 mg) contains 145.5 mg sucrose.<sup>5</sup> In our case, it is possible that the sucrose present in the omalizumab vial influenced the glycemic control. Yalcin et al. described that the glycemic control (HbA1c level) was stable under the administration of omalizumab every two weeks<sup>5</sup>; however, we administered omalizumab once monthly. Therefore, we considered that sucrose included in the omalizumab vial did not influence the glycemic control. Omalizumab inhibits mast cell and basophil activation and release of their profound pro-inflammatory mediators.<sup>2</sup> However, a paradoxical increase in basophil histamine release induced by omalizumab has been reported.<sup>6</sup> Gatifloxacin, a pharmacological agent affecting glucose homeostasis, induces hyperglycemia by histamine release.<sup>7</sup> Therefore, we suggest that an increase in histamine release induced by omalizumab can affect glucose homeostasis. Further investigations are imperative to identify the mechanism underlying the development of omalizumab-induced impaired glucose homeostasis.

Various factors, including diet, lifestyle, body mass index, duration of DM, and comorbidities, influence the glycemic control. Her habits of diet and lifestyle were unchanged and she did not use any OCSs after the administration of omalizumab. Thus, we considered the cause of her deteriorated glycemic control to be omalizumab. However, HOMA-B data revealed lowering of  $\beta$ -cell function.<sup>3</sup> Therefore, it is possible that her DM condition would need insulin therapy regardless of the administration of omalizumab.

Future studies are needed to confirm whether omalizumab can impair glucose homeostasis.

Omalizumab is generally safe and well tolerated. In addition, this drug can help cut down OCS doses and lower the risk of OCS-induced irreversible side-effects, such as DM, in patients with severe asthma requiring OCS. However, consistent with our case, omalizumab can induce the unexpected complication of impaired glucose homeostasis, particularly in patients with DM. Therefore, we should closely monitor patients treated with omalizumab, including their glucose level.

### Conflict of interest

All authors have no conflict of interest regarding to this report.

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S. Hamada<sup>a,\*</sup>, A. Kuroe<sup>b</sup>, M. Tsukino<sup>a</sup>

<sup>a</sup> Department of Respiratory Medicine, Hikone Municipal Hospital, Hikone, Japan

<sup>b</sup> Department of Diabetes and Metabolism, Hikone Municipal Hospital, Hikone, Japan

\* Corresponding author.

E-mail address: [sh1124@kuhp.kyoto-u.ac.jp](mailto:sh1124@kuhp.kyoto-u.ac.jp) (S. Hamada). Available online 8 June 2017

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## Allergic bronchopulmonary aspergillosis treated successfully with omalizumab



Dear Editor,

Allergic bronchopulmonary aspergillosis (ABPA) is caused by a hypersensitivity response of type 2 T helper (Th2) lymphocytes to antigens, mostly *Aspergillus fumigatus* (*A. fumigatus*).<sup>1</sup> This abnormal host response to *A. fumigatus* in a subset of patients with asthma or cystic fibrosis (CF) is likely due to genetic susceptibility that predisposes patients to the risk of developing ABPA. This is characterised by an increased total IgE and *Aspergillus*-specific IgE, IgG, and IgA in the serum and bronchoalveolar lavage.<sup>2</sup> The International Society for Human and Animal Mycology (ISHAM) and the Rosenberg–Patterson criteria are most often used to diagnose ABPA.<sup>3,4</sup>

*Omalizumab* is a humanized monoclonal anti-IgE antibody with licensed indication in severe allergic asthma. There are clinical studies that have also shown benefit in the use of *omalizumab* in ABPA patients without and with cystic fibrosis.<sup>5,6</sup> However, the safety and efficacy of *omalizumab* in ABPA needs further evidence.

The authors described a 45-year-old caucasian man with long standing atopic asthma with frequent exacerbations, and ABPA diagnosed at the age of 42 years. CF was

excluded. At the time of ABPA diagnosis, his predicted forced expiratory volume in 1 s (FEV1) was 58% and after bronchodilator was 62%. All Rosenberg–Patterson criteria were met, including central bronchiectasis with pulmonary infiltrates in all lobes evidenced in a thoracic CT scan. Peripheral blood eosinophils were 570/mm<sup>3</sup> under systemic steroids, total IgE was 2674 IU/mL and AF-specific IgE was 30.50 kU/L. No precipitating antibody against AF antigen was found. The patient was treated with prednisolone 40 mg/day, inhaled salmeterol/fluticasone propionate combination 50/500 mcg twice a day and montelukast 10 mg/day. We could not taper the prednisolone dose because of frequent exacerbations.

Oral itraconazole was not administered because the patient was taking atorvastatin (since a previous cerebral stroke), and also because of his history of hepatotoxicity due to azathioprine (which he has been prescribed in the past for his severe dermatitis).

Despite the optimising treatment, frequent exacerbations of his pulmonary disease occurred. So, one year after ABPA diagnosis the patient began treatment with *omalizumab* 600 mg subcutaneously every 2 weeks (the maximum recommended dosage; dose and dose frequency were based on the patient's weight and on pre-treatment serum IgE IU/mL). The authors evaluated the frequency of exacerbations, the Asthma Control Test score (ACT), lung function, peripheral blood eosinophils, total IgE, and blood AF-specific IgE.