



LETTER 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 β_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.^{1,2} 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 μ g/formoterol, 4.5 μ 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 1 s (%predicted) were 105.5% and 79.5%, respectively. Fractional exhaled nitric oxide level (NIOX VERO[®], Aerocrine Solna, Sweden) was 42 ppb. The peripheral blood eosinophil count was 3.4% (333/ μ L), with a total IgE level of 340 IU/mL. In August 2016, we administered omalizumab (Xolair[®]; 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 μ U/mL and 238 mg/dL, respectively. Homeostasis model assessment (HOMA)-B, which was calculated by the following equation: $(360 \times \text{fasting insulin concentration}) / (\text{fasting glucose concentration} - 63)$,³ 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[®]; 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.⁴ 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.⁵ They concluded that this was because each vial of omalizumab (150 mg) contains 145.5 mg sucrose.⁵ 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 weeks⁵; 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.² However, a paradoxical increase in basophil histamine release induced by omalizumab has been reported.⁶ Gatifloxacin, a pharmacological agent affecting glucose homeostasis, induces hyperglycemia by histamine release.⁷ 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

<http://dx.doi.org/10.1016/j.rppnen.2017.05.002>

2173-5115/© 2017 Sociedade Portuguesa de Pneumologia. Published by Elsevier España, S.L.U. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Please cite this article in press as: Hamada S, et al. Does omalizumab impair glucose homeostasis in a patient with severe persistent asthma and type 2 diabetes mellitus? Rev Port Pneumol. 2017. <http://dx.doi.org/10.1016/j.rppnen.2017.05.002>

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 β -cell function.³ 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.

References

1. Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention; 2014. www.ginasthma.org/ Date last accessed: January 2015. Date last updated: May 2014.
2. Samitas K, Delimpoura V, Zervas E, Gaga M. Anti-IgE treatment, airway inflammation and remodelling in severe allergic asthma: current knowledge and future perspectives. *Eur Respir Rev.* 2015;24:594–601.
3. Cersosimo E, Solis-Herrera C, Trautmann ME, Malloy J, Triplitt CL. Assessment of pancreatic β -cell function: review of methods and clinical applications. *Curr Diabetes Rev.* 2014;10:2–42.
4. Lai T, Wang S, Xu Z, Zhang C, Zhao Y, Hu Y, et al. Long-term efficacy and safety of omalizumab in patients with persistent uncontrolled allergic asthma: a systematic review and meta-analysis. *Sci Rep.* 2015;5:8191.
5. Yalcin AD, Gorczynski RM, Cilli A, Strauss L. Omalizumab (anti-IgE) therapy increases blood glucose levels in severe persistent allergic asthma patients with diabetes mellitus: 18 month follow-up. *Clin Lab.* 2014;60:1561–4.
6. Macglashan DW Jr, Saini SS. Omalizumab increases the intrinsic sensitivity of human basophils to IgE-mediated stimulation. *J Allergy Clin Immunol.* 2013;132:906–11.
7. Ishiwata Y, Yasuhara M. Gatifloxacin-induced histamine release and hyperglycemia in rats. *Eur J Pharmacol.* 2010;645:192–7.

S. Hamada^{a,*}, A. Kuroe^b, M. Tsukino^a

^a *Department of Respiratory Medicine, Hikone Municipal Hospital, Hikone, Japan*

^b *Department of Diabetes and Metabolism, Hikone Municipal Hospital, Hikone, Japan*

* Corresponding author.

E-mail address: sh1124@kuhp.kyoto-u.ac.jp (S. Hamada).