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Hyperamylasemia During Omalizumab Therapy

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ABSTRACT

Objective: Omalizumab safety studies have shown that the drug has an excellent safety profile and is well tolerated in patients with asthma and chronic idiopatic urticaria (CIU) with no blood chemistry monitoring during treatment. Although our clinical experience with drug has pointed out abnormalities in amylase levels. The aim of the present study is to assess blood amylase values during omalizumab therapy and to explain if there is an association between omalizumab therapy and high serum amylase levels.

Materials and Methods: Patients who received omalizumab therapy for severe persistent allergic asthma or CIU between November 2015 and December 2016 were included in the study. Complete blood counts and biochemistry including liver function tests, amylase, pancreatic amylase, and lipase blood levels were evaluated at basal and every visit before omalizumab administration. Patients were evaluated at the time of injection visits that were scheduled every 2 to 4 weeks based on omalizumab dosage. Laboratory assessments followed up at least 1 month to one year. Patients that developed persistent hyperamylasemia carried on with further diagnostic work-up.

Results: Of the total 76 patients, 59 (77.6%) had a diagnosis of CIU and 17 (22.4%) had severe persistent allergic asthma. The median cumulative dose of omalizumab was 4350 (range 900-36000) mg. In the follow-up period, at least one high amylase level was observed in 17 (22.4%) patients. Of these, 11 patients had transient amylase elevation, which returned to the normal range during follow-up. The remaining 6 patients had persistent amylase elevation and underwent further diagnostic examinations. Macroamylasemia was considered as a differential diagnosis and one patient had laboratory tests for macroamylasemia but the results were found within normal limits. There was no statistically significant difference between patients with transient and persistent amylase elevation compared with patients with normal amylase levels in terms of disease, duration of disease, duration of treatment, omalizumab cumulative dose, age, body mass index, and alcohol consumption.

Conclusion: Hyperamylasemia associated with omalizumab therapy is not clear, on the other hand it is a diagnosis of exclusion and all other probable causes of hyperamylasemia were sufficiently excluded. Physicians should be aware of elevated amylase levels in patients treated with omalizumab. To preclude confusion on hyperamylasemia in patients who receive omalizumab, we recommend assessing baseline levels of amylase to clarify if omalizumab causes hyperamylasemia in the treatment period.

Keywords: Amylase, anti-IgE, asthma, urticaria, omalizumab

INTRODUCTION

Omalizumab is a recombinant humanized monoclonal antibody that binds to free IgE at the FceRI binding site (1). It was first approved in 2003 for the treatment of moderate-to-severe persistent allergic asthma that cannot be controlled with optimum treatment in adults and children aged over 12 years.

Clinical safety studies have shown that omalizumab has an excellent safety profile and is well tolerated in patients with asthma and seasonal allergic rhinitis (1). The most commonly reported adverse events with omalizumab treatment were injection site reactions, viral infections, upper respiratory tract infections, sinusitis, headache, and pharyngitis (2).

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In studies that monitored laboratory values during omalizumab treatment, there were no clinically significant changes in values (3-10). Laboratory monitoring has not been recommended during treatment periods.

Post-marketing reports have noted serum sickness disease, thrombocytopenia, Churg-Strauss Syndrome, sarcoidosis, rash, arthralgia, and alopecia attributed to omalizumab (11-13). However, the information leaflet of the drug includes anaphylaxis, malignancy, fever, arthralgia, rash, symptoms such as serum sickness, and eosinophilic conditions (14).

We designed this study based on a patient who was diagnosed as having autoimmune pancreatitis and immunoglobulin (Ig) G4-related disease during omalizumab therapy in our clinic. A women aged 39 years receiving omalizumab treatment for antihistamine-resistant chronic idiopathic urticaria (CIU) at dosage of 300 mg monthly for 9 months was admitted with nausea, vomiting, and abdominal pain with elevated levels of amylase, pancreatic amylase, and lipase. With elevated IgG4 levels and abdominal magnetic resonance imaging (MRI) findings the patient was diagnosed as having autoimmune pancreatitis. This case was diagnosed as having IgG4 related disease and accompanying CIU and as far as we know there has been no reports about their coincidence.

The aim of the present study was to assess blood amylase values during omalizumab therapy and examine if there was an association between omalizumab therapy and high serum amylase levels.

MATERIALS and METHODS

Patients who received omalizumab therapy for the indications of severe persistent allergic asthma or CIU between November 2015 and December 2016 were included in the study. The patients' complete blood counts and biochemistry including aspartate transaminase (AST), alanine transferase (ALT), gamma-glutamyl transpeptidase (GGT), lactate dehydrogenase (LDH), alkaline phosphatase (ALP), total and direct bilirubin, amylase, pancreatic amylase, and lipase blood levels were evaluated at baseline and every visit before omalizumab administration. Patients were evaluated at the time of injection visits that were scheduled every 2 to 4 weeks based on omalizumab dosage. Laboratory assessments continued for at least 1 month to one year. If any abnormality was detected in the values, the patients underwent further tests and screening and were consulted by gastroenterologists to identify the source of abnormal results. Abdominal MRI screening and neck ultrasound examinations were performed when indicated.

Serum amylase activity was measured by the enzymatic colorimetric method. Persistent hyperamylasemia was diagnosed when serum amylase levels were above the upper limit of the reference range (the serum amylase reference interval in adults is 28-100 U/L) lasting more than 3 weeks (15). Transient hyperamylasemia was diagnosed when serum amylase levels were higher than the normal upper limits for less than three weeks, after which normal serum levels were detected in subsequent measurements.

Macroamylasemia was defined as benign, asymptomatic hyperamylasemia due to reduced elimination of amylase because of the high molecular weight of amylase complexes formed with serum IgA, IgG, dextran, and polysaccharide. The clearance of these complexes may be decreased and serum amylase levels may have been detected as higher than the normal limits. Macroamylasemia could be due to renal disease, liver disease, and drugs. Macroamylasemia was tested in one patient for differential diagnosis.

For patients who could not undergo macroamylasemia blood tests, we calculated the amylase-creatinine clearance ratio (ACCR). This was calculated from urine and serum amylase and creatinine measurements. Normal ACCR is 1.6% (16). A decreased ACCR of less than 1% shows a strong possibility for macroamylasemia. Patients whose pancreatic amylase and lipase were normal were considered to have elevated salivary amylase (s-type amylase) levels. One patient's salivary amylase level elevation was documented.

Two patients with persistent hyperamylasemia were excluded from the study; one patient was diagnosed as having IgG4-related disease and the other had multiple myeloma.

The Statistical Package for the Social Sciences (SPSS) Ver. 18 program was used for the statistical analyses; categorical variables were calculated using frequency, and continuous variables were calculated using median and standard deviation. Nominal variables were analyzed using the Chi-square test and the interval variables of the two groups were analyzed using the *t*-test. All study subjects were informed and the written consent was obtained.

The study was approved by Hacettepe University ethics committee with the number 2016/03-34.

RESULTS

Of the 76 patients in total, 59 (77.6%) had a diagnosis of chronic idiopathic urticaria, and 17 (22.4%) had severe asthma. The mean age was 43.7±12.7 years; 52 (68.4%) were women. Half of the patients (n=38) were non-smokers, 22 patients were active smokers, and 16 were former smokers. The median duration of omalizumab therapy was 18.5 (range 3-60) months. The median cumulative dose of omalizumab was 4350 (range 900-36000) mg. In the follow-up period, at least one high amylase level was observed in 17 (22.4%) patients. Of these, 11 patients had transient amylase elevation, which returned to the normal range during follow-up. The remaining 6 patients had persistent amylase elevation and underwent further diagnostic examinations. Macroamylasemia was considered as a differential diagnosis and one patient had laboratory tests for macroamylasemia but the results were found within normal limits.

There was no statistically significant difference between patients with transient and persistent amylase elevation compared with patients with normal amylase levels in terms of diagnoses, duration of disease, duration of treatment, omalizumab cumulative dose, age, body mass index, and alcohol consumption. The characteristics of patients with persistent hyperamylasemia are shown in Table I.

Patients with persistent hyperamylasemia were followed up for two years. Figure 1 shows the course of amylase levels of patients with persistent hyperamylasemia.

The confirmatory gold standard test for macroamylasemia is gel filtration chromatography, which is performed only in specialized laboratories. Among 6 patients with persistent high serum amylase levels, one had elevated levels for 6 months after which the levels were within normal range. The ACCR was calculated in the remaining five patients, four of whom had less than normal levels (3 patients <1.6%, one patient <1%), and one was above 1.6%. The patient who had an ACCR measurement less than 1% underwent further tests for macroamylasemia, but the results were not consistent with macroamylasemia. We could not show macroamylasemia among patients with high serum amylase levels, meaning high serum amylase levels were not due to macroamylasemia.

DISCUSSION

This is the first study that reports elevated serum amylase levels that may be associated with omalizumab treatment. To explain persistent hyperamylasemia among patients treated with omalizumab, we performed all obligatory diagnostic examinations; however, we could not highlight a certain cause. All patients with persistent hyperamylasemia were followed up for two years, we examined them monthly in the first year for amylase and lipase and once in the second year. Persistent hyperamylasemia lasted for at least two years in 5 patients and for 6 months in 1.

All patients were referred to a gastroenterologist, then screened with abdominal MR for pancreatic pathology. Pancreatic amylase was within normal limits in all 6 patients with hyperamylasemia, thus the hyperamylasemia was considered to be caused by elevated salivary amylase

Table I. The characteristics of patients with persistent hyperamylasemia.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age (years)	66	30	64	29	68	72
Gender	Male	Male	Female	Female	Male	Female
Diagnoses	Severe Asthma	Severe Asthma	Chronic Urticaria	Chronic Urticaria	Chronic Urticaria	Chronic Urticaria
Smoking status	Ex-smoker 13 p/yr*	Ex-smoker 9 p/yr	Non-smoker	Non-smoker	Ex-smoker 20 p/yr	Non-smoker
BMI**	26.1	19.03	29.7	28	29.7	27.3
Alcohol consumption	5-6 times per month	1-2 times per month	never	never	never	never
Duration of Omalizumab therapy (months)	60	7	12	18	21	21

*p/yr: packet/years,** BMI: body mass index

levels. Subsequently, one patient underwent a salivary amylase examination and was found to have elevated levels 3-times the upper limits. We then suggested that all patients with hyperamylasemia were salivary-type hyperamylasemia and they were investigated for salivary gland diseases. One patient was diagnosed as having Sjogren disease with biopsy, and another patient had increased vascularity in both submandibular gland parenchyma on ultrasonography. We cannot be certain whether these findings existed before omalizumab treatment. All patients with hyperamylasemia were classified as non-pancreatic hyperamylasemia because of the normal serum pancreatic amylase and lipase levels with no signs of pancreatitis.

Macroamylasemia is one of the causes of elevated salivary amylase, that is a complex between ordinary amylase (usually salivary type) and IgA or IgG in proportions of 70% and 30%, respectively (17). Due to its high molecular weight (greater than 200 kDa) and size, it cannot be eliminated from the kidney and is retained in the plasma with increases in serum amylase activity above the upper reference limits (15). It can be found in 5% of patients with hyperamylasemia (17). Macroamylasemia can be considered in patients with persistently raised total amylase levels and normal lipase. In our study, only one patient had a blood test for macroamylasemia, which was found negative. Ueda et al. reported that serum total and isoamylase activity was higher in elderly women and men beyond the eighth decade, most likely due to age-related decline of renal function (18). We found no correlation between age and amylase levels among patients who were treated with omalizumab.

As mentioned before, ACCR was calculated for patients who could not undergo macroamylasemia blood tests and we found no evidence to consider macroamylasemia.

The use of certain drugs that may increase serum amylase levels such as anti-HIV drugs, azathioprine, clozapine, steroids, paracetamol, aspirin, ranitidine, cimetidine, and cyclosporine was questioned at each visit. Two patients had taken prednisolone for asthma and urticaria. Although the steroid therapy was short-term treatment, hyperamylasemia persisted for two years, independent from steroid therapy.

We found no statistically significant difference between patients with transient and persistent amylase elevation compared to patients with normal amylase levels in terms of diagnoses, duration of disease and treatment, and omalizumab cumulative dose. These results may be due to the small sample size.

The study has some limitations, one of which is the lack of pretreatment amylase levels. Nevertheless, it is a fact that both asthma and CIU investigations do not require amylase measurements before therapy. Also, phase studies of omalizumab do not recommend any laboratory test before treatment and in the follow-up periods of therapy. Although we are not aware of former amylase results, the follow-up period is enough to interpret the results.

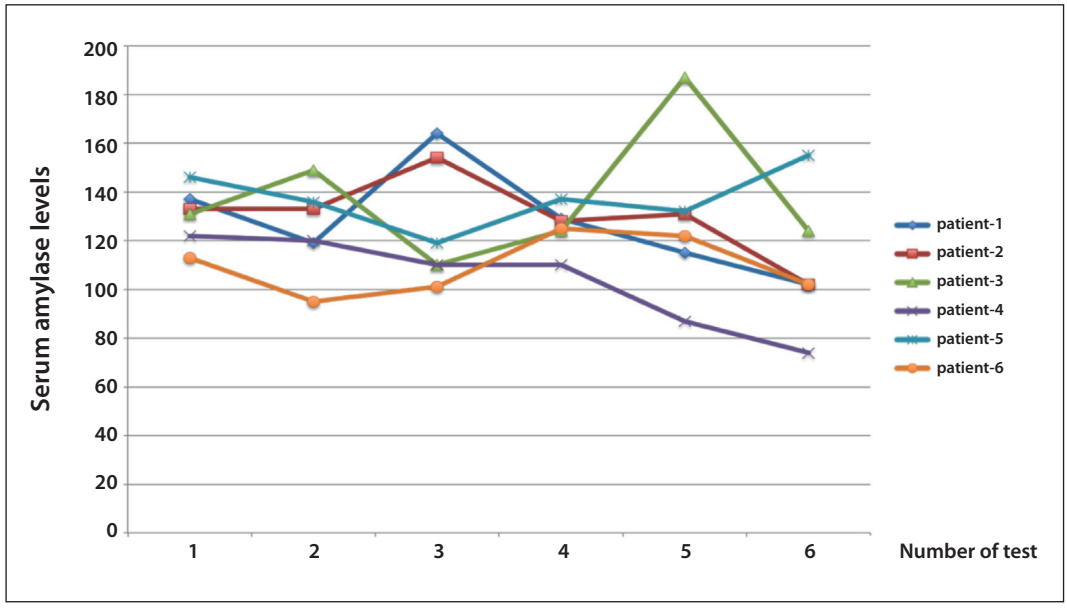

Figure 1. Course of amylase levels of patients with persistent hyperamylasemia.

Even though mandatory diagnostic investigations were performed in all patients, the underlying cause could not be clarified, which makes omalizumab number one in the list as a cause of elevated serum amylase levels. Another limitation is that the study did not have a control group.

Consequently, hyperamylasemia associated with omalizumab therapy is not clear. On the other hand it is a diagnosis of exclusion and all other probable causes of hyperamylasemia were sufficiently excluded. Physicians should be aware of elevated amylase levels in patients treated with omalizumab, and should at least measure baseline levels of amylase to understand if omalizumab causes hyperamylasemia in the treatment period. This approach could help raise awareness of adverse effects and prevent unnecessary clinical and laboratory evaluations. Further prospective studies should be designed to show if there is any significance of elevated amylase levels among patients treated with omalizumab.

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Authorship Contributions

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REFERENCES

1. Babu KS, Arshad SH, Holgate ST. Anti-IgE treatment: An update. Allergy 2001;56:1121-8.
2. Belliveau PP. Omalizumab: A monoclonal anti-IgE antibody. Med Gen Med 2005;7:27.
3. Busse W, Corren J, Lanier BQ, McAlary M, Fowler-Taylor A, Cioppa GD, et al. Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe asthma. J Allergy Clin Immunol 2001;108:184-90.
4. Lanier BQ, Corren J, Lumry W, Liu J, Fowler-Taylor A, Gupta N. Omalizumab is effective in the long-term control of severe allergic asthma. Ann Allergy Asthma Immunol 2003;91:154-9.
5. Milgrom H, Berger W, Nayak A, Gupta N, Pollard S, McAlary M, et al. Treatment of childhood asthma with anti-immunoglobulin E antibody (omalizumab). Pediatrics 2001;108(2):E36.
6. Berger W, Gupta N, McAlary M, Fowler-Taylor A. Evaluation of long-term safety of the anti-IgE antibody, omalizumab, in children with allergic asthma. Ann Allergy Asthma Immunol 2003;91:182-8.
7. Casale TB, Condemi J, LaForce C, Nayak A, Rowe M, Watrous M, et al. Effect of omalizumab on symptoms of seasonal allergic rhinitis. A randomized controlled trial. JAMA 2001;286:2956-67.
8. Adelroth E, Rak S, Haahtela T, Aasand G, Rosenhall L, Zetterstrom O, et al. Recombinant humanized mAb-E25, an anti-IgE mAb, in birch pollen-induced seasonal allergic rhinitis. J Allergy Clin Immunol 2000;106:253-9.
9. Chervinsky P, Casale T, Townley R, Tripathy I, Hedgecock S, Fowler-Taylor A, et al. Omalizumab, an anti-IgE antibody, in the treatment of adults and adolescents with perennial allergic rhinitis. Ann Allergy Asthma Immunol 2003;91:160-7.
10. Nayak A, Casale T, Miller SD, Condemi J, McAlary M, Fowler-Taylor A, et al. Tolerability of retreatment with omalizumab, a recombinant humanized monoclonal anti-IgE antibody, during a second ragweed pollen season in patients with seasonal allergic rhinitis. Allergy Asthma Proc 2003;24(5):323-9.
11. Bekçibaşı M, Barutçu S, Çelen MK, Dayan S, Hoşoğlu S. Churg-Strauss syndrome occurring during omalizumab treatment. Eur J Rheumatol 2015;2(3):129-30.
12. Nazir S, Tachamo N, Fareedy SB, Khan MS, Lohani S. Omalizumab-associated eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome). Ann Allergy Asthma Immunol 2017;118(3):372-4.
13. Yung S, Han D, Lee JK. Cutaneous sarcoidosis in a patient with severe asthma treated with omalizumab. Can Respir J 2015;22(6):315-6.
14. Xolairhcp. Access date: 2021. Available from: https://www.xolairhcp.com/
15. Borovickova I, Bhatt NR, Boran GP, Ridgway PF. Persistent chronic hyperamylasemia: Clinical interpretation and diagnostic approach. J Pancreas 2016;17:349-58.
16. Lawson GJ. Prevelance of macroamylasemia using polyethylene glycol precipitation as a screening method. Ann Clin Biochem 2001;38:37-45.
17. Scheutzel P, Gerlach U. Alpha-amylase isoenymes in serum and saliva of patients with anorexia and bulimia nervosa. Z Gastroenterol 1991;29:339-45.
18. Vissers RJ, Abu-Laban Rb, Mchugh DF. Amylase and lipase in the emergency department evaluation of acute pancreatitis. J Emerg Med 1999;17:1027-37.