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Omalizumab dosing via the recommended card versus use of the published formula

To the Editor:

Before the Food and Drug Administration approval of omalizumab for the treatment of asthma, clinical studies suggested that greater than 90% of the free IgE present in the serum needed to be bound by this antibody to achieve meaningful clinical gains in the management of asthma. Pharmacodynamic studies suggested that to achieve binding of >90% of free IgE, the dosing of omalizumab must be at least equal to 0.016 mg omalizumab/kg body weight/IU/mL of free IgE.¹ In these initial studies, it was stated that the dose of omalizumab was high enough to "ensure for each patient a dosage approximately equal to 0.016 mg/kg IgE (IU/ml)."¹ Using this formula, the dose of omalizumab in milligrams is calculated by multiplying 3 numbers: the patient's body weight in kilograms, the patient's pretreatment free IgE level, and the constant 0.016 (weight $\times$ IgE $\times$ 0.016).

After this formula was developed, a pocket card was created for use in the clinical studies with the purpose of simplifying the dosing of omalizumab. This card was based on the formula presented here. The intent was to insure that patients dosed by means of the pocket card received a dose of omalizumab that was at least equal to (and possibly greater than) that suggested by the formula.

In practice, after dosing a few patients by both the pocket card and the formula used in the early studies, it occurred to us that in several cases, the pocket card produces a significantly greater dose. In some cases, the dose per the pocket card is twice that produced by the formula. For instance, a patient with a serum free IgE level of 107 IU/mL and a body weight of 62 kg would, via the dosing card, receive 300 mg Xolair (Genentech Novartis, South San Francisco, Calif) every 4 weeks. However, when the dose is calculated using the formula ($0.016 \times 107 \text{ IU/mL} \times 62 \text{ kg} = 106 \text{ mg}$ of omalizumab per month), the calculated dose is less than half of this. This discrepancy between the formula and the dosing card tends to be greatest when the serum IgE level and the patient's weight are both at the lower end of the cutoff values that have been placed on the dosing card.

To discover the frequency and magnitude of this problem, we undertook the task of studying this problem by 2 methods.

In the first method, we retrospectively examined the records of patients who had been treated with omalizumab at our institution. We compared the actual dose that was chosen for these patients by use of the pocket card with the dose that would have been given if the formula had been used.

In the second method, we used a random number generator (Microsoft Excel Data Analysis Tools; Microsoft Corp., Seattle, Wash) to create 130 hypothetical patients with asthma. Serum IgE levels, like most biologic variables, fall into a log normal distribution. The Excel random generator was used to create 130 IgE values with a normal distribution, which was then converted to a log normal distribution by raising to the power *e*. The geometric mean IgE level of patients with severe asthma is 112 IU/mL.²

The geometric mean of our hypothetical cohort was 116 IU/mL. Patient weights were taken from 130 consecutive patients seen in an outpatient allergy clinic. We then calculated the dose that would be prescribed and the cost that would be incurred under both methods of determining the dose.

Using the 130 randomly generated patients, the average cost per patient when patients were dosed via the pocket card was \$14,031.71. The average cost per patient when patients were dosed via the published formula was \$9,576.20. Thus, dosing with the pocket card represents a 47% cost increase over dosing with the formula. The formula was created with the goal of administering a dose that would bind up at least 97% of the IgE. It is not clear that there is any additional benefit to be gained by giving more of the medication than the formula prescribes.

Perhaps the results would be different with a real patient cohort. Of 12 patients seen at the Cleveland Clinic Foundation, dosing via the pocket card produced an average cost per patient of \$15,155.00/year. Dosing by using the formula method led to patients requiring \$9,526.00/year of omalizumab. This represents a 59% increase in cost. In some of the these cases, use of the pocket card doubled the yearly cost from \$10,392.00 to \$20,784.00 per patient

per year based on the average wholesale cost of a 150 mg vial of omalizumab of \$433.00.³

Some patients fall into the “do not dose” region on the card because of their high weight and/or IgE value. However, many of these patients could clearly be given enough omalizumab (per the formula) to suppress their IgE and yet not use more than the 750 mg omalizumab considered the dosing ceiling. The aforementioned cost-benefit analysis was based on the subset of patients who could be dosed by both the card and the formula. However, using the formula, 106 of 130 patients would be able to receive omalizumab, whereas only 69 of 130 could be dosed using the pocket card. Therefore, a great many more patients would be able to benefit from omalizumab if the dosing was regularly performed via the formula.

Although use of the formula for dosing of omalizumab could lead to large cost savings, dosing via this method will often lead to a dose that is not equal to a multiple of 150 mg (which is the size of a vial of omalizumab.) This fact could serve to make the cost savings discussed significantly smaller. However, it has occurred to us that although there is not much flexibility in the amount that can be dispensed at a given visit, there is flexibility in the dosing interval. Consider the following patient. PL becomes a candidate for therapy with omalizumab. Her serum IgE is 216 IU/mL, and her weight is 50 kg. Her dose every 28 days would be $50 \text{ kg} \times 216 \text{ IU/mL} \times 0.016 = 173 \text{ mg/28 days}$. Given that omalizumab can be given at either 2-week or 4-week intervals, we see no pharmacologic reason why any interval between these 2 points would be problematic. Therefore, using proportions, PL's dose of 173 mg/28 days could be converted to 150 mg/24 days ($173 \text{ mg/28 days} = 150 \text{ mg/24 days}$). Therefore, this patient could receive her injections every 24 days or every 3 weeks. Alternatively, if a large asthma clinic had a critical mass of patients on omalizumab, vials could be split between 2 patients. Given the 8-hour shelf life in the refrigerator after the solution has been mixed, this approach of splitting vials between patients would not be feasible for smaller clinics. Better cost savings with less waste would also occur if a second smaller vial size were made available.

We are concerned that use of this pocket card may result in increased expense for the health care system without increased efficacy for the patient. Conversely, it may deny Xolair to some patients who should clearly qualify for it. Further research is needed to clarify a more precise method of dosing this expensive medication. We wish to bring this phenomena to the attention of the readership.

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Safety of methacholine challenges in a multicenter pediatric asthma study

To the Editor:

Pharmacologic provocation challenges to evaluate bronchial hyperresponsiveness (BHR) are used as a clinical tool to confirm the diagnosis of asthma in special situations and as a research outcome measure to determine mechanisms and treatment efficacy. BHR is related to various measures of asthma severity¹ and has also been reported as a predictor of persistent asthma and airflow limitation in adulthood.² Most recently, its application as a tool for determining treatment modification has been found to be effective not only at improving clinical parameters of asthma control but also at alleviating airway inflammation.³ Given the relevant applications of bronchoprovocation tests, it is important to standardize and guarantee safety for use in patients. Human subject safety boards and ethics committees are requesting investigators to provide more accurate safety assessments.

The Childhood Asthma Management Program was a multicenter, randomized, clinical trial designed primarily to evaluate the long-term safety and effectiveness of 3 inhaled treatments for mild to moderate childhood asthma over 4 to 6 years, followed by an observational 4-year period (Childhood Asthma Management Program Continuation Study). Before randomization, participants had to have a history of asthma for at least 6 months in the year before screening, evidence of current asthma of mild to moderate severity during a 28-day screening period, and a methacholine FEV₁ PC₂₀ ≤ 12.5 mg/mL.⁴ A written informed consent approved by each clinical center's institutional review board was obtained from all patients and/or the parent. In this report, we evaluate the safety of methacholine provocation performed serially over an 11-year period.

Methacholine testing was performed by trained and certified technicians. Physicians were available on site to evaluate the child and initiate treatment as necessary. The procedure was performed at least 4 hours after the use of a short-acting bronchodilator and 24 hours after the last use of a long-acting bronchodilator or theophylline. The tests were not performed within 4 weeks of an upper respiratory tract infection, other serious illness, or use of oral steroids;