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Mepolizumab in the treatment of severe eosinophilic asthma

Results from a physician in the field

We report our real-world results of using mepolizumab in patients with severe eosinophilic asthma in an office environment. This was a retrospective study; written permission was granted by all patients to use results of their treatment with mepolizumab, a monoclonal antibody directed against the interleukin-5 (IL-5) cytokine.

Mepolizumab (GlaxoSmithKline, Research Triangle Park, North Carolina) is a recombinant humanized immunoglobulin G/K monoclonal anti–IL-5 antibody that inhibits IL-5 from binding to the alpha subunit of the IL-5 receptor complex expressed on the eosinophil cell surface.[1]

Most of the demographics of the patients in the study are listed in Table 1. The average age was 58 years, with a range of 36 to 92 years; 50% were female. Of the 36 patients in the study, 11 were obese (body mass index greater than 36), and 5 were morbidly obese (body mass index greater than 40). Thirty-one of 36 (86%) had allergic rhinitis. Six were receiving immunotherapy. Each patient had an eosinophil count of at least 150 cells/μL, with a range of 150 to 1,700 and an average of 404. Eight patients had a history of smoking, and 3 were currently smoking less than one-half pack per day. The history of asthma ranged from 2 years to 61 years, with an average of 33 years.

Patients received monthly subcutaneous injections of 100 mg of mepolizumab during a period of 6 to 14 months, with an average of 10 months. They all required a high daily dose of inhaled corticosteroid with a long-acting beta-agonist, montelukast, and, at times, additional controller medications, and they had at least 2 exacerbations requiring a burst of prednisone during the past year. Thirteen of 36 required daily prednisone, ranging from 7 to 25 mg per day. Before beginning mepolizumab, when clinically stable, attempts were made to lower the prednisone to the lowest dose that kept them reasonably well controlled. Each patient served as their own control; if they received 14 mepolizumab injections, we compared their clinical history during the previous 14 months. At each visit, before they received mepolizumab, they were examined, pulmonary function tests were performed, and an asthma control questionnaire (ACQ) was completed.[2] Exacerbations were treated with 40 to 60 mg of prednisone per day rather than a Medrol Dosepak (MDP) (Pfizer, New York, New York), because a recent publication highlighted that inappropriate low-dose and automatic taper frequently failed to resolve the exacerbation.[3] Within 24 to 48 hours after the onset of symptoms, patients were seen and treated with 1 to 2 injections of terbutaline, which has been shown to be more effective than simply increasing the number of aerosols.[4]

During the period of 6 to 14 months before treatment with mepolizumab there were 124 exacerbations. After receiving monthly mepolizumab injections there were 25 exacerbations; an average of 3.2 bursts of prednisone before mepolizumab and 0.7 after mepolizumab, an 80% reduction ($P < .01$). Nineteen of 36 patients did not require bursts of prednisone while on mepolizumab. Seven of 13 steroid-dependent asthmatics were able to discontinue prednisone after an average of 6 months, with a range of 1 to 12 months. Six patients still required prednisone from 15 mg to 5 mg per day. The ACQ before mepolizumab ranged from 0.28 to 4.0, with a mean of 1.69. After receiving mepolizumab, the ACQ score ranged from 0 to 2.57 with a mean of 0.93, a 55% reduction ($P < .01$). The frequency of cough, wheeze, dyspnea at rest, and exercise-induced asthma was significantly decreased. They frequently reported feeling significantly better with increased quality of life and had increased energy. Their use of rescue inhalers was markedly decreased. Although the frequency of the upper respiratory infections appeared to be about the same, they did not precipitate exacerbations as frequently as before being treated with mepolizumab, thus frequently obviating the need for bursts of prednisone. Two patients with a long-standing history of anosmia had their sense of smell restored. Antibiotics were not used during the 6- to 14-month period, which was not surprising, because almost all infection-induced asthma attacks are invariably viral.[5]

Mepolizumab was remarkably well tolerated. No significant reactions occurred at the injection site. One patient did develop a mild case of herpes zoster. Another patient developed urticaria on 2 occasions: once 3 days after the injection, which resolved in 3 days, and another episode two weeks after the injection that also resolved within three days. No evidence was seen of respiratory distress with either episode. This patient was pretreated with prednisone, diphenhydramine, and cetirizine for 6 months of injections and then was able to continue receiving mepolizumab without issue for the next 12 injections.

The results of our retrospective study are important for patients requiring daily oral corticosteroids or frequent bursts, because oral corticosteroids are known to be associated with a wide variety of serious adverse side effects. What is not as well known is the increase in the side effects from short-term oral corticosteroids, which can lead to increased rates of sepsis, venous thromboembolism, and fractures, even at relatively low doses.[6] These adverse events have been reviewed by Waljee et al,[6] who compared the rates of these events in nonusers and users of corticosteroids. The rates among nonusers of sepsis, venous thromboembolism, and fractures were 0.02% (n = 293 of 1,221,493), 0.09% (n = 1,054 of 1,221,493), and 0.39% (n = 4,735 of 1,221,493), respectively, in comparison with those of users, which were 0.05% (n = 170 of 327,452), 0.14% (n = 472 of 327,452), and 0.51% (n = 1,657 of 327,452), respectively.

This "real-world study" has complemented the results of multiple randomized controlled trials,[7–11] which is very important in evaluating treatment in a heterogenous disease such as asthma. It is ironic and a testimonial to the efficacy of mepolizumab in patients with severe asthma that most of the patients at the Cleveland Allergy & Asthma Center who require short courses of oral corticosteroids have mild asthma and did not qualify to receive mepolizumab based on their symptoms.

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Table 1
Demographics of Each Patient Including Age, Sex, Past or Present Use of Smoke Tobacco, Eosinophil Count, Number of Mepolizumab Injections in the Study Period, Presence of Allergic Rhinitis, and Whether the Patient Receives Allergy Injections. The Oral Corticosteroid Use, ACQ Scores, and Number of Exacerbations Before and After Receiving Mepolizumab Are Also Given

Patient	Age	Sex	Former smoker	Current smoker	Asthma duration	Allergy injections	Allergic rhinitis	Oral corticosteroid use pre-mepolizumab	Oral Corticosteroid use post-mepolizumab	ACQ pre-mepolizumab	ACQ post-mepolizumab	Eosinophil count	Exacerbations pre-mepolizumab	Exacerbations post-mepolizumab	Number of injections of mepolizumab
1	58	M			50	1				2.10	1.00	192	2	0	14
2	55	M			48					4.00	2.14	210	6	3	14
3	55	F	1	1	10	1	1	15 mg/d	5 mg/d	3.57	2.42	390	4	1	12
4	61	F	1		25		1			1.00	0.14	510	5	0	14
5	52	F		1	3		1			1.43	0.28	370	3	1	14
6	73	F			30	1	1	25 mg/d		3.14	1.14	1010	6	0	12
7	62	F			5		1	20 mg/d	5 mg/d	4.00	2.14	192	5	1	12
8	55	F	1		25		1	20 mg/d	15 mg/d	2.85	2.57	312	5	3	11
9	68	F			28		1			1.14	0.14	270	2	0	13
10	59	M			25	1	1	10 mg/d	5 mg/d	0.42	0.85	160	2	1	12
11	47	M			20			7 mg/d		3.00	1.57	204	4	0	11
12	44	M			40		1			2.14	0.57	300	2	0	11
13	56	F			50	1	1	10 mg/d		0.71	0.71	290	2	1	12
14	48	M			42		1	10 mg/d		3.43	1.42	930	5	1	12
15	57	M			16	1	1			1.29	0.57	162	2	0	12
16	63	M			51		1	15 mg/d	10 mg/d	1.71	1.71	620	2	0	11
17	45	M			39		1			0.28	0.00	820	2	0	12
18	67	F			61		1			0.28	0.57	210	3	0	11
19	70	M			15		1			1.85	0.85	190	2	1	11
20	63	M			50		1			1.43	1.00	250	2	0	11
21	63	M			57					3.85	1.85	1230	6	0	10
22	40	F			18		1			1.00	0.71	220	2	1	9
23	78	M			20		1			2.57	0.85	500	4	0	9
24	77	F	1		12		1			0.71	0.42	150	6	0	9
25	36	F	1		30		1	15 mg/d	8 mg/d	3.14	0.85	400	4	4	9
26	56	M			2		1			2.14	1.14	1210	4	1	9
27	59	F			30		1			3.71	0.57	420	5	0	9
28	54	M			22		1			3.14	0.14	220	2	0	8
29	36	M			30		1			3.14	0.57	1700	4	1	7
30	59	F			56		1	15 mg/d		1.57	0.71	240	3	1	8
31	68	M	1		45		1			1.71	0.00	840	4	0	8
32	52	F			45		1	15 mg/d		0.57	0.28	210	4	0	6
33	62	F			30		1			2.71	1.57	170	2	0	6
34	92	F	1		29		1	10 mg/d		1.57	1.28	160	3	1	7
35	57	F	1	1	14		1			2.28	0.42	180	3	3	7
36	57	M			51					2.28	1.28	320	2	0	6

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Meat reintroduction in a patient with α-gal allergy

A 56-year-old woman presented to a drug allergy clinic for evaluation of a possible allergic reaction to acetaminophen. Two months before presentation, the patient took 1,000 mg acetaminophen for pain relief and 5 hours later awoke with pruritic hives that resolved with diphenhydramine. Two weeks later, she took acetaminophen and developed pruritic hives 4 hours later, this time with vomiting, cramping, pruritic mouth, and sensation of throat closure. These symptoms resolved with diphenhydramine. Her medical history was noncontributory. There were no known food allergies, nor systemic reactions to insect bites/stings.

The patient underwent graded-oral challenge to a cumulative dose of 850 mg acetaminophen in the clinic without reaction. With the possibility of delayed anaphylaxis, diet was questioned. She recalled consuming meals with large amounts of red meat 4 hours before the reactions, with a larger quantity (10 oz beef) before the second. She had abstained from animal meat for religious reasons the 2 weeks preceding the first reaction. She typically consumes a diet rich in chicken, fish, and eggs; however, she likely consumed smaller amounts of red meat infrequently between these episodes without reaction. The patient also recalled a tick bite in New York State 1 year before these episodes, with a local reaction including erythema and pruritus lasting 6 months. Therefore, specific serum galactose-α-1,3-galactose (α-gal) immunoglobulin E (sIgE) was checked and found to be elevated to 46 kU/L. Total serum IgE was 264 IU/mL (Fig 1). The patient was diagnosed with α-gal allergy and advised to abstain from red meat.

On 3-year follow-up, she had avoided red meat and had not experienced any additional reactions. She had continued ingesting other animal products, including dairy. The patient wished to reintroduce meat into her diet. Repeat α-gal testing was 3.5 kU/L, total IgE 60.8 IU/mL, and beef IgE 0.30 kU/L. She underwent an oral challenge with red meat; she was given a cumulative amount of 220 g prosciutto (70 g, then 150 g after 2 hours) and observed for a total of 5.5 hours. She remained asymptomatic. The patient began ingesting modest amounts of meat regularly without reaction. On follow-up 8 months later, α-gal decreased to 1.6 kU/L, total IgE to 49 IU/L, and beef IgE to 0.2 kU/L.

One year after reintroduction, she presented after 1 episode of burning sensation of palms and feet after eating beef. This occurred after a week of increased exercise and sun exposure. She denied additional tick bites. Alpha-gal increased to 3.14 kU/L. Patient self-resumed red meat consumption and has not had any additional reactions. Alpha-gal again decreased to 1.47 kU/L 5 months after this episode. We believe that this is the first reported case of successful, unrestricted reintroduction of red meat for a patient with α-gal allergy.

Alpha-gal is a carbohydrate moiety abundantly expressed on cells and tissues of all mammalian species except primates.[1] The naturally occurring IgG to α-gal was a known cause of hyperacute organ rejection in xenotransplantation.[1] Immunoglobulin E antibodies specific to α-gal have been found to be capable of eliciting serious reactions.

These were initially described after patients receiving cetuximab, a monoclonal antibody chemotherapy for colorectal and squamous-cell carcinoma, developed immediate hypersensitivity reactions.[2] Analysis of the IgE antibodies to cetuximab demonstrated specificity to α-gal residues on the heavy chain portion.[2] High prevalence of hypersensitivity reactions to cetuximuab were reported in the southeastern United States.[2] This distribution was similar to that of Rocky Mountain spotted fever and ehrlichiosis.[3] Within this geographic distribution, individuals (both taking cetuximab and not) were reporting history of tick bite and red meat sensitivity.[1,3] The hypersensitivity reactions included anaphylaxis, angioedema, and urticaria.[4] Thus, the α-gal allergy was defined.[1]

The exact mechanism of this allergy and its natural history remain unknown.[1] Significant evidence supports the role of tick bites in the development of sIgE response to α-gal.[1] Total serum IgE and sIgE to α-gal increased in response to tick bites.[1] Apparently, α-gal sIgE rises by more than 20-fold after a tick bite, with a similar rise in total IgE level.[1] Some evidence suggests that sIgE to α-gal decreases in some patients over time.[5]

Although some foods (eg, egg, peanut, milk) have established threshold sIgE levels for 95% positive predictive values for allergic reactions, such levels have not been well standardized for α-gal allergy.[6] The challenge to red meat was performed in our patient to evaluate safe consumption of red meat. This decision was made after her α-gal levels were found to have decreased from 46 to 3.5 kU/L. Although challenges to red meat have been done with

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