

Could daratumumab be used to treat severe allergy?



To the Editor:

Allergic diseases, such as allergic asthma, rhinitis, and food allergy, affect millions of people worldwide and their prevalence seems to be increasing. Desensitization via allergy immunotherapy (AIT) is available for some allergens, such as pollen and insect venom, and there is a renewed interest in immunotherapy in food allergy. Although a strict and lengthy regimen of AIT is generally able to strongly decrease symptoms, no true curative treatment is available. Therefore, avoidance of the eliciting allergens is often necessary. Still, accidental exposure to culprit allergens occurs. In case of food allergy, this often leads to hospital admission and, in severe cases, treatment in an intensive care unit. A high need exists for curative treatment options.

The specific immune response that defines allergy is characterized by the presence of IgE directed to an allergen (sensitization). After sensitization, exposure to an allergen induces crosslinking of IgE bound to mast cells and basophils, causing a wide release of vasoactive mediators, such as histamine. Therefore, therapy directed against IgE has been a research focus for several years. Therapy using mAbs against IgE (omalizumab) has proven to be effective in allergic asthma, with effectiveness also being researched in other (atopic) diseases, such as allergic rhinitis, and atopic dermatitis.¹ In food allergy, omalizumab might be able to increase allergen tolerability in some patients and its role in (oral) AIT for food allergy is actively investigated. A different method of targeting IgE is by depleting plasma cells that produce (specific) IgE. The effect of B-cell depletion on IgE levels and clinical symptoms of atopic diseases has been studied before. For example, rituximab did not significantly decrease serum IgE levels compared with placebo at 3 or 6 months in patients with Idiopathic thrombocytopenic purpura.² Bortezomib, targeting (malignant) plasma cells via proteasome inhibition, is also being investigated as a treatment option in (auto)antibody-mediated diseases.³ In a mouse model for chronic asthma, bortezomib treatment reduced specific IgE (sIgE) levels.⁴ The effect of plasma cell depletion on sIgE levels in humans remains unknown.

Daratumumab is an mAb targeting CD38, which is highly expressed on malignant plasma cells. Because daratumumab has marked single agent activity in multiple myeloma (MM) and a favorable safety profile, it was recently approved by the Food and Drug Administration for the treatment of relapsed/refractory MM.⁵ We wanted to test the hypothesis that treatment with daratumumab reduces the levels of total and specific IgE via depletion

of IgE-producing plasma cells. To evaluate this, residual blood samples were collected from patients with relapsed or refractory MM treated with daratumumab monotherapy or daratumumab plus lenalidomide-dexamethasone in the University Medical Center Utrecht, Utrecht, The Netherlands, in the period April to August 2014.^{5,6} Routine blood analysis was performed at baseline and after every 4 weeks of daratumumab treatment. In the baseline samples, total IgE level was determined and an ImmunoCAP Phadiatop (ThermoFisher, Uppsala, Sweden) was performed, according to manufacturer's instructions, to indicate sensitization to common inhalant allergens (eg, tree/grass pollen, animal dander, and house dust mite). If the Phadiatop was positive, sIgE levels against birch pollen, timothy grass pollen, and house dust mite were determined using ImmunoCAP (ThermoFisher). These are among the most frequently recognized inhalant allergens in the Netherlands.

A total of 8 patients with MM were included, 5 treated with daratumumab monotherapy (16 mg/kg) and 3 with daratumumab (16 mg/kg) plus lenalidomide-dexamethasone (25 and 40 mg, respectively). Four patients had a detectable IgE level (≥ 2 kU/L) at baseline and are listed in Table I. All 4 subjects demonstrated a decrease in both benign and malignant plasma cells at 8 or 12 weeks of treatment (see Table E1 in this article's Online Repository at www.jacionline.org). Only for patient 1, total IgE levels were elevated above reference levels and a positive Phadiatop as well as sIgE against inhalant allergens were detected. Additional samples from patient 1 at week 4, 8, 12, 16, and 20 were analyzed, demonstrating a decrease of more than 80% in both total and specific IgE levels for timothy grass pollen and house dust mite after 20 weeks (Table II; see Fig E1 in this article's Online Repository at www.jacionline.org). Patient 1 achieved a complete response as determined by evaluation of plasma cell percentages in bone marrow aspirate and M-protein levels (see Tables E1 and E2 in this article's Online Repository at www.jacionline.org). The other 3 patients with detectable IgE levels also demonstrated a decrease in total IgE level after 8 weeks of treatment. For patient 2, total IgE levels decreased 88% (41 to 5 kU/L). For the other 2 patients, baseline IgE levels were very low and dropped below detection limit after 8 weeks.

This proof of concept demonstrates that levels of total and specific IgE gradually decrease during daratumumab treatment in a single patient sensitized to 2 common inhalant allergens. This patient was cotreated with lenalidomide and dexamethasone. The effect of lenalidomide on IgE levels is unknown, although there are reports of increased immunoglobulin levels after lenalidomide treatment in chronic lymphocytic leukemia.^{7,8} Glucocorticoids are known to increase IgE synthesis.⁹ Therefore, the drop in

TABLE I. Measurements at baseline of patients with detectable IgE

Patient	Treatment	Total IgE (kU/L)	Phadiatop	Birch pollen sIgE (kU/L)	Timothy grass pollen sIgE (kU/L)	HDM sIgE (kU/L)
1	D + LD	356	Positive	Negative	9.83	3.23
2	D + LD	41	Negative	ND	ND	ND
3	D	3	Negative	ND	ND	ND
4	D + LD	7	Negative	ND	ND	ND

Reference values: Total IgE, <100 kU/L; ImmunoCAP sIgE birch pollen/timothy grass pollen/HDM, <0.35 kU/L.

D, Daratumumab monotherapy; D + LD, daratumumab plus lenalidomide-dexamethasone; HDM, house dust mite; ND, not determined.

TABLE II. Patient 1 total and specific IgE levels at the investigated time points

IgE levels	Week					
	Week 0	Week 4	Week 8	Week 12	Week 16	Week 20
Total IgE (kU/L)	356	197	185	145	95	44
Timothy grass pollen (kU/L)	9.83	6.07	6.88	6.63	4.1	1.67
HDM (kU/L)	3.23	1.93	1.54	1.06	0.73	0.4

Reference values: Total IgE, <100 kU/L; ImmunoCAP sIgE timothy grass pollen/HDM, <0.35 kU/L.
HDM, House dust mite.

IgE levels observed in this study is unlikely to result from dexamethasone and lenalidomide cotreatment.

Daratumumab is well tolerated both alone and in combination with other agents, with infusion-related reactions as the most frequent adverse reactions. These occur in approximately 50% of patients and mostly during the first infusion.^{5,6} However, adverse reactions as well as long-term effects in a relatively healthy, allergic population could differ from those in patients with MM and require additional studies.

In asthma, IgE depletion by omalizumab treatment resulted in clinical improvement, as well as an increased quality of life and reduced socioeconomic burden of disease, both in clinical trials and in daily practice studies. Although this proof of concept demonstrates the potential value of daratumumab in the management of severe IgE-mediated diseases, its effect on clinical parameters of allergy has yet to be investigated.

Mark A. Blankestijn, MD^a

Niels W. C. J. van de Donk, MD, PhD^b

Kate Sasser, PhD^c

André C. Knulst, MD, PhD^a

Henny G. Otten, PhD^d

From ^athe Department of Dermatology/Allergology, University Medical Center Utrecht, Utrecht, The Netherlands; ^bthe Department of Hematology, VU University Medical Center, Amsterdam, The Netherlands; ^cJanssen Research & Development, Spring House, Pa; and ^dthe Department of Immunology, University Medical Center Utrecht, Utrecht, The Netherlands. E-mail: m.a.blankestijn@umcutrecht.nl.

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Cardiovascular and cerebrovascular events among patients receiving omalizumab: Pooled analysis of patient-level data from 25 randomized, double-blind, placebo-controlled clinical trials



To the Editor:

Omalizumab is an anti-IgE antibody used in the treatment of moderate to severe persistent asthma. EXCELS (An Epidemiologic Study of Xolair [omalizumab]: Evaluating Clinical Effectiveness and Long-term Safety in Patients With Moderate-to-Severe Asthma; NCT00252135) was a prospective observational cohort study conducted as a postmarketing commitment to the US Food and Drug Administration to better understand the long-term safety of omalizumab in clinical practice. Results from EXCELS suggest that omalizumab is not associated with increased risk of malignancy.¹ In a subsequent analysis, however, we reported an imbalance in cardiovascular and cerebrovascular events.² The observational design of EXCELS precluded randomization and blinding to treatment, and thus differences in asthma severity between cohorts at baseline may have contributed to this imbalance, but some increase in risk could not be excluded. Here, we report results from a separate analysis of cardiovascular events using pooled data from randomized controlled trials (RCTs) of omalizumab.

Twenty-five core trials and 2 extension studies met the inclusion criteria for this pooled analysis (see Table E1 in this article's Online Repository at www.jacionline.org); data included patients recruited from 26 countries. Common reasons for exclusion included open-label or single-arm (uncontrolled) design, limited drug exposure (eg, single dose), and pediatric-only studies.

All potential events of interest were identified from the Adverse Event Report Form or Discontinuation Case Report Form using a prespecified search strategy (see Fig E1 in this article's Online Repository at www.jacionline.org). External adjudication was

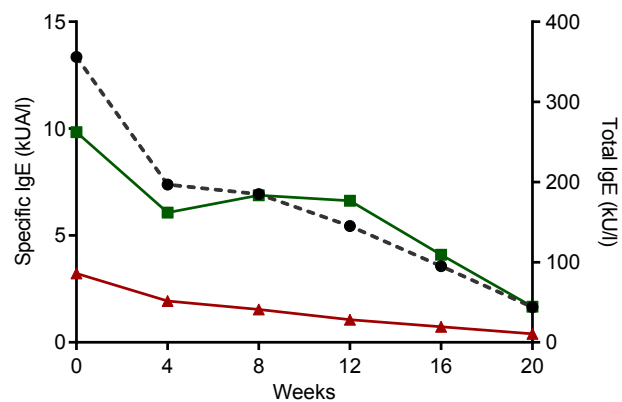


FIG E1. Total IgE and specific IgE (sIgE) levels for patient 1 before and during treatment with daratumumab. The dashed line indicates total IgE levels, the green line sIgE against timothy grass pollen, and the red line sIgE against house dust mite.

TABLE E1. Bone marrow plasma cell numbers for the 4 patients with detectable IgE as determined by flow cytometric analysis, as well as response to treatment

Patient	Response to treatment	% Benign plasma cells		% Malignant plasma cells	
		Pretreatment	At week 8/12	Pretreatment	At week 8/12
1	CR	0.420	0.240	0.226	0.015
2	CR	0.168	0.033	2.485	0.539
3	PD	0.032	0	2.543	0.283
4	CR	0.055	0	6.214	0.025

CR, Complete response; PD, progressive disease.

TABLE E2. M-protein and free kappa light-chain levels for patient 1 at the investigated time points

Time point	M-protein levels quantitative (g/L)	Free kappa light-chains (mg/L)
Week 0	16	52.96
Week 4	5	14.52
Week 8	3	16.40
Week 12	0	14.28
Week 16	0	13.58
Week 20	0	12.69