Successful Desensitization to Irinotecan After Severe Hypersensitivity Reaction

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Irinotecan is an antineoplastic drug that is widely used to treat gastrointestinal malignancies. It prevents DNA from unwinding by inhibition of topoisomerase I [1]. Hypersensitivity reactions (HSRs), which can occur with most drugs, are unpredictable, can affect any organ or system, and range widely in clinical severity from mild pruritus to anaphylaxis. In most cases, the culprit drug is avoided in the future, but for certain patients, the particular drug may be essential for optimal therapy. Under these circumstances, desensitization to the drug in question is a viable option. This approach induces a temporary state of tolerance to the drug responsible for a proven HSR [2].

A 57-year-old man with a personal history of dyslipidemia, high blood pressure, and hyperuricemia and no history of allergy was diagnosed in June 2014 with a low rectal neoplasm 7 cm from the anal margin with synchronous liver metastases (T3N2M1). Short-course radiotherapy was administered, followed by laparoscopic ultralow anterior resection with manual colorectal anastomosis and removal of a surgical specimen through the anus (pass-through) with protective lateral ileostomy.

Postoperative evaluation revealed that the liver tumors had progressed and were nonresectable; consequently, chemotherapy was initiated with CAPOX (capecitabine and oxaliplatin) in combination with bevacizumab (the patient harbored a KRAS mutation), and by April 2015, the patient had received 6 cycles.

The response of the liver metastases to chemotherapy was poor, so it was decided to administer 4 cycles of irinotecan-loaded drug-eluting beads (DEBIRI, BTG) via intra-arterial infusion. The patient received 100 mg of irinotecan in DC Bead (an embolic drug-eluting bead for controlled loading and release of chemotherapeutic agents) (BTG) of 100-300 µm between May and September 2015 and showed no hypersensitivity symptoms.

Owing to disease progression (enlargement of the liver nodules and emergence of new liver foci and pulmonary nodules), treatment was initiated 2 months later with aflibercept in combination with FOLFIRI (irinotecan, calcium levofolinate, and 46-hour 5-fluorouracil in a continuous infusion). In the first cycle, during the administration of irinotecan alone, the patient presented lingual angioedema, generalized urticaria, desaturation, and blurred vision that lasted 6 hours and required various doses of corticosteroids, systemic antihistamines, and oxygen. Given the severity of the reaction, calcium levofolinate and 5-fluorouracil were discontinued. Before the diagnosis of allergy to irinotecan, the patient had received aflibercept, calcium levofolinate, and 5-fluorouracil without symptoms.

The patient was assessed in the allergy department, where skin tests with irinotecan were performed at the concentrations described by Alvarez-Cuesta et al [3]: prick test, 20 mg/mL; and intradermal tests, 2 mg/mL and 20 mg/mL. The result was positive with the 20-mg/mL intradermal test. Drugs for prick and intradermal tests were prepared by the cytotoxic unit of the pharmacy department.

Drug desensitization was programmed using a 12-step protocol adapted from Castells et al [4], which enabled a cumulative dose of 336.4 mg of irinotecan to be administered (Table). Pretreatment was with oral acetylsalicylic acid 500 mg (instead of 325 mg, because of commercial availability) and oral montelukast 10 mg at 48 hours and 24 hours before and on the day of desensitization. The other drugs in the patient's protocol (aflibercept 296 mg, fosaprepitant 150 mg, dexamethasone 12 mg, ondansetron 8 mg, atropine 0.5 mg, calcium levofolinate 373.8 mg, and 5-fluorouracil 4486 mg) were administered following the order, dose, and rate of the oncology department's routine administration protocol. Solutions were prepared by the cytotoxic unit and then administered at the bedside by a specialized nurse from the allergy department. An allergologist experienced in desensitization was present throughout the infusion in the outpatient center.

Desensitization was successful and the patient did not experience a reaction during the infusion or during the following hours. Subsequent cycles were scheduled according to the original desensitization protocol.

We report a successful and rapid protocol for desensitization to irinotecan in a patient who became sensitized to it during

Table. Irinotecan Desensitization Protocol

	Solution Volume		Solution Concentration	Total Dose in Each Solution		
Solution A	500.17 mL		0.007 mg/mL	3.4 mg		
Solution B	501.68 mL		0.067 mg/mL	33.6 mg		
Solution C	516.67 mL		0.645 mg/mL	333.4 mg		
Step	Solution	Rate, mL/h	Time, Min	Volume Administered, mL	Dose Administered, mg	Cumulative Dose Infused, mg
1	A	6	15	1.50	0.010	0.010
2	A	11	15	2.75	0.019	0.029
3	A	23	15	5.75	0.039	0.068
4	A	45	15	11.25	0.076	0.144
5	B	11	15	2.75	0.184	0.329
6	B	23	15	5.75	0.385	0.714
7	B	45	15	11.25	0.753	1.467
8	B	90	15	22.50	1.507	2.974
9	C	23	15	5.75	3.710	6.684
10	C	45	15	11.25	7.259	13.944
11	C	90	15	22.50	14.519	28.463
12	C	180	159.1	477.17	307.937	336.400
Total infusion time:		324 min				

Volume of each solution administered: solution A,21.25 mL;solution B, 42.25 mL; and solution C, 516.67 mL.
Solutions were prepared in the cytotoxicity unit of the pharmacy department. The tubing of each bag is primed with the antineoplastic drug in the pharmacy and connected to a running saline line in close proximity to the patient, thus enabling delivery of small volumes during the initial steps of the desensitization protocol.
The protocol was adapted from Castells et al [4]. Irinotecan is always diluted in 500 mL in our hospital, instead of 250 mL, as per the original protocol, and the infusion rate is adapted to that change. No diluent is removed when a solution is prepared owing to our local safety requirements: the amounts added are 0.17 mL of 20 mg/mL irinotecan (commercial concentration, total volume, 500.17 mL) in solution A, 1.68 mL (total volume, 501.68 mL) in solution B, and 16.67 mL (total volume, 516.67 mL) in solution C.

intra-arterial chemoembolization of liver metastases. The patient experienced a severe HSR to during the first intravenous dose of irinotecan, which was administered 2 months after the last chemoembolization session. We found only 1 other recent case report of desensitization to the drug, although the protocol used differed from ours, especially in terms of premedication [5]: the regimen administered the night before admission comprised intravenous dexamethasone 12 mg, oral fexofenadine 180 mg, and oral cimetidine 400 mg; the regimen administered 2 hours before the procedure comprised intravenous dexamethasone 20 mg, oral promethazine 50 mg, oral fexofenadine 180 mg, and intravenous ranitidine 50 mg.

HSRs are unpredictable, can affect any organ or system, and range widely in clinical severity from mild pruritus to anaphylaxis. In the field of oncology, they have been described with many drugs, and their frequency has been reported to be 5%-27% for platins, 10%-30% for taxanes, and 0.6%-10% for specific monoclonal antibodies [6]. In the study of Alvarez-Cuesta et al [3], irinotecan was the suspected culprit drug in 11 of the 186 patients (5.9%) referred for desensitization over a 3-year period (data confirmed HSR to irinotecan, although the characteristics of the reactions are not provided in the article).

Drug desensitization induces a temporary state of tolerance to the drug responsible for a specific HSR [2]. The 12-step protocol (3 bags) described by Castells et al [6] is the most frequently used, although other protocols should be considered in patients with severe HSRs and anaphylactic reactions [6]. Pretreatment was with oral acetylsalicylic acid 500 mg and oral montelukast 10 mg at 48 hours and 24 hours before and on the day of desensitization. In our department, we use systematic premedication with acetylsalicylic acid and montelukast to improve tolerability of the desensitization protocol [6,7]. We do not use systematic premedication with antihistamines or corticosteroids; these drugs are only used in patients who develop repeated reactions during previous desensitization protocols.

In conclusion, rapid desensitization is a promising method for the delivery of antineoplastic drugs, monoclonal

antibodies, antibiotics, and other drugs after HSRs and should be considered when no acceptable therapeutic alternatives are available.

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Conflicts of Interest

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Hypersensitivity to Quail Egg Proteins: What About Hen Egg?

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Food allergy is a major problem in society today. Since it is consumed throughout the world, hen's egg (HE) is the most common type of egg allergy.

The main HE allergens are proteins from the white, namely, ovalbumin (Gal d 2 [OVA_h]), ovotransferrin (Gal d 3 [OVT_h]), lysozyme (Gal d 4 [LYS_h]), and ovomucoid (Gal d 1 [OVM_h]).

Allergy to egg from other species, especially quail's egg (QE), in patients who tolerate HE is much less frequent, although some cases have been reported [1-3].

The objectives of the present study were to identify the causative allergen in a group of patients with hypersensitivity to QE who tolerate HE and to describe the pattern of hypersensitivity to HE in this group.

We studied 5 patients (4 females and 1 male), with a mean age of 25 years (range, 10-36 years). Symptoms induced by undercooked QE (inclusion criteria) included angioedema (1 patient) and anaphylaxis (4 patients). All patients were atopic. Prior to the anaphylactic reaction, all patients had tolerated QE and HE (at different degrees of cooking), as well as chicken, turkey, and quail meat. After the reaction, all 5 patients tolerated cooked and undercooked HE, and 4 patients tolerated quail, turkey, and chicken meat. The remaining patient has not eaten quail meat since then, but he tolerates turkey and chicken meat.

Informed consent was obtained in all cases. The study was approved by the local ethics committee.

Skin prick-by-prick tests (SPPT) were performed with cooked and uncooked yolk and white from QE. Skin prick tests (SPT) were performed with commercial extracts of common inhalant allergens, OVA_h, OVM_h, OVT_h, LYS_h, and HE yolk and white (Bial-Aristegui, Leti, and ALK-Abelló). The results of the tests are shown in the Table.

Serum total and specific IgE levels against yolk and white from HE and against Gal d 1, 2, and 3 were measured using

Table. Results of SPT, SPPT, and IgE Testing

	Patient 1			Patient 2			Patient 3			Patient 4			Patient 5		
	SPT	SPPT	IgE, kU_A/L	SPT	SPPT	IgE, kU_A/L	SPT	SPPT	IgE, kU_A/L	SPT	SPPT	IgE, kU_A/L	SPT	SPPT	IgE, kU_A/L
QEW	-	P (uncooked) P (cooked)	0.4	P	P (uncooked) N (cooked)	9.7		P (uncooked) N (cooked)	1.0	-	P (uncooked) P (cooked)	4.3	-	P (uncooked) P (cooked)	15.9
QEY	-	P (uncooked) P (cooked)	0.5	P	P (uncooked) N (cooked)	0.7		P (uncooked) N (cooked)	0.7	-	P (uncooked) P (cooked)	4.5	-	P (uncooked) N (cooked)	16.3
HEW	N		<0.35	P		2.1	P		0.5	P		0.4	N		0.84
HEY	N		<0.35	N		<0.35	N		<0.35	N		<0.35	N		<0.35
OVA_h	N		<0.35	P		2.59	P		0.7	P		<0.35	N		0.89
OVM_h	N		<0.35	N		<0.35	P		<0.35	N		<0.35	N		4.38
LYS_h	N		<0.35			-	-		<0.35	N		<0.35	-		-
OVT_h	-		<0.35			<0.35	-		<0.35	N		-	-		-
MS	42 kDa (OVA_q)			42 kDa (OVA_q)			42 kDa (OVA_q)			42 kDa (OVA_q)/ 35 kDa (OVM_q)			42 kDa (OVA_q)/ 35 kDa (OVM_q)		
SYM	Anaphylaxis			Angioedemia			Anaphylaxis			Anaphylaxis			Anaphylaxis		

Abbreviations. HEW, hen egg white; HEY, hen egg yolk; LYS_h, hen lysozyme; MS, mass spectrometry; N, negative; OVA_h, hen ovalbumin; OVA_q, quail ovalbumin; OVM_h, hen ovomucoid; OVM_q, quail ovomucoid; OVT_h, hen ovotransferrin; P, positive; QEW, quail egg white; QEY, quail egg yolk; SPT, skin prick test; SPPT, skin prick-by-prick test; SYM, symptoms.

ImmunoCAP (Thermo Fisher Scientific) according to the manufacturer's instructions. Specific IgE from QE white and yolk was determined using EAST; the solid phase was obtained by coupling the extract solution (10 mg/mL) to 6-mm cyanogen bromide–activated paper discs, as described by Ceska and Lunqvist [4]. The results were expressed in accordance with the manufacturer's instructions for the CAP assay (HYTEC Specific IgE EIA kit) and EAST (HYCOR Biomedical Ltd). Values ≥0.1 and ≥0.35 kU_A/L were considered positive for EAST and CAP, respectively (Table).

QE white and yolk extracts were analyzed using SDS-PAGE, and immunoblotting was performed using the patient's serum, which was incubated overnight and revealed with a second antibody antihuman IgE, as previously described [5].

The result of IgE-immunoblotting with QE white and yolk extracts showed the same IgE-binding profile, although this was much more intense in white than in yolk (data not shown). Two main IgE binding bands were detected: a 42-kDa band, which was revealed in all the assayed sera, and a 35-kDa band, which was detected in 2 sera. In addition, a band of about 97 kDa was detected in patients 3 and 4.

Proteins were identified at the Proteomics Department of the Universidad Complutense de Madrid, a member of the ProteoRed Network.

The 42-kDa and 35-kDa IgE-binding bands were identified and proved to be ovalbumin and ovomucoid from QE (OVA_q, OVM_q), respectively. The molecular weight of OVM_h is about 30 kDa; that of OVMq in a standard 12.5% SDS-PAGE electrophoresis gel is slightly higher [6].

The 97-kDa binding protein was identified as ovotransferrin.

We present 5 cases of hypersensitivity to QE in patients who tolerated HE. As reported by other authors [7], the proteins from different types of egg whites can present cross-reactivity, especially if their phylogenetic homology is high. Since both quail and hen belong to the Galliforme order, their proteins present high homology. In fact, although all patients tolerated cooked and uncooked HE, 3 of the 5 patients were sensitized to OVA_h (most likely by cross-reaction), as deduced from positive SPT and specific IgE results.

All the patients' sera had specific IgE against OVA_q (heat-sensitive), thus explaining why the allergic reaction occurred with undercooked QE (fried, omelette) in all patients. In addition, sera from patients 4 and 5 revealed OVM_q in the immunoblotting assay; the SPPT result to cooked QE white was also positive. In patient 1, the SPPT was performed with QE omelette, whose cooked level is difficult to establish; consequently, the positive SPPT result to QE white, despite being caused by OVM_q, was not observed. Patients whose serum did not reveal OVM_q did not manifest milder reactions than the others.

Only 1 patient had a positive SPT result with OVM_h, and 1 had positive IgE against OVM_h, possibly because of cross-reactive carbohydrate-determining reagents.

Other discrepancies between SPT and ImmunoCAP are probably linked to the difficulties associated with extract standardization: OVM_h in SPT extracts is not as purified as in those used for ImmunoCAP.

All the patients had a positive SPPT result to QE yolk, although no major QE yolk proteins were revealed in the QE

immunoblotting assay. In addition, after the allergic reaction, all patients tolerated poultry meat, indicating that α-livetin (quail albumin) was not involved in any of these cases.

The difficulty in obtaining a QE yolk sample without QE white contamination, as reported elsewhere [7], could explain the positive results for QE yolk in the SPPT and immunoblotting assay.

Although allergy to QE—with or without HE sensitivity—has been reported [2,3,8,9], ours is the first case series in which the causative proteins were identified.

We found only 1 case of non–IgE-mediated food hypersensitivity reaction to QE [10].

In conclusion, in the 5 patients we report, the main QE allergen is ovalbumin. Although proteins from HE and QE showed cross-reactivity, patients commonly tolerate HE consumption even when they have QE allergy. Since patients with QE allergy can show different HE skin test results (positive SPT and/or SSPT and/or specific IgE to HE proteins, with good tolerance to HE), these results should not be used to predict intolerance to HE.

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Is Vitamin D Deficiency a Marker of Severity of Wheezing in Children? A Cross-sectional Study

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Wheezing is a common complaint in pediatric emergency departments, especially in developing countries [1]. The relationship between wheezing in childhood and subsequent development of asthma remains unclear. Individual genetic and immunological factors, environmental factors, lifestyle, dietary habits, and deficiencies of vitamins such as vitamin D (VitD) have been associated with the development of wheezing/asthma [2].

The association between serum VitD levels and various diseases, including asthma, has been extensively studied. However, the results for asthma are controversial [3].

We studied the relationship between serum VitD levels and wheezing in children treated at the Pediatric Program for the Prevention of Asthma (PIPA), Uruguayana, Brazil [4].

All children (3-47 months; n=370) with occasional wheezing (OW; up to 2 episodes of wheezing in the previous year, n=115) and recurrent wheezing (RW; ≥3 wheezing episodes in the previous year, n=255) referred to PIPA (from March 2012 to March 2013; outpatients) were enrolled in this cross-sectional study. Children with other chronic diseases, genetic syndromes, and/or birth defects were not included. At admission, the patient's parents and/or guardians completed a standardized written questionnaire (International Study of Wheezing in Infants; EISL) consisting of 45 questions about demographic characteristics, wheezing and risk factors, as well as the severity of wheezing [5]. RW patients were classified according to the number of episodes in the previous year as having had up to 6 episodes/year (n=150) or >6 episodes/year (n=105).

Peripheral blood samples were obtained from all patients for determination of total serum IgE using ImmunoCap (Thermo Scientific) and VitD levels using electrochemiluminescence. Patients were classified according to VitD level as having deficiency (<20 ng/mL [<50 nmol/L]), insufficiency (21-29 ng/mL [52.5-72.5 nmol/L]), and sufficiency (≥30 ng/mL [75 nmol/L]) [2].

In the initial statistical analysis, OW was compared with RW, and patients with <6 episodes/year were compared with those with ≥6 episodes/year (Table). Categorical variables (gender, visits to the emergency department, use of oral corticosteroids, severe wheezing, hospitalizations due to wheezing, hospitalizations due to pneumonia, and physician-diagnosed asthma) were analyzed using the chi-square or Fisher exact test. Continuous variables (age, weight, height, age at first episode, number of colds and age at first cold, serum VitD levels, total serum IgE levels) were analyzed using the *t* test (normal distribution) or Mann-Whitney test (nonnormal distribution). All analyses were performed with SPSS 18.0 (SPSS Inc), and statistical significance was set at $P<.05$. The study was approved by the local ethics committee, and all parents and/or guardians signed the informed consent.

The Table shows the main characteristics of the patients enrolled in the study. Both groups (OW and RW) were similar in gender, age, and current weight and height. None of the patients were receiving VitD supplements during the month before entering PIPA. RW children were younger at the first episode of wheezing and of upper respiratory tract infection, used oral corticosteroids more frequently than OW patients, and had a higher frequency of upper respiratory tract infection, nighttime awakenings, and hospitalization for wheezing or pneumonia.

These data are consistent with those previously observed in the EISL study [5], in which the analysis of risk factors associated with RW revealed that having a cold during the first 3 months of life indicated a 3-fold higher risk of RW [6]. Viral respiratory infections are considered a major cause of wheezing, particularly when they are recurrent. As observed in the patients we report, early onset of wheezing coincided with the first episode of viral respiratory infection, in addition to being an associated factor for the subsequent development of asthma [6]. A medical diagnosis of asthma was more frequent in RW patients, especially those with >6 episodes of wheezing in the previous year, than in OW patients.

The role of VitD in respiratory antiviral defense has been evaluated in several studies, with conflicting results. In our study, we observed significantly higher serum VitD levels in RW children, especially those with more severe forms, than in OW children and children with milder conditions. Although obvious, these results do not allow us to draw more conclusive findings about the relationship between VitD and wheezing/asthma for the patients in the present study owing to limitations affecting our study, namely, its retrospective design, lack of control with respect to breastfeeding, individual family atopic status, and time of and age at collection of blood samples. Therefore, we were unable to determine the causal connection between VitD and the development of wheezing and/or asthma. In addition, we provide no information about the mother's prenatal VitD levels or on VitD supplements before or during pregnancy. Likewise, we provide no information on the influence of confounders related to maternal diet, socioeconomic factors, lifestyle, or epigenetic changes caused by the environment to which the mothers were exposed [7].

It is important to stress that for a given population, the many factors that can modify the effect of variations in VitD concentrations in children include season, sun exposure, socioeconomic status, ethnicity, age, gender, dietary habits, interaction with other vitamins and trace elements, prenatal

Table. Children With Occasional Wheezing (≤2 Episodes of Wheezing; OW) or Recurrent Wheezing (≥3 Episodes) According to Main Clinical Characteristics and Serum Vitamin D (VitD) and Total IgE Levels: Univariate Analysis

	Recurrent Wheezing					
Characteristic	OW (N=115)	Total (N=255)	*P* Value OR (95%CI)	≤6 episodes n=150	>6 episodes n=105	*P* Value OR (95%CI)
Males, No. (%)	59 (51.3)	145 (56.9)	0.906 0.97 (0.62-1.54)	87 (58.0)	58 (55.2)	0.700 1.05 (0.84-1.31)
Mean (SD) age, mo[a]	18.5 (13.5)	17.6 (12.6)	.788	17.9 (12.9)	17.2 (12.1)[b]	<.0001
Mean (SD) weight, kg[a]	11.4 (4.4)	10.8 (3.5)	.304	11.0 (3.7)	10.5 (3.2)	.349
Mean (SD) height, cm[a]	78.1 (15.4)	77.8 (14.1)	.793	78.5 (14.1)	76.8 (14.1)	.456
Mean (SD) age at first episode, mo[c]	5.3 (4.1)	3.9 (3.0)[b]	.007	4.3 (3.0)	3.3 (3.1)[b]	.005
Mean (SD) number of colds[c]	3.4 (2.0)[b]	4.4 (2.9)	.0001	3.8 (2.2)b	5.3 (3.6)	<.0001
Mean (SD) age at first cold, mo[c]	4.2 (3.1)	3.4 (2.8)[b]	.033	3.6 (2.9)	3.0 (2.6)[b]	.017
Night awakenings/wk, No. (%)[c,d]	82 (71.3)[b]	226 (88.6)	.015 0.46 (0.25-0.84)	127 (84.7)	97 (92.4)	.09 0.46 (0.20-1.06)
Visits to emergency department, No. (%)[e]	76 (66.0)	189 (74.1)	.835 0.91 (0.55-1.53)	105 (70.0)[b]	84 (80.0)	.049 0.53 (0.30-0.94)
Oral corticosteroids, No. (%)[e]	51 (44.3)[b]	147 (57.6)	.018 0.59 (0.38-0.91)	79 (52.7)	68 (64.8)	.07 0.61 (0.36-1.01)
Severe wheezing, No. (%)[e]	88 (76.5)	223 (87.5)	.445 0.74 (0.39-1.40)	131 (87.3)	92 (87.6)	.601 0.77 (0.37-1.59)
Wheezing – hospitalization, No. (%)[e]	12 (10.4)[b]	53 (20.8)	.05 0.49 (0.26-0.96)	30 (20.0)	23 (21.9)	.731 0.86 (0.46-1.58)
Pneumonia – hospitalization, No. (%)[e]	10 (8.7)	44 (17.3)	.082 0.50 (0.24-1.05)	22 (14.7)	23 (21.9)	.148 0.59 (0.31-1.13)
Physician-diagnosed asthma[e]	24 (20.9)[b]	87 (34.1)	.048 0.58 (0.34-0.96)	41 (27.3)[b]	44 (41.9)	.013 0.50 (0.29-0.84)
Mean (SD) VitD serum levels, ng/mL[c]	18.7 (4.9)[b]	37.3 (10.9)	<.001	35.1 (9.7)[b]	39.6 (9.0)	<.001
Mean (SD) total serum IgE levels, IU/L)	178.4 (369.9)[b]	209.6 (347.8)	.007	242.8 (373.0)	164.4 (303.1)	0.126

[a]*t* test.
[b]Significantly lower than the other group.
[c]Mann-Whitney.
[d]Percentage of children who presented ≥1 awakening during any week of the year.
[e]Chi-square/Fisher exact.

and postnatal tobacco exposure, type of delivery, maternal educational level, exposure to paracetamol, and viral infections during the first year of life [8].

Although many studies have focused on the relationship between high serum VitD levels and reduced risk of asthma exacerbations, evidence of an association with the incidence, prevalence, or severity of asthma is scarce.

We observed higher levels of total IgE among RW children, although these were not associated with the frequency of episodes, and found that they were parallel to serum VitD levels. However, high levels of serum IgE were recently reported to be a risk factor for severe asthma in a report stressing the relationship between serum levels of VitD, IgE, and inflammatory T cytokines [10]. The authors postulated that the relationship was U-shaped, ie, both high and low serum VitD levels of were associated with high levels of IgE and a similar immune response [10]. This relationship may explain our findings.

In conclusion, we observed earlier onset and higher severity of wheezing among RW children followed at PIPA than among OW children. We also observed high levels of VitD and total serum IgE. Further cohort studies are necessary to establish a cause-effect relationship.

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Conflicts of Interest

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Psychometric Validation of the Spanish Version of the DHRQoL Questionnaire

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Key words: Drug allergy. Health-related quality of life. Psychometric validation. Questionnaire. Adverse drug reactions.

Palabras clave: Alergia a medicamentos. Calidad de vida relacionada con la salud. Validación psicométrica. Cuestionario. Reacciones adversas a medicamentos.

Drug allergy is a very common condition faced by both primary care physicians [1] and hospital physicians [2] worldwide. Drug allergy is further complicated by the underlying disease, which frequently prevents the use of the usual first-line treatments. Furthermore, allergists know that patients who have experienced an allergic drug reaction, especially those who have had a severe reaction, are increasingly fearful of new allergic reactions and therefore tend to avoid taking any type of medication. In a previous study [3], we validated the Spanish version of the Drug Hypersensitivity Quality of Life (DHRQoL) questionnaire, which was developed in Italy by Baiardini et al [4]. In the present paper, we report the results of our psychometric validation of the questionnaire.

A total of 30 consecutive patients were admitted to the Allergology Service of Bellvitge Hospital, L'Hospitalet de Llobregat, Barcelona, Spain from February to April 2015. Each patient was asked to fill in the DHRQoL questionnaire on 2 occasions separated by a 5-hour interval. No allergy tests were carried out during the interval, and no information that could have influenced the patient's answers to the questionnaire was provided.

The Cronbach α (0 to 1) was used to determine the questionnaire's internal consistency [5]. A factor analysis was also carried out to determine whether 1 or several dimensions could be measured by the questionnaire. Quartimax rotation was used because the existence of a general factor was suspected [4].

Moreover, the Lin correlation coefficient (CC) was used to measure the degree of consistency between the answers to both questionnaires (baseline and retest). A figure was also created following the Bland-Altman plot in order to determine concordance between the questions at 2 different points (baseline and retest).

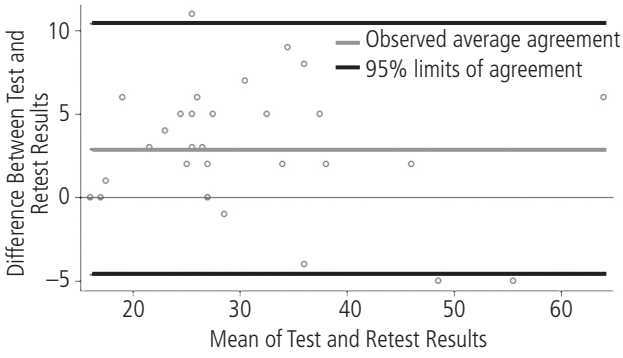
Of the 30 patients who completed the DHRQoL questionnaire, 20 also completed the Psychological General Well-being Index (PGWBI) questionnaire, which consists of 22 items grouped in 6 dimensions: anxiety, depressed mood, positive well-being, self-control, general health, and vitality [6].

The Spearman correlation coefficient was used to analyze the correlation between the DHRQoL and the dimensions of the PGWBI.

The study population comprised 30 patients, 20 of whom were women, with a mean (SD) age of 45 (15.5) years. The median (IQR) time since the allergic reaction was 6 months (3-60 months).

Five of the 30 patients (17%) had experienced an anaphylactic reaction, 14 (47%) had developed urticaria, and the rest (36%) had experienced other types of reactions. The allergist's suspicions before performing the allergy test, combined with the information from each patient's medical history, indicated that 14 patients (47%) may have experienced a drug allergy and that in the remaining 16 patients, the reaction was not a true allergic reaction.

The global result of the baseline DHRQoL questionnaire in all patients was a median (IQR) score of 29 (27-39) and that of the retest questionnaire was a median score of 27 (22-33). Patients with anaphylaxis obtained a median score of 30 (27-35), and those who had not experienced an anaphylactic reaction obtained a median score of 28 (27-39). Furthermore, patients who were suspected of having had a real allergic reaction obtained a median score of 28 (26-35), whereas those in which an allergic reaction was not suspected obtained a median score of 30 (28-43).



y=0 is line of perfect average agreement

The line commencing at zero indicates the expected values (the same in both tests), and the thicker gray line indicates the result obtained from the difference, with a mean value of 2.9 (3.8) points. The agreed minimum and maximum limits were –4.6 and 10.6, respectively.

Figure. Bland-Altman concordance analysis of the difference between both consecutive questionnaires completed by each patient and the mean score of both tests for each patient.

The global CC was 0.911 (95%CI, 0.852-0.970). The question with the greatest concordance was number 13 (CC, 0.919; 95%CI, 0.863-0.975), and that with the lowest concordance was number 7 (CC, 0.575; 95%CI, 0.335-0.815).

The Figure shows the results of the Bland-Altman concordance analysis. The mean difference between the initial test and the retest was 2.9 (3.8) points. Three patients fell outside the expected limits of ±2 SD (–4.6 to 10.4).

Based on the Cronbach α, the questionnaire's global internal consistency was 0.916. Question 3 had the greatest influence (Cronbach α without this question, 0.905), although high internal consistency was observed in general.

The factor analysis carried out with quartimax rotation revealed 3 dimensions: one included all questions except numbers 2 and 9; another included questions 2, 5, 9, and 10; and a third dimension included questions 1, 4, and 7.

A poor correlation was observed between the results of both questionnaires (Spearman ρ, –0.279; *P*=.234). Analysis of the correlation between the DHRQoL questionnaire and the 6 dimensions of the PGWBI questionnaire revealed a negative and statistically significant correlation for the depressed mood dimension (ρ, –0.531; *P*=.016).

This study confirms that the DHRQoL questionnaire has marked internal consistency (Cronbach α, 0.916), which is very similar to that obtained by Baiardini et al [4] (0.928) [4]. Additionally, the test-retest analysis revealed a high degree of concordance, as in the case of the original study carried out to develop the questionnaire [4].

Our factor analysis revealed 3 dimensions. One included all questions except question 2, which is consistent with the data reported by Baiardini et al [4], who studied the questionnaire as a whole. The other 2 dimensions analyzed patients' fear of receiving medications (questions 2, 5, 9, and 10) and the limitations that a possible drug allergy entails for them (questions 1, 4, and 7). These dimensions must be confirmed by means of a confirmatory factor analysis.

The comparison of the results of the DHRQoL and PGWBI questionnaires revealed a negative—albeit not statistically significant—correlation with the depressed mood dimension. This finding differs from that reported by Baiardini et al [4], whose study did not establish a correlation between the DHRQoL questionnaire and any of the PGWBI dimensions.

In conclusion, we confirmed that the DHRQoL questionnaire has the psychometric validity required for a questionnaire developed following appropriate methodology, as in the case of its original Italian version. In the future, it would be of great interest to carry out additional studies to determine to what extent an allergic drug reaction affects the quality of life of the patient who experiences it. It would also be interesting to determine whether the questionnaire's results depend on the type of drug, the severity of the allergic reaction, or other factors.

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Conflicts of Interest

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A Protocol for Induction of Tolerance to Apomorphine in Patients With Parkinson Disease and Hypersensitivity to Apomorphine

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Palabras clave: Apomorfina. Enfermedad de Parkinson. Hipersensibilidad. Desensibilización. Protocolo de inducción de tolerancia.

Apomorphine, a short-acting dopamine D1 and D2 receptor agonist, was the first dopamine receptor agonist used to treat Parkinson disease. Subcutaneous apomorphine is currently used for the management of sudden, unexpected, and refractory levodopa-induced off-states in fluctuating Parkinson disease, either as intermittent rescue injections or continuous infusions [1-3]. Some of the most frequent adverse effects of long-term apomorphine therapy are orthostatic hypotension, nausea, fibrotic nodules at the site of infusion, and sedation [3]. Cutaneous nodules observed in patients with Parkinson disease treated with continuous subcutaneous apomorphine are sometimes characterized by florid eosinophilic panniculitis; however, patch testing is universally negative, and the IgE levels are normal [4]. Delayed hypersensitivity reactions with positive patch test results [5-7] and immediate hypersensitivity reactions have been reported [8].

We present a protocol for induction of tolerance to apomorphine in 2 patients who experienced generalized urticarial reactions to the drug. The first patient (reported elsewhere [8]) was a 56-year-old man with uncontrolled Parkinson disease. Apomorphine injections were administered intermittently via pen over 6 months as rescue therapy for sudden off periods. This regimen was followed by continuous infusion at a rate of 1 mg/h and then increased according to the patient's response. The drug was administered continuously for an additional month via an apomorphine pump with an infusion rate of 2.5 mg/h for 12 hours per day while the patient was awake, stopping at night. The patient developed raised itchy wheals on the underarms, groin, chest, lower back, and buttocks approximately 20 minutes after he reached the cumulative dose of 4 mg apomorphine administered at 2.5 mg/h [8]. The second patient was a 58-year-old man with Parkinson disease treated with continuous infusion of apomorphine for motor fluctuations and dyskinesia. His infusion was programmed based on a 12-hour regimen; however, after the first month of therapy, he experienced progressive generalized itchy wheals when the infusion rate was 3 mg/h. Apomorphine was stopped, and the cutaneous symptoms improved, although Parkinson disease worsened. The patient also had allergic rhinitis due to mite sensitization. He had tolerated tramadol. Neither patient had a history of idiopathic or nonsteroidal anti-inflammatory drug–related anaphylactic reactions or life-threatening vascular collapse. Neither had previously experienced urticaria or angioedema. The patients were not taking antihypertensive medication (angiotensin-converting enzyme inhibitors, ß-blockers, or angiotensin receptor blockers). Apomorphine was considered essential for treatment in both patients.

Allergic-like reactions with apomorphine are rare; therefore, we wanted to record as much information as possible in order to design a desensitization protocol. As we had previously reported [8], patch, prick, intradermal, and challenge testing were considered necessary to collect this information. We performed skin prick tests with apomorphine 10 mg/mL and intradermal tests with diluted apomorphine at concentrations of 0.001 mg/mL, 0.01 mg/mL, and 0.1 mg/mL. An intradermal test at a dilution of 0.1 mg/mL resulted in a 6-mm wheal in the first patient, as previously reported [8]. A negative response was detected in the second patient and 14 controls (6 atopic and 8 nonatopic). Patch testing was performed with apomorphine diluted in water to 50%, 5%, and 1% and in petrolatum 5% and 1%. The results of patch testing with apomorphine were negative in both patients. A single-blind, placebo-controlled challenge test was performed with subcutaneous apomorphine. Symptoms reappeared in both patients. In the first patient, apomorphine produced a positive response after approximately 20 minutes [8]. The second patient experienced urticaria and angioedema 30 minutes after receiving 7 mg of apomorphine and was treated with 5 mg of intravenous dexchlorpheniramine maleate and 30 mg of oral deflazacort. As the commercial preparation of apomorphine contains 0.093% sodium bisulfite, the patients underwent a double-blind, placebo-controlled challenge with sodium metabisulfite, and the results were negative. Although skin testing was negative in the second patient, hypersensitivity to apomorphine was diagnosed taking into account the clinical presentation and reproducibility of the reaction upon reexposure.

A tolerance induction protocol was designed with increasing concentrations of apomorphine (0.03 mg/mL to 10 mg/mL) (Table). The route of administration was subcutaneous, and each dose was administered intermittently. The patients were premedicated with 10 mg of cetirizine 1 hour before starting the protocol. The initial dose was 0.003 mg of apomorphine, and intermittent subcutaneous doses were increased every 15 minutes. The target dose was 3 mg (cumulative dose 4.998 mg of apomorphine). During the third step, the first patient experienced mild pruritus, which resolved with intravenous dexchlorpheniramine maleate (Table). At the end of the procedure, subcutaneous apomorphine infusion was initially continued at 1 mg/h and increased by 0.5 mg/h every 4 hours depending on the patient's response. The first patient continued at 2.5 mg/h for 12 hours per day (no infusion at night) and was completely able to tolerate apomorphine. The second patient continued at 3 mg/h for 12 hours per day (no infusion at night), with complete tolerance of apomorphine.

Table. Tolerance Induction Protocol for Subcutaneous Apomorphine

Step[a]	Solution, mg/mL	Amount, mL	Dose, mg	Cumulative Dose, mg	Findings Patient 1	Findings Patient 2
1	0.03	0.1	0.003	0.003	None	None
2	0.03	0.5	0.015	0.018	None	None
3	0.3	0.1	0.03	0.048	Mild pruritus[b]	None
4	0.3	0.5	0.15	0.198	None	None
5	3	0.1	0.3	0.498	None	None
6	3	0.5	1.5	1.998	Mild dyskinesia	None
7	10	0.3	3	4.998	None	None

[a]Each step was 15 minutes.
[b]Treated with intravenous dexchlorpheniramine 5 mg.

Both patients tolerated continuous subcutaneous apomorphine for more than 12 months after completion of the protocol.

We report 2 cases of hypersensitivity reactions after administration of apomorphine and present the results of a rapid protocol for induction of tolerance to this drug. To our knowledge, no cases of desensitization or induction of tolerance to apomorphine have been reported to date. The cumulative therapeutic dose was reached in 2 hours, and the protocol was completed successfully. The protocol was administered because no alternative treatments were available for Parkinson disease in these cases. The patients responded well to the desensitization procedure and completed the protocol safely.

Apomorphine can cause drug-related reactions, but the exact etiology of these events remains unclear. Both patients in the present report were successfully desensitized to apomorphine. In the first [8], the underlying cause seemed to be an IgE-mediated mechanism; in the second, it was not possible to define the underlying mechanism. However, hypersensitivity to apomorphine was also diagnosed taking into account the clinical presentation and challenge test result.

The desensitization protocol, which was considered an induction tolerance protocol in the second case, worked well in both patients. Therefore, it can be recommended for other cases of adverse reactions to apomorphine.

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Conflicts of Interest

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Aquagenic Urticaria: Report of a Case in an Adolescent Girl

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Key words: Aquagenic urticaria, adolescent, antihistamines, physical urticaria.

Palabras clave: Urticaria acuagénica, adolescente, antihistamínicos, urticaria física.

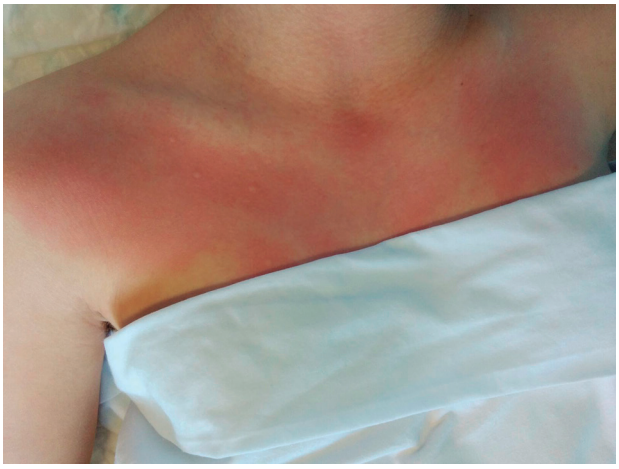

Figure. Wheal and flare reaction 20 minutes after applying a compress soaked in tap water at 35°C to the upper chest.

Aquagenic urticaria is a rare condition. Fewer than 50 cases have been published in the literature and most of these have been in the form of case reports [1]. The clinical picture is characterized by small wheals (1-3 mm), erythema, and intense pruritus occurring within 10 to 30 minutes of exposure to water, regardless of its temperature. The condition resolves within 30 to 60 minutes after the water is eliminated from the skin. Systemic manifestations are rare but have been reported [2]. We report the first case of aquagenic urticaria in a Spanish adolescent.

A 12-year-old girl presented with a 2-month history of erythema, pruritus, and small wheals that developed on her face, neck, and chest after contact with water (showering and diving into a pool). The symptoms appeared within 10 to 20 minutes of contact with water, regardless of temperature, and disappeared without medication in less than an hour.

She did not report angioedema, wheezing, or dyspnea during these episodes. There was also no history of urticaria with physical exercise, sweating, heat, or emotional stress. She tolerated exposure to cold temperatures. There was no present personal or family history of atopy, and none of the girl's relatives reported similar skin reactions related to water exposure.

The physical examination was unrevealing, and dermographism was negative. Additional studies, including a complete blood count and urine analysis, were normal. A water challenge test was performed by applying a compress soaked in tap water at 35°C on the upper chest. Within 20 minutes the patient reported pruritus and developed a micropapular eruption and erythema in the contact area (Figure), confirming the suspected diagnosis of aquagenic urticaria.

Short showers or baths were recommended, and we prescribed medical treatment with oral levocetirizine only for episodes of lasting or uncomfortable urticaria.

Aquagenic urticaria is an uncommon type of physical urticaria that usually appears during puberty or several years later and is more common in female patients [3-5]. Most cases are sporadic, although a small number of familial cases have been reported [6,7]. Its pathogenesis is not fully understood, although several mechanisms have been proposed. Shelley and Rawnsley [8], who described the first cases of aquagenic urticaria in 1964, postulated that water might interact with sebum in the stratum corneum to form a substance capable of acting as a direct mast cell degranulator, resulting in histamine release. Czarnetzki et al [9], in turn, hypothesized that a water soluble antigen at the epidermal layer might diffuse into the dermis, resulting in histamine release from mast cells. Recently, in vitro basophil activation by flow cytometry assay was detected after a water challenge test in a patient with aquagenic urticaria [10].

Cold urticaria and cholinergic urticaria are major considerations in the differential diagnoses for aquagenic urticaria. This condition must be distinguished from aquagenic pruritus, in which intense itching occurs after contact with water, but without visible skin lesions [1,6]. The standard test for aquagenic urticaria is the application of a water compress at 35ºC to the upper body for 30 minutes. Keeping the compress at room temperature avoids confusion with cold-induced or local heat urticaria [1].

Antihistamines are usually recommended to treat aquagenic urticaria, although response varies from one patient to the next. In refractory cases, UV radiation (psoralen-UV-A therapy or UV-B) alone or in combination with antihistamines, barrier methods to protect the skin from water, and even omalizumab, have been successfully used [1,5].

In the case of our patient, given the limited impact of symptoms on her life and their spontaneous resolution within minutes, we indicated symptomatic treatment with antihistamines only if skin lesions worsened.

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Conflicts of Interest

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Yogurt in the Treatment of β-Lactoglobulin–Induced Gastrointestinal Cow's Milk Allergy

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Palabras clave: Alergia a leche de vaca. Alergia gastrointestinal. Betalactoglobulina. Alergia mediada por IgE.

The prevalence of food allergy (FA) is around 3.5% in the general population and 5%-8% in children [1]. Cow's milk (CM) allergy is particularly noteworthy because of the role of this food in children's diet, especially when the child is not breastfed.

Anaphylaxis is the most severe allergic reaction to CM [2] and is currently treated with oral immunotherapy [3]. However, many patients are affected by gastrointestinal (GI) conditions only, including IgE-mediated [4] and non–IgE-mediated disorders [5], which are induced by food antigens with a marked clinical overlap between them [1]. The disorders include eosinophilic esophagitis, eosinophilic gastroenteritis [6], allergic proctocolitis [6], and food protein–induced enterocolitis syndrome [6]. The most common GI condition is immediate GI hypersensitivity, which involves IgE-mediated clinical manifestations that can occur within minutes (immediate reaction) in the upper GI tract or up to several hours later (delayed reaction) in the lower GI tract. Immediate GI hypersensitivity is usually considered a variant of anaphylaxis [7]. The aims of this study were to assess the follow-up of patients with GI allergy mediated by sIgE against β-lactoglobulin [7] after 6 months of dairy products (Group A) and to compare it with that of patients who did not undergo an intervention (Group B, only elimination of CM).

In our area (northern Tenerife, Spain), with 105 910 inhabitants aged <14 years, we selected 40 patients from our center (Infant Allergy Clinic [Northern Region], Tenerife, Spain) who experienced specific GI symptoms 30-120 minutes after intake of a glass of CM. The inclusion criteria also comprised serum specific IgE (sIgE) >0.1 kU_A/L to whole CM or some of the CM proteins such as casein (CAS) and the main whey proteins α-lactalbumin (ALA) and β-lactoglobulin (BLG).

The exclusion criteria included a clinical history of extraintestinal symptoms (cutaneous, ocular, respiratory, and/or cardiovascular) immediately after a glass of CM or sIgE <0.1 kU_A/L to CM, CAS, ALA, and BLG, as well as

Table. Levels of specific IgE in patients from both groups (first line). Levels of specific IgE in group A (second line) treated with daily yogurt and group B (third line) treated with total restriction of CM products at baseline (day 0) and after 6 months (6 mo). Data are expressed as mean specific IgE levels in each group

GI phenotype	Specific IgE							
Total patients N=40	CM n=32 1.36		BLG n=40 4.13		CAS n=28 1.12		ALA n=22 1.09	
Group A n=25	Day 0	6 mo	Day 0	6 mo	Day 0	6 mo	Day 0	6 mo
	1.35	1.2	6.51	4.7	1.51	0.52	0.76	0.50
Group B n=15	Day 0	6 mo	Day 0	6 mo	Day 0	6 mo	Day 0	6 mo
	1.06	1.55	3.38	5.88	1.29	3.98	1.53	1.8

Abbreviations: ALA, α-lactalbumin; BLG, β-lactoglobulin; CAS, casein; CM, cow's milk.

a diagnosis of celiac disease based on the presence of IgA antitransglutaminase antibodies (ELiA Immunocap 250, Phadia) and antideaminated gliadin antibodies (Quanta Lite Gliadin IgA II) and the results of a lactose intolerance inhalation test.

Skin prick tests (SPTs) with commercial extracts (BIAL) were performed with whole CM (5 mg/mL), CAS (10 mg/mL), ALA (5 mg/mL), and BLG (1 mg/mL). The concentration of total immunoglobulin E and sIgE against whole CM, CAS, ALA, and BLG in serum was measured (ImmunoCAP, Phadia AB) based on a detection limit of 0.1 kU_A/L.

Children underwent an open food challenge (OFC) with CM at the hospital allergy unit under clinical observation by experienced personnel. All participants were observed for the 24 hours following the OFC at home by their parents, who could phone the allergy unit at any time. Patients with a positive OFC result were offered a new OFC with yogurt under the same conditions (Group A). Patients who refused the OFC with yogurt were assigned to an elimination diet. During the 6-month study period, participants in the elimination diet group (Group B), were kept on a CM-free diet, whereas those in the dairy products group (Group A) were exposed daily to yogurt. All patients and tutors gave their written informed consent. The protocol was approved by the Regional Ethics Committee (COLIVAC HUNSC P.I-35/11; 24/14).

The most prevalent symptom was abdominal cramps in 36 out of 40 patients (90%), followed by food refusal in 32 patients (80%), abdominal discomfort or distention in 30 patients (75%), diarrhea in 10 patients (25%), and constipation in 5 patients (12.5%).

SPT yielded positive results in only 14 patients (35%). The wheal was greater than 3 mm with CM in 12 patients, CAS in 4 patients, ALA in 6 patients, and BLG in 8 patients.

Specific IgE (sIgE) to whole CM was >0.10 kU_A/L (>0.1) in 32 patients and <0.1 kU_A/L (<0.1) in 8 patients. Mean (SD) sIgE against whole CM was 1.36 (3.34) kU_A/L. sIgE to CAS was >0.10 kU_A/L in 28 patients and <0.1 kU_A/L in 12 patients, with an average of 1.12 (3.21) kU_A/L. sIgE to ALA was >0.10 kU_A/L in 22 patients and 0.1 kU_A/L in 18 patients, with an average of 1.09 (2.45) kU_A/L. sIgE to BLG was >0.10 kU_A/L in 40 patients, with an average of 4.13 (8.30) kU_A/L. No patients had sIgE to BLG <0.1 kU_A/L (Table).

OFC with whole CM in patients in Group A (n=25) was positive, reproducing the initial symptoms of the previous clinical history. The results of OFC with yogurt in patients in Group A were all negative, with good tolerance. Parents/tutors agree that patients were able to take a daily yogurt for 6 months. No symptoms or reactions were recorded after 6 months, and all patients tolerated yogurt every day. Mean levels of sIgE to BLG decreased from 6.51 kU_A/L to 4.7 kU_A/L ($P<.05$). Levels of sIgE to CAS also decreased from 1.51 kU_A/L to 0.52 kU_A/L.

The results of OFC with whole CM in patients in Group B (n=15) were all positive, mimicking the symptoms in the previous clinical history. Parents/tutors reported that patients maintained a diet that eliminated CM and dairy products. After 6 months, no patients experienced symptoms or reactions, and mean levels of sIgE to BLG increased from 3.3 kU_A/L to 5.8 kU_A/L ($P<.05$). Similarly, levels of sIgE to CAS also increased from 1.29 kU_A/L to 3.98 kU_A/L ($P<.01$).

The possible prevalence of β-lactoglobulin–induced GI allergy has been reported to be around 11% in patients with CM allergy [7]. Since BLG is absent or very decreased in many yogurts [8], probably because of polymerization in tetramers of BLG [9], we proposed a 6-month yogurt-only diet after checking tolerance to CM in an OFC. After 6 months, tolerability was excellent in Group A, and levels of sIgE to BLG had decreased significantly. Moreover, sIgE to CAS also tended to decrease. In Group B, levels of sIgE to both BLG and CAS increased significantly. The significance of these trends should be investigated in more detail. In this report, we used yogurt with modified proteins to reduce sensitization to milk proteins, as previously described with casein [10] in this GI phenotype of CM allergy. Yogurt enabled only partial avoidance of cow's milk products. Further reports should evaluate our intervention in order to design a successful protocol, as in other allergy phenotypes.

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Conflicts of Interest

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Cross-reactivity in AED-Induced Severe Cutaneous Adverse Reaction: A Case Report

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Palabras clave: Antiepilépticos. Reactividad cruzada. Síndrome de Stevens-Johnson. Necrolisis epidérmica tóxica. Hipersensibilidad.

Aromatic antiepileptic drugs (AEDs), in particular carbamazepine, phenytoin, phenobarbital, and lamotrigine, are some of the most common medications associated with severe cutaneous adverse reactions, such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reactions with eosinophilia and systemic syndrome (DRESS). The reported incidence of SJS/TEN is 1.2 cases per million inhabitants per year. Cross-reactivity between these aromatic antiepileptic drugs is not uncommon [1]. A large-scale study investigating risk predictors of AED-induced rash found that one of the strongest predictors is a history of rash with another AED [2]. This finding is supported by another study showing a significant association between carbamazepine-, phenytoin-, and oxcarbazepine–induced hypersensitivity skin reactions and a previous history of AED-induced rash [3]. However, to the best of our knowledge, there has only been 1 previous case report, without HLA genotype testing, of cross-reactivity in AED-induced severe cutaneous adverse reactions [4]. We report a case of SJS induced by lamotrigine after a history of carbamazepine-induced SJS, and provide information on HLA genotyping results.

A 63-year-old Indian woman with a diagnosis of right-sided trigeminal neuralgia since 2002 presented with facial pain described as sharp and piercing that lasted approximately 3 to 4 minutes and was aggravated by chewing and moving of the jaw. Magnetic resonance imaging of the brain did not reveal any masses or aberrant vessels compressing the trigeminal nerve roots.

Carbamazepine 200 mg 3 times a day was prescribed and resulted in complete pain relief. Fourteen days later, the patient developed a generalized rash on the trunk and limbs and was diagnosed with carbamazepine-induced SJS. The rash regressed over a month. The algorithm of drug causality for epidermal necrolysis (ALDEN) score was 6. (Table). The patient was put on sodium valproate 200 mg twice a day but

Table. ALDEN (Algorithm of Drug Causality for Epidermal Necrolysis) Scores for Patient

Drug	Delay From Initial Drug Intake to Onset of Reaction; Index Day (Value)	Drug Present in Body on Index Day (value)	Prechallenge/ Rechallenge (Value)	Dechallenge (Value)	Type of Drug (Notoriety)	Other Cause	Final Score[a]
Carbamazepine	14 d (+3)	Drug withdrawn on day of rash (0)	No known previous exposure (0)	Drug stopped (0)	3	None	6
Lamotrigine	20 d (+3)	Drug withdrawn on day of rash (0)	Previous Stevens-Johnson syndrome induced by carbamazepine (2)	Drug stopped (0)	3	None	8

[a]Final score: <0, very unlikely; 0-1, unlikely; 2-3, possible; 4-5, probable; ≥6, very probable.

the adverse effects were intolerable. This drug was substituted with gabapentin 300 mg twice a day, to which baclofen 10 mg 3 times a day was later added.

Ten years later, with increased pain intensity despite increased gabapentin dosage, which caused drowsiness, the patient was started on lamotrigine 25 mg once a day for 1 week, titrated upwards at a rate of 25 mg per week. On day 20, while on lamotrigine 100 mg a day, she developed a second episode of SJS. The ALDEN score was 8 (Table). The patient was subsequently treated with pregabalin 300 mg and amitriptyline 12.5 mg daily and experienced no adverse effects.

HLA-A and B allele genotyping detected HLA-A*02:11 and A*24:17 and HLA-B*40:06 and B*51:06. These alleles have not been reported in association with AED-induced SJS/TEN.

Assessment of causality between the severe cutaneous adverse reaction and the AED was based on ALDEN scores, which, at 6 and higher, supported the causal relationship between the AEDs and SJS.

To our knowledge, cross-reactivity in AED-induced severe cutaneous adverse reactions, such as SJS, has only been reported once in the literature, by Aouam et al [4]. The causal relationship between carbamazepine and lamotrigine and the reaction reported in that case was confirmed with positive skin patch tests at the 48-hour reading. Patch tests were not performed in our case and the causality assessment was based only on ALDEN scores.

Although the incidence is low, there have been reports of cross-reactivity between AEDs and tricyclic antidepressants [5]. Seitz et al [6] observed recurrence of hypersensitivity syndrome in 5 of 36 patients on tricyclic antidepressants with a prior history of hypersensitivity to AEDs. The authors did not observe cross-reactivity between amitriptyline and aromatic AEDs, but caution should be taken when prescribing tricyclic antidepressants to patients with a prior history of hypersensitivity to aromatic AEDs.

Recent studies have reported an association between carbamazepine-induced SJS/TEN and the HLA-B*15:02 allele in populations from Southeast Asia [7,8]. A similar association was subsequently reported for phenytoin- and lamotrigine-induced SJS [7,9]. The findings of a large meta-analysis further implicated HLA-A*31:01 in SJS and generalized rash [10]. Neither of these alleles were detected in our patient.

Negative results for known HLA-alleles associated with AED-induced severe cutaneous adverse drug reactions, such as in our case, does not predict against cross-reactivity. Although these reactions are unpredictable, identification of predisposing risk factors prior to drug selection can reduce the probability of a hypersensitivity reaction. Patients with a history of severe cutaneous adverse reactions to aromatic AEDs such as carbamazepine, phenobarbital, phenytoin, and lamotrigine are best managed with newer AEDs with a lower risk of severe cutaneous adverse reactions.

This case showed cross-reactivity in aromatic AEDs that induced a severe cutaneous adverse drug reaction. Although HLA-genotyping helps to predict reactions, caution should be taken when prescribing alternative AEDs to patients with a previous history of AED-induced severe cutaneous adverse drug reactions, despite negative results for known HLA-alleles.

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Vitiligo Induced by Specific Immunotherapy With Grass Pollen: The Koebner Phenomenon

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Palabras clave: Polen de gramíneas. Fenómeno de Koebner. Inmunoterapia específica. Vitíligo.

Vitiligo is an autoimmune disease of unknown origin that affects approximately 1% of the world's population. It is characterized by local or generalized depigmentation of the skin and/or mucosal membranes [1]. One of the features that may help predict the course of disease and response to treatment is the Koebner phenomenon (KP), also known as the isomorphic response, which represents a basic principle in dermatology. This phenomenon was originally described by the German dermatologist, Heinrich Koebner, who observed the appearance of psoriasis lesions in areas of healthy skin in patients with psoriasis following local trauma, such as excoriations, tattoos, and horse bites [2]. The phenomenon has since been described in relation to other disorders such as vitiligo and lichen planus (true koebnerization) [3]. These posttraumatic lesions are clinically and histologically similar to those of the underlying disease. A recently developed method for the evaluation and classification of KP takes into account different factors such as the patient's clinical history (type 1 KP), physical examination findings (type 2 KP), and experimental induction of skin lesions (type 3 KP) [4]. Vitiligo has been shown to progress differently in the presence of KP, regardless of type, with a larger affected body surface, greater disease activity in the preceding 12 months, and a poorer response to treatment [1].

We present the case of a 42-year-old man, without autoimmune diseases or any other history of interest, who had been undergoing follow-up in the allergology unit since 2007 due to respiratory allergic disease (rhinoconjunctivitis and moderate persistent asthma secondary to grass pollen allergy) and oral allergy to fruits associated with profilin. The allergy study showed positive skin prick tests for grasses, *Cynodon dactylon*, olive, *Platanus acerifolia, Chenopodium album*, birch, ash tree, and profilin (ALK, Abelló, Madrid, Spain). Specific IgE (ImmunoCAP, Thermo Fisher) was determined for grasses (72.40 kU/L), olive (4.18 kU/L),

and the recombinant allergens of *Phleum pratense*: rPhl p 1 (18.20 kU/L), rPhl p 5 (62.40 kU/L), rPhl p 7 (polcalcin), and rPhl p 12 (Phleum p profilin) (6.50 kU/L).

Based on the above findings, the patient received specific allergen immunotherapy (AIT) via the subcutaneous route with Depigoid 100% Grasses group (*Dactylis glomerata, Festuca pratensis, Lolium perenne, Phleum pratense, Poa pratensis*) (Leti, Barcelona, Spain) administered perennially on a monthly basis for 4 years (2008-2012). The therapy resulted in an improvement in respiratory symptoms. The patient showed good tolerance of AIT over the 4 years of treatment, with no early or late local or systemic reactions. Two years after completion of the treatment, the patient was reviewed at our unit and explained that approximately 1 year after the end of AIT he started to develop hypopigmented point lesions on both arms, coinciding with the vaccine dose administration site (Figure). The lesions were more numerous on the right arm, where they merged to form larger hypopigmented areas. The patient explained that the treatment had been administered more often in the right arm, since he had undergone surgery of the left arm and preferred to be injected as little as possible in that arm. There were no other similar lesions elsewhere on the body.

The patient was evaluated in the dermatology department, where he was diagnosed with vitiligo and prescribed topical 0.1% tacrolimus; there had been no repigmentation of the lesions by the time we saw him at our unit. He refused the option of a biopsy because he did not want any more lesions on his arms.

The patient had not been previously diagnosed with vitiligo and had no past history of skin lesions. However, KP has been related to lesions in areas exposed to trauma in patients with no pre-existing dermatosis [5]. None of the patient's relatives had vitiligo, but his father and his grandmother had been diagnosed with rheumatoid arthritis. The literature cites a number of triggering factors for KP, including physical trauma, burns, insect bites, surgical incisions, allergic and irritating reactions, radiation exposure, needle acupuncture, and tattoos [5-7].

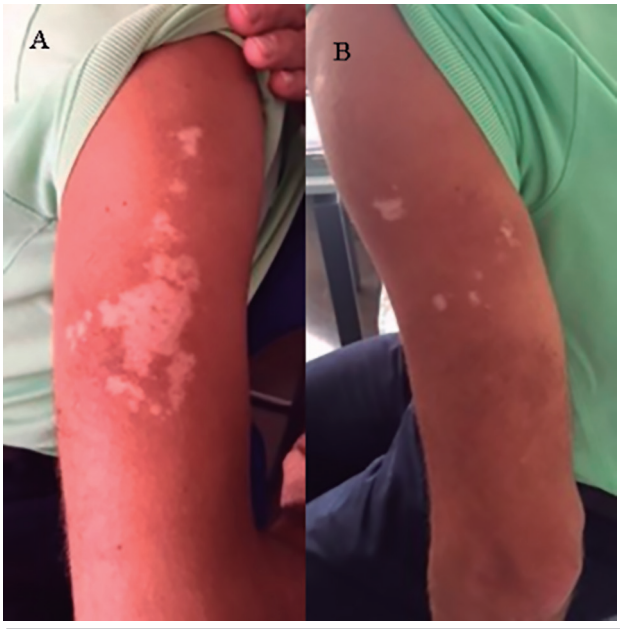

Figure. A, Right arm. B, Left arm.

We have described the case of a patient who started to develop hypopigmented skin lesions 1 year after the end of subcutaneous AIT with grasses, administered on a monthly basis over 4 years. Although the period between skin trauma and the appearance of KP lesions is generally short (10-20 days), the reported latency ranges from 3 days to 2 years [5]. The etiopathogenesis of KP in vitiligo remains unclear, though immune, neural, and vascular factors have been suggested to play an important role [4]. In our case it is difficult to establish whether the triggering cause of KP was repeated trauma due to the needle, as has been described in cases of psoriasis induced by acupuncture [7], or the immune response to administration of the grass extract. To our knowledge, this is the first case of vitiligo associated with KP following the administration of subcutaneous AIT with grass pollen. The possibility of such phenomena in patients who develop vitiligo after a cycle of AIT should be taken into account.

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Conflicts of Interest

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Resolution of Common Variable Immunodeficiency After HIV Infection

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Palabras clave: Inmunodeficiencia común variable. Infección VIH. Hipogammaglobulinemia.

Common variable immunodeficiency (CVID) is the most common of the primary immunodeficiency disorders requiring immunoglobulin replacement, and affects about 1 in every 25 000 white people. The characteristic feature is severe hypogammaglobulinemia, predominantly affecting the IgG and IgA classes. The majority of patients present with recurrent infections, mostly affecting the respiratory tract, although gastrointestinal infections are also common [1,2]. The mechanisms underlying CVID are not known, though evidence points to many different genetic defects inducing abnormalities in B and T lymphocytes [1,3]. Autoimmune diseases and malignancies may also complicate the course of the disease, which is usually favorable with immunoglobulin replacement therapy.

In rare cases, CVID has been reported to resolve transiently or permanently with human immunodeficiency virus (HIV) infection [4-7].

We present the case of a 21-year-old male ex-smoker with a history of repeat sinusitis since childhood. In March 2009 he presented to our allergy service with complaints of dry cough and dyspnea of a few weeks' duration. A physical examination produced no abnormal findings. Skin tests to common inhalants were negative. Spirometry and fraction of exhaled nitric oxide were within normal values. A chest x-ray demonstrated no alterations. A complete blood count showed 5.9% eosinophils, and an analysis of biochemical data revealed no abnormalities.

Immunoglobulin determinations showed a decrease in IgG and IgM and undetectable levels of IgA and IgE (values in mg/dL: IgG, 284; IgA, 0; IgM, 22). Immunophenotyping showed 8% of B lymphocytes and 58% of T lymphocytes and an inverted CD4/CD8 ratio (748/2006 cells/µL). The patient was diagnosed with CVID (SmB+ EUROclass) [8] and began treatment with intravenous human immunoglobulin (IVIG) at a dose of 200 mg/kg once every 3 weeks. Monthly immunoglobulin quantification was performed in order to adjust the treatment and maintain levels of IgG above 500 mg/dL (Figure).

During follow-up, the patient experienced recurrent episodes of urethritis due to his sexual behavior, although

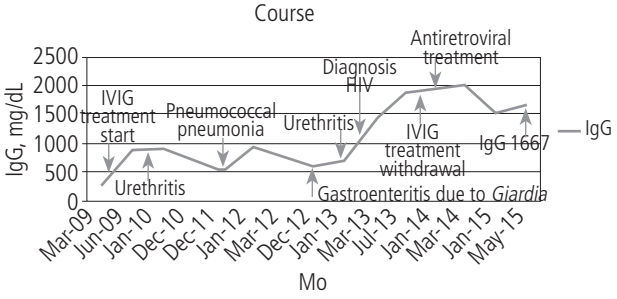

Figure. Clinical course and changes in serum IgG levels in patient. IVIG indicates intravenous immunoglobulin.

in all cases serology tests for sexually transmitted diseases, including HIV, were negative. In 2012, the patient was admitted to the hospital on 2 occasions, the first time for a respiratory infection induced by *Streptococcus pneumoniae*, and the second for a gastrointestinal infection due to *Giardia lamblia*. Both infections coincided with a decrease in IgG levels despite treatment with gamma globulin.

After a new episode of urethritis in June 2013, the patient was diagnosed with HIV infection (positive HIV-1 antibodies and a positive Western blot for gp120,gp41, p31, p24, and p17 from HIV), surprisingly coinciding with an unexpected increase in levels of IgG (>1500 mg/dL). HIV viral load in serum was undetectable.

Over the next 6 months the patient's levels of IgG remained high despite monthly IVIG infusions; the infusions were discontinued in December 2013. Antiretroviral treatment was started in spite of an undetectable HIV viral load. Two years later, the patient still has high levels of IgG but very low levels of IgA (IgG, 1747; IgM, 264; IgA, 2; and IgE, 24). The most recent immunophenotypic study revealed normal total lymphocyte count with a correct distribution of natural killer cells and B and T lymphocytes. The CD4/CD8 ratio (676/1536 cells/µL) was inverted, though the CD4 count remained normal. The level of B lymphocytes was normal, and the proportion of virgin B cells and different types of memory B cells were also within normal range. We observed a correct distribution of immunoglobulin free light chains, and no antigenic data suggested peripheral expression of a monoclonal lymphoproliferative disorder. CD28 and CD27 (lymphoplasmocytoid cells) cells were in normal proportion. No new, relevant infections were reported during this 2-year period (Figure).

This case shows the association of HIV infection and development of hypergammaglobulinemia and recovery of IgG production in a patient with CVID over at least 2 years of follow-up, and adds further evidence to the few similar cases reported in the literature [4-7.]

As in similar reported cases, our patient has shown recovery of IgG, IgM, and IgE while IgA levels remain undetectable. This finding is compatible with the notion that specific genetic—and possibly environmental—factors are required to induce CVID in the context of IgA deficiency [9] .

Hypergammaglobulinemia is a common finding in the early stages of HIV infection due to polyclonal B-cell activation, which could explain the course of these cases [10].

Treatment with antiretroviral drugs does not appear to affect this B-cell activation, since both in our case and in the report by Jolles et al [4], immunoglobulin recovery was maintained in spite of antiretroviral therapy. Nevertheless, the cause behind immunoglobulin recovery in these cases remains unanswered.

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Kounis Syndrome After Levofloxacin Intake: A Clinical Report and Cross-reactivity Study

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Palabras clave: Síndrome Kounis. Levofloxacino. Ciprofloxacino. Test activación basófilos. IgE específica.

Kounis and Zavras [1] described a case of histamine-induced coronary artery spasm in 1991 and this concurrence of an acute coronary event with an acute allergic reaction (anaphylactic or anaphylactoid) is now known as *Kounis syndrome*. It is due to extensive vasodilatation and low cardiac output. In the last 20 years, numerous factors have been implicated in Kounis syndrome, including drugs (eg, β-lactams [2], ibuprofen [3], contrast media), hymenoptera stings, and food.

We describe the case of a 35 year-old man who presented at our allergy department with clinical symptoms (acute coronary syndrome and generalized angioedema with urticaria) and ST decline in several leads in an emergency electrocardiogram performed 30 minutes after the first intake of levofloxacin, which had been prescribed to treat sinusitis. The cardiac evaluation (coronary angiography, cardiac catheterization, plus an exercise stress test) showed normal results. The findings were compatible with a diagnosis of Kounis syndrome. After ruling out all other possible causes, and after obtaining the patient's informed signed consent, we performed a prick test (5 mg/mL) and intradermal test (0.005 mg/mL and 0.05 mg/mL) with levofloxacin. Additional tests included a basophil activation test (BAT) with BasoTest (BD Biosciences), specific IgE to quinolones, and a drug provocation test (DPT) with an alternative drug from the same family.

The prick and intradermal tests were negative in our patient, but positive in 2 patients from a control group of 10 patients with good tolerance of levofloxacin, ciprofloxacin, and ofloxacin. The BAT, performed according to the manufacturer's instructions, showed a positive result for levofloxacin (4.5%) and a negative result for ciprofloxacin and ofloxacin. All the patients in the control group had negative BAT results. Specific IgE (ImmunoCAP, Thermo Fisher Scientific) was negative to ciprofloxacin and positive to levofloxacin (0.67 kU/L); the results in the control group were again negative. With these results, we performed a DPT with ciprofloxacin (placebo-placebo-50-100-100-250 mg) to identify an alternative treatment. The results were negative at the immediate and delayed readings (2 and 48 hours, respectively).

Three types of Kounis syndrome are now recognized [4]: type I, occurring in patients with normal cardiac findings (normal arteriography); type II, occurring in patients with pathological cardiac findings (atherosclerosis in arteriography); and type III, occurring in patients with the type II variant and previous heart problems. Our patient, a healthy man who experienced severe heart failure after levofloxacin intake, was diagnosed with type I Kounis syndrome. This is very important as the fact that no other clinical reasons can explain the symptoms experienced by the patient demonstrates that the drug was the trigger.

To our knowledge, this is the first clinical report of Kounis syndrome due to levofloxacin with a positive in vitro study. As mentioned, several drugs have been implicated in this syndrome, but there has only been 1 report involving a quinolone (ciprofloxacin) [5].

Kounis syndrome is challenging, as few cases are reported annually [6] and there are no established clinical protocols for confirming or excluding a diagnosis, which is established on clinical grounds. Accordingly, the clinical report is the main tool for confirming diagnosis, and it is therefore necessary to focus on ruling out other allergic and nonallergic causes. According to several authors, once the culprit drug has been identified in a patient diagnosed with Kounis syndrome, all other drugs in the same family must be avoided [7]. However, in vitro studies could have an important role in identifying an alternative to recommend to patients: BAT and/or specific IgE are used to confirm a diagnosis and search for alternative treatments, although published results show that an in vitro study cannot rule out hypersensitivity (low sensitivity and/or specificity of the studies) and must be confirmed by a DPT.

In our patient, the results of the in vivo studies for levofloxacin were unclear, as they were negative in our patient but positive in 2 of the control patients. Contradictory results regarding the sensitivity of skin tests in quinolone allergy have been reported, and positive skin tests in controls have been attributed to direct mast cell activation [8]. These conflicting reports led to the proposal for the use of low nonirritating intradermal test concentrations for quinolones, but these have low sensitivity. Based on the positive specific IgE and BAT results for levofloxacin and the negative results for ciprofloxacin, we advised our patient to undergo a DPT with the alternative drug ciprofloxacin, as low cross-reactivity has been reported between ciprofloxacin and levofloxacin [9,10].

Few publications have reported cross-reactivity between quinolones [7,9,10]. In addition, few patients have been studied and the results have been very different (and contradictory). The results show that cross-reactivity between quinolones is unclear and that there are no general rules for predicting cross-reactivity, which should be analyzed on a case-by-case basis.

To conclude, to the best of our knowledge this is the first report of Kounis syndrome due to levofloxacin with a positive in vitro study and tolerance of ciprofloxacin.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Therapeutic Potential of Zoledronate-Activated Autologous γδT Cells in Atopic Dermatitis

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Key words: γδT cells. Vγ9γδT cells. Atopic dermatitis. TARC.

Palabras clave: Células T gamma/delta. Células T V gamma 9 gamma/delta. Dermatitis atópica. Quimiocina regulada y activada del timo (TARC).

Current research on treatment of atopic dermatitis (AD) focuses on creating biological antagonists of the T_H2 cytokine pathway, such as anti-interleukin (IL)-4 receptor α antibody, or finding drug candidates that repair epidermal barrier function [1,2]. In clinical trials, repeated intravenous injections of γδT cells proved feasible and safe for the treatment of patients with malignancies [3]. We demonstrated that zoledronate-activated γδT cells increase the frequency of Vγ9γδT cells and produce mainly T_H1 cytokines but not IL-17 [4]. In cell-based therapy in allergy patients, the use of T_H1-polarized innate cells for establishing robust allergen-specific tolerance is clearly different from that of regulatory T cells (Tregs) or syngeneic hematopoietic stem cells [5,6]. In this study, we evaluated the safety and clinical outcomes of γδT cell therapy in AD patients who received a single intravenous injection of zoledronate-activated γδT cells.

The trial was approved by the Research Ethics Committee of Seta Clinic on February 2, 2012 (approval number: SCG12063). The primary endpoint was the safety of γδT cell therapy; the secondary endpoints were clinical outcome and immunological status. The study population comprised 5 male AD patients (3 with moderate AD and 2 with severe AD), and the median age was 32 years (range, 31-34 years). Peripheral blood mononuclear cells (PBMCs) were collected from the whole blood of each patient and cultured with zoledronate, IL-2, and autologous serum for 14 days. Cell preparations were examined for the presence of bacteria and endotoxins, as previously reported [3,4]. A single intravenous injection of the ex vivo–expanded γδT cells activated by zoledronate was administered to each patient. The use of topical medications was allowed, but the use of systemic corticosteroids and unapproved medicines was prohibited. For assessment of the primary endpoints, adverse events were monitored according to the Common Terminology Criteria of Adverse Events v4.0. The severity and extent of AD were assessed using the AD severity classification of the Japanese Dermatological Association (simple method, maximum 20 points) [7]. The secondary endpoint was the immunological status of the patients, who received a single intravenous injection of zoledronate-activated γδT cells. This was also monitored by flow cytometry of peripheral blood before injection and 1, 2, 4, and 6 months after injection. Levels of the T_H2 biomarker

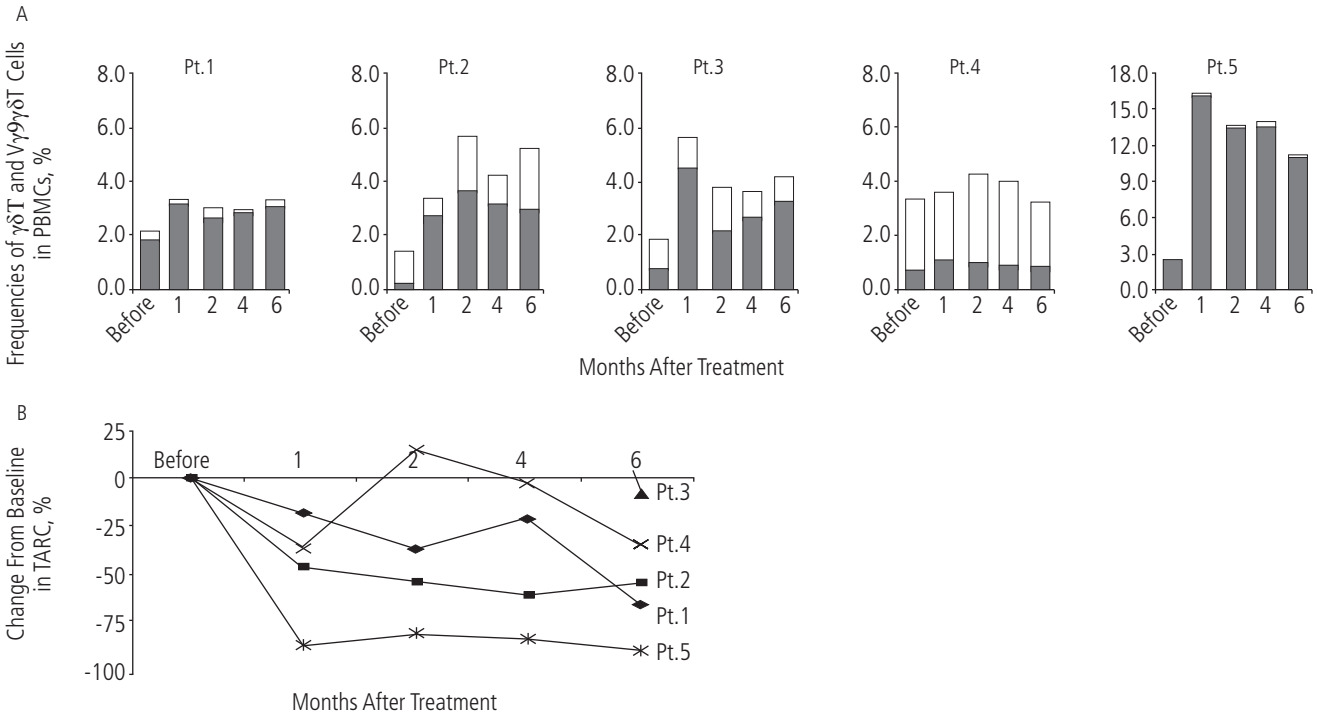

Figure. A, Change in the frequency of γδT (□+ ■) and Vγ9γδT (■) cells in AD patients receiving a single intravenous injection of zoledronate-activated γδT cells. In Patients 2 and 5, the frequencies of Vγ9γδT cells were maintained until 6 months after administration and increased 11.9- and 4.7-fold compared with before treatment, respectively. B, Change in the levels of the T_H2 biomarkers TARC in AD patients who received a single intravenous injection of zoledronate-activated γδT cells. In the 2 patients whose AD severity index improved, the decreases in the levels of TARC 1 month after treatment were 46.2% and 87.7%. TARC indicates thymus and activation-regulated chemokine.

thymus and activation-regulated chemokine (TARC) [8] and levels of IgE and eosinophils of each patient were also evaluated within 6 months of administration of zoledronate-activated γδT cells.

The number of injected zoledronate-activated γδT cells ranged from 5.0 to 9.5 × 10^9. No adverse events were observed during the 6 months after administration. The evaluation of clinical outcome revealed that the clinical index of AD severity improved in 2 of the 5 patients (Patient 2, 7 to 1; Patient 5, 10 to 4). In 1 patient (Patient 1), the clinical index returned to the initial level of the evaluation after a transient improvement; however, no improvement in atopic dermatitis was observed for 2 patients (Patients 3 and 4). Flow cytometry of immune cells in peripheral blood before treatment revealed that the frequencies of γδT and Vγ9γδT cells ranged from 1.2% to 3.5% and from 0.3% to 2.5% of PBMCs, respectively. The change in the frequency of γδT and Vγ9γδT cells in PBMCs is shown in the Figure (Panel A). In the 2 patients whose AD severity index improved, the frequencies of both γδT and Vγ9γδT cells increased markedly and were maintained until 6 months after administration. At this point, the frequencies of Vγ9γδT cells in Patients 2 and 5 increased to 11.9- and 4.7-fold compared with before treatment, respectively. In Patient 3 (no clinical improvement), the frequency of Vγ9γδT cells increased transiently after administration but decreased promptly after 2 months of treatment. Flow cytometry also demonstrated that the frequency of T_H2 cells decreased in 2 patients, with an improvement in the clinical index of AD severity (Patient 2, 1.4 to 0.9; Patient, 5, 7.4 to 4.4), although no decrease was observed for the other 3 patients (data not shown). There were no significant changes in the frequencies of T_H1 cells, B cells, or Tregs after administration of zoledronate-activated γδT cells in any of the 5 patients. The assessment of T_H2 biomarker levels demonstrated that the mean percentage change in TARC levels in Patients 1, 2, and 5 was –35.9%, –54.1%, and –85.9%, respectively, after treatment (Figure, Panel B). However, in Patient 3 (no clinical improvement), TARC levels at 1, 2, 4, and 6 months after the injection were 237.8%, 56.6%, 159.2%, and –7.6%, respectively. In Patients 2 and 5, eosinophil counts fell below half after a month of treatment (data not shown). There was no notable decrease in IgE levels in any of the patients. This is the first study of zoledronate-activated γδT cell therapy for AD patients, in whom therapy was shown to be safe and feasible. In the 2 patients whose clinical index of AD severity improved, we observed a decrease in T_H2 cell frequency, a decrease in TARC levels, and a 5 to 10–fold increase in the frequencies of Vγ9γδT cells in PBMCs compared with before treatment. These data suggest that it is necessary to suppress T_H2-skewed immunity to markedly increase the T_H1-polarized Vγ9γδT cell frequency in PBMCs in AD patients. However, zoledronate-activated γδT cells were not effective for AD patients with T_H1-skewed immunity caused by a bacterial infection [9]. In treatment of cancer patients, more than 3 infusions of zoledronate-activated γδT cells significantly

increased the numbers of Vγ9γδT cells [3,4]. Therefore, in future clinical trials, at least 3 injections of zoledronate-activated γδT cells should be administered to engraft a large number of Vγ9γδT cells in PBMCs. The effect of zoledronate-activated γδT cells for AD patients should be evaluated in randomized controlled trials.

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Conflicts of Interest

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Evaluation of Tolerance in Patients With Type-1 Hypersensitivity Reaction to Wheat After Oral Immunotherapy

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Adverse food reactions are unwanted reactions after ingestion of foods or food additives. The prevalence of wheat allergy is 0.2%-0.9% in adults and 0.4%-1.3% in children [1,2]. IgE-mediated reactions usually begin with acute symptoms within 2 hours after exposure to food [3-6]. In this study, we evaluate the development of tolerance in wheat-allergic patients who had been desensitized according to a known protocol. In our previous study, 13 patients with wheat allergy completed 1 year of follow-up after the maintenance phase of an immunotherapy protocol. These patients were desensitized based on a previously reported protocol [7]. Ten of the 13 patients were aged >5 years. At the time, oral food challenge (OFC) was performed with Senan bread containing 10% protein after a 2-week wheat-free diet. The OFC was performed at intervals of 15 minutes with doses of 0.8, 0.8, 1.6, 3.2, 6.4, 13.5, 26, and 52 g of sliced bread (Senan). The cutoff for clinical tolerance was 52 g of bread. Patients were tested with skin prick test extract (Greer), and the size of the wheal was compared before and after the desensitization period. Moreover, serum-specific IgE was measured using the RIDA qLine Allergy Panel (R-Biopharm) and compared before and after desensitization. Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp). The Fisher exact and chi-square tests were used to compare categorical variables; the Pearson and Spearman rank correlation tests were used to assess the correlation between variables. Mean age was 9.1 years (range, 6-20 years). Two of the 10 patients were females and the rest were males. Patients were divided into 2 groups according to their primary presentations (anaphylaxis or no anaphylaxis). Eight patients had anaphylaxis before desensitization. The allergic manifestations before immunotherapy affected the skin, respiratory tract, and gastrointestinal tract (Table). During desensitization, patients were evaluated for complaints. Seven

Table. Frequency of Symptoms and Complaints Before and During Treatment

Variable		Frequency, No (%)
Primary symptoms of anaphylaxis	Yes	8 (80)
	No	2 (20)
Symptoms before immunotherapy	Facial angioedema	1 (10)
	Urticaria	9 (90)
	Wheezing and shortness of breath	7 (70)
	Rhinorrhea, pruritus, and nasal congestion	2 (20)
	Vomiting and stomach cramps	1 (10)
Symptoms during the wheat-containing diet	Type 1 symptoms (occasionally)[a]	7 (70)
	Initial symptoms[b]	3 (30)
Symptoms during the 1-year immunotherapy period	Urticaria	4 (40)
	Wheezing and dyspnea	2 (20)
	Rhinorrhea	1 (10)
	Generalized pruritus	1 (10)
	Chronic constipation	1 (10)
	Bloating and chronic abdominal distention	1 (10)
Symptoms during the open food challenge	Urticaria	4 (40)
	Ocular pruritus	2 (20)
	Rhinorrhea	3 (30)
	Dyspnea and wheezing	0 (0)
	Gastrointestinal symptoms	0 (0)

[a]Hives, wheezing, rhinorrhea, and pruritus.
[b]Chronic constipation, abdominal bloating, and distension.

patients occasionally had type 1 allergic signs and symptoms. However, clinical manifestations were not as severe as the primary presentations before the desensitization period. The allergic symptoms were urticaria, wheezing, rhinorrhea, and pruritus. A 6-year-old boy experienced chronic constipation when he ate wheat. This symptom may have been related to his wheat-containing diet, although constipation was ruled out by a gastroenterologist. A 9-year-old boy complained of abdominal distention and flatulence after following a wheat-containing diet. Anaphylactic reactions were recorded in 2 patients who did not develop tolerance. The reactions occurred after intake of 12 g and 13 g of bread. In other patients, allergic reactions were less severe and occurred at doses >26 g. In summary, out of the 10 patients evaluated, 4 tolerated 52 g of bread, and 6 patients experienced allergic reactions at doses of 12, 13, 26, 26, 26, and 52 g. Among patients who had an anaphylactic reaction in the initial presentation, 3 developed clinical tolerance. Nevertheless, no significant correlation was found between tolerance and anaphylaxis (P=.747) or between sex and age and development of tolerance (P=.747 and P=.920, respectively). No significant correlation was found between sex and complications during the desensitization period (P=.745). The mean wheal size before and after immunotherapy was 8.7 mm and 5.7 mm, respectively (P<.001). Mean specific IgE before and after desensitization was 53.92 IU/mL and 19.06 IU/mL, respectively (P<.001). Staden et al [8] showed that tolerance was achieved in 36% of milk- or egg-allergic patients who received oral immunotherapy for 21 months and then followed an elimination diet for 2 months. Allergen-specific IgE also decreased in the immunotherapy group. In 2003, Nucera et al [9] desensitized a 7-year-old girl with wheat allergy. After a 6-month treatment, skin prick tests were performed and specific IgE was determined, and no significant change was observed. Burks et al [10] administered oral egg immunotherapy to 55 egg-allergic patients after 12 months of immunotherapy, and the patients followed an elimination diet for 4-6 weeks. In the oral rechallenge, 28% of patients were tolerant [10]. In our study, we eliminated wheat from the patients' diet for 2 weeks in order to respect the duration of immunotherapy. After this period, tolerance was observed in 40% of the patients after the OFC. Although other patients did not achieve tolerance, the incidence of reactions prevented us from administering higher doses.

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Conflicts of Interest

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Induction of Tolerance by Oral Immunotherapy in Patients With Cow's Milk Allergy

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Cow's milk allergy is the most common type of food allergy [1]. In this study, we evaluated the efficacy of oral desensitization in the induction of tolerance in children aged >3 years with a history of cow's milk allergy. The inclusion criteria were a positive history of cow's milk allergy, positive skin prick test result, presence of specific IgE (sIgE) against whole cow's milk proteins or any isolated cow's milk protein, and a positive result in a double-blind, placebo-controlled food challenge (DBPCFC). The exclusion criteria were poor compliance, uncontrolled asthma, cardiovascular disease, and severe systemic disease. The Institutional Review Board approved the study, which was registered with the Iranian Clinical Trials Registry (Registration Code: IRCT2015041621793N1).

All of the patients underwent DBPCFC, in which the test meal consisted of a strawberry-flavored milk-based formula (BioMeal, Fassbel), and the placebo meal consisted of a strawberry-flavored soy-based formula (BioMeal Soy, Fassbel). Initially, 3 drops of the solution were placed in the lower labial fornix, and then oral doses of 0.5, 2, 5, 20, 60, and 162.5 mL were given every 15 minutes. Oral immunotherapy was administered in 3 phases (rush, buildup, and maintenance) [2]. After desensitization, patients were followed for 1 year to monitor allergic reactions. The use of cow's milk and dairy products was prohibited for 1 month in patients who experienced less severe reactions, and an open food challenge (OFC) test was subsequently performed. If the OFC result was negative, the patient was considered to have developed tolerance; if it was positive, the patient was considered to be desensitized.

sIgE against casein and cow's milk protein was measured and a skin prick test (SPT) performed with cow's milk extract (Greer Laboratories). From February 2014 to September 2015, a total of 14 patients (10 male and 4 female) were confirmed to have cow's milk allergy and were enrolled in the final analysis.

The statistical analyses were performed using IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp). The Fisher exact and chi-square tests were used to compare categorical variables, whereas the Pearson test and Spearman correlation coefficient were used to assess the correlation between quantitative and qualitative variables, respectively.

The median age of patients was 4.75 (3.5-7) years, and the median follow-up period before initiation of this study was 14 (6-23) months. Seven patients (50.0%) had a history of atopic disease, and 8 children (57.1%) had a history of adverse reaction to other foods including fish, egg, tree nuts, and peanut. The most common clinical manifestation during the DBPCFC was rhinoconjunctivitis (57.1%). In the buildup phase, 1190 doses of cow's milk (5859 mL) were administered to 13 patients, who completed the buildup phase successfully, and allergic reactions were recorded in 24 doses (2.0%). Details of allergic reactions are shown in the Table. In addition, patient 9 left the study during the sixth week of the buildup phase because of severe allergic reactions (Table). During the maintenance phase, 1170 doses of cow's milk (261 000 mL) were administered and 11 allergic reactions (0.9%) were recorded in 9 patients (patients 1 and 12 had 2 episodes each). The result of SPT showed that the median diameter of the wheal before and after desensitization was 10 and 6 mm, respectively. Moreover, the sIgE level to cow's milk proteins and casein decreased after desensitization from 39.30 to 10.40 kU_A/L and 7.72 to 2.83 kU_A/L, respectively. After oral immunotherapy, the result of the SPT and sIgE levels against casein and milk proteins decreased significantly (P=.002 and .003, respectively). Among 13 patients, the result of the OFC test was negative in 6 cases (46.2%), and tolerance was considered relevant in 4 patients (30.8%); 3 patients (23%) were unable to tolerate milk, and clinical symptoms developed after ingestion of 20 mL of milk. Age, sex, and previous medical history had no significant correlation with the results of the OFC test. Induction of tolerance was significantly more successful in patients with a higher reactive dose in the DBPCFC test and buildup phase, less severe reactions during the immunotherapy protocol, and a shorter duration of immunotherapy. In this study, most of the allergic reactions in the buildup and maintenance phases were mild and could be controlled with oral antihistamines. Short-acting ß-agonists were administered to treat 15 allergic episodes in the build-up phase and 2 episodes in the maintenance phase. Moreover, 2 patients had to be treated with intramuscular epinephrine in the buildup phase (1 received 2 doses). Our results and the results of similar studies show that oral immunotherapy is a relatively safe approach if the necessary precautions are taken [3-5]. We found that the dose tolerated at the beginning of the study correlated with the development of tolerance at the final stage. Our results were similar to those of Staden et al [6]

Table. Results of the Oral Immunotherapy Protocol

Patient No.	Buildup Period, wk	Dose of Allergic Reaction, mL	Allergic Reactions During Buildup Phase	Maintenance Period, d	Maintenance Dose, mL	Allergic Reaction (Maintenance Phase)
1	14	10	Generalized urticaria[a]	90	200	–
		60	Localized urticaria, cough, wheezing[b]			
2	12	10	Localized urticaria[a]	90	250	Localized urticaria, rhinoconjunctivitis[a,e]
3	18	2	Generalized urticaria, cough, rhinoconjunctivitis[b]	90	200	Cough, rhinoconjunctivitis, wheezing[b]
		40	Generalized urticaria, sneezing, wheezing, rhinoconjunctivitis, respiratory distress[c]			
		100	Generalized urticaria, rhinoconjunctivitis, sneezing[a]			
4	10	-	-	90	250	Sneezing, rhinoconjunctivitis[a]
5	18	10	Generalized urticaria, cough, wheezing[b]	90	200	Localized urticaria, throat pruritus[a]
		40	Generalized urticaria, cough, rhinoconjunctivitis[b]			
		100	Generalized urticaria, cough, rhinoconjunctivitis[b]			
6	10	40	Generalized urticaria, sneezing, rhinoconjunctivitis[a]	90	250	Localized urticaria, rhinoconjunctivitis[a]
7	10	-	-	90	250	–
8	12	40	Generalized urticaria, cough[b]	90	250	Localized urticaria[a]
		150	Localized urticaria, cough[b]			
9	10	10	Vomiting, abdominal pain	-	-	–
10	15	10	Cough, wheezing[b]	90	200	Sneezing, rhinoconjunctivitis[a]
		100	Cough, rhinoconjunctivitis[b]			
		5	Sneezing, rhinoconjunctivitis[a]			
11	11	5	Generalized urticaria, cough[b]	90	200	Localized urticaria[a]
		20	Generalized urticaria, cough[b]			
		150	Localized urticaria, throat pruritus, rhinoconjunctivitis[a]			
12	20	5	Cough, rhinoconjunctivitis, wheezing[b]	90	200	Cough, rhinoconjunctivitis[b,e]
		60	Cough, rhinoconjunctivitis, wheezing[b]			
		100	Cough, rhinoconjunctivitis, wheezing, flushing[d]			
13	10	40	Sneezing, rhinoconjunctivitis[a]	90	200	–
		100	Sneezing, throat pruritus, rhinoconjunctivitis[a]			
14	10	60	Throat pruritus, rhinoconjunctivitis[a]	90	250	–

[a]Treatment with oral diphenhydramine.
[b]Treatment with oral diphenhydramine and a short-acting ß-agonist.
[c]Treatment with oral diphenhydramine, a short-acting ß-agonist, and 2 doses of epinephrine and admission to hospital.
[d]Treatment with oral diphenhydramine, a short-acting ß-agonist, and a single dose of epinephrine.
[e]Two episodes of allergic reactions.

and Longo et al [7]. Finally, based on the results obtained in this study and other studies [8-10], it could be concluded that oral immunotherapy leads to tolerance and may accelerate induction of tolerance in patients with cow's milk allergy.

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Conflicts of Interest

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