desensitization procedure which we to date have not been able to explore in clinical practice. Clearly, there is a need for reliable, preferably in vitro diagnostics in order to properly establish the diagnosis and to better understand the underlying immunological mechanism of procarbazine-related DHR. Furthermore, prospective clinical trials comparing drug rechallenge via desensitization or treating through strategies in patients with mild-to-moderate DHR would facilitate optimal clinical decision-making regarding potential drug reintroduction.

In conclusion, desensitization or reintroduction of procarbazine appears to be feasible and safe in patients with mild-to-moderate cutaneous DHR to procarbazine; additional studies in larger patient populations are required in order to make robust recommendations regarding the exact safety profile.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

Hester Van der Valk[1]
Hilda Dijkstra[2]
Annemiek Walenkamp[3]
Marie L.A. Schuttelaar[4]
Hanneke N.G. Oude Elberink[1]
Annick A. J. M. Van de Ven[1]

[1]*Department of Internal Medicine and Allergology, University Medical Center Groningen, Groningen, The Netherlands*
[2]*Department of Clinical Pharmacy and Pharmacology, University Medical Center Groningen, Groningen, The Netherlands*
[3]*Department of Medical Oncology, University Medical Center Groningen, Groningen, the Netherlands*
[4]*Department of Dermatology, University Medical Center Groningen, Groningen, the Netherlands*

Correspondence
Annick A. J. M. van de Ven, MD, PhD, Department of Internal Medicine and Allergology, University Medical Center Groningen, Internal address code AA21, Hanzeplein 1, 9713 GZ Groningen, the Netherlands.
Email: a.a.j.m.van.de.ven@umcg.nl

ORCID

Annick A. J. M. Van de Ven https://orcid.org/0000-0001-7032-9571

REFERENCES

1. Jutras G, Bélanger K, Letarte N, et al. Procarbazine, lomustine and vincristine toxicity in low-grade gliomas. *Curr Oncol.* 2018;25(1):e33-e39.
2. Lee C, Gianos M, Klaustermeyer WB. Diagnosis and management of hypersensitivity reactions related to common cancer chemotherapy agents. *Ann Allergy Asthma Immunol.* 2009;102(3):179–87; quiz 87–9, 222.
3. Baldo BA, Pagani M. Adverse events to nontargeted and targeted chemotherapeutic agents: emphasis on hypersensitivity responses. *Immunol Allergy Clin North Am.* 2014;34(3):565–596, viii.
4. Mahmood T, Mudad R. Pulmonary toxicity secondary to procarbazine. *Am J Clin Oncol.* 2002;25(2):187-188.
5. Shepherd GM. Hypersensitivity reactions to chemotherapeutic drugs. *Clin Rev Allergy Immunol.* 2003;24(3):253-262.
6. Yagmur IT, Guzelkucuk Z, Yarali N, et al. Evaluation of hypersensitivity reactions to cancer chemotherapeutic agents in pediatric patients. *Ann Allergy Asthma Immunol* 2020.124(4):350–356.
7. Caumes E, Guermonprez G, Lecomte C, Katlama C, Bricaire F. Efficacy and safety of desensitization with sulfamethoxazole and trimethoprim in 48 previously hypersensitive patients infected with human immunodeficiency virus. *Arch Dermatol.* 1997;133(4):465-469.
8. Pyle RC, Butterfield JH, Volcheck GW, et al. Successful outpatient graded administration of trimethoprim-sulfamethoxazole in patients without HIV and with a history of sulfonamide adverse drug reaction. *J Allergy Clin Immunol Pract.* 2014;2(1):52-58.
9. Lehmann DF, Hurteau TE, Newman N, Coyle TE. Anticonvulsant usage is associated with an increased risk of procarbazine hypersensitivity reactions in patients with brain tumors. *Clin Pharmacol Ther.* 1997;62(2):225-229.

DOI: 10.1111/all.14430

For hazelnut allergy, component testing of Cor a 9 and Cor a 14 is relevant also in birch-endemic areas

To the Editor,

Diagnosis of nut allergy is usually based on history with a relevant sensitization to the allergen in question and confirmed by allergen challenge. The diagnosis of hazelnut allergy in birch pollen-allergic patients is hampered by cross-reactivity from bich pollen.[1,2] Earlier studies have concluded that Cor a 9 and 14 are the most accurate components for hazelnut allergy diagnostics.[3–5]

Abbreviations: AUC, area under the curve; CI, confidence interval; NPV, negative predictive value; PPV, positive predictive value; ROC, receiver operating characteristic; SPT, skin prick test.

Trial Registration: clinicaltrials.gov: NCT01502878

Avoidance of hazelnut and a fear of an allergic reaction may affect the quality of life, therefore improved in vitro diagnosis and in the case of a negative challenge, reintroduction of hazelnuts into the diet is the goal.

The aim was to study component diagnostics for severe hazelnut allergy in children and adolescents in a region with heavy birch pollination. Further, we assessed the success of reintroduction in patients with a negative challenge.

Eighty-two children and adolescents (aged 1–19 years) with suspected hazelnut allergy were recruited at the Helsinki University Skin and Allergy Hospital. Eligible patients were sensitized to hazelnut (SPT ≥ 3 mm with ground unpeeled nut or IgE ≥ 0.35 kU/L ImmunoCAP whole hazelnut).

Specific IgE was measured against whole hazelnut extract; Cor a 1 (PR-10 protein), 8 (lipid transfer protein), 9 (11 S globulin), and 14 (2S albumin); and birch pollen extract. Skin prick tests were performed with ground hazelnut mixed with 0.9% saline and birch pollen extract.

At the double-blind placebo-controlled challenges (n = 56), on two days, each patient received 5, 50, 200, and 540 mg hazelnut protein, or placebo (Cumulative dose 795 mg, 6 hazelnuts). At open challenges (n = 26), doses were 5, 25, 50, 100, and 500 mg (Cumulat. 680 mg). Reaction severity was assessed by a threshold-adjusted score in Table S1. A questionnaire of hazelnut reintroduction was sent to the challenge-negative patients.

The study (326/13/03/03/2010) was approved by the ethics committee at the Helsinki University Hospital of Children and Adolescents. One of the parents and the patient (≥6 years old) signed written informed consents. See details on methods in the supplemental text.

Of the 82 patients, 33 (40%) showed reaction to hazelnut. Of the challenge reactions, 6 (18%) were severe, 7 (21%) moderate, and 20 (61%) mild. Four patients received adrenaline, and three of them needed more than one dose of adrenaline (2 to 3).

Birch pollen sensitization (SPT and/or IgE) was present in 68 (83%) patients (sIgE ≥ 0.35 kU/L and/or SPT ≥ 3 mm) (median sIgE

TABLE 1 Baseline clinical characteristics and baseline values of the study population by challenge outcome

	Challenge negative or mild (n = 69)	Challenge moderate or severe (n = 13)	*P* value
Gender, female, n (%)	32 (46)	4 (31)	0.37
Age, mean (range)	9.7 (1.9-18.5)	10.1 (5.8-17.4)	0.70
Atopic dermatitis, n (%)	51 (74)	8 (62)	0.50
Asthma, n (%)	34 (49)	5 (39)	0.55
Other food allergy except nuts, n (%)	38 (55)	4 (31)	0.14
Previous history of reacting to some nut, n (%)	46 (67)	9 (69)	0.86
Birch pollen-allergic rhinitis	52 (77%)	6 (46%)	**0.03**
Serum total IgE kU/L[a]	490 (17-14830)	346 (56-1225)	0.21
Hazelnut IgE kU/L[b]	18.5 (0.3-470)	30.9 (0.4-521)	0.58
Hazelnut skin prick wheal size mm[c]	6 (0-18)	9 (0-16)	**0.02**
Birch pollen IgE kU/L[b]	43.3 (0.03-918)	4.52 (0.02-542)	0.050
Birch pollen skin prick wheal size mm[d]	5 (0-13)	4 (0-13)	0.10
Blood eosinophil count E9/l[d]	0.39 (0.08-2.28)	0.27 (0.16-1.39)	0.75
Blood eosinophil percentage[d]	6 (1-29)	5 (3-16)	0.71
IgE to Cor a 1 kU/L[e]	19.1 (0-481)	4.74 (0-230)	0.050
IgE to Cor a 8 kU/L[a]	0.03 (0-6.4)	0.02 (0-0.24)	0.27
IgE to Cor a 9 kU/L	0.21 (0-27.4)	1 (0.07-251)	**0.001**
IgE to Cor a 14 kU/L	0.04 (0-10.5)	6.3 (0-126)	**<0.001**
Sensitization to Cor a 9 and Cor a 14, n (%)	5 (7)	8 (62)	**<0.0001**
Sensitization to Cor a 14 without Cor a 9, n (%)	7 (10)	1 (8)	1
Sensitization to Cor a 9 without Cor a 14, n (%)	25 (36)	4 (31)	0.76
No sensitization to Cor a 9 or Cor a 14, n (%)	32 (46)	0	**0.001**
Cor a 1 monosensitization	27 (39%)	0	**0.008**
Cor a 8 positive	9 (13%)	0	0.34

Note: Significant *P* value < 0.05 is calculated by Pearson chi-square, Fisher's exact, *t* test,or Mann-Whitney U test. Values are represented as medians (range) unless specified. Significant *P* values in bold. Sensitization is defined as IgE ≥ 0.35 kU/L. Number of available results.
[a]n = 75 [b]n = 78, [c]n = 80, [d]n = 76, [e]n = 74, [f]n = 79.

33.8 kU/L [range 0-918], SPT 5 mm [0-13]; Table 1). Correlations between sIgE and SPT to hazelnut, Cor a 1, and birch pollen were moderate to strong (Table S2).

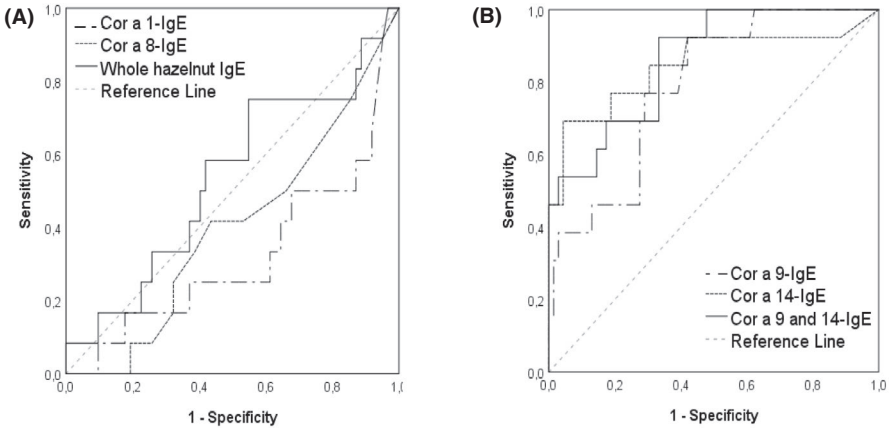
Although the challenge result correlated to some extent with IgE to whole hazelnut extract, moderate-to-severe hazelnut allergy could be most sensitively diagnosed by measuring IgE to both Cor a 9 and 14 (Figure 1; Table 1). Higher levels of specific IgE to Cor a 9 and 14 predicted lower eliciting dose at the challenge: Spearman's rho −0.514, $P = .002$; and −0.413, $P = .017$, respectively. Cor a 14 was superior to Cor a 9 in predicting moderate-to-severe reaction (Figure 1). For the cutoff of 2.04 kU/L, the likelihood ratio was 15.9 and the positive predictive value was 75%. Cor a 9 sensitization without Cor a 14 was present in 29 (35%) patients, of whom 25 (86%) were tolerant at the challenge. By combining the IgE levels of Cor a 9 and 14, diagnostic performance was equally good as with Cor a 14 alone (Figure 1; Table 1).

Fourty-seven of the 49 challenge-negative patients responded to the questionnaire on reintroduction of hazelnut. Of the respondents, 18 (38%) had introduced hazelnut to their diet (full introduction), 24 (51%) had not actively introduced, but reported not specifically avoiding hazelnut (partial introduction), and 5 (11%) reported avoiding hazelnut carefully (no introduction).

This study suggests that asymptomatic sensitization to hazelnut is common and testing for whole extract specific IgE is not a reliable tool when evaluating suspected hazelnut allergy in an area with heavy birch pollination.

Serum IgE to whole hazelnut extract and Cor a 1 associate with diagnostic markers of birch pollen allergy rather than hazelnut allergy. Even high IgE to whole hazelnut can be explained by cross-reactivity from birch pollen. In this study, patients with high whole hazelnut IgE—up to 400 kU/L—without concurrent storage protein sensitization tolerated hazelnut. All Cor a 1 monosensitized patients were asymptomatic or experienced only mild oral allergy symptoms. That specific IgE to whole hazelnut correlated strongly with Cor a 1, can be explained by the fact that hazelnut IgE ImmunoCAP is spiked with Cor a 1.[6] Therefore, in a birch-endemic region, high serum specific IgE concentration to hazelnut is most often caused by cross-reactivity from birch pollen. The association of Cor a 1 sensitization and oral allergy syndrome is in line with studies from Central Europe and birch-endemic areas from the United States.[3,4,7] Obviously, measuring Cor a 1 adds no value to the diagnosis of hazelnut allergy.

Studies from regions with less birch pollen exposure have reported Cor a 14-IgE as the best diagnostic marker for hazelnut allergy. Our results and the cutoff of 2.04 kU/L are in agreement with these reports.[8,9] However, the diagnostic performance of Cor a 14-IgE was superior to Cor a 9-IgE, which is in line with most previous studies including children and adults both from regions with and without birch pollination.[5,7–10] In our patients, sensitization to Cor a 9, without Cor a 14-sensitization, resulted in moderate-to-severe symptoms only in rare cases. By negative IgE testing for Cor a 9 and Cor a 14, true hazelnut allergy can be most accurately ruled out. In patients with a history of birch pollen allergy or sensitization to birch pollen, hazelnut sensitization is frequent due



(C)

	Area under the curve	P value	Asymptotic 95% CI		Cut-off (kU/L)	Sensitivity (%)	Specificity (%)	Likelihood ratio	PPV%	NPV%
			Lower Bound	Upper Bound						
Cor a 9	0.789	.001	0.67	0.91	**0.64**	77	71	2.7	33	94
Cor a 14	0.848	<.001	0.70	0.99	**2.04**	69	96	15.9	75	94
Cor a 9					**0.35**	92	57	2.1	29	98
Cor a 14					**0.35**	69	83	4.0	43	93
Cor a 9					**6.27**	39	96	8.8	63	89
Cor a 9 + 14	0.860	<.001	0.76	0.96	**10.1**	54	96	12.5	70	92

FIGURE 1 Receiver operating characteristic (ROC) analysis of IgE to (A) whole hazelnut, Cor a 1, Cor a 8, and (b and c) Cor a 9, Cor a 14, and sum of IgE to Cor a 9 and 14 to discriminate negative and mild from the moderate and severe challenge reactions. CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value

to cross-reactivity (PR-10 proteins). Sensitization to hazelnut or Cor a 1 is a poor discriminator for hazelnut allergy in this group. This study, however, showed that Cor a 14 and, to a lesser extent, Cor a 9 were a good predictor for true hazelnut allergy. The combination of Cor a 9 and 14 improves allergenic risk assessment.

A follow-up on challenges showed that most patients were reassured by a negative challenge and discontinued the unnecessary avoidance of hazelnut.

KEYWORDS

birch pollen sensitization, Cor a 1, hazelnut allergy, reintroduction, whole hazelnut extract

ACKNOWLEDGMENTS

We sincerely acknowledge registered nurses Jonna Harain and Anssi Koivuselkä for conducting patient visits of this study and Helsinki University Hospital Research Funds, Sigrid Juselius Foundation, Pediatric Research Foundation, Finnish Allergy Research Foundation, and Finnish Society of Allergology and Immunology for the financial support.

CONFLICT OF INTERESTS

The authors declare that they have no conflicts of interest.

AUTHOR CONTRIBUTION

Each named author has made substantial contributions to conception and design, and/or acquisition of data, and/or analysis and interpretation of data, and drafted the article or revised it critically for important intellectual content, and given final approval of the version to be submitted.

FUNDING INFORMATION

Helsinki University Hospital Research Funds, Sigrid Juselius Foundation, Pediatric Research Foundation, Finnish Allergy Research Foundation, and Finnish Society of Allergology and Immunology supported the study financially.

Riikka Uotila
Petteri Röntynen
Anna S. Pelkonen
Helena Voutilainen
Anna Kaarina Kukkonen
Mika J. Mäkelä

Skin and Allergy Hospital, University of Helsinki and Helsinki University Hospital, Helsinki, Finland

Correspondence
Riikka Uotila, Skin and Allergy Hospital, Helsinki University Hospital, P.O. Box 160, 00029 HUCH, Helsinki, Finland.
Email: riikka.uotila@helsinki.fi

ORCID

Riikka Uotila https://orcid.org/0000-0001-5708-2770

REFERENCES

1. Uotila R, Kukkonen AK, Pelkonen A, Mäkelä MJ. Cross-sensitization profiles of edible nuts in a birch-endemic area. *Allergy* 2016;71(4):514-521.
2. Movérare R, Westritschnig K, Svensson M, et al. Different IgE reactivity profiles in birch pollen-sensitive patients from six European populations revealed by recombinant allergens: an imprint of local sensitization. *Int Arch Allergy Immunol*. 2002;128(4):325-335.
3. Faber MA, De Graag M, Van Der Heijden C, et al. Cor a 14: missing link in the molecular diagnosis of hazelnut allergy? *Int Arch Allergy Immunol* 2014;164(3):200-206.
4. Kattan JD, Sicherer SH, Sampson HA. Clinical reactivity to hazelnut may be better identified by component testing than traditional testing methods. *J Allergy Clin Immunol Pract* 2014;2(5):633-4.e1.
5. Masthoff LJ, Mattsson L, Zuidmeer-Jongejan L, et al. Sensitization to Cor a 9 and Cor a 14 is highly specific for a hazelnut allergy with objective symptoms in Dutch children and adults. *J Allergy Clin Immunol* 2013;132(2):393-399.
6. Sicherer SH, Dhillon G, Laughery KA, Hamilton RG, Wood RA. Caution: The Phadia hazelnut ImmunoCAP (f17) has been supplemented with recombinant Cor a 1 and now detects Bet v 1–specific IgE, which leads to elevated values for persons with birch pollen allergy. *J Allergy Clin Immunol* 2008;122(2):413-414.
7. Eller E, Mortz CG, Bindslev-Jensen C. Cor a 14 is the superior serological marker for hazelnut allergy in children, independent of concomitant peanut allergy. *Allergy* 2016;71(4):556-562.
8. Carraro S, Berardi M, Bozzetto S, Baraldi E, Zanconato S. COR a 14-specific IgE predicts symptomatic hazelnut allergy in children. *Pediatr Allergy Immunol* 2016;27(3):322-324.
9. Buyuktiryaki B, Cavkaytar O, Sahiner UM, et al. Cor a 14, Hazelnut-Specific IgE, and SPT as a Reliable Tool in Hazelnut Allergy Diagnosis in Eastern Mediterranean Children. *J Allergy Clin Immunol Pract* 2016;4(2):265-72.e3.
10. Beyer K, Grabenhenrich L, Hartl M, et al. Predictive values of component-specific IgE for the outcome of peanut and hazelnut food challenges in children. *Allergy* 2015;70(1):90-98.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.