Frank A. Redegeld https://orcid.org/0000-0001-8830-7960
Zdenek Dvorak https://orcid.org/0000-0002-3938-3585
Gerlinde Hofstetter https://orcid.org/0000-0003-2077-4479
Franziska Roth-Walter https://orcid.org/0000-0001-5005-9228
Luis F. Pacios https://orcid.org/0000-0002-0585-4289
Erika Jensen-Jarolim https://orcid.org/0000-0003-4019-5765

REFERENCES

1. Hufnagl K, Afify SM, Braun N, et al. Retinoic-acid loading of the major birch pollen allergen Bet v 1 may improve specific allergen immunotherapy: in silico, in vitro and in vivo data in BALB/c mice. *Allergy*. 2020;75(8):2073-2077. doi:https://doi.org/10.1111/all.14259
2. Roth-Walter F, Afify SM, Pacios LF, et al. Cow's milk protein ß-lactoglobulin confers resilience against allergy by targeting complexed iron into immune cells. *J Allergy Clin Immunol*. 2021;147(1):321. doi:https://doi.org/10.1016/j.jaci.2020.05.023
3. Hufnagl K, Jensen-Jarolim E. Vitamin A and D in allergy: from experimental animal models and cellular studies to human disease. *Allergo J Int*. 2018;27(3):72-78. doi:https://doi.org/10.1007/s40629-018-0054-2
4. Bartonkova I, Grycova A, Dvorak Z. Profiling of vitamin D metabolic intermediates toward VDR using novel stable gene reporter cell lines IZ-VDRE and IZ-CYP24. *Chem Res Toxicol*. 2016;29:1211-1222. doi:https://doi.org/10.1021/acs.chemrestox.6b00170
5. Pettipher R. The roles of the prostaglandin D(2) receptors DP(1) and CRTH2 in promoting allergic responses. *Br J Pharmacol*. 2008;153(Suppl 1):S191-S199.
6. Hartmann G, Heine G, Babina M, et al. Targeting the vitamin D receptor inhibits the B cell-dependent allergic immune response. *Allergy*. 2011;66:540-548. doi:https://doi.org/10.1111/j.1398-9995.2010.02513.x
7. Heine G, Francuzik W, Doelle-Bierke S, et al. Immunomodulation of high-dose vitamin D supplementation during allergen-specific immunotherapy. *Allergy*. 2021;76(3):930-933. https://doi.org/10.1111/all.14541

SUPPORTING INFORMATION

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

DOI: 10.1111/all.15053

Sublingual immunotherapy reduces reaction threshold in three patients with wheat-dependent exercise-induced anaphylaxis

To the Editor,

Wheat-dependent exercise-induced anaphylaxis (WDEIA) is a rare IgE-mediated systemic hypersensitivity reaction caused by the combination of wheat product ingestion and cofactors, such as physical exercise, acetylsalicylic acid and alcohol.[1–3] For diagnosis, an appropriate patient's history has to be associated with a sensitization to wheat flour and gluten proteins as detected by skin prick test (SPT), specific IgE and /or basophil activation test (BAT). Confirmation of the diagnosis by oral challenge test (OCT) with gluten and cofactors allows to determine the patient's individual threshold.[4] It has been shown that using high amounts of pure gluten for a challenge, a reaction can even be elicited even without cofactors.[5] Dietary recommendations range from total avoidance of gluten to temporal separation of wheat ingestion from cofactors. Gluten avoidance has been associated with lower reaction thresholds.[6] Currently, no curative treatment such as immunotherapy (IT) has been developed. We describe three patients with WDEIA, who have been treated with a sublingual gluten IT (SLIT) over a course of 3 years. The clinical study was approved by local ethics committee.

For this exploratory study, three female patients with a history of several reactions only to a combination of wheat products plus cofactors and positive challenge with pure gluten were diagnosed with WDEIA and gave their informed consent for SLIT. Titrated SPT with pure wheat gluten and wheat protein hydrolysates (Solpro

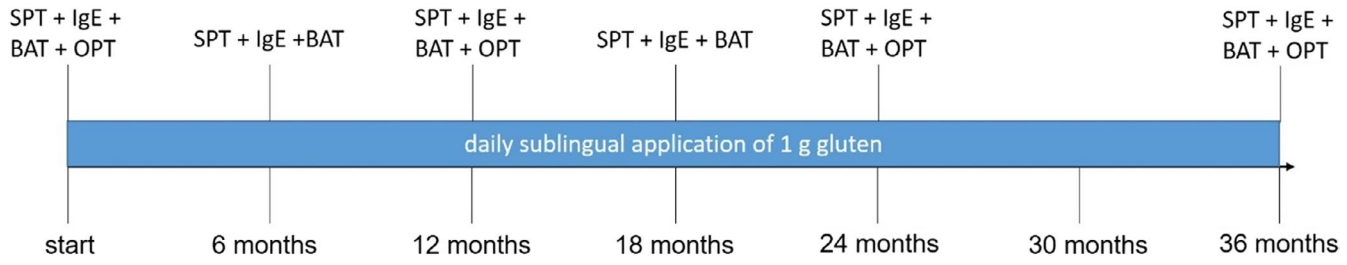

FIGURE 1 Timetable of the study

TABLE 1 Patient's characteristics

	Patient 1	Patient 2	Patient 3
Sex	Female	Female	Female
Age (years)	18	35	39
Race	White Caucasian	White Caucasian	White Caucasian
Asthma	No	No	No
Atopic dermatitis	No	No	No
Allergic rhinitis	No	No	No
Other food allergy	No	No	No
Time period since diagnosis before starting SLIT	6 months	3 months	1 month
Before SLIT			
Specific IgE omega-5 gliadin	0 kU/L	16.6 kU/L	13.9 kU/L
Specific IgE alpha-beta-gamma-gliadin	0.03 kU/L	Not done	3.31 kU/L
Specific IgE wheat flour	0.06 kU/L	Not done	1.05 kU/L
Specific IgE gluten	0.04 kU/L	Not done	2.79 kU/L
SPT gluten	2 mm	8 mm	8 mm
SPT Solpro 508	13 mm	Not done	Not done
Threshold	70 g gluten w/o cofactors	20 g gluten w/o cofactors	5 g gluten w/o cofactors
After 1st year of SLIT			
Threshold	120 g gluten with cofactors (500 mg acetylsalicylic acid and 10 ml alcohol)	20 g gluten with cofactors (1000 mg acetylsalicylic acid and 10 ml alcohol)	15 g gluten w/o cofactors
After 2nd year of SLIT			
Threshold	120 g gluten with cofactors (500 mg acetylsalicylic acid and 10 ml alcohol)	20 g gluten with cofactors (1000 mg acetylsalicylic acid and 10 ml alcohol)	80 g gluten with cofactors (1000 mg acetylsalicylic acid and 10 ml alcohol)
After 3rd year of SLIT			
Specific IgE Omega-5 Gliadin	0 kU/L	10.6 kU/L	12.4 kU/L
Specific IgE Alpha-Beta-Gamma-Gliadin	0 kU/L	0.35 kU/L	1.25 kU/L
Specific IgE wheat flour	0 kU/L	not done	<0.1 kU/L
Specific IgE Gluten	0 kU/L	not done	<0.1 kU/L
SPT Gluten	0 mm	5 mm	7 mm
SPT Solpro 508	15 mm	Not done	Not done
Threshold	120 g gluten with cofactors (500 mg acetylsalicylic acid and 10 ml alcohol)	40 g gluten with cofactors (1000 mg acetylsalicylic acid and 10 ml alcohol)	80 g gluten with cofactors (1000 mg acetylsalicylic acid and 10 ml alcohol)

508) were performed. Levels of specific IgE to wheat flour, gluten, omega-5 gliadin and alpha/beta/gamma-gliadin were measured. BAT was done with wheat gluten and wheat protein hydrolysates in titrated concentrations. The individual threshold for each patient was determined by OCT with gluten and additional cofactors until a reaction was elicited. Immunotherapy was performed by daily sublingual application of 1 mg gluten flour (Kröner, Ibbenbeuren, Germany), which was added with water to form a paste. After 2 min, the gluten had to be chewed and swallowed. All patients were advised to separate wheat ingestion from cofactors by 4 h, but had no formal restrictions. After 6, 12, 18, 24 and 36 months of titrated SPTs, measurements of specific IgE and BAT were repeated. OCT was repeated after 12, 24 and 36 months (overview see Figure 1).

All patients performed SLIT regularly. Patients 1 and 2 had no side effects, whereas patient 3 had local sensation of prickling under the tongue in 50% of applications. The titrated SPT showed no relevant change over time. In patient 2 specific IgE levels to omega-5 gliadin decreased from 16.6 kU/L to 10.6 kU/L and to alpha/beta/gamma-gliadins from 2.42 kU/L to 0.35 kU/L. IgE levels in patient 3 did not change at all and were not detectable at all in patient 1. BAT showed a continuous reduction in basophil activation with gluten and Solpro 508 in patient 1 and had an undulant development in patients 2 and 3.

The individual thresholds of all patients increased during SLIT. In patient 1, it went from 70 g gluten to a cumulative dosage of 120 g gluten with cofactors, in patient 2 from 20 g gluten to 40 g gluten with

cofactors and in patient 3 from 5 g gluten to 80 g gluten with cofactors (Table 1). Of note, no patient developed anaphylaxis despite continuous consumption of wheat products during the treatment. After 6 and 9 months of treatment, patient 2 developed urticaria after eating pancake and patient 3 after consuming spaghetti, both followed by mild exercise. No further systemic reactions occurred afterwards.

The results of this first study demonstrate that SLIT with gluten increases the reaction threshold of tolerated gluten with / without cofactors. Titrated SPT, specific IgE and BAT seem not to be predictive parameters, hence OCT remains gold standard for threshold determination. These results are in agreement with a Danish study assessing the influence of diet on wheat intake tolerance reporting a diet without total avoidance of gluten products to be associated with developing an increased reaction threshold.[6] However, further studies with a larger population are necessary to confirm our results in this pilot study.

FUNDING INFORMATION

Bundesministerium für Bildung und Forschung, Grant/Award Number: 01EA2106A.

ACKNOWLEDGMENTS

This work was supported by the authors' institutes and by research and development grant from the German Federal Ministry of Education and Research (BMBF), project ABROGATE (funding number: 01EA2106A).

CONFLICT OF INTEREST

The authors report no conflict of interest.

Dirk Tomsitz
Tilo Biedermann
Knut Brockow

Department of Dermatology and Allergy Biederstein, School of Medicine, Technical University of Munich, Munchen, Germany

Correspondence
Knut Brockow, Klinik und Poliklinik für Dermatologie und Allergologie am Biederstein, Technische Universität München, Biedersteiner Straße 29, 80802 München, Germany.
Email: knut.brockow@tum.de

ORCID

Dirk Tomsitz https://orcid.org/0000-0003-0036-072X
Knut Brockow https://orcid.org/0000-0002-2775-3681

REFERENCES

1. Scherf KA, Brockow K, Biedermann T, Koehler P, Wieser H. Wheat-dependent exercise-induced anaphylaxis. *Clin Exp Allergy*. 2016;46(1):10-20. doi:https://doi.org/10.1111/cea.12640
2. Christensen MJ, Eller E, Mortz CG, Bindslev-Jensen C. Patterns of suspected wheat-related allergy: a retrospective single-centre case note review in 156 patients. *Clin Transl Allergy*. 2014;4(1):39. https://doi.org/10.1186/2045-7022-4-39
3. Kennard L, Thomas I, Rutkowski K, et al. A multicenter evaluation of diagnosis and management of Omega-5 gliadin allergy (also known as wheat-dependent exercise-induced anaphylaxis) in 132 adults. *J Allergy Clin Immunol Pract*. 2018;6(6):1892-1897. doi:https://doi.org/10.1016/j.jaip.2018.02.013
4. Brockow K, Kneissl D, Valentini L, et al. Using a gluten oral food challenge protocol to improve diagnosis of wheat-dependent exercise-induced anaphylaxis. *J Allergy Clin Immunol*. 2015;135(4):977. doi:https://doi.org/10.1016/j.jaci.2014.08.024
5. Christensen MJ, Eller E, Mortz CG, Brockow K, Bindslev-Jensen C. Exercise lowers threshold and increases severity, but wheat-dependent, exercise-induced anaphylaxis can be elicited at rest. *J Allergy Clin Immunol Pract*. 2018;6(2):514-520. doi:https://doi.org/10.1016/j.jaip.2017.12.023
6. Christensen MJ, Eller E, Mortz CG, Brockow K, Bindslev-Jensen C. Clinical and serological follow-up of patients with WDEIA. *Clin Transl Allergy*. 2019;9:26. doi:https://doi.org/10.1186/s13601-019-0265-8. Published 2019 May 16.

DOI: 10.1111/all.15060

Self-reported nasal hyperreactivity is common in all chronic upper airway inflammatory phenotypes and not related to general well-being

To the Editor,

Chronic upper airway inflammatory diseases like allergic rhinitis (AR), non-allergic rhinitis (NAR), and chronic rhinosinusitis (CRS) are prevalent and relate to higher stress, anxiety, and depression, impacting life quality and raising a large economic burden.[1-3]

Nasal hyperreactivity (NHR)—defined as worsening of upper airway symptoms upon exposure to environmental triggers such as temperature/humidity changes—can be diagnosed objectively by a cold, dry air (CDA) provocation test.[4] However, most studies are questionnaire-based with varying definitions of NHR poorly