Safety and efficacy of immunotherapy with the recombinant B-cell epitope–based grass pollen vaccine BM32

Verena Niederberger, MD,[a] Angela Neubauer, PhD,[b] Philippe Gevaert, MD,[c] Mihaela Zidarn, MD,[d] Margitta Worm, MD,[e] Werner Aberer, MD,[f] Hans Jørgen Malling, MD,[g] Oliver Pfaar, MD,[h,i] Ludger Klimek, MD,[h] Wolfgang Pfützner, MD,[j] Johannes Ring, MD,[k] Ulf Darsow, MD,[k] Natalija Novak, MD,[l] Roy Gerth van Wijk, MD,[m] Julia Eckl-Dorna, MD, PhD,[a] Margarete Focke-Tejkl, PhD,[n] Milena Weber, MSc,[n] Hans-Helge Müller, PhD,[o] Joachim Klinger, PhD,[p] Frank Stolz, PhD,[b] Nora Breit, MSc,[b] Rainer Henning, PhD,[b] and Rudolf Valenta, MD[n,q]

Vienna and Graz, Austria; Ghent, Belgium; Golnik, Slovenia; Berlin, Wiesbaden, Mannheim, Marburg, Munich, and Bonn, Germany; Gentofte, Denmark; Rotterdam, The Netherlands; and Moscow, Russia

Background: BM32 is a grass pollen allergy vaccine based on recombinant fusion proteins consisting of nonallergenic peptides from the IgE-binding sites of the 4 major grass pollen allergens and the hepatitis B preS protein.

Objective: We sought to study the safety and clinical efficacy of immunotherapy (allergen immunotherapy) with BM32 in patients with grass pollen–induced rhinitis and controlled asthma.

Methods: A double-blind, placebo-controlled, multicenter allergen immunotherapy field study was conducted for 2 grass pollen seasons. After a baseline season, subjects (n = 181) were randomized and received 3 preseasonal injections of either placebo (n = 58) or a low dose (80 μg, n = 60) or high dose (160 μg, n = 63) of BM32 in year 1, respectively, followed by a booster injection in autumn. In the second year, all actively treated subjects received 3 preseasonal injections of the BM32 low dose, and placebo-treated subjects continued with placebo. Clinical efficacy was assessed by using combined symptom medication scores, visual analog scales, Rhinoconjunctivitis Quality of Life Questionnaires, and asthma symptom scores. Adverse events were graded according to the European Academy of Allergy and Clinical Immunology. Allergen-specific antibodies were determined by using ELISA, ImmunoCAP, and ImmunoCAP ISAC.

From [a]the Department of Otorhinolaryngology, Medical University of Vienna; [b]Biomay AG, Vienna; [c]the Department Otorhinolaryngology, Ghent University Hospital; [d]the University Clinic of Respiratory and Allergic Diseases, Golnik; [e]the Allergy Center, Charité, Berlin; [f]the Department of Dermatology and Venerology, Medical University Graz; [g]Allergy Clinic Copenhagen University Hospital, Gentofte; [h]the Center for Rhinology/Allergology, Wiesbaden; [i]the Department of Otorhinolaryngology, Head and Neck Surgery, Universitätsmedizin Mannheim, Medical Faculty Mannheim, Heidelberg University, Mannheim; [j]the Department of Dermatology and Allergology, Medical Center Giessen and Marburg GmbH, Marburg; [k]the Department of Dermatology and Allergy Biederstein, Technical University Munich (TUM) and ZAUM-Center of Allergy and Environment, Munich; [l]the Clinic for Dermatology and Allergology, University of Bonn; [m]the Department of Internal Medicine, Erasmus Medical Center, Rotterdam; [n]the Division of Immunopathology, Department of Pathophysiology and Allergy Research, Medical University Vienna; [o]the Institute for Medical Information Technology, Biometrics and Epidemiology, Ludwig-Maximilians-Universität, Munich, and the Institute for Medical Biometry and Epidemiology, Philipps-University, Marburg; [p]SynteractHCR Deutschland GmbH, Munich; and [q]NRC Institute of Immunology FMBA of Russia, Moscow.

Supported by Biomay AG, Vienna, Austria, and research grants F4605 and F4613 of the Austrian Science Fund (FWF). R.V. is recipient of a Megagrant of the Government of the Russian Federation, grant number 14.W03.31.0024.

Disclosure of potential conflict of interest: A. Neubauer is employed by Biomay and is a minor stockholder. W. Aberer has received travel support from Biomay AG. O. Pfaar's institution received grant funds from Biomay, and he has received consultant fees from HAL-Allergy Holding B.V./HAL-Allergie GmbH, Allergy Therapeutics/Bencard Allergie GmbH, Novartis Pharma, Laboratorios LETI/LETI Pharma, MEDA Pharma, ALK-Abelló, Anergis S.A., Biotech Tools S.A., Sanofi US Services, Mobile Chamber Experts (a GA^{2}LEN partner), Pohl-Boskamp, Stallergenes-Greer, Lofarma, and Allergopharma; he has received grants from Stallergenes-Greer, HAL-Allergy Holding B.V./HAL-Allergie, Allergy Therapeutics/Bencard Allergie GmbH, Laboratorios LETI/LETI Pharma, and Anergis S.A.; his institution has received funds from these along with ALK-Abelló, Allergopharma, Lofarma, Nuvo, Circassia, and Biotech Tools S.A.; he has received lecture fees from HAL-Allergy Holding B.V./HAL-Allergie GmbH, Allergy Therapeutics/Bencard Allergie GmbH, Novartis Pharma, Laboratorios LETI/LETI Pharma, ALK-Abelló, Allergopharma, Lofarma, and Stallergenes-Greer; and he has received payment for educational presentations from Stallergenes-Greer. L. Klimek's institution has received consultant fees from ALK-Abelló, Allergopharma, Bionorica, Boehringer Ingelheim, Lofarma, Novartis, MEDA Pharma, and GlaxoSmithKline; has grants with ALK-Abelló, Allergopharma, Bencard, Biomay, HAL, GlaxoSmithKline, LETI, Lofarma, Novartis, and Roxall; has received fees for lectures from ALK-Abelló, Allergopharma, Bionorica, Boehringer, GlaxoSmithKline, Lofarma, Novartis, and MEDA Pharma; receives fees for manuscript preparation from MEDA Pharma and Bionorica; and receives fees for Board membership from MEDA Pharma and Novartis. W. Pfützner and his institution have received clinical study fees from Biomay. He has received consultant fees from ALK-Abelló and lecture fees from ALK-Abelló and Novartis and has grants from ALK-Abelló and Biomay. U. Darsow's institution has received funds as clinical study compensation. N. Novak's institution contributed study patients and has received funding from ALK-Abelló; she received consultant fees from LETI Pharma, ALK-Abelló, and Stallergenes and for lectures from ALK-Abelló, LETI Pharma, Stallergenes, HAL Allergy, and Novartis. R. Gerth van Wijk's institution has received funding for study participation and grant funds from Dutch Lung Foundation and STW, and he has received consultant and lecture fees from ALK-Abelló and Allergopharma and travel funding from the European Academy of Allergy and Clinical Immunology and UEMS. H.-H. Müller received fees from SynteractHCR and Deutschland GmbH for statistical analysis and his institution receives funding from St Jude Medical for statistical analysis not relevant to this work. J. Klinger's institution has received fees for review activities from SynteractHCR. F. Stolz is employed by Biomay. N. Breit has received consulting fees and travel support from Biomay. R. Henning is employed by Biomay AG, holds stock, and has patents with the company. R. Valenta's institution has grant funding from Biomay AG, Thermo Fisher, and Fresenius Medical Care, and he has received consultant fees from Biomay AG, Thermo Fisher, and Fresenius Medical Care. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication April 20, 2017; revised August 3, 2017; accepted for publication September 27, 2017.

Corresponding author: Rudolf Valenta, MD, Division of Immunopathology, Department of Pathophysiology and Allergy Research, Center for Pathophysiology, Infectiology and Immunology, Medical University of Vienna, Waehringer Guertel 18-20, 3Q, 1090 Vienna, Austria. E-mail: rudolf.valenta@meduniwien.ac.at.

0091-6749

https://doi.org/10.1016/j.jaci.2017.09.052

Results: Although statistical significance regarding the primary end point was not reached, BM32-treated subjects, when compared with placebo-treated subjects, showed an improvement regarding symptom medication, visual analog scale, Rhinoconjunctivitis Quality of Life Questionnaire, and asthma symptom scores in both treatment years. This was accompanied by an induction of allergen-specific IgG without induction of allergen-specific IgE and a reduction in the seasonally induced increase in allergen-specific IgE levels in year 2. In the first year, more grade 2 reactions were observed in the active (n = 6) versus placebo (n = 1) groups, whereas there was almost no difference in the second year.
Conclusions: Injections of BM32 induced allergen-specific IgG, improved clinical symptoms of seasonal grass pollen allergy, and were well tolerated. (J Allergy Clin Immunol 2017;■■■:■■■-■■■.)

Key words: *Allergy, grass pollen allergy, allergen, allergen immunotherapy, recombinant allergen, B-cell epitope–based immunotherapy, efficacy, hypoallergenic, clinical trial, safety*

Abbreviations used
AE: Adverse event
AIT: Allergen immunotherapy
API: Active pharmaceutical ingredient
AR/C: Allergic rhinoconjunctivitis
EAACI: European Academy of Allergy and Clinical Immunology
FAS: Full analysis set
GPS: Grass pollen season
HBV: Hepatitis B virus
IDMC: Independent data monitoring committee
LS: Least-squares
MS: Medication score
RQLQ: Rhinoconjunctivitis Quality of Life Questionnaire
SA: Safety analysis
SMS: Symptom medication score
SPT: Skin prick test
SS: Symptom score
VAS: Visual analog scale

Allergen-specific immunotherapy is the only disease-modifying treatment for allergy and has long-lasting effects, even after discontinuation.[1-5]

It has been shown that allergen immunotherapy (AIT) is more cost-effective than pharmacotherapy.[6] However, there are several aspects of current allergen extract–based AIT that can be improved, such as safety and convenience.[7] There is a need for safe AIT forms requiring only few administrations. Recently, a grass pollen allergy vaccine (BM32) has been developed that is based on recombinant fusion proteins consisting of nonallergenic peptides derived from the IgE-binding sites of the 4 major timothy grass pollen allergens (Phl p 1, Phl p 2, Phl p 5, and Phl p 6) and the preS protein derived from the large surface antigen of the hepatitis B virus (HBV).[8] Allergen-specific T-cell epitopes were reduced in the recombinant fusion proteins of BM32. Therefore preS was selected to serve as an immunologic carrier protein providing T-cell help for the production of blocking allergen-specific IgG antibodies. The immunologic characterization of BM32 showed a lack of IgE reactivity and allergenic activity, and at the same time, the vaccine induced allergen-specific IgG in animals, which blocked allergic patients' IgE binding to the grass pollen allergens and inhibited allergen-induced basophil degranulation.[8]

In a subsequent clinical skin test study in human subjects, it was demonstrated that BM32 induced neither immediate type skin reactions nor T cell–mediated late-phase reactions, as evaluated by atopy patch testing.[9] This confirmed the lack of allergenic activity and demonstrated that allergen-specific T-cell epitopes, which in previous synthetic allergy vaccines gave rise to systemic late-phase side effects,[10-13] have indeed been eliminated to a large extent in BM32.

A subsequent safety and dose-finding study conducted as a double-blind, placebo-controlled study in an allergen exposure chamber setting showed that 3 monthly injections of BM32 led to a significant reduction of total nasal symptom scores during a 6-hour grass pollen exposure in patients treated with 80 and 160 μg of BM32, which was accompanied by a reduction of the total ocular symptom score and immediate-type skin sensitivity, as determined by using titrated skin prick tests (SPTs).[14] The clinical effects were associated with an induction of allergen-specific IgG ($IgG_1 = IgG_4 > IgG_2$) production and a reduction in allergen-specific T-cell proliferation by inhibition of IgE-facilitated allergen presentation through allergen-specific IgG antibodies.[14]

Here we report the first double-blind, placebo-controlled, multicenter field trial, which investigated the clinical efficacy and immunogenic effects, as well as tolerability, of BM32.

METHODS

Study subjects

To be eligible for the study, subjects had to be aged 18 to 60 years and of either sex, with a positive history of grass pollen allergy confirmed by a positive SPT response (wheal >3 mm) to grass pollen extract and allergen-specific IgE levels (measured by using ImmunoCAP; Thermo Fisher Scientific, Uppsala, Sweden) of at least 3.5 kU_A/L to both grass pollen extract and rPhl p 1/rPhl p 5 at screening or within 12 months before inclusion. They also had to show moderate-to-severe symptoms of grass pollen allergy during the grass pollen season (GPS) of the screening year 2012. Major criteria for exclusion were symptomatic perennial or seasonal coallergies during the GPS, severe ongoing atopic dermatitis, uncontrolled asthma specified by an FEV_1 of less than 70% of predicted value, nasal polyposis, sensitization to Phl p 7 with allergen-specific IgE levels of greater than 0.35 kU_A/L, and participation in a grass pollen–specific immunotherapy trial or use of marketed grass pollen–specific immunotherapy in the 2 years before study start. The complete list of inclusion and exclusion criteria can be found in the study protocol in the Study Protocol and Table E1 in this article's Online Repository at www.jacionline.org. Table I shows that subjects were evenly distributed regarding age, sex, symptoms, and immunologic characteristics regarding the treatment groups.

Study design

This study was a multicenter, double-blind, placebo-controlled, parallel-group, prospective study to investigate the safety and efficacy of 2 years of treatment with BM32 in patients with grass pollen allergy with allergic rhinitis, mild asthma, or both. The trial has been registered under EudraCT no. 2012-000442-35 and ClinicalTrial.gov Identifier NCT01538979. The Study Protocol is available in this article's Online Repository. This study was carried out in 11 centers in 5 European countries (5 sites in Germany, 2 sites in Austria, and 1 site each in Belgium, Denmark, The Netherlands, and Slovenia) and was conducted in accordance with the Declaration of Helsinki and in compliance with Good Clinical Practice guidelines. The study