



Real-life safety study of an accelerated cluster immunotherapy with a house dust mite native extract in patients with allergic rhinitis or rhinoconjunctivitis

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Received: 8 January 2021 / Accepted: 15 February 2021

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Keywords Allergen immunotherapy · Accelerated cluster schedule · Compliance · Natural allergen extract · House dust mites

To the editors

Adherence with allergen immunotherapy is an important weakness of subcutaneous immunotherapy as approximately 50% of patients do not complete the required minimum treatment (3 years) [1]. An accelerated cluster build-up immunotherapy schedule may offer patients a more convenient treatment option. However, this is not usual because of the concerns of immunotherapy-induced systemic reactions. This study aims to assess the safety of a 3-step accelerated cluster immunotherapy based on a natural allergen extract of mites (Beltavac® Depot Plus; Probelte Pharma, Murcia, Spain).

This retrospective study was conducted for patients receiving this 3-step cluster schedule between 2015 and 2020 at the Nuestra Señora de Guadalupe Hospital, (Gomera, Canary Islands, Spain). Patients were aged 5 to 67 years old and diagnosed with mite-induced allergic rhinitis or rhinoconjunctivitis. The build-up cluster immunotherapy protocol consists of three physician's office visits during the first month of treatment (Table 1). Afterwards, the maintenance doses were administered every 4 weeks up to the end of the treatment. Patients were observed for a period

of 30 min after each injection. The main outcome was the number of local and systemic adverse reactions in accordance with the World Allergy Organization Subcutaneous Immunotherapy Systemic Reaction Grading System [2]. The study was approved by an independent ethics committee.

In all, 57 patients met inclusion criteria and 54 completed the build-up phase. The three missing cases did not attend the follow-up appointment and the medical team was unable to locate them. Therefore, adherence to the treatment during this period was 95%. The average patient age was 33 and approximately 50% were polysensitized. All had moderate or severe allergic rhinitis, most associated with conjunctivitis, and in 46% of cases, associated with mild or moderate asthma. All patients were taking a medication to control both rhinitis and asthma symptoms. The vast majority of patients (82%) received an extract with *Dermatophagoides* mixture (50% *D. pteronyssinus* and 50% *D. farinae*). The remainder received a mixture of *Dermatophagoides* and *Blomia tropicalis* at 30 or 50%. This depot extract was adsorbed on aluminum hydroxide and contained 3 µg/ml Der p 1, 2.3 µg/ml Der p 2, 4.5 µg/ml Der f 1 and 2.6 µg/ml Der f 2. A total of 25 adverse reactions were reported among the 280 doses administered (8.9% of doses administered) in 19 patients (33%). All reactions were local, had a papule size of less than 5 cm and occurred within 30 min after administration. Most occurred after the administration of 1 ml at visit 3 (Table 1). All resolved within a few hours and only six patients needed treatment, an oral antihistamine. No patient had to discontinue treatment as a result of an adverse reaction. No systemic reactions were reported.

In conclusion, this preliminary study on the safety of this 3-step accelerated cluster immunotherapy schedule with a native mite extract (Beltavac® Depot Plus) seems to have an acceptable safety profile. Data

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Table 1 Accelerated cluster build up schedule and adverse reactions recorded per visit

Visit No. (day)	Injection No.	Vial concentration (CR ^a /ml)	Schedule (ml)	Total doses	Adverse reactions (No.)	Adverse reactions (%)
Visit 1 (0)	1	1.5	0.2 + 0.2	114	0	–
	2					
Visit 2 (15 ± 7)	3	1.5	0.4 + 0.4	112	6	5.3
	4					
Visit 3 (30 ± 7)	5	1.5	1	54	19	35.1

^aCR (cutaneous response): An allergen extract has an activity of 1 CR/ml when its prick test induces a cutaneous reaction (papule) equal to that produced by a solution of histamine dihydrochloride 10 mg/ml in a population not less than 20 patients clinically allergic to the tested allergen extract

regarding the safety and efficacy with this extract at the standard dose have not been published. However, according to the literature, local reactions associated with conventional allergen immunotherapy are fairly common, ranging from 26 to 82% of patients [3]. On the other hand, systemic reactions are much less frequent, approximately 2 to 5% of patients [2, 4]. Our results seem consistent with previous data; however infrequent adverse reactions may not have been detected because of the small sample size and further research in a larger population will be necessary to confirm these results. To our knowledge, this is the first study assessing the safety of a 3-step accelerated cluster build-up in one month. We suggest that with the appropriate selection of patients the risk of this schedule may be similar to other schedules and, additionally, it may improve patient adherence. We hope this result will encourage research in the area and promote the use of the cluster schedule, which is essential for patients with restricted access to the immunotherapy services.

Author Contribution Elena Rodríguez Plata: Concepcion, acquisition, interpretation, draft of the work and final version approval. Guacimara L. Hernández Santana: Acquisition, revision of the work and final version approval. Estefanía Cubas Mesa: Acquisition, revision of the work and final version approval. Kevin Coello Valeriano: Acquisition, revision of the work and final version approval. María Matas Ros: Analysis, revision of the work and final version approval. Inmaculada Buendía Jiménez: Design, analysis and interpretation, draft of the work and final version approval.

Declarations

Conflict of interest M. Matas Ros is an employee of Probelte Pharma. I. Buendía Jiménez is an employee of Probelte Pharma. E. Rodríguez Plata, G.L. Hernández Santana, E. Cubas Mesa and K. Coello Valeriano declare that they have no competing interests.

Ethical standards The study was approved by the ethic Committee from the *Complejo Hospitalario de Canarias* on September 26, 2019.

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