ORIGINAL ARTICLE

Postmarketing Study for Assessment of Tolerability of a Grass Allergen Immunotherapy Tablet (GRAZAX) in Patients With Rhinitis or Rhinoconjunctivitis

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Abstract

Background and Objective: Many patients with grass pollen allergy in Spain have concomitant sensitization to other allergens such as profilin. Since this type of sensitization is more common in Mediterranean countries than in countries where most patients were enrolled in clinical trials on GRAZAX (*Phleum pratense* 75,000 SQ-T/2,800 BAU, ALK), the aim of this study was to analyze tolerability to GRAZAX under clinical practice conditions in patients with grass pollen allergy.
Methods: A total of 155 patients were enrolled consecutively in a prospective, open-label, observational study. Adverse reactions were recorded during the first month of treatment at 3 different timepoints: after the first dose, when patients were kept under observation for 30 minutes, and on days 15 and 30 after starting treatment
Results: With the first dose, 117 adverse reactions were recorded in 63 patients (40.7%). The commonest reactions (>10% patients) were oral pruritus (25.2%) and throat irritation (24.5%). Ear pruritus was recorded in 7.7%. All reactions but 1 occurred within 30 minutes of administration and all were mild-to-moderate.
At the end of treatment, the percentage of patients with adverse reactions had decreased significantly (21.3%). Most adverse reactions (95.2%) were mild-to-moderate and only 3 (1.4%) were severe. No serious adverse reactions were recorded.
Conclusion: GRAZAX seems to be well tolerated, and most reactions were mild-to-moderate. Many of these reactions occur with the first dose. Therefore, according to the Summary of Product Characteristics, the first dose has to be administered under medical supervision.

Key words: Allergen immunotherapy tablets. Rhinoconjunctivitis. Tolerability. Satisfaction. Grass pollen allergy.

Resumen

Antecedentes y Objetivo: Muchos de los pacientes alérgicos a gramíneas en España presentan sensibilizaciones concomitantes a otros alérgenos como profilina. Dado que este tipo de sensibilización es más frecuente en países mediterráneos que en aquellos otros en los que se incluyeron la mayoría de pacientes de los ensayos clínicos realizados con GRAZAX® (*Phleum pratense* 75,000SQ-T/2,800BAU, ALK, Dinamarca), el objetivo del estudio es recoger datos de tolerabilidad en condiciones de práctica clínica en pacientes con alergia al polen de gramíneas.

Métodos: Se incluyeron 155 pacientes de forma consecutiva en un estudio prospectivo, abierto y observacional. Las reacciones adversas se recogieron durante el primer mes de tratamiento: tras administración de la primera dosis, permaneciendo los pacientes en observación 30 minutos, y 15 y 30 días tras iniciarse el tratamiento.
Resultados: Con la primera dosis se registraron 117 reacciones adversas (RA) en 63 pacientes (40.7%). Las reacciones más comunes (>10% pacientes) fueron prurito oral (25.2%), e irritación de garganta (24.5%). Prurito ótico se registró en el 7.7% de los pacientes. Todas las reacciones excepto una ocurrieron dentro de los 30 minutos tras la administración del tratamiento y todas ellas fueron leves-moderadas. Al finalizar el primer mes de tratamiento el porcentaje de pacientes con RA descendió al 21.3%. La mayoría (95.2%) fueron leves-moderadas y sólo 3 (1.4%) fueron severas. No hubo reacciones graves.
Conclusión: GRAZAX® parece ser un producto bien tolerado, siendo la mayoría de reacciones leves-moderadas. Como muchas de ellas ocurren con la primera dosis, es importante que ésta se administre bajo supervisión del especialista.

Palabras clave: Liofilizado oral de gramíneas. Rinoconjuntivitis. Tolerabilidad. Satisfacción. Alergia al polen de gramíneas.

Introduction

Allergic rhinitis is a major health problem. In a survey conducted in Europe, prevalence was found to be about 23% (17%-29%) [1]. Such high prevalence means that this disease represents a considerable economic burden on health systems. In several countries, the costs of allergic rhinitis are highly significant: in the United States, the indirect costs (US$0.1-9.3 billion, including lost productivity) are even higher than the direct costs (US$1.6-4.9 billion). The indirect costs are also higher in allergic rhinitis than in conditions such as stress, migraine, and depression [2]. Grasses are one of the commonest causes of allergic rhinitis and have a clear impact on patients' quality of life [3]. Current recommended symptomatic treatment for allergic rhinitis includes topical nasal corticosteroids and antihistamines. However, a recent survey in the UK found that over 40% of patients were dissatisfied with this type of treatment [4]. Allergen-specific immunotherapy is an etiological treatment that acts on the immunopathogenic mechanisms of the allergic reaction. It can prevent the onset of symptoms and reduce the need for medication by changing the natural course of the allergic disease [5].

In 2006, GRAZAX (*Phleum pratense*, 75,000 SQ-T/2,800 BAU, ALK) was registered in Europe under the mutual recognition procedure and approved for disease-modifying treatment of grass pollen–induced rhinitis and rhinoconjunctivitis in adults and children aged >5 years [6]. Its efficacy, safety, and sustained effect have been demonstrated in various randomized controlled trials [7-15]. We present the first observational study on this product in Spain. Such a study is interesting in our setting for 2 reasons: first, many patients with grass pollen allergy in Spain are subject to high grass pollen concentrations; second, many patients with grass pollen allergy have concomitant sensitization to other allergens, such as profilin [16-17]. Since this type of sensitization is more common in Mediterranean countries [18] than in countries where most patients were enrolled in clinical trials with GRAZAX, our objective was to collect data on tolerability in clinical practice among patients living in Spain.

Methods

Patients and Study Design

The study population comprised 155 patients who were enrolled consecutively at 10 hospitals. Patients were aged ≥18 years and had been diagnosed with grass pollen–induced rhinitis or rhinoconjunctivitis, according to ARIA guidelines [19]. Diagnosis was by prick test (grass mix prick test [ALK], wheal diameter ≥3 mm), positive IgE to *P pratense* (CAP ≥class 2), or both. The inclusion and exclusion criteria were in accordance with the GRAZAX Summary of Product Characteristics (SmPC). In addition to applying the contraindications set out in the SmPC, we also excluded patients who had received immunotherapy for grasses in the 5 years prior to study entry, since treatment-experienced patients could have shown better tolerability of the product under study.

Sensitization to profilin was assessed using prick test (profilin prick test [ALK], wheal diameter ≥3 mm).

The postauthorization study had a prospective, open-label, observational design and was approved by the health authorities of the different autonomous communities where the study was conducted and by local ethics committees. All participants gave their written informed consent to participate in the study.

Treatment

Treatment was administered in the form of a tablet (GRAZAX®. *Phleum pratense*, 75,000 SQ-T/2,800 BAU, ALK).

In accordance with the SmPC, patients were kept under observation for 30 minutes after taking the first dose. The duration of follow-up was 1 month.

Assessment of Response

Adverse reactions were recorded during the first month of treatment at 3 different timepoints: during the observation period and on days 15 and 30 after starting treatment. Patients were given a purpose-designed form where they noted any reactions and which they returned to the doctor at each follow-up visit. The investigators assessed the severity of adverse

reactions using the following definitions: mild (transient symptoms, no interference with daily activities), moderate (marked symptoms, moderate interference with daily activities), and severe (unacceptable symptoms, considerable interference with daily activities). Adverse reactions were coded in accordance with MedDRA terms (version 13.1). The analysis included all patients who had received at least 1 dose of treatment.

Results

Of the 155 patients included in the study, 19 did not continue treatment after the first month and a further 9 said they would discontinue treatment after the first month. The reasons for discontinuation were adverse reactions in 16 cases, patient's decision in 3, and doctor's decision in 1. The cause was unknown in 8 patients.

Table 1. Symptoms Recorded and Medication Taken During the Pollen Season Prior to Study Entry

Symptoms	No.	%
All patients (1 missing)	154	100
Nose symptoms		
– No symptoms	0	0
– Mild	7	4.55
– Moderate	94	61.04
– Severe	53	34.42
Eye symptoms		
– No symptoms	2	1.30
– Mild	16	10.39
– Moderate	98	63.64
– Severe	38	24.68
Respiratory symptoms		
– No symptoms	77	50.00
– Mild	36	23.38
– Moderate	37	24.03
– Severe	4	2.60
Skin symptoms		
– No symptoms	140	90.91
– Mild	6	3.90
– Moderate	8	5.19
– Severe	0	0
Medication		
AH (topical)	39	25.15
AH (oral)	148	95.47
Corticosteroids (oral)	4	2.58
$ß_2$-agonists (inhaled)	51	32.90
Corticosteroids (topical)	93	59.99
Missing	3	1.93

Abbreviation: AH, antihistamines.

Table 2. Adverse Reactions to the First Dose

	No.	%	Events
All patients	155		
All adverse events	63	40.65	117
Gastrointestinal disorders			
– All adverse events	47	30.32	55
– Oral pruritus	39	25.16	41
– Dysphagia	3	1.94	3
– Lip edema	3	1.94	3
– Flatulence	1	0.65	1
– Edema mouth	1	0.65	1
– Nausea	1	0.65	1
– Cheilitis	1	0.65	1
– Glossitis	1	0.65	1
– Dyspepsia	1	0.65	1
– Abdominal pain	1	0.65	1
– Hyperchlorhydria	1	0.65	1
Respiratory, thoracic and mediastinal disorders			
– All adverse events	41	26.45	46
– Throat irritation	38	24.52	38
– Cough	3	1.94	3
– Asthma	1	0.65	1
– Dysphonia	1	0.65	1
– Pharyngeal disorder	1	0.65	1
– Larynx irritation	1	0.65	1
– Oropharyngeal swelling	1	0.65	1
Ear and labyrinth disorders			
– All adverse events	12	7.74	12
– Ear pruritus	12	7.74	12
Eye disorders			
– All adverse events	2	1.29	2
– Lacrimation increased	1	0.65	1
– Eye pruritus	1	0.65	1
Nervous system disorders			
– All adverse events	1	0.65	1
– Dizziness	1	0.65	1
General disorders and administration site conditions			
– All adverse events	1	0.65	1
– Sensation of foreign body	1	0.65	1

Demographic and Clinical Characteristics

The mean (SD, range) age of the patients was 31.9 (9.8, 18-62) years with an equal distribution by sex (50% women, 50% men). Age at onset of allergy was 16.1 (8.7) years. Of the patients comprising the final study sample, 16.1% were sensitized to profilin, 8.4% had food allergy, and 41% had asthma associated with rhinoconjunctivitis. The type and severity of symptoms during the season prior to study entry as well as the type of medication used for symptom control are presented in Table 1. Before taking the study medication,

Table 3. Adverse Reactions at Visits 2 and 3

	No.	%	Events
All adverse events	71	52.21	206
Gastrointestinal disorders			
– All adverse events	48	35.29	104
– Oral pruritus	24	17.65	53
– Edema mouth	10	7.35	14
– Dyspepsia	5	3.68	9
– Lip swelling	6	4.41	7
– Vomiting	1	0.74	5
– Dysphagia	3	2.21	3
– Tongue edema	2	1.47	2
– Abdominal pain	1	0.74	1
– Nausea	1	0.74	1
– Tongue eruption	1	0.74	1
– Flatulence	1	0.74	1
– Oral disorder	1	0.74	1
– Salivary hypersecretion	1	0.74	1
– Gastroesophageal reflux disease	1	0.74	1
– Hypoesthesia oral	1	0.74	1
– Abdominal pain upper	1	0.74	1
– Aphthous stomatitis	2	1.47	2
Respiratory, thoracic and mediastinal disorders			
– All adverse events	36	26.47	71
– Throat irritation	30	22.06	49
– Oropharyngeal discomfort	1	0.74	1
– Rhinitis allergic	4	2.94	6
– Wheezing	2	1.47	3
– Rhinorrhea	2	1.47	2
– Dyspnea	1	0.74	2
– Oropharyngeal swelling	2	1.47	2
– Cough	2	1.47	2
– Asthma	1	0.74	1
– Dry throat	1	0.74	1
– Asphyxia	1	0.74	1
– Laryngeal edema	1	0.74	1
Ear and labyrinth disorders			
– All adverse events	12	8.82	12
– Ear pruritus	10	7.35	11
– Ear congestion	1	0.74	1
Eye disorders			
– All adverse events	6	4.41	8
– Allergic conjunctivitis	4	2.94	6
– Conjunctival hyperemia	1	0.74	1
– Eye pruritus	1	0.74	1
Nervous system disorders			
– All adverse events	4	2.94	6
– Dizziness	3	2.21	5
– Headache	1	0.74	1
Skin and subcutaneous tissue disorders			
– All adverse events	2	1.47	5
– Pruritus	2	1.47	5
General disorders and administration site conditions			
– All adverse events	2	1.47	2
– Face edema	1	0.74	1
– Sensation of foreign body	1	0.74	1

57% of patients were dissatisfied or very dissatisfied with the results of symptomatic treatment received during the grass pollen season.

Tolerability

With the first dose, 117 adverse reactions were recorded in 63 patients (40.7%). The commonest reactions (>10% patients) were oral pruritus (25.2%) and throat irritation (24.5%). Ear pruritus was recorded in 7.7%. The full list of reactions is given in Table 2. All reactions but 1 occurred during the 30-minute observation period (86.3% occurred in the first 15 minutes): 66.7% were mild, and the remaining 32.5% were moderate. No serious or severe reactions were recorded. Only 18 of the reactions required pharmacological treatment, and the patient recovered completely in all 18 cases.

At the second visit, the percentage of patients with adverse reactions (41.3%) was similar to that at the first visit, while at the end of the month of follow-up, the percentage had decreased significantly (21.3%).

The adverse reactions reported at visits 2 and 3 are shown in Table 3. Most (95.2%) were mild-moderate; 3 (1.4%) were severe. No serious adverse reactions were recorded, and 24 (11.5%) required treatment (mainly antihistamines).

The 3 severe reactions occurred in 2 patients. The patient who had 2 severe adverse reactions suffered from cough and laryngeal edema, which remitted with antihistamine treatment (cetirizine). These reactions occurred after 10 days of treatment and resolved in 1 day. The patient was 18 years old and had rhinoconjunctivitis and asthma. With the first dose he experienced a mild reaction consisting of an itchy throat. The third severe reaction was in a 19-year-old patient who had rhinoconjunctivitis and urticaria. The reaction consisted of facial edema, which remitted after 3 days of treatment with antihistamine (levocetirizine), and occurred after 14 days of treatment. The patient did not have a reaction to the first dose.

For profilin-sensitized patients (diagnosed by prick test), the tolerance profile did not differ from the global profile in terms of severity of adverse

events. Adverse reactions were recorded in 44% of patients sensitized to profilin.

Global Tolerability Assessment

At the end of the study, each patient was asked about how adverse reactions had influenced their perception of treatment. According to 96.6% of the patients who answered the questions, the adverse reactions had little or no impact on their state of health, and 91.3% said they had little or no impact on their degree of satisfaction with treatment.

Discussion

This multicenter study assessed the tolerability of GRAZAX under real conditions of use and in geographical areas with high grass pollen levels [20-22]. Therefore, patients exposed to such high pollen concentrations, especially in the case of grasses, have a higher incidence of concomitant sensitization to minor allergens such as profilin, which has a prevalence of over 50% in certain areas [16]. Consequently, the aim of this study was to obtain data from clinical practice on the tolerability of a product that has been documented as safe in clinical trials [9,11,18].

The adverse reactions observed were mainly local (oral pruritus, throat irritation) and consistent with those observed in clinical trials with GRAZAX [7-11]. The same pattern was also found for the severity of the reactions. In more than 95% of cases, reactions were mild or moderate, and no serious adverse reactions were recorded. The percentage of patients who discontinued treatment because of adverse reactions was somewhat higher than in clinical trials performed with the same product [8,11]. Further studies with a different design would be necessary to explain this difference.

In accordance with the SmPC, the first dose should be administered under medical supervision. This approach also enables the physician to prepare the patient for expected adverse reactions and to inform the patient that, if the treatment is continued, the adverse reactions will decrease. The fact that almost all the reactions to the first dose were immediate (within 15 minutes of administration) justifies this recommendation. Medical supervision at this time also increases adherence, since it enables the physician to adequately explain the safety profile to the patient, who will subsequently administer the drug at home.

The results of a phase 1 clinical trial with GRAZAX [9] showed that the frequency of adverse reactions decreased significantly after the first week of treatment. In our study, we also observed a decrease in the percentage of patients with adverse reactions throughout the study. Compared with the first dose, the number of patients with adverse reactions was 40.7%, which is similar to the percentage recorded at the second visit (41.3%), although both figures decreased by around 50% after 1 month of treatment (21.3%). It has been suggested that this rapid onset of improved tolerability with the allergen immunotherapy tablet administered daily may be due to downregulation of immunoglobulin E–mediated signaling pathways in inflammatory cells (eg, mast cells and basophils), particularly reduced Syk protein levels [9].

In conclusion, GRAZAX seems to be well tolerated in clinical practice, and most reactions were mild-to-moderate. Many of these reactions occur with the first dose. Therefore, according to the SmPC, the first dose has to be administered under medical supervision.

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Conflicts of Interest

Fernando de la Torre works for ALK, Spain. The remaining authors declare that they have no conflicts of interest.

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