A major step forward for sublingual immunotherapy: the quality of 5-grass pollen tablet is recognized also in Italy

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Dear editor

After a century of allergen immunotherapy (AIT), for the first time, the Italian Agency for Drugs (AIFA [Agenzia italiana per il farmaco]) has just approved the full reimbursement (A class) for an AIT product, such as the 5-grass pollen tablet with the indication for treating allergic rhinitis (AR).

On the other hand, AR represents a relevant health issue as the worldwide prevalence is approximately 20%.¹ AR is sustained by an IgE-mediated inflammatory reaction that in turn induces typical symptom occurrence. Allergic inflammation is promoted by an allergen-specific defect of T-regulatory cells and a Th2 polarization.² This impaired immune response characterizes the two main peculiarities of allergic reaction: systemic IgE production and nasal eosinophil infiltrate.³ AR has also a significant social burden both in terms of high costs and individual complaints, mainly negatively affecting quality of life. AR treatment is traditionally based on drug prescription, such as antihistamines and topical corticosteroids. However, the main limit of drug therapy is that it is essentially symptomatic and its efficacy quickly stops after suspension. On the contrary, AIT is the unique causal therapy of AR as it is able of inducing a long-lasting immunological and clinical tolerance toward the causal allergen.⁴ The mechanism of action of AIT is based on restored T-regulatory function and re-direction of immune response to a physiological Th1-oriented pathway.⁵ AIT consists of administering increasing doses of the causal allergen extract able to reduce allergic symptoms.⁶ There is strengthened evidence that AIT is effective and safe as recognized by the meta-analysis approach.⁷ At present, sublingual immunotherapy is commonly prescribed for AR patients as effective and well tolerated.

The 5-grass pollen tablet according to a pre-co-seasonal course, has the indication for AR and/or conjunctivitis treatment in adult or pediatric (over 5 years) patients with severe symptoms as documented by two regulatory studies.^{8,9} AIFA's decision of full-reimbursement for the 5-grass pollen tablet has been based on the qualified requirements of this product: allergen panel composition, effectiveness, safety, standardization, adequate dosage, and pharmaco-economic impact. First, sublingual tablets are composed of 5-grass pollens, belonging to Pooideae family (*Dactylis glomerata*, *Anthoxanthum odoratum*, *Lolium perenne*, *Poa pratensis*, and *Phleum pratense*). This 5-grass mixture is appropriate according to the production of pollen by the grasses as evidenced by phenological studies.¹⁰ In fact, the approach by phenology demonstrated that the different grasses yield their pollen in dissimilar times of the season in

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a specific geographical area in Italy and that some grasses, such as *P. pratense*, produce their pollen in periods out of the pollen peaks in the atmosphere, when patients have no more intense symptoms.¹⁰ Of course, the presence of a given grass species is closely related to symptom appearance in grass allergic patients. Thus, the 5-grass mixture extract has optimal characteristics to cover the whole grass pollination period, so assuring a clinical effectiveness for a large population of grass pollen allergic patients. In addition, it has been reported that the 5-grass pollen mixture has ideal immunological capability of inducing immunization in AR patients,^{11,12} considering that 5-grass pollen tablet contains a large array of allergens naturally occurring in the atmosphere, that trigger allergic symptoms. An immunological study demonstrated that in children living in the Mediterranean area the 5-grass mixture is more alike to natural grass exposure than *P. pratense* extract alone.¹³ Another interesting issue is the molecular aspect, because among the grass species there is a lot of differences in the amino acid sequence of the allergens from the group 1 and 5, as confirmed by a study of Moingeon et al¹⁴ who highlighted by mass spectrometry the different three-dimensional structure of these allergens between the Pooideae that results in a large number of epitopes that are not shared among the various species. Indeed, the characteristics of 5-grass pollen tablet have a clinical relevance as the administration of the 5-grass-pollen mixture allows to obtain quick effectiveness. In this regard, a study using the “Vienna chamber” model showed that 5-grass pollen tablet significantly reduced allergic symptoms after 7–30 days.¹⁵ Moreover, an economic evaluation stated that 5-grass pollen tablet is a cost-effective treatment in patients with grass pollen-induced seasonal AR.¹⁶ Another intriguing aspect is that its cost-effectiveness increases with the severity of AR symptoms as evidenced by a recent analysis concerning the higher clinical efficacy of the 5-grass pollen tablet treatment in patients with more severe AR.¹⁷ These outcomes should be thoroughly taken into consideration in the management of AR patients. It is also of note that 5-grass pollen tablet is a drug listed as treating grass allergy with AIT by the Canadian Drug Expert Committee.

In conclusion, the AIFA decision about the full reimbursement of an AIT product for AR treatment has an outstanding importance for 5-grass pollen tablet, this fact provides a new

consideration of AIT and paves the way to a new era in the centenary AIT history.

Disclosure

Giorgio Ciprandi is a scientific consultant for Stallergenes Italy, and has no other conflicts of interest to disclose.

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