

Allergic rhinoconjunctivitis: pathophysiological mechanism and new therapeutic approach

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Summary. Allergic rhinoconjunctivitis (AR) is the most common IgE-mediated disease. A type2 immune response is involved in AR pathogenesis. Allergic inflammation is characterized by eosinophilic infiltrate and mediators release. AR treatment is usually based on medication prescription, including antihistamines and intranasal corticosteroids. However, medications may be prescribed for long periods and sometimes may be scarcely effective, thus aggressive strategy should be used. Therefore, complementary medicine is becoming attractive for patients at present. Nutraceuticals represent interesting therapeutic options in clinical practice. In this regard, a new compound has been designed containing Vitamin D3, *Perilla* extract, and quercetin. (www.actabiomedica.it)

Key words: allergic rhinoconjunctivitis, inflammation, immune response, nutraceuticals

Allergic rhinoconjunctivitis (AR) is the most common IgE-mediated disorder as its prevalence has exceeded the 40% of the general population; in particular, the most worrying aspect is that AR prevalence has approximately doubled over the past 20 years (1). Thus, the term Allergy Epidemic has been coined to emphasize this alarming phenomenon. Many hypotheses have been proposed to explain this exponential growing: the most updated is the Microbiota Hypothesis (2). This theory concerns the pivotal role exerted by the intestinal microbiota in manipulating the immune response, mainly in infancy and childhood. An altered composition of the human microbiota, namely a reduction of quality and quantity of microbial strains, impairs the physiological maturation of the immune system (3). In other words, the microbiota represents a reservoir of antigens that are crucial to stimulate the developing the immune function in infants and children (4). An adequate antigenic “pressure” is necessary

to ensure the correct immunological maturation that is physiologically oriented toward a type1 polarization (Figure 1). Type1 immune response is necessary to guarantee a correct defence against infectious agents. Therefore, a defective composition, i.e. qualitative and/or quantitative, of the human microbiota promotes the maintenance of Type2-polarized immune response that is typical of the foetal period (5,6). Actually, the foetus would represent for the mother a non-self-antigen and consequently should be rejected. To avoid this negative situation, the foetal-placental unit develops a type2 milieu able to preserve the foetus from the potential maternal reject. The foetus grows therefore in an environment that is Type2-polarized and the infant maintains that arrangement. Therefore, the physiological maturation from a type2-polarized toward a type1-oriented immune response is promoted by a correct, such as quantitatively and qualitatively, antigenic exposure, insured by the “good” microbiota. However,

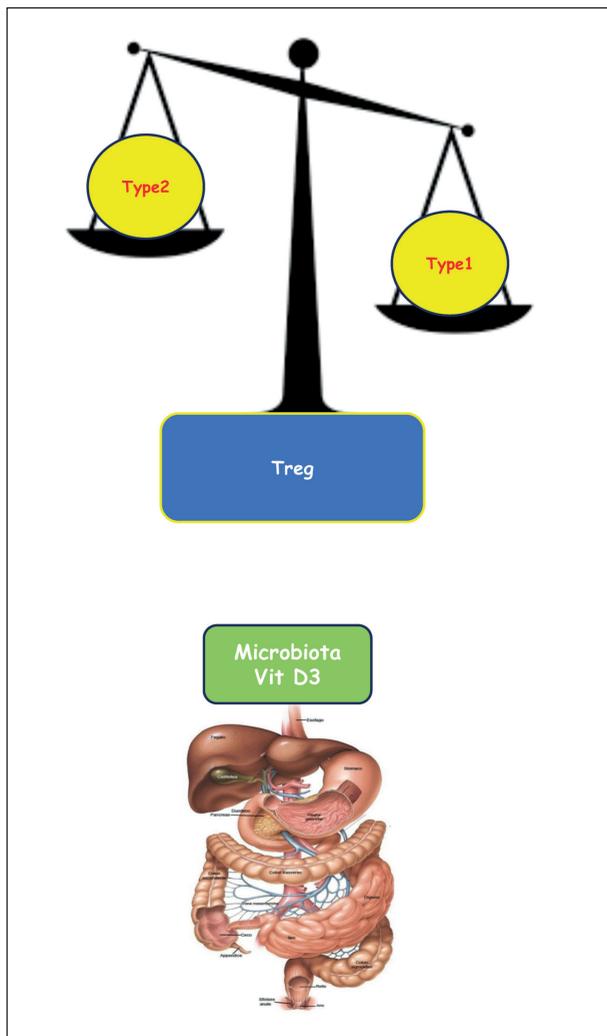


Figure 1. Balance between type1 and type2 immune response in healthy subjects. Treg= T regulatory cells

the present life-style, mainly occurring in the western countries, is characterized by a low fibre diet, vaccinations, reduced infections, antibiotics overuse, in other words a “over-hygienic” environment. This situation alters the normal composition of the microbiota, impairs the maturation of the immune system, and ultimately allows the increase of allergic disorders. In this context, Vitamin D₃ exerts synergic activity with microbiota to guarantee a correct immune function.

As explained, the immune response is dysregulated in allergic patients and is polarized toward the type2. The main cellular factor involved in this imbalance is the T regulatory cell subset. Allergic patients paradigmatically present an allergen-specific functional

defect of T regulatory cell. This defect depends also on both impaired microbiota and Vitamin D₃ deficiency (2). However, this unbalanced arrangement may be reversible as may be corrected by specific treatments. The defect of T regulatory cells maintains the type2 polarization that results in the sensitization phenomenon, i.e. the ongoing production of immunoglobulin class E (IgE) characterized by the same allergen-specificity of T regulatory cells (2). The IgE are abundantly present on the surface of the primary effector cells, such as mast cell and basophil. When the allergen enters into the nose and the eye, it binds with the specific IgE, covering the mast cell surface, and immediately starts the allergic reaction (Figure 2). Really, this antigen-IgE link activates mast cell that releases pre-formed mediators, including primarily histamine, and cytokines, and produces neo-formed mediators, including arachidonic acid metabolites. Histamine is the main mediator involved in allergic reaction and is of primary importance

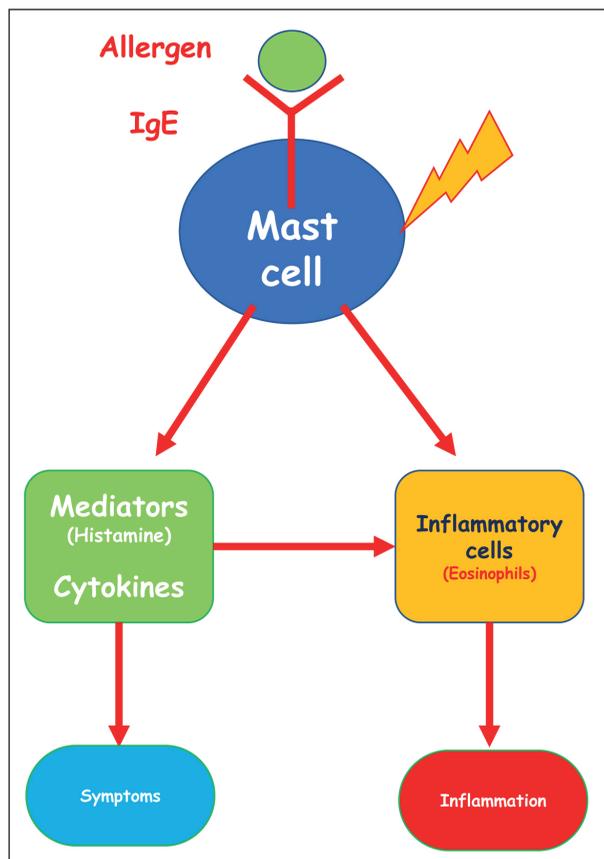


Figure 2. Allergic reaction consequent to allergen exposure

as it elicits all allergic symptoms. On the other hand, mast cell-derived cytokines induce the cascade of inflammatory phenomena typical of allergic inflammation. Allergic inflammation is in turn responsible to cause other clinical events, mainly concerning mucosal swelling and vascular congestion and leakage.

The pivotal pathophysiological characteristic of allergic reaction is the presence of a typical inflammatory pattern at the level of the target organ, i.e. the nose and the eye in AR patients (7). In particular, an abundant eosinophilic infiltrate represents the typical feature during allergic reaction. A fundamental concept has been evidenced some years ago: the persistence of allergic inflammation until the allergen exposure occurs. This paradigm is essential to recognize the need of using anti-inflammatory medication to treat allergic patients for long time.

From a clinical point of view, AR is characterized by nasal and ocular symptoms (such as ocular and nasal itching, nasal congestion, sneezing, watery rhinorrhoea, eye redness, and lacrimation), and also general complaints such as fatigue and cough. In particular, the most disturbing symptoms are nasal congestion and ocular itching.

AR has also detrimental effects on mood, sleep, social activities, work and scholastic performance. If there is asthma comorbidity, uncontrolled AR may aggravate the asthmatic symptoms. Moreover, quality of life is significantly impaired in children and adolescents with AR (7). Therefore, all allergic patients should be adequately treated.

In addition, AR is characterized by two clinically relevant aspects. First, AR frequently precedes the asthma onset as the airways share common pathogenic mechanisms (8). In addition, AR patients have more infections than non-allergic subjects because of an impaired type1 immune response and a mucosal inflammation that promote infections (9-11).

AR treatment is usually pharmacological, including antihistamines and intranasal corticosteroids, even though these drugs exert a merely symptomatic effect as do not cure allergy; in addition, medications could not completely relieve symptoms (12). However, it is well known that aggressive therapy and prolonged use of medications may produce significant side effects, thus these strategies should be limited or avoided al-

together in children (13). As a consequence, more and more people prefer to use complementary medicine, for example herbal medications and vitamins (14). In this regard, there is a growing interest around nutraceuticals.

Nutraceuticals are just substances of natural origin that can have a positive effect on the state of health. At present, nutraceuticals, with proven efficacy, are popularly associated with conventional therapy to speed up recovery, make it long lasting, and avoid aggressive therapeutic regimens, including systemic corticosteroids, or at least limit their duration if they are needed (15,16). Their use is popular, but methodologically correct studies (randomized controlled trials, RCT) are very few.

Recently, a new compound has been developed for the treatment of allergic rhinoconjunctivitis: Lertal®. The current Supplement will present and discuss its components, the published evidence, and new experiences conducted in clinical practice.

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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