

Principles of successful immunotherapy

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DEFINITION OF SUCCESSFUL IMMUNOTHERAPY

The clinical efficacy of allergen-specific immunotherapy in hayfever has been convincingly documented [1]. The majority of controlled studies in asthmatics published during the last decade, shows a tendency towards a beneficial effect [2]. Immunotherapy seldom has the capacity to act as a curative treatment. The expected magnitude of symptom and drug reduction is important, as in the case of asthma, immunotherapy often only results in a reduction in disease severity. A significant reduction in drug intake will, however, imply a reduced risk of the pharmacological drug treatment, thus improving the quality of life [3]. However, if the expectations from immunotherapy are a complete abolishment of symptoms, the treatment will be considered a failure. The claim of critics, that immunotherapy has to show its superiority to available pharmacotherapy alternatives, is to me a fundamental mistake. The clinical efficacy of immunotherapy should not be compared with drug treatment, but immunotherapy should be used as a supplement to drug treatment in order to achieve a multifactorial treatment approach interfering broadly with the pathophysiology of allergic diseases.

INDICATION FOR IMMUNOTHERAPY

Contraindications

Immunotherapy means a severe manipulation of the patient's immune system. Even when large studies fail to reveal increased collagenous, auto-immune or lympho-proliferic disease in patients treated with immunotherapy over many years, this treatment would normally be avoided in patients with an underlying immune system disorder (systemic disease, immune deficiencies, cancer or chronic infections) [4].

Since a reasonable result of immunotherapy is dependent upon active participation of both patient and therapist, lack of cooperation is a contraindication for starting treatment [4].

Immunotherapy should not be undertaken in patients with diseases rendering the treatment of anaphylactic reactions difficult like coronary heart diseases, arterial hypertension, and treatments with β -blockers [4].

Even though multiple studies have failed to show any teratogenic damage during immunotherapy, treatment should not be started during pregnancy due to the risk of anaphylactic shock and the consequent abortion or detrimental effect on the foetus. However, an already commenced immunotherapy, perhaps with reduced dose, gives a risk of anaphylactic shock which is so minimal that it is advisable to continue treatment if pregnancy occurs. The slightest hesitation from the patient's side, however, should lead to the termination of treatment [4].

Factors to consider before using immunotherapy

Immunotherapy has only shown effect in unequivocally IgE-mediated allergic conditions, i.e. IgE-mediated rhinoconjunctivitis, IgE-mediated bronchial asthma and IgE-mediated anaphylaxis due to insect allergy [5].

In order to increase the probability of a satisfactory clinical response in immunotherapy, it is crucial that exacerbations and the overall severity of the disease are caused by allergen exposure. This can only be ascertained from the history, since there is no convincing correlation between the severity of disease judged by the symptom score and the reactions in diagnostic tests [6].

The value of allergen avoidance can be discussed, but in practice immunotherapy should not be commenced unless attempts have been made to eliminate the allergen in cases where it is technically feasible [4]. This is not possible for pollen allergy. Animal dander allergens can be reduced in the patient's home (by removing pets, etc.) but unless the patient's social life is to be severely restricted, it is not possible to totally eliminate the indirect exposure of the patient in e.g. nursery schools, work, schools, public transport, social contacts, etc. In theory, elimination of house dust mite is possible, but in practice it has proved difficult to reduce the amount of mites with ordinary cleaning. Elimination of mould spores is not possible outdoors.

When considering immunotherapy, it is important to evaluate whether the overall severity of the disease is sufficient to warrant this type of therapy. In case of life-threatening disease like anaphylaxis caused by allergy to *Hymenoptera*, immunotherapy represents the only acceptable alternative [7]. Inhalant allergy may be treated with drugs, but in fact the mortality of asthma has increased despite the introduction of potent and more efficacious anti-asthmatic drugs [8]. Several recent studies have focused on the modulation of inflammation by immunotherapy caused by a capacity to inhibit the release of allergic mediators from mast cells [9]. The treatment of asthma should aim at preventing bronchial inflammation and epithelial damage in order to avoid the development of a non-reversible chronic obstructive pulmonary disease. A substantial number of patients with hayfever develop asthma at a later stage of the disease, but several studies have shown a significant capability of immunotherapy to reduce the further development of rhinitis into asthma. Theoretically, the

reduction in airway inflammation may impede the development of new allergies and in that way alter the spontaneous course of the disease.

ALLERGEN EXTRACTS

The availability of an adequate allergen preparation is equally important as the indication for immunotherapy. Immunotherapy may be insufficient regarding the qualitative and quantitative composition of the allergenic components in the extracts [10]. Therefore it is essential to use well-characterized, standardized allergen extracts in sufficiently high doses. In an attempt to make immunotherapy more effective with reduced side effects, modified allergen extracts have been developed [11]. Clinical trials of the effect of modified allergen extracts have shown the same efficacy as non-modified extracts and a reduced occurrence of side effects. With routine immunotherapy, allergen extracts containing allergen determinants to which the patient does not have IgE antibodies, are used. By isolating the allergenic determinants in a mixed extract, to which the patient has a specific IgE-reaction, tailor-made extracts can be produced and used for immunotherapy. The clinical effect of immunotherapy is dose-related and it is recommended that the maximum tolerated dosage is used. This may be defined as a clinically effective allergen dose inducing a minimum of side effects.

SAFETY OF IMMUNOTHERAPY

In the evaluation of the potential risks and benefits, it is hard to obtain a strictly scientific attitude as to whether immunotherapy should or should not be added to the pharmacological treatment of allergic diseases. Immunotherapy implies injection of allergens in an IgE-sensitized person and thereby a potential risk of eliciting anaphylactic reactions.

Immunotherapy and side effects

When investigating side effects in immunotherapy it is important to distinguish between the almost inevitable large local reactions i.e. diffuse swellings which may persist for a day or more. These local reactions are annoying, but in no way dangerous. Immediate systemic reactions may be subdivided into mild and life-threatening ones. The mild reactions include rhinitis, mild asthma, and urticaria responding well to minimal treatment. The life-threatening side effects like severe exacerbations of asthma, anaphylaxis, and infrequent fatalities represent the major problem in immunotherapy [12]. The life-threatening side effects should be treated intensively and without any delay. With the use of standard allergen extracts, what could be called the immunotherapy balance implies that the allergen dose injected constitutes a delicate balance between a dosage resulting in optimal clinical efficacy, and a dosage resulting in severe life-threatening systemic side effects.

Measures to reduce side effects

Patients should be carefully informed of the principle of immunotherapy and contraindications observed. The allergic disease should be treated optimally with relevant drugs in order to normalize lung function etc. before injections. Patients should be instructed to report recent exacerbations in allergic diseases and infections as well as local and systemic reactions following the preceding injection.

Physicians should be given adequate training in practical immunotherapy and be supplied with facilities for treating anaphylaxis including supplies of adrenaline, oxygen, and intravenous fluids [13]. Since a significant proportion of life-threatening side effects are due to errors in dosage and timing, meticulous care must be taken when attending to procedures. Likewise, clinical evaluation and whenever possible peak flow (or equivalent) readings in asthmatics should be made before each injection and repeated before the patient leaves the clinic.

Allergen extracts should be standardized, optimally in relation to the IUIS International Standards. Only high-quality extracts with a minimal batch variation and documented stability should be used.

Direct medical supervision of allergen administration is recommended including an adequate observation period after each injection, with a view to the early recognition of local and systemic reactions, and prompt treatment [4, 5].

CONCLUSION

The inflammatory nature of the allergic reaction calls for an intensive treatment to prevent the initially completely reversible bronchospastic reaction from evolving into a chronic, irreversible, obstructive airway disease with persistent reduction of pulmonary function. Recent studies indicate that immunotherapy may have the capacity of turning off the allergic reaction thereby interrupting the chain of events resulting in the smouldering clinical picture characterizing allergic disease of the lower respiratory tract. Immunotherapy has the obvious advantage of regular consultations implying a closer and more intensive observation of patients with severe disease. This is of special importance in the attempts to increase monitoring to avoid under-medication of asthma, and enhances the possibilities of more intensive treatment during acute exacerbations. A second advantage of immunotherapy in the treatment of allergy is the fundamental interference in the pathophysiological mechanisms responsible for the disease. In our opinion immunotherapy has some obvious advantages over non-specific drug treatment on condition that patients are selected using the right indication, high-quality extracts, and that allergists are educated to take all necessary steps to reduce side effects and to treat adequately.

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