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REVIEW

Dose dependence of efficacy and safety of subcutaneous immunotherapy

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ABSTRACT: ***Dose dependence of efficacy and safety of subcutaneous immunotherapy. C. Incorvaia, F. Frati, P. Puccinelli, G.G. Riario-Sforza, S. Dal Bo.***

A number of experimental and clinical evidence has shown that exposure to high amounts of allergen molecules favours the development of tolerance. This is true also for subcutaneous immunotherapy (SCIT), for which a dose dependence of clinical efficacy was clearly demonstrated. The effective doses, measured as μg of major allergens, to be administered during maintenance treatment were established for the main allergens. Regarding pollens, the range of effectiveness corresponds to 25-41 and 13-20 μg of major allergens Phl p 5 and Phl p 6 for grasses, to 10-47 μg of Amb a 1 for ragweed, to 12 μg of Bet v 1 for birch, and to 6.2 μg of Par j 1 for *Parietaria*. With house dust mites, a maintenance dose of 5-11.5 μg of the major allergen from *Dermatophagoides pteronyssinus* Der p 1 is associated to clinically relevant effects, and with cat epithelium the clinical success is observed using a dose of 13-15 μg of Fel d 1.

Nevertheless, there are adverse reactions facing SCIT, which are related to the amount of injected allergen. In fact, the safety decreases when the administered doses increase. This has led to "optimal doses" being defined which show a good balance between efficacy and safety (corresponding for example to a dose of 7 μg for Der p 1 and of 13 μg for Fel d 1). The dose dependency with respect to both efficacy and safety makes essential to accurately consider the risk/benefit ratio in each patient eligible for SCIT.

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Introduction

Allergen specific immunotherapy is generally recognised as an effective treatment for rhinitis and asthma caused by sensitisation to inhalant allergens and of Hymenoptera venom allergy [1, 2]. However its efficacy is strictly related to the fulfilment of some prerequisites regarding the selection of patients and the performance of the treatment. A pivotal aspect is represented by the dose dependence of efficacy, which first emerged in the fifties in a study by Johnstone [3] and was later confirmed for both aeroallergens [4] and Hymenoptera venoms [5].

A number of scientific observations support the importance of the quantitative relationship between the allergenic molecules and the immune system. It is well known that a cytokine pattern typical of Th2 lymphocytes favours the allergic response to antigens, while a cytokine pattern typical of Th1 cells favours tolerance [6]. There is evidence to suggest that higher antigen doses are associated to the development of Th1 cells producing IFN-γ both in an experimental model [7] and in atopic subjects [8].

With foods, it has been established that the induction of oral tolerance is highly dose-dependent and changes for different foodstuffs, requiring significantly higher amounts for peanut than for ovalbumin [9]. As to the role of antigen presenting cells, dendritic cells were shown to increase both the rate of internalising cells and the number of internalised allergen molecules by exposure to increasing amounts of allergen [10].

Moreover, in studies on natural exposure, the contact with high doses of allergens was related to the development of tolerance to animal epithelia [11] and to honeybee venom [12]. With the latter model, receiving more than 50 stings per year was associated to tolerance to venom [12].

On considering specific immunotherapy, the uniqueness of the effective dose was facilitated with Hymenoptera venom through the common use of materials standardised in micrograms (μg), while for aeroallergens the heterogeneity of the different units proposed by the various manufacturers made it difficult to achieve such a goal. In fact, when measurements in μg of major allergens became available, it was possible to identify the doses related to clinical efficacy [1]. Nevertheless, with conventional subcutaneous immunotherapy (SCIT) the problem of adverse reactions has to be faced, which are related to the amount of the injected allergen [13].

Dose dependence of efficacy of SCIT

The optimal maintenance doses in μg of major allergens as defined by specifically designed controlled studies were accurately analysed in the

WHO Position paper on allergen immunotherapy, which stated that *"a maintenance dose of 5-20 μg of major allergen per injection is associated with significant improvement in patient symptom scores"* [1]. It is useful to review such recommendations according to the different allergens.

Pollens

For grass pollen, a study by Osterballe identified the amounts of the major allergens Phl p 5 and Phl p 6 from *Phleum pratense* in a respective range of 25-41 μg and 13-20 μg which are required as maintenance dose to ensure clinical efficacy during the grass pollen season [14].

For ragweed pollen, four studies are available, with a quite wide range of optimal doses of the major allergen Amb a 1 corresponding to 2-19 μg and to 4-47 μg in the first trials [15, 16]; this range was later narrowed to 12-24 μg [17] and more recently defined in 10 μg [18].

For birch pollen one placebo-controlled study reported a clinical effectiveness on rhinoconjunctivitis and asthma symptoms during the pollen season using for active treatment a maintenance dose containing 12 μg of the major allergen Bet v 1 [19].

Also in a controlled study with a *Parietaria* pollen extract, in actively treated patients there were significantly lower symptom-medication scores than placebo treated patients, accompanied by significant decrease of target organs reactivity and a significant increase in the specific IgG antibodies using a maintenance dose of 6.2 μg of the major allergen Par j 1 [20].

House dust mites

As defined by two controlled studies, a maintenance dose of 5-7 μg of the major allergen from *Dermatophagoides pteronyssinus* Der p 1 is associated with clinically relevant effects in patients with mite allergy [21, 22]. A trial on children treated with two different extracts prepared from mite bodies or whole mite culture identified in a range from 0.5 to 11.5 μg the effective maintenance dose of Der p 1 [23].

Cat epithelium

This is the most investigated allergen with regard to the optimal maintenance dose, with quite similar results. In fact, in initial studies a dose of 8-16 μg of the major allergen Fel d 1 was suggested to be effective [24, 25], and confirmation was offered by way of subsequent trials, respectively identifying in 15 μg [26], and in 13 μg [27] the optimal dose. A recent study compared three different maintenance doses – 0.6, 1.3, and 15 μg – and found significant differences in clinical and immunologic effectiveness in favour of the highest dose [28].

Hymenoptera venom

Regarding the total amount of venom administered with the maintenance dose of immunotherapy, Golden *et al*. reported a lower efficacy in preventing systemic reactions to stings of the dose of 50 μg compared to the generally recommended dose of 100 μg [5], and Rueff *et al*. observed that patients not fully protected by the 100 μg dose achieved complete protection by doses of 200 μg or higher [29]. Some studies investigated the effective amounts of single venom allergens, which suggested 3 μg for Dol a 5 and Dol m 5 respectively from *Dolichovespula arenaria* and *Dolichovespula maculata*, 5 μg for Ves g 5 from *Vespula germanica*, and in 12 μg for Api m 1 from *Apis mellifera* [30, 31].

Dose dependence of safety of SCIT

The safety aspects were mainly evaluated in the same studies investigating the SCIT efficacy. In the 1996 study by Creticos *et al*. [18] the maintenance dose of 4 μg of Amb a 1 was less than optimal with regard to the effectiveness but caused systemic reactions in 19% of patients, with two treatment withdrawals because of the reactions.

The study by Haugaard *et al*. was aimed at evaluating the efficacy and safety profile of different maintenance doses of Der p 1 in subjects treated for mite allergy: systemic reactions occurred in 15% of patients with the dose of 0.7 μg, in 20% with the dose of 7 μg, and in 43% with the dose of 21 μg. The authors suggested the dose of 7 μg as being appropriate for safety [22].

Regarding cat immunotherapy, in two studies using the maintenance dose of 16 μg of Fel d 1 respective rates of systemic reactions corresponding to 60% [24] and 40% [25] were reported. These rates were too high to be acceptable, however in both trials rush protocols – which are usually associated to a lower safety – were used. In the trial conducted by Alvarez-Cuesta *et al*. [27] the maintenance dose of 13 μg was instead related to reactions – all mild and not requiring stopping of SCIT – in 21% of patients, and this indicates such dose to be the most suitable.

Concluding remarks

There is a considerable body of evidence on the dose dependence of SCIT regarding both efficacy and safety. This makes it essential to accurately consider the risk/benefit ratio in each patient eligible for this treatment.

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