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REVIEW

Accelerated subcutaneous immunotherapy in pediatric population – Systematic review☆

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Abstract
Background: Accelerated subcutaneous immunotherapy (SCIT) schedules represent an alternative to conventional SCIT, providing immunotherapy benefits in a shorter period of time. The objectives of this systematic review were to assess clinical and immunological efficacy as well as safety of accelerated SCIT build-up schedules for the treatment of respiratory allergy in pediatric patients.
Methods: Studies were located by searching PubMed, using ''immunotherapy'' and ''desensitization'' as keywords. The selection of studies, published from January 1st, 2006, to December 31th, 2015, was performed in two stages: screening of titles and abstracts, and assessment of the full papers identified as relevant, considering the inclusion criteria. Data were extracted in a standardized way and synthesized qualitatively to assess efficacy and safety of accelerated schedules in respiratory allergy.
Results: Eleven trials were included: two evaluated rush SCIT and nine assessed cluster SCIT. This review demonstrated that rush and cluster schedules are clinically and immunological efficacious, with faster effect than conventional schedules. No relevant difference with respect to clinical outcomes was noticed between subgroups (pediatric, adult and mixed populations). Regarding safety, most local adverse reactions were mild and there were neither life-threatening systemic reactions nor fatal events. No relevant differences in the incidence and severity of either local or systemic reactions between the accelerated schedule group and control group were registered.

Abbreviations: CT, controlled trial; cysLT, cysteinyl leukotrienes; EAACI, European Academy of Allergy and Clinical Immunology; ECP, eosinophilic cationic protein; eNO, exhaled nitric oxide; FEV_1, forced expiratory volume at one second; ITT, intention-to-treat; MS, medication score; PEF, peak expiratory flow; QLQ, quality of life questionnaire; QOL, quality of life; RCT, randomized controlled trial; SCIT, subcutaneous immunotherapy; SIT, specific immunotherapy; SMS, symptom and medication score; SS, symptom score.

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Conclusions: Accelerated SCIT build-up schedules are effective in the treatment of respiratory allergy in pediatric patients, representing a safe alternative to the conventional schedules with the advantage of achieving clinical effectiveness sooner.

Introduction

Currently three therapeutic approaches are employed for IgE-mediated respiratory allergies treatment: specific allergen avoidance, symptomatic drugs such as antihistamines, corticosteroids, mast cell stabilizers, antileukotrienes, β_2-agonists and anti-IgE monoclonal antibodies, and allergen-specific immunotherapy (SIT). SIT is an immune-modifying therapeutic since it restores mechanisms of immune tolerance to allergens, resulting in a significant reduction of symptoms and symptomatic medication usage, as well as in an improvement of quality of life and productivity at school and/or work.[1–4] It is of particular interest in pediatric population because of its capacity to change the response to allergens at an early phase and, thus, to prevent disease progression.[5]

Subcutaneous immunotherapy (SCIT) protocols are performed in two stages: build-up (up-dosing) phase which involves the administration of increasing doses of allergen extracts until the effective (or maintenance) dose is reached, and maintenance phase. Conventional immunotherapy schedules generally involve one or two weekly injections during up-dosing phase, over a 16-week period, followed by monthly maintenance injections for a period of three to five years. Rush and cluster immunotherapy schedules are accelerated build-up schedules which allow the patient to reach the maintenance dose and, thus, the benefits of immunotherapy, more rapidly. In a cluster up-dosing regimen, two to four repeated injections are given to the patient in a single day of treatment on nonconsecutive days, in most cases reaching the maintenance dose in four to eight weeks. A rush up-dosing schedule involves the subcutaneous administration of increasing amounts of allergen extracts at intervals of 15–60 min over a period ranging from one to three days.[4,6]

It is estimated that only a few allergic patients accept this therapeutic option mainly because of time inconvenience. Thus, accelerated schedules represent an alternative to conventional time-consuming schedules, allowing a reduced number of office visits (and associated costs), while preserving clinical efficacy. Despite their advantages, these schedules have not been widely used, mainly due to safety issues.[6]

The main objectives of this systematic review were to evaluate clinical and immunological efficacy as well as safety of accelerated SCIT build-up schedules for the treatment of respiratory allergy in pediatric patients.

Methods

The protocol was developed following international guidelines for systematic reviews.[7]

Studies were obtained by searching PubMed, from January 1st, 2006, to December 31st, 2015. The search strategy used two keywords: ''immunotherapy'' and ''desensitization''. Inclusion criteria used to select studies were: (i) population: studies of participants diagnosed with IgE-mediated allergic respiratory disease, confirmed by objective measures (positive skin prick test and/or serum-specific IgE to sensitizing allergens); (ii) intervention: rush or cluster SCIT; (iii) comparative intervention: placebo, conventional SCIT or pharmacotherapy; (iv) outcomes: symptoms and medication scores, quality of life, functional measures (lung function, rhinometry), allergen specific reactivity (cutaneous, nasal, conjunctival, and bronchial allergen reactivity), immunological and inflammatory parameters, safety; and (v) study design: randomized controlled trial (RCT). Only studies written in English were included.

The first stage of studies selection was a screening of titles and abstracts against the inclusion criteria to identify potentially relevant articles. When a definite decision based on title or abstract was not possible, the full papers were assessed. Rejected studies were grouped into those that did not meet the review objectives and those that addressed the topic of interest but failed on one or more inclusion criteria. Studies were also excluded when there was no abstract available. The second stage was the assessment of the full papers identified as relevant at time of the initial screening. If there were no full papers to access, those studies were excluded.

Only essential information for descriptive purposes of the systematic review were included in data extraction forms, namely: first author; publication year; study design; subjects characteristics (age, disease and co-morbidities) and number of subjects allocated to intervention and control groups; intervention description (type of vaccine, build-up schedule, duration and number of injections per up-dosing visit, gap between increasing doses) and control group; co-interventions description; treatment duration; outcome measures; and key results of the study analysis. The Cochrane Collaboration's recommended tool for assessing risk of bias[7] was the quality assessment process used in this review.

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