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[Intervention Protocol]

Immunotherapy (oral and sublingual) for food allergy to fruits

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To determine the efficacy and safety of oral and sublingual immunotherapy in children and adults with food allergy (FA) to fruits, when compared with placebo or elimination strategy.

BACKGROUND

Description of the condition

The National Institute of Allergy and Infectious Diseases (NIAID) defines FA as an "adverse immune response that occurs reproducibly on exposure to a given food and is distinct from other adverse responses to food, such as food intolerance, pharmacologic reactions, and toxin-mediated reactions" (Chafen 2010). This definition encompasses immune responses that are IgE mediated (immediate), non–IgE mediated (delayed), or a combination of both, and is in agreement with other international guidelines (Burks 2012).

Food allergy (FA) is a disease on the increase, and affects around 6% of young children in US and 3 to 4% of adults in UK (Sicherer 2011). According to The National Center for Health Statistics, 3.9% of US children in 2007 reported an FA (Kim 2011; Beyer 2012), with an increase of 18% in prevalence from 1997 to 2007 (Branum 2008). There are several hypotheses for this increase, of which the 'hygiene hypothesis' has received significant attention, but does not provide a sufficient immunological explanation. Other hypotheses describe associations between environmental and genetic factors, and also include food allergens (Mousallem 2012). There is a lack of accurate data on the prevalence of FA, particularly with regard to fruits, vegetables, nuts, and other edible plants. The prevalence of allergy to fruits has been estimated to be between 0.1 to 4.3% (Zuidmeer 2008). However, if prevalence is measured only by skin tests, this figure may be closer to 1% (Dalal 2002; Rance 2005). The prevalence of allergy to fruits as diagnosed by the patient's perception, is between 0.4% to 3.5% in adults and in children under three years, can be 11.5% (Eggesbo 1999). In this latter age group, Zuidmeer 2008 found the prevalence of allergy dependant on fruit species as 8.5% to apple, and 6.8% to orange and/or lemon.

The FA treatment, for allergy, including that to fruit, is the elimination of the allergen. Unfortunately, many patients accidentally ingest allergenic foods, which can result in severe anaphylactic reactions (Bock 1989). While it is advisable to use intramuscular adrenaline as emergency treatment in cases of accidental ingestion of allergenic food (Kim 2011), allergen-specific immunotherapy has also been studied as a longer-term treatment option in cases where avoidance of allergenic foods may prove difficult (Enrique 2005).

Description of the intervention

The concept of 'allergen immunotherapy' refers to a modulation of the immune system (Krishna 2011), which is expected to perform an allergen involved hyposensitization, in this case, to a food allergen (Scott-Taylor 2005). Recently, studies have been conducted on different types of immunotherapy for the treatment of FA, including oral immunotherapy (OIT) and sublingual immunotherapy (SLIT). Oral immunotherapy involves the ingestion of small amounts of the allergen (milligrams to grams) in the form of a flour combined with a food vehicle; while sublingual immunotherapy (SLIT) involves the administration of micrograms to milligrams of allergen extract under the tongue. Despite the good results obtained with OIT, further studies are needed to consolidate these findings (Jones 2009; Clark 2009; Patriarca 2003). SLIT offers an alternative that also requires additional studies for routine use (Kim 2011).

How the intervention might work

Desensitization is defined as the ability to increase the amount of food protein required to induce a clinical reaction, while still on regular immunotherapy. 'Tolerance' is the ability to consume large amounts of the food protein after treatment cessation. Thus food allergy immunotherapy aims to establish a permanent state of tolerance. While the mechanism by which immunotherapy induces tolerance maybe unclear, immunotherapy appears to alter the T cell responses to the allergen by skewing the Th2 response to a Th1 response and via the induction of Tregs (regulatory T cells). These Tregs can be natural (thymus derived) or inducible (antigen-specific), and both can suppress the immune responses by different mechanisms, including secretion of IL-10 and transforming growth factor (TGF)-b. Tregs in turn can suppress the allergic immune response, including secretion of IL-10 and transforming growth factor (TGF)-b (Shevach 2009). Both these cytokines have been found to be important in FA (Mousallem 2012; Chehade 2005; Maggi 2010; Perez-Machado 2003).

Why it is important to do this review

OIT and SLIT seem to be the most novel approaches for treating food allergies. OIT appears to be more effective than sublingual (Scott-Taylor 2005). At the time of writing this protocol, the effectiveness and safety of these interventions are as yet unclear. This review will provide a rigorous summary of the available evidence regarding the efficacy associated with OIT and SLIT for the management of allergy to fruits.

OBJECTIVES

To determine the efficacy and safety of oral and sublingual immunotherapy in children and adults with food allergy (FA) to fruits, when compared with placebo or elimination strategy.

METHODS

Criteria for considering studies for this review

Types of studies

This review will include clinical randomised controlled trials (RCTs) in which oral or sublingual immunotherapy is compared with placebo, or an elimination diet. We may also include any non-randomised controlled trials found.

Types of participants

We will include children and adults diagnosed with food allergy (FA): 'immediate fruit'. 'Immediate' allergic reactions are IgE mediated and defined as: 1) a suggestive history and positive skin prick test to fruit represented by a wheal ≥ 3 mm, compared with saline control or with an elevation of serum IgE specific to fruit (cut point defined by each centre); 2) an open oral challenge test or simply double-blind placebo-controlled trial. The methodology, application and interpretation of provocation tests in patients with serum IgE-mediated reactions have been established recently by the European Academy of Allergology and Clinical Immunology (Bindslev-Jensen 2004).

Types of interventions

We will include oral or sublingual immunotherapy for fruits administered through any protocol. Oral immunotherapy is

the introduction of the food allergen (in this case fruit) in incremental doses and intervals, over a period of time. We will include comparative studies, incorporating placebo and a continuous elimination diet, with or without carriage of epinephrine autoinjector. Sublingual immunotherapy will also be included and the results will be analysed separately.

Types of outcome measures

Primary outcomes

- Evidence of desensitization: an increase in the amount of fruit that can be tolerated while receiving immunotherapy (oral or sublingual).
- Evidence of immunologic tolerance: a complete recovery from allergy to fruits after completion of immunotherapy (oral or sublingual), or after a period of not having eaten the fruit involved.

Secondary outcomes

- Number of days free of symptoms.
- Changes in quality of life related to health assessed by generic and specific instruments for FA.
- Local adverse reactions: Oral Allergy Syndrome (OAS), angioedema, rash, gastrointestinal symptoms.
- Systemic Adverse Reactions: anaphylaxis (commitment of two or more systems).
- Immunological Changes:
  - decrease in the size of the wheal obtained through the prick test
  - decrease in the level of specific serum IgE for the fruit
  - increased levels of specific IgG4 for the fruit.

Search methods for identification of studies

Electronic searches

We will identify trials including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, CINAHL, and AMED.

We will also conduct a search of ClinicalTrials.gov. We will search all databases from their inception to the present, and we will impose no restriction on language of publication.

Searching other resources

We will check reference lists of all primary studies and review articles for additional references. We will contact authors of identified trials and ask them to identify other published and unpublished studies. We will also contact manufacturers and experts in the field.

Data collection and analysis

Selection of studies

Two independent evaluators (JJYN and JBT) will screen the titles and abstracts, identified through the electronic searches, to identify studies to include in the review. We will discuss any disagreements and consult with a third reviewer (FPL or EEM). If additional information or any clarification is needed from any article, we will contact the trial authors.

Data extraction and management

Two independent evaluators (JJYN and JBT) will read all reports in detail and will summarise the pertinent details in a standard data extraction sheet (which will include the kind of study; methodology; number and description of participants; type, drug doses, and duration of intervention; type, timing, and method of outcome measurement; as well as evaluation of methodology). We will discuss any disagreements, and aim to reach agreement by consensus with a third reviewer (FPL or EEM).

Assessment of risk of bias in included studies

Two review authors (FPL and MR) will independently assess risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions (* Higgins 2011). We will resolve any disagreement by discussion, or by involving a third assessor. We will assess risk of bias according to the following domains.

Sequence generation (selection bias)

For each included study, we will describe in detail, the methodology used to generate the allocation sequence, and we will evaluate the methodology to determine if it can produce comparable groups. We will assess sequence generation as: low risk of bias (any truly random process, e.g. random number table, computer random number generator); high risk of bias (any non-random process, e.g. odd or even date of birth, hospital or clinic record number); or unclear risk of bias.

Allocation concealment (selection bias)

For each included study, we will describe in detail the methodology used to conceal the allocation sequence and we will evaluate the methodology to determine whether intervention allocation could have been foreseen in advance, during recruitment, or changed after assignment. We will evaluate allocation concealment as: low risk of bias (e.g. telephone or central randomisation, consecutively numbered sealed opaque envelopes); high risk of bias (e.g. open random allocation, unsealed or non-opaque envelopes, alternation, date of birth); or unclear risk of bias.

Blinding (performance bias)

For each included study, we will describe the methodology used, if any, to blind study participants and personnel from knowing the intervention that a participant received. We will also provide information on whether the intended blinding was effective. Where blinding is not possible, we will assess whether the lack of blinding was likely to have introduced bias. We will assess blinding separately for different outcomes or classes of outcomes. We will evaluate blinding as: low risk of bias, high risk of bias, or unclear risk of bias for participants, and outcome evaluators.

Incomplete outcome data (attrition bias through withdrawals, dropouts, or protocol deviations)

For each included study and for each outcome or class of outcomes, we will include a description of data completeness, including attrition and exclusions from the analysis, as well as an assessment of the reasons of attrition or data exclusion (if available). We will record the number of attrition and exclusions, as well as the number of patients included in the analysis at each stage (compared with the total randomised participants).

Selective outcome reporting

We will assess selective outcome reporting for each included study. We will evaluate selective outcome reporting as: low risk of bias (where it is clear that all of the study's prespecified outcomes and all expected outcomes of interest to the review have been reported); high risk of bias (where not all of the study's prespecified outcomes have been reported, one or more reported primary outcome(s) were not prespecified, outcomes of interest are reported incompletely and so cannot be used, study fails to include results of a key outcome that would have been expected to have been reported); or unclear risk of bias.

Overall risk of bias

We will classify all studies according to the following criteria: low risk of bias (all individual items were at 'low risk of bias'); moderate risk of bias (one or more individual item(s) was at 'unclear risk of bias' while the remaining were at 'low risk of bias'); or high risk of bias (one or more individual item(s) was at 'high risk of bias').

Measures of treatment effect

We will assess treatment effect through mean differences (MDs) or standardized mean differences (SMDs) for continuous outcomes, and risk ratios (RRs) for dichotomous outcomes. We will present all measures with 95% confidence intervals (CIs). We will run all statistical analyses with Review manager 5.1 (RevMan 2011).

Unit of analysis issues

The unit of analysis will be the patient, i.e. for dichotomous outcomes such as presence or absence of tolerance, partial tolerance and adverse effects.

Dealing with missing data

The main analysis will be an available data analysis in each of the papers. If a paper presents both intention-to-treat and per protocol data, we will use the former in the analyses.

Assessment of heterogeneity

We will assess clinical heterogeneity by examining the trials in terms of patient characteristics, interventions, controls and definition of results.

We will the evaluate statistical heterogeneity through the I^2 statistic. We will use a cut-off point of $I^2 > 50\%$ to indicate relevant statistical heterogeneity. We will determine causes of heterogeneity through sensitivity analyses and analysis of subgroups.

Assessment of reporting biases

We will explore publication bias by means of a funnel plot (Egger test; Egger 1997), if ten or more studies are available (Higgins 2011).

Data synthesis

We will perform meta-analyses using a random-effects model and using the inverse variance method. We will present forest plots for each result, where we are able to extract data.

Subgroup analysis and investigation of heterogeneity

We will carry out a subgroup analysis according to:

- immunotherapy regimen: oral vs sublingual
- type of fruit allergenic: peach, apple, banana, kiwi, melon, strawberry and citrus fruits
- according to age: children, adults.

Sensitivity analysis

We will carry out sensitivity analyses to determine the effect of the following parameters on the treatment effect estimates.

- risk of bias: including only low risk of bias studies.
- meta-analysis model: applying a fixed-effect model compared to a random-effects model.

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None

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CONTRIBUTIONS OF AUTHORS

All of the authors have contributed to the conception, development and drafting of this protocol.

DECLARATIONS OF INTEREST

None

INDEX TERMS

Medical Subject Headings (MeSH)

Desensitization, Immunologic [*methods]; Food Hypersensitivity [etiology] [*therapy]; Fruit [*adverse effects]; Malus [*adverse effects]; Pyrus [*adverse effects]; Randomized Controlled Trials as Topic; Sublingual Immunotherapy [methods]

MeSH check words

Adult; Humans