Immunotherapy

Recommendations

1. Physicians should consider injection immunotherapy using appropriate allergens for the treatment of allergic asthma only when the allergic component is well documented (level I).
2. Physicians should not recommend the use of injection immunotherapy in place of avoidance of environmental allergens (level III).
3. Physicians may consider injection immunotherapy in addition to appropriate environmental control and pharmacotherapy when asthma control remains inadequate (level IV).
4. Immunotherapy is not recommended when asthma is unstable (level III). Exposure to allergens,[1] the presence of atopy[2] and high serum IgE[3,4] levels have been associated with persistent asthma. IgE attached to mast cells, basophils and other airway cells activates the cells when specific allergens are encountered, resulting in the release of inflammatory mediator molecules. Infiltration of the airway with eosinophils is a consistent feature of acute inflammation in most people with chronic persistent asthma. Insights into the inflammatory profile in asthma have led not only to a re-evaluation of the disease-modifying effect of allergen-specific immunotherapy, but also to the development of new approaches targeting specific pro-inflammatory molecules such as IgE and cytokines.

Literature review

A search was carried out from 1996 to present using MEDLINE and additional references from those reports retrieved through MEDLINE as appropriate. Key words included: "children," "asthma," "allergy," "immunotherapy," "immune modulation" and "desensitization."

Current evidence

Rationale for allergen immunotherapy

Immune modulation offers the only opportunity to modify the underlying disease processes of asthma in the long-term as no pharmacologic therapeutic agents, including inhaled corticosteroids, have been shown to do this. Subcutaneous allergen immunotherapy is accomplished by the administration of increasing doses of allergen extracts over prolonged periods until a therapeutic level that will cause immune deviation is reached. There are believed to be 2 main types of helper T-lymphocytes characterized by the cytokines they produce[5]: TH1 cells synthesize interferon-gamma and IL2,12,18 and TNF α and β, which are important in the development of protective immunity to infectious agents; TH2 cells synthesize IL4, 5, 6, 9 and 13, which mediate allergic (eosinophilic) inflammation. The effect of allergen immunotherapy is to increase the number of T regulatory cells, reduce TH2 and maintain or reduce TH1 cells, resulting in reconstitution of normal immune regulation and correction of allergy.[6,7] This is associated with increased allergen-specific IgG4, decreased allergen-specific IgE and downregulation of effector cells including eosinophils and mast cells.

Subcutaneous immunotherapy

Although subcutaneous immunotherapy has been used since 1911 for allergic disorders, its value in the treatment of childhood asthma continues to be debated despite numerous studies that have demonstrated its efficacy.

Three analyses have demonstrated improvement in asthma. Sigman and Mazer[8] reviewed 12 studies of immunotherapy in childhood asthma performed between 1966 and 1994, 8 of which were double blinded, 3 were single blinded and 1 was unblinded. Changes in bronchial hyperreactivity were measured in 50% and medication use in 25%. Antigens used in the studies varied widely and may reflect improvements in antigen standardization over time. Five studies used house dust mite (HDM) allergen and 2 of the blinded studies showed significant improvement in bronchial responsiveness ($p < 0.01$). In the larger of these, 35 of 52 treated subjects no longer responded to HDM allergen compared with 7 of 28 subjects treated with placebo. As well, decreases in symptom scores (85% decrease in antigen-treated group v. 50% decrease in the placebo group, $p < 0.05$) and drug scores (weighted score for medication: 10 v. 250, respectively, $p = 0.007$) and loss of the late asthmatic response on bronchial provocation with *Dermatophagoides pteronyssinus* ($p < 0.05$) were found after 1 year of treatment. This is likely of clinical importance given the association of the late asthmatic response to airway inflammation.

Abramson and colleagues[9] evaluated 54 studies of immunotherapy performed up to 1997: 25 trials of immunotherapy for HDM allergy; 13 pollen allergy trials; 8 animal dander allergy trials; 2 *Cladosporium* mould allergy; and 6 trials looking at multiple allergens. Concealment of allocation was assessed as clearly adequate in only 11 of these trials, and significant heterogeneity was present in many of the findings. However, overall, there was a significant reduction

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in asthma symptoms and medication use following immunotherapy. There was also a significant improvement in asthma symptom scores (standardized mean difference –0.52, 95% CI –0.70 to –0.35). People receiving immunotherapy were less likely to report a worsening of asthma symptoms than those receiving placebo (OR 0.27, 95% CI 0.21–0.35) and were less likely to require medication (OR 0.28).

Ross and coworkers[10] reviewed all studies of specific immunotherapy (SIT) in patients with asthma published in English between 1966 and 1998. All prospective, randomized, double blind, placebo-controlled studies of SIT (24 studies involving 962 asthmatic patients with documented allergy) were included in a meta-analysis. Immunotherapy was judged effective in 17 (71%) of the 24 studies, ineffective in 4 (17%), and equivocal in 3 (12%) ($\chi^2 = 15.25$, $p = 0.0005$). Symptoms of asthma were more likely to improve in patients who received SIT than in patients who received placebo (OR 2.76, 95% CI 2.22–3.42). Results also favoured the immunotherapy group in terms of improvement in pulmonary function (OR 2.87, 95% CI 1.82–4.52), protection against bronchial challenge (OR 1.81, 95% CI 1.32–2.49) and reduction in the need for medications (OR 2.00, 95% CI 1.46–2.72).

Since these meta-analyses were published, other studies have continued to look at the effect of immunotherapy on asthma. Adkinson and colleagues[11] performed a randomized double-blind placebo-controlled study in children with moderate to significant asthma, but used various regimens of immunotherapy and followed up for an average of only 3 months. No significant difference was noted between study groups.

Hedlin and associates[12] studied 29 children, 7–16 years of age, over a 3-year period. They were randomly allocated to receive birch–timothy pollen and either cat–dust mite or placebo immunotherapy. Specific bronchial allergen challenge (PC_{20}) with HDM allergen increased significantly in the active immunotherapy group ($p < 0.001$) but also increased in the placebo + pollen group ($p < 0.05$). Bronchial histamine challenge (PC_{20}) increased continuously in the active HDM immunotherapy group ($p < 0.05$ and $p = 0.002$ after 1 and 3 years, respectively) and increased after 3 years in the placebo + pollen immunotherapy group ($p < 0.05$). There was no significant change in the dose of inhaled budesonide needed for symptom control in either group.

Pifferi and colleagues[13] conducted a randomized investigator-blinded clinical trial after a 1-year run-in period. During the 3-year treatment period, 15 children receiving SIT for HDM (no drop-outs during the study) and 14 age- and sex-matched children served as controls (4/14 drop-outs) were studied. In the SIT group, significant improvement in asthmatic symptoms and marked reduction in drug intake was observed (an average of 1 day steroids per subject in the SIT group v. 11 days of systemic steroids per subject in the control group). The SIT group showed a significant decrease in bronchial hyperreactivity (70% improved v. 15% improved in the control group). The SIT group had no new sensitivities during the study period. No major local or systemic side effects were reported.

In a retrospective study, Cools and associates[14] studied asthmatic patients, who were allergic to either HDM (*D. pteronyssinus*) ($n = 34$) or to both HDM and grass pollen ($n = 14$) and who were treated with SIT during childhood (mean duration of therapy 61 ± 9.70 months). They were re-evaluated in early adulthood (mean age of treated group 23.1 years; control group 22.7 years) after cessation of therapy for an average of 9.3 ± 2.76 years. The results were compared with those of a control group of asthmatic patients ($n = 42$) with comparable asthma features, who were treated with appropriate anti-asthmatic drugs during childhood, but who never received SIT. At re-evaluation, the risk of frequent asthmatic symptoms was 3 times higher in the control group than in the SIT-treated group (prevalence ratio 3.43, $p = 0.0006$).

Paul and colleagues[15] looked at the effect of a combination of environmental precautions and immunotherapy on asthmatic children (encasings for mattresses, blankets and pillows in combination with HDM allergen reduction on the floor have proved effective in reducing bronchial hyperreactivity of mite-allergic children). They compared the effect of HDM-proof mattress encasements and SIT with a partially purified mite extract ($n = 8$) with using encasings alone. Twenty mite-allergic children with asthma and high domestic exposure to HDM allergen (>2 μg Der p 1 + f 1/g mattress dust) were studied. Initially both groups were comparable. In 80% of children, encasements reduced Der p 1 and Der f 1 concentrations on the mattress to below 3% of the initial values. PC_{20} histamine increased from 0.4 to 1.4 mg/mL in the group with SIT and encasings but remained unchanged in the control group. SIT with allergen extracts was found to be an effective adjunct to the encasings.

Gruber and colleagues[16] studied 26 children with asthma, who were allergic to HDM. After 24 months, the SIT group showed a significant reduction in bronchial responsiveness assessed by cold dry air challenge, whereas no changes were observed in the control group. In the SIT group, more patients lost bronchial hyperresponsiveness than in the control group (6 of 14 v. 1 of 12; $p < 0.05$). One year after terminating SIT, the treatment group showed a tendency toward increasing bronchial responsiveness.

Basomba and coworkers[17] conducted a double-blind, placebo-controlled study in 55 asthmatic patients sensitized to HDM. They were randomly assigned vaccination with *D. pteronyssinus* extract encapsulated in liposomes or placebo for 12 months. Nearly half (45.8%) of the patients actively treated reduced their symptom and medication scores by at least 60% versus only 12% of patients receiving placebo treatment ($p < 0.05$). Percentage of healthy days in the active group rose from 10.5% before treatment to 64.5% afterward ($p = 0.0008$). Reduction in sensitivity was demonstrated by skin-prick test responses ($p < 0.01$), late-phase response after intradermal testing ($p = 0.009$) and bronchial challenge test results ($p = 0.026$) in the active group. Serum levels of specific IgG increased throughout the treatment, whereas specific IgE levels showed only an

initial transient increase. No change in these parameters was observed in the placebo group.

Altinatas and colleagues[18] conducted an open, randomized study of 3 different groups of immunotherapy materials and a placebo in 34 patients with HDM sensitive asthma. The maximum tolerated dose with the bronchial provocation test increased significantly after immunotherapy with a geometric mean of 36 307 units of HDM tolerated in the active immunotherapy group compared with 7100 units in the placebo group. There were local reactions that prevented 4 of 10 patient in one group from receiving an "ideal" maintenance dose.

Overall, data from these studies suggest a potential benefit for the treatment of asthma in children using immunotherapy. However, issues relating to the most appropriate timing and approach to immunotherapy as well as potential for adverse effects have limited the usefulness of currently available approaches.

Immunotherapy for secondary prevention

To study the ability of SIT to modify the progression of allergic sensitization, Pajno and colleagues[19] studied 134 children (age range 5–8 years), who had intermittent asthma with or without rhinitis, with single sensitization to mite allergen. SIT was proposed to all the children's parents, but was accepted by only 75 of them. The remaining 63 children were treated with medication only and were considered the control group. SIT with mite mix was administered for 3 years and all patients were followed for a total of 6 years; 123 children completed the follow-up study. Fifty-two out of 69 children (75.4%) in the SIT group showed no new sensitization, compared with 18 out of 54 children (33.3%) in the control group ($p < 0.0002$).

Eng and coworkers[20] examined a group of patients who had received pre-seasonal SIT to grass pollen 6 years after discontinuation of treatment. Thirteen of 14 patients with previous SIT and 10 out of 14 patients of the control group were followed. Scores for overall hay-fever symptoms (peak score 20 v. 10, $p < 0.004$) and individual symptoms for nose (peak score 9 v. 10, $p < 0.04$) and chest (peak score 4 v. 2, $p < 0.01$) remained lower in the group treated with SIT. Only 23% of patients with previous pollen-asthma who had received SIT experienced pollen-associated lower respiratory tract symptoms compared with 70% in the control group ($p < 0.05$). There was no significant difference in the use of pharmacologic treatment during the pollen season except for asthma medication. Six years after cessation of SIT the immediate skin response to grass pollen remained decreased compared with the reaction of the controls. Of the initially pollen-monosensitized children, 61% had developed new sensitization to perennial allergens compared with 100% in the control group ($p < 0.05$). SIT in children with pollen allergy reduces the onset of new sensitization and may be able to modify the natural course of allergic disease

Similarly, in a retrospective study, Purella-D'Ambrisio and colleagues[21] examined 8396 monosensitized patients with respiratory symptoms in an open, retrospective study. The treatment group consisted of 7182 patients, who had previously been treated with SIT; they received SIT and anti-allergic drugs when needed for 4 years and then were treated with drugs for at least another 3 years. The control group consisted of 1214 patients treated only with drugs for at least 7 years. All patients underwent skin-prick tests with a standard panel of allergens and total and specific IgE determination. After 7 years, 26.9% of the treated participants were polysensitized compared with 76.8% of the control group ($p < 0.0001$). Asthmatic participants were significantly more likely to become polysensitized than those suffering only from rhinitis (32.14% v. 27.29% after 4 years, 36.5% v. 31.33% after 7 years; $p < 0.0001$). Total IgE decreased by 17.5% in SIT-treated patients and increased by 13.7% in control patients ($p < 0.0001$).

Adverse effects of subcutaneous immunotherapy

Akcakaya and colleagues[22] retrospectively evaluated the incidence of local and systemic reactions to injections of adsorbed extracts of HDM (*D. pteronyssinus* and *D. farinae*) applied according to a conventional schedule in children. Eighty-eight patients, aged 6–15 years, suffering from allergic asthma or asthma together with rhinitis were included. Local reactions occurred after 206 injections (3.57%; 144 were <20 mm in diameter, 62 were >20 mm) and systemic reactions were seen after 12 injections (0.2%). Twelve patients experienced 12 systemic reactions (11 males and 1 female). Of these, 7 patients (58.3%) experienced no local reactions before a systemic reaction. Most of both local and systemic reactions occurred within less than 30 minutes after the injection. The study supported the safety of immunotherapy with HDM in children. Although 5 of the 12 patients who experienced systemic reactions had local reactions before a systemic reaction, in general the presence of local reactions was not helpful in predicting which patients would develop a systemic reaction. Males and patients with asthma together with rhinitis appeared to be at greater risk for systemic reaction.

Karaayvaz and coworkers[23] evaluated conventional allergen immunotherapy with aqueous extracts in 1506 patients. There were 125 systemic reactions in 109 patients (1 per 1831 injections), of which 52.8% involved the skin, 12% were respiratory, 30.4% involved respiratory symptoms and the skin, 0.8% caused hypertension alone and 4% caused hypotension with respiratory symptoms (bronchospasm or rhinorrhea) and skin reactions. Most of the systemic reactions (84.8%) occurred within the 30 minutes after injection. Of the systemic reactions, 41% were observed in the build-up period and 58.4% in the maintenance injection period. The 30-minute waiting period appeared to be adequate for conventional immunotherapy; however, a longer waiting period may be necessary for high-risk subjects.

Taber and associates[24] studied the safety of immunother-

apy with a biologically standardized depot extract of *Alternaria tenuis* containing 5 BU/mL used according to a conventional immunotherapy schedule in 129 patients. Most of the adverse reactions were systemic and mild. The risk of adverse reactions was significantly higher in children, patients with asthma and during the initial phase of treatment. Patients who suffered from adverse reactions had a significantly higher level of total and specific IgE.

Adverse effects of immunotherapy in children, although usually mild, remain a concern. The potential for severe and life-threatening systemic anaphylaxis has tended to limit the use of immunotherapy in children.

Conclusions

Subcutaneous immunotherapy has been shown to be effective in allergic asthma by randomized studies and by meta-analyses (level I). Early intervention with immunotherapy may prevent the progression from monosensitization to polysensitization (level I). Administration of immunotherapy appears to be safe; however systemic reactions are more likely in asthmatics; therefore, poorly controlled asthma is a contraindication to administration of immunotherapy.

Sublingual immunotherapy

Sublingual therapy is the most widely used non-injection route for allergen immunotherapy in Europe, although it is not currently available in Canada.[25] There are 6 blinded randomized controlled trials[25–32] dating back to 1990 in children with asthma, although all of the studies have been of small scale, half with fewer than 30 participants. Treatment is well tolerated apart from occasional minor abdominal discomfort.[33,34] Large-scale trials, over prolonged treatment periods using commercially available allergens extracts and well-standardized protocols, are needed.

Other immunotherapeutic strategies

Anti-IgE therapy

Allergic asthma is frequently initiated by IgE molecules binding antigens. Monoclonal antibodies, developed in mice, which bind the portion of IgE that interacts with the FceR1 receptor have been modified by grafting a human Fc receptor from an IgG1 molecule to humanize the mouse antibody. This creates an antibody that does not allow IgE to bind to its receptor and does not pose a risk of anaphylaxis or allergic symptoms for the patient.[35,36] This molecule effectively neutralized free IgE in subjects in clinical trials. Several large studies have used anti-IgE therapy as an adjuvant therapy for asthma in adults, but no data are yet available for a pediatric population.[37–42] The main drawbacks include price, in keeping with other monoclonal antibody therapies, and lack of any long-term data.

Intravenous immunoglobulin

Intravenous immunoglobulin has been shown in a number of fairly small studies to decrease oral steroid requirements in those with severe asthma,[43–46] but the cost and potential side effects preclude its more extensive use pending further trials.

Methotrexate

A recent Cochrane review[47] analysed 10 studies of methotrexate in steroid-resistant asthma. The net effect was a small decrease in oral steroid use and no real improvement in pulmonary function. This modest benefit, associated with some risk of hepatotoxicity, outweighed the benefits for routine use.[48,49]

Gold therapy

Gold therapy has the advantage of being administered orally or by injection, improving compliance and physician control. There have been multiple small and medium-sized trials of oral gold therapy.[50,51] A recent Cochrane review[52] assessed 3 studies with 311 patients. The review found a small but significant decrease in use of steroids, but determined that the side effect profile precludes the use of this agent in the treatment of steroid-dependent asthma. There have been no published pediatric trials.

Cytokine therapies

Several novel cytokine-based therapies have been used in preliminary studies in adult asthma;[53] however, no substantive data on any of these approaches exist for children.

In summary, anti-IgE and other immunomodulators such as IVIG may be considered in the limited number of cases where high doses of inhaled steroids and add-on therapy do not control asthma.

Implications for research

1. Large-scale trials over prolonged periods of time are required to assess outcome.
2. Commercially available allergen extracts should be used.
3. Standardized protocols for dose and outcome variables should be developed.

Implementation strategies

1. This approach should be fully explored for its disease-modifying effects and long-term outcomes that are especially important in children.
2. A working group of investigators should be formed for protocol design, development of funding and implementation.

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