LEUKOTRIENE ANTAGONIST THERAPY

ANTI-LEUKOTRIENES AS ADD-ON THERAPY TO INHALED GLUCOCORTICOIDS IN PATIENTS WITH ASTHMA: SYSTEMATIC REVIEW OF CURRENT EVIDENCE

Ducharme FM. *BMJ*. 2002;324:1545–1551

Purpose of the Study. To examine the evidence for the efficacy and glucocorticoid-sparing effect of oral anti-leukotrienes taken daily as add-on therapy to inhaled glucocorticoids in patients with asthma.

Study Population. Systematic review of randomized, controlled trials of children and adults with asthma comparing the addition of anti-leukotrienes or placebo to inhaled glucocorticoids.

Methods. Medline, Embase, Cinahl, and Central databases up to August 2001 were used. Trials were included if they were randomized, controlled trials, if they pertained to children and adults with asthma who were taking inhaled glucocorticoids for maintenance, if they compared the addition of anti-leukotrienes or placebo daily to inhaled glucocorticoids for a minimum of 28 days, and if they documented measures of efficacy other than compliance. Primary outcome measures were number of asthma exacerbations when the intervention was compared with the same or increased dose of inhaled glucocorticoids. It also included the change from baseline dose of inhaled glucocrticoids required to maintain control when the intervention was aimed to establish the steroid-sparing effect. Secondary outcomes were changes in pulmonary function tests, symptoms, use of rescue β_2-agonists, quality of life, exacerbations requiring hospital admission, adverse effects, and withdrawals.

Results. Of 376 citations, 13 were included (12 in adult patients; 1 in children). The addition of licensed doses of anti-leukotrienes to inhaled glucocorticoids resulted in a nonsignificant reduction in the risk of exacerbations requiring systemic steroids (2 trials; relative risk: 0.61; 95% confidence interval: 0.36–1.05). No trials comparing the use of anti-leukotrienes with double the dose of inhaled glucocorticoids could be pooled. The use of anti-leukotrienes resulted in no overall group difference in the lowest achieved dose of inhaled glucocrticoids (3 trials; weighted mean difference: −44.43 μg/day, −147.87 to 59.02: random effect model) but was associated with a reduction in withdrawals owing to poor asthma control (four trials; relative risk: 0.56; 95% confidence interval: 0.35–0.89)

Conclusions. The addition of anti-leukotrienes to inhaled glucocorticoids may modestly improve asthma control compared with inhaled glucocorticoids alone but this strategy cannot be recommended as a substitute for increasing the dose of inhaled glucocrticoids. The addition of anti-leukotrienes is possibly associated with superior asthma control after tapering of glucocorticoids, but the glucocorticoid-sparing effect cannot be quantified at present.

Reviewer's Comments. This systematic review summarizes the evidence available through August 2001 and emphasizes the shortage of relevant trials testing the role of anti-leukotrienes as add-on therapy to inhaled glucocorticoids. Although no firm conclusion can be made, the addition of anti-leukotrienes to inhaled glucocorticoids may modestly improve the control of asthma, but there is little evidence to consider their use as a substitute for increasing doses of inhaled glucocrticoids. There is also one pediatric trial showing modest benefit, and extrapolation of adult data to children remains speculative. Additional studies are needed to evaluate the true role of anti-leukotrienes as a steroid-sparing agent, and until more evidence is available, the gold standard should remain that clinicians use inhaled corticosteroids at the lowest effective dose to maintain asthma control.

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OTHER THERAPIES

THE ROLE OF ANTICHOLINERGICS IN ACUTE ASTHMA TREATMENT

Rodrigo GJ, Rodrigo C. *Chest*. 2002;121:1977–1987

Purpose of the Study. To determine the evidence in the literature of randomized, controlled trials supporting the use of anticholinergics in the treatment of acute asthma. The study was a metanalysis of both pediatric and adult studies, but only results of the review of pediatric studies will be reported here.

Study Population. Study subjects were between the ages of 1 and 17 years, and the studies were performed in the United States and Europe between 1985 and 2000. A total of 17 pediatric studies were included in the analysis.

Methods. The question that was proposed to answer from the literature search was: "Does the addition of inhaled anticholinergic agents to standard treatment of β_2-agonist agents decrease the likelihood of hospital admission or improve pulmonary function in the course of the emergency department (ED) visit?" A literature review using MEDLINE 1966–2001, EMBASE 1980–2001, CINAHL 1982–2001, Cochrane Review, and hand-searching major journals with cross-searching of references was performed. Studies were ranked for level of evidence with highest rank given to large randomized, controlled trials or systematic reviews of randomized trials and lower ranks for cohort and case studies. Studies were analyzed for methodology and assigned a Jadad score based on quality, with scores of 3 or higher considered of good quality. Only studies performed on asthmatics in acute care settings such as EDs were included. The primary outcome assessed by the review was need for hospitalization and secondary outcomes included pulmonary function tests, clinical or physiologic results and adverse effects.

Results. A total of 4 studies (2 systematic reviews and 2 randomized, controlled trials) involving pediatrics patients presenting to the ED with acute asthma who had been treated with anticholinergic agents were examined. The dose of nebulized ipatropium bromide used in these trials was usually 250 μg per dose every 20 minutes. Frequency of dosing versus β_2-agonists was not noted in the analysis. Hospital admissions were reduced by about 30% in the subjects that were treated with multiple doses of anticholinergic agents in addition to β_2-agonists. A moderate difference was noted between the groups for change in pulmonary function. There was less benefit to adding a single dose of an anticholinergic agent to the β_2-agonists treatment of children with mild to moderate acute asthma (forced expiratory volume in 1 second [FEV_1] >50%). No apparent increase in adverse events was noted.

Conclusions. The authors conclude that the addition of anticholinergic therapy to usual β_2-agonist therapy was beneficial in pediatric patients presenting with acute asthma that was more severe by reducing the need for hospitalization and by improving lung function.

Reviewer's Comments. This metanalysis is further evidence to support the common practice in pediatric EDs of

adding anticholinergic therapy to standard β_2-agonist therapy in patients presenting with more severe acute asthma.

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OMALIZUMAB PROVIDES LONG-TERM CONTROL IN PATIENTS WITH MODERATE-TO-SEVERE ALLERGIC ASTHMA

Buhl R, Soler M, Matz J, et al. *Eur Respir J*. 2002;20:73–78

Purpose of the Study. To examine the ability of omalizumab, an anti-immunoglobulin E (anti-IgE) agent, to maintain long-term disease control in patients with moderate-to-severe allergic asthma.

Study Population. Four hundred eighty-three patients with moderate-to-severe allergic asthma maintained on beclomethasone diproprionate.

Methods. Four hundred eighty-three patients with physician-diagnosed moderate-to-severe allergic asthma were investigated in a 24-week double-blind extension trial. These patients were a subset of 546 patients that were maintained on randomized treatment of omalizumab during a 28-week double blind steroid reduction phase of the core trial. During the 28-week steroid reduction phase of the core trial, the lowest sustainable dose of beclomethasone diproprionate was established. Patients in this trial had positive prick skin tests to common inhalant allergens and IgE levels of >30 to <700 IU/mL. The extension part of the trial was a 24-week double blind extension with placebo control. Standard doses of omalizaub were used throughout the 24-week extension period and given every 2 to 4 weeks based on body weight and IgE level. The use of concomitant asthma medication was permitted and investigators were allowed to adjust the beclomethasone diproprionate dose or switch patients from beclomethasone diproprionate to other asthma medications if deemed necessary. Patients were followed clinically for asthma symptoms and exacerbations. Mean doses of inhaled corticosteroids and other asthma medications were recorded, and forced expiratory volume in 1 second (FEV_1) by spirometry was recorded.

Results. More omalizumab-treated patients (33.5%) than placebo-treated patients (13.5%) were able to complete the extension period without requiring inhaled corticosteroid treatment. The mean beclomethasone diproprionate equivalent dose throughout the extension period was lower in the omalizumab group (25 μg/day) than the placebo group (43 μg/day). Disease control was sustained in 76% of omalizumab patients compared with 59.4% of placebo patients free from an asthma exacerbation during the extension period. Compared with placebo, fewer patients in the omalizumab group used other concomitant asthma medications during the extension. Treatment with omalizumab was well-tolerated and the incidence of adverse events was similar between groups.

Conclusions. These results suggest that omalizumab is a promising new agent for the long-term control of allergic asthma.

Reviewer's Comments. The role of anti-IgE therapy in asthma and other allergic diseases is a topic of increasing interest as these drugs may soon come to market. This study nicely shows that omalizumab provides long-term benefit and hints of a possible steroid-sparing effect, which is always of increasing interest with the widespread use of inhaled corticosteroids. However, additional long-term studies are needed to better assess the overall cost benefit analysis of these products. They are likely to be very expensive and if only a minimal steroid-sparing effect is found, their role may be very limited.

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SELECTIVE INTRACELLULAR DELIVERY OF DEXAMETHASONE INTO ACTIVATED ENDOTHELIAL CELLS USING AN E-SELECTIN-DIRECTED IMMUNOCONJUGATE

Everts M, Kok RJ, Ásgeirsdóttir SA, et al. *J Immunol*. 2002;168:883–889

Purpose of the Study. To determine if a dexamethasone-anti-E-selectin conjugate can be specifically delivered to activated endothelial cells and exert its biological effects in a cell-specific manner.

Study Population. Experiments were performed using human and mouse endothelial cell cultures.

Methods. Dexamethasone was conjugated to anti-human E-selectin and the resulting immunoconjugate was characterized in terms of its ability to bind to E-selectin and endothelial cells, to be internalized, and to exert biological activity on the endothelial cells. Binding of the dexamethasone-anti-E-selectin conjugate to endothelial cells was analyzed by immunohistochemistry and flow cytometry. Internalization and localization of the dexamethasone conjugate was studied with confocal laser scanning microscopy (CLSM) and immuno-transmission electron microscopy (Immuno-TEM). Activity of the drug was analyzed using a mouse endothelial cell line transfected with a glucocorticoid-responsive reporter gene construct and the drug's effect on interleukin (IL)-8 expression was assayed using Northern blotting.

Results. The dexamethasone conjugate bound to activated, but not resting, human endothelial cells when the drug-treated cell cultures were stained with antibodies directed against anti-human E-selectin or dexamethasone. Flow cytometry confirmed these results. CLSM and Immuno-TEM demonstrated binding of the dexamethasone conjugate to activated, but not resting, cell surfaces 10 and 20 minutes after incubation and after 1 hour, cell surface staining began to decrease and intracellular staining increased. The dexamethasone conjugate was able to activate a glucocorticoid-responsive reporter gene to a similar degree to that seen with free dexamethasone. Northern blotting demonstrated downregulation of IL-8 expression in activated human endothelial cells treated with the dexamethasone conjugate. Again, this effect was similar to that seen with free dexamethasone.

Conclusions. Conjugated dexamethasone-anti-E-selectin is specifically targeted to active endothelial cells and internalized by these cells. The results also suggest that the conjugate drug retains the ability to regulate transcription.

Reviewers' Comments. Although targeted drug therapy is not a novel concept, these experiments suggest that a noncytotoxic drug can be targeted to a specific cell type and retain biological activity. Unlike a drug targeted to kill cancer cells, this approach utilizes an antiinflammatory drug to downregulate proinflammatory cytokines and cell surface receptors with the idea that the toxicity associated with immune suppression would be minimized.

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THE ROLE OF ANTICHOLINERGICS IN ACUTE ASTHMA TREATMENT

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