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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