LONG-TERM EFFECT OF BUDESONIDE ON HYPOTHALAMIC-PITUITARY-ADRENAL AXIS FUNCTION IN CHILDREN WITH MILD TO MODERATE ASTHMA


**Purpose of the Study.** To determine the safety of 36 months of inhaled budesonide administration on hypothalamic-pituitary-adrenal (HPA) axis function in children with mild to moderate asthma.

**Study Population.** Sixty-three children enrolled in the previously published Childhood Asthma Management Program (CAMP) study with mild to moderate asthma (mean age: 9.5 ± 1.9 years). CAMP participants were between 5 and 12 years of age.

**Methods.** Children received placebo, nedocromil (16 mg/day by metered-dose inhaler), or budesonide (400 mg/day by Turbuhaler). HPA axis function was assessed at baseline and after 12 and 36 months of continuous treatment using serum cortisol levels at 0, 30, and 60 minutes after administration of 0.25 mg of adrenocorticotropic hormone (ACTH) and 24-hour urinary free-cortisol (UFC) excretion. Data for children treated with placebo and nedocromil were combined and compared with those treated with budesonide.

**Results:** Serum cortisol measurements were obtained for 54 children at 12 months (5 missed the study visit, and 4 had declines in cortisol after ACTH) and 56 children at 36 months (5 missed the visit, and 2 declined participation). After adjusting for age at randomization, race, gender, clinic, body surface area, and baseline serum cortisol level, there were no differences in serum cortisol levels during ACTH simulation testing between treatment groups. During the study, the serum cortisol levels at successive time points tended to decrease in both treatment groups. Additionally, cortisol levels of children who did and did not receive supplemental ICSs during the study were similar. Oral corticosteroids were prescribed to 6 participants before randomization (3 budesonide and 3 placebo/nedocromil), and additional courses were used during the study for exacerbations. When all groups were combined, oral corticosteroid use 4 months preceding the 12- and 36-month visits did not affect cortisol levels after ACTH stimulation. Subgroup analyses confirmed these findings, adjusting for any supplemental corticosteroid use. Technical problems allowed UFC measurement at only the 36-month visit for 56 patients. Although UFC levels were similar in both treatment groups, ICS use within the 4 months before the 36-month visit was borderline significantly lower (22 vs 34 µg/m² per 24 hours; P = .05); however, oral prednisone did not show any effect. Finally, there was no difference in serum cortisol or UFC between treatment groups based on cumulative ICS dose.

**Conclusions.** No effect on HPA axis function was observed after chronic budesonide treatment at 400 mg/day in children with mild to moderate asthma. There was no cumulative effect on HPA axis function over a 3-year period.

**Reviewer’s Comments.** Despite the proven efficacy of ICSs, there remains concern regarding the long-term effects of their use with resultant underutilization. Several short-term studies of systemic effects related to low-dose ICSs have demonstrated little effect on HPA axis activity, but studies on long-term use are lacking. This study is the first of long-term studies to help detect or refute potential long-term effects of ICSs in children and thus far dispels fears regarding the use of ICSs for asthma control.

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INHALED CORTICOSTEROIDS AND THE RISK OF FRACTURES IN CHILDREN AND ADOLESCENTS

Schlienger RG, Jick SS, Meier CR. *Pediatrics.* 2004;114:469–473

**Purpose of the Study.** To determine if children or adolescents who are exposed to inhaled corticosteroids (ICS) (ie, beclomethasone, budesonide, fluticasone) are at a higher risk of having bone fractures compared with non-exposed individuals.

**Study Population.** This was a population-based study using the United Kingdom General Practice Research database that contains data for >3 million people.

**Methods.** Within a base population of 273 456 individuals aged 5 to 79 years, the authors used International Classification of Diseases codes to identify children or adolescents who were aged 5 to 17 years with a fracture diagnosis and up to 6 control subjects per case matched to cases on age, gender, general practice attended, calendar time, and years of history in the database. They compared the use of ICS steroids before the index date between fracture cases and control patients.

**Results.** There was no increased fracture risk associated with current exposure to ICS when compared with nonusers even in individuals with current longer-term exposure, ie, ≥20 prescriptions (adjusted odds ratio: 1.15; 95% confidence interval: 0.89, 1.48). For individuals with current or previous exposure to oral steroids, the adjusted odds ratio for current long-term inhaled steroid use compared with nonuse was 1.21 (95% confidence interval: 0.99, 1.49).

**Conclusions.** The conclusions of the authors were that exposure to ICS does not substantially enhance the fracture risk in children and adolescents when compared with non-exposed individuals.

**Reviewer’s Comments.** This excellent study verifies general consensus in the literature that ICS used in recommended doses do not increase fracture risk in children or adolescents when compared with controls. There are some
Immunodeficiency

PRIMARY IMMUNODEFICIENCY

IMMUNODEFICIENCY AND INFECTIONS IN ATAXIA-TELANGIECTASIA


Purpose of the Study. To describe immunodeficiency in ataxia-telangiectasia (A-T) and its clinical manifestations and course.

Study Population. Patients with A-T who underwent multidisciplinary assessment at Johns Hopkins Hospital (Baltimore, MD).

Methods. Charts from the first 100 consecutive patients with A-T who were assessed at Johns Hopkins Ataxia-Telangiectasia Clinical Center were reviewed. Specific criteria for the diagnosis of A-T had to be met. Immunologic data were obtained by reviewing laboratory assessments of patients’ immune systems. Infections were determined by patient and family interviews and chart review.

Results. A large percentage of patients had immunoglobulin deficiencies at the time of first immunologic assessment: 65% had IgG4 deficiency, 63% had IgA deficiency, 48% had IgG2 deficiency, and 23% had IgE deficiency. Deficiencies did not correlate or progress with age. Lymphopenia occurred in 71% of patients. CD19 B lymphocytes were reduced in 75% of patients. CD4 T cells were decreased in 69% of the patients, and CD8 T cells were decreased in 51% of the patients. Patients had no untoward effects from live viral vaccines. Recurrent upper respiratory infections occurred in one third of the patients regardless of age. Lower respiratory tract infections increased with age. Viral and opportunistic infections were not common.

Conclusions. Patients with A-T have a wide array of laboratory-based immunodeficiencies. However, there seems to be no correlation between laboratory values and clinical manifestation of immunodeficiency in this population.

Reviewers’ Comments. This study confirms previously characterized immunodeficiencies in A-T patients. However, the large number of patients involved in this study allowed for a more extensive review of immunodeficiencies as well as clinical correlation of laboratory values. At this time it seems that clinical immunodeficiency is not common in A-T. Rather, the high rate of respiratory infections may be attributable to other factors of A-T such as neurologic deficits leading to aspiration.

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AUTOSOMAL RECESSIVE HYPERIMMUNOGLOBULIN E SYNDROME: A DISTINCT DISEASE ENTITY


Purpose of the Study. To describe the clinical and immunologic features of a distinct subgroup of patients with hyper-IgE syndrome (HIES) having autosomal recessive inheritance (AR-HIES) as distinct from the form having autosomal dominant inheritance (AD-HIES).

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CLINICAL AND IMMUNOLOGICAL EFFECT OF LOW-DOSE IFN-α TREATMENT IN PATIENTS WITH CORTICOSTEROID-RESISTANT ASTHMA


Purpose of the Study. To evaluate the clinical and immunologic effects of interferon (IFN)-α in patients with corticosteroid-resistant asthma with and without Churg-Strauss syndrome.

Study Population. Ten patients with severe steroid-resistant asthma, 3 of whom had Churg-Strauss syndrome, were studied.

Methods. Subjects were given 3 × 10^6 IU/day of recombinant IFN-α for at least 5 months. The prior systemic corticosteroid doses were maintained until clinical improvement was seen, and then they were decreased gradually. Spirometry, immunophenotyping of peripheral blood mononuclear cells, cytokine measurements, and lymphocyte proliferation assays were performed.

Results. IFN-α rapidly improved patient clinical status as assessed by improved lung-function parameters and decreased prednisone requirements. Immunologic changes included decreased leukocyte numbers, decreased numbers of eosinophils in patients with prior eosinophilia, increased relative numbers of CD4+ T cells, increased differentiation of T-helper (Th)1 cells, and increased interleukin 10 and IFN-γ levels in peripheral blood mononuclear cells.

Conclusions. Treatment with IFN-α in patients with steroid-resistant asthma with and without Churg-Strauss syndrome was associated with clinical improvement. Possible mechanisms of action include induction of anti-inflammatory interleukin 10 and establishment of a correct Th1/Th2 balance.

Reviewers’ Comments. Although this study involved only a few patients and additional elucidation of the underlying mechanisms is needed, these patients with steroid-resistant asthma improved with IFN-α treatment. Although this study involved only adults, the use of IFN-α as a potential steroid-sparing medication for use in children may also prove beneficial, especially given justified patient, parental, and physician concerns about using long-term oral corticosteroids in children because of the potential for significant toxicity. The use of IFN-α, however, would have to outweigh its inherent potential adverse effects including influenza-like symptoms, nausea, and liver toxicity, to name a few. This preliminary study, however, does make a case for the need for additional, longer-term clinical trials.

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Inhaled Corticosteroids and the Risk of Fractures in Children and Adolescents
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