Review: Clinical Trial Outcomes

CLINICAL INVESTIGATION

Inhaled corticosteroids: the last 5 years

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This review will highlight new information on the use of inhaled corticosteroids (ICSs) for management of asthma with regard to long-term side effects and new treatment approaches. Variability in response to ICSs has been increasingly recognized and contribution of pharmacogenomic, phenotypes and environmental factors have been identified and discussed here. As ICSs remain the cornerstone of persistent asthma management, the CAMP trial provides more data in long-term adverse effect of ICSs. In order to minimize the side effects of ICSs, different asthma management approaches have been proposed in different patient populations. In addition, potential advantages of fine particle ICSs for improving small airway disease have been discussed.

Keywords: adverse events • asthma • intermittent therapy • inhaled corticosteroids • intermittent treatment • pharmacogenetics • small airways • vitamin D

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In 2007, the National Heart, Lung and Blood Institute published its update of the guidelines for the diagnosis and management of asthma the Expert Panel Report 3 [101]. In 2009, the update of the International Global Initiative for Asthma guidelines was published [102]. Both the Expert Panel Report 3 and Global Initiative for Asthma guidelines recommended that inhaled corticosteroids (ICSs) be the foundation of treatment for all ages of patients with persistent asthma with little variation between them. Although ICSs are well-established therapies and very effective for many patients with asthma, ongoing clinical investigations have continued to assess best dosing strategies, determinants of responsiveness and potential risks from long-term use of ICSs. It is the purpose of this paper to report on the past 5 years of these investigations that may affect future guidelines.

Determinants of response

■ Pharmacogenomic

It has become clear over the years of many clinical trials that while the majority of patients with asthma respond well to ICS therapy, the response can be highly variable with up to 10–15% of patients not responding and as many as 24% having a poor lung function response [1]. A number of investigations have assessed both genetic, as well as phenotypic, explanations for the relative lack of response. Utilizing a genome wide association analysis, a functional variant (rs37973) in the *GLCCI1*, was shown to be associated with a decreased response in lung function (forced expiratory volume in 1 s) to ICS in children participating in the CAMP clinical trial [2]. Patients who were homozygous for the variant allele had only a third of the response to budesonide than those homozygous for the wild-type allele. This finding was replicated in four other distinct populations with asthma. The variant allele occurs in approximately 16% of the population and the genotype accounted for approximately 6.6% of the response variability in those who had it, as well as the increased risk of a poor response. This study has added to previous studies in the CAMP cohort by this group, demonstrating a diminished

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lung function response to ICSs secondary to minor alleles of the *FCER2* gene and in the *CRHR1* gene [1].

Phenotype & environment

Phenotypic and environmental factors can also alter response to the ICSs. Asthma-related factors predictive of a response to ICSs in children in terms of improved asthma control, include increased concentrations of fraction of exhaled nitrous oxide (FENO), increased eosinophil counts and eosinophil cationic protein, increased IgE, lower lung function, increased airway hyper-responsiveness as measured by methacholine bronchoprovocation, increased bronchodilator responsiveness to short-acting β_2 agonist and a parental history of asthma [1,3]. However, only FENO, airway hyper-responsiveness and parental history of asthma predicted a greater response to ICSs than leukotriene modifier [3]. Interestingly, asthma characteristics that predict poor lung function response do not necessarily predict a poor response for preventing asthma exacerbations and vice versa [1].

A major nonasthma specific phenotype predictive of poor response to ICSs is elevated BMI and obesity [4,5]. Clinically, this has resulted in both decreased lung function response and protection against asthma exacerbations from ICSs [5]. This effect appears to be related decreased clearance of apoptotic inflammatory cells by airway macrophages, which is normally improved by corticosteroids in nonobese patients with asthma [6]. The decreased response, defined by forced expiratory volume in 1 s, asthma symptom score, and albuterol use also occurs with combination therapy of ICSs with long-acting inhaled β agonists (LABAs), despite the fact that the addition of LABAs has been shown to produce a synergistic activation of the glucocorticoid receptor and improved anti-inflammatory activity [7,8]. It is notable that, although the response to ICS/LABA combination is diminished in obese patients compared with normal weight patients, the obese patients have a superior response to ICS/LABA compared to montelukast [7].

Environmental factors that blunt the response to ICSs include smoking and vitamin D insufficiency and deficiency [9,10]. Although it has been known for a long time that smoking impairs the response to ICSs, a recent report found that *in utero* smoke exposure reduced improvement in airway responsiveness to ICS therapy in children 5–12 years of age [11]. Whether the mechanism for the decreased response from smoking and *in utero* exposure is similar, is unknown. Recent evidence suggests that the oxidative stress from smoking increases the activity of PI3Kδ, which leads to the inactivation of histone deacetylase-2, which prevents transactivation of corticosteroid responsive genes [9]. This finding may allow the development of therapeutic strategies for improving the response to ICS in patients who smoke or are past smokers or have severe asthma where the inflammation produces oxidative stress. An *in vitro* study found that nortriptyline, a direct inhibitor of PI3Kδ, restores corticosteroid sensitivity induced by oxidative stress in monocytic cells [12]. Whether this approach will improve response in patients awaits clinical trials. Up to 35% of children with persistent asthma are vitamin D insufficient (<30 ng/ml serum concentration) and the decreased corticosteroid responsiveness may, in part, explain the association between vitamin D insufficiency and increased risk of severe exacerbations, decreased asthma control and increased ICS and oral corticosteroid usage [13–15]. In addition, vitamin D deficiency is associated with decreased lung function improvement from ICSs [16]. While the exact mechanism by which vitamin D insufficiency reduces corticosteroid responsiveness is unknown, it has been shown to increase levels of the immune-modulatory cytokines TGF-β, MKP1 and IL-10 from T-regulatory cells [15]. A large multicenter clinical trial stratified by vitamin D status is underway to determine whether supplementation of vitamin D improves outcomes in patients requiring ICSs.

Long-term adverse effects of ICSs

Growth

Corticosteroids can produce a variety of adverse systemic effects when taken either continuously or frequently over many years, including: decreased linear growth; decreased bone mineral density (BMD) and osteoporosis; decreased hypothalamic–pituitary–adrenal axis activity; and posterior subcapsular cataracts. Patients receiving high doses of ICSs have shown an increased risk of experiencing these effects [101,102]. In addition, patients receiving low to medium doses of some ICSs have demonstrated small (1–2 cm) reductions in growth in the first 1–2 years of initiation of ICS therapy; however, it was unknown what the long-term consequences were on adult height from the initial reduction [101,102]. In the first long-term prospective trial of ICS therapy in children 5–12 years of age followed into adulthood, the initial -1.2 cm difference in height seen in the budesonide group at year 2 of the CAMP trial persisted into the final adult height in comparison with the group that received the placebo [17]. Although the mean effect over all the patients was small, a significant dose-response effect was found (-0.1 cm/μg/kg budesonide) so that the younger, smaller children experienced a greater reduction in height. Two additional studies demonstrated dose-response effects on growth in preschool and school aged children. A study by the Childhood Asthma Research and Education Network

of the National Heart, Lung, and Blood Institute reported a significant reduction in height (mean: -1.6 cm) in preschoolers 2 years of age weighing <15 kg who received fluticasone propionate 176 µg/day by chlorofluorocarbon propelled metered dose inhaler (MDI) via Aerochamber™ valved holding-chamber (VHC) [18]. The importance of these results is amplified by a recent study comparing the delivery of the newer hydrofluoroalkane propelled fluticasone propionate MDI with the Aerochamber™ Max made with antistatic polymers [19]. Both preschool and school aged children (1–4 and 5–9 years old, respectively) achieved significantly higher steady state plasma fluticasone propionate concentrations than 5–18 year olds not using the antistatic VHC with the MDI. In addition, the concentrations they reported were threefold greater than those seen using the same doses in children ≥12 years with an older static VHC. Thus, safety data from older MDI formulations and VHCs should not be extrapolated to newer preparations and devices. Low doses of the newer hydrofluoroalkane propelled beclomethasone dipropionate (80 µg/day) produced significant reduction in growth (-1.1 cm over 1 year) in children 5–18 years old [20]. However, low to medium dose mometasone furoate (100–200 µg/day) by dry powder inhaler produced little to no significant growth suppression in 4–9 year olds over 1 year [21]. The results of this study were interesting in that 100 µg twice daily did not produce a difference from placebo, but 200 µg once in the morning did produce a significant reduction (-0.70 cm). This suggests that the peak serum concentration may be as or more important as the total daily dose. These results are similar to the lack of a growth effect from fluticasone propionate by dry powder inhaler at 100 and 200 µg/day, which is to be expected as fluticasone propionate and mometasone furoate have very similar potencies and pharmacokinetic properties [22]. Unfortunately, fluticasone propionate by hydrofluoroalkane MDI alone or with a VHC has not been evaluated for growth effect. The newer ciclesonide was studied but in dosages that did not produce a therapeutic effect in children so it is unclear whether ciclesonide's apparently improved therapeutic index in adults as measured by adrenal axis suppression extends to growth in children [22,23]. This is particularly important because the effects of ICSs on growth occur at doses that do not affect the adrenal axis [22].

■ Bone-mineral density

High-dose ICSs have been associated with decreased bone-mineral density (BMD), osteoporosis and increased risk of fracture in patients with other high-risk factors [101,102]. However, long-term prospective controlled trials in children had not been completed. The CAMP cohort of children (n = 877) were followed with dual-energy X-ray absorptiometry scans of the lumbar spine for a median duration of just over 7 years and the effect of both cumulative ICS and oral corticosteroid doses for acute exacerbations on mean bone mineral accretion over that time was assessed [24]. No effect was found for ICS on bone mineral accretion or risk of osteoporosis or fracture risk. Interestingly, a decreased bone mineral accretion and an associated increased risk of osteopenia was found in boys who received approximately two oral courses of prednisone per year. This shows that effects on growth do not translate into effects on BMD. A recent follow up to this study found that the decreased BMD and osteopenia risk only occurred in those patients with vitamin D insufficiency or deficiency [25]. Based upon the previous discussion, this suggests that vitamin D may have a twofold beneficial effect in children with asthma in preventing severe exacerbations, reducing the risk of receiving courses of prednisone and preventing mineral resorption from the bone due to oral corticosteroids.

■ Cataracts

Finally, 232 patients from the original CAMP cohort received slit lamp exams 12–13 years after the initial randomization [26]. Following the initial CAMP trial of 4–6 years there was one patient in the budesonide group that had a small post-subcapsular cataract. At the final exam, 16 patients had findings consistent with cataracts, but there was no significant difference in the percentage of patients who received corticosteroids or never received corticosteroids over CAMP and follow up (6.7 vs 8.3%, respectively). Oral corticosteroid use did not have an effect on the development of cataracts.

■ Summary

The relative lack of long-term adverse effects of ICSs in children with persistent asthma is important because an almost 5-year follow up of the CAMP study found that the patients who had received ICSs for a mean of 4.3 years did not differ in lung function, airway hyperresponsiveness or asthma control [27] and that less than 10% had their asthma in remission [28]. In addition, all the children in the follow-up cohort, despite the initial randomized treatment, required ICSs for asthma control during 30% of the post-trial period [27].

Intermittent versus continuous ICSs

■ Children & adults

Due to the fact that it has become increasingly clear that continuous ICS therapy does not alter the natural progression of asthma, investigators have been exploring the use of intermittent ICSs for both adults and children with mild persistent asthma [20,29]. A recent

meta-analysis of the comparative trials found that continuous ICS therapy provided greater improvement in measures of the impairment domains from the guidelines including: lung function, asthma control days, symptom-free days and as-needed short-acting inhaled β_2 agonists for rescue, as well as biomarkers of inflammation such as FENO [29]. However, there was no discernible difference in the risk domain (hospitalization, emergency department visits, or withdrawals from treatment failure). The two most recent trials illustrate the differences in approach to intermittent therapy. In the first, school aged children, with mild-to-moderate persistent asthma, were first controlled with medium dose budesonide (800 µg/day), then the daily dose reduced or discontinued [30]. The intermittent therapy consisted of 2 weeks of budesonide 800 µg/day for any children with worsening asthma and who were not responding to six doses of short-acting inhaled β_2 agonist in the first 24 h, whether or not they were receiving continuous low doses of budesonide [30]. In the other trial the ICS was given continuously and as needed whenever the short-acting inhaled β_2 agonist was administered or just as needed [20]. Children 6–18 years of age were randomly assigned to one of four treatment arms after a run-in period confirming well-controlled asthma. The treatment arms were beclomethasone dipropionate 40 µg one puff twice daily plus a combination of beclomethasone dipropionate 40 µg and albuterol one puff as needed, placebo daily plus a combination of beclomethasone dipropionate and albuterol one puff each as needed, beclomethasone dipropionate, 40 µg one puff twice daily plus albuterol as needed, or placebo daily plus albuterol as needed. The primary outcome was time to first exacerbation requiring prednisone. Both studies demonstrated a reduction in exacerbations and median time to exacerbation in the continuous ICS arms of the study, but their definitions of exacerbation differed [20,30]. However, both studies also demonstrated reductions in growth velocity in the continuous ICS arms of the trial while the intermittent-only periods did not (see discussion on growth above).

Infants & preschool children

Infants and preschool children often have intermittent wheezing episodes, primarily associated with upper respiratory viral infections without detectable symptoms in between episodes, and may represent a different phenotype from older children and adults [101,102]. Current recommendations state that patients 0–4 years with two or more exacerbation in 6 months or four or more wheezing episodes/year and risk factors for asthma (i.e., a positive modified asthma predictive index [101,102]), should be treated as persistent asthma and a systematic review and meta-analysis reported a 40% reduction in asthma exacerbation rate in preschool children with asthma and recurrent wheezing on daily ICS therapy [31,101]. However, many clinicians and parents are unwilling to prescribe and administer chronic medication for what they perceive as an intermittent problem. Recent clinical trials have shed more light on appropriate therapy for these patients. In a comparison study of budesonide 1 mg by nebulizer solution twice daily with montelukast 4 mg orally once daily and placebo for 7 days at the start of a respiratory illness, no treatment arm reduced the use of oral corticosteroids; however, those children with a positive modified asthma predictive index experienced symptom reduction during the episodes with both active treatments [32].

In a placebo-controlled trial of very high dose fluticasone propionate (750 µg twice daily via MDI and VHC) at the start of respiratory illness for up to 10 days in children 1–6 years old, asthma exacerbation rate, which was defined as the use of oral corticosteroid, was reduced by 50% [33]. There was no difference between the groups in the number of upper respiratory tract infections. However, the high dose of ICS was associated with a significantly reduced height and weight gain compared with those receiving the placebo over the median period of 40 weeks of the study. Infants (n = 276) between 1 and 4 years of age with frequent wheezing were randomized to three arms for 3 months: nebulized beclomethasone dipropionate 800 µg twice daily plus salbutamol 2500 µg as needed, daily placebo plus combination of beclomethasone dipropionate 800 µg and salbutamol 1600 µg as needed, or daily placebo plus salbutamol 2500 µg as needed [34]. Only children on regular daily beclomethasone dipropionate had significantly higher symptom-free days compared with those on only rescue salbutamol. However, the children on as-needed therapy were not significantly different from those on continuous therapy with ICS. Interestingly, children with risk factors for persistent asthma did not differ in response. Finally, the Childhood Asthma Research and Education clinical trials network of the National Heart, Lung and Blood Institute assessed the use of nebulized budesonide 0.5 mg daily versus intermittent budesonide, 1 mg twice daily for 7 days at the start of a respiratory illness usually associated with exacerbations in children aged 12 to 53 months and a positive modified asthma predictive index [35]. At the end of the 1-year trial, there was no difference in the rate of asthma exacerbation as defined by use of oral corticosteroids, asthma symptoms or severity of episodes between the treatment arms. The linear growth was the same in both groups.

Summary

In adults and school aged children with mild persistent asthma, the use of as-needed or intermittent ICSs may

prevent some use of prednisone bursts for acute exacerbations but reduce the beneficial effect on daily and night time symptoms, short-acting β_2 agonist use and biomarkers of inflammation (i.e., FENO). In children and adults with truly intermittent or seasonal asthma, the use of continuous treatment during the season is appropriate. In infants and preschool children with intermittent viral associated exacerbations intermittent high dose ICS therapy, may prevent exacerbations requiring systemic corticosteroid therapy; however, the appropriate dose and formulations have yet to be determined.

Targeting small airways

Since the mid-1990s, inflammation in small airways has been increasingly recognized as a major contribution to the pathology of asthma and chronic obstructive pulmonary disease (COPD) [36–39]. Small airways (<2 mm diameter) inflammation results in increased air-trapping and bronchial hyper-responsiveness and is associated with increased nocturnal asthma and severe uncontrolled asthma phenotypes, as well as COPD [36–39]. A primary difficulty for assessing treatment of small airways inflammation has been the identification of a standardized tests and relating the improvement in those tests with overall improvement in patients [38,39]. It has been posited that the newer small particle generating (or ultrafine particle) ICS MDIs may provide enhanced control because of their improved delivery to the peripheral small airways, and this position has high face validity [38,39]. Studies have clearly demonstrated improved overall lung deposition and greater peripheral lung deposition of the ultrafine particles [39,40]. Some investigators have suggested the improved delivery in small airways indicates that ultrafine preparations be the delivery of choice for infants and young children who by definition have smaller airways [41]. Clinical studies using radiolabeled ICSs have confirmed greater delivery in young children for ultrafine particle devices [42]. However, no clinical studies of efficacy or on the safety of using ultrafine particles have been completed in infants and children. Investigations in small numbers of adult patients have demonstrated preferential improvement in some measures of small airways disease from the newer ultrafine particle devices; however, results have been inconsistent and confounded by differential dosing of the ultrafine versus standard particle delivery devices and study design flaws [36,39]. Unfortunately, large comparative trials of ultrafine and standard particle ICSs have not recruited patients specifically with small airways dysfunction that occurs in 50% or less of patients [36,39]. As a result, those comparisons do not support a differential improved asthma outcomes for the ultrafine [36,39]. Improved methods of measuring small airways disease and large-scale trials targeted at patients with significant small airways inflammation are required to determine if targeted therapy provides clinically relevant improvement in asthma and COPD control [36–39].

Future perspective

ICSs are likely to remain the foundation of therapy for asthma in the next 5–10 years, as no other single mediator inhibitor or other classes of anti-inflammatories have demonstrated as robust efficacy. However, there are ongoing investigations of newer products that provide longer durations of action [44]. Whether these products will provide improved effectiveness with fewer adverse effects is speculative at this point in time. Preclinical studies investigating corticosteroids and other glucocorticoid receptor agonists that preferentially stimulate the repression of inflammatory genes, but do not activate the genes responsible for systemic adverse effects, are also in development. In addition, methods of overcoming corticosteroid resistance are being investigated, although most will not be available in the next 5 years. Although the addition of LABAs to ICS have been shown to provide enhanced glucocorticoid receptor activation [45] and reduced exacerbations, which is considered an anti-inflammatory effect [46], there remains concern in the USA that ICSs may not prevent the rare association of severe life-threatening exacerbations from LABAs [47]. Based upon studies adding LABA monotherapy to patients' usual asthma therapy, which demonstrated an increased risk of death from asthma in adults and hospitalization in children, all LABA containing products, including combination products with ICSs, contain a boxed warning of those risks [47]. However, even the US FDA meta-analysis of all the studies with LABAs as monotherapy and in combination with ICSs found no increased risk of death or hospitalization with simultaneous use of the combination [48]. The FDA determined that the data on combination therapy were of insufficient power to conclude ICSs mitigated the risk, and therefore, mandated large ongoing clinical trials to address this issue; however, results will not be available for at least 5 years [47]. A large clinical trial of vitamin D supplementation will help answer the question of whether it reverses some corticosteroid insensitivity. In infants and young children, we have good evidence that preemptive use of high-dose ICSs prevents the use of oral corticosteroids; however, we need much more information on appropriate dose, duration, and safety, particularly for the newer hydrofluoroalkane MDIs that generate smaller particles. Hopefully more clinical trials will be performed in this patient population.

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Executive summary

- Although inhaled corticosteroids (ICSs) remain the foundation of care for patients with persistent asthma, new clinical studies have identified genetic and environmental causes of corticosteroid resistance that should allow the discovery of methods for improving efficacy.
- While the long-term use of ICSs at medium doses has a strong safety profile, their inability to alter the natural progression of asthma has spurred investigations of intermittent dosing strategies to minimize exposure; however, continuous therapy will remain preferred in persistent asthma.
- Intermittent ICS therapy of infants and young children who have primarily intermittent asthma associated with viral respiratory tract infections is effective but more information on appropriate dosing is required.
- There is an increasing interest in targeting small airways inflammation to improve outcomes in asthma as more ultrafine particle generating devices are developed. Early studies are promising but have suffered from inconsistencies, design flaws and ease of assessing small airways and response to therapy.

References

Papers of special note have been highlighted as:

- ▪ of interest
- ▪▪ of considerable interest

1 Rogers AJ, Tantisira KG, Fuhlbrigge AL *et al.* Predictors of poor response during asthma therapy differ with definition of outcome. *Pharmacogenetics* 10(8), 1231–1242 (2009).

▪ **Investigates both genetic and asthma phenotypic associations with poor lung function response in the 311 patients randomized to inhaled corticosteroid (ICS) in the CAMP clinical trial of 4–6 years. They found younger age, higher pre-bronchodilator forced expiration volume in 1 s percentage predicted, lower bronchodilator response to albuterol, and lower airway hyper-responsiveness were associated with poor response, but that only bronchodilator response and two genetic polymorphisms were associated with poor response in the multivariate model.**

2 Tantisira KG, Lasky-Su J, Harada M *et al.* Genomewide association between GLCCI1 and response to glucocorticoid therapy in asthma. *N. Engl. J. Med.* 365(13), 1173–1183 (2011).

▪▪ **The first genomewide association study to assess response to ICS in asthma. They utilized 118 trios (patients and families) for the initial analysis and then four independent populations for a total of 935 persons for confirmation.**

3 Knuffman JE, Sorkness CA, Lemanske RF *et al.* Phenotypic predictors of long-term response to inhaled corticosteroid and leukotriene modifier therapies in pediatric asthma. *J. Allergy Clin. Immunol.* 123(2), 411–416 (2009).

4 Sutherland ER, Goleva E, Strand M, Beuther DA, Leung DYM. Body mass and glucocorticoid response in asthma. *Am. J. Resp. Crit. Care Med.* 178(7), 682–687 (2008).

▪ **The first study to demonstrate decreased *in vitro* corticosteroid response in leukocytes from patients with asthma who had vitamin D insufficiency.**

5 Forno E, Lescher R, Strunk R, Weiss S, Fuhlbrigge A, Celedón JC. Decreased response to inhaled steroids in overweight and obese asthmatic children. *J. Allergy Clin. Immunol.* 127(3), 741–749 (2011).

▪▪ **Used the CAMP cohort to evaluate ICS response in asthmatic children. In this case, they demonstrated decreased protection against risk of exacerbations as well decreased lung function response.**

6 Fernandez-Boyanapalli R, Goleva E *et al.* Obesity impairs apoptotic cell clearance in asthma. *J. Allergy Clin. Immunol.* 131(4), 1041–1047 (2012).

7 Camargo CA Jr, Boulet LP, Sutherland ER *et al.* Body mass index and response to asthma therapy: fluticasone propionate/salmeterol versus montelukast. *J. Asthma* 47(1), 76–82 (2010).

▪▪ **The primary importance of this study is not the finding of decreased response to ICS from increased BMI and obesity, but that the diminished response affects other therapies as well. Thus, a decreased response to one form of therapy does not imply that patients should necessarily be treated with alternatives.**

8 Essilfie-Quaye S, Ito K, Ito M, Kharitonov SA, Barnes PJ. Comparison of Symbicort® versus Pulmicort® on steroid pharmacodynamic markers in asthma patients. *Respir. Med.* 105(12), 1784–1789 (2011).

9 Marwick JA, Caramori G, Casolari P *et al.* A role for phosphoinositol 3-kinase delta in the impairment of glucocorticoid responsiveness in patients with chronic obstructive pulmonary disease. *J. Allergy Clin. Immunol.* 125(5), 1146–1153 (2010).

▪ **While it has been known for some time that smoking and oxidative stress reduces the response to corticosteroids, this study first identified a causal mechanistic link that can be explored to potentially develop therapies for intervening (see [14]).**

10 Sutherland ER, Goleva E, Jackson LP, Stevens AD, Leung DYM. Vitamin D levels, lung function and steroid response in adult asthma. *Am. J. Respir. Crit. Care Med.* 181(7), 699–704 (2010).

11 Cohen RT, Raby BA, Van Steen K *et al.* In utero smoke exposure and impaired response to inhaled corticosteroids in children with asthma. *J. Allergy Clin. Immunol.* 126(3), 491–497 (2010).

12 Mercado N, To Y, Ito K, Barnes PJ. Nortriptyline Reverses Corticosteroid Insensitivity by Inhibition of Phosphoinositide-3-Kinase-d. *J. Pharmacol. Exp. Ther.* 337(2), 465–470 (2011).

13 Brehm JM, Schuemann B, Fuhlbrigge AL *et al.* Serum vitamin D levels and severe asthma exacerbations in the childhood asthma management program study. *J. Allergy Clin. Immunol.* 126(1), 52–58 (2010).

■ **One of the first studies with the ability to assess prospectively the effects of vitamin D insufficiency due to the long-term nature of the CAMP trial. After adjusting for factors associated with an increased risk of exacerbations including age, sex, BMI, income and treatment group, insufficient vitamin D status was associated with higher odds of severe exacerbation over a 4-year period (overall response: 1.5; 95% CI: 1.1–1.9; p = 5.01).**

14 Gupta A, Sjoukes A, Richards D *et al.* Relationship between serum vitamin D, disease severity, and airway remodeling in children with asthma. *Am. J. Respir. Crit. Care Med.* 184(12), 1342–1349 (2011).

15 Searing DA, Zhang Y, Murphy JR, Hauk PJ, Goleva E, Leung DY. Decreased serum vitamin D levels in children with asthma are associated with increased corticosteroid use. *J. Allergy Clin. Immunol.* 2125(5), 995–1000 (2010).

16 Wu AC, Tantisira K, Li L, Fuhlbrigge AL, Weiss ST, Litonjua A. Effect of vitamin D and inhaled corticosteroid treatment on lung function in children. *Am. J. Respir. Crit. Care Med.* 186(6), 508–513 (2012).

17 Kelly HW, Sternberg AL, Lescher R *et al.* Effect of inhaled glucocorticoids in childhood on adult height. *N. Engl. J. Med.* 367(10), 904–912 (2012).

■■ **The only prospective clinical trial to follow children who had a growth suppressive effect from early ICS therapy into adulthood. As 90.6% of the initial cohort were followed into adulthood, it was also the first study allowing an intention-to-treat analysis and found that the children did not outgrow the effect as it persisted into adulthood.**

18 Guilbert TW, Mauger DT, Allen DB *et al.* Growth of preschool children at high risk for asthma 2 years after discontinuation of fluticasone. *J. Allergy Clin. Immunol.* 128(5), 956–963 (2011).

■ **A *post hoc* analysis of the decreased growth from the use of fluticasone propionate 200 µg/day in 2–4 year-olds with a risk of developing asthma (positive asthma predictive index). This study assessed the growth 2 years after discontinuing the medication and further established a dose-response aspect.**

19 Elmallah MK, Khan Y, Hochhaus G, Shuster JJ, Hendeles L. Systemic exposure to fluticasone MDI delivered through antistatic chambers. *J. Allergy Clin. Immunol.* 128(5), 1113–1115 (2011).

20 Martinez FD, Chinchilli VM, Morgan WJ *et al.* Use of beclomethasone dipropionate as rescue treatment for children with mild persistent asthma (TREXA): a randomized, double-blind, placebo-controlled trial. *Lancet* 377(9766), 650–657 (2011).

■■ **This study compared the relative efficacy of continuous low dose ICS (beclomethasone dipropionate 80 µg/day via hydrofluoroalkane propelled metered dose inhaler) to as needed ICS in children with mild asthma. They also compared the addition of as needed ICS with the low-dose daily ICS. Only the low-dose-continuous-ICS arms were significantly better than placebo in preventing exacerbations requiring oral corticosteroids and there was no advantage of adding as needed ICS to low-dose continuous therapy. They also reported a significant reduction in growth on the low-dose arms. This was the first placebo comparison of the newer ultrafine particle beclomethasone dipropionate on growth.**

21 Skoner DP, Meltzer EO, Milgrom H, Stryszak P, Teper A, Staudinger H. Effects of inhaled mometasone furoate on growth velocity and adrenal function: a placebo-controlled trial in children 4–11 years old with mild persistent asthma. *J. Asthma* 48(8), 848–859 (2011).

22 Kelly HW. Comparison of inhaled corticosteroids: an update. *Ann. Pharmacother.* 43(3), 519–527 (2009).

■ **A review of the pharmacokinetic/pharmacodynamic characteristics of the ICS that determine efficacy and safety and relative dose equivalency.**

23 Skoner DP, Maspero J, Banerji D, Ciclesonide Pediatric Growth Study Group. Assessment of the long-term safety of inhaled ciclesonide on growth in children with asthma. *Pediatrics* 121(1), e1–e14 (2008).

24 Kelly HW, Van Natta ML, Covar RA, Tonascia J, Green RP, Strunk RC for the CAMP Research Group. Effect of long-term corticosteroid use on bone mineral density in children: A prospective longitudinal assessment in the Childhood Asthma Management Program (CAMP) study. *Pediatrics* 122(1), e53–e61 (2008).

25 Tse SM, Kelly HW, Litonjua AA *et al.* Corticosteroid use and bone mineral accretion in children with asthma: Effect modification by vitamin D. *J. Allergy Clin. Immunol.* 130(1), 53–60 (2012).

26 Raissy HH, Sternberg AL, Williams P, Jacobs A, Kelly HW; CAMP Research Group. Risk of cataracts in the Childhood Asthma Management Program Cohort. *J. Allergy Clin. Immunol.* 126(2), 389–392 (2010).

27 Strunk RC, Sternberg AL, Szefler SJ *et al.* Long-term budesonide or nedocromil treatment, once discontinued, does not alter the course of mild to moderate asthma in children and adolescents. *J. Pediatr.* 154(5), 682–687 (2009).

■■ **A very important study that follows the CAMP cohort for an additional 4.5 years after discontinuing randomized therapy. It further establishes the lack of a disease altering effect of the ICSs as patients lose the benefit of the corticosteroids once discontinued and lung function either improves or worsens despite whether patients received ICS or placebo for 4–6 years.**

28 Covar R, Strunk R, Zeiger RS, Wilson LA, Liu AH, Weiss S *et al.* Predictors of remitting, periodic, and persistent childhood asthma. *J. Allergy Clin. Immunol.* 125(2), 359–366 (2010).

29 Chauhan BF, Chartrand C, Ducharme FM. Intermittent versus daily inhaled corticosteroids for persistent asthma in children and adults. *Cochrane Database Syst. Rev.* 12, CD009611 (2012).

■ **A new systematic review of the benefit or lack of from the use intermittent ICS therapy in asthma in both children and adults with persistent asthma.**

30 Turpeinen M, Nikander K, Pelkonen AS *et al.* Daily versus as-needed inhaled corticosteroid for mild persistent asthma (The Helsinki intervention childhood asthma study). *Arch. Dis. Child.* 93(8), 654–659 (2008).

31 Castro-Rodriguez JA, Rodrigo GJ. Efficacy of inhaled corticosteroids in infants and preschoolers with recurrent wheezing and asthma: a systematic review with meta-analysis. *Pediatrics* 123(3), e519–e525 (2009).

32 Bacharier LB, Phillips BR, Zeiger RS *et al.* Episodic use of an inhaled corticosteroid or leukotriene receptor antagonist in preschool children with moderate-to-severe intermittent wheezing. *J. Allergy Clin. Immunol.* 122(6), 1127–1135 (2008).

33 Ducharme FM, Lemire C, Noya FJ *et al.* Preemptive use of high-dose fluticasone for virus-induced wheezing in young children. *N. Engl. J. Med.* 360(4), 339–353 (2009).

■ **The first trial to clearly demonstrate a benefit from high-dose ICS for infants and young children with intermittent wheezing associated with viral infections. Unfortunately, they used very high doses that produced significantly decreased growth so we do not know whether lower and safer doses may be equally effective.**

34 Papi A, Nicolini G, Baraldi E *et al.* Regular vs prn nebulized treatment in wheeze preschool children. *Allergy* 64(10), 1463–1471 (2009).

35 Zeiger RS, Mauger D, Bacharier LB *et al.* Daily or intermittent budesonide in preschool children with recurrent wheezing. *N. Engl. J. Med.* 365(21), 1990–2001 (2011).

■■ **A second trial demonstrating that intermittent high-dose nebulized budesonide was as effective as low-dose continuous nebulized budesonide in preventing preschool children from progressing to oral corticosteroids. This study suggests that more moderate ICS doses may be as effective as the very high dosage used by Ducharme *et al.*** [34].

36 Kelly HW. Alveolar nitric oxide concentration, small airways inflammation, and targeted asthma therapy: are we there yet? *J. Allergy Clin. Immunol.* 126(4), 736–737 (2010).

37 van den Berge M, Ten Hacken NH, van der Wiel E, Postma DS. Treatment of the bronchial tree from beginning to end: targeting small airway inflammation in asthma. *Allergy* 68(1), 16–26 (2013).

38 van den Berge M, ten Hacken NH, Cohen J, Douma WR, Postma DS. Small airway disease in asthma and COPD: clinical implications. *Chest* 139(2), 412–423 (2011).

■ **A nicely done review of the trials of ICSs in improving obstruction in the small aiways. It includes a table of the various methods of assessing small airways disease with advantages and disadvantages, as well as whether they have shown responsiveness to intervention.**

39 Usmani OS, Barnes PJ. Assessing and treating small airways disease in asthma and chronic obstructive pulmonary disease. *Ann. Med.* 44(2), 146–156 (2012).

40 Leach CL, Kuehl PJ, Chand R, Ketai L, Norenberg JP, McDonald JD. Characterization of respiratory deposition of fluticasone-salmeterol hydrofluoroalkane-134a and hydrofluoroalkane-134a beclomethasone in asthmatic patients. *Ann. Allergy Asthma Immunol.* 108(3), 195–200 (2012).

41 Amirav I, Newhouse MT, Minocchieri S, Castro-Rodriguez JA, Schüepp KG. Factors that affect the efficacy of inhaled corticosteroids for infants and young children. *J. Allergy Clin. Immunol.* 125(6), 1206–1211 (2010).

■ **An excellent review of the many factors affecting delivery of ICS to infants and small children and the various studies documenting delivery. Unfortunately, it also illustrates a dearth of efficacy and safety studies for the newer ultrafine particle ICSs yet recommends their use over older more established preparations.**

42 Schueepp KG, Devadason SG, Roller C *et al.* Aerosol delivery of nebulised budesonide in young children with asthma. *Respir. Med.* 103(11), 1738–1745 (2009).

43 Van Muylem A, Kerckx Y, Michils A. Acinar effect of inhaled steroids evidenced by exhaled nitric oxide. *J. Allergy Clin. Immunol.* 126(4), 730–735 (2010).

44 Bleecker ER, Bateman ED, Busse WW *et al.* Once-daily fluticasone furoate is efficacious in patients with symptomatic asthma on low-dose inhaled corticosteroids. *Ann. Allergy Asthma Immunol.* 109(5), 353–358 (2012).

45 Essilfie-Quaye S, Ito K, Ito M, Kharitonov SA, Barnes PJ. Comparison of Symbicort® versus Pulmicort® on steroid pharmacodynamic markers in asthma patients. *Respir. Med.* 105(12), 1784–1789 (2011).

46 Ducharme FM, Ni Chroinin M, Greenstone I, Lasserson TJ. Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma. *Cochrane Database Syst. Rev.* 14(4), CD005533 (2010).

47 Chowdhury BA, Seymour SM, Levenson MS. Assessing the safety of adding LABAs to inhaled corticosteroids for treating asthma. *N. Engl. J. Med.* 364(26), 2473–2475 (2011).

■ **Outlines the stance of the US FDA on whether ICSs mitigate the risk of rare life-threatening asthma exacerbations associated with long-acting inhaled β agonists monotherapy and why they have mandated large prospective trials to determine the answer.**

48 McMahon AW, Levenson MS, McEvoy BW, Mosholder AD, Murphy D. Age and risks of FDA-approved long-acting β_2-adrenergic receptor agonists. *Pediatrics* 8(5), e1147–e1154 (2011).

■ Websites

101 National Institutes of Health, National Heart, Lung, and Blood Institute. National Asthma Education and Prevention Program. Full report of the Expert Panel: guidelines for the diagnosis and management of asthma (EPR-3) 2007. www.nhlbi.nih.gov/guidelines/asthma (Accessed 15 May 2013)

102 Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention. www.ginasthma.org (Accessed 15 May 2013)