

Guideline-defining asthma clinical trials of the National Heart, Lung, and Blood Institute's Asthma Clinical Research Network and Childhood Asthma Research and Education Network

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Because of an increasing prevalence, morbidity, and mortality associated with asthma, the National Heart, Lung, and Blood Institute created the Asthma Clinical Research Network and the Childhood Asthma Research and Education Network to improve public health. The objectives of these clinical research networks are to conduct multiple, well-designed clinical trials for rapid evaluation of new and existing therapeutic approaches to asthma and to disseminate laboratory and clinical findings to the health care community. These trials

comprise a large proportion of the data driving the treatment guidelines established and reviewed by the National Asthma Education and Prevention Program. This article will review the basic design and major findings of selected Asthma Clinical Research Network and Childhood Asthma Research and Education Network trials involving both adults and children with asthma. Collectively, these studies have helped refine the therapeutic role of existing controller medications, establish standard models for side-effect evaluation and risk-benefit models, validate symptom-based assessments for asthma control, and identify baseline characteristics that might predict individual patient responses. Remaining challenges include shaping the role of novel therapeutics in future guidelines, incorporating pharmacogenomic data in treatment decisions, and establishing better implementation strategies for translation to community settings, all with the goal of reducing the asthma burden on society. (*J Allergy Clin Immunol* 2007;119:3-11.)

Key words: *Asthma, clinical trial, treatment guidelines*

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The Asthma Clinical Research Network (ACRN) and the Childhood Asthma Research and Education (CARE) Network were initiated in 1993 and 1999, respectively, from requests for proposals that were developed and funded by the National Heart, Lung, and Blood Institute. The ACRN and the CARE Network were developed to specifically address therapeutic issues in asthma in both adults and children based on concerns related to the increase in the incidence and prevalence of worldwide asthma and in response to clinical researchers who desired a mechanism by which dispassionate therapeutic trials in asthma could be conducted to answer important and relevant therapeutic questions that were unlikely to be addressed by industry.

The ACRN was initially funded and developed with 6 clinical centers (University of California, San Francisco, Calif; National Jewish Medical and Research Center, Denver, Colo; University of Wisconsin, Madison, Wis; Thomas Jefferson Medical College, Philadelphia, Pa;

Abbreviations used

ACD:	Asthma control day
ACRN:	Asthma Clinical Research Network
BAGS:	Beta Agonist Study
BARGE:	Beta-Adrenergic Response by Genotype
BDP:	Beclomethasone dipropionate
CARE:	Childhood Asthma Research and Education
CFC:	Chlorofluorocarbon
DPI:	Dry powder inhaler
eNO:	Exhaled nitric oxide
FP:	Fluticasone propionate
HPA:	Hypothalamic-pituitary-adrenal
ICS:	Inhaled corticosteroid
IMPACT:	Improving Asthma Control Trial
MDI:	Metered-dose inhaler
NAEPP:	National Asthma Education and Prevention Program
NNT:	Number needed to treat
PACT:	Pediatric Asthma Controller Trial
PEF:	Peak expiratory flow
SLIC:	Salmeterol ± Inhaled Corticosteroids
SOCS:	Salmeterol or Corticosteroids Study

Harlem Lung Center, New York, NY; and Brigham and Women's Hospital, Boston, Mass) and 1 data-coordinating center (Pennsylvania State University, Hershey, Pa).¹ The CARE Network was next developed in 1999 and consisted of 5 clinical centers (University of California, San Diego, Calif; University of Arizona, Tucson, Ariz; Washington University, St Louis, Mo; University of Wisconsin, Madison, Wis; and National Jewish Medical and Research Center, Denver, Colo) and 1 data-coordinating center (Penn State University, Hershey, Pa). The research mission for both networks was 2-fold: (1) to provide a mechanism for evaluating new and existing therapeutic approaches for asthma to contribute to the evidence base of the National Asthma Education and Prevention Program (NAEPP) guidelines and (2) to provide avenues for the rapid dissemination of the clinical and laboratory findings that resulted from any protocols to the health care community. The following is a review of selected trials that have been conducted to date by these networks, which are also summarized in [Table I](#).

ACRN**The Beta Agonist Study**

In the early 1990s, because of observations made primarily with the use of fenoterol, considerable controversy existed regarding the safety of regular β_2 -agonist use in asthma. Some investigators reported that the regular use of this class of compounds had the potential of increasing both morbidity and mortality from asthma,² whereas others were not convinced that such angst was warranted.³ To directly address this controversy, the first protocol developed by the ACRN was the Beta Agonist Study (BAGS).⁴ BAGS was designed to answer the following

question: Is the regular use of β -agonists in asthma safe? BAGS enrolled 255 patients with mild asthma (age, 12–55 years; FEV₁, $\geq 70\%$ of predicted value; methacholine PC₂₀, ≤ 16 mg/mL; no inhaled corticosteroids [ICSs] for 6 weeks before enrollment; and β -agonist use in a specified range). Subjects were treated for 16 weeks with albuterol, 2 inhalations 4 times daily, or matching placebo, followed by a 4-week withdrawal period. The major outcome measure evaluated was change in morning peak expiratory flow (PEF), which was collected and recorded daily. The trial results provided the following answer: regular β -agonist treatment was found to be neither harmful nor beneficial compared with as-needed use. On the basis of these results, it was concluded that inhaled albuterol should be prescribed for patients with mild asthma on an as-needed basis. The NAEPP incorporated this evidence into its recommendations that as-needed, short-acting β -agonist use was an essential component of both categorizing the severity of asthma and controlling it.

The Salmeterol or Corticosteroids Study

Whereas long-acting β_2 -agonists were known to provide greater symptom relief compared with short-acting β_2 -agonists and the addition of salmeterol was shown to be more effective than increasing the dose of ICS,^{5,6} the role of long-acting β_2 -agonists as monotherapy in asthma was undocumented. Therefore the Salmeterol or Corticosteroids Study (SOCS) was designed to test the question of whether salmeterol substitution could maintain asthma control first established by use of ICSs.⁷ This randomized, placebo-controlled, triple-blind trial enrolled 164 subjects with moderate persistent asthma on entry who were able to achieve control, as demonstrated by an FEV₁ value of greater than 80% of predicted value and PEF variability of less than 20% after a 6-week run in period with 400 μ g of inhaled triamcinolone twice daily. The 3 intervention arms were designed to continue participants taking this fixed dose of triamcinolone or switch to either inhaled salmeterol (42 μ g twice daily) or placebo. The primary end point was a change in morning PEF after 28 weeks of therapy. Secondary end points included a change in FEV₁, asthma symptom scores, rescue bronchodilator use, treatment failures, exacerbations, bronchial methacholine responsiveness, and both sputum eosinophil and exhaled nitric oxide (eNO) levels as markers of airway inflammation.

Although there was no significant difference in morning PEF between the active treatments, those subjects who continued triamcinolone demonstrated a lower rate of treatment failures (6%, 24%, and 36%) and exacerbations (7%, 20%, 29%) compared with participants switched to either salmeterol or placebo, respectively. These results translate to a number needed to treat (NNT) of 8 favoring triamcinolone over salmeterol and an NNT of 5 versus placebo with respect to the numbers of patients needed to treat with triamcinolone to prevent 1 exacerbation in 28 weeks. Additionally, there was good consistency for the secondary end points in that all patients' symptoms were stable on ICSs and all were worse on either salmeterol or

TABLE I. Synopsis of reviewed trials

Trial	Summary
BAGS	Scheduled albuterol use is neither beneficial nor harmful.
SOCS	Salmeterol cannot be used as monotherapy for moderate disease.
SLIC	Control gained with salmeterol addition allows ICS dose reduction.
BARGE	Genotype at the 16th amino acid residue of the β_2 -adrenergic receptor affects the long-term response to albuterol use.
DICE	Partial suppression of overnight plasma cortisol levels is a reliable method for comparing ICS side-effect potency.
MICE	Maximum improvement in FEV ₁ after a 6-wk ICS trial occurs at lower doses with less HPA-axis suppression than those required to affect airway hyperresponsiveness.
IMPACT	Symptom-driven intermittent use of ICSs in mild disease is not associated with increased exacerbation rates.
PEAK	ICSs are effective in reducing pediatric asthma symptom burden but do not modify asthma natural history.
CLIC	More children have improved FEV ₁ values with ICSs than with montelukast.
PACT	Low-dose fluticasone provides children more ACDs than does montelukast.
SLIMSIT	Compares ICS-salmeterol versus leukotriene receptor antagonist-salmeterol as controller strategies for moderate asthma.
PRICE	Establishes biomarker predictors of short- and long-term ICS responses.
AIMS	Compares conventional therapy with the addition of a high-dose ICS or montelukast at the onset of viral upper respiratory tract infections for the reduction of subsequent asthma symptoms in preschool-aged children.

In each case, the study acronym is followed by a brief summary of the main conclusions of the trial. The last 3 studies in the table have recently been submitted for publication. These are Combination Therapy With a Long-acting β -agonist and a Leukotriene Antagonist in Moderate Asthma (SLIMSIT) and Predicting Response to Inhaled Corticosteroid Efficacy (PRICE) through the ACRN and Acute Intermittent Management Strategies (AIMS) by the CARE Network.

placebo. The benefits of 28 weeks of triamcinolone were not maintained during a placebo run-out period, demonstrating the validity in the randomization scheme and suggesting the need for daily ICS therapy in this defined population. Thus salmeterol monotherapy could not be recommended in persistent asthma, and the trial results contributed to the need for reevaluation of the value of lung function measures as the primary end point for future asthma studies.

The Salmeterol \pm Inhaled Corticosteroids trial

Adding salmeterol to a medium-dose ICS was emerging as a better strategy than increasing the ICS dose,⁸⁻¹⁰ but the question of reducing ICS doses after control was established still remained. The Salmeterol \pm Inhaled Corticosteroids (SLIC) trial was designed to address this question. This randomized, blind, double-dummy controlled study performed in parallel with SOCS and sharing the 6 week run-in period on 400 μ g of triamcinolone inhaled twice daily enrolled asthmatic subjects whose symptoms remained uncontrolled (FEV₁ \leq 80% or PEF variability $>$ 20%) despite documented adherence to a medium-dose ICS.¹¹ The hypothesis tested was that subjects who attain symptom control after the addition of salmeterol to an ICS could safely reduce or eliminate the dose of triamcinolone without increased risk of treatment failure. Subjects with moderate asthma ($n = 175$) who remained symptomatic after the 6-week ICS run-in period were randomized to added inhaled salmeterol (42 μ g twice daily) or placebo (the placebo-minus group) for 18 weeks with a 13:2 randomization weight scheme favoring salmeterol. After 2 weeks, the salmeterol group was 1:1 randomized to continue the 400- μ g triamcinolone inhaled twice daily (the salmeterol-plus group) or to taper and eliminate the ICS dose (the salmeterol-minus group). The placebo-minus and the salmeterol-minus groups received 200 μ g

of triamcinolone inhaled twice daily for 8 weeks, followed by ICS-placebo for another 8 weeks. The primary end point was the time to treatment failure, as defined by prospectively identified lung function measurement decreases, increases in rescue albuterol use, oral or parenteral corticosteroid use, or physician clinical judgment on the basis of safety concerns.

During the ICS reduction phase, there was no difference in the rates of treatment failures between the salmeterol-plus and salmeterol-minus groups (2.8% and 8.3% with an insignificant relative risk of 2.2 [95% CI, 0.5-9.2]). However, after the ICS elimination phase, the salmeterol-plus group had significantly fewer treatment failures (13.7%) compared with the salmeterol-minus group (46.3%), with a relative risk of 4.3 (95% CI, 2.0-9.2) associated with the latter. Examination of sequential effects showed that the mean presalmeterol FEV₁ value was the only secondary end point with a between-group difference favoring the salmeterol-plus group after ICS reduction, whereas after ICS elimination, this group had improved peak flows and symptom and quality-of-life scores and less rescue bronchodilator use. The SLIC trial provided crucial evidence that patients with moderate asthma achieving symptom control on the addition of salmeterol to a medium-dose ICS could safely undergo a 50% ICS dose reduction but could not have their ICS regimen eliminated.

The Beta-Adrenergic Response by Genotype trial

As discussed above, the conclusion of the BAGS trial was that regularly scheduled use of albuterol in patients with mild asthma is neither beneficial nor harmful when compared with as-needed use.⁴ The discovery of β_2 -adrenergic receptor functional differences encoded by common genetic differences raised the possibility that select patients with asthma might not benefit from or might even be harmed by frequent exposure to albuterol, an idea

supported by retrospective studies evaluating genotypes for the 16th amino acid of the receptor.¹²⁻¹⁴ In this regard the Beta-Adrenergic Response by Genotype (BARGE) trial was designed to prospectively answer the proof-of-principal question of whether patients with mild asthma and different β_2 -adrenergic receptor genotypes have altered lung function measures when treated with regularly scheduled albuterol versus placebo.¹⁵ After a 6-week placebo run-in period, 78 genotype-stratified (Arg/Arg and Gly/Gly at amino acid 16) and FEV₁-matched subjects with mild asthma were randomized in a double-blind crossover trial to receive 16 weeks of scheduled albuterol or placebo, followed by an 8-week washout period on scheduled placebo and then 16 weeks on the opposite treatment arm, using ipratropium bromide as the rescue inhaler throughout. The primary outcome was the change in morning PEF at the end of the 16-week treatment periods (scheduled albuterol vs placebo) within a given genotype; the between-genotype comparison of PEF was a secondary outcome.

The Gly/Gly genotype subjects experienced an increase in PEF while taking scheduled albuterol that did not occur during the placebo treatment. By contrast, the Arg/Arg genotype subjects had no change in PEF while taking albuterol but showed improvement while taking placebo, with a genotype-attributable difference of 24 L/min ($P = .0003$). Secondary outcome variables were consistent in that the Arg/Arg subjects had a lower FEV₁ value, higher symptom scores, and more rescue bronchodilator use while taking scheduled albuterol compared with those subjects with the Gly/Gly genotype. An effect on exacerbations was not observed given the relatively short treatment periods in subjects with mild disease. Whereas the mechanism or mechanisms at the genetic, cellular, and physiologic levels remain to be determined, this study was the first prospectively designed, genotype-stratified trial to suggest that patients with the Arg/Arg genotype might benefit from avoiding short-acting β_2 -adrenergic receptor agonists.

The SOCS/SLIC salmeterol response by genotype analysis

The higher adverse event rates in patients with moderate or severe asthma suggest that there might be a select group of patients in whom long-acting β_2 -adrenergic receptor agonist use promotes risk of exacerbation or even asthma-related death.^{6,16,17} The ACRN was in a unique position to begin to address the question of whether Arg/Arg genotype individuals also respond poorly to salmeterol because the SOCS and SLIC trial prospectively collected DNA samples on consenting participants. Genotyping was performed on 53 subjects receiving salmeterol and 43 subjects receiving placebo in the SOCS trial, as well as on 74 subjects receiving salmeterol and a fixed dose of triamcinolone in the SLIC trial.

In the 2 trials combined, there were 25 subjects who were Arg/Arg homozygotes and 48 who were Gly/Gly homozygotes.¹⁸ Baseline characteristics of these 2 subject groups were comparable, with the exception that the Arg/

Arg subjects in the SOCS were slightly older than those with the Gly/Gly genotype (36.99 ± 12.64 vs 29.14 ± 10.59 years, $P = .03$). At the end of the treatment periods in both studies, subjects with the Arg/Arg genotype had worse morning PEF compared with the Gly/Gly subjects (-51.4 and -36.8 L/min in the SOCS and SLIC trial, respectively), despite a transient improvement in SLIC subjects with the Arg/Arg genotype receiving both salmeterol and triamcinolone. A genotype-attributable difference in exacerbation rates was not observed in either trial; however, Arg/Arg subjects in the SLIC trial had lower FEV₁ values, higher morning symptom scores, and more rescue bronchodilator use compared with those with the Gly/Gly genotype. In sum, this retrospective study suggests B16 Arg/Arg homozygotes have a reduced therapeutic response to salmeterol, providing the foundation for the ongoing prospective Long Acting Bronchodilator Response by Genotype trial.

The Dose of Inhaled Corticosteroids with Equisystemic Effects study

Numerous factors influence the specific choice of ICS in asthma management. Because little comparative data existed with respect to the incidence of side effects, the goal of the Dose of Inhaled Corticosteroids with Equisystemic Effects (DICE) study was to establish the dose of 6 different ICS products that caused similar degrees of hypothalamic-pituitary-adrenal (HPA) axis suppression.¹⁹ ICS-naive subjects ($n = 156$) with mild-to-moderate asthma were randomized to a 6-week escalating dose regimen of one of 6 ICSs or matching placebo. The study medications included beclomethasone dipropionate (BDP)-chlorofluorocarbon (CFC), flunisolide-CFC, fluticasone propionate (FP)-CFC, and triamcinolone acetonide-CFC, which were all delivered through metered-dose inhalers (MDIs). Additionally, budesonide and FP were delivered through dry powder inhalers (DPIs). Several methods were used for assessing HPA-axis suppression, including serial urine and plasma cortisol concentrations; serum osteocalcin measurements were also made. Using the dose causing 10% HPA-axis suppression assessed on the basis of overnight plasma cortisol levels, a rank order of side-effect potency was established according to labeled doses: flunisolide-CFC (1), triamcinolone acetonide-CFC (1.19:1), BDP-CFC (1.69:1), FP-DPI (2.08:1), budesonide-DPI (3.45:1), and FP-CFC (8.33:1). Thus the DICE results support ICS dose equivalence estimates in the NAEPP guidelines, although HPA-axis suppression from FP-DPI was less than expected.

The Measuring Inhaled Corticosteroid Efficacy study

The objective of the Measuring Inhaled Corticosteroid Efficacy (MICE) study was to establish a standard model for making benefit/risk assessments for controller therapies.²⁰ This protocol used a feasibility design enrolling 30 subjects with mild-to-moderate asthma who were then randomized to 18 weeks of escalating doses of either BDP-CFC or FP-CFC MDIs, followed by a 3-week

administration of high FP-DPI to assess maximum effects. Major end points for efficacy included changes in FEV₁ and methacholine PC₂₀ values, as well as prevention of exercise-induced bronchospasm. Changes in eNO levels and measures of sputum eosinophils were also evaluated. ICS risk was assessed on the basis of suppression of overnight plasma cortisol concentrations. Despite equivalent dosing strata, low-dose FP-CFC was associated with the maximum improvement in FEV₁ values, whereas medium-dose BDP-CFC was required to achieve a similar effect size. For both agents, HPA-axis suppression was observed at doses higher than that needed to achieve the maximum FEV₁ improvement. The optimum improvement in airway reactivity occurred at 1 dose step higher than that needed to achieve the FEV₁ benefit (medium and high, respectively). Significant variability was noted among subjects, and a secondary cohort analysis suggested that subjects with a good FEV₁ response (defined as $\geq 15\%$ improvement) to either ICS could be predicted on the basis of baseline characteristics, including increased eNO levels, higher bronchodilator reversibility, and lower FEV₁/FVC ratios. Finally, about a third of the subjects had poor responses ($< 5\%$ improvement in FEV₁) to ICSs, which is consistent with the notion that patients with more severe disease might require higher ICS doses to prevent exacerbations. The MICE findings also substantiate the variability in ICS responses in this defined asthma population.

The Improving Asthma Control Trial

National and international guidelines have recommended daily anti-inflammatory “controller” therapy, even for mild persistent asthma, a classification characterized by consistent but low morbidity.^{21,22} This recommendation was prompted by studies reporting that such treatment improves PEF, FEV₁, severity of symptoms, exacerbation frequency, and quality of life,²³⁻²⁵ which was reinforced by reports that ICS therapy might prevent progressive loss of lung function.²⁶⁻²⁸ These latter findings, noted in studies conducted in both adults and children, strongly influenced guideline recommendations for early recognition and continuous treatment of patients with mild persistent asthma.^{21,22} However, these studies involved small numbers of participants, and their design was not ideal to provide solid evidence that would convincingly validate these recommendations.

Moreover, despite this emphasis on the prescribing of daily controller therapy, anecdotal reports and analysis of pharmacy records indicated that many patients were not diligent about renewing their prescriptions for controller medications (ICSs and leukotriene receptor antagonists).²⁹ Thus patients with mild persistent asthma appeared to be using their controller medications intermittently because they did not perceive the need to use therapy daily. To more firmly establish whether daily controller therapy was essential in patients with mild persistent asthma, not only to control symptoms and reduce exacerbations but also to prevent any future loss of lung function, the ACRN formulated the following research

question and designed and conducted a year-long clinical study, the Improving Asthma Control Trial (IMPACT), to answer it: In patients with NAEPP guideline definitions of mild persistent asthma, is it essential to administer controller therapy on a daily basis to establish and maintain adequate asthma control and to prevent loss of lung function?

The inclusion criteria for IMPACT included the following: physician-diagnosed asthma, age 18 to 65 years, and FEV₁ of 70% or greater of predicted value, with either 12% or greater (and ≥ 200 mL) improvement after albuterol inhalation or bronchial hyperreactivity (methacholine PC₂₀ < 16 mg/mL). Patients were randomized to one of 3 treatment arms: (1) budesonide (200 μ g twice daily), (2) oral zafirlukast (20 mg twice daily), and (3) placebo (intermittent-only treatment). All were instructed to take open-label budesonide or prednisone, as guided by a symptom-based action plan. The run-in and treatment phases both ended with a 14-day period of intense combined therapy, called PICT (prednisone, 0.5 mg/kg/d; budesonide, 800 μ g 2 times daily; and zafirlukast, 20 mg 2 times daily) and acute treatment with albuterol (540-720 μ g). The primary outcome was morning PEF, and secondary outcomes included those directly perceived by patients, namely asthma exacerbations, days lost from work or school, symptom-free days, and asthma-related quality of life. Other secondary outcomes included a panel of physiologic and biologic measures of asthma activity.

There were 225 randomized patients (73 taking budesonide, 76 taking zafirlukast, and 76 taking placebo) in IMPACT. The 3 groups yielded similar increases in morning PEF (7% to 9%, approximately 32 L/min; $P = .90$) and similar rates of asthma exacerbation (14/73 taking budesonide, 6/76 taking zafirlukast, and 10/76 taking placebo; $P = .238$), even though the intermittent-only group took budesonide for an average of only 0.5 weeks of the year. The budesonide group displayed greater improvement in prebronchodilator FEV₁ values ($+4.02\% \pm 1.20\%$; zafirlukast, $-1.06\% \pm 1.00\%$; and intermittent only, $+0.66\% \pm 1.09\%$; $P = .005$) but not in postbronchodilator FEV₁ value ($P > .25$). Budesonide treatment was associated with improvements in questionnaire scores for asthma control and symptom-free days but not for quality of life.

The results of IMPACT suggested that guideline criteria for mild persistent asthma might define a condition so mild that patients instructed in an action plan could decide whether to take daily anti-inflammatory therapy on the basis of their assessment of the importance of their symptomatic improvements.³⁰ These findings clearly were unexpected and have led many asthma researchers to compare and contrast these results with those of other studies to determine how treatment recommendations for mild persistent asthma might need to be modified.³¹⁻³³ Alternatively, it is conceivable that the criteria used to define mild persistent asthma might need to be redefined as well. Nonetheless, the findings from IMPACT are indeed provocative and will no doubt influence the design of future clinical trials focused on providing additional evidence that would solidify the definition of mild

persistent asthma and its appropriate treatment in both the short- and long-term.

CARE NETWORK

The Prevention of Early Asthma in Kids trial

Based on data generated in both pediatric²⁸ and adult^{26,34} patients with asthma, current asthma guidelines recommend that daily controller therapy should be initiated in individuals whose symptoms place them in the mild persistent asthma category. However, in preschool-aged children wheezing is a common manifestation of viral respiratory tract infections,³⁵ and properly diagnosing asthma in this age group so that appropriate treatment can be initiated has posed a challenge for many clinicians. On the one hand, early recognition and treatment might be important in altering the natural history of the disease in terms of both symptom and exacerbation control, as well as loss of lung function. On the other hand, treating children who only have a transient wheezing phenotype might be putting them at unnecessary potential risk from medication side effects (eg, reduced growth velocity from ICSs).³⁵⁻³⁷ To address these critical questions in childhood asthma, the first trial conducted by the CARE Network was the Prevention of Early Asthma in Kids (PEAK) trial.³⁸ The main research question posed by the PEAK trial was as follows: Can early recognition and treatment of children at increased risk of asthma prevent its clinical expression or any alterations in lung function measures that occur as a result of it?

The PEAK trial was a 3-year-long, double-blind, randomized, parallel-group design trial in which children ages 2 to 3 years with a positive modified asthma predictive index were treated for 2 years with either fluticasone, 44 μ g per puff administered through an MDI, 2 puffs twice daily through a spacer and face mask, or matching placebo. At the end of this treatment period, all children were taken off active medications for a 1-year observation period. Treatment algorithms (step-up and step-down controller regimens) were used throughout the trial to maximize participant safety while minimizing prolonged interventions that would dampen the ability to document that this type of intervention was indeed therapeutic in both the short- and long-term.

The primary outcome was the difference between the study groups in the proportion of episode-free days during the year-long observation period. Episode-free days were defined as those during which there were no asthma-like symptoms, no unscheduled medical visits for respiratory tract symptoms, and no use of any supplementary asthma medications, including pre-exercise albuterol. Secondary outcomes included the proportion of episode-free days during the treatment period. Other outcomes during both the treatment and observation periods included the number and time to systemic corticosteroid courses and controller medications and blood eosinophilia. Impulse oscillometry was performed by using established procedures to assess the contribution of resistance and reactance to the total impedance of the respiratory system; reactance at low

frequencies reflects the elastic properties of the respiratory system and will be more negative in patients with airway dysfunction.³⁹⁻⁴¹ An exacerbation was defined as the need for a prednisolone course to control asthma-like symptoms. In addition, the potential effects of long-term use of the ICS on growth velocity were assessed.

During the observation year, no significant differences in the proportion of episode-free days, number of exacerbations, or lung function were observed between the 2 groups. During the 2-year treatment period, ICS use was associated with a 4.8% greater proportion of episode-free days ($P = .006$), a 32.0% lower rate of exacerbations ($P < .001$), and a 53.0% reduction in supplementary ICS use ($P < .001$). Although symptom control during the treatment period was clearly improved with daily ICS therapy, some side effects from the treatment on linear growth were observed. The mean increase in height in the ICS group was 1.1 cm less than that seen in the placebo group at 24 months ($P < .001$). However, after cessation of daily therapy, the ICS group had a similar growth velocity compared with that seen in the placebo group during the last 12 months of treatment and a higher velocity during the observation year, resulting in a mean increase in height that was 0.7 cm less in the ICS group at the end of the trial ($P = .008$). The participants in the PEAK trial are currently being followed more long-term to determine the overall effects that ICS treatment could have on growth velocity.

The results of the PEAK trial have clearly provided new insights into the success of potential interventions that might alter the natural history of asthma disease expression in early childhood. It is clear from the PEAK trial data that during treatment, ICSs reduced symptom burden, exacerbations, and respiratory system reactance. Thus treatment was very effective in controlling symptom burden. Although growth velocity diminished early in treatment, it subsequently accelerated, despite continued therapy. The long-term consequences of this therapeutic intervention on growth are currently under study. Despite these positive benefits in terms of the control of symptom burden during therapy, once it was stopped, symptoms returned in approximately 2 to 3 months. Thus the natural history of asthma in high-risk preschool-aged children was not altered by 2 years of ICS therapy. The PEAK trial supports the disease-controlling but not the disease-modifying effects of ICS therapy.

Characterizing the Response to a Leukotriene Receptor Antagonist and an Inhaled Corticosteroid trial

Evidence from the ACRN DICE and MICE trials suggested that considerable interindividual variability in response to ICSs exists in adults with persistent asthma and that phenotypic attributes might predict such a response. Therefore the CARE Network designed the Characterizing the Response to a Leukotriene Receptor Antagonist and an Inhaled Corticosteroid (CLIC) trial⁴² to examine the variability of responses to both ICSs and leukotriene receptor antagonists in children with asthma to identify patient features that would serve as indicators for selection of

the controller medications most likely to achieve a favorable response in individual patients. Children 6 to 17 years of age with mild-to-moderate persistent asthma were enrolled. Children were excluded if they had FEV₁ values of less than 70% of predicted value or had evidence of severe disease. All participants demonstrated improvement in FEV₁ values of 12% or greater after maximal bronchodilator or a methacholine PC₂₀ value of 12.5 mg/mL or less. Eligible children were randomized to one of 2 crossover sequences, including 8 weeks of FP-DPI, 100 µg twice daily, and 8 weeks of montelukast, 5-10 mg nightly (depending on age), in a double-masked design.

Response was assessed on the basis of improvement in FEV₁ from baseline to the end of each treatment period and defined as an improvement in FEV₁ of 7.5% or greater. On the basis of this definition, 17% of 126 participants responded to both study medications, 23% responded to FP alone, 5% responded to montelukast alone, and 55% responded to neither medication. Similar to the adult studies, responses to FP and montelukast varied considerably.

The CLIC trial also provided the opportunity to assess medication responses for relationships to baseline asthma phenotype-associated biomarkers. Greater differential responses to FP over montelukast (defined on the basis of FEV₁ improvement) were associated with higher bronchodilator use, bronchodilator response, eNO levels, and eosinophil cationic protein levels and lower methacholine PC₂₀ and pulmonary function values.

Because of the poor correlation of pulmonary function responses to controller therapy with many nonpulmonary clinical control outcomes,⁴³ the CARE Network also reported additional CLIC asthma clinical control outcomes in a subsequent article.⁴⁴ As expected, improvements in most clinical asthma control measures occurred with both FP and montelukast. However, clinical outcomes (asthma control days [ACDs], Asthma Control Questionnaire scores, and albuterol use), pulmonary responses (FEV₁/forced vital capacity, PEF variabilities, morning PEF, and measures of impedance), and inflammatory biomarkers (eNO) improved significantly more with FP than with montelukast treatment. eNO served as both a predictor of ACDs and a response indicator in documenting the difference in ACD response between FP and montelukast. The short-term results of the CLIC trial both supported the guidelines' preference of ICSs as first-line therapy for mild-to-moderate persistent asthma in children and the potential role of eNO to individualize choice of controller therapy.

The Pediatric Asthma Controller Trial

The Pediatric Asthma Controller Trial (PACT) was designed to compare 3 contemporary asthma controller regimens as first-line therapy for the management of mild-to-moderate persistent asthma in school-aged children.⁴⁵ The guideline recommendations to date had largely relied on trials in adults with more moderate diseases, resulting in extrapolations to the pediatric population. Whereas important data to manage childhood asthma was provided in the CLIC trial, the trial was too short-term to adequately assess the important outcome of asthma exacerbations.

Therefore PACT enrolled 285 children (age, 6-14 years) with mild-to-moderate persistent asthma based on symptoms but who all purposefully had baseline FEV₁ values of 80% of predicted value or greater. Bronchodilator reversibility was collected but was not an entry criterion. All children demonstrated methacholine FEV₁ PC₂₀ values of 12.5 mg/mL or less. During the baseline placebo run-in period, PACT participants averaged only 27% ACDs, documenting their need for controller therapy. Children were randomized to one of 3 double-blind 48-week treatments: 100 µg of FP-DPI twice daily (FP monotherapy); 100 µg of FP/50 µg of salmeterol in the morning and 50 µg of salmeterol in the evening (PACT combination); and 5 mg of montelukast in the evening. The primary outcome was ACDs; a multitude of secondary outcomes were determined, including asthma exacerbation, humanistic measurements, and pulmonary function measurements.

All 3 PACT controller therapies resulted in an improvement in ACDs during the 48 weeks compared with that documented at baseline. However, the FP monotherapy group gained an average of 42 ACDs per year compared with the montelukast monotherapy group ($P = .004$). FP monotherapy and PACT combination were comparable in many patient-measured outcomes, including percentage of ACDs and prevention of asthma exacerbations, but FP monotherapy was superior for clinic-measured FEV₁/FVC maximum bronchodilator response and PC₂₀ values. FP was superior to montelukast for ACDs and for all other PACT control outcomes. The NNT for both FP monotherapy and PACT combination compared with montelukast is approximately 6.5, meaning that 7 children would need to be treated with FP monotherapy or the PACT combination instead of montelukast to achieve 1 additional treatment response (*a priori* defined as a 20% increase in ACDs). Importantly, growth over 48 weeks was not statistically different in the 3 treatment groups (FP, 5.3 cm; PACT combination, 5.3 cm; montelukast, 5.7 cm).

Of the regimens tested, the PACT findings favor FP monotherapy because of its overall success in improving asthma control outcomes. Therefore this study provides the definitive evidence in support of guideline recommendations of low-dose ICSs in treating children with mild-to-moderate persistent asthma with FEV₁ values of 80% of predicted value.

SUMMARY

This review has highlighted the major contributions of the ACRN and CARE Network trials to the current NAEPP asthma treatment guidelines, as depicted in Fig 1. First, the stepwise positioning (level of severity between intermittent and persistent) of as-needed short-acting β₂-agonists was established (BAGS), and later, whether a subgroup of patients might be at risk if these agents were used on a regular basis (the BARGE trial) was established. Second, the use of the long-acting β-agonist salmeterol was evaluated to determine whether it could be used

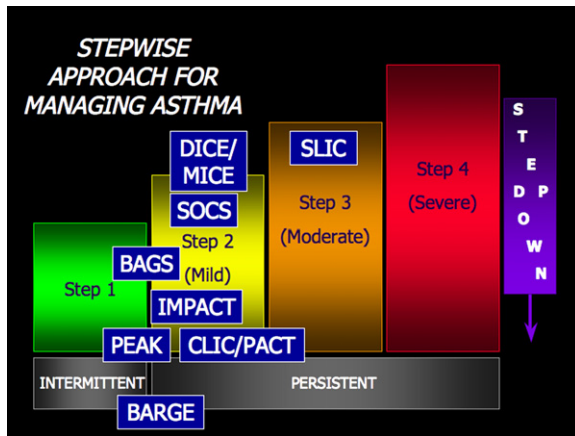


FIG 1. Past and present ACRN and CARE Network clinical trials separated by NAEP severity steps. The acronyms refer to trials reviewed herein. Escalation of controller therapy selection and dose is appropriate for the moderate and severe strata. Patients who remain symptomatic despite oral corticosteroids and other agents in the severe class should be reevaluated for medication compliance issues, aggressive treatment of other coexisting conditions (eg, vocal cord dysfunction, gastroesophageal reflux, or chronic sinusitis), or both.

as monotherapy in mild persistent asthma (SOCS) and whether it would enable steroid reduction, elimination, or both in more moderate disease (the SLIC trial). Both studies clearly demonstrated that long-acting β -agonists should not be used as monotherapy, and later retrospective analyses based on β -adrenergic receptor genotypes indicated that the results seen in the BARGE trial with short-acting β -agonists were applicable to long-acting β -agonists as well. Third, models for standardized assessment of controller therapy side-effect comparisons and risk/benefit calculations were established (the MICE and DICE studies). Fourth, for individuals with mild persistent asthma (using strict NAEP2 guideline criteria), intermittent ICS use directed by symptoms was found not to be associated with higher rates of exacerbations compared with daily use with ICSs (IMPACT). Fifth, despite concerns of the transient effects on growth, ICS use in school-aged children and in adolescence was found to be safe and preferable to montelukast for improving pulmonary function and establishing symptom control (CLIC and PACT). Finally, in preschool-aged children at high risk of having asthma, daily treatment with an ICS was able to control symptom burden and exacerbations but was unable to alter the natural history of asthma once the therapy was discontinued (the PEAK trial). Both the ACRN and CARE Network continue to develop protocols that will provide answers to questions regarding both the short- and long-term management of asthma in both adults and children that will assist clinicians in providing optimal care for their patients.

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