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Guideline-Defining Asthma Clinical Trials of the NHLBI ACRN and CARE Networks

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Abstract

Due to an increasing prevalence, morbidity and mortality associated with asthma, the National Heart, Lung and Blood Institute created the Asthma Clinical Research Network (ACRN) and the Childhood Asthma Research and Education (CARE) 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 ACRN and CARE 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 may 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.

Introduction

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 (RFPs) that were developed and funded by the National Heart Lung and Blood Institute. The ACRN and CARE 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

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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 six clinical centers (University of California, San Francisco; National Jewish Medical and Research Center, Denver; University of Wisconsin, Madison; Thomas Jefferson Medical College, Philadelphia; Harlem Lung Center, New York; Brigham and Women's Hospital, Boston) and one data coordinating center (Pennsylvania State University, Hershey).¹ The CARE Network was next developed in 1999 and consisted of five clinical centers (University of California, San Diego; University of Arizona, Tucson; Washington University, St. Louis; University of Wisconsin, Madison; National Jewish Medical and Research Center, Denver) and one data coordinating center (Penn State University, Hershey). The research mission for both networks was twofold. First, to provide a mechanism for evaluating new and existing therapeutic approaches for asthma in order to contribute to the evidence-base of the NAEPP guidelines. Second, 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, also summarized in Table 1.

Asthma Clinical Research Network

The beta agonist study (BAGS)

In the early 1990's, due to observations made primarily with the use of fenoterol, considerable controversy existed regarding the safety of regular beta₂ 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 asthma², while 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 beta agonists in asthma safe?" BAGS enrolled 255 patients with mild asthma (age 12–55 yrs; FEV₁ ≥ 70% predicted; methacholine PC₂₀ ≤ 16 mg/ml; no inhaled corticosteroids for 6 weeks prior to enrollment; beta agonist use in a specified range). Subjects were treated for sixteen 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), collected and recorded daily. The trial results provided the following answer: regular beta agonist treatment was found to be neither harmful nor beneficial compared to as needed use. Based on 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 beta agonist use was an essential component of both categorizing the severity of asthma and controlling it.

The salmeterol or corticosteroids study (SOCS)

Whereas long acting β₂-agonists (LABA) were known to provide greater symptom relief compared to short acting β₂-agonists and the addition of salmeterol was shown to be more effective than increasing the dose of inhaled corticosteroids (ICS),^{5, 6} the role of LABAs 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 ICS.⁷ This randomized, placebo-controlled, triple-blinded trial enrolled 164 subjects with moderate persistent asthma on entry, who were able to achieve control, demonstrated by an FEV₁ > 80% of predicted and peak expiratory flow variability < 20%, after a 6-week run in period on 400 μg inhaled triamcinolone twice daily. The three intervention arms were designed to continue participants on this fixed dose of triamcinolone, or switch to either inhaled salmeterol (42 μg twice daily) or placebo. The

primary endpoint was a change in morning (PEF) after 28 weeks of therapy. Secondary endpoints included a change in FEV₁, asthma symptom scores, rescue bronchodilator usage, treatment failures, exacerbations, bronchial methacholine responsiveness, and both sputum eosinophils and exhaled nitric oxide 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 to 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 one exacerbation in 28 weeks. Additionally, there was good consistency for the secondary endpoints in that all were stable on ICS, and all were worse on either salmeterol or 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 endpoint for future asthma studies.

The salmeterol ± inhaled corticosteroids (SLIC) trial

Adding salmeterol to medium dose ICS was emerging as a better strategy than increasing the ICS dose,^{8–10} but the question of reducing ICS after control was established still remained. To address this, the SLIC Trial was designed. This randomized, blinded, double-dummy controlled study, performed in parallel with SOCS and sharing the 6 week run-in period on 400 µg triamcinolone inhaled twice daily, enrolled asthmatic subjects who remained uncontrolled (FEV₁ ≤ 80% or PEF variability > 20%) despite documented adherence to medium-dose ICS.¹¹ The hypothesis tested was that subjects who attain control after the addition of salmeterol to 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 were randomized to added inhaled salmeterol (42 µg twice daily) or placebo (designated placebo-minus) for 18 weeks with a 13:2 randomization weight scheme favoring salmeterol. After two weeks, the salmeterol group was 1:1 randomized to continue the 400 µg triamcinolone inhaled twice daily (salmeterol-plus) or to taper and eliminate the ICS dose (salmeterol-minus). The placebo-minus and the salmeterol-minus groups received 200 µg triamcinolone inhaled twice daily for 8 weeks followed by ICS-placebo for another 8 weeks. The primary endpoint was the time-to-treatment failure as defined by prospectively identified lung function measurement declines, 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 of 0.5 to 9.2)). However after the ICS-elimination phase, the salmeterol-plus group had significantly fewer treatment failures (13.7%) compared to 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 pre-salmeterol FEV₁ was the only secondary endpoint with a between group difference favoring the salmeterol-plus group after ICS reduction, whereas after ICS elimination this group had improved peak flows, symptom and quality of life scores, and less rescue bronchodilator usage. SLIC provided crucial evidence that moderate asthmatics achieving control upon the addition of salmeterol to 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 (BARGE) 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 to as-needed usage.⁴ The discovery of β_2 -adrenergic receptor functional differences encoded by common genetic differences raised the possibility that select patients with asthma may not benefit or may even be harmed from 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 vs. placebo.¹⁵ After a 6 week placebo run-in, 78 genotype-stratified (Arg/Arg and Gly/Gly at amino acid 16), FEV₁-matched subjects with mild asthma were randomized in a double-blind, cross-over 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 comparisons of PEF was a secondary outcome.

The Gly/Gly genotype subjects experienced an increase in PEF while on scheduled albuterol that did not occur during the placebo treatment. By contrast, the Arg/Arg genotype subjects had no change in PEF on albuterol, but improved while on placebo, with a genotype-attributable difference of 24 L/min ($p=0.0003$). Secondary outcome variables were consistent in that the Arg/Arg subjects had a lower FEV₁, higher symptom scores, and more rescue bronchodilator use while on scheduled albuterol, compared to 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(s) at the genetic, cellular and physiological 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 suggests that there may be a select group of patients in whom long-acting β_2 -adrenergic receptor agonist usage 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, as SOCS and SLIC prospectively collected DNA samples on consenting participants. Genotyping was performed on 53 subjects on salmeterol and 43 on placebo in the SOCS trial, as well as on 74 subjects on salmeterol and a fixed dose of triamcinolone in the SLIC study.

In the two trials combined, there were 25 subjects who were Arg/Arg homozygotes and 48 who were Gly/Gly homozygotes.¹⁸ Baseline characteristics of these two subject groups were comparable with the exception that the Arg/Arg subjects in SOCS were slightly older than those with the Gly/Gly genotype (36.99 ± 12.64 vs 29.14 ± 10.59 , $p = 0.03$). At the end of the treatment periods in both studies, subjects with the Arg/Arg genotype had worse morning PEF compared to the Gly/Gly subjects (-51.4 and -36.8 L/min in the SOCS and SLIC trials respectively), despite a transient improvement in SLIC subjects with the Arg/Arg genotype on both salmeterol and triamcinolone. A genotype-attributable difference in exacerbation rates was not observed in either trial, however, Arg/Arg subjects in the SLIC study had lower FEV₁, higher morning symptom scores, and more rescue bronchodilator usage compared to those with the Gly/Gly genotype. In sum, this retrospective study suggests B16 Arg/Arg

homozygotes have a reduced therapeutic response to salmeterol, providing foundation for the ongoing prospective trial named LARGE (Long Acting Bronchodilator Response by Genotype).

The dose of inhaled corticosteroids with equisystemic effects (DICE) study

Numerous factors influence the specific choice of ICS in asthma management. As little comparative data existed with respect to the incidence of side effects, the goal of the DICE study was to establish the dose of six different ICS products that rendered similar degrees of hypothalamic-pituitary-adrenal axis suppression.¹⁹ ICS-naïve subjects (n=156) with mild to moderate asthma were randomized to a six week-escalating dose regimen of one of six ICS or matching placebo. The study medications included beclomethasone dipropionate-chlorofluorocarbon (BDP-CFC), flunisolide (FLU-CFC), fluticasone propionate (FP-CFC), and triamcinolone acetonide (TAA-CFC) were all delivered by metered dose inhalers (MDIs). Additionally, budesonide (BUD-DPI) and fluticasone propionate (FP-DPI) were delivered by 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 by overnight plasma cortisol levels, a rank order of side effect potency was established according to labeled doses: FLU-CFC (1), TAA-CFC (1.19:1), BDP-CFC (1.69:1), FP-DPI (2.08:1), BUD-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 (MICE) study

The objective of the MICE study was to establish a standard model for making benefit-to-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 three-week administration of high FP-DPI to assess maximum effects. Major endpoints for efficacy included changes in FEV₁ and methacholine PC₂₀ as well as prevention of exercise-induced bronchospasm. Changes in exhaled nitric oxide (eNO) and measures of sputum eosinophil were also evaluated. ICS risk was assessed by suppression of overnight plasma cortisol concentrations. Despite equivalent dosing strata, low dose FP-CFC was associated with the maximum improvement in FEV₁ while 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 one 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 by baseline characteristics including elevated eNO, higher bronchodilator reversibility, and lower FEV₁/FVC ratios. Finally, about a third of the subjects had poor responses ($< 5\%$ improvement in FEV₁) to ICS, consistent with the notion that more severe patients may 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 (IMPACT)

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 may 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 (ICS 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 if daily controller therapy was essential in 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, IMPACT, to answer it. In patients with NAEPP Guideline definition of mild persistent asthma, is it essential to administer controller therapy on a daily basis in order 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 18–65 years, and FEV₁ ≥ 70% of predicted, with either ≥ 12% (and ≥ 200 ml improvement) following albuterol inhalation or bronchial hyperreactivity (methacholine PC₂₀ < 16 mg/ml). Patients were randomized to one of three treatment arms: (1) budesonide (200 µg bid); (2) oral zafirlukast (20 mg bid); (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 µg 2x/d, and zafirlukast 20 mg 2x/d) and acute treatment with albuterol (540–720 µg). 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 physiological and biological measures of asthma activity.

There were 225 randomized patients (73 on budesonide, 76 on zafirlukast, and 76 on placebo) in IMPACT. The three groups yielded similar increases in morning PEF (7–9%, ~32 L/min; *p* = 0.90) and similar rates of asthma exacerbation (14/73 on budesonide, 6/76 on zafirlukast, and 10/76 on placebo, *p* = 0.238), 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 pre-bronchodilator FEV₁ (+4.02% ± 1.20%; zafirlukast, −1.06% ± 1.00%; “intermittent only,” +0.66% ± 1.09%; *p* = 0.005) but not in post-bronchodilator FEV₁ (*p* > 0.25). 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 may define a condition so mild that patients instructed in an action plan may 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 lead many asthma researchers to compare and contrast these results with other studies to determine how treatment recommendations for mild persistent asthma may need to be modified.^{31–33} Alternatively, it is conceivable that the criteria used to define mild persistent asthma may 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 both short and long term.

Childhood Asthma Research and Education (CARE) Network

The prevention of early asthma in kids (PEAK) 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 may 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 may be putting them at unnecessary potential risk from medication side effects (e.g. reduced growth velocity from ICS).^{35–37} To address these critical questions in childhood asthma, the first trial conducted by the CARE network was Prevention of Early Asthma in Kids (PEAK) study.³⁸ The main research question posed by PEAK was as follows: can early recognition and treatment of children at increased risk of developing asthma prevent its clinical expression or any alterations in lung function measures that occur as a result of it?

PEAK was a three year long, double blind, randomized, parallel group design trial in which children ages 2–3 years with a positive modified asthma predictive index (API) were treated for two years with either fluticasone 44 mcg/puff MDI, 2 puffs twice daily via a spacer and face mask, or matching placebo. At the end of this treatment period, all children were taken off active medications for a one-year observation period. Treatment algorithms (step up and step down controller regimens) were utilized 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 both 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 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 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, 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 two groups. During the two-year treatment period, ICS use was associated with a 4.8% greater proportion of episode-free days ($p=0.006$), a 32.0% lower rate of exacerbations ($p<0.001$), and a 53.0% reduction in supplementary ICS use ($p<0.001$). 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 the placebo-group at 24 months ($p<0.001$). However, following cessation of daily therapy, the ICS-group had a similar growth velocity compared to 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 ($p=0.008$). The participants

in PEAK are currently being followed more long term to determine the overall effects that ICS treatment could have on growth velocity.

The results of PEAK have clearly provided new insights into the success of potential interventions that may alter the natural history of asthma disease expression in early childhood. It is clear from the PEAK data that, during treatment, ICS 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 even in spite of 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 two to three months. Thus, the natural history of asthma in high-risk preschool aged children was not altered by two years of ICS therapy. PEAKs supports the disease controlling, but not modifying effects, of ICS therapy.

Characterizing the response to a leukotriene receptor antagonist and an inhaled corticosteroid (CLIC)

Evidence from the ACRN DICE and MICE trials suggested that considerable interindividual variability in response to ICS exists in adults with persistent asthma, and that phenotypic attributes might predict such response. Therefore, the CARE Network designed the CLIC trial⁴² to examine the variability of responses to both ICSs and LTRAs 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 < 70% predicted, or had evidence of severe disease. All participants demonstrated improvement in FEV₁ of 12% or greater after maximal bronchodilator or methacholine PC₂₀ ≤ 12.5 mg/ml. Eligible children were randomized to one of two crossover sequences, including 8 weeks of FP-DPI 100 mcg 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%. Based on this definition, 17% of 126 participants responded to both study medications, 23% responded to FP alone, 5% to montelukast alone, and 55% responded to neither medication. Similar to the adult studies, responses to FP and montelukast varied considerably.

CLIC 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) was associated with higher bronchodilator use, bronchodilator response, eNO levels, and eosinophil cationic protein levels and lower methacholine PC₂₀ and pulmonary function values.

Due to the poor correlation of pulmonary function responses to controller therapy with many nonpulmonary clinical control outcomes⁴³, the CARE Network also reported additional CLIC asthma clinical control outcomes in a subsequent manuscript.⁴⁴ As expected, improvements in most clinical asthma control measures occurred with both FP and montelukast. However, clinical outcomes (asthma control days, the Asthma Control Questionnaire, 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 asthma control days (ACD) 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 ICS as first-line therapy for mild-to-moderate persistent asthma in children and the potential role of eNO to individualize choice of controller therapy.

Pediatric asthma controller trial (PACT)

PACT was designed to compare three 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 CLIC, the trial was too short-term to adequately assess the important outcome of asthma exacerbations. Therefore, PACT enrolled 285 children (ages 6–14 years) with mild-to-moderate persistent asthma based on symptoms, but who all purposefully had baseline $FEV_1 \geq 80\%$ predicted. Bronchodilator reversibility was collected, but was not an entry criterion. All children demonstrated methacholine FEV_1 $PC_{20} \leq 12.5$ mg/ml. During the baseline placebo run-in, PACT participants averaged only 27% ACDs, documenting their need for controller therapy. Children were randomized to one of three double-blind 48 week treatments: FP DPI 100 mcg twice daily (FP monotherapy); FP 100 mcg/salmeterol 50 mcg in the morning and salmeterol 50 mcg in the evening (PACT combination); montelukast 5 mg 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 three PACT controller therapies resulted in an improvement of ACDs during the 48 weeks, as compared to that documented at baseline. However, the FP monotherapy group gained an average of 42 asthma control days per year, compared to the montelukast monotherapy group ($p=0.004$). FP monotherapy and PACT combination were comparable in many patient-measured outcomes, including percent of ACDs and prevention of asthma exacerbations, but FP monotherapy was superior for clinic-measured FEV_1/FVC maximum bronchodilator response, and PC_{20} . FP was superior to montelukast for ACDs and for all other PACT control outcomes. The NNT for both FP monotherapy and PACT combination as compared to montelukast is approximately 6.5, meaning that 7 children would need to be treated with FP monotherapy or PACT combination instead of montelukast in order to achieve one additional treatment response (a priori defined as a 20% increase in asthma control days). Importantly, growth over 48 weeks was not statistically different in the three treatment groups (FP 5.3 cm, PACT combination 5.3 cm, montelukast 5.7 cm).

Of the regimens tested, the PACT study findings favor FP monotherapy due to its overall success in improving asthma control outcomes. Therefore, this study provides the definitive evidence in support of guideline recommendations of low dose ICS in treating children with mild-to-moderate persistent asthma with $FEV_1 \geq 80\%$ predicted.

Summary

This review has highlighted the major contributions of the ACRN and CARE Network trials to the current NAEPP asthma treatment guidelines, depicted in Figure 1. First, the stepwise positioning (level of severity between intermittent and persistent) of as-needed short acting β_2 -agonists was established (BAGS) and later, whether or not a subgroup of patients may be at risk if these agents were used on a regular basis (BARGE). Second, the use of the long acting beta agonist, salmeterol, was evaluated to determine if it could be used as monotherapy in mild persistent asthma (SOCS), and if it would enable steroid reduction and/or elimination in more moderate disease (SLIC). Both studies clearly demonstrated that long acting beta agonists should not be used as monotherapy, and later retrospective analyses based on beta adrenergic receptor genotypes indicated that the results seen in the BARGE trial with short acting beta agonists were applicable to long acting beta agonists as well. Third, models for standardized

assessment of controller therapy side-effect comparisons and risk-benefit calculations were established (MICE, DICE). Fourth, for individuals with mild persistent asthma (using strict NAEPP2 guideline criteria), intermittent ICS use directed by symptoms was found not to be associated with higher rates of exacerbations compared to daily use with ICS (IMPACT). Fifth, despite concerns of the transient effects on growth, ICS usage in school-aged children and adolescence was found to be safe and preferable to montelukast for improving pulmonary function and establishing symptom control (CLIC, PACT). Finally, in preschool-aged children at high risk of developing 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 (PEAK). 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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Figure 1.

Past and present ACRN and CARE Network clinical trials separated by NAEPP 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 and/or aggressive treatment of other coexisting conditions such as vocal cord dysfunction, gastroesophageal reflux, or chronic sinusitis.

Table 1

Synopsis of reviewed trials. In each case, the study acronym is followed by a brief summary of the main conclusions of the trial. The last three 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.

Trial	Summary
BAGS	Scheduled albuterol usage 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 beta2-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 ICS in mild disease is not associated with increased exacerbation rates
PEAK	ICS are effective in reducing pediatric asthma symptom burden but do not modify asthma natural history
CLIC	More children have an improved FEV ₁ on ICS than on montelukast
PACT	Low dose fluticasone provides children more asthma control days than does montelukast
SLIMSIT	Compares ICS-salmeterol versus LTRA-salmeterol as controller strategies for moderate asthma
PRICE	Establishes biomarker predictors of short- and long-term ICS responses
AIMS	Compares acute high dose ICS to montelukast or albuterol at the onset of viral upper respiratory tract infections to reduce subsequent asthma symptoms in preschool children