

## The American Lung Association: Asthma Clinical Research Centers network: addressing real life questions in asthma management

Clinical trials are designed to answer specific questions regarding the safety, efficacy and effectiveness of biomedical or behavioral interventions in human subjects. Results from clinical trials have led to many breakthroughs in disease prevention and treatment, and provided evidence to support optimal standards of care into clinical or public health practice. Clinical trials form the evidence base for clinical treatment guidelines. The American Lung Association Asthma Clinical Research Centers network is a multicenter clinical trials' network based in the USA that has significantly contributed to the evidence base for asthma management in both adults and pediatric patients. The purpose of this paper is to provide an overview of how selected Asthma Clinical Research Center studies have affected the treatment and the management of asthma over the past 13 years.

**Keywords:** asthma • clinical trials • network • research

### The Asthma Clinical Research Centers network

Established in 1999, the Asthma Clinical Research Center (ACRC) was the creation of the scientific leadership of the American Lung Association in response to recognizing the critical gap in information related to treatment and care for asthma during a time when disease rates were rising to epidemic proportions. Existing research on asthma at that time was focused on the safety and efficacy of specific drugs or on the mechanistic understanding of the complex pathology of asthma. As such, the ACRC was established to examine issues that would be directly relevant to the everyday practice of medicine. The concept was to fund research centers to answer clinical research questions through the recruitment of large number of subjects and provide results that are directly relevant to treatment decisions facing patients and their physicians. The American Lung Association provides infrastructure support to establish and maintain the research centers while support for individual protocols and provision of study medications and/or devices

would be sought from both public and private sources.

Today, the ACRC network consists of 18 academic clinical centers across the country, a data coordinating center and a network chairman. A Steering Committee, which consists of the Principal Investigator at each center, Data Coordinating Center staff and representatives from the American Lung Association, meets in person three times a year to discuss and vote on potential protocols that have been previously reviewed by a protocol committee. The network has, thus far, successfully completed ten clinical trials, which recruited over 5000 patients with asthma. These studies have advanced our understanding of the care and treatment of people with asthma. The consistent core support of the American Lung Association has been essential for providing seed monies for investigators to develop ideas, infrastructure and seek additional funding mostly from the National Institute of Health and occasionally from the pharmaceutical industry to conduct specific trials. To date, the Network's work has led to over 40 published papers in high-

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impact journals; the inclusion of asthma to the Advisory Committee on Immunization Practice (ACIP) recommendations regarding high-risk groups who should receive influenza vaccination; and the recognition of the clinical practice impact of many trials, for example, designated as a 'trials that matter' in one accompanying editorial [1]. In addition, the ACRC has had a stellar record for completing recruitment and publishing trial results on schedule. In this article, an overview of some of the key achievements of the network is provided.

### Comparative effectiveness trials

Comparative effectiveness trials (CER) are designed to compare the effectiveness, benefits and harm of treatment options with the overall goal of assisting patients, clinicians, payers and policy-makers in making informed and timely healthcare decisions at both the individual and national levels. As a multicenter network, the ACRC is well poised to conduct this type of research due to its ability to enroll large numbers of patients from diverse populations from different regions of the USA to ensure that the research findings have external generalizability and are relevant to large groups of patients. As such, CER type trials are central to the mission of the network, which is 'to improve asthma care through clinical research in diverse populations'.

In one of its first trials, the ACRC examined whether a relatively inexpensive asthma medication, theophylline, that had fallen out of favor due to concerns over side effects, could be used as safely and effectively as more commonly used asthma medication, montelukast, as an add-on to existing asthma therapy. Known as the LODO trial, 489 participants, aged 15 years and older, with poorly controlled asthma were randomized into one of three groups: theophylline, montelukast or placebo and followed up for a period of 6 months to determine the frequency of asthma exacerbations between groups. Results of the study demonstrated that neither the use of montelukast nor low-dose theophylline, when used as add-on medications, reduced the rate of asthma exacerbations in subjects with poorly controlled asthma compared with placebo [2]. Furthermore, reports of adverse effects were similar among the three groups. However, subgroup analyses indicated that in patients not taking inhaled corticosteroids (ICS), low-dose theophylline as an add-on therapy significantly reduced the rate of asthma exacerbations by 31% compared with placebo (1.8 vs 5.7%;  $p = 0.002$ ). This somewhat unexpected finding provided clinicians with a safe and viable alternative option for treating patients unable or unwilling to take ICS. More importantly, theophylline being considerably less costly than montelukast may be more accessible to the poor and uninsured populations.

In another CER trial, the LOCCS Trial, the network examined whether therapy could be reduced among well-controlled asthmatics receiving low dose of the ICS, fluticasone. A treatment regimen of twice-a-day inhaled fluticasone was compared with once-a-day oral montelukast as well as once-a-day inhaled fluticasone/salmeterol combination in 500 patients (adults and children) with well-controlled asthma. Results of the study indicated that the simpler regimen of a once-a-day inhalation of fluticasone/salmeterol combination was as effective as the twice-daily treatment with low-dose inhaled fluticasone in patients with mild persistent asthma, determined by the reduction of treatment failures, nocturnal awakenings and improvement of lung function as well as asthma composite scores [3]. These results offered immediate benefits for patients, as a simpler treatment plan with only one dose per day would not only result in fewer prescription refills – reducing the cost for medications and perhaps a decrease in side effects – but would potentially lead to improved treatment compliance. Treatment with montelukast was associated with an increase in the rate of treatment failures compared with the other groups but patients remained symptom free on close to 80% of treatment days.

The ACRC is currently conducting a third CER trial examining three potential approaches to step down treatment in 400 patients with well-controlled asthma, while receiving combination inhaled corticosteroids/long-acting  $\beta$ -agonists (ICS/LABA). Current asthma guidelines recommend stepping down therapy once asthma is controlled for at least 3 months; however, the best approach to stepping down patients with moderate-to-severe persistent asthma is unclear. Determining an optimal approach is of particular interest to practitioners due to the ongoing controversy regarding LABA safety as well as the potential of treatment failure among patients. The LASST trial is a 56-week multicenter, prospective, randomized, three-arm parallel trial that has been designed with clinically relevant primary outcomes and longer term follow-up after reduction of asthma treatment, in order to provide definitive evidence to guide clinicians how to safely minimize medication in patients with moderate-to-severe asthma [4]. The trial is expected to be completed in 2015.

### Adjunctive treatment trials

Trials conducted by the ACRC have also examined several questions related to adjunctive treatments in asthma care such as appropriate preventative care through vaccination, and the treatment of comorbid conditions.

In 2000, the network embarked on its first study, the SIIVA trial, to evaluate the safety of the inactivated influenza vaccine in patients with asthma. At this time, less than 30% of patients with asthma were being vac-

cinated against influenza due to practitioners concern regarding the possibility of vaccination-associated exacerbations of asthma. A total of 2032 patients aged 3 to 64 years were randomized to receive an injection of the influenza vaccine and an injection of placebo in random order with 4 weeks between injections. Results from the study demonstrated no difference in asthma exacerbations rates between the two groups within 14 days of injection [5]. As such, the network concluded that the influenza vaccine was safe for asthmatics and that annual influenza vaccinations should be recommended for asthmatics to protect against influenza and related complications. Based on these findings, the Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices now recommends annual influenza vaccination for all patients with asthma. Latest evidence suggests that 47% of people with asthma received the influenza vaccine in 2009; an increase of 20% since 2001 when results from the SIIVA trial were published. It has been estimated that an increase in the influenza vaccination rate by 20% would decrease the number of asthma hospitalizations due to influenza each by almost 18,000, saving over US\$137 million per year in healthcare expenditures [AMERICAN LUNG ASSOCIATION, UNPUBLISHED DATA].

In patients with asthma, gastroesophageal reflux (GER) is a common co-morbidity and, as such, it was common for practitioners to treat asymptomatic GER with proton pump inhibitors (PPI) in an attempt to improve asthma control in patients with difficult to control symptoms. The network examined whether the empiric use of PPI for the treatment of asymptomatic GER would improve asthma control in children and adults with poorly controlled asthma while on ICS treatment. In the SARA trial, 412 adult subjects with uncontrolled asthma and concurrent ICS therapy were randomly assigned to receive either the PPI, esomeprazole or a placebo for 24 weeks to determine whether empiric treatment with a PPI would improve asthma control. In total, 40% of trial subjects had pH probe-diagnosed GER but no differences in asthma control was seen in study patients, irrespective of pH probe results [6]. In a subsequent study of 306 children with uncontrolled asthma on ICS therapy, the SARCA trial, results mirrored those of the adult trial. Despite the fact that 43% of children had pH probe-diagnosed GER, empiric treatment with the PPI, lansoprazole, did not improve asthma control [7]. Additionally, the study demonstrated that PPI treatment was associated with more upper respiratory tract infections, sore throat and bronchitis in children. Results of these studies suggest that the investigation and treatment of GER in patients with asthma should be dictated by the presence of GER symptoms, not asthma symptoms. As such, practitioners

may want to rethink their prescription habits of PPIs to their asthma patients with asymptomatic GER as the disease is not a likely cause of poorly controlled asthma and the use of PPIs may be associated with unwanted adverse risks. Of note, these studies did not examine the role of non-acid GER in patients.

One of the ACRC current studies is examining whether the treatment of chronic sinonasal disease through nasal steroids will improve asthma control. Much like GER, rhinitis and sinusitis are common co-morbidities in asthma patients and these conditions have been reported in over 30% of trial participants. In the STAN trial, 380 patients with uncontrolled asthma and sinonasal disease will be randomized to receive nasal steroids or placebo. The primary objective of the trial will be to evaluate whether the addition of 6 months of treatment with nasal steroids improves asthma control. The results of the study will be reported later on this year.

### **Novel diagnostics & treatments**

Another type of studies conducted by the ACRC are those that are directed toward improving ways practitioners diagnose asthma or related co-morbidities and/or discovering novel ways to treat asthma.

Sinusitis and rhinitis are commonly reported among asthma patients and both have been associated with uncontrolled asthma. While treatment guidelines recommended screening patients with asthma for sinusitis and rhinitis, there had been no simple way to validate diagnosis. As such, the network commissioned the SIRNA trial with the goal of developing a clinical tool to reliably diagnose sinusitis and rhinitis among those with poorly controlled asthma. Through the evaluation of 59 participants, the network was able to develop a five-item questionnaire that had a sensitivity of 0.90 (95% CI: 0.77–0.97) and a specificity of 0.94 (95% CI: 0.71–1.00) to diagnosis chronic sinonasal disease [8]. This five-item questionnaire was then successfully utilized to screen asthmatic patients for chronic sinonasal disease in the STAN trial mentioned above.

The ACRC is currently conducting a proof-of-principle clinical trial, the CPAP trial, to determine whether the use of CPAP, an effective treatment for sleep apnea, could improve airway hyper-responsiveness and asthma control in asthmatics without sleep apnea. CPAP increases airway pressure by applying external pressure through the nose or mouth to prevent airway collapse during sleep. Researchers in the network propose that same pressure will reduce the airway constriction that occurs during an asthma attack. The study will evaluate whether treatment for 12 weeks with nocturnal CPAP will reduce airway hyperresponsiveness measured by methacholine challenge for patients with asthma. The results of this study may lead to prescribing

CPAP, a non-pharmaceutical treatment, to patients with difficulties in achieving asthma control.

### Future perspective

After 14 years, the ACRC remains focused on conducting clinically relevant research and contributing important new knowledge in the quest to help the millions of people with asthma. Two important metrics of the networks' success are our competitive funding record and our publication record. We have successfully competed for financial support from both the National Institutes of Health and the pharmaceutical industry. Second, our results have been consistently published in high impact medical journals [2,3,5–10]. Most importantly, the findings have had a direct impact on the lives of asthma patients and the cost of their care.

The ACRC is a collaborative effort of many individuals. First, the support of the American Lung Association through its infrastructure support enables individual sites to recruit the number of patients needed to definitively establish whether some widely used asthma treatments are beneficial or ineffective. Second, the network employs the best researchers in the field of lung health to gather to discuss emerging trends and areas of research interests to pursue. Engaging the unique intellectual capital and scientific resources available from each of the network centers has been a key component of our success thus far. This includes the mentorship of younger investigators who have contributed significantly to the productivity of the ACRC. Finally, the Data Coordinating Center at Johns Hopkins provides the expertise and logistic support to enable the network to conduct multiple concurrent studies efficiently.

The American Lung Association is now in discussions to expand the ACRC network to include research on COPD. Although at an early stage, it is hoped that the ACRC will be ready to start recruiting for COPD patients by 2015. In summary, the ACRC has conducted clinical trials that have provided important information that allows asthma practitioners to deliver care to their patients based on a solid evidentiary footing.

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### Executive summary

- The American Lung Association Asthma Clinical Research Centers network is the largest not-for-profit network dedicated to improving asthma care through clinical research in diverse populations.
- Since its inception, the network has completed ten clinical trials, recruited more than 5000 patients with asthma and published over 40 articles.
- Research findings have significantly contributed to the evidence base for asthma management in both adults and pediatric populations.

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