Asthma Therapy: What’s New and Is It Necessarily Better?

Asthma has been a major disease focus for the past 7 years due to the increasing morbidity and mortality. In 1991, the National Asthma Education and Prevention Program (NAEPP) published the first guidelines from an expert panel on the diagnosis and management of asthma. Following this were the International Consensus Report and Global Initiatives for Asthma. Recently, a second expert panel report was released on the guidelines for the diagnosis and treatment of asthma. Yet, asthma continues to be an important lung disorder for both respiratory subspecialists and primary care physicians in terms of cost, office visits, and hospitalizations. Unfortunately, there appears to be no cure in the near future. Thus, asthma therapy is directed at controlling airway inflammation, educating the patient, and improving the patient’s quality of life.

For years inhaled corticosteroids have been the mainstay of chronic asthma therapy. There are multiple brands of inhaled corticosteroids, yet comparative studies have been poorly designed to answer the clinically important questions: is one corticosteroid better than the others? Also, what is meant by high-dose inhaled corticosteroids? Furthermore, what is the best parameter to evaluate asthma on a chronic basis?

Clinical trials of inhaled corticosteroids use symptom control, reduction in rescue medication, attack frequency, and improvement in $FEV_1$ to determine efficacy. In this issue of CHEST (see page 34), Nathan and associates do not address any of these questions, yet they do present, albeit hidden, information about dose-response characteristics of one common inhaled corticosteroid, beclomethasone dipropionate. Higher doses (1.344 mg per day vs 336 mg per day) given to asthmatic patients under controlled situations showed a greater improvement in $FEV_1$ over 4 weeks. The authors also showed that changing the formulation to a higher dose per puff (84 mg) is equivalent to older preparations (42 mg). In addition, bid dosing resulted in better patient compliance than qid or tid dosing. Interestingly, these patients supposedly were already using inhaled corticosteroids, but over the course of the study they demonstrated further improvements in their $FEV_1$ values.

Recent studies also raise questions about the risks and benefits of chronic inhaled corticosteroid therapy for asthma. Garbe et al. report that 3 months of inhaled corticosteroids (>1500 to 1600 mg per day) increase the risk of glaucoma or ocular hypertension in elderly patients. Other known risks from chronic use of inhaled corticosteroids include growth suppression in children, skin thinning and purpura, adrenal suppression, cataracts, oral candidiasis, and osteoporosis.

Potency of the inhaled corticosteroids deserves comment in that potency is based on dose-response characteristics using reduction in skin erythema. With inhaled corticosteroids, potency cannot be directly assessed unless specific lung parameters common to asthma are evaluated (eg, eosinophil influx, cytokine production, or mast cell mediator release). Studies should evaluate different dosages of inhaled corticosteroids in the same asthmatic patient and should possibly include BAL measurements of these parameters. Blocking or blunting pulmonary responses to allergens assesses only a small subset of asthmatic patients. In addition, the newest inhaled corticosteroid, fluticasone propionate, failed to demonstrate a dose-response by $FEV_1$ improvement in asthmatic patients.

More important in asthma management has been the advent of new antileukotriene medications.
of these pharmacologic agents, zileuton, inhibits the 5-lipoxygenase enzyme and ultimately the production of leukotrienes B4, C4, and subsequently C4 metabolites, leukotrienes D4 and E4. Another anti-leukotriene medication, zafirlukast, works by blocking leukotriene D4 receptors. Review of clinical studies shows that these pharmacologic agents improve FEV\textsubscript{1} by 8 to 16%. Are they truly better than the current medications available for asthma or should these be added to current therapy? The implications that these products be used as monotherapy for asthma needs to be questioned until data from these studies clearly identify the subset or subsets of asthmatic patients who respond significantly to these pharmacologic agents. These agents are not approved for children under 12 years of age, and monitoring of liver function is necessary with zileuton.

The last issue about asthma therapy is the microgram vs microgram controversy. Is there any study truly comparing 50 \( \mu \)g of one corticosteroid to 50 \( \mu \)g of another corticosteroid in asthmatic patients? Until such a comparative trial is performed, this debate will continue.

How should health-care providers proceed in the management for asthma? Clearly, physicians should document the total microgram dose per day of inhaled corticosteroids for patients (ie, beclomethasone 336 \( \mu \)g \times 4, triamcinolone 600 \( \mu \)g \times 4, fluticasone 440 \( \mu \)g \times 4, or budesonide 1000 \( \mu \)g \times 4 per day). Second, compliance of all inhaled medications demands some objective evaluative method. We must assume that our patients are noncompliant with their daily medications, so having an inhaler with a counting device would be a major benefit for monitoring patients. Third, the issue of benefits and risks from chronic inhaled corticosteroids needs to addressed and widely disseminated so that patients and physicians can be appropriately informed about their use. The last issue concerns the appropriate daily monitoring method for our asthmatic patients: should we continue with peak flows, or use FEV\textsubscript{1} instead? For those involved with asthma research, lung pharmacology of any inhaled medication should be carried out to inform the clinician prescribing these medications. Comparative trials are desperately needed using only equivalent doses of these medications. Further investigations of new pharmacologic agents for asthma should be continued, especially antileukotrienes, anticytokines, anti-IgE agents, and antiplatelet activating factor products. Lastly, does early diagnosis and aggressive treatment truly alter the natural history of a patient’s asthma?

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In Pursuit of Tuberculosis Control

Civil Liberty vs Public Health

In 1987, based on a steady annual decline in the number of tuberculosis (TB) cases in the United States, the Advisory Council for the Elimination of Tuberculosis was established. At that time, it was considered a realistic expectation that TB would be eliminated by the year 2010. In 1993, TB was declared a global health emergency by the World Health Organization. Currently, the eradication of TB is no longer considered a feasible target.

Numerous factors contributed to the resurgence of TB. While more than 90% of the global incidence of and mortality from *Mycobacterium tuberculosis* infection occurs in the developing world, the rising incidence of this disease and the emergence of multidrug-resistant TB (MDRTB) led to renewed interest in TB on the part of health-care workers, consumers, and policy makers worldwide. Subsequently, some limited success has been achieved in reestablishing control of TB.

The resurgence of this disease illustrates the failure of public health policies during the 1970s and 1980s and led to a reappraisal of the medical, legal, and ethical implications of disease control measures considered necessary for this disease. Directly observed treatment (DOT) programs, initially advocated in 1958, combined with the principles of intermittent therapy, utilized as early as 1961, are currently considered the standard of care for TB treatment, at least for areas with TB treatment completion rates below 90%. The ensuing expansion of DOT programs in the United States has not occurred without controversy and subsequent compromise. The call for a policy of universal DOT is supported by the following: high rates of treatment failure; the associated morbidity, mortality, and cost of treating MDRTB; the inability of professionals to distinguish compliant patients from noncompliant patients in advance; the attempt to avoid discrimination based on race, socioeconomic conditions, or other factors that providers may believe will affect compliance; and the likelihood that the application of universal DOT as a standard of care would serve to reduce the potential stigma of this treatment. These arguments have all been challenged by opponents who characterized universal DOT as a waste of limited resources (ie, wasting funds on individuals who would be compliant with therapy), an unethical intrusion upon autonomy, and a violation of the constitutional requirement that the least restrictive alternative be used. Currently, DOT is viewed as a service, and the general consensus appears to be in support of a policy of offering it to all patients, but of mandating it only in cases of documented nonadherence to prescribed therapy.

While DOT may continue to engender controversy, it is indubitably an effective treatment policy that results in a decrease in the number of reported TB cases, and in the incidence of multidrug-resistant cases. However, as illustrated in the article by Burman and colleagues in this issue of *CHEST* (see page 57), the use of DOT does not, in and of itself, ensure adherence to a prescribed regimen; the use of more restrictive measures may be required.

Short-term incarceration has been used for the management of noncompliance by the Denver Metro Tuberculosis Clinic, which for decades has employed a consistent approach to the treatment of tuberculosis, emphasizing DOT and enforcing local and state public health laws for control of contagious cases. Many components of the Denver treatment program are considered essential to expedite patients’ access to and utilization of treatment (ie, free treatment, extended hours, facilitators, assignment to a nurse-clinician, etc). In addition, patients are notified at treatment initiation of the Tuberculosis Clinic’s legal obligation to ensure effective quarantine of infectious patients, indicating that chemical quarantine (chemotherapy) can be substituted for physical quarantine. Despite what is apparently a well-established, supported, and functional TB treatment program, nearly 5% of the patient population was nonadherent to outpatient treatment and required...