role to play in OAC therapy for the foreseeable future. Any efforts at maximizing their potential use, both safely and efficaciously, remains a great priority.

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Reducing Oral Steroids With Inhaled Steroids
Is That All That Can Be Achieved?

When inhaled corticosteroids were first investigated, some of the earliest clinical trials that showed compelling evidence of their efficacy were performed in patients who were dependent on oral corticosteroids. Although the design of these studies was far from ideal, the efficacy of even low-dose inhaled steroids in reducing or frequently eliminating the need for oral corticosteroids was striking.1

This was confirmed when they became available in clinical practice; the first target groups of patients were those dependent on oral steroids or requiring frequent rescue courses of steroids. The next major development of inhaled corticosteroids was the introduction of high-dose inhaled beclomethasone dipropionate (BDP).2 Again, clinical experience with this preparation preceded well-performed clinical trials, but the efficacy of high-dose inhaled BDP in reducing the requirement of oral steroids was quite striking.3 Since then, a feature of the development of each new inhaled corticosteroid has been a trial demonstrating the ability to reduce or eliminate oral steroid requirement in severe asthma.4–7 Typically, in comparison with placebo, more than three fourths of patients are able to eliminate regular oral steroids, and consequently the mean dose of inhaled corticosteroids is markedly reduced. A superficially surprising result of these trials6,7 is that despite the elimination of oral steroids, lung function improves. The explanation for this phenomenon is probably that clinicians, when prescribing oral steroids, perform a balancing act; rather than administer a higher dose of oral steroids, with the aim of producing better lung function, they prefer to administer a lower dose of oral steroids, leaving lung function impaired and patients symptomatic but with fewer side effects. When more effective treatment is administered, there is still room for lung function to improve.

Although most inhaled steroids have been investigated for their oral steroid-sparing ability, the number of well-designed and controlled trials is still limited and some important questions remain. No controlled trial of inhaled steroids > 2,000 mcg/d has been reported; although inhaled steroids are used by clinicians above these doses, the value is unclear. No head-to-head comparisons of different inhaled steroids have been performed to compare oral steroid sparing. Although there is clearly a difference between low-dose and high-dose inhaled steroids in terms of efficacy and oral steroid sparing, the evidence that there is a dose-response relationship...
> 1,000 μg/d is not well founded. The current study has used the new inhaled corticosteroid ciclesonide. Small-scale clinical pharmacology studies have suggested that even at high doses, ciclesonide has minimal adrenal cortical suppression activity compared with currently available inhaled steroids. The trial has investigated well-characterized patients who are dependent on oral steroids, despite receiving relatively high doses of inhaled steroids. Two doses of ciclesonide, 640 μg/d and 1,280 μg/d, were compared with placebo. The exact dose-response relationship between ciclesonide and conventional inhaled steroids is not fully established, but based on receptor binding studies it would be anticipated to have a potency between budesonide and fluticasone. The results of the study demonstrate that both doses of ciclesonide were able to reduce the mean dose of oral steroids and enable approximately 30% of patients to completely stop oral steroids. As with previous studies, lung function improved despite the elimination of oral steroids. There was a nonsignificant trend to the higher dose of ciclesonide leading to a greater reduction in mean oral steroid dose. The study in this issue of CHEST (see page 1176), therefore, confirms that oral inhaled steroids reduce oral steroid dose and, similar to previous studies, hints at a dose-response relationship. However, the study has a number of important shortcomings. It was of short duration, only 12 weeks; this means that the maximum reduction in oral steroid dose may not have been achieved. Basal cortisol levels were measured, but there was no significant difference between placebo- and active-treated groups at the end of the study; this is probably because recovery of adrenocortical function is slow and was not maximum by study end. Furthermore, it is possible that with a longer study, even more patients will have stopped oral steroids and consequently the mean oral steroid dose would have decreased. For a new inhaled steroid with a potentially advantageous therapeutic ratio, use of higher doses in oral steroid-dependent doses is an attractive positioning. To understand the potential value, we now need active comparative studies rather than placebo-controlled trials. These trials need to enroll patients who are oral-steroid dependent, despite high-dose inhaled steroids; the trial needs to be at least 26 weeks long and preferably longer to fully understand the overall potential. It would also be of value to investigate doses > 2,000 μg/d to determine if even higher doses could eliminate steroid requirement in a greater percentage of patients. Although oral steroid-dependent asthmatic patients are now a small minority, they suffer greatly both from their disease and the side effect of oral steroids. For health-care providers, these patients are expensive to treat, as they tend to have poorly controlled disease and suffer from the side effects of oral steroids. These patients remain an important group for whom other therapies are needed, and the potential for high-dose inhaled steroids in this group may not be completely exhausted.

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