

## STEROID-RESISTANT ASTHMA

by Donald Y.M. Leung, M.D., Ph.D., & Stanley S. Szeffler, M.D.

### Steroid Resistance

Inhaled glucocorticoids have become the mainstay of asthma therapy. Treatment with oral glucocorticoids is the most potent therapy available for acute asthma exacerbations and as a maintenance regimen for patients with severe disease. Unfortunately, however, a small fraction of asthmatics are steroid resistant and do not benefit from standard treatment.

Obviously it is critical to identify these patients as soon as possible. Patients who do not respond to low steroid doses are often placed on higher doses, which in steroid-resistant (SR) asthmatics can cause significant adverse effects without providing significant benefit. In addition, because steroids are the cornerstone of asthma therapy the definition of an effective alternative treatment for these patients is a challenging medical problem.

There are no definitive statistics on the prevalence of SR asthma, but a rough estimate is that it occurs in less than 5% of the asthmatic population. This translates into a sizeable number of patients, based on estimates that there are more than 25 million asth-

matic patients in the United States. More importantly, because these patients are the most difficult asthmatics to treat they may appear in disproportionately high numbers in hospital emergency rooms. In addition, many SR patients go unrecognized.

### Diagnosing Steroid Resistance

Steroid resistance, which was first described in 1968, is a clinical diagnosis that is made after an asthmatic patient fails to respond to a prolonged course of systemic glucocorticoid therapy. The standard definition of resistance is a patient who fails to respond to high-dose, oral glucocor-

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ticoid therapy, e.g. a two-week course of 40mg prednisone per day. These patients often become cushingoid in appearance because of their high steroid dose.

Failure to respond is documented by monitoring the morning forced expiratory volume in 1 sec (FEV<sub>1</sub>), prior to treatment with a bronchodilator. During two weeks of steroid treatment, the pre-bronchodilator FEV<sub>1</sub> of a SR patient will not improve by more than 15%. Other objective measures

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of airflow, including peak expiratory flow monitoring, may also need to be followed. Other markers of treatment failure are a need to raise the steroid dose, overuse of an inhaled beta-agonist, and a high frequency of hospitalizations and emergency room visits.

Resistance to inhaled steroids is not as well studied, but the fraction of patients who fall into this category may be even higher. The logical strategy for managing a patient who fails to respond to inhaled steroids is to try a more potent topical steroid, or a course of oral medication. As a result, failure to respond to inhaled steroids alone does not classify a patient as SR.

In the vast majority of cases steroid resistance is acquired by a process that we will discuss later in this article. There is no known association between the development of steroid resistance and age, but patients with SR asthma tend to have more severe disease. The best associations with resistance appear to be the duration of a patient's asthma, and the patient's rate of pulmonary function deterioration over time. Patients with long-standing, poorly controlled disease, a poor response to inhaled steroids, and those who encounter difficulty in being weaned off systemic steroids are most likely to develop resistance.

Once a primary-care physician identifies a likely SR patient it is important that the patient be referred to a center such as National Jewish that specializes in managing these cases. Our institution is the foremost center in the United States doing research on the etiology and pathogenesis of SR asthma.

The first step in the patient's workup is to confirm that the patient really has asthma by ruling out the other disorders that are the differential diagnosis for recurrent

wheezing. Many of these diagnoses are unresponsive to glucocorticoid therapy, which could explain the SR disease that the patient shows.

The differential diagnosis includes sinusitis, gastroesophageal reflux, congestive heart failure, an anatomic abnormality, immunodeficiency, interstitial lung disease, and bronchopulmonary dysplasia. Other conditions that could masquerade as SR asthma include poor patient compliance with therapy, drug interactions with glucocorticoids, abnormal glucocorticoid absorption or elimination, food sensitivity, environmental factors, and psychosocial factors.

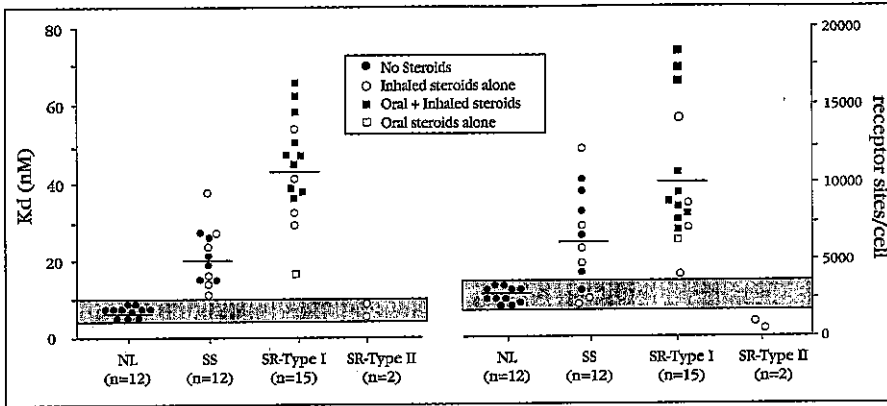
If the patient's diagnosis of asthma is confirmed, the next step is to attempt to identify factors in the patient's environment that may contribute to poor asthma control, such as allergens. The third step is to perform steroid pharmacokinetic studies to determine whether the patient has a defect in the absorption or clearance of various systemic steroids.

Finally, we carry out studies that examine whether the patient's steroid receptors are abnormal, and whether the patient has ongoing inflammation and immune activation that is unresponsive to systemic steroid treatment. These final studies relate to recent findings we have made regarding the cellular and molecular mechanisms of steroid resistance.

## **Type I or Type II**

SR patients are divisible into two types. The vast majority, perhaps 90%, are Type I, which is characterized by a reversible, decreased binding affinity of T cells for glucocorticoids. The remaining SR patients are Type II's; it appears that all cells in Type II patients carry an abnormally low number of glucocorticoid receptor binding sites.

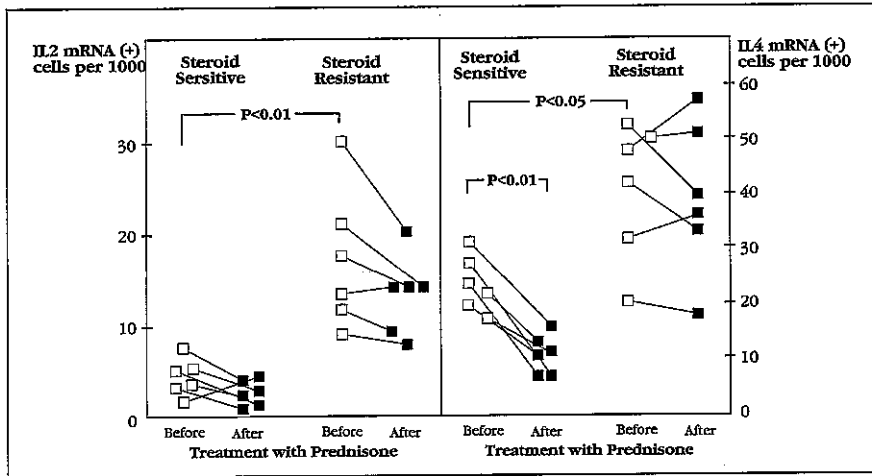
Fig. 1



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The GR binding parameters of 12 normal (NL) controls, 17 SR asthma patients, and 12 SS asthma patients. Normal ranges for both GR parameters are indicated by the shaded bar. The solid bar indicates the mean for each group. All groups were significantly different ( $P = 0.0001$ , ANOVA) from each other.

Fig. 2



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Number of cells with positive hybridization signals for IL-2 and IL-4 mRNA in BAL fluid from six patients with SR asthma obtained before and after treatment with prednisone.

Because there is only one human glucocorticoid-receptor gene, the observations that Type I patients can develop severe side effects from chronic, systemic steroid treatment, and that their glucocorticoid receptor defect is limited to T cells suggest that Type I SR asthma is an acquired disorder, possibly the result of an immune-activation pathway.

In contrast, Type II SR asthma is not associated with the development of steroid-induced side effects and is not limited to T cells. Type II resistance has the hallmarks of an irreversible, innate (primary) defect.

Findings made in our laboratory suggest

that the glucocorticoid receptor defect that appears in Type I SR occurs in response to the release of certain cytokines, such as interleukin (IL)-2 and IL-4. In addition, results from clinical studies indicate that the level of cytokine activation is much higher in SR asthma patients compared to those who are steroid sensitive. Bronchoalveolar lavage cells from the airways of patients with SR asthma have a distinct pattern of cytokine gene expression, which may alter a patient's therapeutic response to glucocorticoids.

These and other observations raise the possibility that Type I SR asthma is the end

result of ongoing immune activation that is no longer controlled by the immunosuppressive effects of steroids. We believe that this immune activation occurs because of the high level secretion of specific cytokines, such as IL-2 and IL-4, by activated T cells, the cells that are believed to have a central role in the pathogenesis of asthma. A patient's lost ability to respond to steroids leads to a vicious cycle of unchecked immune activation.

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### **The reduction of steroid binding in steroid-sensitive patients is not as pronounced as in the SR asthmatics.**

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of the allergen-trigger factors--is critical to successful management of the patient's asthma. Another possible route to successful treatment may be use of the new generation, inhaled, synthetic glucocorticoids, which have an enhanced binding affinity for the glucocorticoid receptor.

Critical aspects for future investigation will be identification of the specific cells involved in SR asthma, identification of a primary allergen or possibly a microbial superantigen that triggers immune activation in these patients, and the development of new intervention strategies. A key will likely be early identification of these patients and early use of novel treatments. With time, some aspects of severe SR asthma may become irreversible, requiring the use of cytotoxic drugs or, perhaps, transplantation.

Even steroid-sensitive asthmatics have a reduced glucocorticoid binding affinity compared to non-asthmatic, control patients, although the reduction of steroid binding in steroid-sensitive patients is not

This hypothesis is particularly intriguing because it suggests that early intervention with anti-inflammatory therapy—including the identification and elimination

as pronounced as in the SR asthmatics. This finding suggests that chronic asthma may be associated with a spectrum of glucocorticoid-receptor binding abnormalities; Type I SR asthma may represent the extreme form of this condition.

Modest doses of inhaled glucocorticoids may also have the potential to influence steroid sensitivity, which means that the mechanisms that underlie Type I SR asthma have important implications for controlling inflammation in patients with mild asthma. Given the increasing use of steroids in asthma treatment, an important, immediate lesson from these observations is that steroids should always be used cautiously. The dose must be carefully titrated so that a patient only receives the minimum amount required to exert the desired therapeutic effect.

In addition to providing new insights for therapy, increased understanding of the causes of SR asthma may also have diagnostic implications. Studies are underway to assess new markers of steroid resistance, such as the appearance of activation antigens on T cells, the secretion of an eosinophil protein, or elevated cytokine levels.

## **Management**

Once a patient is diagnosed as having SR asthma, the next step is to determine whether it is Type I or II. This is followed by patient education about steroid resistance, adjustment of the steroid dose, and introduction of other immunomodulatory therapies.

As of now there are no clear alternatives to oral steroids for treating patients with SR asthma. Our group has had some success using combined treatment with troleanomycin and methylprednisolone in several SR patients. This regimen led to normaliza-

# Clinical and Laboratory Features of Steroid Resistant Asthma

Features	Type I	Type II
Glucocorticoid-induced Side Effects	Yes	No
AM Cortisol*	Suppressed	No
GR binding affinity	Decreased	Normal
GR number	High	Low
Reversibility of GR defect	Yes	No

\* Feature on high dose systemic steroids

tion of T cell sensitivity. Another group has reported success using cyclosporine to improve the symptoms of patients with SR asthma. Other potentially useful agents include methotrexate, gold, intravenous gamma globulin, hydroxychloroquine, dapsone, and interferon- $\gamma$ . Two anti-inflammatory drugs that are often used to treat mild to moderate asthma, cromolyn and nedocromil are not sufficiently potent for patients with more severe disease.

The prognosis of a patient with SR asthma is poor. The best approach to managing this disease is to recognize it early, before the patient's airway becomes so damaged that the asthma is irreversible.

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