REVIEW

Steroid resistant asthma: what is the clinical definition?

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Abstract: Asthma is usually a steroid-responsive disease. A few patients respond poorly to these drugs, and others need such high doses to control the disease that side-effects become a serious problem. The term steroid-resistant asthma is used for both groups. In some patients, factors may be operating to make the asthma worse and, thus, to increase the requirement for steroids. In order to make a clinical diagnosis of steroid-resistant asthma, it is therefore necessary to investigate the factors that could be operating to prevent a "normal" response to steroids. These factors include wrong diagnosis, insufficient steroid reaching the airway mucosa, continuing exposure to sensitizing agents, unrecognized aggravating agents, excessive use of beta-agonist aerosols, and failure to undertake regular management according to a strict management plan.

Using a strict clinical definition of steroid-resistant asthma leads to better investigation and treatment of individual patients, allows steroids to be stopped when they are not indicated, allows other anti-inflammatory drugs to be used with confidence, and provides a well-defined group of patients for further research relating to the mechanisms of action of steroids.

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Soon after the introduction of adrenocorticotrophic hormone (ACTH) in 1949 [1], it became evident that asthma is a steroid-responsive disease. It appeared that the disease could be controlled by oral steroids in almost all patients, but their side-effects rapidly limited their use. In 1968, Schwarz et al. [2] described six patients whose disease appeared to be relatively resistant to steroids, because they required larger doses for poorer control, had a decreased eosinopenic response, and had only mild Cushing-like changes. They used the term "steroid resistant asthma" (SRA) to describe these patients. It is now well-established that there is a group of patients whose tissue (skin, blood leucocytes and airways) respond poorly to steroids, and a number of researchers are studying the mechanisms involved [3, 4].

Some patients with severe asthma respond to oral steroids, but only to very high doses, and it is not clear if they have SRA, a severe form of the disease, or both [5]. Some appear to be responsive initially, and to become progressively unresponsive with time, although this sequence of events is not documented in the literature. The introduction of inhaled steroids has largely overcome the problem of side-effects for those who do respond but only to high oral doses, and in most patients inhaled steroids in adequate doses allow oral steroids to be greatly reduced or withdrawn completely [6, 7]. Today, most doctors expect that their patients will improve once the regular use of a sufficient dose of the inhaled form is introduced [8, 9], and a poor response is usually diagnosed as SRA. Sometimes there are reasons, other than true SRA, for the apparent poor response, and this is the subject of this review.

Why is a clinical definition of steroid resistant asthma important?

Clinical practice

The presence of SRA may be an indication for the use of anti-inflammatory drugs, such as methotrexate, cyclosporin or gold, in order to try to reduce the dose of steroids in those taking large oral doses, or to try to improve the control of the disease in those who appear genuinely steroid resistant. Because of the toxicity of these drugs, physicians need to be sure that SRA is in fact present. Additionally, in some patients, the steroids can simply be stopped [5]. In the process of defining the steroid-resistant state, factors may be recognized that are preventing the expected response to inhaled steroids.

Research

Patients in whom steroid resistance is well-defined are needed, so that the nature of the abnormalities present can be studied and, hopefully, corrected. Studies of steroid resistance also provide mechanisms for understanding the action of steroids.
Bronchial biopsies can be performed safely in patients with asthma, being widely used in asthma for research, and guidelines have been described [19, 20].

Question 2

Are adequate doses of steroids reaching the airways? It seems likely that inhaled steroids, by acting at the surface of the airway, have an effect that can be achieved only by large doses of oral steroids [21]. Thus, unless adequate inhaled forms of the drugs are reaching the airways, SRA cannot be established. There are many reasons why sufficient drug may not be reaching the airways of a patient who has been prescribed inhaled steroids. Firstly, the dose prescribed may have been too low. Secondly, the patient may have misunderstood the instructions (confusing the dose, or even mistaking the steroid for a bronchodilator and using it intermittently). Thirdly, the patient may not be using the drug properly, e.g., a metered dose inhaler without a large volume spacing device. Fourthly, the patient may dislike the inhaled form and simply not be taking it because of the local side-effects (thrust, dysphonia). Others experience symptoms on withdrawing oral steroids and return to using them, instead of the inhaled form prescribed.

It is necessary to check the actual device and drug being used by the patient, as well as the inhaler technique. In addition, the help of the family, the pharmacist, and other medical persons involved in the management of the patient, must be sought, in order to be satisfied that the drug is being inhaled properly and in adequate doses. The appearance of the patient is not particularly helpful. The presence of steroid side-effects indicates that there is steroid in the systemic circulation, and can be present from either the inhaled or the oral form. Lack of evidence of any steroid effect in someone claiming to have taken large doses (e.g., 2 mg or more daily of inhaled steroid) for 6 or more months, suggests either that inadequate doses are being taken, or that true steroid resistance is present.

How much inhaled steroid should be prescribed? It seems likely that 2 mg·day$^{-1}$ in divided doses is sufficient in almost all patients, and there is no published evidence that increasing doses above 2 mg·day$^{-1}$ increases the response. In a recent study, 1.5 mg was no more effective than 0.3 mg·day$^{-1}$ in patients taking oral steroids [22]. However, many of the factors addressed in this review were not controlled in that study.

Usually, the problem preventing adequate doses of inhaled steroid from reaching the airway mucosa can be identified and corrected (although dysphonia remains a problem in a few patients). A trial of the correct use of the inhaled steroid for several months is then indicated.

Question 3

Have all provoking stimuli, especially domestic allergens or occupational sensitizers, been removed from the daily environment of the patient? The answer to this
question requires a knowledge of the allergens to which the patient is sensitized. The majority of patients with severe asthma, if allergic, are sensitized to house dust mites, and a measurement of mite allergen in the patient's bed is needed. In the case of occupational sensitizers, the history is extremely important, and a visit to the place of work may be needed. A lot of effort is needed to control exposures. If allergy to house dust mites exists, the bedding must be treated thoroughly, with mattress and pillow covers, and hot washing of all bedclothes [23]. Most importantly, the humidity of the bedroom should be kept as low as possible [24, 25].

In the occupational setting, removal from the sensitizer is essential (although this may be difficult for financial reasons). Continued exposure is certainly associated with deteriorating asthma [26]. If doubt exists about continuing exposure to sensitizing workplace or domestic agents, it may be necessary for the patient to leave work, and/or the house, for a period of time.

**Question 4**

Have all potential aggravating factors such as gastrooesophageal reflux, obstructed breathing during sleep and drugs been removed? Gastro-oesophageal reflux is very common in patients with severe asthma, and sometimes the disease improves when it is treated [27]. Obstructive sleep apnoea can make asthma worse, as can snoring induced by severe nasal obstruction due to rhinitis. Keeping the nasal airway open at night, and treating sleep apnoea, improves the control of asthma in some patients [28].

Several drugs make asthma worse. Most notably aspirin and related compounds, and beta-blockers. Although these problems are well-known, asthmatics continue to be prescribed them, usually by a second medical practitioner. A careful drug history is indicated.

The presence of aspirin sensitivity needs to be established, or the drugs stopped, at least for a trial period. Sometimes, asthma improves even though the patient has not previously been recognized as having, aspirin induced attacks. Although removing natural salicylates from the diet usually does not improve the control of asthma, a diet that is totally free of preservatives sometimes results in greatly improved control of the disease [29]. A trial of treatment with leukotriene antagonists, once they become widely available, may be indicated in such patients [30].

Beta-blocking drugs are widely used and, although their deleterious effects in asthma are well-known, including the fact that eye drops can make asthma worse [31], patients occasionally continue to be prescribed them. They should be stopped, at least for a trial period.

Although the treatment of the above conditions and the removal of these drugs usually improves the symptoms, a dramatic improvement in the disease, or in the response to steroids, rarely occurs. Nevertheless, a small improvement occurring in conjunction with improvement consequent to other measures, such as allergen avoidance, sometimes leads to an improvement in the severity of the disease, and in the requirement for steroids.

**Question 5**

Has the patient stopped taking regular doses of inhaled beta-agonists? It is now known that regular doses of some beta-agonists in high doses can increase the severity of asthma [32], although it is not known if all beta-agonists affect all patients. It may be that regular use of relatively small amounts (e.g. two inhalations of salbutamol four times a day) is sufficient to make asthma worse and to affect the response to steroids in some patients. A few patients take large amounts of these drugs on a regular basis, and there is increasing anecdotal evidence for improvement in some patients when beta-agonists are withdrawn.

Thus, SRA should not be diagnosed while the patient is taking more than eight puffs a day of any of the six hour duration aerosols. It is possible to reduce beta-agonist use over a period of weeks, by introducing or increasing theophylline [33] and/or anticholinergics, by avoidance of known trigger factors, and by giving support and reassurance [34].

**Question 6**

Has the patient followed a strict management plan, aimed at reducing the severity of the disease, for at least 6 months? Improvement in the severity of asthma can take up to six months, especially when the disease is severe, both with treatment [35], and with withdrawal from allergen exposure [36]. It is, therefore, important to manage the patient under ideal conditions for a period of six months, with an asthma management plan [37, 38].

In addition to appropriate doses of inhaled steroids, minimal amounts of beta-agonists, removal from causal agents, and treatment of aggravating factors, the management plan should include formal assessment of severity, asthma education and support, and a written plan for prompt treatment of exacerbations with adequate doses of oral steroids.

**Practical considerations**

In many instances, the best way to address the first five questions is to admit the patient to hospital for a week for investigation, for supervision of therapy, including reduction of beta-agonists, and for removal from causal agents. If the severity of the disease (as judged from symptoms, morning peak flows and bronchodilator use) improves in hospital but deteriorates on discharge, it is likely that environmental factors are present, and a diagnosis of true SRA cannot be made. Deterioration on leaving hospital indicates that the factors involved must be identified and readdressed.

**The steroid resistant state**

Failure to improve or to maintain improvement of the severity of asthma on doses of 2 mg of inhaled steroids per day (regardless of the oral doses given) after all these
factors have been addressed indicates SRA. In addition, obtaining definite answers to the six questions means that the patient will have been investigated thoroughly, and have been given the opportunity to understand the disease, the drugs being used, and the options available for further treatment.

Once a diagnosis of SRA is established, the use of other anti-inflammatory drugs can be considered, especially in those patients who are partially controlled on high oral doses. If steroids are reduced, theoretically at least, the patient's disease may become steroid sensitive again [3].

Other anti-inflammatory drugs including methotrexate, [39, 40] cyclosporin [41] or gold [42] can be tried. However, these drugs are toxic, and methotrexate, in particular, has limited usefulness because it is not uniformly effective [43], or effective only as long as adequate doses are being taken [44], and has even been a cause of asthma [45]. For these reasons, and because inhaled steroids are so effective, these toxic drugs should be given only when there is good evidence of resistance to the action of inhaled corticosteroid.

References
23. McDonald LG, Tovey E. - The role of water temperature and laundry procedures in reducing house dust mite populations and allergen content of bedding. J Allergy Clin Immunol 1992, 90: 599-608.