 Steroid Resistant Asthma

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Abstract
Inspite of very safe and effective treatment, Bronchial asthmatics do not respond well in 5 – 10% of cases which are labelled as Refractory Asthma. Besides compliance, presence of psychogenic and trigger factors and comorbid illness, steroid insensitiveness or resistance may play a significant role in the poorly controlled/ responding asthmatics. Type I Steroid resistance is due to lack of binding affinity of steroids to glucocorticoid receptors and may respond to higher doses of steroids while type II steroid resistance is because of reduced number of cells with glucocorticoid receptors, which is very rare and do not respond to even higher doses of systemic steroids and these cases require alternative/ novel therapies. Future treatment of steroid resistant and severe refractory asthma is likely to be targeted towards cytokines and Bronchial Thermoplasty.

Introduction

Bronchial asthma is the commonest chronic respiratory disorder world wide affecting about 300 million individuals globally, with prevalence of 1 to 18%. 1 An estimated 25.7 million people including 7.1 million children have asthma in united states. 2 A recent study has reported the overall prevalence of asthma is 8.7% among school children aged 12-15 years in India. 3 Thus world wide the economic costs associated with asthma are estimated to exceed those of TB and HIV /AIDS combined.

Airway inflammation and Immune activation are key factors in the aetiopathogenesis of asthma and about 95% patients respond well to β2 agonist and corticosteroids with or without add on therapies like montelukast and long acting theophyllines. However 5-10% of patients do not respond well to this treatment. These cases are labelled as difficult/ therapy resistant asthma. 4

Incorrect diagnosis, non adherence with therapy and various co-morbidities contribute a lot to the poor control of asthma. A study from the Brompton Hospital over 100 patients with difficult asthma revealed alternative or additional diagnosis in 32%, non-adherence with therapy in 50% and Psychiatric Co-morbidity in 11% patients. 5

Although most patients with chronic asthma have significant improvement in their airway function with corticosteroid therapy, a subset of asthmatics are insensitive to corticosteroid. 6 Clinical studies have revealed suboptimal response to ICS in about 50% of asthmatics. 7 Failure to detect corticosteroid insensitivity early in the course of illness may affect the treatment strategy and outcome.

It should be noted that the term steroid resistant (SR) asthma refer to a relative insensitivity to corticosteroid (Corticosteroid dependent asthma) rather than absolute resistance (Corticosteroid resistant asthma) which is very rare and found in less than 1:1000 asthmatics.

Definition

Corticosteroid resistant asthma is defined as less than 15% improvement in baseline FEV1 after 14 days course of oral prednisolone (40 mg/day) in patients who demonstrate more than 15% improvement in FEV1 following the inhaled β2 agonist, Salbutamol. Furthermore the patients who show FEV1 improvement of 30% or more are considered corticosteroid sensitive. 8

Immunopathology

The majority of SR asthma patients have cytokine induced corticosteroid resistance that is likely to be acquired as a result of exposure to environmental factors like allergens, infection, smoking, obesity, stress, Ethnicity, Vitamin D deficiency etc. Laboratory studies have demonstrated that cytokines like Interleukin -2 (IL-2) and

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Interleukin-4 (IL-4) can induce steroid resistance. Neutrophilic inflammation in SR asthmatics have been associated with the increased bacterial colonisation of the airways particularly Chlamydia pneumoniae and H. Influenzae.

**Mechanism and Types of Steroid Resistance**

There are at least two mechanisms responsible for SR. In type 1 SR asthma patients, the gluco-corticoid receptor (GCR) binding affinity is abnormally reduced with an increase in receptor sites per cell while in type 2 SR asthma the GCR binding capacity is normal but there is marked reduction in the number of GCR cells. Further the GCR defect in the TYPE 1 SR is reversible with the deprivation of cytokine like IL-2 and IL-4 while it is irreversible in type 2 SR. Type 1 SR asthma which accounts for the large majority of patients is acquired and restricted to T cells while as type 2 SR asthma is a form of primary cortisol resistance and is not limited to T cells only and is rare (Table1).

**Diagnosis**

When an established patient of asthma is poorly controlled in terms of chronic symptoms, frequent nocturnal or episodic exacerbations, persistent and variable airways obstruction and continued requirement of short acting β2 agonist (SABA) despite being given a total daily dosage in excess of 2000 mcg beclomethasone (800 mcg in children) or equipotent dosage of other ICS in adults is considered to be therapy resistant asthma. These patients may require oral corticosteroid regular or off and on basis to maintain reasonable control of the disease. Rarely such patients may not respond to even higher dose of steroids.

**Table 1 : Showing difference between type 1 and type 2 steroid resistance**

<table>
<thead>
<tr>
<th></th>
<th>Type 1</th>
<th>Type 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basic defect</td>
<td>Decrease GCR binding affinity</td>
<td>Reduced number of GCR cells</td>
</tr>
<tr>
<td>Cells affected</td>
<td>Only T cells</td>
<td>Both T and non T mononuclear cells</td>
</tr>
<tr>
<td>Reversibility of defect</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Cause Improvement with higher dose of steroid</td>
<td>Usually Acquired</td>
<td>Genetic</td>
</tr>
<tr>
<td>Cushingoid side effects with higher dose of steroid</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Morning cortisol levels</td>
<td>Suppressed</td>
<td>Normal</td>
</tr>
</tbody>
</table>

Diagnosis of steroid resistant asthma in these patients can be established by means of follow up for a period of ≥ 6 months during which time asthma management is carried out according to published asthma guidelines and issues such as compliance with treatment, identification of exacerbating factors, exclusion of other diagnosis are dealt with.

The following steps may help in the diagnosis of steroid resistant or insensitive asthma.

1. Patient should have a prebronchodilator morning FEV1 < 70% of predicted with a 15% improvement following a rapidly acting bronchodilator treatment. This value of FEV1 is recorded as baseline.
2. These patients should be given oral steroid (prednisolone 40 mg/day) for at least two weeks.
3. These patients fail to show increase in prebronchodilator morning FEV1 by 15% over baseline value even after 2 weeks of oral steroid.

The steroid resistant asthma should be differentiated from “Brittle asthma”, where patient experience recurrent episode of severe airways narrowing that appear rapidly over minute to hours, occurring any time of the day with no obvious trigger. These patients have either normal lung function between episodes which cannot be prevented by steroid or a persistent background of wide variability in airways obstruction. Such episodes may respond to either subcutaneous adrenaline or terbutaline.

**Management**

The management of autoimmune and inflammatory pulmonary diseases associated with the steroid resistance poses a significant challenge to the clinician. In case of asthma clinical studies have suggested that favourable response to inhaled steroid is associated with high levels of exhaled nitric oxide, high bronchodilator response and sputum eosinophilia. The patient with suspected steroid resistance should be managed in a stepwise manner as mentioned below:

- **Step 1**: Confirm diagnosis of asthma and rule out concomitant medical disorder such as vocal cord dysfunction, gastro-oesophageal reflux, chronic sinusitis, tracheomalacia, allergic bronchopulmonary aspergillosis, tropical pulmonary eosinophilia or Churg–Strauss syndrome etc.
- **Step 2**: Identify and remove potential allergens at home, in school and at work place that might trigger the patient’s disease.
- **Step 3**: Review the patient’s compliance and inhaler technique. Spacer device should be used to optimise medication delivery and reduce adverse effects.
- **Step 4**: Evaluate for psychological factors affecting
adherence and response to therapy. Develop strategies to improve compliance by simplifying medication regimen and implementing a written action plan.

**Step 5**: Evaluate for the potential microbial infection (e.g. Mycoplasma or Chlamydia) which can trigger airway inflammation and steroid insensitivity in chronic asthmatics. These individuals might respond to a prolonged course of antibiotics such as clarithromycin.

**Step 6**: Consider factor that affect life style and steroid responsiveness. Maximise combination (Long acting β2 agonist or Theophylline ) therapy, assessment and correction of vitamin D deficiency, control and treatment of obesity, cessation of smoking etc may improve steroid responsiveness.

The above steps are helpful in type 1 steroid resistant asthma. While patient with type 2 steroid resistant asthma need further workup and alternative approaches for treatment.

**Step 7**: Evaluate systemic corticosteroid pharmacokinetics to determine whether there is incomplete corticosteroid absorption, failure to convert into active form or rapid elimination. Patient with poor absorption usually respond to oral liquid preparations, in case of rapid elimination a split dosing regimen is suggested with the first dose in the morning and the second dose in the afternoon.

**Step 8**: Assess evidence for persistent tissue inflammation despite treatment with high dose steroids such as exhaled Nitric oxide (FeNo), sputum eosinophils, BAL or bronchial biopsy specimens, studies on peripheral blood mononuclear cells (PBMCs) etc.

**Step 9**: The final step is to consider alternative anti-inflammatory and immunomodulator approach such as IV Immunoglobulin, Cyclosporin –A, Methotrexate, Azathioprine, Gold, anti IgE antibodies (Omalizumab) in allergen triggered airways disease. Particularly in type 2 SR asthma Leukotriene modifiers like Montelukast is also a good choice in such cases.

The novel therapies in SR asthma like antagonist to pro-inflammatory cytokines like IL-2, IL-4, IL-5, IL-13, TNF – α and anti inflammatory cytokine IL-10 may find a great role as anti-inflammatory and steroid sparing agent. Further bronchial thermoplasty has also shown significant improvement in asthma control in severe asthmatics. Recently IL-1 targeted therapies in corticosteroid resistant neutrophilic asthma are also being tried.

**Conclusion**

Thus absolute corticosteroid resistance is very rare and therefore poorly responding asthmatic patients should be evaluated and managed in a stepwise manner before switching over to alternative anti-inflammatory therapies. Probably cytokine based approach and Bronchial Thermoplasty will be more useful in patients with SR asthma.

**References**