STEROID RESISTANT ASTHMA

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Individuals with steroid resistant asthma which was first described in 1968 are often the most difficult to manage asthmatic patients in that they have severe disease yet fail to respond to glucocorticoids. To make the diagnosis of steroid resistant asthma, the patient must fail to respond to a 7 to 14 days course of daily prednisolone as measured by less than a 15% improvement in morning prebronchodilator FEV₁ following the glucocorticoids course. Ongoing inflammation is thought to play a major role in the pathogenesis of steroid resistant asthma, and recent studies have demonstrated diminished glucocorticoid receptor to DNA binding as possible mechanisms for diminished glucocorticoids responsiveness. Alternative asthma therapies, such as methotrexate, cyclosporine and intravenous gammaglobulin are often used in this group of asthmatic patient.

Dr. Donal Y. M. Leung of National Jewish Medical & Research Center in Denver, Colorado, says that:

Cytokine – induced increases in glucocorticoid receptor beta expression may account for the steroid insensitivity seen in some asthmatics and could serve as a marker for the early identification of these patients.

If you read the asthma guidelines you get the feeling that everyone should be taking inhaled steroids but atleast 10 – 15% of asthmatics don’t respond to inhaled steroids, and 5% don’t respond to oral steroids.

Others say that “steroid resistance” is simple under treated asthma or possibly a cellular abnormality which could be a consequence of the inflammatory process or could be due to drug induced desensitization or a genetic abnormality in the glucocorticoid receptor. Certain mediators such as interleukin-1 and interferon-Y can alter glucocorticoid response, while the mechanism of action of interferon-Y is unknown, it appears that interferon-1 decreases the density of glucocorticoid receptor.

Steroid resistant patients are divisible into two types. The vast majority, perhaps 90% are Type I, which is characterized by a reversible, decreased biding 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.

Because there is only one human glucocorticoid – receptor gene, the observation that type I patients can develop severe side affects 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 asthma is not associated with the development of steroid-induced side effect and is not limited to T-cells. Type II resistance has the hallmarks of an irreversible innate (primary) defect.

It is suggested 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. Level of cytokine activation is much higher in SR asthma patients compared to those who are steroid sensitive.

There is a 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. This immune activation occurs because of the high level secretion of specific cytokines, such as IL-2 and IL-4 by activated T-cell; the cells that are believed to have central role in the pathogenesis of asthma. A patient lost ability to respond to steroid leads to a vicious circle of unchecked immune activation. It suggests that early intervention with anti-inflammatory therapy–including the identification and elimination of the allergen-trigger factors is critical to successful management of the patient’s asthma.

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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.

Management:
Try and determine the type of asthma.
Patient education about steroid resistance, adjustment of steroid dose, and
Introduction of other immunomodulatory therapies.
Different combination of treatments with troleandomycin & methylprednisolone in several SR patients. This regimen led to normalization of T-cells sensitivity.
Other agents tried are cyclosporine, methotrexate, gold, intravenous gammaglobulin, hydroxychloroquine, dapsone and interferon-Y.

Prognosis:
For SR patient is poor. The best approach is to recognize it early before the patient’s airway becomes so damaged that the asthma is irreversible.

References: