Steroid Resistant Asthma

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Global burden of Asthma

- 300 million people worldwide suffer from asthma, with 250,000 annual deaths.
- More than 100 million will add up by 2025.
- 30 million are suffering from severe asthma accounting for 50% of total asthma related health expenditure.

Asthma and allergies strike 1 out of 4

- Parkinson's: 5.2 million
- Alzheimer's: 24.2 million
- Stroke: 30.7 million
- Coronary Heart Disease: 54 million
- Cancer: 50 million
- Diabetes: 220.5 million
- Asthma & Allergies: 300 million people
Economic burden of Asthma

- The annual economic cost of asthma is ~$100 billion USD.
- Healthcare expenditure for poorly controlled asthma accounts for ~50 billion USD.

Burden of Asthma in Bangladesh: Annual loss ~ 1200 Crore BDT

- **1999**
  - Total affected: 7 Million
  - Children: 4 Million

- **2011**
  - Total affected: 11.1 Million
  - Children: 4.1 Million

Ref: Conclusion of NAPS 1 study 1999 & NAPS 2, 2010
Definition of Asthma

Asthma is a **chronic inflammatory disease** of the airways in which many **cells and cellular elements** play a role. The chronic inflammation is associated with airways **hyperresponsiveness (AHR)** that leads to episodes of wheezing, breathlessness, chest tightness, and coughing, particularly night and in the early morning. These episodes are usually associated with widespread, but variable, airflow obstruction within the lung that is often reversible spontaneously or with treatment.

Ref: Global initiative for Asthma (GINA) 2011 updated definition
First breakthrough in Asthma management

- In 1949 Boardley and colleagues were the first to describe that some asthmatic patients improved rapidly with intramuscular injections of adrenocorticotropic hormone.

- In 1951, oral administration of cortisone was found to be effective in patients with difficult to control asthma.

Scenario change of Asthma management

In 1970s with the advent of inhaled Steroid therapy the scenario of Asthma management changed drastically.
Current management of Asthma

The mainstay of Asthma therapy is broad-spectrum anti-inflammatory agents, in the form of inhaled steroids with or without long acting β2-agonists as preventer medication and use of short acting β2-agonists as reliever medication.

Schwartz and colleagues were the first to report a group of asthmatic patients who were poorly managed by high dose systemic glucocorticoid therapy in 1968.

Steroid Resistance

- It has been observed that 5-10% of Asthmatics do not respond to optimum dosage of inhaled and systemic steroid therapy.

- This resistance is not related to age or severity of the disease.

- These group of patients were referred as steroid resistant Asthmatics.
Steroid Resistant asthma is defined as failure to improve morning prebronchodialator FEV1 >15% from baseline following 2 weeks of oral administration of glucocorticoid at a dose of 20mg b.i.d.

To understand the mechanism of Steriod Resistance

We have to understand

- Cellular action of inflammatory mediators
- The molecular mechanism of Steriod action
Key cellular players of inflammation

- Eosinophil
- Lymphocyte
- Mast cell
- Macrophage
- Dendritic Cell
- Epithelial cell
- Smooth muscle cell

Ref: Current Drug Targets, 2010, 11, 957-970
Cellular action of inflammatory mediators

Inflammatory stimulus

Receptor

Cytoplasm

MAPKs

- p38
- JNK

Nucleus

SRE

NF-kB

AP-1

Increased expression of inflammatory gene
Corticosteroid

Cytoplasm

GR

hsp90

Hsp90 dissociation

Nucleus

AP-1
MAPK
NFκB

Inflammatory gene transcription

A

CBP
(HAT activity)

Inflammatory gene transcription

C

B

Anti-inflammatory Gene Transcription
Eg. MKP-1, IL-10

Glucocorticoid Responsive Element

HDAC

Management of Steriod resistant Asthma
Correct diagnosis of Steroid resistant Asthma.

Patient then should be evaluated by highly skilled asthma specialists for clinical and lab confirmation of steroid resistance.

Management of Steriod resistant Asthma

- Identification of cellular site of Steriod resistance.
  - Lab test of PBMC
  - Bronchoalveolar Lavage Cells

Where Steroid resistance occurs?

**Cytoplasm**
- At receptor level
  - GR
  - Hsp90 dissociation

**Nucleus**
- At pro-inflammatory gene level
  - AP-1
  - MAPK
  - NFκB

- At anti-inflammatory gene level
  - CBP
  - (HAT activity)
  - HDAC

- Inflammatory gene transcription
- Glucocorticoid Responsive Element
- Anti-inflammatory Gene Transcription
  - Eg. MKP-1, IL-10

Where Steroid resistance occurs?
- At receptor level
- At pro-inflammatory gene level
- At anti-inflammatory gene level

Management of Steroid resistant Asthma

- Selection of targeted pharmaco therapy
  - Bypassing corticosteroid insensitivity
  - Overcoming corticosteroid insensitivity
  - Restoring corticosteroid sensitivity

Bypassing corticosteroid insensitivity

- Biological molecules.
  - Omalizumab (acting against IgE)
  - Mepolizumab (acting against IL-5)
  - Etanercept (acting against TNF alpha)
Overcoming corticosteroid insensitivity

- Newer Steriod molecule
  - dissociated corticosteroids
Restoring corticosteroid sensitivity

- Enhanced sensitivity at the level of receptor (low dose methotrexate)
Restoring corticosteroid sensitivity

- Overcoming steroid resistance.

Vitamin D3, p38 MAPK inhibitors

- Anti-inflammatory gene transcription
  - Eg. MKP-1, IL-10

Glucocorticoid Responsive Element
Restoring corticosteroid sensitivity

- Overcoming steroid resistance.

Upregulating HDAC 2 (Nortriptylin, low dose theophylin, non antibiotic macrolide and HDAC 2 activator, sulforaphane.)
Future direction

- Now it is clear that Steroid Resistant asthma is a distinct phenotype
- It requires a different therapeutic approach
- Easy lab test with bio markers for site of steroid resistance should be made available
- PBMC/ Macrophage of affected patients can guide individual site of resistance and targeted therapy
- Large number of pharmacological agents are on Phase-1 trial to be available in near future.
Thank you
Back up slides
Restoring corticosteroid sensitivity

This might be achieved in one of two ways. First, the molecular mechanisms which underlie corticosteroid insensitivity could be reversed. Second, the aetiological factors responsible for corticosteroid insensitivity could be removed.
In addition, incubation of T cells from normal subjects in the presence of IL-2 and IL-4 induces GCR binding defects. In contrast the binding affinity of GCRs in type II SR asthma is not defective and IL-2 and IL-4 do not affect GCR binding capacity of peripheral blood mononuclear cells (PBMCs) from these patients.

In response to these observations, Nair et al., used anti-IL-5 (Mepolizumab) in a small pilot study to suppress IL-5 and eosinophilia. They showed that this treatment led to the improvement of clinical symptoms of SR asthma\(^1\)

However, a larger study with the same antibody by Haldar et al., demonstrated that neutralization of IL-5 and decrease of eosinophilia was not associated with improvement of clinical symptoms and airway responsiveness in these patients\(^2\).


Glucocorticoid Resistance in SR Asthma

Our knowledge of how resistance to glucocorticoid therapy develops has greatly expanded in recent times. It is now recognized that the mechanisms leading to glucocorticoid resistance in SR asthma are heterogeneous and include abnormal expression of GCRs, defective transcriptional activator function and histone acetylation, and epigenetic factors such as microRNAs.

Ref: Current Drug Targets, 2010, 11, 957-970
Management of Steroid resistant Asthma

- Identification of sub group of severe asthma patients who are truly steroid resistant.
- Diagnostic approach.
- Reversal of steroid resistance.
Reversal of SR Asthma

Substantial recent progress has been made in understanding the activity of glucocorticoids and the molecular mechanisms that underpin the pathogenesis of SR asthma. The mechanisms of action of glucocorticoids are multifactorial and numerous mediators may potentially contribute to the development of SR asthma.

Ref: Current Drug Targets, 2010, 11, 957-970
Therapeutic Drugs or Targets

Cyclosporine A

Model of Action
Inhibits calcineurin and inactivates NF-AT Prevents IL-2 expression and reduces T cell function

Possible Side Effect
Increased opportunistic infections Kidney or liver dysfunction Peptic ulcers, pancreatitis or pruritus
Therapeutic Drugs or Targets

Rapamycin

Model of Action

Inhibits mTOR pathway Prevents IL-2 response and anti-proliferative Blocks T- and B- cell activation

Possible Side Effect

Increased opportunistic infections Increased risk of lymphoma or skin cancer Kidney dysfunction
Therapeutic Drugs or Targets

Mycophenolate

Model of Action
Inactivates IMPDH pathway Induces apoptosis of activated T cells Suppresses T- and B- cells functions

Possible Side Effect
Increased opportunistic infections Increased risk of thrombophlebitis and thrombosis Associated with miscarriage, esophagitis and gastritis
Therapeutic Drugs or Targets

Basiliximab

Model of Action

Neutralizes IL-2 and prevents T cell replication
Suppresses T- and B- cell functions

Possible Side Effect

Increased opportunistic infections Hypersensitivity, allergic and gastrointestinal reactions
Therapeutic Drugs or Targets

p38 MAPK inhibitors
(e.g. SB203580)

Model of Action
Predominantly inhibits p38 MAPK Suppresses MAPKAP kinase 2

Possible Side Effect
Drug toxicity Impact on fetal or neonatal development
Therapeutic Drugs or Targets

PI3K inhibitors
(e.g. wortmannin and PX-886)

Model of Action
Inhibits PI3K pathways

Possible Side Effect
Antagonism of cell survival pathways
Dysregulation of host defence system
Drug toxicity
Therapeutic Drugs or Targets

Vitamin D3

Model of Action
Enhances IL-10 production by T cells Promotes T regulatory responses

Possible Side Effect
Vitamin D poisoning by excess usage including hypercalcemia, hypertension, anorexia, dehydration, vomiting, constipation and fatigue
Therapeutic Drugs or Targets

P-glycoprotein 170

Model of Action
ATP-binding transporter Transports glucocorticoids out of cells

Possible Side Effect
Not known but targeting this protein may cause malfunction of cell-membrane transportation
Macrophage Migration Inhibitory Factor (MIF)

Model of Action
Modulates macrophage function Counter-regulates anti-inflammatory effects of glucocorticoids

Possible Side Effect
Not known but may interfere with host immune responses
Corticosteroid insensitivity in severe asthma

Corticosteroid Dose

Clinical Response

No Asthma

Non-severe asthma ‘steroid-sensitive

Severe asthma ‘steroid-insensitive

Therapeutic approaches to
corticosteroid insensitivity
Gene Repression

Histone Acetylation
HATs CBP, P300, TAF_{II} 250

Histone Deacetylation
HDACs 1-14

Gene Transcription

Inflammatory Gene Transcription