
بسم الله الرحمن الرحيم

Phenotype Guided Asthma Therapy

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Heterogeneity Of Asthma

- Asthma is a heterogeneous disease, and different asthma patient groups probably have different underlying pathophysiology.
- Severity of the asthma syndrome and the impairment in the individual patient can substantially vary between different patients.

Endotyping

- Asthma is a complex disease with multiple phenotypes representing several heterogeneous underlying immunologic endotypes.
- Identified 4 phenotypic clusters, 3 of which were atopic with differentiation based on their level of lung function.
- In asthma phenotyping sex gender and race also are important.

Endotyping.

- The variability in response to non targeted therapy, such as corticosteroids, further supports this theory that there are various pathobiological pathways involved in asthma.

- Defining patients based on the underlying pathophysiologic mechanism of the disease. This approach has been named endotyping.

Endotyping.

- The main purpose of these classifications is to identify patients groups, which differ in terms of natural course of the disease or which will respond differently to specific therapy.
- Several different phenotypes and endotypes have been described :
- Early onset allergic asthma
- Late onset eosinophilic asthma
- Exercised induced, obesity related
- Non-eosinophilic asthma

Endotyping.

- Identification of biomarkers: increasing value to identify patients, which would respond to novel targeted therapies.
- For Th2-mediated asthma, three biomarkers have been described: number of sputum/blood eosinophils, FeNO fractional exhaled nitric oxide and periostin .

Endotyping.

- Patients with inadequately controlled asthma despite treatment with medium-to high-dose ICSs were classified based on:
- periostin level and TH2 signature, as defined by an IgE level of greater than 100 IU/mL and a peripheral eosinophil count of greater than 0.14 × 109 cells/L.

Periostin

- Periostin is a product of bone turnover, which would suggest higher baseline levels in growing children compared with adults, thereby limiting its use.
- periostin levels are 2- to 3-fold higher in children than in adults, those patients with asthma by 6 years of age had significantly higher periostin levels than children who did not have asthma by that age.

Early onset allergic asthma

- T helper 2 (Th2) cells play a pivotal role in allergen-induced inflammation in such patients.
- <12 years -atopic constitution – allergen induced asthma.
- Higher degree of bronchial hyperresponsiveness,
- Higher serum IgE levels
- Increased numbers of eosinophils in blood or sputum.

Late onset eosinophilic asthma

- >12 years .
- Increased numbers of eosinophils in their sputum and blood
- Sometimes not allergic
- Do not have an atopic constitution

Late onset eosinophilic asthma

- Need for high-dose ICS
- Often requirement of OCS because of corticosteroid refractory symptoms
- Associated with sinus disease, nasal polyps, and higher urine leukotrienes
- Aspirin-sensitive asthma.

Late onset eosinophilic asthma

- At least two-third of patients with severe asthma
- Severe asthmatics are mostly female and have an atopic constitution
- Eosinophilic inflammation is observed more in severe asthma than in the general population of asthmatics.

Non-allergic asthma

- Air pollutants
- contact with certain microbes and glycolipids
- Contact with these stimuli causes activation of epithelial cells which results in increased numbers of neutrophils in the sputum and in production of different cytokines such as IL-25, IL-33 and thymic stromal lymphopoietin (TSLP).

Other asthma phenotypes

- obesity related asthma
  important role of mechanical limitations due to obesity.
- Asthma-COPD overlap syndrome (ACOS).

Severe asthma

- The definition of severe or therapy-resistant: patients who remain uncontrolled despite maximum inhaled therapy (high-dose ICS and LABA).

Asthma Medication

- Three twice-daily ICS/LABA combinations are currently FDA approved for the treatment of asthma, budesonide/formoterol, and mometasone/formoterol, with only fluticasone propionate/salmeterol approved for patients as young as 4 years old and the other 2 approved for patients as young as 12 years.

Asthma Medication

- Vilanterol is a LABA with 24-hour activity developed as a once-daily treatment in combination with a novel ICS, fluticasone furoate, approved by the FDA for the treatment of chronic obstructive pulmonary disease (COPD) in 2013 and for asthma in patients 18 years and older in 2015.

Anti Cholinergic Drugs

- Patients with acute asthma exacerbations due to cholinergic activation, in viral infections, air pollution exposure, and allergy, may benefit from anticholinergic treatment.

Anti Cholinergic Drugs

- The addition of tiotropium is advised in the current update of the GINA guidelines at steps 4 and 5 on top of inhaled ICS and LABA. Recent studies have shown that tiotropium is also effective as a bronchodilator in patients with non-severe asthma.

Anti Cholinergic Drugs

- Tiotropium was superior both to a doubling dose of ICS and to the addition of salmeterol for pre bronchodilator and post bronchodilator FEV1 improvement.

Anti Cholinergic Drugs

- The addition of tiotropium to ICS/LABA treatment reduced the risk of a severe exacerbation by 21%.

Anti Cholinergic Drugs

- Tiotropium once-daily add-on to medium-dose ICS reduces airflow obstruction and improves asthma control comparable to a LABA .
- Tiotropium so far has not been approved as first-line treatment in this patient group.

CROMOLIN

- Additionally, cromolyn plays a role in management of exercise-induced asthma.
- It appears to affect one of the specific postulated causes of exercise induced asthma, namely heat and water loss at the airway mucosa.

Macrolides

- Macrolide antibiotics :not anti-microbial but also immunomodulatory and anti-inflammatory effects.
- Clarithromycin resulted in a decrease of IL-8 levels and a decrease of neutrophil accumulation in the airway lumen, suggesting a primary effect on neutrophlic airway inflammation .
- Macrolides :potential treatment for patients with non-eosinophilic asthma.

Macrolides

- Macrolid improved airway hyperresponsiveness .
- These results were independent of the patient's airway colonisation status with Mycoplasma pneumoniae or Chlamydia pneumoniae.

Macrolides

- However, a predefined subgroup analysis of patient without signs of eosinophilic inflammation (low FeNO and < 200 eosinophils/µl blood) revealed a reduction of exacerbations in the group treated with macrolide antibiotic .

Novel targeted therapies

- Novel targeted therapies, which inhibit certain immunological pathways, have been developed but these novel treatments are not effective in all patients with severe asthma, but only certain phenotypes.

Novel targeted therapies

- This includes monoclonal antibodies against IgE, against interleukin (IL)-5 and antibodies targeting IL-13 pathways.

Anti –IgE

- Omalizumab
- Decreases free IgE levels
- inhibits binding of IgE with its high- and low-affinity receptors (FcεRI and CD23)
- Down regulates these receptors on mast cells basophils, and circulating dendritic cells
- Start if IgE more than 30 IU and eosinophil more than300 in mm.

Anti-IgE

- Omalizumab:
- additional controller medication in steps 5 and 6 of the EPR3 guidelines for patients ≥ 12 years whose disease is not adequately controlled with ICSs alone.
- Omalizumab in adolescents and adults decreases rates of asthma exacerbations (seasonal variability of exacerbations in the fall and spring).

Anti-IgE

- patients with signs of Th2-inflammation (such as high eosinophils in blood, high FeNO and increased periostin in serum) show a higher clinical effectiveness and reduction in exacerbations compared to patients which lack signs of Th2-driven inflammation .

pediatric patients with severe asthma

- Bronchoalveolar lavage of pediatric patients with severe therapy-resistant asthma has shown increased eosinophil counts compared with those in control subjects but no increase in IL-4, IL-5, or IL-13 levels.
- This suggests that the new immunomodulators directed toward these TH2 cytokines might not be effective in pediatric patients with severe asthma.

Anti-IL-5

- Mepolizumab
- A humanized mAb directed against IL-5
- IL-5 induces the maturation, activation, and recruitment of eosinophils.
- Bind to IL-5, inactivate the cytokine
- Promote programmed cell death of eosinophils
- Leading to a disappearance of eosinophils from systemic circulation and organ tissue.

Anti-IL-5

- These could range from numbers of eosinophils in blood ≥ 400/µl or using sputum eosinophil count of ≥ 3% .
- There is increasing evidence that the efficacy of anti- IL-5 increases in the population of patients with higher baseline eosinophil counts and higher number of exacerbations.

Anti-IL5

- Reductions in the rate of clinically significant exacerbations with mepolizumab
- correlated with baseline patient blood eosinophil counts and numbers of exacerbations in the year
- but not atopic status, IgE concentrations, FEV1, or bronchodilator response.

Anti-IL-4/13 and anti-IL-4 receptor

- IL-13, which is a central mediator for development of airway hyperresponsiveness and mucus production .
- IL-13 directly acts on epithelial cells and induces the expression of
- 1- mucin genes
- 2-periostin
- 3-serpin B2
- 4-calcium-activated chloride channel protein1

Anti-IL-4/13

- Inhibition of IL-4/13 in patients with a Th2-inflammatory profile is encouraging and results in:
- Less exacerbations
- Improved lung function
- Improved symptoms

Anti-IL-4/13

- Significant reduction in FeNO and serum IgE were observed in the anti- IL-4Ra-treated group.
- Dupilumab added to combination therapy demonstrated an improvement in lung function, a reduction in severe asthma exacerbations and a decrease in FeNO levels .

Anti-IL-4/13

- Dupilumab, a human monoclonal antibody to the IL-4 receptor:
- Decrease asthma exacerbations
- Improve lung function
- Decrease Th2-related inflammatory markers in moderate-to-severe asthmatic patients with elevated eosinophil levels.

Anti-IL-4/13

- The anti- IL-13 antibody lebrikizumab has been tested in patients with asthma patients who were uncontrolled with ICS.
- Increase in lung function especially in patients with showed increased levels of periostin in serum at baseline .
- In contrast, patients with low levels of periostin showed no significant increase in lung function following anti-IL-13 administration.

Anti-TSLP

- Epithelial cells have been play important part in inducing and mediating immune responses also in the lung.
- In patients with asthma airway epithelial cells can be activated by exposure to allergens, viruses, or environmental pollutants.
- Results in the production of TSLP (thymic stromal lymphopoietin) IL-25, and IL-33 by these epithelial cells

Anti-TSLP

- TSLP is an interesting target to reduce inflammation.
- Treatment with anti-TSLP result in a reduced late-phase response and airway inflammation in patients with allergic asthma after an allergen challenge .

Conclusion

- These antibodies bind specific cytokines or cytokine receptors and inhibit specific pathobiological pathways.
- This makes it necessary to better understand the underlying pathophysiological pathway in individual patients, to choose an adequate treatment.