T2-low Asthma

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Abstract

T2-low asthma represents between 30-40% of severe asthma patients. It is less well defined compared to the allergic and eosinophilic asthma (T2-high asthma). There are no specific biomarkers for T2-low asthma but is often connected with the smoking, air pollution and obesity. Most of the patients have late onset asthma with more symptoms that are induced by exercise and cold exposure with frequent infective exacerbations and bronchiectasis. The responce to inhaled steroid treatment is poor, so the available therapeutic options and the targeted therapies effective in both T2-high and T2-low asthma like new anti-TSLP monoclonal antibody tezepelumab are discussed. Ongoing trials with sophisticated transcriptomic and proteomic characterisations of different T2-low asthma patients should provide us tools to better characterise these patients and choose the precise therapeutic approaches.

Keywords: T2-low asthma, neutrophylic asthma, paucigranulocytic asthma

Introduction

Non-eosinophilic (T2-low) severe asthma is somewhat an „orphan" entity in the severe asthma spectrum[1]. Severe asthma is a heterogeneous disease involving diverse pathobiological mechanisms (endotypes) with different clinical presentations (phenotypes). While the allergic asthma and non-allergic eosinophilic asthma (T2-high asthma) are better defined and their pathobiology is better described with increasing number of specific treatment options, non-eosinophillic (T2-low asthma) is less defined, different mechanisms are involved in its pathobiology. The pathways are likely different in individual patients, vary over time and circumstances, and are more complex than a simple division into arbitrary groups: T (Type) 2 and non-T2 inflammation. More likely, the end product of airway inflammation will be a mixture of both pathways with either T2 or the non-T2 being dominant, and possibly reflecting a therapeutic target for greater disease control[2].

Clinical Characteristics

T2-low asthma represents between 30-40% of severe asthma patients. Persistently non-eosinophilic asthma prevalence has been reported up to 47% but most patients (>90%) considered to have neutrophilic bronchitis may have a re-emergence of sputum eosinophils when their steroid doses are tapered for long enough[3].

T2-low asthma is more frequent in the late-onset asthma patients, obese females and high symptomatic patients and has a poor responce to inhaled steroid treatment. Neutrophilic inflammation is frequently associated

https://doi.org/10.26493/978-961-293-157-5.105-113

with smoking, air pollution, obesity, very late onset (>50 or > 65 years of age), exercise and cold induced asthma, infective asthma exacerbations and bronchiectasis[1,4].

Pathophysiology

Non-type 2 inflammation (T2-low) mediated asthma is difficult to define due to lack of signature biomarkers. It exists in the absence of T2-high or eosinophilic inflammation and includes neutrophilic and paucigranulocytic subtypes. Several cell types and cytokines, including Th1, Th17, IL-6, and IL-17, contribute to mechanisms of non-T2 asthma[5].

In response to industrial pollutants, infectious agents, tobacco smoke, and other nonspecific stimuli, injured airway epithelial cells release a multitude of factors that initiate innate and adaptive immunity with subsequent release of toll-like receptors (TLRs). TLR2 and TLR4 are innate immune receptors that are inducing the shift toward Th1 and Th17 response so the dominant T cells in T2-low asthma are Th1 and Th17 that generate pro-inflammatory cytokines as IL-8, IFN-γ, IL-6, IL-17A/F, TNF-α and IL-1ß. T helper 17 (Th17) cell-derived cytokines and immune factors mediate neutrophilic influx to the airways. Th17-secreted interleukin-17A (IL-17A) is an independent risk factor for severe asthma that impacts airway smooth muscle (ASM) remodeling. Transforming growth factor-β1 (TGF-β1) correlates with enhanced Th17 activity and is essential to Th17 differentiation and IL-17A production. Vice versa, IL-17A enhance activation of TGF-β1 signaling pathways augmenting the immune response[6].

The application of cluster analysis in asthma has gained increasing attention as a departure from traditional hypothesis-based approaches to phenotyping asthma. This analysis is accomplished through "omics" methods, which refers to a large dataset derived from a single sample to gain insight into previously unrecognized molecular host-environment interactions and mechanisms of disease (RNA Transcriptomics - study of gene expression and metabolomics - measurement of mediators or metabolic products). Minimally invasive analytic tools have been reported for asthma, using blood, sputum, or bronchial brushings[1]. The omics approach has been helpful in understanding the molecular mechanisms of T2-low asthma. The potential chemosensory and remodeling signatures recently described in asthmatic airways may point to new endotypes relevant in T2-low patients[7-9].

Beside the inflammation, some structural abnormalities of the airway smooth muscles and heightened neuronal dysfunction can lead to the increased cough reflex sensitivity connected with the poor asthma control[10].

There is a negative correlation between airway cytotoxic T cells (CD8+) and body mass index in severe asthma patients. Desreased expression of CD8+ cytotoxic T cell network in individuals with T2-low asthma[11] is strongly related to obesity and systemic inflammation. A primary function of CD8+ T cells is host defense against viral infection and an impaired immune response to viral infections could be a mechanism of exacerbations in T2-low asthma.

Airway mucus hypersecretion is associated with greater asthma severity, reduced lung function, increased number of exacerbation and is a predictor of a poorer response to anti-inflammatory treatment with glucocorticoids. Mutations or polymorphisms in the cystic fibrosis transmembrane conductance regulator (CFTR) gene were detected in hypersecreting patients with neutrophilic asthma, bronchiectasis, pansinusitis and recurrent respiratory infections[12].

Depending on the cellularity, T2-low asthma can be further classified into neutrophilic and paucigranulocytic but there are no strict borders between those groups.

Neutrophylic Asthma

Key cytokine involved in T2-low asthma, IL-17, promotes neutrophil migration by inducing IL-6 and IL-8 release from bronchial epithelial cells. IL-8 (CXCL8) is the most potent chemoattractant in the lung that correlates with both increased neutrophil percentage and absolute neutrophil counts. Moreover, neutrophils have also been demonstrated to secrete IL-8 creating a positive feedback loop that promotes further neutrophilic inflammation.

Receptor for advanced glycation endproducts (RAGE) is a pattern-recognition receptor that interacts with various endogenous ligands involved in host response to injury, infection, and inflammation. Asthmatics with neutrophilic inflammation have a deficiency in soluble form of RAGE (sRAGE). sRAGE serves as a decoy receptor by sequestering RAGE ligands and thus inhibiting RAGE dependent cellular responses. It is not known whether that deficiency is causative factor or the result of neutrophilic inflammation[13].

It is wrong to consider neutrophils as only negative cells in asthma. Activated neutrophils can eliminate pathogens by phagocytosis, degranulation or formation of neutrophil extracellular traps (NETs). Because of their role in mediating persistent inflammation and causing airway damage, they have been thought of as primitive killers. However, they can have immunomodulatory effects and play a role in tissue repair and healing through production of anti-inflammatory cytokines like IL-1RA, IL-10, TGFß1 and TGFß2. High extracellular DNA concentrations in sputum mark a subset of patients with more severe asthma who have NETs and markers of inflammasome activation in their airways[14,15].

The particular effect of the neutrophils is dependent on location of the cells, comorbidities and surrounding inflammatory milieu and nowadays we can recognise multiple neutrophil phenotypes with distinct morphological and functional characteristics. They can either activate a pro-inflammatory cascade or differentiate into immunomodulatory role. This knowledge is crucial in programming the treatment strategies because the treatment not adapted to the specific underlying pathobiology may lead to undue adverse effects[16].

Impact of Corticosteroids on Sputum Neutrophilia

Th1 cell activation leads to production of IFN-γ which in combination with the low secretory leukocyte protease inhibitor (SLPI) expression leads to high airway resistance and corticosteroid refractoriness. Use of corticosteroids (ICS and OCS) has been even shown to contribute to sputum neutrophilia[17] because the corticosteroids, while they promote apoptosis of eosinophils, have been demonstrated to inhibit neutrophil apoptosis. Sputum neutrophil count was higher in patients receiving moderate-to-high dose ICS than those receiving low-dose ICS.

Paucigranulocytic Asthma

Paucigranulocytic asthma encompasses patients with absence of airway inflammation (eosinophilia and neutrophilia) with persistent symptoms and evidence of AHR[5]. Activation of Type 1 ILCs with excessive IFN-γ production leads to reduced numbers of eosinophils and neutrophils resulting in paucigranulocytic inflammation. Mechanisms of this endotype can be changes in ASM or inflammation not reflected in the bronchial lumen.

Numerous stimuli, including inflammatory cytokines, pollutants, altered airway microbiome and mechanical strains, can predispose ASM to become nonspecifically hyper-responsive.

AHR independent of inflammation can be caused by the altered neuronal control of ASM contractility. Nerve growth factor (NGF) can induce AHR, activate inflammatory cells and cause airway remodeling. Neuroimmune cross-link dysregulation of critical

signaling molecules, including G protein-coupled receptors, transmembrane proteins, and growth transcriptional factors, can be possible mechanisms promoting AHR independent of airway inflammation.

Secretion of mast cell mediators could lead to bronchial obstruction, airway remodeling and AHR so the mast cell infiltration in ASM can play a role in the pathogenesis of this asthma phenotype.

Some patients may show both Th17 and Th2 mediated inflammation and mixed granulocytic inflammation might be a transition between neutrophilic and eosinophilic phenotypes.

Management of T2-low Asthma

No specific therapies have shown any clinical benefits in patients with asthma that is associated with a non-T2 inflammatory process. It remains to be seen if such an endotype truly exists and to identify treatments to target that endotype. There is a high unmet need in the endotype-driven approach for the T2-low asthma[1].

Meanwhile, identifying intense airway neutrophilia as an indicator of airway infection and airway hyperresponsiveness as an indicator of smooth muscle dysfunction, and treating them appropriately, and not increasing glucocorticosteroids in patients who do not have obvious T2 inflammation, seem reasonable[3].

First, we should confirm the T2-low nature of asthma with documented AHR and the absence of T2 inflammation (normal blood or sputum eosinophils, serum IgE or FeNO) or high sputum neutrophil. This is important because most of such patients (with the exception of mast-cell mediated disease) may not benefit from increasing the dosage of maintenance ICS.

Neutrophilic bronchitis can mask the underlying eosinophillic component so it is important to recheck the cell counts after the blood neutrophilia has resolved. In unresolved cases, investigations of transcriptome and proteome in sputum may lead to the better differentiation of T2 high and T2 low asthma.

Non-pharmacological Treatment

Active or passive smoking can induce neutrophilic inflammation, so the first measure in those patients is to promote smoking cessation.

Low-fat diet should be tried especially in obese patients. The high-calorie and high-fat meal can increase the neutrophil recruitment in the airways. Because of that, in obese patients weight reduction program with weight loss can lead to significant improvement in asthma control and forced vital capacity, reduction in symptom days, rescue-medication use and emergency room visits[18].

Bariatric surgery can be considered in morbid obese patients If there is no effect of weight reduction programs.

Bronchial thermoplasty (BT) can improve asthma control, peak expiratory flow, quality of life, symptom-free days and decrease the rescue medication use, severe exacerbations, emergency department visits and days missed from work/school. BT should be reserved for uncontrolled asthmatics with persistent symptoms, frequent exacerbations and severe AHR[19]. One limitation of bronchial thermoplasty is the difficulty of predicting clinical responders, so the discussion with experts about the feasibility and necessity of bronchial thermoplasty is adviced[20].

Mucus clearance procedures: In the patients with mucus hypersecretion, smoking cessation, physiotherapy in different body positions with high-frequency chest wall oscillation and eduaction about deep breathing with effective coughing can improve mucus clearance and alleviate the symptoms. In addition, intermittent positive end-expiratory pressure (PEEP) can dilate the small airway, reduce small airway obstruction, promote the sputum drainage and accelerate

mucus clearance. Inhalation therapies should be prefferentialy administered via humidified inhalation or aerosol inhalation in order to moisturize the airway, dilute sputum and facilitate expectoration[21].

Pharmacological Treatment

ICS could be discontinued or reduced in two thirds of non-eosinophilic asthma patients with no worsening of asthma control or exacerbation. Sometimes that reduction can reveal an eosinophilic inflammation and lead to the change in patient classification and treatment[22].

Tezepelumab is an anti-TSLP monoclonal antibody that binds human TSLP, prevents interaction with its receptor and, consequently, inhibits multiple downstream inflammatory pathways. Blocking of this pathways can improwe the severe asthma control in both T2 and non-T2 asthma[23].

Long acting bronchodilators (LAMA and LABA) can be effective in increasing the time to first exacerbation and improving lung function and symptoms[24].

Antibiotic treatment can be effective in patients with recurrent infective exacerbations. Molecular microbiology and mycology with extended cultures, including 16s deep sequencing, may be considered to direct the treatment.

Immunoglobulin replacement may improve asthma control in patients with infective exacerbations and immunoglobulin deficiency[25].

Azithromycin in long-term non-antibiotic doses of (250 mg daily three times per week) can result in decrease of severe asthma exacerbations frequency, improvement of the quality of life and reduced frequency of respiratory infections with no significant adverse events[26].

Selective antagonists of cysteinyl leukotrienes receptors in vitro can inhibit superoxide generation, production of LTB4 and release of elastase by activated neutrophils[27,28].

Theophylline in vitro promotes apoptosis of neutrophils, inhibits neutrophils from generating reactive oxygen species and causes a decline in neutrophil chemotaxis[29].

Roflumilast, a phosphodiesterase-4 inhibitor, can cause the reduction of neutrophil counts and TNF-α levels and can improve FEV1 in mild to moderate asthmatics when added to ICS[30].

Antifungal treatment should be considered in the patients with the persistent presence of Aspergillus in the respiratory tract[31,32].

Immunoglobulin replacement therapy: Patients with severe asthma and recurrent respiratory infections should be screened and (if appropriate) treated for immunoglobulin deficiency since that can improve asthma outcomes[33].

A proposal of algorithm to T2 low asthma approach is shown in the Figure 1.

Investigational Products

Because of an unmet need for new therapeutic agents in T2-low asthma, there are plenty of investigational products in development for that indication[3,34].

CXCR2 antagonists in preliminary studies showed significantly reduced sputum and blood neutrophilia in patients with severe neutrophilic asthma and decreased number of mild exacerbations.

Etanercept blocks TNF and in a small study demonstrated improvement in AHR, FEV1, and symptoms. Other investigated anti-TNF-α compounds showed unacceptable toxicity, mainly increased risk of infections.

Antibody against IL-17 receptor did not result in any statistically significant benefit uptill now.

Anakinra (IL-1 receptor antagonist) in healthy volunteers significantly reduced sputum neutrophilia and caused the rise of sputum IL-1β, IL-6, and IL-8 levels.

*Anti-IL6 b*locking might be a potential therapeutic target in T2-low asthma, but

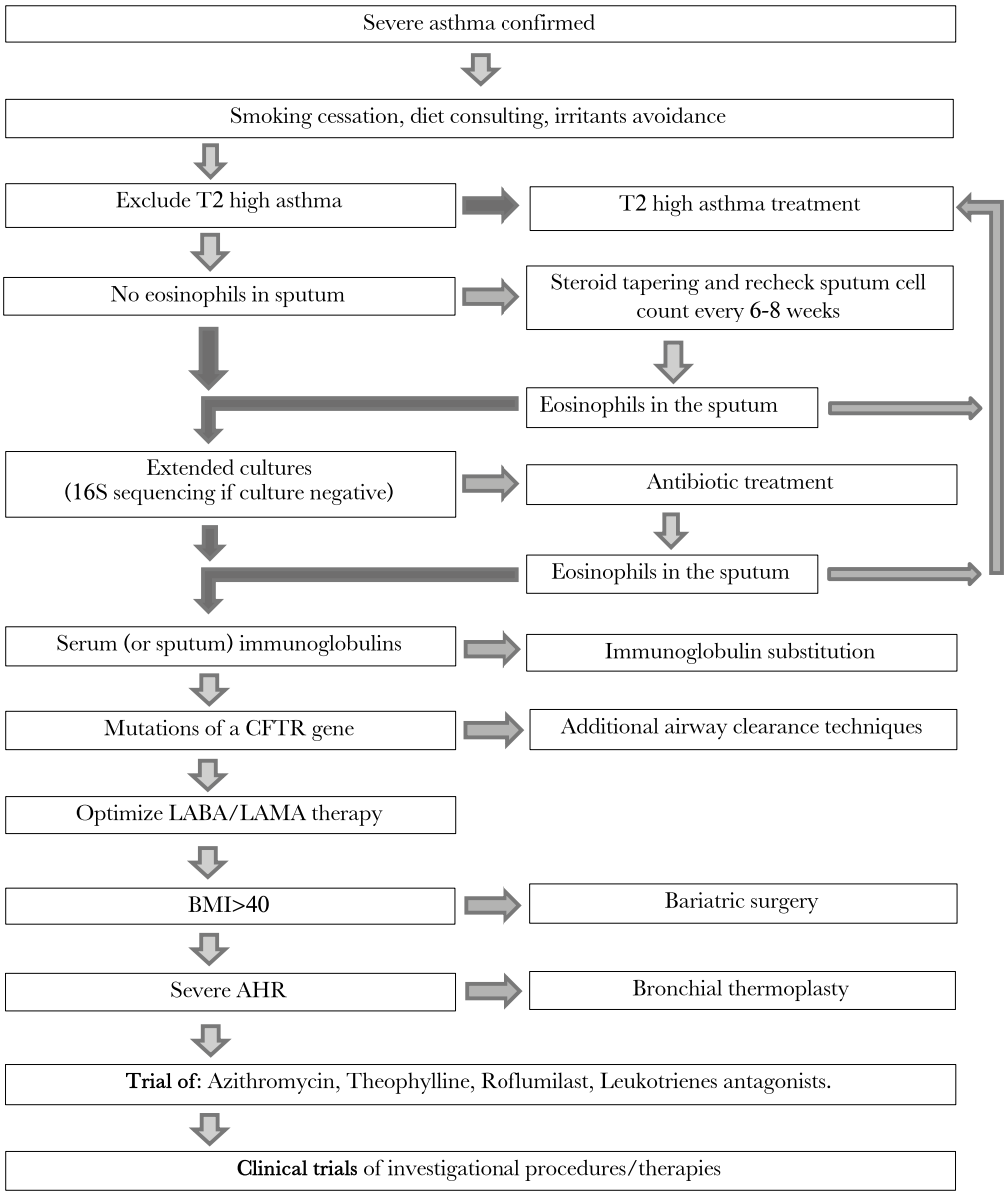

Figure 1. A proposal of algorithm to T2low asthma approach.
16S sequencing: 16S rRNA gene (DNA sequence corresponding to rRNA encoding bacteria, which exists in the genome of all bacteria)
CFTR gene: gene for a Cystic Fibrosis Transmembrane conductance Regulator protein
LABA: Long-Acting Beta Agonists
LAMA: Long-Acting Muscarinic Antagonists
BMI: Body Mass Index
AHR: Airway Hyperresponsiveness

there is no clinical trial data available for intervention in asthma.

Nebulized IFN-β treatment at the onset of viral upper respiratory tract infections shown to improve morning peak flow, increase in serum CXCR10 and reduced sputum CCL4 concentrations which suggested this treatment might improve outcomes of URTI induced asthma exacerbations.

Imatinib inhibits tyrosine kinase of KIT, induces mast cell apoptosis and reduces bone marrow mast cell burden. It can reduce airway mast cell burden and improve AHR in severe asthma.

5-lipoxygenase-activating protein (FLAP) inhibitors can reduce the sputum LTB4 levels but there are no significant effects on sputum neutrophil counts.

Modification of airway dysbiosis: Several novel approaches beyond antibiotics that may modify dysbiosis, including phage therapies, prebiotic nutrients, microbe-derived products (bacterial extracts, immune stimulants), and specific live microbial species (probiotics) may represent novel therapeutic avenues[35].

Targeting Mucus Hypersecretion: Quantitative imaging has been applied using computed tomography to develop validated mucus plugging scores in severe asthma. Novel inhaled and oral mucolytics and biologics that target IL-13–driven goblet cell metaplasia could help solve that problem.

Treating Comorbidities

A number of comorbid diseases, including rhinitis, rhinosinusitis, gastroesophageal reflux, and obstructive sleep apnea, are associated with severe or difficult-to-treat T2-low asthma. If present and untreated, these conditions may adversely affect asthma control, quality of life, and/or lung function, despite adequate treatment with step-up asthma controller therapy. Failure to recognize these comorbidities may divert appropriate care and increase disease burden. Assessment and management of these risk factors may contribute to improved asthma outcome[36].

Conclusion

Lately, the heterogeneity of asthma phenotypes is recognised and the treatment options are tailored according to those differences. T2-low asthma is still less well defined with different subtypes characterized by the low expression of T2 inflammatory markers and normal to low eosinophils.

Several treatment options for T2-high asthma have been developed and some of those treatments like new anti-TSLP monoclonal antibody tezepelumab are effective also in T2-low asthma. The results of ongoing trials with sophisticated transcriptomic and proteomic characterisations of different T2-low asthma patients will provide us tools to better characterise these patients and choose the precise therapeutic approaches.

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