Targeting Endophenotypes In Asthma – Personalized Treatment Strategy Driving Drug Development

Asthma, a major chronic inflammatory disease of the airways, affects over 235 M people globally. Despite optimization of standard therapies including inhaled corticosteroids and long-acting bronchodilators, ~3-10% of patients have severe asthma while ~17% have difficult-to-treat disease.

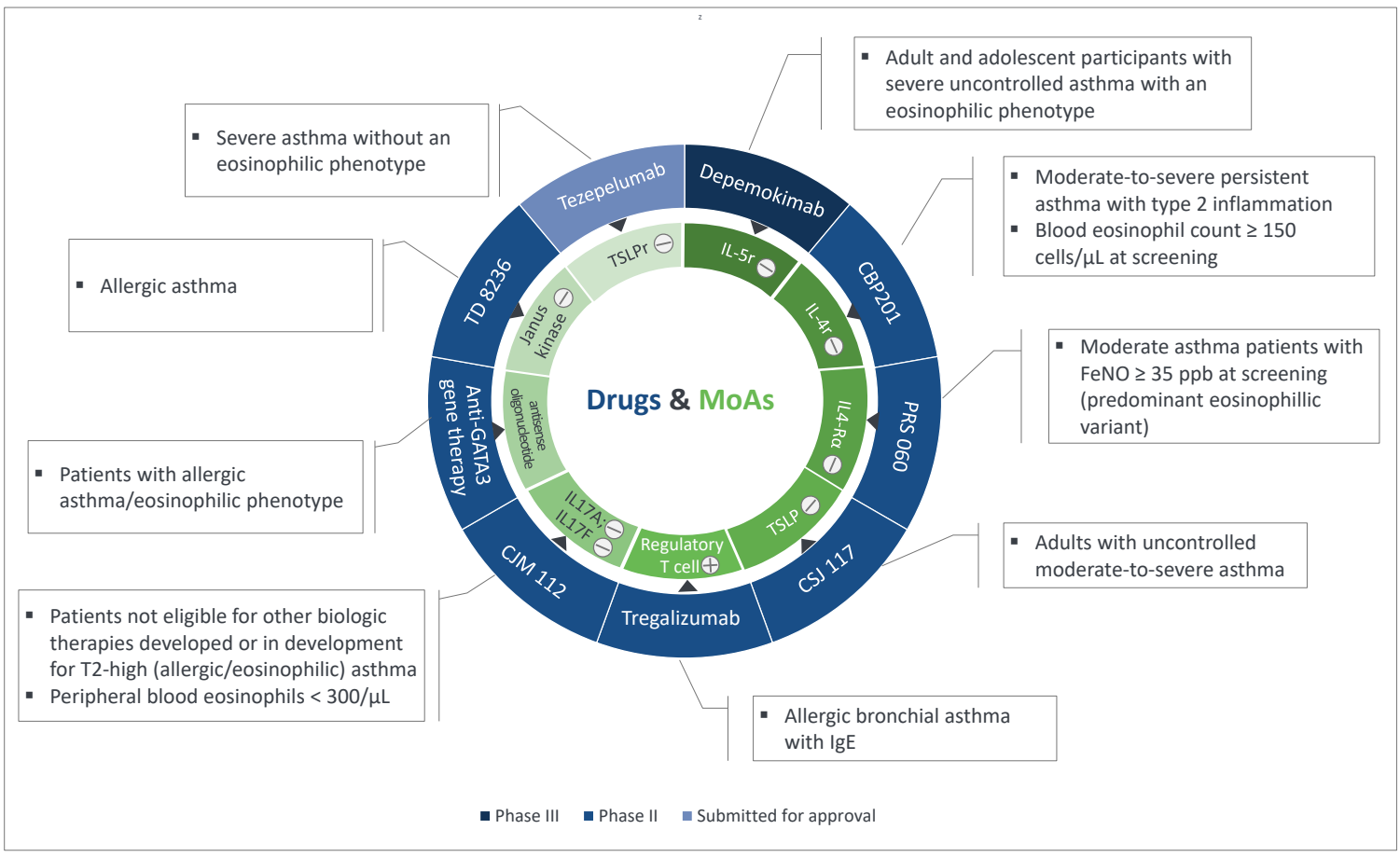
In 2020, the European Academy of Allergy and Clinical Immunology published guidelines on the treatment of severe asthma using biologics. The selection of a biologic is driven by the availability of biomarkers (peripheral blood eosinophil count, fractional exhaled nitric oxide [FeNO], and total and allergen specific IgE), parameters of age, comorbidity, and medical infrastructure required for drug administration. However, there are a high number of suboptimal responders, especially if airway eosinophilia and/or T2 airway inflammation persist. Non-adherence to either the biologic or the background controller therapy could also induce suboptimal response.

Despite the failure of some biologics in advanced clinical development, there are other biologics targeting novel mechanisms including tezepelumab that targets the novel thymic stromal lymphopoietin (TSLP), bi-specific antibodies in early development targeting IL-4Ra/IL-5, or anti-IL-13/IL-17 antibody, a potential treatment option for patients with combined eosinophilic and neutrophilic inflammation (mixed granulocytic asthma) or in patients with counter-regulated non-type 2 inflammation after targeted treatment of type 2 inflammation (Phase I).

Other pathways are also being targeted such as inhibition of transcription factors by catalytically active antisense oligonucleotides targeting GATA-3, a key transcription factor in the type 2 inflammatory pathway. Similarly, small molecules selectively inhibiting eosinophil maturation leading to clinical improvement as measured by improvement of pre-bronchodilator FEV1 are in development (dexpramipexole, Phase II).

The next generation of biologics targeting upstream cytokines may be very promising as they interfere early in the type 2 inflammatory cascade. To address the remaining unmet need, the treatment of asthma is moving toward a personalized treatment strategy based on patient-specific characteristics and underlying endotype rather than disease severity alone.

Some potential assets in development:



Inhibitor/Antagonist: ⊖; TSLP: Anti-thymic stromal lymphopoietin (TSLP) antigen-binding antibody fragment; antisense oligonucleotide: DNAzyme hgd40 antisense oligonucleotide, enabled to cleave the target mRNA molecule, GATA3 mRNA, downregulating the expression of downstream cytokines such as IL-4, IL-5, and IL-13; TSLPr: Blocks the interaction of thymic stromal lymphopoietin (TSLP) with its receptor complex.

SmartAnalyst is partnering with leading bio-pharma companies to deliver insights on current challenges with diseases of the immune system. We are helping clients address key questions that will influence future drug development:

1. With the discovery of upstream pathways of inflammation in asthma, how will the overall disease landscape evolve?
2. What are the targets against which the drugs are being developed for management of moderate-to-severe asthma?
3. What biomarkers could be used to assess the efficacy of therapy?
4. What insights can be drawn from real-world data on management of patients with moderate-to-severe asthma?
5. Based on the residual unmet needs, what is the likely positioning of new biologics or small molecules in development?
6. How do KOLs view the unmet needs in the management of patients with moderate-to-severe asthma?

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