Cytokine antagonists are monoclonal antibodies that offer new treatment options for refractory asthma but will also increase complexity because they are effective only for patients with certain asthma subtypes that remain to be more clearly defined. The clinical and inflammatory heterogeneity within refractory asthma makes it difficult to manage the disease and to determine which, if any, biologic therapy is suitable for a specific patient. The purpose of this article is to provide a data-driven discussion to clarify the use of biologic therapies in patients with refractory asthma. We first discuss the epidemiology and pathophysiology of refractory asthma. We then interpret current evidence for biomarkers of eosinophilic or type 2-high asthma so that clinicians can determine potential treatments for patients based on knowledge of their effectiveness in specific asthma phenotypes. We then assess clinical data on the efficacy, safety, and mechanisms of action of approved and pipeline biologic therapies. We conclude by discussing the potential of phenotyping or endotyping refractory asthma and how biologic therapies can play a role in treating patients with refractory asthma. © 2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2016;:–): 2)

Key words: Severe asthma; Refractory asthma; Biologic therapy; Monoclonal antibody; Eosinophil; FeNO; Periostin

Although a substantial proportion of suboptimal outcomes in asthma is related to poor adherence as well as both avoidable and unavoidable environmental exposures, increasing evidence suggests that there remain a group of patients with refractory asthma in whom standard therapies are ineffective. Cytokine antagonists are monoclonal antibodies that offer new treatment options for refractory asthma but are effective only for patients with certain asthma subtypes. These specific asthma subtypes and the best measures to identify responders are still becoming recognized. Clinicians need to be able to distinguish between difficult-to-treat asthma, in which the patient is capable of asthma control with currently available treatments, and refractory asthma, in
Asthma. Although we recognize that non-clinical data on the efficacy, safety, and mechanisms of action of emerging biologics and to discuss and debate the distinguishing characteristics of severe asthma, asthma phenotypes in treatment selection, the role of T helper cell type 2 (Th2) pathways in asthma control. This type of high-intensity treatment is referred to as Step 5 or Step 6 in the National Asthma Education and Prevention Program (NAEPP) Expert Panel Report 3 (EPR-3) Guidelines for the Diagnosis and Management of Asthma and Step 5 in the Global Initiative for Asthma (GINA) Global Strategy for Asthma Prevention and Management. However, for those in whom control is poor due to adherence issues and comorbidities, the term applied is “difficult-to-control” asthma. A recent study from the Netherlands reported that 17.4% of the asthma patient population had difficult-to-control asthma despite high-intensity treatment, but once poor medication adherence and incorrect inhaler technique were factored, 3.6% of the asthma patient population had severe refractory asthma.

COSTS OF REFRACTORY ASTHMA

The 2000 ATS Workshop on Refractory Asthma estimated that less than 5% of patients with asthma have high medication requirements to maintain good asthma control or have persistent symptoms, exacerbations, or airflow obstruction despite high medication use. This subset of patients has disproportionately high health care utilization. Such patients account for much of the morbidity, mortality, medical resource use, and costs related to asthma care. Moreover, both adults and children with uncontrolled asthma have significant health care use as measured by rates of hospitalization in the previous year and the lifetime history of intubation. The cost, both direct and indirect, is particularly high in children with very poorly controlled asthma versus children with not-well-controlled or well-controlled asthma. In the Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) observational study of children aged 6-12 years, mean annual total asthma costs in children with very poorly controlled asthma were more than twice as those in children with not-well-controlled asthma or well-controlled asthma.

HETEROGENEITY OF ASTHMA

Clinically, there are differences among patients in terms of symptoms, airway function (eg, forced expiratory volume in 1 second [FEV1]), airway architecture, airway hyperresponsiveness, degree and type of inflammation, susceptibility to exacerbations, and response to corticosteroids. In addition, clinicians encounter many types of populations, including patients who respond well to standard treatment with ICSs and/or long-acting β-agonists (LABAs), patients with comorbidities, and patients who are exacerbation-prone but between exacerbations require very little medication.

IDENTIFYING THE PATIENT WITH REFRACTORY ASTHMA

Guidelines and publications have referred to poorly controlled asthma by a variety of terms: severe asthma, refractory asthma, severe refractory asthma, difficult/therapy-resistant asthma, difficult-to-treat asthma, and uncontrolled asthma. Definitions of these terms often overlap, but the terms do not necessarily refer to the same patient population or the same underlying reasons for poor asthma control.

We define refractory asthma per the definition of Bel et al and the 2014 international European Respiratory Society (ERS)/American Thoracic Society (ATS) guidelines, in which patients with refractory asthma are those for whom alternative diagnoses have been excluded, comorbidities have been treated, triggers have been removed, and compliance with treatment has been checked, but remain poorly controlled or with frequent, severe exacerbations despite the prescription of high-intensity treatment or who require systemic corticosteroids to maintain asthma control. This type of high-intensity treatment is referred to as Step 5 or Step 6 in the National Asthma Education and Prevention Program (NAEPP) Expert Panel Report 3 (EPR-3) Guidelines for the Diagnosis and Management of Asthma and Step 5 in the Global Initiative for Asthma (GINA) Global Strategy for Asthma Prevention and Management.
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