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Special article

Guidelines for Severe Uncontrolled Asthma☆

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ABSTRACT

Since the publication, 9 years ago, of the latest SEPAR (Spanish Society of Pulmonology and Thoracic Surgery) Guidelines on Difficult-to-Control Asthma (DCA), much progress has been made in the understanding of asthmatic disease. These new data need to be reviewed, analyzed and incorporated into the guidelines according to their level of evidence and recommendation. Recently, consensus documents and clinical practice guidelines (CPG) addressing this issue have been published. In these guidelines, specific mention will be made of what the previous DCA guidelines defined as "true difficult-to-control asthma". This is asthma that remains uncontrolled after diagnosis and a systematic evaluation to rule out factors unrelated to the disease itself that lead to poor control ("false difficult-to-control asthma"), and despite an appropriate treatment strategy (Spanish Guidelines for the Management of Asthma [GEMA] steps 5 and 6): severe uncontrolled asthma. In this respect, the guidelines propose a revised definition, an attempt to classify the various manifestations of this type of asthma, a proposal for a stepwise diagnostic procedure, and phenotype-targeted treatment. A specific section has also been included on DCA in childhood, aimed at assisting healthcare professionals to improve the care of these patients.

Normativa sobre asma grave no controlada

Palabras clave:
Asma grave
Asma no controlada
Fenotipado del asma
Tratamiento del asma

RESUMEN

Desde la publicación, hace ya 9 años, de la última normativa de la Sociedad Española de Neumología y Cirugía Torácica (SEPAR) sobre asma de control difícil (ACD), se han producido avances en los conocimientos de la enfermedad asmática, que hacen necesario realizar una puesta al día de los datos disponibles e incorporarlos tras su análisis en el nivel de evidencia y recomendación más adecuado. Recientemente han aparecido documentos de consenso y guías de práctica clínica (GPC) que abordan este problema. En esta normativa se hará mención explícita a lo que la previa guía de ACD definía como «verdadera asma de control difícil»; es decir, al asma que tras haber verificado su diagnóstico, realizado un abordaje sistematizado para descartar factores ajenos a la propia enfermedad que conducen a un mal control de la

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misma («falsa asma de control difícil»), y realizar una estrategia de tratamiento adecuado (escalones 5 y 6 de la Guía española para el manejo del asma [GEMA]), no se consigue alcanzar el control: «asma grave no controlada» (AGNC). En esta línea la normativa propone una revisión de la definición, un intento de clasificación de las diferentes manifestaciones de este tipo de asma, una propuesta del abordaje diagnóstico por pasos y un tratamiento dirigido según fenotipo, conjuntamente con un apartado específico sobre este arquetipo de asma en la infancia, con el objetivo de que pueda servir de ayuda a los profesionales sanitarios y repercutir en el cuidado de estos pacientes.

Introduction

Asthma is a worldwide problem, and severe uncontrolled asthma (SUCA) in particular has far-reaching socioeconomic repercussions. For this reason, all healthcare professionals treating these patients must be aware of the situation, and have the proper tools for providing the best approach to this problem.

The first obstacle encountered is the exact terminology for defining these patients, since there is no common agreement.

"Difficult-to-treat asthma" is a term used for patients who find it difficult to achieve control as a result of poor compliance, incorrect inhalation techniques, exposure to allergens or other triggers, or associated comorbidities. The term "refractory or treatment-resistant asthma" refers to subjects who, when a diagnosis of asthma has been confirmed and comorbidities identified and treated, require treatment with high-dose inhaled corticosteroids (IC) plus another second controller (long-acting β_2-agonist [LABA] and/or systemic corticosteroids [SC]) to prevent their asthma becoming uncontrolled, or who remain uncontrolled despite this therapy. SUCA includes patients with refractory asthma and those with incomplete response to treatment.[1]

Methodology

These guidelines were drawn up following SEPAR recommendations for the development of guidelines. All citations used by the various authors, experts in severe asthma, were recorded in an EndNote database and classified according to their levels of evidence, using the Grading of Recommendations (GRADE) approach.[2]

Among the studies selected from a systematic search as a basis for these guidelines, very few were identified as randomized controlled trials with a low risk of bias that would provide direct, consistent and precise evidence. Most recommendations proposed are based on indirect evidence, retrieved from studies performed in moderate persistent asthma, and to a lesser extent, studies in patients with severe asthma. The result is imprecise levels of evidence and recommendations, although all the studies were evaluated and classified using the GRADE system.

Quality of evidence was classified as high, moderate, low and very low, based on different considerations for presence of direct bias (and the direction), consistency and directness of the estimates (Fig. 1).

Definition

The definition set out in the ATS/ERS consensus statement[1] was used throughout this paper. This defines severe asthma as "asthma requiring treatment with high-dose IC, plus a second controller and/or SC to prevent it from becoming uncontrolled or that remains uncontrolled despite this therapy" (evidence D-R2). Severe uncontrolled asthma is defined in Table 1.

Epidemiology

The lack of well-designed studies using homogeneous definitions means that available data on the epidemiology of severe asthma are disparate, particularly in adults. Severe asthma varies in prevalence between one country and another (18% in Western Europe, 19% in the United States and 32% in Central Europe)[3] and about 50% of these severe patients are thought to have poor disease control.[3] In Spain in 2011, the prevalence of severe uncontrolled asthma, according to medical criteria, was reported to be 3.9% of all asthma cases[4] (evidence C). Moreover, this small proportion of patients is responsible for much higher use of resources than other asthmatic patients[5] (evidence D-R2).

Genetics

Asthma is a complex syndrome resulting from the interaction of numerous genes and environmental exposure. The lack of studies in severe asthma make it impossible to determine precisely which genes are responsible for making an individual susceptible to developing severe asthma. Currently, genome wide association approaches (GWAS) are analyzing hundreds of thousands of polymorphisms located throughout the genome in the search for variants associated with susceptibility to developing severe asthma[6] (evidence C-R2). Single nucleotide polymorphisms (SNPs) in the interleukin-4 receptor subunit alpha (IL4Rα) are associated with poorer lung function, higher immunoglobulin E (IgE) levels, severe asthma exacerbations and tissue inflammation[7] (evidence C-R2). An IL-6 receptor (IL6R) variant is associated with severe asthma phenotypes and poorer lung function[8] (evidence C-R2). Other genetic mutations associated with severe asthma are variations in genes involved in tumor necrosis factor (TNF) and multiple SNPs in the RAD50-IL13 regions of chromosome 5q31.1 and the HLA-DR/DQ region of chromosome 6p21.3, respectively[9] (evidence C-R2).

Severe Asthma Phenotypes

Clinicians have identified markedly different asthma patient subtypes or profiles, suggesting that asthma remains a poorly classified syndrome.

Several studies that merge objective clinical variables have been performed in an attempt to categorize patients into clinical phenotypes, or on their pathophysiological basis (endotypes)[10] which, in the case of SUCA, will have therapeutic implications (evidence D-R2).

These studies share several multivariate statistical techniques, especially cluster analyses[11–13] (evidence C-R2). The overall conclusion is that there are at least 4 reasonably well defined phenotypes/endotypes in severe asthma, characterized according to natural history, pathobiology, clinical features and therapeutic response.