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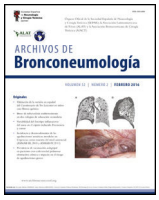

Editorial

Biologics in Asthma: Don't Let the Magic Bullets Sink the Boat☆

Biológicos en asma: que las balas mágicas no hundan el barco

At the beginning of the last century, Paul Ehrlich, Nobel Laureate in 1908, created the concept of "magic bullets", referring to the selective toxicity of treatments.[1] It should be the goal of all physicians to prescribe the ideal treatment for each patient, combining the maximum therapeutic benefit with the fewest side effects.

In respiratory medicine, magic bullets are of particular relevance in individuals with severe uncontrolled asthma. Although the proportion of asthma patients in this category is small, between 5% and 10%, this group generates most of the cost of the disease, while at the same time experiencing reduced working capacity, loss of quality of life, and exacerbations that are sometimes life-threatening.[2–6]

Before prescribing a monoclonal drug, it seems essential to ensure that the diagnosis of asthma is correct, that the patient is receiving the appropriate treatment, and that their compliance is good. It is well established that the diagnosis of asthma by physicians may be erroneous in around 33.1% of cases.[7] It has also been reported that about 42% of patients with an episode of life-threatening asthma (LTA) were not receiving inhaled corticosteroids (ICS) before admission, but even more worryingly, after admission for an episode of LTA, 21.5% were discharged from the hospital without a prescription for ICS.[6]

The therapeutic landscape for this group of patients changed dramatically in 2003 when the Food & Drug Administration approved the use of omalizumab in patients with severe allergic asthma. This event was followed by some years of relative stagnation until mepolizumab was approved in 2015. Since then, reslizumab, benralizumab, and dupilumab have also been approved, all for use in severe eosinophilic asthma.[8] The use of these treatments has had a significant impact on patients with asthma by reducing the rate of exacerbations, although differences between these molecules in terms of better quality of life and symptom control, lower systemic corticosteroid doses, and improved lung function[8] have been observed in clinical trials.

Being able to choose between various options raises questions as to what the best therapeutic decision would be – questions that have not been definitively answered. On the one hand, the indication for any of these drugs clearly overlaps, since in most severe asthmatics more than one biological drug may be suitable.[9,10] On the other, studies carried out in routine clinical practice have also shown that the original indications could and should be expanded, as these products were also effective in patients other than the initially defined population. Omalizumab, for example, has been shown to be effective in non-allergic patients.[11,12] This is a common occurrence in drug research, as evidence from clinical trials is important for determining the efficacy of these treatments. However, patients who are managed in routine clinical practice are clearly different from those included in the studies, and this may at least partially compromise the external validity of the available data.[3]

Another important lesson we have learnt from research in routine clinical practice is the possibility that a patient who does not respond to treatment with one monoclonal antibody may respond to another. In this respect, data from the OSMO study clearly show that patients who did not respond to omalizumab and were switched to mepolizumab achieved a significant improvement in both asthma control and quality of life, with a 64% decrease in the rate of exacerbations.[13]

In the absence of direct comparisons, some authors have attempted to compare the efficacy of these drugs by making indirect comparisons using network meta-analyses, but these studies provide less robust conclusions than direct comparisons: even though they may be based on placebo-controlled studies, there is always interference from other treatments that are not exactly the same (such as ICS or beta-agonists), and they do not use the same inclusion criteria.[14,15] Another possible source of divergence is the measurement of results: the definition of exacerbation, for example, despite being similar, is not homogeneous between studies, nor is the method used to determine disease control. This all goes to explain, at least in part, the differences in results between these studies.[14,15]

Biologics are a clear advance in asthma management, but they are costly. However, it is just as inefficient to prescribe these drugs for patients who do not need them (which will result in high direct costs), as it is to *not* prescribe them for patients who would clearly benefit from their use: despite initial savings in direct costs, overall costs will be higher, whether direct (health expenditure associated with more hospital admissions), or indirect (quality of life of patients and their families; increased incidence of temporary or permanent occupational disability). Nevertheless, some things are clear: these treatments are effective; failure of one or more should not prevent us from trying others; and improved indicators to guide us towards making the most appropriate choice are needed.

The indication for these treatments is still based on scant data. It seems that we will have to look beyond allergy and eosinophilia to

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find the magic bullet for each patient, one that performs its function efficiently and does not torpedo our health system.

Higher-precision medicine seems necessary in this context. While we await definitive answers, we would do well to remember Kant's advice: someone's intelligence is measured by the quantity of uncertainties he can bear.

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