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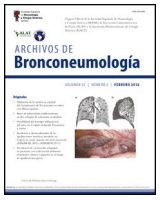

Editorial

Initiating Biological Treatment of Asthma: When is the Right Time?

Six monoclonal antibodies (biological agents or biologics)[1,2] are currently available to effectively and safely treat severe uncontrolled asthma, revolutionizing the treatment of such cases. Treatment with biologics significantly improves the disease and even potentially achieves four-domain clinical remission, i.e., no exacerbations, no need for oral corticosteroid (OCS) cycles, controlled asthma, and normal or stabilized lung function measured as forced expiratory volume in 1 second (FEV_1).[3]

Asthma is a risk factor for loss of lung function, with some asthmatics, especially severe asthmatics, developing bronchial obstruction that is not fully reversible. Observed in large cohort studies is that patients who experience recurrent severe exacerbations tend to experience accelerated lung function decline, which may, in turn, lead to a poorer treatment response.[4–6] This decline is even more pronounced when exacerbations occur in young people with asthma.[4] Exacerbations are an independent risk factor associated with poor lung function, which seems to be caused by bronchial remodelling that independently accompanies exacerbation-related inflammation.[7]

While their anti-inflammatory efficacy is essential treatment for asthma, the ability of inhaled corticosteroids (ICS) to reverse bronchial remodelling is limited. Studies of children addressing early ICS intervention for mild asthma have reported no benefits for long-term lung function.[8] For adults, it is not clear whether this strategy could slow down lung function decline, or what might happen in patients with severe disease.[9,10] While there is as yet no effective treatment that counters remodelling, different biologics have been observed to show an unexpected anti-remodelling effect.[11–14]

In general terms, biologics reduce the deposition of molecules closely related to remodelling, such as transforming growth factor (TGF) and procollagen,[11] and also reduce bronchial hyperresponsiveness[12]; moreover, observed in patients who receive them early on is a slowdown in lung function decline.[13,14] When the time of disease onset is considered, patients whose disease has evolved over longer periods respond less vigorously, not only in terms of lung function (lower magnitude of obstruction reversal), but also in terms of achieving clinical remission.[14–16] A recent analysis of pre-biologic characteristics and post-biologic remission in patients included in the International Severe Asthma Registry (ISAR) reported that the odds ratio of achieving four-domain remission decreased by 15% for each additional decade living with asthma (0.85; 95% CI: 0.73–1.00).[16]

For all the above reasons, a number of authors have recently proposed bringing forward the start of biological treatment, arguing that, if administered in less advanced phases, the decline in lung function could possibly be slowed down, thus modifying the natural history of the disease.[17] Currently, biologics are largely reserved for patients with severe uncontrolled asthma taking high doses of ICS combined with long-acting β2 agonist (LABA) and long-acting antimuscarinic antagonists (LAMA) treatment, and also, in many cases, needing daily OCS.[1,2] This represents the worst possible clinical scenario for very advanced stages of asthma, with perhaps a lower probability of a favourable response to treatment.

Are we arriving late? The question is pertinent but uncomfortable. If the answer is yes, it opens up an important margin for improving disease treatment and possibly preventing severe asthma, but also implies unsustainable direct costs for public health systems if prescription was extended to young patients with non-severe asthma. Responding appropriately to the question requires a rational analysis of current information and implications.

The early administration of biologics for asthma could reduce exacerbations and the need for cortisone cycles, improve lung function and daily symptoms, reduce the use of inhaled drugs and their long-term side effects, and probably improve therapeutic adherence, patient satisfaction, and quality of life. However, certain issues need to be considered. Firstly, the benefits of early administration of biologics are documented in a limited number of studies that have not been specifically designed to explore such benefits, or the benefits have been deduced from post-hoc analyses of those studies. Hence, we need more solid evidence in the form of long-term prospective studies with sufficiently large population samples that compare the use of biologics to the usual inhaled treatment and clinical practice, most especially between patients with severe and with moderate asthma. Secondly, we need to analyse the specific effectiveness of each biologic, as not only are there likely to be differences between biologics, but also, for reasons that are unclear, some biologics lose effectiveness over the medium term. Finally, we lack studies that confirm the safety of biologics over the long term, as potential adverse effects may not be justified in patients with non-severe asthma.

Since, given the potential cost, it would be impossible to prescribe biologics to the entire population with asthma, suitable candidates would need to be selected. However, based on which criteria, variables, or biomarkers? We do not as yet have the answer, although in the future artificial intelligence might help with candidate selection. And for moderate or mild asthma? While the cost would clearly be more affordable for moderate asthma, by this stage, administration may come too late.

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Leaving aside the aforementioned sustainability issue, the cost effectiveness of biologics compared with other treatments for non-severe asthma is also relevant, especially from the perspective of the funder. Public health systems, which would ultimately decide whether or not to assume the cost, usually only consider direct costs (including, in this instance, the cost of the biologic), whereas a comprehensive cost analysis should additionally incorporate indirect and intangible costs. Furthermore, an important health system issue, as yet unresolved, is geographical inequalities in access to treatments, which would be aggravated in this new scenario. A recent study by Almonacid et al.[18] found significant geographical inequalities in the Spanish health system, with patients with asthma in some areas receiving an unacceptably high annual number of prednisone cycles. Furthermore, many patients who should be receiving biologics today are not receiving them.

In short, although the concept of early-stage biological treatment of asthma is undoubtedly attractive, many questions remain unanswered. Given that the current evidence on biologics as treatment for non-severe asthma is incomplete, further robust information is needed. Although the development of biosimilar drugs may reduce costs in the future, those currently available are unacceptably costly for public health systems with broad coverage like that in Spain. At the moment, therefore, it seems that we should ensure that biological treatment of asthma is "on time" rather than "soon".

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Authors' Contributions

- VP: designed content and wrote the manuscript draft.
- GG: revised, corrected, and approved the final manuscript.
- LPLL: revised, corrected, and approved the final manuscript.
- SQ: revised, corrected, and approved the final manuscript.

Conflicts of Interest

- VP in the last three years has received honoraria for speaking at sponsored meetings from Astrazeneca, Boehringer-Ingelheim, Chiesi, Gebro, GSK, Luminova-Medwell, and Sanofi; has received assistance for travel from Astrazeneca and Chiesi; and has acted as a consultant for Astrazeneca, Chiesi, GSK, and Menarini.
- GG in the last three years has received honoraria for speaking at sponsored meetings from Chiesi, GSK, Novartis, and Sanofi; has received assistance for travel from GSK and Sanofi; has acted as a consultant for GSK and Sanofi; and has received honoraria for clinical trials investigations from GSK, Sanofi, Chiesi, WorldWide, PPD, Insmed, Fortrea, Areteia, and Astrazeneca.
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- SQ has been on advisory boards for and has received honoraria from Allergy Therapeutics, Astrazeneca, Chiesi, GlaxoSmithKline, Gebro, Novartis, and Sanofi.

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