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Biologics and global burden of asthma: A worldwide portrait and a call for action

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ABSTRACT

Biologics for severe asthma can significantly impact on the burden of disease and also have the potential to reduce asthma mortality. By reviewing the literature and contacting the pharmaceutical companies, the present paper aims at providing a worldwide snapshot of biologic drugs availability, related with the trend of asthma mortality rate, as a marker of the burden of the disease.

A decline in the global rate of annual asthma mortality was observed until the 1980s, but overall no further reduction occurred, and the current mortality estimation is 0.19 deaths per 100.000 people. A higher mortality rate has been registered in low and middle-income countries (LMICs), where poor socioeconomic conditions and lack of access to the medical resources are more relevant. The availability of monoclonal antibodies is mainly limited to the developed and high-income countries. Furthermore the overall "asthma management system" in LMICs suffers from a number of restrictions that hamper the widespread availability of biologics besides their costs. The availability of generic drugs in the field of biologics for severe asthma could contribute to facilitate their widespread accessibility. But before that, awareness and expertise regarding severe asthma, and proper tools to assess and manage it, deserve to be shared worldwide. Collaboration projects involving physicians from all the countries through the scientific Academies network and with the support of the Companies active in the field may provide an initial concrete opportunity.

Keywords: Severe asthma, Severe asthma prevalence, Asthma mortality, Biologics, Asthma costs

DEAR EDITORS,

Bronchial asthma is one of the most common non-communicable respiratory diseases, and it affects more than 300 million people in the world.[1] According to recent epidemiological studies, its prevalence among the general population is 4.5% on average, with substantial variation in different areas and countries.[2] Asthma prevalence is currently higher in developed countries, but in less developed nations it is still increasing.[3]

Severe asthma affects less than 5% of asthmatic patients, even though epidemiological studies specifically addressing the issue in different countries are still missing,[4,5] as well as an accurate estimation of fatal asthma cases.[6,7]

Severe asthma is a heterogeneous disease characterized by different clinical and biologic phenotypes.[8] The recent introduction of biologic drugs fostered a radical change in the therapeutic approach of severe asthma, at least of the T2 high phenotype. An increasing number of different molecules is going to enlarge the available options, besides oral corticosteriods, for difficult to treat patients. The monoclonal antibodies targeting IgE, IL4/IL13, and IL5 driven

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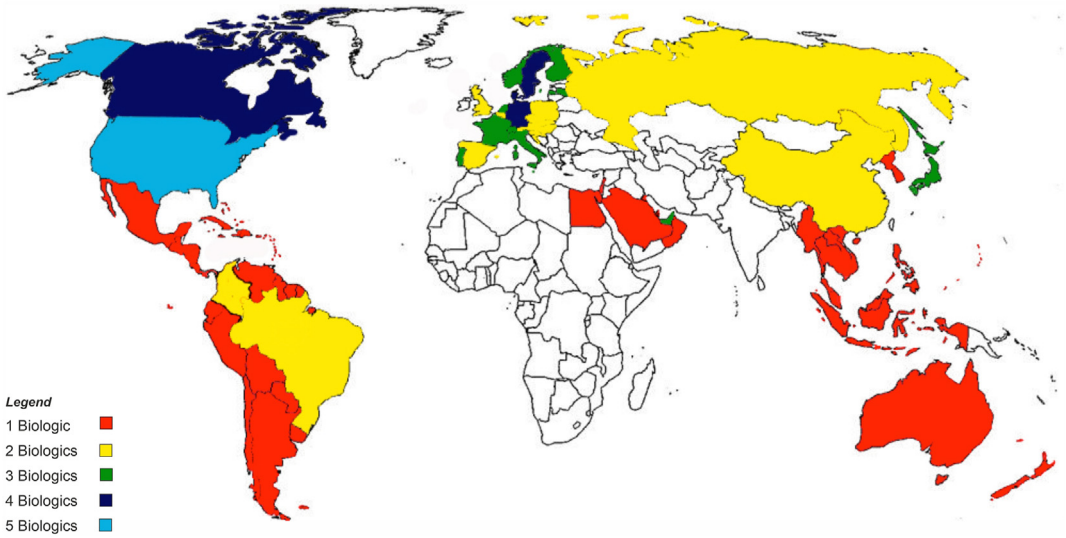

Fig. 1 Worldwide availability of biologics for severe asthma. The different colors identify the number of marketed biologics in each country.

inflammation have been proven to significantly reduce exacerbations and hospitalizations in severe asthmatic patients as well as the use of oral corticosteroids.[8] In other words, biologics for severe asthma are going to have a significant impact on the burden of the disease and on its mortality rate. However, access to these treatment options is still very limited in some areas.

The present paper provides a worldwide snapshot of biologic drugs availability, combined with the trend of asthma mortality rate as a marker of the burden of the disease in different countries. This approach is not free of bias; in fact, risk factors for asthma mortality may differ from risk factors for asthma morbidity and poorly controlled asthma.[9] On the other hand, defining asthma outcomes specifically related to asthma morbidity or asthma control is not easy in low- and middle-income countries (LMICs). In fact, in those areas the access to health care services (which means proper diagnosis and treatment), or the possibility to get controller medications besides oral corticosteroids is very limited due to personal income restrictions or poor health care systems resources.[10] Also, data on the social and indirect economic burden in those settings remain especially scarce.[11] For those reasons, more than in high-income countries, in LMICs asthma mortality may reflect the extreme consequences of improper asthma management due to the above-mentioned limitations, besides specific risk factors for morbidity or mortality.

A literature review has been performed on PubMed and Medline including the following key words: asthma mortality, fatal asthma. Furthermore the availability of biologics for severe asthma in each country was verified by exploring marketing data and by contacting the pharmaceutical companies. Benralizumab, mepolizumab, omalizumab, reslizumab, and dupilumab were included in the investigation.

As far as asthma mortality is concerned, generally speaking the decline observed since the late 1980s seems to have flattened. In fact, no further reduction has been registered from 2006 to 2012.[1,3] In the United States, after increasing during the 1980s, annual rates were relatively flat until the late 1990s, and then progressively declined.[12]

According to the available evidence, the current asthma mortality rate is 0.19 deaths per 100 000 people.[3] Of note, the study by Ebmeier and colleagues included 46 countries, 30 high-income countries, and the 16 middle-income countries, and evaluated only patients aged from 5 to 34 years, in order to exclude chronic obstructive pulmonary disease (COPD) in those 35 years and older, and bronchiolitis in those younger than 5 years as potential confounding factors; however, the above mentioned 2016 World Health Organization (WHO) Mortality Database from 46 countries estimated 420 000 fatalities due to asthma, around 1000 per day.[3] Differently from the

prevalence data, a striking higher mortality for asthma has been registered in LMICs.[3,13] Whereas asthma prevalence seems to be affected by urbanization and environmental allergy, its fatality is more influenced by poor socioeconomic conditions and difficult access to health care resources.[13] In fact, according to the report by Sinharoy et al,[13] poverty, lack of education, and accessibility to both chronic and lifesaving medications in Asian and African countries have a significantly higher impact on asthma prevention, diagnosis, and treatment in comparison to European and other countries. The higher levels of air pollution in those areas further hamper the achievement of an optimal disease control, despite not directly being associated with asthma mortality.[14] Of note, the increased asthma-related mortality is not considered a result of higher asthma prevalence as much as poor socioeconomic conditions.[15]

At the same time, as shown in Fig. 1, the availability of monoclonal antibodies for the treatment of severe T2 asthma is mostly limited to the developed and high-income countries, where at least 1 of the currently approved biologics is available on the market.

Omalizumab is the most accessible biologic drug, namely in Europe, with the exception of East European countries (eg, Serbia, Bulgaria, Albania, Romania, Ukraine, and Belarus), in North America, Central America, much of Latin America, in Australia and in Asia, including United Arab Emirates (UAE), though it is not available in India and in many countries of the middle East, except Israel. In Africa the availability of omalizumab is limited to Egypt.

The areas where mepolizumab is accessible are more limited. It is marketed in Europe, Russia, United States, and Canada. In Eastern Countries, Central and South America, and Africa mepolizumab is not available. In Asia, it is available in UAE, China, Japan, and South Korea only.

Reslizumab is even less accessible, being limited to North America, and North and Mediterranean European countries (Switzerland excluded).

Regarding benralizumab, it is currently available in North America and in few European countries.

Dupilumab was marketed in the United States in 2018. In the last 2 years it became available in Japan, South Korea, Russia, Arabian Peninsula (with the exception of Yemen and Bah rein), Israel, Brunei, Colombia, and Brazil. The European Medicines Agency (EMA) approved dupilumab for severe asthma in 2019, but its distribution is currently limited to Germany, Netherlands, Luxembourg, Sweden, Denmark, Norway, Finland, France, and Latvia.

The picture of biologics availability in the world is very dynamic at the moment; all the companies producing monoclonal antibodies for severe asthma are committed to enlarge the market worldwide for their drugs. However, the gap between high-income countries and low-income/less developed countries is still substantial, and probably the situation will not change in the near future. In fact, the panorama is quite complex and different determinants hamper a more extensive accessibility to biologics worldwide. The cost of drugs probably represents a major limitation. In LMICs the resources from both national health systems and private insurance systems are not enough to cover the costs related to biologic drugs, from acquisition from pharmaceutical companies to storage and final delivery to patients.[10,11] On the other hand, the overall "asthma management system" in LMICs suffers from a number of restrictions that limit the widespread availability of biologics besides their costs. In fact, in many areas health care services lack the basic tools for a proper asthma assessment, and physicians' expertise regarding biologics is scarce. Or, the accessibility to adequate healthcare resources is difficult due to patients' income restrictions and poor disease awareness.[13]

All the above-mentioned conditions may represent a critical drawback for the correct and regular treatment with inhaled steroids, which have a well-known role in promoting the decline of asthma mortality,[16] in favor of an overuse of short acting beta agonists (SABA) and oral corticosteroids (OCS). In fact, they are inexpensive and more easily available/accessible. The same trend has been observed in Western countries,[7,17–19] but in the case of LMICs it even might be enhanced[10,13] and more connected with asthma morbidity and mortality reflecting

the extreme consequences of improper asthma management.

Severe asthma still represents a global challenge worldwide, in terms of burden and economical impact. Optimizing severe asthma management besides biologics availability and implementing different strategies and interventions, tailored on the specific geographic and socio-economic setting in different countries, is a priority. It might entail improving the referral to specialized centers and increasing the adherence rate to inhaled corticosteroids (ICS) in high-income countries or strengthening the overall asthma management system in LMICs.

However, each one of the currently recommended therapies for asthma control, including biologic drugs, should be accessible worldwide as a major strategy for reducing OCS use and their costs in terms of morbidity.[20] This should be considered a priority by the National Health Systems and by the stakeholders in the field, as a major strategy to reduce asthma morbidity and mortality.

Educational initiatives currently ongoing in several African nations are a significant step forward in terms of healthcare pathways optimization.[13] The availability of generic drugs in the field of biologics for severe asthma could contribute to an overall cost reduction and facilitate their widespread accessibility.[21] But before that, awareness and expertise regarding severe asthma, and proper tools to assess and manage it, deserve to be shared worldwide. Collaboration projects involving physicians from all the countries through the scientific Academies network, with the support of the Companies active in the field, may provide an initial concrete opportunity.

Abbreviations
ICS: inhaled corticosteroids; LMICs: low- and middle-income countries; OCS: oral corticosteroids; UAE: United Arab Emirates; WHO: World Health Organization.

Author contributions
MC and GS conceived the manuscript and drafted the first version. MMA, EB, GWC, IA, CB critically revised the manuscript and substantially contributed to the final draft.

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