Comment

Title:
EXTERNAL VALIDITY OF TRIALS SHOULD BE TAKEN INTO ACCOUNT BEFORE ASTHMA DRUG CANDIDATES REACH MARKET AUTHORISATION.

Authors:

Orestis Briasoulis MD[1], Ross Breckenridge FRCP[1], Andrew Nunn MSc[2]

Affiliations:

[1] Division of Medicine, University College London, UK
[2] MRC Clinical Trials Unit at UCL, Institute of Clinical Trials & Methodology, London, UK

Correspondence:
Orestis Briasoulis MD
Division of Medicine, University College London
Gower Street, WC1E 6BT, London
Email: orestis.briasoulis.15@ucl.ac.uk
Phone: +44 7783 911179

Authors' contributions:
All authors contributed equally.

Conflicts of interests:
The authors declared no conflicts of interest.

Significant advances have been made during the last decade in asthma treatment, but concerns have been raised about the validity of trial results with respect to the entire asthma population, given the considerable heterogeneity of asthma sub-groups and short time duration of trials (1, 2). A basic reason for questioning general applicability of asthma therapeutics, is that participants of randomized controlled trials (RCTs) often represent only 5% of the asthma population due to strict trial eligibility criteria (3). Since the risk-benefit profile of new drugs can be unpredictable for the majority of asthma patients, we need to re-examine the issue of external validity of RCT results.

Several groups of asthmatics are under-represented in RCTs. Patients prone to small airway disease such as those with refractory asthma, nocturnal asthma, exercise-induced asthma, smokers and those with co-existing allergic rhinitis (4) are often excluded from trials. Yet, these groups are likely to show a different response to inhaled corticosteroid treatment depending on the particle size of formulation (5). Despite the fact that patients with uncontrolled asthma can develop fixed airway obstruction, irreversible bronchoconstriction is often set as an exclusion criterion and disqualifies approximately 75% of asthma trial participants (3). In addition, patients with a smoking history of more than 10 pack-years are often excluded, even though it has been estimated that one out of four asthmatics in Europe are smokers (6), and smoking is associated with impaired therapeutic response to corticosteroids. Moreover, although significant comorbidity is present in roughly one third of asthmatics, more than half of RCTs exclude comorbidities (7, 8). If all the above mentioned asthma groups are excluded from RCTs it is very likely to result in uncertainty on the use of drugs in real-life clinical settings.

It is, therefore, clear that development of alternative trial design approaches should be pursued, addressing the incorporation of external validity. This way we could avoid the debatable approval of drugs that apply to a small proportion of asthma patients and address the currently seeming unavoidable efficacy-effectiveness gap (9).

To establish high external validity of trials as a requirement for drug approval, generalizability needs to be quantified in an objective manner. A useful tool to assess this could be the Pragmatic-Explanatory Continuum Indicator (PRECIS-2) (10). This tool was originally created to assist trial design; nevertheless, it can also be used for critical assessment since it evaluates the eligibility criteria, recruitment process, trial setting, resources and expertise needed for the treatment, flexibility and adherence of treatment, follow-up of patients, relevancy of outcomes and extent of analysis. The parts of a trial design that relate to applicability are evaluated on a numeric scale, making it an objective and reproducible way to assess generalizability of trials.

More specifically, we propose that external validity could be facilitated by a specific adaptive trial design composed of three phases [Fig1]. An initial exploratory phase would be characterized by strict eligibility criteria, controlled settings and follow-up in order to study the PK-PD relationship and determine the proposed dose. In a subsequent explanatory phase, the efficacy and safety of the drug would initially be assessed in a controlled and tightly defined patient population so that efficacy can be demonstrated. After confirmation of the risk/benefit profile, the study population will be enhanced, at an interim point. Population enhancement can be performed in two ways, either by broadening eligibility criteria of the pre-existing arms or by adding additional arms with broader eligibility criteria. The second method, would enable the parallel study of efficacy-safety in highly selected populations and in real world patients, generating data with both high internal and external validity at the same time, enabling greater generalizability of results and precision in patient subgroups.

We conclude that regulatory authorities need to request the submission of confirmatory data that demonstrates the generalizability and predictability of results to the whole patient population for whom the drug will finally be prescribed. Moreover, we propose to integrate external validity to RCTs of asthma drugs by developing novel trials characterized by an adaptive trial design and population enhancement at an interim point.

Figures:

Fig. 1: Trial design incorporating external validity.

References:

1. Butler MG, Zhou EH, Zhang F, Wu YT, Wu AC, Levenson MS, et al. Changing patterns of asthma medication use related to US Food and Drug Administration long-acting beta2-agonist regulation from 2005-2011. J Allergy Clin Immunol. 2016;137(3):710-7.
2. Kew KM, Evans DJ, Allison DE, Boyter AC. Long-acting muscarinic antagonists (LAMA) added to inhaled corticosteroids (ICS) versus addition of long-acting beta2-agonists (LABA) for adults with asthma. Cochrane Database Syst Rev. 2015;6:CD011438.
3. Travers J, Marsh S, Williams M, Weatherall M, Caldwell B, Shirtcliffe P, et al. External validity of randomised controlled trials in asthma: to whom do the results of the trials apply? Thorax. 2007;62(3):219-23.
4. Bonini M, Usmani OS. The role of the small airways in the pathophysiology of asthma and chronic obstructive pulmonary disease. Ther Adv Respir Dis. 2015;9(6):281-93.
5. Leach C, Colice GL, Luskin A. Particle size of inhaled corticosteroids: does it matter? J Allergy Clin Immunol. 2009;124(6 Suppl):S88-93.
6. Cerveri I, Cazzoletti L, Corsico AG, Marcon A, Niniano R, Grosso A, et al. The impact of cigarette smoking on asthma: a population-based international cohort study. Int Arch Allergy Immunol. 2012;158(2):175-83.
7. Van Spall HG, Toren A, Kiss A, Fowler RA. Eligibility criteria of randomized controlled trials published in high-impact general medical journals: a systematic sampling review. JAMA. 2007;297(11):1233-40.
8. Herland K, Akselsen JP, Skjonsberg OH, Bjermer L. How representative are clinical study patients with asthma or COPD for a larger "real life" population of patients with obstructive lung disease? Respir Med. 2005;99(1):11-9.
9. Eichler HG, Abadie E, Breckenridge A, Flamion B, Gustafsson LL, Leufkens H, et al. Bridging the efficacy-effectiveness gap: a regulator's perspective on addressing variability of drug response. Nat Rev Drug Discov. 2011;10(7):495-506.
10. Zuidgeest MG, Goetz I, Grobbee DE, Consortium WPotG. PRECIS-2 in perspective: what is next for pragmatic trials? J Clin Epidemiol. 2016.