Phase three studies of biologics for severe asthma: could do better?

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It is an exciting time for those of us treating patients with severe asthma. We now have more effective ways of assessing patients, monitoring adherence, and defining airway inflammation [1–5]. Current trials should inform on the role of biomarkers in determining treatment response [6], as we move away from a one-size-fits-all approach with oral prednisolone as the best alternative available. We can now select patients for intervention with biologics.

As we have previously stressed, protocolised assessment including objective measures of adherence are essential before categorising someone as having severe asthma [7, 8]. In much of Europe and the UK, care is delivered through standardised assessment protocols at defined specialist services linked to research units [1, 2]. We now have licensed biologics targeting key inflammatory pathways: IgE with omalizumab and eosinophils with mepolizumab, with over 10 years clinical experience with the former, and extensive trial data with the latter [9–11]. A surprising feature of omalizumab in clinical practice has been that, unlike for most drugs, outcomes in clinics [12] have often been better than those seen in clinical trials [9]. In the context of severe asthma, selection of patients for treatment with biologics may be more rigorous than for trials, since in many settings payers have set the bar high and require full protocolised assessment, and frequent oral prednisolone courses, in addition to treatment of comorbidities and confirmation of treatment adherence. Future trials should only select protocol-assessed patients who remain symptomatic despite optimisation of management, or who require long term oral prednisolone.

One can learn the importance of treating the right patient with the right drug from the mepolizumab studies. It took many years to define the subgroup of patients with severe asthma who respond to anti-IL-5 treatment: in retrospect it is not a great surprise that those with residual eosinophilia (detectable in blood or sputum) respond, while those who are not eosinophilic do not [10, 11, 13, 14]. Defining the relevant clinical outcome, specifically eosinophilic exacerbations, was also a critical part of defining the benefit of this class of therapy in severe disease. However, this concept of subtypes of asthma is new and clinically still evolving. Much has been made of endotypes, with many different pathways described as potentially contributing to the asthma phenotype [15]. There has been much debate about type 2 (IgE and eosinophilia driven by IL-4, IL-5 and IL-13) and non-type 2 asthma [16, 17]. Whether real non-type 2 asthma exists in the severe asthma population is still an open question: some patients have symptoms despite high dose inhaled steroids without residual type 2 inflammation, but the precise mechanism of

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persistent symptoms in this group is unclear. The current RASP-UK study adjusting therapy according to type 2 biomarkers, exhaled nitric oxide, blood eosinophils and serum periostin (an IL-13 induced epithelial protein) should help define which patients have controlled type 2 disease, and which (if any) have a non-type 2 mechanism driving their symptoms [6].

Recent publications have shown benefit in large clinical trials of anti-IL-5 approaches with mepolizumab [10, 11, 14], reslizumab [18] and benralizumab [19, 20] (all target interleukin-5), and dupilumab (anti-IL4/IL-13) [21]. However, in all studies with exacerbation rates and/or oral steroid reduction as outcomes there were very large placebo effects. Large phase III studies of lebrikizumab (anti-IL-13) did not show significant clinical benefit compared to placebo [22]. Of note, the lebrikizumab phase 3 studies did not enrich for exacerbations by requiring a pre-specified exacerbation history in the previous year [22].

We would argue there are important lessons for future development of "add-on" therapies to standard optimised care for severe asthma.

Firstly, with the availability of licenced anti-IgE and anti-IL-5 therapy, it is becoming difficult to argue ethically that in studies of these "add-on" therapies for patients who remain uncontrolled despite optimised standard care with high dose inhaled steroids with or without additional controllers, one could treat one arm with placebo. Companies, regulators, clinicians and patients need to consider whether comparator studies should be performed with the currently best available treatment including biologic therapies (as is the case for new cancer treatments or rheumatogical diseases).

Secondly, it is notable that the current large phase III studies tend to recruit from many sites, which may not all be specialist severe asthma centres, and it is unclear whether all patients have had detailed assessment, management of co-morbidities and objective measures of adherence. There have been a number of studies which have highlighted the comorbidity and complexity of a difficult-to-manage asthma population [1–5]. Most published studies have made little or no mention of other organ involvement or effects on common comorbidities, despite the systemic effect of treatment. In particular, co-existent nasal symptoms from rhinitis, rhinosinusitis or nasal polyps have seldom been assessed, despite separate trials suggesting potential benefit [23, 24]. This may reflect regulatory rules, but that is not an excuse of not considering all aspects of our patients' illness. Importantly, we should also be aware that current dosing for these products is extrapolated from the clinical trials and there may be room for more personalised treatment regimens depending on defined clinical or inflammatory features of disease and individual patient responses.

Thirdly, many phase III trials in severe asthma have been designed to show a reduction in exacerbations in a type-2 biomarker high population and consistently these studies enrich for both relevant (or what is predicted as relevant) biomarker profile and a history of prior exacerbations. Adherence studies in severe asthma have consistently shown a higher exacerbation rate in poorly adherent patients [25] and our suspicion is that less than ideally optimised asthma management and medication adherence in large phase three studies accounts at least in part for the high placebo response.

Finally, when a drug is eventually licenced, payers impose additional criteria on access to restrict the population on the basis of questionable economic models. For example in the UK for both omalizumab and mepolizumab, a protocolised assessment at a severe asthma centre multidisciplinary team is required and only patients with four or more courses of oral prednisolone or long term oral prednisolone are eligible for reimbursement under criteria produced by the National Institute for Health and Care Excellence [26, 27]. All of these issues mean that the patient population for whom the drug is eventually made available may be very different from the population recruited to the pivotal clinical trials.

Unless there is a re-evaluation of how we perform phase III "add-on" clinical trials in asthma, we anticipate that it may become difficult to recruit to large trials, and the problems discussed above will increase. It is perhaps time to move towards detailed systematic clinical assessment and objective assessment of adherence before recruitment to clinical trials that will allow comparator studies with currently available and effective treatments in optimised patients. This would ideally be done during phase 2 development, using monitored adherence to inhaled treatment so that the true effect size of the "add-on" treatment can be estimated in patients with severe disease optimised on best standard of care therapies. This may also lead to a better estimate of the anticipated "placebo effect" in larger studies and consequently lead to smaller and more cost-effective studies in phase 3 by implementing the systematic clinical assessment and objective measurements of adherence developed in the phase 2 programme.

The emergence of biologics has led to optimism and excitement in this new era of severe asthma medicine: at last new treatments are available with the potential to transform the quality of life of our patients. We owe it to them to assess these novel agents effectively to optimise the benefits, avoiding over-optimistic expectations but also making sure we do not throw the baby out with the bath water!

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