Biologics for paediatric severe asthma: Trick or TREAT?

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While most asthma in UK children can be controlled with low-moderate dose inhaled corticosteroids (ICS), there remains a small group with severe disease and poor control despite maximal treatment whose needs are unmet because of discrimination compared to adults. Severe asthma is a commissioned service for adults with only named specialist centres able to assess patients and prescribe biologics. A systematic assessment at a dedicated severe asthma centre is associated with improved quality of life and asthma control and a reduction in health-care utilisation(1). This multidisciplinary assessment helps to identify remediable factors such as poor adherence and ensures that appropriate patients are started on costly biologics. In contrast, although international guidelines exist(2), there is no such service provision or specification for children, despite clear evidence of their long-term morbidity, including development of chronic obstructive pulmonary disease in adulthood(3), and the potential risks associated with the prescription of biologics.

Children with severe, therapy resistant asthma (STRA) and refractory difficult asthma(4) should be considered for biologics(2), but until July 2018, the only one licenced for children was the anti-IgE monoclonal antibody, omalizumab. However, the restricted prescribing guidelines including a narrow serum IgE range, and the variable clinical response in STRA(5), has left a significant proportion of children with unmet therapeutic needs. The exciting pipeline of biologics could help to address the needs of a wider group of children with STRA. However, we have three key concerns; firstly, that the appropriate studies are not being carried out in children; secondly, that drug development is aimed at therapeutic targets from adult models of disease; and thirdly, there are very little data to guide choosing the optimal biologic for individual patients.

Mepolizumab (monoclonal antibody to IL-5) dramatically reduces asthma attacks in adults. Although adolescents (>12 years) were eligible for the trials, the actual numbers included were tiny (about 30 of the total 800 plus participants). However, mepolizumab was licensed for use in children aged 6-17 years by the European Medicines Agency (EMA) in August 2018, despite absence of efficacy data in this age group. This is clearly discriminatory and contravenes European Paediatric regulation (https://www.ema.europa.eu/en/human-regulatory/overview/paediatric-medicines/paediatric-regulation). In stark contrast, omalizumab was only licenced after efficacy was shown in children aged 6-16 years(5). Although most children with STRA have steroid resistant eosinophilic airways disease(6,

7) which is likely to respond to mepolizumab, this cannot be assumed. IL-5 has only been infrequently detected in paediatric STRA broncholaveolar lavage and endobronchial biopsy(8). Furthermore, in the context of a maturing immune system, and knowing the regulatory function of eosinophils in immune homeostasis(9, 10), their circulatory depletion in children could be deleterious.

We are concerned that, having achieved approval for a paediatric licence by extrapolation of adult data for one biologic, the pharmaceutical industry will adopt the same approach for the many other biologics currently being approved for adult severe asthma(11). Worryingly, benralizumab, which targets the IL-5 receptor on eosinophils and basophils and results in complete depletion of circulating eosinophils, resulted in worse asthma in clinical trials(12-14). However, it has been approved by the US Food and Drug Administration for children >12 years despite only 4% of all participants in the five Phase 3 studies being aged 12-17 years(15). Surely robust efficacy and safety data are mandatory before a paediatric licence is granted for drugs whose potential harmful effects cannot be predicted from adult studies.

To address the current discrimination against children in the UK, we have united as a paediatric respiratory community to undertake a clinical trial funded by the National Institute of Health Research (NIHR). We will use a unified clinical protocol including at least 8 weeks electronic adherence monitoring(16) prior to randomisation. The "**Treating severe paediatric asthma; a randomised trial of mepolizumab and omalizumab (TREAT) trial"** will compare the efficacy of omalizumab and mepolizumab in children with STRA. It is a non-inferiority trial over 52 weeks with asthma attacks as the primary outcome, also investigating potential biomarkers for response in children. As with the adult PREDICTUMAB trial(17) endorsed by the European Respiratory Society, TREAT is a pragmatic trial to determine which biologic is best for which individual child. Importantly, we will also demonstrate the advantages of specialist paediatric centres and optimise our ability to undertake future paediatric clinical trials. This framework should also be attractive for the pharmaceutical industry for future trials. The need for pragmatic trials will increase exponentially and we are grateful to the NIHR for having the foresight to fund TREAT. UK children with severe asthma cannot continue to be treated as second class citizens.

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