

Biologics for paediatric severe asthma: trick or TREAT?



Although most asthma in UK children can be controlled with low to moderate doses of inhaled corticosteroids, there remains a small group with severe disease and poor control despite maximal treatment whose needs are unmet. There are stark differences in the health care received by this group compared with that of adults with similar clinical characteristics. Unlike adults, children with severe asthma are not treated at specialist centres, clinical trials of novel therapeutics are not tailored for children, and novel biologics are being approved without evidence of efficacy. In adults, severe asthma is managed in a commissioned service, and only named specialist centres can 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 use.¹ This multidisciplinary assessment helps to identify remediable factors, such as poor adherence, and ensures that appropriate patients are started on costly biologics. By contrast, despite international guideline recommendations,² there is no such service provision or specification for children in the UK and most other parts of the world, even though children with severe asthma have associated long-term morbidities, including development of chronic obstructive pulmonary disease in adulthood.³ Without specialist services, children could be exposed to potential harm associated with inappropriate prescribing of biologics, or they could be denied an appropriate therapy, and an absence of accurate monitoring will result in a missed opportunity to assess the benefit of biologics across the lifespan as disease modifying drugs.⁴

Children with severe therapy-resistant asthma (STRA) and refractory difficult asthma⁵ should be considered for biologics² but, until July, 2018, the only biologic licensed for children was the anti-immunoglobulin (Ig) E monoclonal antibody, omalizumab. However, the restricted prescribing guidelines, including a narrow serum IgE range, and the variable clinical response in STRA,⁶ has left a substantial 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: first, that the appropriate studies are not being done in children (for instance, inappropriate endpoints such as FEV₁ are selected); second, that drug development

is aimed at therapeutic targets from adult models of disease; and finally, there are very little data to guide choosing the optimal biologic for individual patients.

Mepolizumab (the monoclonal antibody to interleukin-5) substantially reduces the frequency of asthma attacks in adults. Although adolescents (older than 12 years) were eligible for the trials, the actual numbers of adolescents included were small (about 30 of more than 800 participants). However, mepolizumab was licensed for use in children aged 6–17 years by the European Medicines Agency in August, 2018, despite the inadequate efficacy data in adolescents older than 12 years, and the complete absence of efficacy data in those aged 6–11 years. This decision is clearly of huge concern and contravenes European Paediatric regulations. By contrast, omalizumab was only licensed after its efficacy was shown in children aged 6–16 years.⁶ Although most children with STRA have steroid-resistant airway eosinophilia,^{7,8} which should respond to mepolizumab, the eosinophilia may not be due to T helper 2 cytokines—which have been difficult to detect in paediatric STRA—highlighting the need for paediatric studies.⁹ Biomarkers for the subgroup most likely to respond also need to be identified in studies of children. Furthermore, in the context of a maturing immune system and because of the regulatory function of eosinophils in immune homeostasis,¹⁰ the circulatory depletion of these cells 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 being approved for adult severe asthma.¹¹ Worryingly, benralizumab, which targets the interleukin-5 receptor on eosinophils and basophils and results in complete depletion of circulating eosinophils^{12–14} has been approved by the US Food and Drug Administration for children older than 12 years despite only 4% of all participants in the five published phase 3 studies¹⁵ being aged 12–17 years. We accept that trials are ongoing in adolescents, and that studies in children are challenging. We also acknowledge that regulatory agencies might have provided paediatric approval to avoid children being denied access to novel drugs while evidence is collated. However, robust efficacy and safety data are surely mandatory before a paediatric



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For the European Medicines Agency paediatric regulations see <https://www.ema.europa.eu/en/human-regulatory/overview/paediatric-medicines/paediatric-regulation>

licence is granted for drugs whose potential harmful effects cannot be predicted from adult studies. If licences are granted, then post-marketing surveillance must be mandated. Without steps like these, biologics for children will creep into the Global Initiative for Asthma and other guidelines without any evidence base.

To address the age discrimination against children in the UK, we have united as a paediatric respiratory community to undertake a clinical trial funded by the UK National Institute for Health Research. We will use a unified clinical protocol that includes at least 8 weeks of electronic adherence monitoring before randomisation. The so-called 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. This is a non-inferiority trial for 52 weeks, with asthma attacks as the primary outcome, but we will also investigate biomarkers of response in children. As with the adult PREDICTUMAB trial¹⁶ endorsed by the European Respiratory Society, TREAT is a pragmatic trial to determine which biologic is best for each individual child. Importantly, we will aim to demonstrate the advantages of specialist paediatric severe asthma centres and thereby encourage childhood STRA to also be commissioned as a specialist service. This framework should also be attractive for the pharmaceutical industry to engage with paediatricians to design future trials specifically for children and to enable efficient recruitment and regulatory approval. The need for pragmatic trials will increase exponentially and we are grateful to the National Institute for Health Research 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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