ORIGINAL RESEARCH LETTER

Childhood-onset severe hypereosinophilic asthma: efficacy of benralizumab

To the Editor:

Hypereosinophilic syndrome (HES) is a group of rare chronic disorders that are defined by an absolute blood eosinophil count (BEC) of at least 1.500×10^9 cells·L^{-1} on at least two occasions [1] with absence of secondary causes of eosinophilia (including parasitic infections, malignancy as myeloproliferative variants) and end-organ eosinophilic infiltration with associated damage [2]. In 2006, a working group modified the definition of HES to include other previously distinct disease entities associated with eosinophilia, such as eosinophilic granulomatosis with polyangiitis (EGPA, formerly known as Churg–Strauss syndrome) and chronic eosinophilic pneumonia [3]. EGPA typically occurs in middle-aged adults with asthma, and childhood-onset is rare with a prevalence of 10–13 patients per million people [4, 5]. We report here a series of six children with childhood-onset asthma with oral corticosteroid (OCS) dependence associated with hypereosinophilic asthma with a long-term follow-up and the marked efficacy of benralizumab. The study was declared to the French Data Protection Authority (CNIL) according to the reference methodology MR004. All of the included patients or their parents received an information note and were given the opportunity to oppose the use of their personal data, but no refusals were received.

The median age of the children at the beginning of care was 5.5 years (range 5 to 10 years) and four were male. A descriptive history of the children (at diagnosis and after follow-up) is reported in table 1. All of the patients had severe refractory asthma partially controlled or uncontrolled with multiple attacks often requiring intensive care despite step 5 Global Initiative for Asthma (GINA) treatment [6] including OCS treatment. Pulmonary function revealed an obstructive pattern (forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) median 70%; range 57–84% of predicted value) associated with intermittent hypoxaemia for all patients. They all had abnormal chest computed tomography (CT): pulmonary infiltrates and nodules (n=6), pulmonary hyperinflation (n=6) and bronchial wall thickening (n=4). At the time of diagnosis, all patients had upper airway disease: nasal polyposis (n=3) and chronic rhinosinusitis (n=3), associated with vernal kerato-conjunctivitis (n=1). Other likely eosinophilic involvement was refractory gastro-oesophageal reflux (n=1) and cutaneous manifestations (urticaria n=1, atopic dermatitis n=1). All had a normal electrocardiographic pattern and echocardiogram. No signs of renal vasculitis were present. HES was confirmed by repeated high levels of absolute BEC, median peak BEC 1.955×10^9 cells·L^{-1} (range 1.550 to 40.400×10^9 cells·L^{-1}) and median peak fractional exhaled nitric oxide 110 ppb (range 35–247 ppb). Four had eosinophilia: median 7% (range 0–45) in bronchoalveolar lavage. All other causes of HES were ruled out: negative FIP1L1 platelet-derived growth factor receptor A; absence of eosinophilic leukaemia (bone marrow analysis for one patient); and normal blood tryptase levels. None of the patients had allergic bronchopulmonary aspergillosis, autoimmune disease or parasitic infection. Antineutrophil cytoplasmic antibody (ANCA) were negative and C-reactive protein (CRP) values were normal in all patients. Serum IgE levels were elevated in three patients with a median of 217 kU·L^{-1} (range 66–1447). Positive specific IgE$\geqslant$0.35 kU·L^{-1} was found in five patients, specifically for staphylococcal toxins in four.

All patients had received long-term treatment with continuous OCS (>1 year) resulting in growth retardation for four. All had received a biologic – omalizumab (6–48 months) then mepolizumab

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Severe hypereosinophilic asthma in children is extremely rare. This letter adds to the existing literature by providing long-term follow-up, and is the first report of the marked efficacy of benralizumab after failure of other biologic treatments. https://bit.ly/2G7Tc2k

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TABLE 1 Patient characteristics

Age years; sex	Follow-up years	Lung disease			Personal and familial history		Biomarkers		Treatments		
		Severe asthma	Recurrent hypoxaemia; FEV_1/FVC %	Chest CT	Other eosinophilic organ involvement	Familial history	BEC $\times 10^9$ cells·L^{-1}; F_{ENO} ppb; % eosinophil BAL; total IgE IU·mL^{-1}; specific IgE IU·mL^{-1}	ANCA and CRP	OCS years; bolus of CS; impact on growth; normalised LF	Biologics: follow-up years – TC, PC, NC	Benralizumab follow-up months; possibility of OCS discontinuation; BEC$\times 10^9$ cells·L^{-1}; F_{ENO} ppb
8; girl	4	Multiple hospitalisations /multiple intensive care	Yes; 84	PIN; SA	Chronic rhinosinusitis; GOR	Atopic dermatitis	1.810; 247; 0; 342; HDM 15.6	Negative ANCA and CRP	1; no; yes	Omalizumab: 1 – NC	5 –TC; yes; 0.58; NA
7; boy	8	Multiple hospitalisations	Yes; 69	PIN; HI	Nasal polyposis; VKC; epilepsy	Food allergies	1.550; 150; NA; 66; positive SAE	Negative ANCA and CRP	5; yes; yes	Omalizumab: 1 – TC and relapse; mepolizumab: 0.5 – TC and relapse	10 – TC; yes; 0; NA
5; boy	4	Multiple hospitalisations	Yes; 71	PIN; BWT; HI; IST	Nasal polyposis	Allergic rhinitis	5.000; 35; 5; 92; positive SAE	Negative ANCA and CRP	3; multiple; yes; yes	Omalizumab: 1 – PC; Mepolizumab: 1.5 – PC and relapse	12 – PC; yes; 0; NA
6; boy	8	Multiple hospitalisations /multiple intensive care	Yes; 71	PIN; BWT; HI; DMA	Chronic rhinosinusitis Chronic urticaria	None	1.700; 120; 45; NA; negative	Negative ANCA and CRP	3; multiples; yes; yes	Omalizumab: 4 – TC and relapse; mepolizumab: 0.5 – PC and relapse	6 – PC; no; 0; 111
9; boy	4	Multiple hospitalisations	No; 68	PIN; BWT; HI	Chronic rhinosinusitis Atopic dermatitis	Asthma	40.400; 49; 38; 1447; positive SAE	Negative ANCA and CRP	1; multiples; no; yes	Omalizumab: 0.5 – NC; cyclosporine: 0.5 – PC; mepolizumab: 0.5 – NC	10 – TC; yes; 0; NA
5; girl	10	Multiple hospitalisations /multiple intensive care	Yes; 57	PIN; BWT; HI; IST; DMA	Nasal polyposis	Type 1 diabetes	2.100; 100; 7; 226; positive SAE	Negative ANCA and CRP	4; yes; no	Omalizumab: 4 – PC and relapse; mepolizumab: 0.5 – NC	6 – TC; yes; normalised LF 0; NA

FEV_1: forced expiratory volume in 1; FVC: forced vital capacity; CT: computed tomography; F_{ENO}: exhaled nitric oxide fraction; CS: corticosteroid; PIN: pulmonary infiltrates and nodules; SA: segmental atelectasis; BWT: bronchial wall thickening; HI: hyperinflation; IST: interlobular septal thickening; DMA: diffuse mosaic attenuation; GOR: gastro-oesophageal reflux; VKC: vernal kerato-conjunctivitis; peak BEC: blood eosinophil count; BAL: bronchoalveolar lavage; peak total IgE (measured by ImmunoCAP): specific IgE towards common specific inhaled mould, food allergens and staphylococcal toxins (ImmunoCAP Phadiatop Infant; Uppsala, Sweden); HDM: house dust mites-specific IgE (⩾0.35 kU·L^{-1}); SAE: *Staphylococcus aureus* enterotoxins-specific IgE (⩾0.35 kU·L^{-1}); ANCA: anti-neutrophil cytoplasmic antibody; CRP: C-reactive protein; OCS: oral corticosteroid; LF: lung function; TC: total control; PC: partial control, as defined by the Global Initiative for Asthma; NC: no control; NA: not available.

(6–18 months) at recommended doses for children of school age for both biological treatments, which failed to control their asthma. One patient received cyclosporine with partial control but relapsed after 6 months. Finally, all patients received benralizumab for 5 to 12 months (at the same dosage as used in teenagers), which resulted in total asthma control for four and discontinuation of OCS for five.

All of the children of our series were diagnosed as having severe hypereosinophilic asthma. A diagnosis of EGPA was not retained even though they all had four of the six clinical findings for EGPA in accordance with the American College of Rheumatology classification [7] (*i.e.* asthma, eosinophilia, mononeuropathy/polyneuropathy, non-fixed pulmonary infiltrates on radiography, paranasal sinus abnormality, bloods vessel with extravascular eosinophils). They all received long-term treatment with daily OCS and immunomodulatory agents such as cyclosporine with substantial toxic effects as described in the literature [8]. However, in a more recent paper, Cottin *et al.* [9] state that a diagnosis of EGPA requires asthma, hypereosinophilia and at least one new-onset extra bronchopulmonary organ manifestation of disease (other than rhinosinusitis or other ear, nose and throat manifestations), which was not present in our cases.

Moreover, conversely to adults, Gendelman *et al.* [10] showed that children with EGPA were significantly more likely to have lung involvement ($p<0.001$) and eosinophilic gastroenteritis ($p=0.02$). Unlike Zwerina's paediatric cases [11], but similar to ours, none of the children in Gendelman *et al.*'s series [10] had positive ANCA.

Interleukin-5 is a cytokine with a selective role in eosinophil maturation, differentiation, mobilisation, activation and survival, so interleukin-5 inhibition is a logical therapeutic target for EGPA.

In the literature, mepolizumab (a fully humanised, anti-interleukin-5 (anti-IL-5)) has been largely explored in the context of HES syndrome. After proof-of-concept studies [12, 13], a randomised, double-blind, placebo-controlled trial [14] showed that treatment with mepolizumab led to significant reduction, and often discontinuation, of OCS in patients with HES who were negative for FIP1L1-PDGFRA.

Benralizumab, a humanised, afucosylated interleukin-5 receptor α monoclonal antibody with a different mechanism of action compared to other anti-IL-5 agents, reduces BEC by enhancing antibody-dependent cellular cytotoxicity, which represents a potential advantage of this biologic in the treatment of EGPA [15]. It has been explored for the treatment of diseases other than asthma with prominent tissue eosinophilia: a phase II placebo-controlled trial showed that benralizumab reduced BEC and MPO-ANCA in patients with FIP1L1-PDGFR-negative HES, with an improvement in symptoms of bronchial asthma [16].

Our description of severe hypereosinophilic asthma in children adds to the existing literature by providing long-term follow-up. Furthermore, we are the first to report the efficacy of benralizumab after failure of other biologic treatments for five out of six children. Nevertheless, a long follow-up is necessary to confirm the absence of relapse as we have seen with the other biologics in our population. International multicentre controlled studies must confirm this therapeutic option for reducing the rates of steroid-related adverse effects and the risk of mortality in paediatric patients with severe hypereosinophilic asthma.

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