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 $1.500 \times 10^9 \text{cells} \cdot \text{L}^{-1}$ 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 $1.955 \times 10^9 \text{cells} \cdot \text{L}^{-1}$ (range 1.550 to 40.400 $\times 10^9 \text{cells} \cdot \text{L}^{-1}$) and median peak fractional exhaled nitric oxide (FE(NO)) 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 $\geq 0.35$ 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.
| Age years; sex | Follow-up years | Severe asthma | Recurrent hypoxaemia; FEV₁/FVC % | Lung disease | Personal and familial history | Biomarkers | Treatments | Biologics: follow-up years – TC, PC, NC | Benralizumab follow-up months; possibility of OCS discontinuation; BEC×10⁹ cells·L⁻¹; FENO ppb |
|---------------|----------------|---------------|---------------------------------|-------------|-------------------------------|------------|-----------|-----------------------------------------|---------------------------------------------|
| 8; girl       | 4              | Yes; 84       | PIN; SA                         | Chronic rhinosinusitis; GOR | Atopic dermatitis | BEC ×10⁹ cells·L⁻¹; FENO ppb | 1; no; yes | Omalizumab: 1 – NC | 5 – TC; yes; 0.58; NA |
| 7; boy        | 8              | Yes; 69       | PIN; HI                         | Nasal polyposis; VKC; epilepsy | Food allergies | 1.810; 247; 0; 342; HDM 15.6 | Negative ANCA and CRP | 5; yes; yes | Omalizumab: 1 – TC and relapse; mepolizumab: 0.5 – TC and relapse |
| 5; boy        | 4              | 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 |
| 6; boy        | 8              | 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 |
| 9; boy        | 4              | 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 | 6 – PC; no; 0; 111 |
| 5; girl       | 10             | Yes; 57       | PIN; BWT; HI; IST; DMA          | Nasal polyposis | Type 1 diabetes | 2.100; 100; 7; 224; positive SAE | Negative ANCA and CRP | 4; yes; no | Omalizumab: 4 – PC and relapse; mepolizumab: 0.5 – NC | 6 – TC; yes; normalised LF; NA |

FEV₁: forced expiratory volume in 1; FVC: forced vital capacity; CT: computed tomography; FENO: 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/polynuropathy, non-fixed pulmonary infiltrates on radiography, paranasal sinus abnormality, blood 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.

Jocelyne Just1,2, Melisande Bourgoin1,2, Flore Amat1,2, Nathalie Cottel1, Nathalie Lambert1,2 and Stephanie Wanin1,2

1AP-HP, Groupe hospitalier Trousseau-La Roche Guyon, Centre de l’Asthme et des Allergies, Paris, France. 2Sorbonne - université, Paris, France.

Correspondence: Jocelyne Just, Centre de l’Asthme et des Allergies, Groupe hospitalier Trousseau-La Roche Guyon, 26 Avenue du Dr Arnold Netter, 75012 Paris, France. E-mail: jocelyne.just@aphp.fr

Received: 2 June 2020 | Accepted after revision: 21 Sept 2020

Conflict of interest: J. Just reports grants and personal fees from Novartis, grants from ALK-Abello, and personal fees from Stallergenes, AstraZeneca and Thermo Fisher, outside the submitted work. M. Bourgoin reports grants from Stallergènes and ALK-Abello, and personal fees from Novartis, outside the submitted work. F. Amat has nothing to disclose. N. Cottel has nothing to disclose. N. Lambert has nothing to disclose. S. Wanin has nothing to disclose.

References

1 Simon H, Rothenberg M, Bochner B, et al. Refining the definition of hypereosinophilic syndrome. J Allergy Clin Immunol 2010; 126: 45–49.
2 Allen JN, Davis WB. Eosinophilic lung diseases. Am J Respir Crit Care Med 1994; 150: 1423–1438.
3 Klion AD, Bochner BS, Gleich GJ, et al. Approaches to the treatment of hypereosinophilic syndromes: a workshop summary report. J Allergy Clin Immunol 2006; 117: 1292–1302.
4 Watts RA, Scott DG. Epidemiology of the vasculitides. Curr Opin Rheumatol 2003; 15: 11–16.
Mahr A, Guillemin L, Poissonnet M, et al. Prevalences of polyarteritis nodosa, microscopic polyangiitis, Wegener’s granulomatosis and Churg-Strauss syndrome in a French urban multiethnic population in 2000: a capture-recapture estimate. *Arthritis Rheum* 2004; 51: 92–99.

Global Initiative for Asthma (GINA). https://ginasthma.org/tag/children/

Masi AT, Hunder GG, Lie JT, et al. The American College of Rheumatology 1990 criteria for the classification of Churg-Strauss syndrome (allergic granulomatosis and angiitis). *Arthritis Rheum* 1990; 33: 1094–1100.

Ogbogu PU, Bochner BS, Butterfield JH, et al. Hypereosinophilic syndrome: a multicenter, retrospective analysis of clinical characteristics and response to therapy. *J Allergy Clin Immunol* 2009; 124: 1319–1325.

Cottin V, Bel E, Bottero P, et al. Revisiting the systemic vasculitis in eosinophilic granulomatosis with polyangiitis (Churg-Strauss): a study of 157 patients by the Groupe d’Etudes et de Recherche sur les Maladies Orphelines Pulmonaires and the European Respiratory Society Taskforce on eosinophilic granulomatosis with polyangiitis (Churg-Strauss). *Autoimmun Rev* 2017; 16: 1–9.

Gendelman S, Zelt A, Spalding SJ. Childhood onset eosinophilic granulomatosis with polyangiitis (formerly Churg-Strauss syndrome): a contemporary single-center cohort. *J Rheumatol* 2013; 40: 929–935.

Zwerina J, Eger G, Englbrecht M, et al. Churg-Strauss syndrome in childhood: a systematic literature review and clinical comparison with adult patients. *Semin Arthritis Rheum* 2009; 39: 108–115.

Koury MJ, Newman JH, Murray JJ. Reversal of hypereosinophilic syndrome and lymphomatoid papulosis with mepolizumab and imatinib. *Am J Med* 2003; 115: 587–589.

Rosenwasser L, Rothenberg M. IL-5 pathway inhibition in the treatment of asthma and Churg-Strauss syndrome. *J Allergy Clin Immunol* 2010; 125: 1245–1246.

Rothenberg M, Klion A, Roufosse F, et al. Treatment of patients with the hypereosinophilic syndrome with mepolizumab. *N Engl J Med* 2008; 358: 1215–1228.

Kolbeck R, Kozhich A, Koike M, et al. MEDI-563, a humanized anti-IL-5 receptor alpha mAb with enhanced antibody dependent cell-mediated cytotoxicity function. *J Allergy Clin Immunol* 2010; 125: 1344–1353.

Takenaka K, Minami T, Yoshihashi Y, et al. Decrease in MPO-ANCA after administration of benralizumab in eosinophilic granulomatosis with polyangiitis. *Allergol Int* 2019; 68: 539–540.