Childhood-onset severe hypereosinophilic asthma: efficacy of benralizumab

J. Just, M. Bourgoin, F. Amat, N. Cottel, N. Lambert, S. Wanin

ERJ open research
THE BEST IN OPEN ACCESS BASIC, TRANSLATIONAL & CLINICAL RESPIRATORY RESEARCH

Early View

Research letter

Childhood-onset severe hypereosinophilic asthma: efficacy of benralizumab

J. Just, M. Bourgoin, F. Amat, N. Cottel, N. Lambert, S. Wanin

Please cite this article as: Just J, Bourgoin M, Amat F, *et al*. Childhood-onset severe hypereosinophilic asthma: efficacy of benralizumab. *ERJ Open Res* 2020; in press (https://doi.org/10.1183/23120541.00339-2020).

Childhood-onset severe hypereosinophilic asthma: efficacy of benralizumab

Severe hypereosinophilic asthma and benralizumab

Word 12

J. Just MD,PhD[1,2] , M. Bourgoin MD,MSc [1,2,], F. Amat MD,PhD[1,2], N. Cottel MD[1], N. Lambert MD[1,2], S. Wanin MD[1,2,]

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

Corresponding author

Pr. Jocelyne Just, M.D., Ph.D., 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 Tel. +33 1 71 73 68 47; Fax: +33 1 44 73 53 15

No declaration of funding for the research reported in this manuscript.

Dear Editor,

Hypereosinophilic syndrome (HES) is a group of rare chronic disorders that are defined by an absolute blood eosinophil count (BEC) of at least 1.500×10^9cells/L on at least two occasions[i] with absence of secondary causes of eosinophilia (including parasitic infections, malignancy as myeloproliferative variants) and end-organ eosinophilic infiltration with associated damage[ii]. 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[iii]. EGPA typically occurs in middle-age adults with asthma and childhood-onset is rare with a prevalence of 10-13 patients per million people[iv,v]. 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 the included patients or their parents received an information note and could have opposed 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 the Table. All the patients had severe refractory asthma partially or uncontrolled with multiple attacks often requiring intensive care despite step 5 GINA treatment[vi] including OCS treatment. Pulmonary function revealed an obstructive pattern (FEV_1/FVC median 70%; range 57-84 % of predicted value) associated with intermittent hypoxemia for all the patients. They all had abnormal chest CT: pulmonary infiltrates and nodules (n=6), pulmonary hyperinflation (n=6), and bronchial wall thickening (n=4). At the time of diagnosis, all the patients had upper airway disease: nasal polyposis (n=3), chronic rhinosinusitis (n=3),

associated with vernal kerato-conjunctivitis (n=1). Other likely eosinophilic involvement was refractory gastroesophageal reflux (n=1), 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 attested by repeated high levels of absolute BEC, median peak BEC 1.955 $\times 10^9$cells/L (range 1.550 to 40.400 $\times 10^9$cells/L), 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 leukemia (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 CRP values were normal in all the patients. Serum IgE levels were elevated in three patients with a median of 217 kU/l (range 66-1447). Positive specific IgE $\geq$ 0.35 kU/L were found in five patients, specifically for staphylococcal toxins in four.

All the 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 (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 the 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[vii] (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[viii]**.** However**,** in a more recent paper, Cottin et al.[ix] 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 ENT manifestations) which was not present in our cases.

Moreover, conversely to adults, Gendelman et al.[x] 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 pediatric cases[xi], but similar to ours, none of the children in Gendelman and al.'s series[9] had positive ANCA.

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

In the literature, mepolizumab (a fully humanized, anti–interleukin-5 (anti-IL-5)), has been largely explored in the context of HES syndrome. After proof-of-concept studies[xii, xiii]. a randomized, double-blind, placebo-controlled trial[xiv] 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 humanized, 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[xv]. 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[xvi].

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 5/6 children. Nevertheless, a long follow-up is necessary to attest 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.

Table: Patient characteristics

Demographic data		**Lung disease**			**Personal and familial history**		**Biomarkers**		**Treatments**		
Age year; Gender	**Follow-up years**	**Severe Asthma**	**Recurrent hypoxemia; FEV_1/CVF (%PV)**	**Chest CT**	**Other eosinophilic organ involvement**	**Familial history**	**BEC; FeNO; % eosinophil BAL; Total IgE; Specific IgE**	**ANCA; 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; FeNO**
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 years-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

Abbreviations: CT (computed tomography); PIN (Pulmonary Infiltrates and Nodules); SA (Segmental Atelectasis); Bronchial Wall Thickening (BWT); HI (hyperinflation); Interlobular Septal Thickening (IST); DMA (Diffuse Mosaic Attenuation); GOR (Gastroesophageal reflux); VKC (vernal kerato-conjunctivitis); peak BEC (Blood Eosinophil Count, $\times 10^9$cells/L.); Peak FeNO (Fraction of exhaled Nitric Oxide) ppb; % eosinophil in BAL (Broncho-Alveolar Lavage) ; Peak total IgE (measured by ImmunoCAP), IU/mL); specific IgE toward common specific inhaled, mold, food allergens and staphylococcal toxins (ImmunoCAP Phadiatop Infant; Uppsala, Sweden). HDM (House Dust Mites-specific IgE $\geq$ 0.35 kU/L); SAE (Staphylococcus Aureus Enterotoxins- specific IgE $\geq$ 0.35 kU/); ANCA (Anti neutrophil cytoplasmic antibody); CRP ;OCS (Oral Corticosteroid); LF (Lung Function); TC (Total Control); PC (Partial Control) as defined in the GINA guidelines; NC (No Control); NA (Not Available)

Reference

[i] Simon H, Rothenberg M, Bochner B, Weller P, Wardlaw A, Wechsler M, Rosenwasser L, Roufosse F, Gleich G, Klion A. Refining the definition of hypereosinophilic syndrome. J Allergy Clin Immunol 2010; 126: 45–49.

[ii] Allen JN, Davis WB. Eosinophilic lung diseases. Am J Respir Crit Care Med 1994; 150: 1423–1438.

[iii] Klion AD, Bochner BS, Gleich GJ Thomas B Nutman, Rothenberg M, S Hans-Uwe, Wechsler M, Weller P, The Hypereosinophilic Syndromes Working Group. Approaches to the treatment of hypereosinophilic syndromes: a workshop summary reports. J Allergy Clin Immunol 2006; 117: 1292–1302.

[iv] Watts RA, Scott DG. Epidemiology of the vasculitides. Curr Opin Rheumatol 2003; 15: 11-6.

[v] Mahr A, Guillevin L, Poissonnet M, Ayme S. 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: 92-9.

[vi] https://ginasthma.org/tag/children/

[vii] Masi AT, Hunder GG, Lie JT, Michel BA, Bloch DA, Arend WP, 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.

[viii] Ogbogu PU, Bochner BS, Butterfield JH, Gleich GJ, Huss-Marp J, Kahn JE, Leiferman KM, Nutman TB, Pfab F, Ring J, Rothenberg ME, Roufosse F, Sajous MH, Sheikh J, Simon D, Simon HU, Stein ML, Wardlaw A, Weller PF, Klion AD. Hypereosinophilic syndrome: a

multicenter, retrospective analysis of clinical characteristics and response to therapy. J Allergy Clin Immunol 2009; 124: 1319-1325.

[ix] Cottin V, Bel E, Bottero P, Dalhoff K, Humbert M, Lazor R, Sinico RA, Sivasothy P, Wechsler ME, Groh M, Marchand-Adam S, Khouatra C, Wallaert B, Taillé C, Delaval P, Cadranel J, Bonniaud P, Prévot G, Hirschi S, Gondouin A, Dunogué B, Chatté G, Briault C, Pagnoux C, Jayne D, Guillevin L, Cordier JF. 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.

[x] GendelmanS, ZeftA, SpaldingSJ.Childhoodonset eosinophilic granulomatosis with polyangii tis (formerly Churg-Strauss syndrome): a contemporary single-center cohort. J Rheumatol 201; 40: 929-935.

[xi] Zwerina J, Eger G, Englbrecht M, Manger B, Schett G. Churg-Strauss syndrome in childhood: A systematic literature review and clinical comparison with adult patients. Semin Arthritis Rheum 2009; 39: 108-115.

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

[xiii] 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.

[xiv] Rothenberg M, Klion A, Roufosse F, Kahn J, Weller P, Simon H, Schwartz L, Rosenwasser L, Ring J, Griffin E, Haig A, Frewer P, Parkin J, Gleich G; Mepolizumab HES Study Group. Treatment of patients with the hypereosinophilic syndrome with mepolizumab. N Engl J Med 2008; 358: 1215-1228.

[xv] Kolbeck R, Kozhich A, Koike M, Peng L, Andersson C, Damschroder M, Reed J, Woods R, Dall'acqua W, Stephens J, Erjefalt J, Bjermer L, Humbles A, Gossage D, Wu H, Kiener P, Spitalny G, Mackay C, Molfino N, Coyle A. MEDI-563, a humanized anti-IL-5 receptor alpha mAb with enhanced antibodydependent cell-mediated cytotoxicity function. J Allergy Clin Immunol 2010; 125: 1344-1353.

[xvi] Takenaka K, Minami T, Yoshihashi Y, Hirata S, Kimura Y, Kono H. Decrease in MPO-ANCA after administration of benralizumab in eosinophilic granulomatosis with polyangiitis, Allergol. Int. 2019; 68: 539–540.