The Severe Paediatric Asthma Collaborative in Europe (SPACE) ERS Clinical Research Collaboration: enhancing participation of children with asthma in therapeutic trials of new biologics and receptor blockers

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The Severe Paediatric Asthma Collaborative in Europe (SPACE) ERS Clinical Research Collaboration is devoted to describing phenotypes of children with severe asthma and to enhancing their participation in therapeutic trials of new drugs http://ow.ly/zxgB30m01zR

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Asthma is one of the most common chronic diseases of childhood. Fortunately, most children with asthma have a mild or moderate form of the disease [1], and symptom control can be achieved by ensuring adequate provision of care and continuously addressing the basics in asthma management through shared decision-making with patients and their families. However, asthma remains difficult to treat for a small proportion of children who may be symptomatic despite aggressive maintenance therapy and after management issues like adherence to treatment have been addressed [2, 3]. The expression "a small proportion" is anecdotal, since estimating the "true" prevalence of severe asthma in childhood has proved challenging. Epidemiological research on this topic is hampered by the heterogeneity in criteria used to define and classify paediatric severe asthma, as well as the scarcity of validated monitoring and outcome-assessment tools [2, 3]. Moreover, even with the adoption of a more standardised and internationally acknowledged definition, an accurate estimate of severe asthma prevalence should be based on very large population cohort studies including information on therapy not only by questionnaires but also from pharmacy-dispensed prescriptions.

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Data from two population-based cohort studies performed in the general population of school-aged children in Sweden and in Norway [4, 5] reported a prevalence of 0.5% and 0.23%, respectively, but confidence intervals around these estimates are large due to the small sample size. Prevalence is also affected by factors such as suboptimal asthma prevention strategies and access to healthcare and medication [6]. Notwithstanding, there is no doubt that children with severe asthma account for a consistently larger amount of resource expenditure in comparison with peers with less severe disease, with a burden for children, parents and families, and a reduced health-related quality of life [7]. Importantly, patients carry this burden forward as they transition to adulthood, with impairments in lung function and possible progression to chronic obstructive pulmonary disease [8].

While the well-known saying among paediatric care providers that "children are not small adults" may seem overused, it remains true for paediatric severe asthma. A strong body of evidence from translational studies has shown that mechanisms at work in severe asthma, patterns of inflammation, and pathophysiology are not necessarily the same in children and in adults [9–11]. Extrapolating clinical characteristics and severity patterns from adults may also be incorrect [12]. In a few studies on small samples, most children with severe asthma were atopic, with a history of eczema, allergic rhinitis and food allergy [7, 13, 14]; others report a number of children with severe exacerbations but pauci-symptomatic between the episodes, with lung function values in the normal range for their age, while adults are more likely to have a persisting disease expression pattern, including reduced lung function [15, 16].

Furthermore, despite a promising pipeline of biologics, oral receptor blockers and other new compounds in severe asthma [12, 17], novel interventions have been slow to arrive to paediatrics. Pharmaceutical companies have faced key challenges in designing and implementing paediatric drug development plans, leaving unmet needs in this field. Issues include the choice of adequate eligibility criteria for entering into clinical trials (*e.g.* inhaled or systemic corticosteroid dose thresholds, and lung function parameters), complicated research protocols that may be too demanding, especially for young children, and the selection and measurement of validated and patient-important outcomes, both of which need special consideration in paediatric trials. In addition, biomarkers that may predict response to treatment in adults, such as blood eosinophils, may be different for children given the different asthma endotypes in childhood [15, 18]. Hurdles in recruitment and underrepresentation of children in severe asthma trials (with or without adults) have ensued. This leads to uncertainties regarding the efficacy and safety of potentially valuable new treatments in paediatric severe asthma, which may not always be extrapolated from evidence in adult trials.

These considerations provide a strong rationale to set up studies that could provide more information on children and adolescents with severe asthma both to better define the disease, and in particular sub-phenotypes, and to personalise treatment. The two things are complementary as emerging phenotype-directed therapies proposed in adults still need to be approved in children. There is therefore an urgent need for collaborative trials on new anti-asthmatic drugs specifically recruiting children and adolescents, as expressed also by the European Medicines Agency, which officially supported the European Respiratory Society (ERS) Clinical Research Collaboration (CRC) on severe asthma in children, Severe Paediatric Asthma Collaborative in Europe (SPACE).

SPACE aims

The main aims of SPACE are as follows: 1) to provide a comprehensive real-life description of characteristics of patients with severe paediatric asthma in secondary/tertiary care centres across Europe, by setting up a prospective web-based database, incorporating baseline and annual follow-up data; 2) to establish a platform to enhance participation and retention of children with severe asthma in collaborative therapeutic trials of new biologics and receptor blockers specifically devoted to paediatric patients; and 3) to ameliorate treatment and care of children and adolescents with severe asthma and improve their quality of life, also taking into account possible differences by age and sex.

What SPACE has achieved so far

An overview of the protocol for the SPACE registry has been recently published in *Breathe* [19]. As definition of criteria for severe asthma is one of the problems, we worked on the identification of eligibility criteria for paediatric patients aged 6–17 years with severe asthma mainly based on the ERS/American Thoracic Society guidelines [20]. A complete list of inclusion and exclusion criteria can be found in *Breathe* [19], while data items to be included in order to characterise the clinical phenotypes of these patients are shown in table 1 [21]. The goal is to identify patients who can potentially benefit from specific therapies, and to explore aspects that could be crucial in evaluating efficacy of treatment, including quality of life. For the moment, the SPACE database will provide a comprehensive real-life description of baseline characteristics of severe paediatric asthma in 11 major secondary and tertiary care centres across Europe [19].

TABLE 1 Severe Paediatric Asthma Collaborative in Europe (SPACE) case report form sections

Demographics
Personal and family history
Inclusion criteria
Clinical management at a specialised centre >6 months
Confirmation of asthma (symptoms, spirometry)
High-dose inhaled corticosteroids (as defined by Liu *et al.* [19]), plus long-acting β_2-agonists or leukotriene modifiers or theophylline or systemic corticosteroids for ⩾6 months
Exclusion criteria
Symptoms primarily due to a condition that might mimic asthma (*e.g.* foreign body, malformation, cystic fibrosis)
Comorbidities and risk factors
Obesity
Symptomatic gastro-oesophageal reflux
Mental health disorders (*e.g.* anxiety, depression)
Disordered breathing (*e.g.* vocal cord dysfunction, hyperventilation syndrome)
Obstructive sleep apnoea
Nasal polyposis
Chronic rhinosinusitis
Atopic dermatitis
Allergic rhinitis or conjunctivitis
Environmental triggers
Poor adherence
Recreational drug use
Adherence to therapy
Parental/patient report
Prescription refill rate
Electronic monitoring
Prednisolone/theophylline levels
Symptoms likely due to non-adherence
Asthma-related Paediatric Quality of Life questionnaire
Asthma background information
Lung function
Fractional exhaled nitric oxide
Atopic markers
Blood and sputum eosinophils
Bronchoscopic and lung imaging findings
Asthma exacerbations in the last 12 months
Asthma control at entry
Asthma Control Questionnaire score
Asthma Control Test score
GINA assessment
Respiratory treatment at entry

GINA: Global Initiative for Asthma.

The web-based SPACE database has been developed in close collaboration with the Health Informatics Centre at the University of Dundee (UK), which already developed the European Multicentre Bronchiectasis Audit and Research Collaboration (EMBARC) registry of adult non-cystic fibrosis bronchiectasis [22].

A first round of enrolment across the included centres is expected by early 2019.

SPACE's potential and next steps

A long-term sustainability of this platform would allow several lines of development. The first and simplest step is to refine the database and, at the same time, to include more centres and patients. The SPACE steering committee will define the characteristics of the centres to be involved. As already underlined, the severity of asthma in childhood is often related to good asthma control, which could possibly be more easily achieved in large centres with multidisciplinary teams; above all, these centres also have the possibility to distinguish cases of true severe asthma from cases with a disease that can mimic asthma and cases in which asthma control is not achieved due to comorbidities or lack of compliance [23].

The second important line of development is connected to the final goal of the SPACE network: to use the registry to recruit children and adolescents into trials of new therapies for asthma, and in addition to

prospectively evaluate the characteristics of those already currently on biologic therapy. The database would in fact provide information to academia and to industry on the number and characteristics of children eligible for trials of new and existing drugs. Centres participating in the registry could develop into a virtual clinical trials network to perform trials in Europe where only a few children with asthma are eligible per centre. In this respect, the ERS would have a central role, for communication with national societies and ERS researchers/members, for patient engagement through the European Lung Foundation (ELF) and for an independent liaison with industry partners.

SPACE will collaborate with a similar ERS CRC in adults: Severe Heterogenous Asthma Research collaboration, Patient-centred (SHARP) [24]. This will hopefully allow SPACE to implement two further goals: to rethink the critical passage from adolescence to adulthood in the management of severe asthma, and to give a deeper attention to patients', especially adolescents', and parents' input, in collaboration also with ELF.

Finally, in the near future, biomarkers in urine, blood and breath could be collected and measured. This will require additional consent and ethics committee approvals but could also represent an outstanding tool for a better definition of severe asthma phenotypes in children and adolescents, in addition to clinical and common laboratory findings, and for more personalised therapies. The availability of biomarkers will allow performance of mechanistic studies, *e.g.* to assess associations between biomarkers and risk of exacerbation or lung function decline, or biomarkers of response in children where biologic therapy is about to be initiated. One of the greatest achievements in the last years in asthma research has been the study of the immune responses and their consequent inflammatory profiles in response to triggers such as allergens, viruses and microbes. This has uncovered key mechanisms and has led to the successful adoption of new biologics targeting T2-mediated immunity, namely immunoglobulin (Ig)E, the interleukin (IL)-5 pathways, and more recently anti-IL4Rα and small molecules in late phase development [12, 17]. The success in clinical trials, especially in adults with severe asthma, has largely been due to the recognition that these mechanisms are of greatest importance in severe disease and in driving asthma attacks. A similar work for paediatric patients is at the moment only at the initial stage [25].

In conclusion, more precise definition of the phenotypes of severe asthma in children and adolescents, and better targeting of therapy based upon these, together with a network implementing these features to improve identification of children for clinical trials, are likely to facilitate an *ad hoc* and more successful approach rather than extrapolation from studies conducted in adults. This will lead to improved care and quality of life for young people with severe asthma. Furthermore, a better control of severe asthma early in life could represent a window of opportunity to modify the life-course of the disease.

Jonathan Grigg and Franca Rusconi are Chairs of the SPACE Clinical Research Collaboration. Members of the SPACE Clinical Research Collaboration: Jonathan Grigg (Queen Mary University of London, UK); Franca Rusconi (Meyer Children's University Hospital, Florence, Italy); Wim van Aalderen and Niels W.P. Rutjes (Academical Medical Centre, Amsterdam, the Netherlands); Karin C.L. Carlsen (Oslo University Hospital, Oslo, Norway); Courtney Coleman (European Lung Foundation, Sheffield, UK); James D. Chalmers (University of Dundee, UK); Steve Cunningham (University of Edinburgh, UK); Ricardo M. Fernandes (Hospital de Santa Maria, Lisbon, Portugal); Louise J. Fleming (Imperial College, London, UK); Betty Frankemölle (member of the SHARP patient advisory group); Monika Gappa (Marien Hospital, Wesel, Germany); Bülent Karadag (Marmara University, Istanbul, Turkey); Norrice M. Liu (Queen Mary University of London, UK); Fabio Midulla (Sapienza University, Rome, Italy); Marielle W.H. Pijnenburg (Erasmus MC-Sophia, University Medical Centre Rotterdam, Rotterdam, the Netherlands); European Lung Foundation severe asthma patient advisory group.

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