NOVELTY: a landmark study in phenotyping and endotyping chronic obstructive airway diseases in real clinical practice

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Shareable abstract (@ERSpublications)
NOVELTY is a prospective real life observational study that investigates asthma, COPD and asthma/COPD overlap over a period of years with the purpose to relate phenotype and endotype to clinical outcomes and disease trajectories https://bit.ly/3qERZRD

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Asthma and COPD are two common chronic airway diseases associated with high morbidity and mortality [1, 2]. It is estimated that approximately 20% of asthma and COPD have diagnosis or features of both [3]. There is growing appreciation of the need to tease out phenotypes and endotypes across the spectrum of chronic airway diseases [4, 5], to evolve towards precision medicine [6, 7]. While there have been recent large cohort studies following either severe asthma [8] or COPD [9], there is paucity of large real life longitudinal studies investigating both asthma and COPD together with the asthma/COPD overlap across the all disease severity spectrum without any predetermined pharmacological intervention.

NOVELTY is a 3-year, observational, prospective, longitudinal cohort study in patients with a diagnosis or suspected diagnosis of asthma, COPD or asthma/COPD overlap [10]. This study is important for several reasons. First, it is an important study by its size and its worldwide design, having investigated more than 12 000 patients recruited across different parts of the world, which makes it the largest real-life study dedicated to asthma and COPD so far. Second, it enrolled patients from different care settings, including university hospitals, other hospitals, private specialist clinics and, most importantly, primary care settings, in which the majority of asthma and COPD diagnosis are made and managed. Third, it is a longitudinal study which investigates patient reported outcomes, lung function, inflammatory and "omic" biomarkers and healthcare resource utilisation. This gives a comprehensive view of patient status that will support analysis of the relationship between phenotype/endotype of chronic airway diseases and clinical outcomes as well as disease trajectories.

In this issue of the *European Respiratory Journal*, Reddel *et al*. [11] report on the first results of the NOVELTY study by describing in great detail the baseline features of the enrolled patients. The authors classified the patients into three groups, asthma, COPD and asthma/COPD overlap, and graded each group according to physician assessed severity into mild, moderate and severe. Asthma accounted for 53% and COPD for 35%, while asthma/COPD overlap was found in 12% of the enrolled patients. The study brings some expected findings but also surprising data. As anticipated, asthma patients showed a dominant female gender and were younger than COPD and asthma/COPD overlap patients. Asthma more often featured atopic status, chronic upper airway diseases such as rhinitis, sinusitis and nasal polyposis, while COPD was more often associated with smoking history and cardiovascular comorbidities. From the figures provided in the current study, it can be deduced that asthma/COPD overlap was observed in 19% of all patients receiving an asthma diagnosis whereas 26% of those qualified as COPD displayed asthma features, according to the physician. When the diagnosis of asthma/COPD was mentioned, asthma preceded COPD in the majority of cases but in one third of cases, the two diagnoses were made at the same time, indicating that typical features of both diseases may concomitantly express at the moment of diagnosis. Another expected finding is that physician graded disease severity was well correlated with the intensity of

the dyspnoea, as well as the impairment in expiratory flow rate (FEV_1), the severity of airway obstruction (FEV_1/FVC ratio) and the exacerbation rate, thereby highlighting the importance clinicians give to these features in both diseases.

A strong message of the current paper, confirming a previous study [12], is the discrepancy between physician based diagnosis in real life and theoretical criteria needed to support the diagnosis as recommended by guidelines. Indeed, there was a high proportion of mild to moderate COPD patients who do not satisfy the criterion of the disease with a FEV_1/FVC lower than 0.7 or the lower limit of normal, an observation likely to reflect insufficient use of spirometry in real life. Similarly frustrating, but perhaps less unexpected, is the large majority of patients with moderate to severe asthma do not show significant reversibility to bronchodilation (figure 1). This finding definitively confirms what has already been shown in smaller cohorts recruited from clinical practice or from large epidemiological studies, in which reversibility was only found in 12% of patients who had previously received an asthma diagnosis [13]. Of course, lack of reversibility in the current study may partly be due to previous stabilisation of the disease by inhaled corticosteroid (ICS) therapy, as the large majority (>90%) of the patients were receiving maintenance treatment at inclusion, or due to airway remodelling in the more severe patients [14]. Unfortunately, NOVELTY has not planned bronchial challenge to assess bronchial hyperresponsiveness and performing bronchial challenge is much more sensitive for asthma diagnosis than resorting to the use of a sole bronchodilator test as a proof of increased airway fluctuation [15, 16]. Therefore, we can assume that a proportion of patients qualifying as asthmatic but not showing significant bronchodilation could have received diagnostic confirmation had they undergone a bronchial challenge. However, high rate of false asthma diagnosis in the community has been repeatedly reported [17]. Incorrect diagnosis of asthma and COPD may not only be a cause of concern and anxiety for the patient him/herself, but it may have unfavourable consequences in terms of public health spending by leading to unjustified drug prescriptions.

If the current study shows that exacerbation rate increased with the disease severity, the authors also want to highlight that the asthma/COPD overlap had the greatest exacerbation rate, that even mild disease may exacerbate and that approximately half of the patients quoted as severe in each group had no exacerbation in the previous 12 months before entering the study, thereby highlighting the unpredictable nature of exacerbation. The concept of exacerbation in the current study is, however, blurred by the rather loose definition. Indeed, an exacerbation was defined as a "yes" answer to the question "has your patient experienced an exacerbation of their asthma or COPD beyond the patient's usual day to day variance".

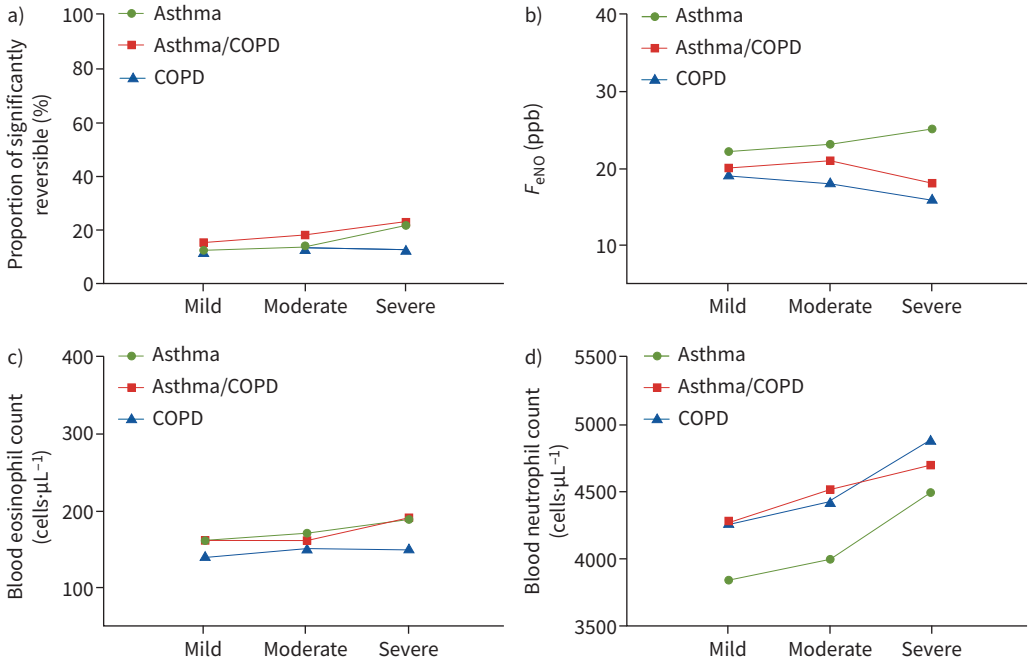

FIGURE 1 a) Proportion of patients with positive bronchodilator test (12% and 200 mL) in asthma, asthma/COPD and COPD, according to disease severity. Evolution of b) fractional exhaled nitric oxide (F_{eNO}), c) blood eosinophil and d) blood neutrophil counts classified according to disease severity. Adapted from REDDEL *et al.* [11].

No reference was made to the type of medication used to control the exacerbation nor to alteration in airway calibre during exacerbation. In disease such as asthma, the roots of which are the fluctuation of airway calibre and symptoms, we have to admit that the definition of exacerbation chosen by the authors of this study may be tricky. We would have preferred that exacerbations were defined by oral corticosteroid (OCS) or antibiotic course, even if this definition may harbour a part of subjectivity as prescription criteria of an OCS course were found to be highly variable among chest physicians and general practitioners alike [18, 19]. More solid to us, also less subject to bias recall, is the outcome of hospital admission in the year prior to entering the study, which concerned only 1% of mild asthma patients and 3% of those with mild COPD, while occurrence of this event reached 9% and 19% in those with severe asthma and COPD, respectively.

Perhaps the most surprising and intriguing data of the current study are the values of blood biomarkers and fractional exhaled nitric oxide (F_{eNO}) across the groups. Although inflammation heterogeneity within asthma and COPD is now recognised, there is still a tendency to qualify asthma as an eosinophilic/F_{eNO} high and COPD as a neutrophilic/F_{eNO} low disease. Although F_{eNO} values may appear rather similar across the groups at first sight, it is worth noting that the F_{eNO} evolved in the opposite direction in asthma and COPD when graded from mild to severe (figure 1). The average difference in F_{eNO} levels between severe asthma and severe COPD is appreciable, reaching 9 ppb (25 ppb *versus* 16 ppb), although values remained within the normal range. Blood eosinophil count did not markedly differ across the groups when expressed as absolute cell counts per µL (figure 1), even if patients with asthma had a slightly greater proportion of eosinophils when expressed as percentage of circulating leukocytes, probably related to the higher atopic status in asthma than in COPD. Similar blood eosinophil counts may, however, not imply similar airway eosinophilic inflammation. Indeed, airway eosinophilic inflammation measured by induced sputum cannot be entirely captured by blood analysis, with discordance being observed of up to 25% [20, 21], and latest GINA guidelines recommend the procedure of induced sputum in severe asthma patients to better define airway inflammatory status, where it is feasible. It is perhaps disappointing that such a big study intending to go deep into endotyping has not planned sputum induction in the groups of severe asthmatics in some expert centres. Not only did blood eosinophil count not clearly differ between those with asthma and COPD, but, even more surprising, there was no clear difference between mild and severe diseases. Moreover, the geometric mean appears to be below 200 cells μL^{-1} in all groups of asthmatics, meaning that a substantial part of them are below 150 cells μL^{-1}, a threshold under which it may be inadequate to prescribe continuous ICS, as suggested by a recent study by Pavord *et al.* [22]. The lack of relationship between asthma severity and blood eosinophil count goes against the assumption that a large proportion of severe asthma patients show severe eosinophilic inflammation refractory to corticoids, as evidenced by the recent publication of baseline data of SHARP across severe asthma registries, in which median blood eosinophil counts are generally well above 250 cells μL^{-1} in most countries [23]. This apparent contradiction indicates that the group of severe asthma exhibiting intense systemic eosinophilia, highlighted in current European registries, actually represents a minority of the patients deemed to be severe in common clinical practice. Even more unexpected is the relationship between disease severity and blood circulating neutrophils in asthma (figure 1). However, we believe this relationship may be driven by the greater amount of ICS and OCS taken by the severe patients. It is well known that OCS markedly increases blood circulating neutrophils by reducing their adherence to vascular endothelium. Therefore, it is likely that high dose of ICS may result in the same effect, albeit to a lesser extent. It is intriguing to observe that real-life studies in which the burden of ICS or OCS dose was decreased in asthma patients were associated with a reduction in blood circulating neutrophils [23–26]. Whether neutrophils play a detrimental role in the diseases, and in severe asthma in particular, has long been a matter of debate [27] and is still questionable, as a drug reducing circulating and airway neutrophils fail to improve asthma clinical outcomes [28]. Having accepted that lots of severe asthma patients are probably non-eosinophilic, we must ask what we can do to improve the health status of these patients in whom biologics targeting T2 molecular pathways are useless. Targeting the epithelial derived alarmin TSLP seems to hold promise [29]. Perhaps trying anti-IL-6, a cytokine found to be related to exacerbation in the SARP3 [30], or promoting regular low intensity physical activity, a care well validated in COPD [31], are also avenues worth being explored in the future.

Thanks to its comprehensive approach to the different domains of chronic airway diseases and its longitudinal design, NOVELTY holds great promise. No doubt it will deliver some key discoveries that will advance our understanding and management of airway obstructive diseases beyond the labels of asthma and COPD.

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