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EDITORIAL

Assessing inflammatory phenotypes and improving the cost-effectiveness of asthma and COPD care in the community

See linked article by Tilemann *et al*. on pg 407

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Asthma and chronic obstructive pulmonary disease (COPD) are common diseases, but diagnosis can be difficult within the constraints of primary care. The presenting symptoms of both conditions are non-specific and overlapping. Although questionnaires on symptoms and exposures can help in screening for and differentiating between asthma and COPD, objective confirmation is required before a diagnostic label is applied (generally for life) and long-term treatment commenced.

COPD diagnosis is relatively straightforward where there is access to spirometry; demonstration of fixed airways obstruction, usually in a smoker or ex-smoker, defines the disease. Diagnosing asthma is more difficult; lung function is often normal in the absence of triggers, and 'pseudo-asthma' (for example dysfunctional breathing) may spuriously suggest variable airflow obstruction. Under-diagnosis and misdiagnosis of COPD,[1] and over-diagnosis of asthma,[2] are commonly reported. Up to a quarter of patients labelled as having asthma lack objective confirmation of the disease. The reason for distinguishing between asthma and COPD is that they are different diseases with different pathophysiological characteristics and different guideline-defined treatment algorithms. In particular, low-dose inhaled corticosteroids (ICS) have an early and pivotal role in most cases of asthma but should be used more selectively and at higher doses in COPD. Long-acting bronchodilators are used as monotherapy in COPD, but only as an additional treatment to ICS in asthma. But making such a distinction is itself difficult. So how can we do better and why should we?

The use of alternative objective tests, such as biomarkers, is one possibility. A biomarker is a surrogate measurement designed to characterise and quantify an underlying disease process[3] and may correlate only weakly with symptoms. Airways and systemic inflammation play an important role in the pathogenesis and clinical manifestations of asthma and COPD. Heterogeneity in the type and intensity of inflammation occurs between and within individuals over time in both diseases, with implications for therapy and for prognosis.[4,5] Biomarker-based assessment of inflammation may therefore have a role in diagnosis and targeting treatment.

A number of potentially useful respiratory biomarkers have been described, although how we can integrate these into routine care is less clear.[3] The simplicity of measurement and relatively low cost of some biomarkers indicate their potential for routine use. In primary care it is feasible to obtain prognostic markers based on blood tests – e.g. C-reactive protein (CRP), serum immunoglobulin E (IgE) levels, and blood eosinophil counts. Measurement of the fraction of exhaled nitric oxide (F_ENO), a simple and inexpensive technology for assessing eosinophilic airway inflammation,[6] is also viable in routine general practice.[7] F_ENO measurement has a role where there is diagnostic difficulty,[8] in recognising different patterns of disease (i.e. phenotypes),[9] and in identifying those at risk of adverse outcomes (e.g. exacerbations).[10] F_ENO is most useful in targeting those patients who will benefit from anti-inflammatory treatment.[8] In difficult, poorly controlled asthma, where symptoms may be due to more than one cause, F_ENO measurement can be used predictively to avoid unnecessary and futile increases in steroid therapy.[11]

In this issue of the *PCRJ*, Tilemann *et al*. report the utility of biomarkers in the diagnosis and differentiation of asthma and COPD.[12] Over 200 symptomatic undiagnosed patients underwent a standardised evaluation centred firstly on physiological assessments. Based on the outcomes, patients were then placed into four groups: 'asthma', 'COPD', 'partial

reversibility' and 'no obstructive lung disease'. In addition, four biomarkers were measured: CRP, IgE, blood eosinophil count and F_ENO. The relationship between each biomarker and the subsequent diagnosis was investigated. Differences were observed between groups. COPD cases had significantly higher levels of CRP than asthma patients, although with considerable scatter and overlap. Asthma cases had higher F_ENO, blood eosinophil and IgE, although again there was wide scatter and overlap. These results are intuitively correct; one would expect that those patients with COPD would have greater systemic inflammatory activation and those with asthma more atopy and eosinophilic inflammation.

When assessing diagnostic tests it is important to know the performance characteristics based on sensitivity (the ability to identify positive results, so helping 'rule out' a diagnosis if negative) and specificity (the ability to identify negative results, helping 'rule in' if positive). In Tilemann *et al*'s paper,[12] receiver-operating characteristic (ROC) curves for each biomarker were constructed, and optimal cut-off values estimated. Consistent with other research, the sensitivities and specificities of F_ENO showed that it is a good test for ruling asthma out but not so good at ruling it in. Similar but less discriminatory findings were reported for blood eosinophilia (possibly an under-rated investigation) and raised IgE. CRP had reasonable sensitivity but a specificity of only 50% for COPD, so had a high false positive rate.

Where does this leave us? In patients with non-specific respiratory symptoms, a raised CRP makes COPD more likely, especially if spirometry is abnormal. Markers of eosinophilic inflammation or allergy make asthma more probable. Clearly, exploring the relationship between these biomarkers and treatment responsiveness would be the next logical step in these authors' investigations. A limitation of this paper[12] is that it focusses on the differentiation between asthma and COPD but doesn't 'drill deeper'. This is understandable but unfortunate. Our current guideline-based approach encourages us to treat patients as if they were all the same once they are diagnosed. However, given that asthma and COPD are such heterogeneous conditions, with recognisable but overlapping phenotypes, a multi-dimensional assessment of patients with airways diseases is required.[13] We should perhaps pay less attention to the diagnostic label and more to risk stratification and targeted treatment. For example, eosinophilic inflammation is a marker of steroid responsiveness regardless of diagnosis.[14] Arguably, it is more important to characterise the underlying pathology – i.e. airway inflammation – rather than physiology, in guiding therapy. Even in primary care, phenotype-specific treatment may lead to better outcomes and more appropriate targeting of therapy.

In these days of financial constraints, there is an additional reason for this approach. Approximately 30% of patients with asthma do not achieve good control despite maximum doses of ICS.[15] Approximately 85% of patients with COPD do not respond symptomatically to inhaled steroid (although in a subset, exacerbations may be reduced). Yet in asthma, guidelines recommend a step-wise increase in anti-inflammatory treatment for all patients, and in COPD the majority of patients receive ICS, often sooner rather than later. The cost implication of ineffective treatments is large. There is potential for reducing this cost substantially, and simultaneously improving the quality of patient care by more accurate phenotypic assessment and targeted treatment. This should be applicable in primary care and should not just be the prerogative of secondary and tertiary care.

Conflicts of interest

MT is an Associate Editor of the *PCRJ*, but was not involved in the editorial review of, nor the decision to publish, this article. DRT declares that he has no conflicts of interest in relation to this article.

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