Morbidity associated with oral corticosteroids in patients with severe asthma

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Cross-sectional primary care record studies show that 0.9% of the adult population receive regular oral corticosteroids (OCS). Prescriptions have increased steadily over the past 20 years, presumably reflecting an increasingly elderly and infirm population.[1] Respiratory conditions (mainly airway diseases) are responsible for 25–40% of these OCS prescriptions,[1 2] by some way the largest proportion of any specialty. Against this background, it is surprising and disappointing that little is known about morbidity due to OCS usage in patients with airway disease and we remain in the unsatisfactory position of having to extrapolate from studies carried out in non-respiratory conditions. Better information in an airway disease population is important as we are approaching the biological treatment era and have within our sights treatments that offer a realistic potential to be alternatives to OCS and to allow patients already taking them to withdraw therapy safely.[3–9] High quality data will be key to inform cost-effectiveness analyses for these new asthma therapies.

The paper by Sweeney *et al*[10] in this issue of the journal is therefore timely. The authors present data from two large severe asthma populations derived from the Optimum Patient Care Research Database (OPCRD) and British Thoracic Society (BTS) Difficult Asthma Registry on the occurrence of corticosteroid associated comorbidities. OPCRD is a respiratory database that contains anonymous longitudinal medical records supplemented by information from patient-completed questionnaires from over 525 general practices across UK. This data set was used to examine potentially OCS-related morbidity in a severe asthma cohort requiring regular OCS and two age and gender-matched control cohorts: one with mild/moderate asthma requiring minimal OCS use and the other without asthma. The BTS Difficult Asthma Registry consists of anonymised data collected from Specialist UK Difficult Asthma Services. Potentially OCS-related morbidity was compared in patients with severe asthma requiring daily OCS therapy to maintain asthma control and patients who were not on regular OCS but required frequent rescue corticosteroid courses. Their findings from both databases mirror findings on regular OCS-related adverse effects in non-asthmatic patient groups.[11–13] The most prevalent comorbidities linked to previous OCS exposure identified in subjects with severe asthma were dyspeptic disorders, obesity, psychiatric disorders, hypertension, hypercholesterolaemia, osteoporosis and osteopenia, type 2 diabetes mellitus, cardiovascular disease and sleep disorders. The odds for having morbidities linked to OCS exposure in severe asthma compared with control cohorts varied between 1.5 times higher for hypertension to over 5 times higher for osteoporosis and osteopenia.

Although it is difficult to tease out completely morbidities due to severe asthma from those due to systemic corticosteroid exposure, the information obtained from the work done by Sweeney *et al* represents the best estimate yet of the burden of OCS treatment in severe asthma. Particular merits of their analysis include assessment of two large severe asthma populations with complementary strengths and weaknesses, and the use of relevant control cohorts. The OPCRD severe asthma cohort from primary care (808 subjects) was larger and included high-quality information on comorbidities that are routinely monitored in primary care, whereas the BTS severe asthma cohort was smaller (328 subjects) but potentially benefited from a more systematic screening for corticosteroid-induced comorbidities and better identification of poor treatment adherence. Despite these differences, the observed prevalence rates for corticosteroid-induced comorbidities were similar, providing confidence that they are reflective of the true impact of regular systemic corticosteroid exposure. Additional strengths include the much more careful definition of asthma severity and systemic corticosteroid exposure than in previous studies,[14–17] and the availability of quality-of-life assessments and socioeconomic information so that the burden on individual patients and healthcare systems linked to OCS-related comorbidities could be examined. Finally, the well-chosen control groups made it possible to get some idea of comorbidities as a result of asthma per se and identify the point where a step up in OCS-associated comorbidities occurs.

However, as with all good papers, there are important remaining questions. The analysis provides only limited information on the relationship between risk estimates of corticosteroid-related morbidities and dosage and duration of OCS given. In addition, in a cross-sectional study such as this, it is difficult to determine chronology and causality of relationships. Is there a threshold dose or duration or both for the emergence of individual morbidities? Is there a different dose–response relationship for different morbidities? If there is a different relationship, why is this so? What patient factors, including but not limited to age and gender, would put a patient at higher risk of corticosteroid-related adverse events when dose and duration of corticosteroid usage are equal? Studies have shown that women gain more weight than men with increasing doses of inhaled corticosteroids.[18] Might men better tolerate OCS treatment? Are frequent rescue courses of OCS truly innocuous or are they also associated with an effect on development of corticosteroid-related comorbidities and, if so, when do adverse effects become equivalent to those seen in a patient on daily OCS but no rescue courses. Future studies are needed to address these important remaining questions.

Sweeney and group's findings support the presence of a dose–response relationship by showing that regular daily corticosteroid exposure is associated with a measurably greater prevalence of corticosteroid associated morbidities than frequent rescue courses of OCS. These findings would certainly impact on our decision in starting regular long-term OCS and will inform screening programmes in patients exposed to regular systemic corticosteroids. What is also clear from the study is that OCS-associated morbidity is substantial and places a significant burden on patients, healthcare systems and payers.[19–23] The findings provide a strong hint of a step up in treatment-associated morbidity when patients transition from step 4 to step 5 treatment and emphasise the importance of a thorough root and branches review before

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this step is taken. Basic measures such as ensuring that the diagnosis is correct, that treatment is being adhered to and is taken correctly and that there are no obvious environmental factor leading to poor control are crucially important. Case series suggest that around 30% of patients referred to a severe asthma clinic have apparently severe disease because of a failure in one or more of these basic steps.[24]

Current treatment guidelines advise a 'step-wise' increase of corticosteroids in asthma with long-term regular OCS considered when the managing physician thinks they have exhausted other forms of inhaled or oral therapies.[25] In many cases, the clinical problem is poor symptom control and the assumption is made that this reflects a persistent corticosteroid-responsive pathophysiological process. There is increasing evidence that this is often not the case. Cross-sectional and longitudinal studies have shown that eosinophilic, corticosteroid responsive inflammation is often divorced from the traditional symptoms and the physiological abnormalities of asthma.[26 27] Persistent symptoms often reflect corticosteroid unresponsive factors such as fixed airflow obstruction or a breathing pattern disorder.[24] Even worse, symptoms could be due to a condition that is worsened by regular OCS use such as obesity. Titration of corticosteroid treatment on the basis of objective measures of corticosteroid responsive airway inflammation results in improved outcomes and more economical use of treatment compared with a traditional symptom-based management approach.[26 28–30] We suggest that this evidence is sufficiently compelling to restrict a step up to regular OCS to patients who have good evidence of a corticosteroid responsive process in the form of raised biomarkers of eosinophilic airway inflammation such as a blood eosinophilia and/or a raised exhaled nitric oxide.

There should be very active exploration of alternative treatments and a real deal of caution exercised before introducing regular OCS in patients who have persistently suppressed biomarkers of eosinophilic airway inflammation. Management is more difficult in 'biomarker low' but symptomatic patients already established on regular OCS. This population has a low risk of serious asthma attacks[26] and some may well be better served by reduced corticosteroid treatment and the introduction of alternative therapies. This possibility will be investigated definitively by the important Refractory Asthma Stratification Programme UK consortium study.[31]

What about the population with severe asthma and raised biomarkers who have mastered the basics of asthma management and are adherent with high-intensity inhaled therapy? Recurrent asthma attacks are often a dominant clinical problem and many patients will be receiving frequent rescue courses of OCS. The introduction of regular OCS can have a large positive impact in this population[26] but, in our experience, this is often transient and offset by the OCS-related morbidity documented by Sweeney *et al*. This is the population where biological therapy will have a role. Omalizumab, an anti-IgE monoclonal antibody, and the first of such biologic-based therapies, has a disappointing effect as a OCS sparing agent[32] and can only be used in a minority of patients because of atopy, serum IgE and weight-related restrictions. Mepolizumab[3 6 7] an anti-IL-5 monoclonal antibody, has been recently licensed for use and looks like a better bet as an alternative to regular OCS and as an OCS sparing agent. Phase III trials[3 6] have shown that treatment is associated with a 50% reduction in exacerbation frequency, improved FEV1, reduced asthma control questionnaire scores and a 50% reduction in the dose of OCS required to control asthma. The impact of treatment is particularly large in patients with frequent exacerbations and blood eosinophilia.[7] The related monoclonal antibody benralizumab,[4] which targets the IL-5 receptor and causes a rapid eosinopenia, may have potential as an alternative to rescue doses of OCS in patients presenting with an eosinophilic exacerbation. In addition, other emerging targeted therapies including dupilumab (an anti-IL-4Rα antibody),[9] lebrikizumab (anti-IL-13)[5] and the orally active CRTH2 antagonist QAW039[8] are showing great promise, too. How big a role these targeted therapies will have, and which therapy to use in which patient are important research questions for the future. We suggest that it is not beyond the realms of possibility that these therapies will completely replace the use of OCS in airways disease. The work of Sweeney *et al* suggests that this would be a very significant and important development for patients with severe asthma.

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