Prevalence and recovery of adrenal insufficiency in steroid-dependent asthma patients receiving biologic therapy

To the Editor:

Asthma is a complex and heterogeneous inflammatory disease of the airways. Regular inhaled corticosteroid (ICS) therapy suppresses airway inflammation and treats asthma symptoms sufficiently in most patients. However, a small, but significant, proportion of patients with severe disease suffer from persistent daily symptoms and are reliant on oral corticosteroids (OCS), for short-term control in acute exacerbations, or as long-term maintenance therapy [1].

OCS are highly effective but have significant adverse effects [2], including anxiety, osteoporosis, weight gain, hypertension, diabetes mellitus, and both Cushing’s syndrome and adrenal insufficiency; it has been suggested that overall asthma-related mortality is increased compared with cohorts with less severe disease, not requiring OCS [3]. Secondary adrenal insufficiency, from hypothalamo-pituitary-adrenal (HPA) axis suppression is a predictable outcome from prolonged corticosteroid exposure, whether oral, inhaled, parenteral or topical, and patients have a high risk of adrenal crisis which can be life-threatening [4]. With the successful introduction of biological agents for severe asthma, patients previously dependent on maintenance OCS are increasingly able to wean their maintenance steroids [5, 6]. Testing the integrity of the HPA axis has therefore become mandatory for physicians caring for these patients.

There are a variety of techniques to assess adrenal reserve [7]; the insulin tolerance test is the gold standard test but impractical outside specialist centres; the short tetraacosactide test (SST; serum cortisol measured before and 30 and 60 min after parenteral injection of 250 µg tetraacosactide [8]) is often considered mandatory for the reliable assessment of adrenal reserve, but is resource intensive, with some risk of hypersensitivity reactions or anaphylaxis. Conversely, morning serum cortisol measurement is simple, cheap and can be done in an outpatient or primary care setting.

We present our experience of the prevalence of adrenal insufficiency in an OCS dependent asthma cohort receiving biologic therapy, and of the resolution of adrenal suppression in this cohort and further discuss the potential role of the SST in the assessment of adrenal insufficiency.

We conducted a retrospective review of 92 consecutive patients with confirmed adherence to OCS maintenance therapy who were initiated on the anti-IL-5 or anti-IL-5R monoclonal antibody (mAb) mepolizumab or benralizumab respectively, between May 2017 and September 2018. Baseline characteristics including sex, age, dose and duration of OCS, fraction of exhaled nitric oxide, spirometry, body mass index and asthma control (ACQ-6 score) were collected. Serum cortisol was assayed on a Roche Gen II, with 7.9% cross reactivity to prednisolone, and interpreted using our local reference ranges.

All patients whose clinical symptoms allowed for a reduction of their prednisolone dose to ≤5 mg daily had an assessment of adrenal reserve with a serum morning cortisol having omitted OCS for at least 24 h and ICS for 12 h prior to testing.

Patients were considered to have adrenal insufficiency if the cortisol was <133 nmol·L⁻¹. Those patients continued on their current dose, maintained steroid precautions and were followed over 12 months with repeat cortisol measurements every 4–8 weeks when attending for their biologic injections. Patients who reported symptoms suggestive of adrenal insufficiency did not wean prednisolone further and underwent

Adrenal insufficiency is common in previously steroid-dependent asthma patients. Morning serum cortisol is a valid and important first line test which can indicate adrenal insufficiency and can guide who might need dynamic testing. http://bit.ly/2IVGNfI

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Group A: all subjects</th>
<th>Group B: no AI</th>
<th>Group C: AI</th>
<th>Group D: AI recovered</th>
<th>Group E: AI not recovered</th>
<th>95% CI of difference B versus C</th>
<th>95% CI of difference D versus E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects n</td>
<td>92 (59%)</td>
<td>16 (59%)</td>
<td>37 (57%)</td>
<td>26 (54%)</td>
<td>11 (65%)</td>
<td>−13.3−50.3</td>
<td>−35.6−2.6</td>
</tr>
<tr>
<td>Female</td>
<td>54±14</td>
<td>57±13</td>
<td>54±15</td>
<td>54±14</td>
<td>52±16</td>
<td>−9.3−3.7</td>
<td>−8.5−8.5</td>
</tr>
<tr>
<td>Age years</td>
<td>3.5 (1.4−11.1)</td>
<td>2.2 (1.1−7.7)</td>
<td>3.9 (1.4−11.6)</td>
<td>3.8 (1.5−10.1)</td>
<td>3.9 (1.6−15.9)</td>
<td>−7.0−21.9</td>
<td>−1.5−6.2</td>
</tr>
<tr>
<td>Total OCS exposure</td>
<td>10±5.8</td>
<td>11±6.9</td>
<td>10±5.4</td>
<td>9.5±4.7</td>
<td>7±5.7</td>
<td>−4.2−1.2</td>
<td>−2.4−3.6</td>
</tr>
<tr>
<td>Duration of maintenance OCS treatment weeks</td>
<td>52 (24−160)</td>
<td>32 (20−110)</td>
<td>60 (28−187)</td>
<td>66 (31−285)</td>
<td>55 (26−126)</td>
<td>−4.0−44.0</td>
<td>−104−20</td>
</tr>
<tr>
<td>Blood eosinophil count cells·μL⁻¹</td>
<td>631±294</td>
<td>652±321</td>
<td>610±270</td>
<td>620±20</td>
<td>644±314</td>
<td>−1.5−0.1</td>
<td>−1.5−0.2</td>
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<td>FENO</td>
<td>59±41</td>
<td>61±38</td>
<td>58±42</td>
<td>61±44</td>
<td>46±36</td>
<td>−22.5−15.1</td>
<td>−40.9−10.5</td>
</tr>
<tr>
<td>ACQ-6</td>
<td>3±1.2</td>
<td>2.8±1.4</td>
<td>3.1±1.1</td>
<td>3.2±1.1</td>
<td>2.8±1</td>
<td>−1.7−0.9</td>
<td>−1−0.2</td>
</tr>
<tr>
<td>Post-bronchodilator FEV₁ % pred</td>
<td>65±21.7</td>
<td>64±20.7</td>
<td>67±22.1</td>
<td>67±20.7</td>
<td>63±27</td>
<td>−7.5−12.3</td>
<td>−17.6−8.8</td>
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<tr>
<td>BMI</td>
<td>30±5.9</td>
<td>30±5.5</td>
<td>30±6.2</td>
<td>30±6.6</td>
<td>29±5.1</td>
<td>−2.8−2.7</td>
<td>−4.6−2.6</td>
</tr>
</tbody>
</table>

Data are presented as mean±sd or median (interquartile range), unless otherwise stated. #: in year prior to starting biologic therapy, in g prednisolone; ¶: prior to biologic therapy. AI: adrenal insufficiency; OCS: oral corticosteroids; ACQ: Asthma Control Questionnaire; FEV₁: forced expiratory volume in 1 s; BMI: body mass index.

Testing with the SST. Patients with cortisol levels >133 nmol·L⁻¹ weaned prednisolone by 1 mg every month and were assessed at biologic visits 4–8 weeks. A cortisol level of >350 nmol·L⁻¹ (between 95 and 99% specific for a normal HPA axis [9]) was regarded as in keeping with normal adrenal function as per our institution’s guideline, allowing discontinuation of OCS.

Results are expressed as means±sd for parametric data, and medians and interquartile ranges (IQR) for non-parametric data. For comparison of single variables, t-tests have been used (or non-parametric equivalents) with paired analysis where appropriate.

92 (54 female) patients were included in this analysis. Baseline clinical characteristics are summarised in table 1. All patients were on high dose ICS (beclometasone diproprionate equivalent 2000 µg per day) in addition to maintenance OCS. 65/92 (71%) patients had a low cortisol level (<133 nmol·L⁻¹) with a median (IQR) of 68 (37–98) nmol·L⁻¹ diagnostic of adrenal insufficiency. Of these, 48/65 (74%) recovered adrenal function within 1 year with a median (IQR) time to recovery of 20 (12–28) weeks.

17 (26%) patients had a persistently low morning cortisol and needed to remain on low dose prednisolone 3–5 mg beyond 12 months: four patients remained on prednisolone to control their asthma, three for rheumatoid arthritis but 10 did so for persistent adrenal insufficiency. Although there was no statistically significant correlation between developing adrenal insufficiency and total duration or cumulative dose of OCS, it was noteworthy that patients with adrenal insufficiency had received nearly double the dose of OCS and for a longer period of time, compared to patients without adrenal insufficiency (table 1).

35 of 92 (38%) patients had an SST in addition to a morning cortisol as part of their HPA-axis assessment. Patients who failed the SST (15/35; 43%) had a median morning cortisol of 86 nmol·L⁻¹ (IQR 55–132, range 13–214 nmol·L⁻¹), and they were taking a median of 5 mg prednisolone daily. 20/35 (57%) patients who passed their SST had a median morning cortisol of 220 nmol·L⁻¹ (IQR 183–250, range 146–350 nmol·L⁻¹) and were taking a median of 3 mg prednisolone daily.

To our knowledge, we present the first real world data on the prevalence of adrenal insufficiency in steroid-dependent asthma patients who are receiving biologic therapy, and the resolution of adrenal insufficiency as OCS are weaned. Almost three in four patients had low morning serum cortisol, indicative of adrenal insufficiency.

Diagnosing adrenal insufficiency, and maintaining steroid precautions, is essential to reduce the risk of adrenal crisis, a life-threatening medical emergency [10]. Weaning OCS and encouraging recovery of the intact HPA allows the patient to safely stop steroid precautions and avoids unnecessary exposure to a harmful drug. It is important to acknowledge, however, that adrenal insufficiency can persist for prolonged periods and can be caused by high dose inhaled steroids as well as OCS.

There are studies reporting a link between dose and duration of OCS and adrenal insufficiency [7, 8], but we did not find such correlation, nor did others [11]. Our sample size, recall bias regarding duration of adrenal insufficiency.
steroid exposure, varying degrees of adherence to OCS and inter-individual variability in glucocorticoid action and metabolism may account for this.

Measuring morning cortisol levels is a practical and safe first step to assess adrenal function once the underlying disease allows for a reduction of the prednisolone dose <5 mg daily: the level widely considered to be the physiological threshold equivalent to endogenous daily production [12]. Our experience has shown that dynamic testing of the adrenal axis should be avoided in patients with low morning cortisol levels and on prednisolone doses >5 mg daily, as both were highly indicative of adrenal insufficiency.

In summary, we report that adrenal insufficiency appears to be highly prevalent in OCS-dependent severe asthma patients who have been able to reduce their steroid exposure following introduction of biologic therapies. Whilst we observed that adrenal insufficiency will resolve in the majority of patients it persists in a significant minority who require ongoing close monitoring. Assessment of HPA function, using morning cortisol measurements in patients on ≤5 mg of prednisolone daily must form part of the routine care of OCS-dependent asthma patients receiving steroid-sparing biologic therapies, with the SST being a useful second line test for a selected group of patients.

Alexandra M. Nanzer1, Aqib Chowdhury2, Asma Raheem2,1, Cris Roxas1, Mariana Fernandes1, Louise Thomson1, Linda Green1, Jasdeep Dhariwal1, Grainne D’Ancona3, Brian D. Kent1, Philip A. Kelly1 and David J. Jackson1,2

1Guy’s and St Thomas’ NHS Foundation Trust, Thoracic Medicine, Guy’s Severe Asthma Service, London, UK. 2King’s College London, London, UK. 3King’s College Hospital NHS Foundation Trust, Dept of Acute Medicine, London, UK.

Correspondence: Alexandra Nanzer, Guy’s and St Thomas’ Hospitals, Guy’s Severe Asthma Service, Great Maze Pond, London SE1 9RT, UK. E-mail: alexandra.nanzerkelly@gstt.nhs.uk

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References