EUROPEAN RESPIRATORY *journal*

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

Research letter

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Alexandra Nanzer, Aqib Chowdhury, Asma Raheem, Cris Roxas, Mariana Fernandes, Louise Thomson, Linda Green, Jaideep Dhariwal, Grainne D'Ancona, Brian Kent, Philip Kelly, David Jackson

Please cite this article as: Nanzer A, Chowdhury A, Raheem A, *et al*. Prevalence and Recovery of Adrenal Insufficiency in Steroid-Dependent Asthma Patients Receiving Biologic Therapy. *Eur Respir J* 2020; in press (https://doi.org/10.1183/13993003.02273-2019).

Prevalence and Recovery of Adrenal Insufficiency in Steroid-Dependent Asthma Patients Receiving Biologic Therapy

Authors:

*corresponding author: alexandra.nanzerkelly@gstt.nhs.uk

Alexandra Nanzer, Guy's and St Thomas' NHS Foundation Trust, Thoracic Medicine, Guy's Severe Asthma Service, London, UK

Aqib Chowdhury, Kings College London, UK

Asma Raheem, King's College London, UK

Cris Roxas, Guy's and St Thomas' NHS Foundation Trust, Thoracic Medicine, Guy's Severe Asthma Service, London, UK

Mariana Fernandes, Guy's and St Thomas' NHS Foundation Trust, Thoracic Medicine, Guy's Severe Asthma Service, London, UK

Louise Thomson, Guy's and St Thomas' NHS Foundation Trust, Thoracic Medicine, Guy's Severe Asthma Service, London, UK

Linda Green, Guy's and St Thomas' NHS Foundation Trust, Thoracic Medicine, Guy's Severe Asthma Service, London, UK

Jaideep Dhariwal, Guy's and St Thomas' NHS Foundation Trust, Thoracic Medicine, Guy's Severe Asthma Service, London, UK

Grainne D'Ancona, Guy's and St Thomas' NHS Foundation Trust, Thoracic Medicine, Guy's Severe Asthma Service, London, UK

Brian Kent, Guy's and St Thomas' NHS Foundation Trust, Thoracic Medicine, Guy's Severe Asthma Service, London, UK

Philip Kelly, King's College Hospital NHS Foundation Trust, Department of Acute Medicine, London, UK

David Jackson, Guy's and St Thomas' NHS Foundation Trust, Thoracic Medicine, Guy's Severe Asthma Service, London, UK and King's College London, UK

Take Home Message

Adrenal insufficiency is common in previously steroid-dependent asthma patients who successfully wean their maintenance steroids upon starting biologic therapy. Morning serum cortisol levels are a valid and important first line test which can indicate adrenal insufficiency and can guide who might need dynamic testing.

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 biologic 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 tetracosactide test (SST; serum cortisol measured before and 30 and 60 minutes after parenteral injection of 250µg tetracosactide (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 as an outpatient or in primary care.
We present our experience of the prevalence of AI 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 AI.

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 (FeNO), spirometry, BMI 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 ≤ 5mg/daily had an assessment of adrenal reserve with a serum morning cortisol having omitted OCS for at least 24 hours and ICS for 12 hours prior to testing.

Patients were considered to have AI if the cortisol was <133 nmol/L. 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 AI did not wean prednisolone further and underwent testing with the SST. Patients with cortisol levels > 133nmol/L weaned prednisolone by 1mg every month and were assessed at biologic visits 4-8 weekly. A cortisol of > 350nmol/L (between 95-99% 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 inter-quartile ranges for non-parametric data. For comparison of single variables, *t*-tests have been used (or non-parametric equivalents) with paired analysis where appropriate.

Ninety-two (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/day) in addition to maintenance OCS. 65/92 (71%) patients had a low cortisol (<133nmol/l) with a median of 68 nmol/L (IQR 37-98) diagnostic of AI. Of these, 48/65 (74%) recovered adrenal function within one year with a median time to recovery of 20 weeks (IQR 12-28).

Seventeen (26%) patients had a persistently low morning cortisol and needed to remain on low dose prednisolone 3-5mg beyond 12 months: 4 patients remained on prednisolone to control their asthma, 3 for rheumatoid arthritis but 10 did so for persistent AI. Although there was no statistically significant correlation between developing AI and total duration or cumulative dose of OCS, it was noteworthy that patients with AI had received nearly double the dose of OCS and for a longer period of time compared to patients without AI (table 1).

Thirty-five 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 86nmol/l (IQR: 55-132, range 13-214), and they were taking a median of 5mg prednisolone daily. 20/35 (57%) patients who passed their SST had a median morning cortisol of 220 nmol/l (IQR: 183-250, range 146-350) and were taking a median of 3mg prednisolone daily.

To our knowledge we present the first real world data on the prevalence of AI in steroid-dependent asthma patients who are receiving biologic therapy, and the resolution of AI as OCS are weaned. Almost 3 in 4 patients had low morning serum cortisol, indicative of AI.

Diagnosing AI, 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 AI 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 AI (7, 8), but we did not find such correlation, nor did others (11). Our sample size, recall bias regarding duration of 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 <5mg 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 > 5mg daily as both were highly indicative of AI.

In summary, we report that AI 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 AI 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 ≤5mg 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.

Group	A	B	C	D	E		
Characteristics	All subjects n=92	No AI n=27	AI n=65	AI recovered n=48	AI not recovered n=17	95% CI of difference B vs C	95% CI of difference D vs E
Female, (%)	54 (59%)	16 (59%)	37 (57%)	26 (54%)	11 (65%)	-13.3 - 50.3	-35.6 - 2.6
Age (years), mean (SD)	55 (14)	57 (13)	54 (15)	54 (14)	52 (16)	-9.3 - 3.7	-8.5 - 8.5
Total OCS exposure in year prior to starting biologic (gram prednisolone), median (IQR)	3.5 (1.4-11.1)	2.2 (1.1-7.7)	3.9 (1.4-11.6)	3.8 1.5-10.1)	3.9 (1.6-15.9)	-7.0 - 21.9	-1.5 - 4.2
Baseline maintenance OCS (mg), mean (SD)	10 (5.8)	11 (6.9)	10 (5.4)	9.5 (4.7)	7.5 (7.3)	-4.2 - 1.2	-2.4 - 3.6
Duration of maintenance OCS treatment prior to biologic (weeks), median (IQR)	52 (24-160)	32 (20-110)	60 (28-187)	66 (31-285)	55 (26-126)	-4.0 - 44.0	-104 - 20
Blood eosinophil count prior to biologic therapy cells/mcL, mean (SD)	631 (294)	652 (321)	610 (270)	620 (20)	644 (314)	-1.5 - 0.1	-1.5 - 0.2
FeNO, mean (SD)	59 (41)	61 (38)	58 (42)	61 (44)	46 (36)	-22.5 - 15.1	-40.9 - 10.5
ACQ-6, mean (SD)	3 (1.2)	2.8 (1.4)	3.1 (1.1)	3.2 (1.1)	2.8 (1)	-1.7 - 0.9	-1 - 0.2
Post-bronchodilator FEV1% predicted, mean (SD)	65 (21.7)	64 (20.7)	67 (22.1)	67 (20.7)	63 (27)	-7.5 - 12.3	-17.6 - 8.8
BMI, mean (SD)	30 (5.9)	30 (5.5)	30 (6.2)	30 (6.6)	29 (5.1)	-2.8 - 2.7	-4.6 - 2.6

Table 1: Baseline characteristics; SD Standard Deviation; OCS Oral Corticosteroids; IQR Interquartile Range; FeNO Fractional exhaled Nitric Oxide; ACQ Asthma Control Questionnaire; BMI body mass index

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