



## Adrenal insufficiency during low-dose chronic steroid treatment

Editors  
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### Introduction

Adrenal insufficiency related to steroid treatment of inflammatory or autoimmune disorders is an underestimated clinical problem. No standardised protocol addresses evaluation of adrenal function during the course of therapy, or following its cessation. A clinician who is unaware may fail to recognise and treat an adrenal crisis, with potentially serious consequences.

In patients on high-dose steroids, adrenal insufficiency may manifest only when the treatment is halted. Patients on chronic low-dose steroid treatment, on the other hand, may develop adrenal insufficiency even during the course of therapy when confronting a stressful event calling for a surge in cortisol production, a demand which the adrenal gland is unable to meet due to lack of stimulus from the hypothalamus and the pituitary.

### The study

A recent cross-sectional study from Denmark (1) investigated 42 Caucasian patients aged  $\geq 18$  years affected by rheumatoid arthritis and receiving prednisolone at the dose of 5 mg/day for at least 6 months (median 66, range 6-444 months). Exclusion criteria included inability to provide written consent, pregnancy, oestrogen treatment in the 6 weeks prior to adrenal evaluation and any condition precluding the suspension of steroids for 48 hours.

Adrenal function was assessed with an intravenous ACTH (Synacthen<sup>®</sup>, 250  $\mu$ g) stimulation test, carried out in the morning after a mean of 48 hours (range 36-96 hours) from the last dose of prednisolone. Cortisol serum levels were measured before and 30 minutes after the injection of Synacthen<sup>®</sup>, with a normal response being defined as a cortisol serum level of at least 420 nmol/L (15.2  $\mu$ g/dL) at 30 minutes. In order to rule out primary adrenal failure, ACTH and anti-adrenal antibodies were also assessed.

In the study, 20/42 (48%) of patients failed to mount a sufficient cortisol response to ACTH stimulation. Even after restriction of the analysis to patients without supplementary steroid doses for 3 months, 13/33 patients (39%) showed an inadequate adrenal response. ACTH serum levels (tested in 41 patients) were reduced, while anti adrenal antibodies (tested in 38 patients) were negative in all.

There was no correlation between duration of steroid treatment and serum cortisol peak at 30 minutes, and no significant differences were reported in relation to sex or the presence of rheumatoid factor in the serum.

### Discussion

The clinical manifestations of adrenal insufficiency are not specific and easy to misinterpret as a flare up of the underlying disorder, which may contribute to the diagnostic delay. This study shows that even low chronic doses of steroid (e.g. 5 mg of prednisolone per day) carry a significant risk of hypoadrenalism. It is paramount that patients on long-term steroid treatment be made aware of the risk of adrenal failure and instructed to increase the steroid (preferably hydrocortisone) when facing a potential adrenal crisis. Adrenal function should be evaluated during low-dose steroid treatment as well at its cessation, in order to identify patients who may need to continue steroid replacement until normalization of the hypothalamic-pituitary-adrenal axis. There is a need for prospective trials to establish the best way to approach adrenal function during chronic steroid treatment.

### References

1. Borresen SW, Klohe M, Baslund B, et al. Adrenal insufficiency is seen in more than one-third of patients during ongoing low-dose prednisolone treatment for rheumatoid arthritis. *Eur J Endocrinol* 2017, 177: 287-95.