Endocrine CONNECTIONS

RESEARCH

Efficacy and safety of a 30-day methylprednisolone treatment protocol for subacute thyroiditis: a prospective study

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Abstract

Objective: The optimal corticosteroid treatment regimen for subacute thyroiditis has not yet been established. To avoid side effects, tapering of the initial dose of corticosteroid is recommended. With reducing dose, the symptoms can recur.

Design: In a prospective clinical study, a 30-day methylprednisolone (MPSL) treatment protocol with a starting dose of 24 mg/day and tapered by 4 mg every 5 days was assessed for effectiveness and safety regarding possible adrenal insufficiency.

Methods: Fifty-nine patients with subacute thyroiditis were included. At visit 1, after establishing the diagnosis, a short stimulation adrenocorticotrophic hormone (ACTH) test was performed and methylprednisolone treatment was prescribed. At visit 2 (40 ± 5 days after visit 1), clinical, laboratory (including short stimulation ACTH test), and ultrasound evaluation were repeated.

Results: Forty-eight patients (81.4%) were cured by the prescribed protocol, having significantly lower cortisol levels after stimulation at visit 1 than patients who were not cured (mean, 674.9 nmol/L and 764.0 nmol/L, respectively, $P = 0.012$). Seven patients (12.3%) developed adrenal insufficiency; this group had significantly lower cortisol levels after stimulation at visit 1 than patients without adrenal insufficiency development (mean, 561.5 nmol/L and 704.7 nmol/L, respectively, $P = 0.005$). Using stimulated cortisol level at visit 1 as the explanatory variable, logistic models were optimized to determine treatment efficacy (AUC = 0.745, optimal threshold 729 nmol/L, specificity 71%, sensitivity 73%) and adrenal function (AUC = 0.861, optimal threshold 629 nmol/L, specificity 73%, sensitivity 100%).

Conclusions: The described protocol was efficient for more than 80% of patients. Using this protocol, the corticosteroid treatment interval is shorter than proposed in current guidelines.

Significance statement: A short but effective protocol for treatment of subacute thyroiditis with methylprednisolone is presented in this article. Using this protocol, the treatment interval is shorter than proposed in current guidelines. Its safety regarding possible adrenal insufficiency is assessed.

Key Words

- subacute thyroiditis
- corticosteroids
- methylprednisolone
- adrenal insufficiency

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Introduction

Subacute thyroiditis (ST), also called subacute granulomatous or de Quervain's thyroiditis, is a transient inflammatory thyroid disease (1, 2). The diagnosis of ST is based on medical history, physical examination, thyroid ultrasound, laboratory results, and/or thyroid scintigraphy. Rarely, a fine-needle aspiration biopsy of the thyroid is needed. Patients with mild symptomatic ST are usually treated with nonsteroidal anti-inflammatory drugs (NSAID). Sometimes, beta-adrenergic-blocking drugs are added. In patients who fail to respond to NSAID or present initially with moderate-to-severe pain and/or thyrotoxic symptoms, corticosteroid (CS) treatment is recommended (1).

The optimal CS treatment regimen for ST has not yet been established (1, 3, 4). Several approaches to treatment regarding the CS formulation, starting dose, and duration of treatment are used (1, 3, 4, 5, 6, 7, 8). To avoid side effects of CS treatment, tapering of the initial dosage of CS over several weeks is recommended; however, as the dose of CS is reduced, the symptoms can recur (1).

Although it is generally accepted that low doses of CS do not suppress the hypothalamic–pituitary–adrenal (HPA) axis, it has been reported that adrenal insufficiency after discontinuation of CS occurs frequently and might often be underdiagnosed in clinical practice (9, 10, 11, 12). Adrenal insufficiency often presents with only minimal and unspecific clinical prodromal symptoms but may suddenly become life threatening if left untreated upon acute stress (13). Administration of exogenous CS, even in small doses for only a few days, leads to a measurable suppression of the HPA axis resulting in the inability of the adrenal cortex to secrete additional cortisol if needed (14).

In accordance with this, a 30-day treatment protocol with a starting dose of 24 mg/day of methylprednisolone (MPSL) as the initial treatment for ST and tapered by 4 mg every 5 days is employed in our center. The following study was designed to assess the effectiveness of this treatment protocol and its safety regarding possible adrenal insufficiency.

Methods

In a single-center prospective clinical study, 59 Caucasian patients with moderate/severe ST referred to the Outpatient Thyroid Clinic of the Department of Nuclear Medicine, University Medical Centre Ljubljana, in the period between August 2019 and May 2022, were examined. The study was approved by the Republic of Slovenia National Medical Ethics Committee (No. 0120-515/2018/7). A written informed consent was obtained by all patients included in the study.

At visit 1, ST was diagnosed by an experienced thyroid specialist (according to American Thyroid Association, there are no definitive criteria for the diagnosis of ST; all the patients included in the study met the proposed diagnostic criteria by Stasiak *et al.*: elevated sedimentation rate (SR) and typical hypoechoic lesions with blurred margin and decreased vascularization on thyroid ultrasound, and at least one of the following – thyroid swelling; pain and tenderness of the thyroid gland/lobe; decreased serum level of thyrotropin (TSH); elevated serum level of free thyroxine (free T_4) and/or free triiodothyronine (free T_3); suppressed thyroid scan with technetium-99m pertechnetate; and fine-needle aspiration biopsy result typical for ST) (1, 2, 15). Since this was a prospective study, we decided to include a suppressed thyroid scan with technetium-99m pertechnetate as an additional inclusion criterium in all patients to further establish a firm study group and minimize the possibility of including patients with other etiology of hyperthyroidism although this is not a required criterium for the diagnosis by American Thyroid Association guidelines or the proposed diagnostic criteria by Stasiak *et al.* (1, 2). Exclusion criteria for the study were pregnancy and age below 18 years. A low-dose ACTH stimulation test was performed in all patients after the diagnosis of ST. C-reactive protein (CRP), thyroid peroxidase antibodies (TPOAb), thyroglobulin antibodies (TgAb), TSH-receptor antibodies (TSH-R Ab), and thyroglobulin (Tg) were also measured. The height and weight of the patients were recorded and BMI was calculated.

Patients were treated with MPSL by the protocol described in Fig. 1. Proton-pump inhibitor and cholecalciferol were prescribed simultaneously (16, 17).

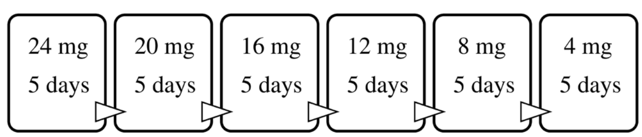

Figure 1
A 30-day methylprednisolone (MPSL) treatment protocol: 24 mg/day of MPSL was prescribed as the initial dose for the treatment of ST and was tapered by 4 mg every 5 days.

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Visit 2 followed 40 ± 5 days after visit 1 when clinical examination, complete laboratory tests (including low-dose ACTH stimulation test), and thyroid ultrasound were repeated. Remission of ST was evaluated by an experienced thyroid specialist and was defined by the disappearance of clinical symptoms and signs of ST in correlation to biochemical parameters and thyroid ultrasonographic findings (1). If adrenal insufficiency was confirmed, patients were educated and hydrocortisone treatment was prescribed (18).

However, the patients were instructed at visit 1 to come for an earlier evaluation if the pain in the thyroid worsened during the tapering of MPSL dose or if they had elevated body temperature. The attending clinician decided on the subsequent dose of MPSL and the duration of treatment.

Laboratory tests

All laboratory measurements were performed at the biochemical laboratory of the Department of Nuclear Medicine at the University Medical Centre Ljubljana. Serum concentrations of cortisol (Immulite 2000 XPi till January 2021, afterward Atellica, both Siemens Healthineers), TSH, free thyroxine (T_4), free tri-iodothyronine (T_3), TPOAb, and TgAb were measured using a chemiluminescence immunoassay (Advia Centaur till January 2021, afterward Atellica, both Siemens Healthineers, Erlangen, Germany). TSH-R Ab and Tg concentrations were measured by a chemiluminescence immunoassay (BRAHMS Kryptor Gold, Thermo Fisher Scientific). SR was measured semi-automatically (Sediko m10, Laboratorijska tehnika Burnik, Slovenia). CRP level was measured by a latex immunoturbidimetric assay (Advia 1800/2400, Siemens).

For a low-dose (1 µg) ACTH test, a blood sample was taken in the morning between 8 and 10 a.m., at 0 min for the assessment of basal cortisol and again 30 min after intravenous administration of 1 µg of corticotropin (synthetic ACTH) for the measurement of stimulated serum cortisol concentrations. A cutoff value 460 nmol/L of stimulated cortisol was used to define adrenal insufficiency (19).

Thyroid US was performed by a US machine (Samsung HS70A) with a 7.5 MHz linear transducer. The volume of the thyroid was calculated by the formula width × length × thickness × π/6 (20).

Thyroid scintigraphy was performed using a gamma camera equipped with a pinhole collimator (Siemens BASICAM) after intravenous administration of 100 MBq of Tc-99m pertechnetate.

Statistical analysis

The statistical analysis was performed with R Core Team, 2014 (R version 3.1.1; The R Foundation for Statistical Computing; Mathsoft, Cambridge, MA, USA). Values are expressed as mean ± s.d. (range), and 95% confidence interval levels were computed as the Wilson score interval for associated binomial distributions. Mann–Whitney *U*-test was used to test for correlation of variables with treatment efficacy and adrenal function; $P < 0.05$ was considered statistically significant. For statistically explanatory variables, box-plot graphs were drawn and logistic regression was performed. The resulting logistic model predictions were checked using the receiver operator characteristic (ROC) curve and associated area under the curve (AUC) computation. The optimum cutoff threshold was determined using the Youden's index.

Sample sizes were estimated using effect size analysis for the unpaired Student's *t*-test statistics, assuming a normal distribution of parameters under study. Under such conditions, a cohort of 50 patients was targeted in the study. Calculations were performed using statsmodels 0.14.0 software package. Such a group allows for the detection of significant differences of parameters with a Cohen's effect size of 1 and distribution ratio of 1 over 4 in treatment affected group assuming a significance level of $\alpha = 0.05$ and statistical power $\beta = 0.8$.

Results

Forty-six (88%) female and 13 (22%) male patients were included in the study. The baseline characteristics of the patients are depicted in Table 1.

Table 1 Baseline characteristics of the patients included in the study.

Parameter	Value mean ± s.d. (range)	Normal range
Age (years)	47.3 ± 10.1 (29–72)	–
TSH (mIU/L)	0.067 ± 0.223 (0.01–1.63)	0.59–4.23
fT_4 (pmol/L)	35.6 ± 14.8 (11.1–77.3)	11.5–22.7
fT_3 (pmol/L)	11.6 ± 5.4 (4.5–27.2)	3.5–6.5
Tg (µg/L)	207.4 ± 191.8 (9.7–816.0)	0.5–58
Thyroid volume (mL)	19.8 ± 8.2 (5.4–41.5)	–
CRP (mg/L)	51.3 ± 34.7 (5–157)	<5
SR (mm/h)	66.4 ± 22.4 (29–113)	<20

CRP, C-reactive protein; fT4, free thyroxine; fT3, free triiodothyronine; SR, sedimentation rate; Tg, thyroglobulin; TSH, thyrotropin.

Table 2 Biochemical parameters of patients cured (group A) or not cured (group B) by a 30-day MPSL treatment protocol at visit 2.

Parameter	Group A (*N* = 48), mean ± s.d. (range)	Group B (*N* = 11), mean ± s.d. (range)	*P*-value
TSH (mIU/L)	5.207 ± 7.703 (0.010–53.970)	1.803 ± 1.550 (0.020–4.530)	0.003
fT_4 (pmol/L)	12.2 ± 2.3 (6.1–18.5)	16.1 ± 3.3 (11.8–22.6)	<0.001
fT_3 (pmol/L)	4.8 ± 0.5 (3.8–6.0)	6.0 ± 1.2 (4.9–8.0)	<0.001
Tg (µg/L)	56.9 ± 55.7 (12.5–297.3)	144.5 ± 214.3 (6.3–659.9)	0.626
Thyroid volume (mL)	10.5 ± 6.4 (3.1–42.6)	17.7 ± 10.5 (4.3–42.7)	0.006
CRP (mg/L)	13.6 ± 7.3 (5–32)	42.1 ± 39.6 (6.0–124.0)	<0.001
SR (mm/h)	15.9 ± 10.3 (4–44)	46.0 ± 31.4 (11–115)	<0.001

CRP, C-reactive protein; fT4, free thyroxine; fT3, free triiodothyronine; SR, sedimentation rate; Tg, thyroglobulin; TSH, thyrotropin.

Efficacy of the 30-day MPSL treatment protocol

For evaluating the efficacy of the 30-day MPSL treatment protocol, the patients were divided into group A (the patients whose ST improved by the prescribed treatment protocol and did not recur, *N* = 48; 81.4%) and group B (the patients whose ST was not cured by the prescribed treatment protocol, *N* = 11; 18.6%). The biochemical parameters of group A and group B are outlined in Table 2. In group B, two patients experienced a worsening of symptoms before the conclusion of the 30-day protocol and needed an elevation of the MPSL dose (the cumulative MPSL treatment lasted 80 days for one and 42 days for the other patient). Four patients complained of repeated symptoms and signs at visit 2 and after evaluation, they were prescribed a repeated 30-day MPSL scheme. One patient was prescribed a 20-day 16 mg MPSL scheme and one was advised to take analgesic drugs only (both at visit 2). Three patients complained of recurrent signs and symptoms after 1 month of the visit 2 and were prescribed a repeated 30-day MPSL treatment protocol.

Patients in group B had significantly higher cortisol levels after stimulation at visit 1 in comparison to group A ($P = 0.012$) (Fig. 2). No other significant difference in patients' age, BMI, thyroid volume, basal cortisol, TSH, free T_4, free T_3, CRP, SR, Tg, or thyroid antibody levels between the two groups was found.

Figure 3 shows the fit of the logistic regression curve to the model predicting treatment efficacy with cortisol level after stimulation at visit 1 as the explanatory variable. The ROC curve was calculated and an AUC of 0.745 was obtained, the optimal stimulated cortisol threshold level of 729 nmol/L yielded a test specificity of 71% (95% CI (57, 82)) and a test sensitivity of 73% (95% CI (43, 90)) (Fig. 4).

Adrenal function before and after MPSL treatment

At visit 1, basal mean cortisol value was 400.7 ± 135.2 (range, 127.0–693) nmol/L and after stimulation 692.4 ± 119.8 (range, 461–999) nmol/L. At visit 2, basal mean cortisol value was 376.5 ± 110.0 (range, 109–575) nmol/L and after stimulation 597.5 ± 116.0 (range, 349–902) nmol/L.

Of the two patients who needed an elevation of MPSL dosage during the treatment, adrenal insufficiency developed in the patient whose continuous MPSL treatment lasted 42 days (and still did not recover at repeat testing after 6 months) but not in the patient whose continuous MPSL treatment lasted 80 days.

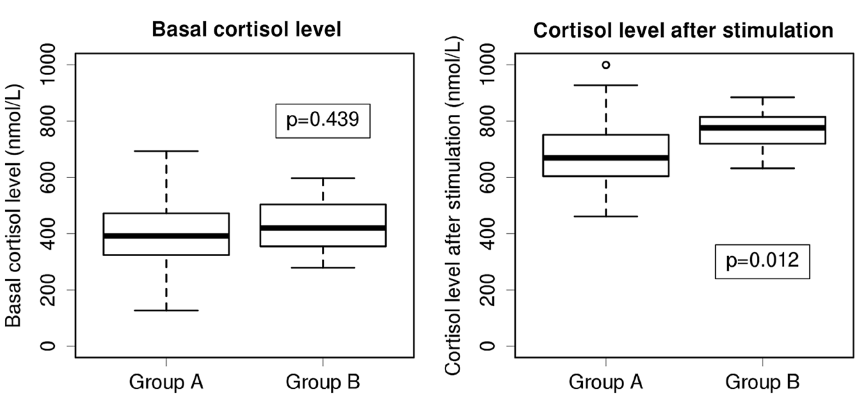

Figure 2
Basal and stimulated cortisol level at visit 1 in patients who were cured (group A, *N* = 48) or not cured (group B, *N* = 11) after the 30-day MPSL treatment protocol.

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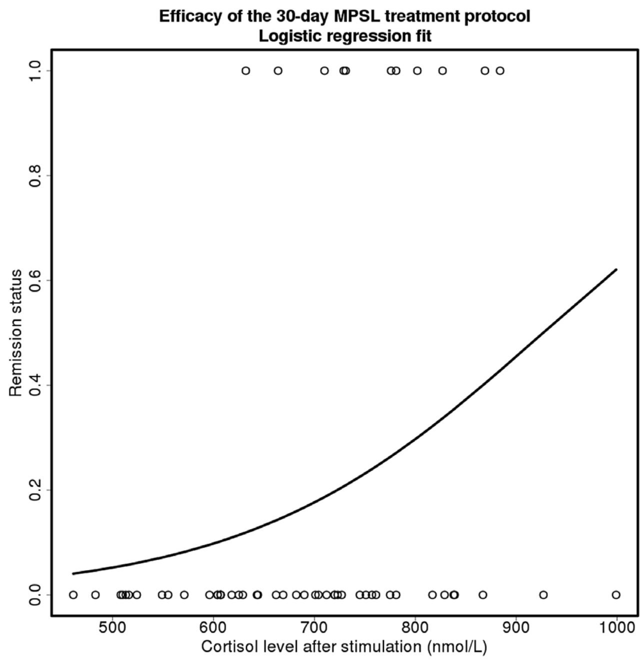

Figure 3
Fit of the logistic regression curve to model predicting treatment efficacy with cortisol level after stimulation at visit 1 as the explanatory variable. Dots indicate patient data, and continuous line represents probability of recurrence as a function of cortisol level after stimulation. On *y*-axis, 0 indicates remission, 1 indicates not cured.

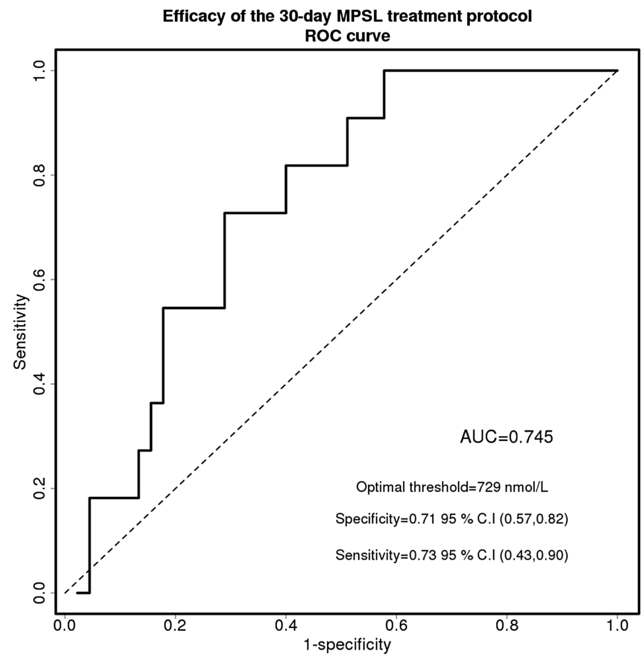

Figure 4
The ROC curve for logistic regression model that uses stimulated cortisol level at visit 1 as the explanatory variable in evaluating the efficacy of the 30-day MPSL treatment protocol.

The 57 patients who completed the 30-day MPSL treatment were divided into two groups: group 1–50 patients with normal adrenal function at visit 2 and group 2–7 patients (12.3%, 95% CI (6.1%, 23.2%)) with adrenal insufficiency at visit 2. In group 2 at visit 2, basal mean cortisol value was 282.0 ± 68.6 (range 174–350) nmol/L and after stimulation 422.5 ± 14.7 (range 400–444) nmol/L. The development of adrenal insufficiency significantly correlated with cortisol level after stimulation at visit 1 (Fig. 5). No other significant difference in patients' age, BMI, thyroid volume, basal cortisol, TSH, free T4, free T3, CRP, SR, Tg, or thyroid antibody levels between the two groups was found.

Figure 6 shows fit of the logistic regression curve to model predicting development of adrenal insufficiency with cortisol level after stimulation at visit 1 as the explanatory variable. The ROC curve was calculated and an AUC of 0.861 was obtained. The optimal stimulated cortisol threshold level of 629 nmol/L yielded a test specificity of 73% (95% CI (59, 83)) and a test sensitivity of 100% (95% CI (61,100)) (Fig. 7).

A repeated stimulation test after 3 months showed normal adrenal function in all seven patients

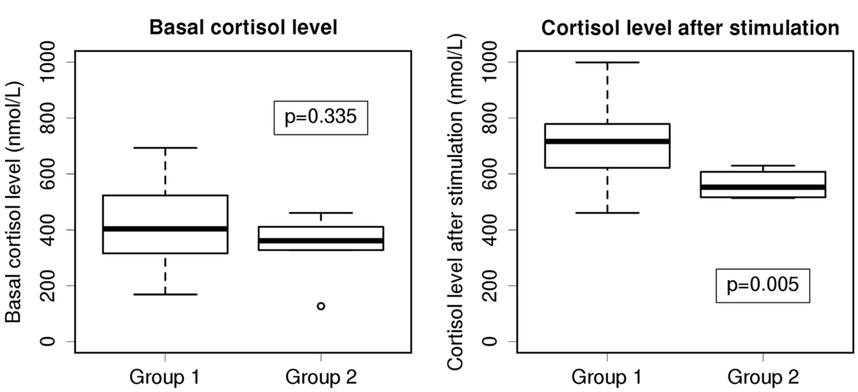

Figure 5
Basal and stimulated cortisol level in patients who did not (group 1, *N* = 50) and in patients who did (group 2, *N* = 7) develop adrenal insufficiency after 30-day MPSL treatment protocol (visit 1).

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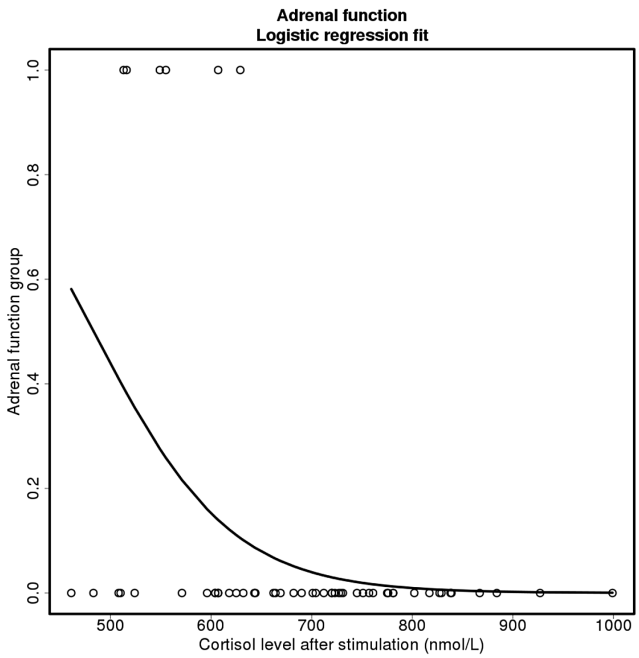

Figure 6
Fit of the logistic regression curve to model predicting development of adrenal insufficiency with cortisol level after stimulation at visit 1 as the explanatory variable. Dots indicate patient data, and continuous line represents probability of developing adrenal insufficiency as a function of cortisol level after stimulation at visit 1. On *y*-axis, 0 indicates normal adrenal function, 1 indicates adrenal insufficiency.

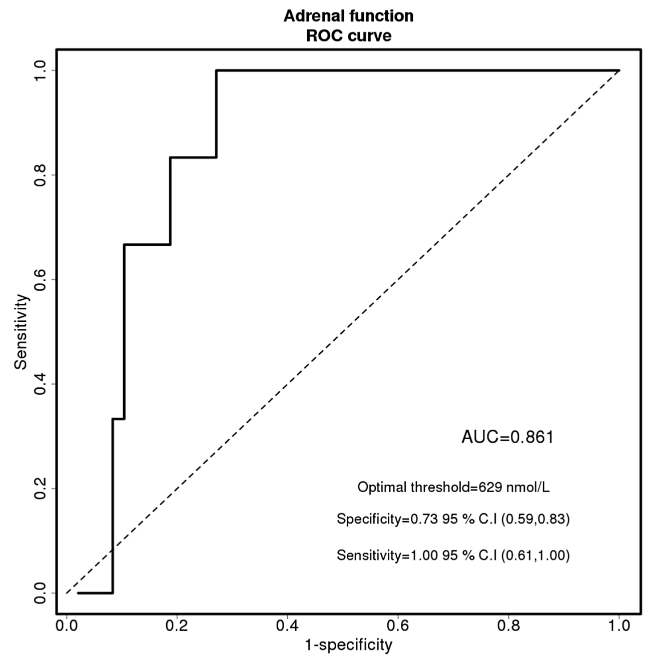

Figure 7
The ROC curve for logistic regression model that uses stimulated cortisol level at visit 1 as the explanatory variable for developing adrenal insufficiency after the 30-day MPSL treatment protocol.

in group 2. Until the recovery of adrenal function, no other clinical complications were registered in this group.

Discussion

In our study, we report the results of a prospective clinical study evaluating efficacy and safety with respect to the adrenal function of a 30-day MPSL treatment protocol with a starting dose of 24 mg tapered by 4 mg every 5 days for treating moderate/severe forms of ST.

The 30-day MPSL protocol was efficient for more than 80% of patients. It is important to emphasize that the initial dose of CS in our treatment protocol was lower and the duration of treatment shorter than recommended in the current ATA and AACE guidelines (1, 21) and reported by a previous study summarizing decades of experience (22). Our results showed a similar recurrence rate as the results of a recent study by Sencar *et al.* where a higher initial MPSL dose was prescribed and a longer treatment duration was employed (15) as well as a similar recurrence rate as the study by Mizukoshi *et al.*, which used a similar starting dose of CS but longer treatment interval (23). In a study where a similar starting dose of CS was employed but was replaced by NSAID after 1 week, the recurrence rate was a bit higher (8). A study that reported much lower initial dose of CS was successful to treat only 50% of patients over a 6-week period (4). The initial MPSL dose in our study was higher but the treatment duration much shorter than that proposed by a recent systematic review which suggested at least 6 weeks of therapeutic period before tapering to a minimum CS dose (24).

In our study, a strict cutoff value for determining adrenal insufficiency was employed (19). Using these criteria, adrenal insufficiency was confirmed after a 30-day MPSL treatment protocol in a small subgroup of patients. Adrenal insufficiency resolved after 3 months and no further complications were registered. The development of adrenal insufficiency was significantly associated with stimulated cortisol level at visit 1 which could be explained that there is probably a subgroup of individuals with an intrinsic tendency to be more susceptible to develop adrenal insufficiency. Therefore, in such individuals, adrenal insufficiency can develop earlier and prolonged treatment with a lower CS dose can represent an additional risk for these individuals. Importantly, clinical signs and symptoms are unreliable and unable to predict an impairment of the HPA axis (9, 10, 25). Whether a patient with an insufficient response

to an adrenal stimulating test develops clinically significant complications depends on the presence of stress and can change relatively fast. Adrenal insufficiency should therefore always be taken seriously (10, 25). We believe this insight is important to have in mind when constructing the optimal CS treatment protocol for ST which should be as short as possible. In our opinion, it is better to completely stop CS treatment for a short interval to make it possible for adrenals to recover and then repeat treatment if needed. However, since many authors believe that longer corticosteroid treatment with low doses is more beneficial and not related to significant side effects (4, 15, 23, 24), possible adverse effects of such protocols should be evaluated in further studies.

One of the strengths of our study is the adrenal function evaluation before and after CS treatment which is not routinely employed in clinical practice. To our best knowledge, no study evaluating the HPA axis in ST patients treated with CS has been published. We have shown that there is a susceptible group of individuals who develop adrenal insufficiency. Therefore, our results suggest that even if low doses of CS are used for a relatively short time, the threshold to test for adrenal insufficiency in CS-treated patients should be low in clinical practice, especially if non-specific symptoms after cessation of CS treatment are present (9). Furthermore, all patients included in our study were Caucasian. A recent systematic review of ST treatment protocols reported that most studies were conducted in Japan and China and the results cannot be directly extrapolated to other races (26). Therefore, our results contribute to evaluating modalities of CS treatment of ST in people of Caucasian race.

One of the limitations of the study is a relatively short interval for adrenal testing after finishing treatment. However, since this was a clinical study, all efforts for optimal patient care including early clinical evaluation after finishing the 30-day treatment period were implemented. Another limitation of the study are relatively small subgroups of analyzed patients (group A vs group B when analyzing treatment efficacy and group 1 vs group 2 in analyzing adrenal function). Further studies targeting larger sample sizes should be performed to confirm the statistical significance established in our study. Larger cohorts are also expected to narrow confidence intervals on specificity and sensitivity at the optimal cutoff. Furthermore, despite careful planning of the study, the immunoassay method for measuring laboratory parameters was changed during the course of the study for reasons not associated with the study. The consistency of normal ranges provided by the same manufacturer indicates the comparability of the obtained results.

In conclusion, we report that the 30-day MPSL treatment protocol was efficient for more than 80% of patients. With this protocol, a small subgroup of patients developed a mild form of adrenal insufficiency which recovered after 3 months. Since clinical signs and symptoms of adrenal insufficiency are unreliable, the threshold to test should be low in individuals with unspecific symptoms after cessation of CS treatment, even if low doses of CS for a short time were used.

Declaration of interest
The authors declare no conflict of interest.

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