Hypothalamus-Pituitary-Adrenal Axis Function in Patients with Rheumatoid Arthritis Treated with Nighttime-Release Prednisone

RIEKE ALTEN, GISELA DÖRING, MAURIZIO CUTOLO, ERIKA GROMNICA-IHLE, STEPHAN WITTE, RAINER STRAUB, and FRANK BUTTGEREIT

ABSTRACT. ***Objective.*** To investigate the effects of longterm low-dose chronotherapy with modified-release (MR) prednisone for rheumatoid arthritis (RA) on the hypothalamus-pituitary-adrenal (HPA) axis as part of the Circadian Administration of Prednisone in Rheumatoid Arthritis (CAPRA-1) study. This consisted of a 3-month active-controlled phase and a 9-month open-label extension with MR prednisone including patients previously treated with prednisone (Clinical Trials.gov number NCT00146640).

Methods. Corticotropin-releasing hormone (CRH) tests were performed on 28 patients at 3 timepoints: at baseline on prestudy immediate-release (IR) prednisone, after the 3-month double-blind phase on either IR prednisone or MR prednisone, and after the 9-month open-label extension on MR prednisone. Changes of cortisol were assessed and compared to individual patients' efficacy and safety data.

Results. The increase (mean, SD) of cortisol plasma concentrations after injection of corticorelin was 5.5 (4.37) μg/dl on IR prednisone at baseline (n = 21) and 5.3 (4.07) μg/dl on MR prednisone at 12 months (n = 22). Numbers of normal/suppressed/no response reactions did not differ among treatments. Switching from IR to MR prednisone did not influence responses, nor did longterm treatment of up to 12 months with MR prednisone. No worsening of adrenal impairment was observed on treatment with nighttime-release prednisone in patients with low responsiveness to CRH testing before the treatment with MR prednisone.

Conclusion. Treatment with nighttime-release prednisone did not change adrenocortical function over 12 months. We presume that chronotherapy with this nighttime-release prednisone may improve the efficacy of longterm low-dose glucocorticoid treatment in patients with RA. (J Rheumatol First Release August 1 2010; doi:10.3899/jrheum.100051)

Key Indexing Terms:
CHRONOTHERAPY CIRCADIAN RHYTHMS GLUCOCORTICOID
PROINFLAMMATORY CYTOKINES INTERLEUKIN 6

Rheumatoid arthritis (RA) is a chronic inflammatory disease in which circadian rhythms of proinflammatory and antiinflammatory mediators play key roles[1,2,3,4]. Early morning increase of proinflammatory cytokines, particularly interleukin 6 (IL-6), has been shown to coincide closely with the diurnal variations of RA symptoms and also with changes in the physiologic rhythm of endogenous cortisol and reduced hypothalamic-pituitary-adrenal (HPA) axis function[2,3,4,5,6,7,8,9]. Glucocorticoids (GC) have been among the most important drugs for the treatment of RA as well as for other inflammatory diseases[10,11], despite their potential to cause frequent and sometimes serious side

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effects. In particular, higher doses and longer treatment durations are still matters of concern[4,12,13,14]. Nevertheless, evidence-based knowledge on the effects of prednisone therapy in RA is rather limited, especially concerning longterm nighttime application, which to our knowledge has not been investigated yet. This is particularly true for effects of such a treatment scheme on the HPA axis function.

The low-dose regimen for longterm treatment of RA recommends < 10 mg/day prednisone as a single dose early in the morning[14]. This in general reduces the risk of adverse effects, but patients with RA still wake up in the morning with painful joint stiffness despite otherwise effective standard treatments. Chronotherapy in RA, with application of prednisone before the daily increase of proinflammatory activity, was realized for the first time with a novel modified-release (MR) prednisone formulation, which releases prednisone at about 2 A.M. when taken at bedtime[15]. Hence prednisone is released during the rising phase of the circadian cortisol cycle[4]. This mechanism by itself overcomes an inadequate cortisol release in RA, presumably leading to better clinical effects, and it mimics the physiological circadian rhythm of endogenous cortisol. The HPA axis might be less disturbed by this timing of prednisone application.

The clinical benefit of these characteristics of the new MR formulation was shown in the Circadian Administration of Prednisone in Rheumatoid Arthritis trial (CAPRA-1), an active-controlled clinical trial in which MR prednisone demonstrated a clinically relevant reduction of morning stiffness of the joints and of IL-6 after 3 months[15]; both effects were sustained over the entire study period of up to 12 months[16].

We report, for the first time, the effects of longterm, low-dose prednisone chronotherapy on the HPA axis function in patients with RA. These are the results of an additional investigation with corticotropin-releasing hormone (CRH) stimulation tests in a subgroup of patients. Our investigation was included in the CAPRA-1 protocol, in addition to the controlled study and the open-label extension[15,16,17].

MATERIALS AND METHODS

We performed our study between August 2004 and January 2007 in 28 patients with RA who participated in the CAPRA-1 trial[15]. The protocol was reviewed and accepted by the responsible national ethics committees in Germany (University Hospital Charité, Berlin) and Poland (University Hospital Wroclaw) and was conducted according to the principles set up in the Declaration of Helsinki. The study is registered in Clinical Trials.gov number NCT00146640.

Study protocol of the CAPRA-1 clinical study. CAPRA-1 was a randomized, multicenter, double-blind, active-controlled phase III study to investigate the safety and efficacy of the application of MR prednisone at bedtime in comparison with standard immediate-release (IR) prednisone given in the morning. A total of 288 patients, previously treated with stable doses of low-dose glucocorticoids (2.5–10 mg/day prednisone or equivalent), disease-modifying antirheumatic drugs, nonsteroidal antiinflammatory drugs, and nonantiinflammatory analgesics were randomized to 3–10 mg/day IR or MR prednisone with no change of individual doses for 3 months. During the 9-month open-label extension with MR prednisone, dose changes were allowed for MR prednisone as well as for the other RA treatments. The treatment periods with MR prednisone were up to 9 months for those patients randomized to IR prednisone (IR/MR group) and up to 12 months for those treated with MR prednisone in the double-blind phase (MR/MR group).

Patients treated at German centers with 5 mg prednisone/prednisolone or equivalent and complying with all other entry criteria of the study were eligible to participate in the test series if additional informed consent was given. The tests were performed during the screening phase on treatment with prestudy IR prednisone, at the end of the double-blind phase, and at the end of open-label extension. For this additional CRH stimulation testing, 32 patients (16 patients per group at the end of the double-blind phase) were considered appropriate. Due to an inadequate recruitment of volunteers for the test series, the initial dose restriction to 5 mg prednisone was lifted and patients with doses 5 to 10 mg per day, as well as patients who took part in only 1 test at the end of the study, were also included per protocol amendment.

Study design, types of treatment, visit schedule, and number and timepoints of tests are summarized in Figure 1.

CRH testing. According to the test kit manufacturer's instructions, intervals of at least 24 hours from the last dose of prednisone to the test drug injection were mandatory[18]. During the screening phase, for Test 1 on IR prednisone, no morning medication was given on the test day. At the end of the double-blind phase, for Test 2, with randomized double-dummy study medication being either IR prednisone in the morning or MR prednisone in the evening, no evening dose was taken the day before and no morning dose on the test day. At the end of the open-label study on MR prednisone, for Test 3, no evening dose was applied before the test day. This resulted in intervals between the last glucocorticoid intake and the tests of > 24 hours for IR prednisone and > 36 hours for the tests for MR prednisone. Tests were performed in the morning. They consisted of an intravenous 30-second bolus injection of 100 μg of human corticorelin (CRH Ferring, Ferring Pharmaceuticals Inc., Tarrytown, NY, USA). Blood samples of 1 ml were drawn 15 min prior to and immediately before, and 60 and 90 min after injection. Cortisol plasma concentrations were analyzed centrally by the Bio Analytical Research Corporation, Ghent, Belgium.

Statistical analysis. The data were analyzed by means of exploratory descriptive statistics. In the CAPRA-1 protocol, no tests for significance of findings were defined, because at that time we were not aware of any published experience on longterm nighttime application of prednisone in patients with RA, which could have been used for a statistical sample size calculation and hypotheses to be tested.

Cortisol concentrations of each blood sample were analyzed. Serum cortisol values measured immediately before the test injection, and the higher one of the 2 postinjection values per test, are reported as mean (SD) and median (minimum/maximum).

Descriptive comparisons of treatments were calculated for pairs of tests done by the same patient on the same treatment (Tests 1 and 2 for the IR/MR group; Tests 2 and 3 for the MR/MR group) and after change of treatments (Tests 2 and 3 for the IR/MR group; Tests 1 and 2 for the MR/MR group).

Test results were interpreted according to the 3 ratings of response as normal (change ≥ 5 μg/dl), suppressed (change > 0 to < 5 μg/dl), and no response (no increase, or reduction of cortisol). Efficacy data, such as duration of morning stiffness, Disease Activity Score for 28 joints (DAS28), IL-6, and C-reactive protein (CRP) of patients with "no response" in any of the tests, and of those with preinjection cortisol < 10 μg/dl, were extracted from the CAPRA-1 database and compared with the individual patients' test responses[15,16].

The safety database was scrutinized for incidence of Addison disease–like symptoms, such as fatigue, anorexia, asthenia, abdominal pain, hypotension, and circulatory failure[10,12,13,14]. Only safety data of patients who took CRH tests were included in our analysis. Serum sodium and potassium values were extracted for those patients from the biochemistry

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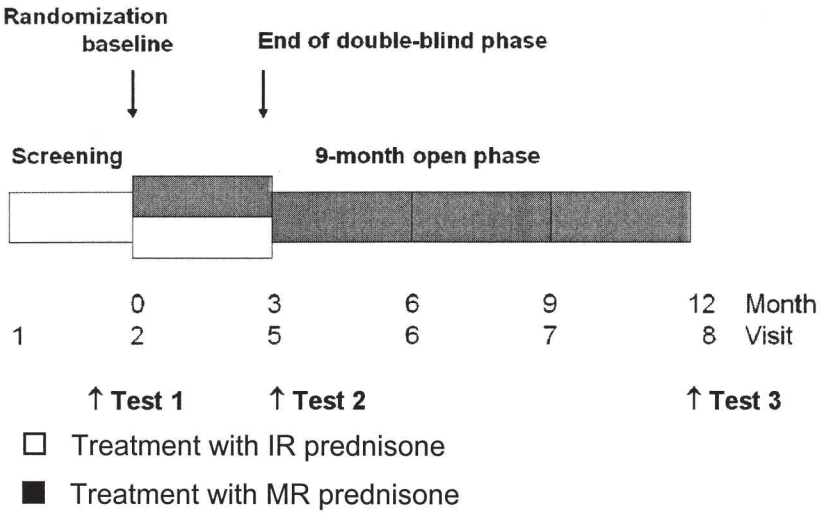

Figure 1. The study design.

data of CAPRA-1 as an additional means of scrutiny for any corticoid-related changes of these electrolytes.

RESULTS

Patients, number of tests, and pretest prednisone dosages. At least 1 CRH test was done by 28 patients, including 6 patients who did only the 1 test at the end of the study. Patient characteristics are shown in Table 1.

A total of 64 tests were performed — 32 tests with each of the 2 drugs. Two tests performed at the end of the study were not valid due to incorrect dosing intervals before testing. In total, 62 valid tests were analyzed. The prednisone dose before the tests was 5 mg in 54 out of the 64 tests. Altogether, 6 patients, taking 10 tests, were taking higher dosages. For 3 patients taking 5 tests in the IR prednisone group, these dosages were 7.5 mg (twice at Test 1) and 7.0 mg (once at Test 1; twice at Test 2). Five patients completed Test 3 after treatment with higher doses of MR prednisone, which were 7.0 mg in 2 tests and 10 mg in 3 tests. None of these 5 patients had "no response" in any of the tests, according to the general definition. Two patients had a "normal response" and 2 a "suppressed reaction" in all 3 tests. Only 1 of these 5 patients presented a cortisol concentration below 10 μg/dl at any time (both tests on IR prednisone). After 9 months of MR prednisone treatment, the cortisol level before the testing was above 10 μg/dl in this patient.

Table 1. Demographic characteristics of all patients who took at least 1 CRH test. N = 28. Cohort includes 22 patients who consented to the test series with 3 tests, and 6 patients who consented to 1 test at the end of the study.

Characteristic	
Age, yrs	
Mean (SD)	56.1 (9.6)
Range	33 to 69
Age, yrs, n (%)	
≤ 45	4 (14.3)
> 45 and ≤ 65	18 (64.3)
> 65 and ≤ 75	6 (21.4)
Weight, kg	
Mean (SD)	79.7 (14.3)
Range	52.5 to 112.0
Men/women, n (%)	3 (10.7)/25 (89.3)
Ethnic origin, n (%)	
White	28 (100)

CRH: corticotropin-releasing hormone.

The mean daily dose of IR prednisone administered was 5.3 mg (SD 0.82) before the 32 tests (21 tests in the screening phase and 11 tests at the end of the double-blind phase). The mean daily dose of MR prednisone administered was 5.6 mg (SD 1.56) before the 30 tests eligible for analysis (8 tests at the end of the double-blind phase and 22 tests at 12 months). An effect of this minimal dose difference on the CRH test results was not expected.

Cortisol change after corticorelin injection. Prednisone chronotherapy for up to 12 months did not change CRH test results. There was no difference between the changes of cortisol levels from baseline on IR prednisone (21 tests) to end of study on MR prednisone (22 tests). This result suggests that no new HPA axis suppression developed and no further aggravation of adrenocortical suppression, which had already been established by prestudy GC treatments, occurred in our patients during our study. Mean (SD) and median (minimum/maximum) cortisol concentrations are shown in Table 2.

Individual patients' test responses in repeated tests. Although the number of tests in the controlled phase of the study was small, results indicate that there was no difference between the treatments (Test 2: 11 tests on IR prednisone and 8 tests on MR prednisone). CRH test results on treat-

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Table 2. Plasma cortisol levels (μg/dl) after stimulation with corticorelin; highest changes of the 2 postinjection values per test by treatment and time.

Treatments	No. Tests	Mean ± SD, μg/dl	Median, μg/dl	Minimum/Maximum μg/dl
Test 1				
IR prednisone				
Screening phase	21	5.5 ± 4.37	5.00	–0.98/15.00
Test 2				
MR prednisone	8	3.3 ± 5.76	2.50	–3.98/13.85
End of double-blind phase[15]				
Test 2				
IR prednisone	11	4.5 ± 3.91	3.01	–1.02/12.00
End of double-blind phase[15]				
Test 3				
MR prednisone	22	5.3 ± 4.07	5.00	–2.00/13.01
At end of study				

IR: immediate release; MR: modified release.

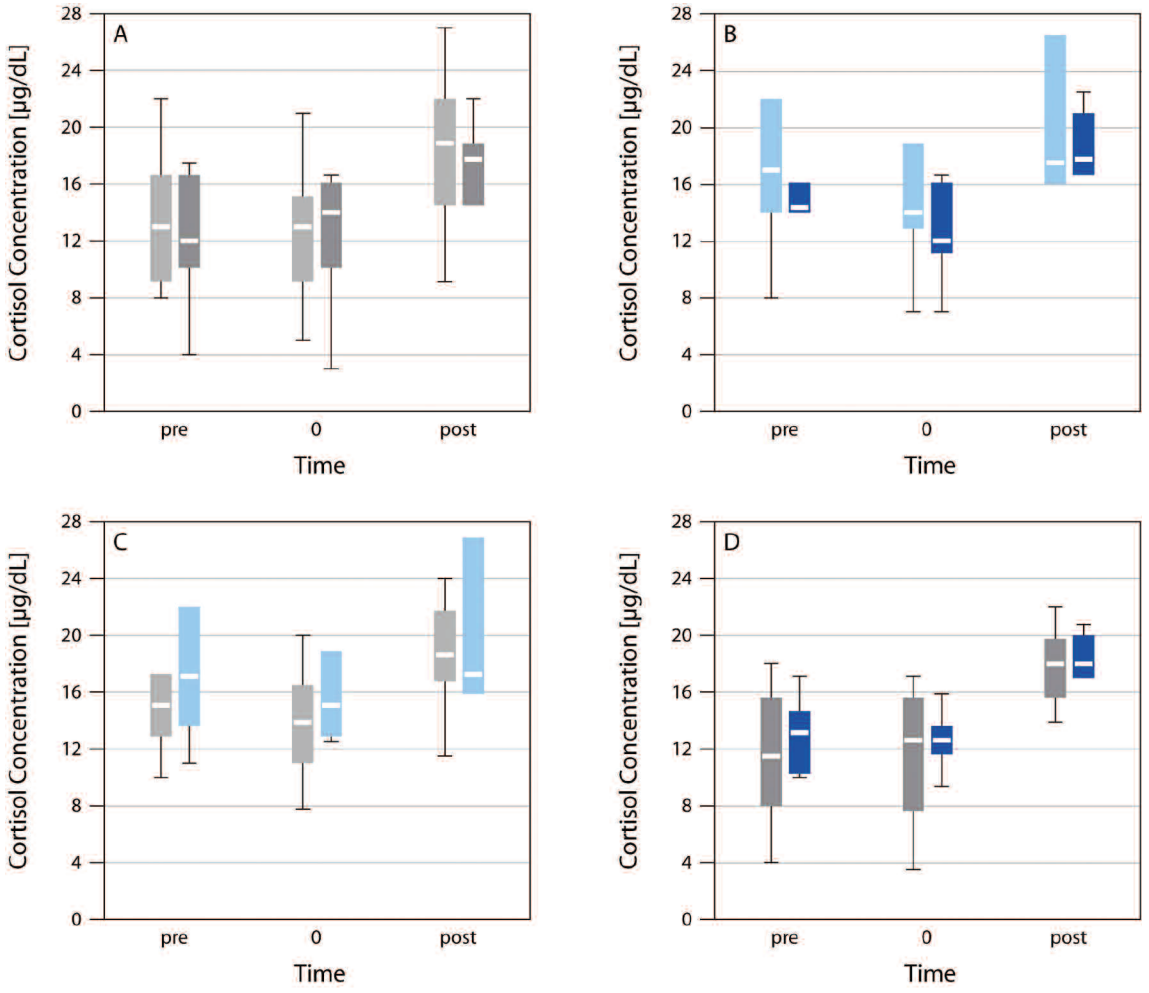

Figure 2. Maximum changes of cortisol after corticorelin injection in repeated tests of individual patients. Timepoints "pre" and "0" are before corticorelin injection. "Post" denotes highest value of the 2 assessments at 30 or 60 minutes after injection. (A) Repeated tests on unchanged immediate-release (IR) prednisone. Pale gray indicates score after Test 1; dark gray after Test 2, n = 11. (B) Repeated tests on unchanged modified-release (MR) prednisone. Pale blue indicates score after Test 2; dark blue after Test 3, n = 7. (C) Results after the change of treatments from IR to MR prednisone after randomization. Pale gray: Test 1, MR/MR; pale blue: Test 2, after double-blind MR, n = 7. (D) Repeated tests after change at end of double-blind phase from IR to MR prednisone. Dark gray: Test 2 after double-blind IR prednisone; dark blue: after 9 months of open MR prednisone, n = 9.

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ments with IR or MR prednisone, as shown in Figure 2, also confirmed that no additional suppression of the HPA axis regulation occurred in these previously GC-treated patients. Panel A (data of patients with 2 tests on IR prednisone, Test 1 and 2) and Panel B (data of patients with 2 tests on MR prednisone, Tests 2 and 3) describe the repeated tests on unchanged treatments. There was no difference on repetition of the test on the same treatments. Further, no difference in the test results was detected when the test was repeated in the MR/MR group after 9 months, i.e., after an exposure to MR prednisone of 12 months altogether. Panels C and D describe the test results after the change of treatments from IR to MR prednisone after randomization (MR/MR group, Test 1) or at the start of the open-label phase (IR/MR group, Test 2). There was no difference in the test results when the treatments were switched from IR to MR prednisone.

Global ratings of test results. The distribution of the 3 ratings, i.e., normal, suppressed, and no response, did not change during the course of the study. This was particularly true for the suppressed and no response outcomes (Table 3).

Preinjection serum cortisol. The preinjection cortisol values did not show any relevant difference between treatments with either IR prednisone or MR prednisone during the course of our study; although under IR prednisone the minimum and maximum pretest cortisol values were numerically lower than later under treatment with MR prednisone. Preinjection cortisol values below 10 μg/dl were found in 5 patients in Test 1, when all patients had been treated with IR prednisone, and in 1 further patient on MR prednisone (at Test 2), who had no Test 1. The overall lowest preinjection cortisol concentration of 3 μg/dl was measured in a patient on IR prednisone (Test 2). Low preinjection values increased to above 10 μg/dl in 3 of the 6 patients at the end of the study on MR prednisone. In Test 3, when all patients were on MR prednisone, only 1 patient still had a preinjection cortisol value below 10 μg/dl. This patient had a similarly low cortisol value at Test 1 on IR prednisone.

The efficacy data as assessed in the CAPRA-1 study of the patients with marked low outcomes of the CRH tests were individually scrutinized for any signs and symptoms of HPA axis impairment. The comparison of the test outcomes of patients with no response or low preinjection cortisol levels with their individual efficacy data, particularly duration of morning stiffness, DAS28, and signs of inflammation, such as elevation of erythrocyte sedimentation rate, CRP, or IL-6, did not show a relationship between the test results and the therapeutic effects of cortisol on disease activity.

Safety. One patient out of the 28 CRH test volunteers terminated the double-blind phase after 48 days on IR prednisone due to a flare of RA. This patient had a normal response to the corticorelin injection at Test 1 but no further test. The most frequently reported treatment-emergent adverse event in the 28 patients was flushing (14 events in 10 patients on IR prednisone; 17 events in 14 patients on MR prednisone). Additionally, but less frequently, feeling hot (3 events in 2 patients on IR and 6 events in 5 patients on MR prednisone) and hot flushing (once on IR) was reported. Often a patient reported more than 1 of these symptoms. Such events were only reported in connection with and within minutes of the injection of corticorelin, and were in all cases causally attributed to the corticorelin injection. At the same time and in connection with these test-related symptoms, a few patients reported tachycardia (n = 2) and chest pain (n = 1) on MR prednisone, and palpitations (n = 1) and vertigo (n = 1) on IR prednisone.

The observation period for all other adverse events, attributable to IR prednisone, included only the 3 months of the double-blind phase, but up to 12 months for MR prednisone. This resulted in a 5-fold longer exposure to MR prednisone, or in terms of patient-years (PY), this related to 4.21 PY and 22.41 PY for IR prednisone treatment and MR prednisone treatment, respectively. Deterioration of RA or symptoms pertaining to RA were reported by 12 patients while on treatment with MR prednisone compared to 4 patients in the IR prednisone group, which also reflects the difference in duration of observation.

No Addison disease–like symptoms were reported for the 288 patients included in the CAPRA-1 study and no clinically relevant changes, for example, altered Na/K ratios, were found in the biochemistry investigations[15,16]. This also includes the 28 patients of the CRH test series. Further, investigators of the CAPRA-1 study did not judge any of the adverse events as being related to HPA axis impairment.

Table 3. Global rating of responses to corticorelin injection.

Response	IR Prednisone			MR Prednisone		
	Test 1, n = 21	Test 2, n = 11	Total, n = 32 (%)	Test 2, n = 8	Test 3, n = 22*	Total, n = 30 (%)
Normal	11	5	16 (50.0)	2	13	15 (50.0)
Suppressed	7	5	12 (37.5)	4	7	11 (36.7)
No response	3	1	4 (12.5)	2	2	4 (13.3)

* Two tests with too short or unknown intervals from last dose not counted. Normal: increase of cortisol ≥ 5 μg/dl; suppressed: increase of cortisol > 0 – < 5 μg/dl; no response: no increase or reduction of cortisol. IR: immediate-release prednisone; MR: modified-release prednisone. n: number of tests.

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Importantly, there was also no indication that adrenal insufficiency, induced by nighttime application of MR prednisone, compromised the safety of the patients by reducing the therapeutic efficacy.

DISCUSSION

There was no indication that changing treatments from IR prednisone to chronotherapy with the novel MR prednisone increased the risk of HPA axis insufficiency, or deterioration of preexisting suppression. Patients with low pretest cortisol levels and/or small increases of cortisol after stimulation during the screening phase, which may indicate suppressed HPA axis function, did not show higher RA disease activity or clinical signs of secondary hypocortisolism. Suppressed CRH test responses or low pretest cortisol values had no influence on the patients' safety in our study. No adverse events attributable to HPA axis disturbance were observed during the treatment with MR prednisone for up to 12 months.

In overviews on GC toxicity in the literature, generally the borderline between high and low GC doses varies from below 10 mg/day to below 15 or 20 mg/day[12,13,14]. Timepoints of application during the day are hardly ever specified. Moreover, evidence-based information on nighttime application of GC for longterm treatments in RA was very scarce before the CAPRA-1 study was conducted. Our test results confirm newer findings from basic science, indicating that clinical efficacy of prednisone should improve when the release takes place between 2 and 3 A.M., i.e., before the rise of proinflammatory activity and during the rise of endogenous cortisol[4,15]. Nighttime drug application in the context of chronotherapy or chronobiology implies a close synchronization of treatment with the endogenous rhythms of the disease. This is what was achieved by the development of the new MR prednisone tablet.

RA and other rheumatic diseases, such as polymyalgia rheumatica, show changes of HPA axis function that are independent of any treatment with glucocorticoids[8,19,20,21,22]. Regarding the HPA axis, low doses of prednisone on longterm treatment may, theoretically, be as harmful as high doses given for shorter periods[13,14]. This also includes low-dose treatment regimens with doses below 10 mg/day. Santen, *et al* measured reduced HPA axis function by CRH testing in patients with chronic obstructive pulmonary disease (COPD) who were treated with 5 mg prednisolone/day over at least 3 months[23]. Although the pathophysiology of COPD differs from that of RA, GC treatments may have similar effects on the HPA axis. Most recently, Kirwan, *et al* demonstrated in previously GC-naive patients with RA that 7.5 mg/day prednisolone suppressed HPA axis responses to adrenocorticotropic hormone stress testing, but the authors also stated that there is no definitive evidence of severity and frequency of such deficiencies[24].

Moreover, side effects of low-dose GC treatments of RA, related to HPA axis deficiency, were not mentioned in recent extensive reviews[10,11,22]. Symptomatic adrenal insufficiency, with a variety of possibly serious effects, may also occur when high doses of GC are withdrawn too rapidly[13,23,25]. In CAPRA-1, which included 288 patients with RA, we did not observe HPA axis-related adverse events. For interpretation of the relevance of our findings, it is important to point out once more that in the CAPRA-1 trial, nighttime-release MR prednisone was more efficacious than the standard morning application of IR prednisone in previously GC-treated patients with RA[15,16].

The CRH test series presented here was conducted in a random sample of patients from the CAPRA-1 trial, the main criterion of eligibility for participation in the test series being the prestudy prednisone dose of 5 mg. The tests were done in the morning in an outpatient setting, which compares well with the normal daily life of patients with RA. Although the number of patients participating in the test series was rather small, this study provided unique additional insights. The series of tests, including the double-blind comparison of the 2 different prednisone preparations, as well as the switch from IR to MR prednisone, with treatment times of up to 12 months with MR prednisone, made it possible to compare CRH test responses in patients with their individual clinical efficacy results. It also allowed evaluation of whether an imbalance of HPA axis function would cause any safety concerns. Low serum cortisol before the test, and low responsiveness of the HPA axis to stimulation with corticorelin, did not coincide with higher disease activity, for example with longer duration of morning stiffness, higher DAS28 scores, or more elevated levels of serum CRP or IL-6. Similarly, the magnitude of the response to CRH stimulation seemed to be independent of preinjection cortisol levels. As shown in 4 of the 5 patients with cortisol below 10 μg/dl (at least in 1 test) who repeated their tests, response ratings did not change. Nevertheless, in all but 1 of these patients the duration of morning stiffness of the joints was clearly reduced between Tests 1 and 3. The same applies to the DAS28 score, which was clinically relevantly reduced during our study in 4 of these patients. CRP was normal in all 5 patients, indicating efficient antiinflammatory disease control (these individual patients' data are not shown here).

The type and number of adverse events observed in these 28 CRH test patients must be interpreted with caution. Only 3 months of the entire study were conducted under blinded conditions, allowing an objective comparison between the 2 treatments for only very few tests. As data from the double-blind phase of the CAPRA-1 study showed, there was no difference in the safety profile between the treatments[15]. The monitored observation time for the CRH test patients treated with MR prednisone was 5 times longer than that of patients treated with IR prednisone, due to the extended drug exposure to MR prednisone during the open phase of our study.

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Further, it is known that corticorelin causes facial flushing and similar symptoms. Such symptoms, persisting only for some minutes, were observed during almost all tests and were in all cases directly related to corticorelin as reported by the investigators. None of the other events suggested any relationship with corticoid-induced adrenocortical insufficiency. This applies to the adverse events reported during the study, as well as to the findings in routine clinical laboratory investigations[15,16]. Our data, derived from the CRH test series, further support the safety of low-dose GC chronotherapy with MR prednisone in RA.

CRH testing in these previously GC-treated patients with RA did not show any new or further deterioration of HPA axis function after switching treatment from IR prednisone to nighttime-release MR prednisone, or after up to 12 months of treatment with MR prednisone. The results of our study may lead to the assumption that nighttime prednisone can successfully substitute the extra dose of endogenous cortisol at the timepoint when it is most needed. MR prednisone may thereby provide a physiological stimulus and optimize the replacement therapy in an altered circadian rhythm of endogenous cortisol production in patients with inadequately controlled RA.

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