Hypothalamic-Pituitary-Adrenal Axis Function in Patients with Rheumatoid Arthritis Treated with Different Glucocorticoid Approaches

Rieke Alten Edgar Wiebe

Schlosspark-Klinik, Charité University Medicine Berlin, Berlin, Germany

Key Words

Hypothalamic-pituitary-adrenal axis function ·
Glucocorticoids · Modified-release prednisone ·
Rheumatoid arthritis

Abstract

Glucocorticoids (GCs) continue to be an important treatment option in rheumatoid arthritis (RA) – despite their multitude of side effects. Amongst those, suppression of the hypothalamic-pituitary-adrenal (HPA) axis plays a dominant role. In clinical practice, low-dose GC therapy of 5 mg or less per day seems to be safest in eschewing these undesirable effects and assuring function of the HPA axis. Further research has shown that, apart from dosage, the degree of HPA axis suppression by exogenous GCs is not only dependent on the duration of therapy, but that it also underlies a significant diurnal variation. The recent development of a novel modified-release (MR) prednisone formula reflects an attempt at targeting these circadian neuroendocrine pathways of the HPA axis' function and their interplay with the immune system in RA. Data from a subset of 28 patients included in the CAPRA-1 study indicated that chronotherapy with MR prednisone has no adverse effect on HPA function. Whether adapting GC therapy to a pathophysiological circadian pattern might even be beneficial will have to be further investigated.

© 2014 S. Karger AG, Basel

Introduction

The groundbreaking discovery of the anti-inflammatory and immunosuppressive properties of 'Compound E' or cortisone by Hench and Kendall in 1948 marked the beginning of the ability of physicians to treat and control autoimmune diseases. Ever since, GCs have been a cornerstone in the treatment of rheumatic diseases – with treatment regimens and administration forms changing constantly in the past decades by adapting to the latest scientific findings. In fact, soon after the successful use of pharmaceutically manufactured cortisone, Hench became aware of its mineralocorticoid adverse effects – namely sodium/water retention and potassium loss [1]. Not much later, the initial enthusiasm was further dampened by a report in 1952 by Fraser et al. [2]. They reported the post-operative collapse and death of a woman who had received prednisolone for 6 months. In the postmortem analysis, an atrophy of both adrenal glands was found. Further reports accumulated showing corticosteroid-induced adrenal suppression to result in severe post-operative complications [3]. With increasing knowledge on the complications of long-term corticosteroid therapy in patients with rheumatoid arthritis (RA), the essential role of the hypothalamic-pituitary-adrenal (HPA) axis and its susceptibility to

suppression by exogenous glucocorticoids (GCs) were pinpointed and the exact role and benefits of corticosteroids in the treatment of RA put under considerable debate. Against the background of GC-related adverse effects, it continues to be a major challenge to find a therapeutic regimen that minimizes the constraining side effects while guaranteeing an optimal control of symptoms and autoinflammatory processes. This article provides an overview of current knowledge on different GC treatment approaches and their effects on HPA function.

Dose-Dependent HPA Axis Function

Confronted with the adverse effects on the HPA axis, findings by Danowski et al. [4] could show that the probability of HPA axis suppression was related to the duration and dosage of GC therapy, i.e. higher doses over a longer period of time caused more pronounced suppression of the pituitary-adrenal function. In 1993, LaRochelle et al. [5] outlined a correlation between prednisone dose and HPA axis response to stimuli, favoring less than 5 mg per day for normal HPA function. These results reflected previous findings by Daly et al. [6], who, in 1967, showed that median plasma cortisol levels only remained in normal ranges in patients when receiving less than 5 mg of prednisolone per day. Yet, interestingly, in the latter study, there seemed to be no definite correlation between individual plasma cortisol levels and dose and duration of prednisolone treatment. Similarly, in 1992, Schlaghecke et al. [7] tested the degree of pituitary-adrenal function in patients treated with different doses of synthetic GC medication for different periods by measuring the pituitary-adrenal response after stimulation with corticotropin-releasing hormone (CRH). They concluded that the pituitary-adrenal function could not be estimated from dose, duration of therapy or basal plasma values of cortisol. Even EULAR recommendations on GC therapy state that 'hypothalamic-pituitary-adrenal axis suppression may vary greatly from person to person and continues to be difficult to predict' [8]. Current EULAR guidelines integrate the concept of dose-dependent HPA axis effects of GCs and underline that HPA axis suppression is likely to occur with treatment that exceeds the equivalent of 7.5 mg of prednisolone for more than 3 weeks [9].

The low-dose GC approach as an initial or maintenance therapy originated mainly from findings that showed that low-dose therapy was as effective in reliev-

ing patients from symptoms and preventing disease progression in the short and medium term, and at the same time reduced the adverse effects of long-term therapy [10–12]. Several other studies have shown that the benefit/risk ratio is favorable for low-dose therapy. Still, most recently, Kirwan et al. [13] demonstrated in a randomized, double-blind, placebo-controlled trial that in previously GC-naïve patients, 7.5 mg of prednisolone per day also suppressed HPA activity (measured after ACTH stimulation test). Thus, it seems that GC therapy and its effects on the HPA axis remains likely to also be defined by the treatment regimen, rather than dosage alone.

Targeting the Time of Day of GC Administration

In the early beginnings of systematic GC therapy of RA, different regimens were investigated in order to find a way of administering GCs effectively with the least suppression of the HPA axis. In a special report from 2011, Kirwan [14] gives a detailed overview of the historical development of how the current treatment rationale evolved in favor of targeting the time of day of GC delivery. Briefly, midnight administration of GCs was shown by Nichols et al. [15] to completely suppress cortisol production for 24 h, while giving the same dose at 8 a.m. or 4 p.m. would suppress GC secretion from the adrenal gland only transiently and less intensely. This diurnal variation indicated that HPA axis function goes beyond a simple negative feedback mechanism and represented a clear case for adapting GC therapy to the timing of the day. In addition, findings in which HPA axis suppression was shown to be more severe in multiple daily dose administration with more pronounced side effects while being less potent in controlling symptoms [16], supported the recommendation of a single morning dose regimen [17]. This concept was further substantiated by analyses by Weitzman et al. [18], who outlined the episodic secretion of cortisol, making morning doses of exogenous GCs the optimal timing in theory – just after the physiological endogenous GC peak.

However, data remained controversial, especially in regard to controlling morning symptoms, such as morning stiffness, because some patients favored a nocturnal dose of prednisolone [19, 20]. Thus, treatment options were in a somewhat stymieing situation where safety was potentially traded off against efficacy – paving the way for new treatment approaches that targeted the circadian pathophysiology of RA.

Fig. 1. Responses to CRH testing in subgroups of patients included in the CAP-RA-1 study according to treatment [38]. Data are presented from assessments made 15 min before (Pre), immediately before (0) and the highest of 30 or 60 min after (Post) CRH testing. **a** Patients (n = 11) remaining on treatment with conventional prednisone. **b** Patients (n = 7) remaining on treatment with MR prednisone. **c** Patients (n = 7) switched from conventional (at screening) to MR prednisone (measure at the end of double blind phase). **d** Patients (n = 9) switched from conventional (during double blind phase) to MR prednisone (measured at the end of open-label treatment). Figure modified after Alten et al. [38].

Circadian Rhythms and HPA Axis Deficiency in Patients with RA

With recent insights into the role of endogenous and exogenous GCs [21], and a better understanding of the involvement of neuroendocrine pathways in the function of the HPA axis and their interplay with the immune system in RA [22–26], new treatment options arose. The basis was found by Arvidson et al. [27] when proposing that key symptoms such as morning stiffness in RA were likely to be attributable to circadian rhythms of plasma concentrations of IL-6 (which peaked in the morning and abated during the day).

Mastorakos et al. [28] showed in 1993 that recombinant IL-6 stimulated the HPA axis and led to a marked and prolonged elevation of plasma ACTH and cortisol levels. A plethora of studies investigating the HPA axis function of patients with RA strengthened the concept,

that although the HPA axis seems to function normally in patients with RA, its defect lies in its insufficiency to react with adequately high levels of cortisol to increased inflammation [29–31].

The link between diurnal endogenous GC production and stimulation by (auto-) inflammatory cytokines formed the basis for attempting a new strategy in which this ‘HPA axis insufficiency’ would be tackled by administering GCs at a time point where elevated GC levels are needed the most to control rising pro-inflammatory cytokines responsible for the main symptoms, such as morning stiffness [24]. This approach, where a group of patients received low-dose prednisolone at 2 a.m. as compared to a group receiving the same dose at 7.30 a.m. proved extremely effective in reducing circadian symptoms [32].

These early findings were the cradle for the development of a preparation of a novel modified-release (MR)

Table 1. Plasma cortisol levels after stimulation with CRH [38]

Treatment and assessment time	n	Mean plasma cortisol ($\pm$ SD), μ g/dl	Maximum plasma cortisol, μ g/dl
Conventional prednisone (pre-study)	21	5.5 $\pm$ 4.37	15.00
Conventional prednisone (after 12 weeks double-blind phase)	11	4.5 $\pm$ 3.91	13.85
MR prednisone (after 12 weeks double-blind phase)	8	3.3 $\pm$ 5.76	12.00
MR prednisone (after 9 months open-label phase)	22	5.3 $\pm$ 4.07	13.01

prednisone formulation, which, when taken at bedtime, releases the drug at around 2 a.m. prior to the rise of pro-inflammatory cytokines. In the past few years, two large studies on GC chronotherapy with MR prednisone – Administration of Prednisone in Rheumatoid Arthritis (CAPRA)-1 plus open-label extension and CAPRA-2 – have clearly shown its clinical efficacy [33–35], safety and tolerability [36–38]. Yet, although the safety profile of MR prednisone is favorable and clinically not different from conventional prednisone [37], the question was raised as to what the impact of this new formula specifically on the HPA axis might be.

Chronotherapy and Its Effect on the HPA Axis: Current Data

In the pilot study by Arvidson et al. [32], it was pointed out that from a theoretical point of view, administration of nocturnal GCs could be controversial since it does not coincide with the circadian rhythm of endogenous GC secretion. Although chronotherapy with MR prednisone represents an approach to targeting the pathophysiological pattern of the circadian neuroendocrine-immune system in RA, the exact effect on the HPA axis could not be predicted a priori. With limited knowledge on the effects of long-term night-time prednisone application, it was therefore important to assess the impact of MR prednisone on the HPA axis.

The function of the HPA axis was tested in a subset of 28 patients included in the CAPRA-1 study – for a detailed description, see Alten et al. [38]. Briefly, CRH-stimulation tests were performed at three different time points: at baseline, at 12 weeks of treatment with either conventional or MR prednisone, and after the 9-month open-label extension phase with MR prednisone. Exogenous human CRH was administered and cortisol plasma

levels analyzed 15 min before, immediately before and 60 and 90 min after injection. The response to CRH was rated as either normal (52.4%), suppressed (33.3%) or no response (14.3%).

Over a period of 12 months, no deterioration or onset of adrenal insufficiency was noted. Mean cortisol response did not differ between time points (table 1; fig. 1), and the proportion of responders remained constant. Switching from conventional to MR prednisone (during the open-label phase) also did not negatively influence the response. This clearly indicated that chronotherapy with MR prednisone has no adverse effect on HPA axis function. Also, although the plasma cortisol level in this study did not change between the start and endpoint, a separate detailed study of plasma cortisol concentrations in patients treated with MR prednisone showed an enhanced nocturnal cortisol peak after 2 weeks of treatment [39]. This potential beneficial effect of chronotherapy on HPA axis function was corroborated by a within-patient analysis of the CAPRA-1 patients who, after being on conventional prednisone from baseline for the first 12 weeks, switched to MR prednisone for 9 months. The statistically significant ($p < 0.05$) 12% increase in maximum cortisol response even suggested an improved HPA axis responsiveness in RA patients with chronotherapy compared to conventional morning prednisone treatment [40].

Conclusion

Our experience with exogenous GC therapy has shown us that the effects on HPA axis function are strongly related to the respective treatment approach, including dosage, duration, disease activity and circadian rhythms. In the light of the current concept of insufficient endogenous GC secretion due to a disturbed HPA axis in RA, it

seems that adapting GC therapy to a pathophysiological circadian pattern does not only reduce symptoms associated with circadian rise of pro-inflammatory cytokines, but may also possibly improve HPA function. Despite these encouraging results, further studies with larger populations and in a long-term setting are warranted to substantiate the potential beneficial effects of MR prednisone on HPA function. Regardless, it will remain a challenge

to offer a GC approach that completely reduces the risk of HPA suppression. The most promising approach in this regard is future research that aims at further revealing the interplay between the neuroendocrine and immune systems – it will help us to better understand the variability in HPA function of patients undergoing GC treatment, especially in regard to GC resistance, and make GC therapy safer and more effective.

References

- 1 Ward E, Slocumb CH, Polley HF, Kendall EC, Hench PS: Clinical effects of cortisone administered orally to 100 patients with rheumatoid arthritis. *Ann Rheum Dis* 1951;10:477–484.
- 2 Fraser CG, Preuss FS, Bigford WD: Adrenal atrophy and irreversible shock associated with cortisone therapy. *J Am Med Assoc* 1952; 149:1542–1543.
- 3 Jasani MK, Boyle JA, Greig WR, Dalakas TG, Browning MCK, Thompson A, et al: Corticosteroid-induced suppression of the hypothalamo-pituitary-adrenal axis: observations on patients given oral corticosteroids for rheumatoid arthritis. *Q J Med* 1967;36:261–276.
- 4 Danowski TS, Bonessi JV, Sabeh G, Sutton RD, Webster MW Jr, Sarver ME: Probabilities of pituitary-adrenal responsiveness after steroid therapy. *Ann Intern Med* 1964;61:11–26.
- 5 LaRoche GE Jr, LaRoche AG, Ratner RE, Borenstein DG: Recovery of the hypothalamic-pituitary-adrenal (HPA) axis in patients with rheumatic diseases receiving low-dose prednisone. *Am J Med* 1993;95:258–264.
- 6 Daly JR, Myles AB, Bacon PA, Beardwell CG, Savage O: Pituitary adrenal function during corticosteroid withdrawal in rheumatoid arthritis. *Ann Rheum Dis* 1967;26:18–25.
- 7 Schlaghecke R, Kornely E, Santen RT, Ridderskamp P: The effect of long-term glucocorticoid therapy on pituitary-adrenal responses to exogenous corticotropin-releasing hormone. *New Engl J Med* 1992;326:226–230.
- 8 Duru N, van der Goes MC, Jacobs JW, Andrews T, Boers M, Buttgerit F, et al: EULAR evidence-based and consensus-based recommendations on the management of medium to high-dose glucocorticoid therapy in rheumatic diseases. *Ann Rheum Dis* 2013;72: 1905–1913.
- 9 Hoes JN, Jacobs JW, Boers M, Boumpas D, Buttgerit F, Caeyers N, et al: EULAR evidence-based recommendations on the management of systemic glucocorticoid therapy in rheumatic diseases. *Ann Rheum Dis* 2007; 66:1560–1567.
- 10 Bijlsma JW, van der Goes MC, Hoes JN, Jacobs JW, Buttgerit F, Kirwan J: Low-dose glucocorticoid therapy in rheumatoid arthritis: an obligatory therapy. *Ann NY Acad Sci* 2010;1193:123–126.
- 11 Svensson B, Boonen A, Albertsson K, van der Heijde D, Keller C, Hafstrom I: Low-dose prednisolone in addition to the initial disease-modifying antirheumatic drug in patients with early active rheumatoid arthritis reduces joint destruction and increases the remission rate: a two-year randomized trial. *Arthritis Rheum* 2005;52:3360–3370.
- 12 Kirwan JR, Buttgerit F: Symptom control with low-dose glucocorticoid therapy for rheumatoid arthritis. *Rheumatology* 2012; 51(suppl 4):iv14–iv20.
- 13 Kirwan JR, Hickey SH, Hallgren R, Mielants H, Björck E, Persson T, et al: The effect of therapeutic glucocorticoids on the adrenal response in a randomized controlled trial in patients with rheumatoid arthritis. *Arthritis Rheum* 2006;54:1415–1421.
- 14 Kirwan JR: Targeting the time of day for glucocorticoid delivery in rheumatoid arthritis. *Int J Clin Rheumatol* 2011;6:273–279.
- 15 Nichols T, Nugent CA, Tyler FH: Diurnal variation in suppression of adrenal function by glucocorticoids. *J Clin Endocrinol Metab* 1965;25:343–349.
- 16 Klinefelter HF, Winkenwerder WL, Bledsoe T: Single daily dose prednisone therapy. *JAMA* 1979;241:2721–2723.
- 17 Diraimondo VC, Forsham PH: Pharmacophysiological principles in the use of corticoids and adrenocorticotropin. *Metabolism* 1958;7: 5–24.
- 18 Weitzman ED, Fukushima D, Nogeire C, Roffwarg H, Gallagher TF, Hellman L: Twenty-four hour pattern of the episodic secretion of cortisol in normal subjects. *J Clin Endocrinol Metab* 1971;33:14–22.
- 19 Deandrade JR, McCormick JN, Hill AG: Small doses of prednisolone in the management of rheumatoid arthritis. *Ann Rheum Dis* 1964;23:158–162.
- 20 De Silva M, Binder A, Hazleman BL: The timing of prednisolone dosage and its effect on morning stiffness in rheumatoid arthritis. *Ann Rheum Dis* 1984;43:790–793.
- 21 Buttgerit F, Burmester G-R, Straub RH, Seibel MJ, Zhou H: Exogenous and endogenous glucocorticoids in rheumatic diseases. *Arthritis Rheum* 2011;63:1–9.
- 22 Cutolo M, Straub RH, Buttgerit F: Circadian rhythms of nocturnal hormones in rheumatoid arthritis: translation from bench to bedside. *Ann Rheum Dis* 2008;67:905–908.
- 23 Straub RH, Schaible HG, Wahle M, Schedlowski M, Neeck G, Buttgerit F: Neuroendocrine-immunologic mechanisms in rheumatic diseases – a congress report (in German). *Z Rheumatol* 2002;61:195–200.
- 24 Straub RH, Cutolo M: Circadian rhythms in rheumatoid arthritis: implications for pathophysiology and therapeutic management. *Arthritis Rheum* 2007;56:399–408.
- 25 Eijsbouts AM, van den Hoogen FH, Laan RF, Hermus AR, Sweep CG, van de Putte LB: Hypothalamic-pituitary-adrenal axis activity in patients with rheumatoid arthritis. *Clin Exp Rheumatol* 2005;23:658–664.
- 26 Perry MG, Kirwan JR, Jessop DS, Hunt LP: Overnight variations in cortisol, interleukin 6, tumour necrosis factor alpha and other cytokines in people with rheumatoid arthritis. *Ann Rheum Dis* 2009;68:63–68.
- 27 Arvidson NG, Gudbjörnsson B, Elfman L, Ryden AC, Totterman TH, Hallgren R: Circadian rhythm of serum interleukin-6 in rheumatoid arthritis. *Ann Rheum Dis* 1994;53: 521–524.
- 28 Mastorakos G, Chrousos GP, Weber JS: Recombinant interleukin-6 activates the hypothalamic-pituitary-adrenal axis in humans. *J Clin Endocrinol Metab* 1993;77:1690–1694.
- 29 Harbuz MS, Jessop DS: Is there a defect in cortisol production in rheumatoid arthritis? *Rheumatology* 1999;38:298–302.
- 30 Harbuz MS, Korendowycz E, Jessop D, Crown AL, Lightman SL, Kirwan JR: Hypothalamo-pituitary-adrenal axis dysregulation in patients with rheumatoid arthritis after the dexamethasone/corticotrophin releasing factor test. *J Endocrinol* 2003;178:55–60.
- 31 Cutolo M, Villaggio B, Otsa K, Aakre O, Sulli A, Serio B: Altered circadian rhythms in rheumatoid arthritis patients play a role in the disease's symptoms. *Autoimmun Rev* 2005;4: 497–502.
- 32 Arvidson NG, Gudbjörnsson B, Larsson A, Hallgren R: The timing of glucocorticoid administration in rheumatoid arthritis. *Ann Rheum Dis* 1997;56:27–31.

- 33 Alten R: Chronotherapy with modified-release prednisone in patients with rheumatoid arthritis. *Expert Rev Clin Immunol* 2012;8: 123–133.
- 34 Buttgereit F, Doering G, Schaeffler A, Witte S, Sierakowski S, Gromnica-Ihle E, et al: Efficacy of modified-release versus standard prednisone to reduce duration of morning stiffness of the joints in rheumatoid arthritis (CAPRA-1): a double-blind, randomised controlled trial. *Lancet* 2008;371:205–214.
- 35 Buttgereit F, Doering G, Schaeffler A, Witte S, Sierakowski S, Gromnica-Ihle E, et al: Targeting pathophysiological rhythms: prednisone chronotherapy shows sustained efficacy in rheumatoid arthritis. *Ann Rheum Dis* 2010; 69:1275–1280.
- 36 Buttgereit F, Mehta DP, Kirwan JR, Szechinski J, Boers M, Alten R: Safety data for low-dose glucocorticoid chronotherapy of rheumatoid arthritis with 5 mg modified-release (MR) prednisone in a randomized, double-blind placebo-controlled trial. *Ann Rheum Dis* 2010;63(suppl 3):219.
- 37 Buttgereit F, Szechinski J, Doering G, Witte S, Knauer C, Grahn A: Integrated summary of safety for modified-release prednisone compared to immediate release prednisone: results from the Circadian Administration of Prednisone in Rheumatoid Arthritis (CAPRA) studies. *Ann Rheum Dis* 2011;70(suppl 3):88.
- 38 Alten R, Doring G, Cutolo M, Gromnica-Ihle E, Witte S, Straub R, et al: Hypothalamus-pituitary-adrenal axis function in patients with rheumatoid arthritis treated with nighttime-release prednisone. *J Rheumatol* 2010;37: 2025–2031.
- 39 Kirwan JR, Clarke L, Hunt LP, Perry MG, Straub RH, Jessop DS: Effect of novel therapeutic glucocorticoids on circadian rhythms of hormones and cytokines in rheumatoid arthritis. *Ann NY Acad Sci* 2010;1193:127–133.
- 40 Kirwan JR: Targeting the time of day for glucocorticoid delivery in rheumatoid arthritis. *Int J Clin Rheumatol* 2011;6:273–279.