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 relieving 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.
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)
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

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

<table>
<thead>
<tr>
<th>Treatment and assessment time</th>
<th>n</th>
<th>Mean plasma cortisol (± SD), μg/dl</th>
<th>Maximum plasma cortisol, μg/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional prednisone (pre-study)</td>
<td>21</td>
<td>5.5 ± 4.37</td>
<td>15.00</td>
</tr>
<tr>
<td>Conventional prednisone (after 12 weeks double-blind phase)</td>
<td>11</td>
<td>4.5 ± 3.91</td>
<td>13.85</td>
</tr>
<tr>
<td>MR prednisone (after 12 weeks double-blind phase)</td>
<td>8</td>
<td>3.3 ± 5.76</td>
<td>12.00</td>
</tr>
<tr>
<td>MR prednisone (after 9 months open-label phase)</td>
<td>22</td>
<td>5.3 ± 4.07</td>
<td>13.01</td>
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</tbody>
</table>
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


References

