The Importance of Chronotherapeutics in the Treatment of Rheumatoid Arthritis

René Westhovens

Head of Clinic, Department of Rheumatology, University of Leuven

Abstract

While important progress has been made in treating rheumatoid arthritis (RA), there is still a need for research into the use of glucocorticoids (GCs). There is strong evidence for an impact of circadian rhythms in the symptoms of RA, and a wealth of evidence for an association between elevated levels of a number of pro-inflammatory cytokines, including interleukin-6 (IL-6), levels of which most closely follow disease symptoms. The recent surge of interest in the field of chronobiology has highlighted the importance of optimising timing of treatment administration. Traditionally, GCs were given in the morning; however, evening administration has recently been associated with improvements in response. In this article we discuss the chronobiology of RA and the availability of a new programmed-release prednisone tablet that, when taken at bedtime, releases prednisone at 2am. The impact of such therapies on the optimal treatment of RA patients is evaluated. With chronotherapeutics becoming ever more popular, more consideration is being given to the timing of therapy for a number of chronic diseases.

Keywords

Rheumatoid arthritis, glucocorticoids, chronobiology, programmed release, circadian rhythms

Circadian Rhythms in Rheumatoid Arthritis

The circadian rhythms of disease symptoms for RA have been well studied and are widely accepted. In patients with RA, disease symptoms such as joint pain, morning stiffness and functional disability increase in the early morning, with abatement during the day and a smaller new increase in the early evening. Circadian changes in the metabolism or nocturnal secretion of endogenous corticosteroids are responsible, in part, for the time-dependent changes observed in the inflammatory response of RA. A relationship between elevated levels of a number of pro-inflammatory cytokines and the symptoms of RA has been established. Interleukin-6 (IL-6) is one such cytokine that has pro-inflammatory properties. It is a multifactorial cytokine that was originally identified as a B-cell differentiation factor involved in the maturation of antibody-producing cells. Since then, IL-6 has been found to have a wide array of additional activities, including effects on T cells, blood vessels and neurons. Among the pro-inflammatory cytokines involved in circadian changes, IL-6 is of particular relevance as its levels most closely follow the daily pattern of RA symptoms (see Figure 1).

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Patients with RA have elevated levels of IL-6 in the synovial fluid and the serum compared with age-matched controls and patients with osteoarthritis. Assuming that IL-6 serum levels mirror its production and are associated with a flare in inflammatory activity early in the morning, the timing of GC administration might be important for its effect on the inflammatory process.
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Timing of Glucocorticoid Treatment

Over the years, GCs have been used in a variety of ways in the treatment of RA. In short-term regimens, treatment is often aimed at controlling symptoms in periods of high disease activity, either with unchanged background antirheumatic therapy or while awaiting the effects of newly started disease-modifying drugs. This type of treatment is known as bridge therapy. Among those patients for whom other drugs have failed to control symptoms sufficiently, GCs are used for prolonged periods of time. GCs can also be used specifically to prevent progression of joint damage as assessed by radiological scores.

The investigation of the optimal timing of GC administration is not a new area of interest. While traditionally GCs were, and often still are, given in the morning, more recently many studies have compared morning and evening administration, with varying conclusions (see Table 1). The reasons for this trend in morning administration include minimised suppression of the hypothalamic–adrenocortical axis when GCs are taken in the morning to coincide with endogenous plasma cortisol levels. The importance of the timing of GC administration has been highlighted in the European League Against Rheumatism (EULAR) evidence-based recommendations on systemic GC therapy in rheumatic diseases.

Furthermore, patient and rheumatologist perspectives on glucocorticoids have been explored to enhance the implementation of these recommendations.

Investigations into the optimal timing of GC administration started as early as 1964, when De Andrade et al. compared morning and evening administration of 5mg prednisolone and reported that 23 out of 49 patients preferred evening dosing. Patient preference for an evening dose was also reported in a study by De Silva et al. in 1984. In this study, patients receiving prednisolone at 10–11pm experienced significantly less morning stiffness than those receiving prednisolone at 6–7am (p=0.0001). Other studies, including one by Kowanko et al., have suggested that the timing of GC administration does not have a significant effect on efficacy, and that prednisolone can therefore be prescribed at any of the three times investigated (8am, 1pm and 11 pm) if it results in fewer side effects.

Interestingly, in the majority of studies investigating the optimal timing of administration of GCs, no safety results are reported (see Table 1). As concerns about the safety of GCs have been expressed in a number of studies and highlighted by patient and rheumatologist perspectives, safety should form an important component in decision-making about optimal GC therapy in RA.

In contrast to the studies detailed above, one study reported methylprednisolone administration in a single dose at 8am to be most effective, as it showed adequate clinical results as well as a reduced disturbance of cortisol circadian behaviour. However, it is evident that in the most recent clinical trials, evening administration of GCs has been favoured over traditional morning administration.

It has been suggested that traditional administration of GCs between 6 and 8am is not optimal as night-time pathophysiological processes may already have led to inflammation. Owing to the short half-life of prednisone (two hours), evening administration of standard prednisone would result in the peak in prednisone being too early. Therefore, unless the patient is woken up at 2am, it has been difficult to deliver GCs correctly and optimally. In a study by Arvidson et al., patients with active RA were randomised to two groups and were allocated to prednisolone at either 2am or 7.30am. Patients were assessed at 7.30am on day one (before treatment) and after treatment for five days. Although this study found that administration of GCs at 2am had better effects on severe morning RA symptoms and serum IL-6 levels than administration at 7.30am, there have been criticisms about the trial due to the lack of a placebo arm and the fact that the trial did not have a cross-over design. Unfortunately, no other studies have been conducted to verify these findings. However, it has sparked an interest in the development of novel, programmed-release GC medications, which offer more convenient and suitable delivery; in theory, if the timing of GC administration could be optimised, it might be possible to reduce/lower the GC dose.

A programmed-release low-dose prednisone tablet is currently in phase III clinical development. This formulation aims to synchronise prednisone release to the circadian rhythm of cortisol and symptoms of RA, which both have their peaks in the early morning hours. This programmed-release tablet releases prednisone approximately four hours after ingestion, so when given at bedtime, prednisone is released at approximately 2am. In addition, the pharmacokinetic profile and total drug exposure of this tablet are almost identical to those of conventional prednisone (see Figure 2).

The Circadian Administration of Prednisone in Rheumatoid Arthritis (CAPRA1) study is a multicentre, randomised, double-blind, active-controlled study investigating the efficacy and safety of this programmed-release prednisone tablet in 288 patients with active RA. All patients had advanced-stage disease and had been on stable-dose GC for at least three months before the study. Patients were randomised (1:1) to 12 weeks of double-blinded treatment with either programmed-release prednisone or conventional immediate-release prednisone at a dose equivalent to pre-study doses (3–10mg/day). The primary end-point was the relative change from baseline in duration of morning stiffness of the joints. Buttgereit et al. reported that the relative mean decrease in duration of morning stiffness from baseline was significantly greater in patients treated with the programmed-release prednisone tablets compared with those who received conventional prednisone (-22.7 versus -0.4%; p=0.045). At the end of treatment, patients treated with programmed-release
Prednisone achieved a mean reduction in duration of morning stiffness of 44 minutes compared with baseline. The absolute difference between the treatment groups was reported to be 29.2 minutes (95% confidence interval [CI] -2.59–61.09) in favour of the programmed-release tablet; p=0.072). With regard to the secondary end-point of serum IL-6 levels, patients in the programmed-release prednisone group achieved a reduction in IL-6 levels of 29% compared with those in the conventional prednisone group, in which IL-6 levels remained constant. This difference between the two groups was statistically significant (p=0.002).\textsuperscript{13} Programmed-release prednisone was equivalent to standard prednisone in terms of quality of life variables and pain intensity, including recurrence of joint pain during the day and quality of sleep.\textsuperscript{39}

There is conflicting evidence for the long-term efficacy of GCs. Trials by Everdingen et al. and Kirwan et al. reported that the anti-inflammatory effects of GCs decrease and eventually disappear with time.\textsuperscript{22,26} By contrast, Tengstrand et al. found that prolonged GC use still exhibits anti-inflammatory properties.\textsuperscript{39,40} In addition, the long-term use of low-dose GCs has been found to retard radiographic progression.\textsuperscript{24–28} The efficacy results from the CAPRA1 nine-month extension study of programmed-release prednisone\textsuperscript{41} provide further support for the long-term use of GCs. In this section of the study, patients who had completed the 12-week double-blind phase of the study continued on programmed-release prednisone. The results of this open-label extension study demonstrated sustained long-term efficacy of programmed-release prednisone. After 12 months of treatment, the mean relative reduction of morning stiffness was 46.1% (p<0.001), and the mean absolute change was 83.9 minutes. In addition, the reduction in IL-6 was maintained throughout the 12 months,\textsuperscript{39} and a correlation between IL-6 reduction and reduced morning stiffness for the combined groups was demonstrated.\textsuperscript{39} Secondary variables also showed improvements at the end of the 12 months, with American College of Rheumatology 20 (ACR20) response being achieved in 37% of the long-term treated patients. The Disease Activity Score for 28 Joints (DAS28) change for the open-phase population between baseline and the end of the study was from 5.8 to 4.8.\textsuperscript{39}

In the 12-week randomised, double-blind phase of the CAPRA1 study, no clinically relevant differences between the safety profiles of

### Table 1: Studies Investigating the Optimal Timing of Glucocorticoid Therapy for the Treatment of Rheumatoid Arthritis

<table>
<thead>
<tr>
<th>Publication</th>
<th>n</th>
<th>Glucocorticoid</th>
<th>Glucocorticoid Dose Times</th>
<th>Cross-over Design?</th>
<th>Efficacy Results</th>
<th>Safety Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>De Andrade et al., 1964\textsuperscript{49}</td>
<td>49</td>
<td>Prednisolone</td>
<td>Morning and 10pm</td>
<td>Yes</td>
<td>Evening dose preferred in the majority of patients</td>
<td>Not reported</td>
</tr>
<tr>
<td>Kowanko et al., 1982\textsuperscript{12}</td>
<td>12</td>
<td>Prednisolone</td>
<td>8am, 1pm or 11pm</td>
<td>Yes</td>
<td>Prednisolone equally effective when given at 8am, 1pm or 11pm. Stronger grip</td>
<td>Not reported</td>
</tr>
<tr>
<td>De Silva et al., 1984\textsuperscript{26}</td>
<td>41</td>
<td>Prednisolone</td>
<td>10–11pm and 6–7am</td>
<td>Yes</td>
<td>Less MS with night administration (p=0.0001). Patient preference for night-time</td>
<td>Not reported</td>
</tr>
<tr>
<td>Fisher et al., 1992\textsuperscript{6}</td>
<td>6</td>
<td>Methylprednisolone</td>
<td>8am and 4pm</td>
<td>Yes</td>
<td>Drug clearance was 28% greater with administration at 4pm. A single dose administered in the morning provides adequate clinical effects and less disturbance of cortisol circadian behaviour.</td>
<td>Not reported</td>
</tr>
<tr>
<td>Arvidson et al., 1997\textsuperscript{26}</td>
<td>26</td>
<td>Prednisolone</td>
<td>2am and 7.30am</td>
<td>No</td>
<td>Less MS with night administration (p=0.001). Less joint pain with night administration (p=0.01). Reduction in IL-6 with night administration (p=0.01).</td>
<td>Not reported</td>
</tr>
<tr>
<td>Buttgeret et al., 2008\textsuperscript{28}</td>
<td>28</td>
<td>Prednisone and modified-release prednisone</td>
<td>6–8am and 10pm</td>
<td>Yes</td>
<td>Greater change in duration of MS with night modified-release administration (p=0.045). Greater mean reduction in MS with night modified-release administration (p=0.072).</td>
<td>Did not differ between treatment groups, overall profile of AEs consistent with underlying disease</td>
</tr>
</tbody>
</table>

AEs = adverse events; IL-6 = interleukin-6; MS = morning stiffness.
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programmed-release and conventional-release prednisone were noted. In this phase of the study, 41% of the patients in each group experienced an adverse event, and the overall profile of adverse events was consistent with the underlying disease and the known safety profiles of prednisone and the concomitant drugs for RA. The safety of long-term low-dose GC use has been an area of great debate, with studies reporting conflicting data. Several investigations have documented an increased incidence of both osteoporosis and fractures in patients receiving long-term low-dose GCs. Others have failed to confirm these observations, especially with respect to steroid-induced osteoporosis. A study by Wassenberg et al. in 2005 was the first controlled trial to demonstrate that a daily prednisone dose as low as 5 mg substantially reduces radiographic progression in early RA over two years. This study, in contrast to the conclusions drawn from retrospectively examined trials, found only minor side effects associated with long-term use. It reported that increased osteoporotic incidence was not associated with low-dose prednisone – a conclusion supported by Kirwan et al. and van Staa et al. Overall, recent evidence suggests that low-dose GCs may have an improved adverse event profile compared with higher-dose GCs, with the adverse events associated with long-dose GCs being modest and often not statistically different from those seen with placebo. Results from the nine-month extension phase of the CAPRA1 study support these claims, as the sustained safety profile of programmed-release prednisone was demonstrated, with low adverse event rates throughout the study.

Conclusions

Over the years, the dose and timing of GCs for the treatment of RA have been much debated and researched areas. With increasing awareness of the benefits of chronobiology and mounting evidence for the impact of circadian rhythms in RA, it is important to explore the possibility of using medications that can synchronise GC release with the night-time surge of inflammatory components. The availability of a programmed-release formulation of prednisone has brought fresh hope for the treatment of RA. Results from the CAPRA1 study are encouraging and provide support for the use of night-time programmed-release low-dose GCs, allowing administration at bedtime with a delayed release of the drug at 2am.

The initial results from trials investigating this programmed-release low-dose prednisone suggest that it may be the first step towards the development of a low-dose GC regimen that accounts for the chronobiology of RA and provides an efficacious and well tolerated approach to the treatment of patients with RA. Further trials are required and results are eagerly awaited. One such trial is the ongoing CAPRA2 study, which aims to compare the safety and efficacy of programmed-release prednisone versus placebo in combination with standard disease-modifying antirheumatic drug treatment in patients with active RA.

It also remains to be determined whether circadian rhythms and the use of chronobiology may also play a role in determining an optimal treatment algorithm in other diseases, such as polymyalgia rheumatica, asthma, hypertension, myocardial infarction and peptic ulcer. However, it is true that advances in our understanding of the importance of chronobiology indicate that more consideration should be given to the timing of drug dosing to achieve optimal therapeutic results. Incorporating the assessment of patient preferences for the dose and timing of treatment into future research might also stress the importance of chronobiology in treatment strategies for several diseases.
23. EMPIRE Rheumatism Council, Multi centre controlled trial comparing cortisone acetate and acetyl salicylic acid in the long term treatment of rheumatoid arthritis; results up to one year, Ann Rheum Dis, 1950;19:353–70.


52. Van der Goes MC, Jacobs JW, Boers M, et al., Patients' and rheumatologists' perspectives on glucocorticoids