Review Article

Modified-release Prednisone in Rheumatoid Arthritis: Rationale for Chronotherapy, Mechanistic Considerations, and Clinical Implications

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Abstract

Pain, stiffness of joints, and functional disability of rheumatoid arthritis (RA) are maximum in the morning. Cytokines, especially interleukin (IL)-6, demonstrate a circadian variation in patients with RA and contribute to the severity of aforementioned symptoms. Perturbed cortisol response in patients with RA is not effectively able to negate the effects of interleukin 6 rise in the early morning. Modified-release (MR) prednisone is a polymer-based drug delivery system which releases the drug 4 h after the ingestion of tablet closely simulating the cortisol rise and peak in patients with RA. In this review, we focus on the rationale for chronotherapy, mechanistic considerations, and clinical implications of MR prednisone.

Key Words: *Circadian rhythm, glucocorticoids, interleukin-6, modified release, morning stiffness*

Introduction

Rheumatoid arthritis (RA) is a chronic systemic autoimmune inflammatory disease which is associated with progressive disability, poor quality of life, and systemic complications. Glucocorticoids (GCs) with their multiple mechanisms of action are an effective tool to treat RA.[1,2] Available evidence also underscores their disease-modifying effect on the structural damage in RA without any convincing toxicity when used in low doses.[3,4] Three factors, namely, GC resistance, concerns regarding toxicity of GC, and unproven superiority and safety of GC molecules such as Deflazacort, continue to drive the quest to develop GCs with better risk–benefit ratio.[1,5,6] Novel GCs that induce transrepression but stimulate little or no transactivation are investigated. In addition, novel drug delivery systems and combinations are also being developed. In this review, we appraise a novel drug delivery system of prednisone, i.e., modified-release (MR) prednisone.

Circadian Rhythms in Rheumatoid Arthritis

Various diurnal variations or circadian rhythms of the human body are rooted to the suprachiasmatic nucleus (SCN) in the hypothalamic region of the brain. Sleep-wake cycle, body temperature, heart rate, blood pressure, hormone regulation, and immunity are the physiological functions that fall under the purview of circadian control.[7] The SCN and paraventricular nucleus modulate circadian rhythms in the sympathetic and parasympathetic neurons, thereby influencing diurnal variations in gene transcription in different lymphoid tissues (which regulate the immune system) through positive modulators (CLOCK; circadian locomotor output cycles kaput and BMAL1; brain and muscle aryl hydrocarbon receptor nuclear translocator like-1) and negative regulators (PER; period and CRY; cryptochrome).[8]

Reduced production of cortisol in the early morning and increased production of melatonin in the night influence the severity of early morning symptoms of RA.[9] The hypothalamic-pituitary-adrenal (HPA) axis and its associated circadian variations in cortisol (which can counter the effects of increased interleukin [IL-6] levels) are also disturbed in RA.[10]

In one of the early studies, a diurnal variation in the grip strength and joint stiffness in RA was reported.[11] There was about 28% improvement in grip strength at 6.00 pm compared to 6.00 am and the joint stiffness reduced by

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40% at 6.00 pm compared to 6.00 am.[11] In another study, patients reported minimal grip strength and maximal joint swelling in the morning, while subjective pain and stiffness scores were also highest in the morning.[12] Alterations in circadian rhythm of circulating serum cortisol, melatonin, and IL-6 correlate with the hypofunctioning of the HPA axis in patients with RA.[13]

The **cortisol** peak and nadir shifted to earlier times of the day in those patients with low erythrocyte sedimentation rates (ESRs up to 40 mm/h) and medium disease activity (ESR between 40 and 80 mm/h) in a study.[13] On the contrary, the circadian rhythm was lost or markedly reduced in patients with high activity (i.e., those with >80 mm/h).[13] In another study, a significant correlation was also noted between inflammatory activity in RA and adrenal cortisol secretion (coefficient of regression $r = 0.63$, $n = 26$, $P < 0.001$).[14]

IL-6 is a potent activator of the HPA axis as well as an important systemic mediator of the acute phase response in active RA. In one study, IL-6, ESR, and C-reactive protein (CRP) significantly correlated with serum cortisol, which is elevated in active RA, depending on disease activity.[15] In another study in comparison to normal subjects, plasma IL-6 levels were significantly elevated in patients with RA with a circadian rhythm observed [Figure 1].[16]

Melatonin works on immune system by regulating cytokine production of immunocompetent cells. Melatonin stimulates the production of IL-2, interferon γ, IL-12, and IL-6.[17] The concentration of these cytokines peaks in the early morning, and at the same time, the serum melatonin levels also peaks. In fact, the melatonin levels have been found to be significantly higher in patients with RA compared to controls. Although progressive increase in melatonin was observed in those with RA and control subjects from 8.00 pm up to 1st h of the morning, the peak serum melatonin concentration was reached earlier by at least 2 h in RA patients than in control subjects ($P < 0.05$). The melatonin plateau was sustained for 2–3 h in RA patients but not in control subjects. After 2.00 pm, there was no difference in decrease of melatonin levels in both RA patients and control subjects.[18] Hence, the nocturnal melatonin rhythm is altered in patients with RA with earlier peak and a longer duration in the early morning.

Prolactin is also thought to have a pathogenic role in RA.[19] The prolactin levels were found to be elevated in the serum as well as in the synovial fluids in patients with RA.[20] A significant correlation was found between high prolactin levels and the duration of RA ($r = 0.23$; $P = 0.01$) as well as functional stage ($r = 0.24$; $P = 0.01$).[21]

Chronotherapy with Glucocorticoids

Chronotherapy exploits the known disturbed circadian rhythms to optimize treatment outcomes and minimize adverse effects. Aforementioned observations suggest that the optimal time for delivery of GC treatment is during the night, to mimic the normal circadian rhythm of cortisol secretion and target the effects of nocturnal proinflammatory stimuli. The initial chronotherapies involving GCs were timed in the morning, which coincided with the commencement of diurnal activity of RA symptoms.[22] A trial tested administration of low-dose prednisolone (5 or 7.5 mg daily) at 2.00 am which showed favorable effects on the duration of morning stiffness, joint pain, articular indices, and morning serum concentrations of IL-6 ($P < 0.01$).[22]

In the 1980's, a unique twice-a-day GC combination chronotherapy (Dutimelan 8–15™) was introduced to mimic the endogenous circadian cortisol rhythm. The 8.00 am tablet contained 7 mg prednisolone acetate plus 4 mg prednisolone alcohol and 3.00 pm tablet contained 3 mg prednisolone alcohol and 15 mg prednisolone acetate. As safe as the conventional GCs, it fell out of favor due to poor patient compliance.[23]

In a subsequent study, no difference in the circadian rhythms of finger joint swelling and of grip strength was noted when the GC was dosed at different times

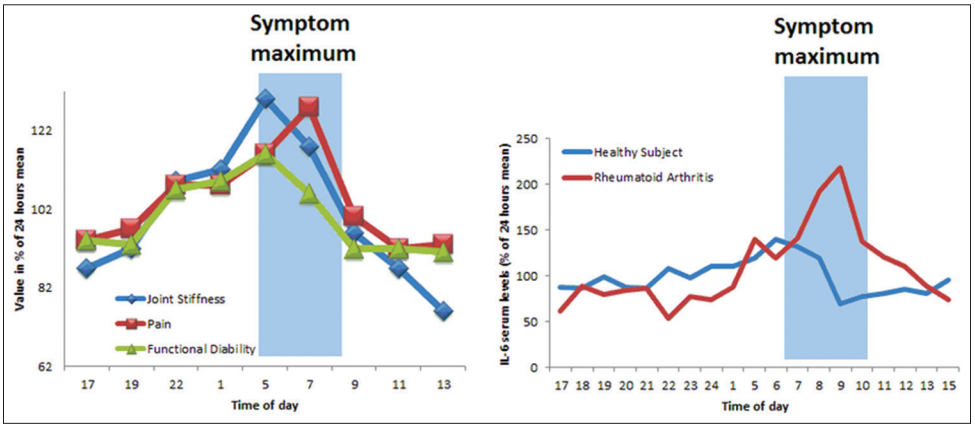

Figure 1: Circadian rhythm of symptoms and interleukin-6 (modified from reference 16)

(once-daily at 8.00 am, 1.00 pm, or 11.00 pm).[24] However, in a different study, nighttime dosing of low-dose GCs significantly reduced the duration of morning stiffness when compared to morning-time once-daily, driving home the point that the optimum time of GC dosing is at night.[25]

Modified-release Prednisone

The main difference between MR prednisone and conventional/immediate-release (IR) prednisone is the time-delayed release of the active agent. Following oral ingestion (at 10.00 pm) of the MR tablet of prednisone, water penetrates the tablet as it passes through the gastrointestinal tract and the coating bursts approximately 4 h after the ingestion and releases prednisone at about 2.00 am.[26] This closely simulates the normal physiological rise of cortisol which negates the IL-6-related early morning disease manifestations of RA.

Clinical Efficacy of Modified-release Prednisone

a. Randomized controlled studies

Circadian Administration of Prednisone in Rheumatoid Arthritis (CAPRA-1) was a 12-week, multicenter, randomized, double-blind trial which compared the efficacy of MR prednisone with that of IR prednisone in 288 patients with active RA who were receiving stable doses of disease-modifying antirheumatic drugs (DMARDs).[27] Their average daily duration of morning stiffness was 45 min or more.[27] 12 weeks of treatment with evening administration of MR prednisone resulted in a substantially greater decrease in duration of morning stiffness of the joints than was recorded after morning administration of IR prednisone (relative change; from baseline 164.1 [101.4] min vs. 182.5 [125.0] min to at the study end − 22.7% [89.1] min vs. −0.4% [89.0] min, $P = 0.045$).[27] At the end of treatment, patients in the prednisone MR group achieved a mean reduction of 44 min in the morning stiffness compared with baseline. This improvement in morning stiffness with MR prednisone was already evident after 2 weeks of treatment, with a difference of 10% between the two treatment groups. With continued treatment, this difference increased and plateaued at around 38% from week 7 to the end of the 12-week treatment period. However, secondary outcomes for efficacy such as pain intensity during the day, quality of sleep, DAS28, physician's global assessment of disease activity, laboratory variables (ESR, CRP), and health assessment questionnaire disability index did no differ between the two groups.[27]

CAPRA-2 investigated the efficacy and safety of low-dose prednisone chronotherapy in patients with active RA receiving standard DMARD treatment in a 12-week, double-blind, randomized, parallel-group, placebo-controlled multicenter study.[28] At week 12, 48% of patients receiving MR prednisone achieved an ACR20 response, compared with 29% in the placebo group ($P < 0.001$).[28] The response was achieved rapidly: A significant difference in ACR20 response rate between treatment groups was evident at week 2, and the difference remained significant throughout the study ($P < 0.005$). ACR50 responder rates were numerically greater with MR prednisone than with placebo at all time points, and the difference was significant at weeks 6 and 12 (22% vs. 10% at week 12, $P < 0.006$).[28] Significantly greater decreases in the severity of morning stiffness and recurrence of stiffness later in the day were also seen for MR prednisone compared with placebo ($P \leq 0.01$) as well as in the morning and evening pain.

b. Switching to modified-release prednisone

Of patients with RA originally randomized to MR or IR prednisone, all eligible 249 patients received MR prednisone chronotherapy (2–10 mg/day) in the 9-month open-label extension of CAPRA-1.[29] Irrespective of whether patients were continued on MR prednisone (MR/MR group) or switched from IR to MR prednisone (IR/MR group), there was sustained reduction in morning stiffness. After 6 months of treatment, morning stiffness was reduced in the IR/MR group by 54% and in the MR/MR group by 56%; morning stiffness reduction after 12 months was 45% in IR/MR group and 55% in MR/MR group.[29] DAS28 and pain showed clinically relevant improvements with no differences between the treatment groups. Of the 219 patients who completed the entire study, 37% achieved an ACR20 response.[29]

In an open-label observational study, 950 RA outpatients who were treated with GCs and DMARDs were switched from IR prednisone or 6-methyl (6M)-prednisolone to low-dose MR prednisone and followed for 4 months.[30] At 4 months, treatment with MR prednisone significantly decreased the duration of morning stiffness [Figure 2].[30] Switching over to MR prednisone significantly alleviated the intensity of pain as measured on numerical rating scale [Figure 3].[30] Patient and physician global assessment

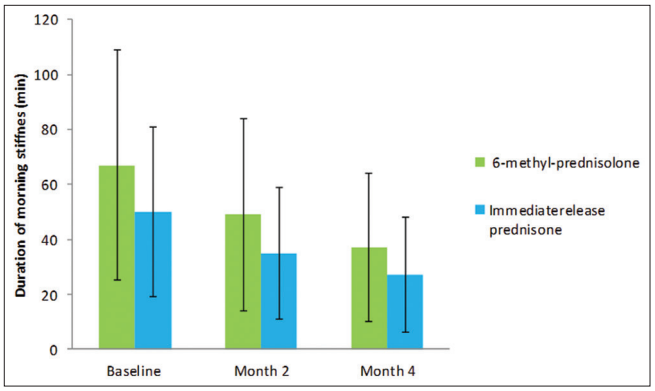

Figure 2: Switching over to modified-release prednisone from either 6-methyl prednisone or immediate-release prednisone resulted in significant reduction in morning stiffness ($P < 0.001$) (drawn from data in reference 30)

scores of disease activity also improved significantly from baseline ($P < 0.001$).[30]

Effect of modified-release prednisone on cytokines and hormones

In the CAPRA-1 study, IL-6 levels decreased in MR prednisone group but remained constant in the IR group (relative reduction of nearly 29% vs. 0%).[27] In the long-term extension of the CAPRA-1 study, the same reduction by about 50% was seen at the end of the study in the IR/MR group.[29] Low levels of IL-6 were sustained, but no further reduction was observed in the MR/MR group.[29] In CAPRA-2 study compared to placebo, the decrease in IL-6 was greater in the MR prednisone group.[28] No change in the TNFα levels was observed between the two treatment arms.[28] In another study, the high pretreatment peak of IL-6 was abolished following treatment with MR prednisone.[31] Moreover, the changes in IL-6 correlated with the changes in morning stiffness. There was a reduction in afternoon and evening serum cortisol, but the early morning cortisol peak concentration increased.[31]

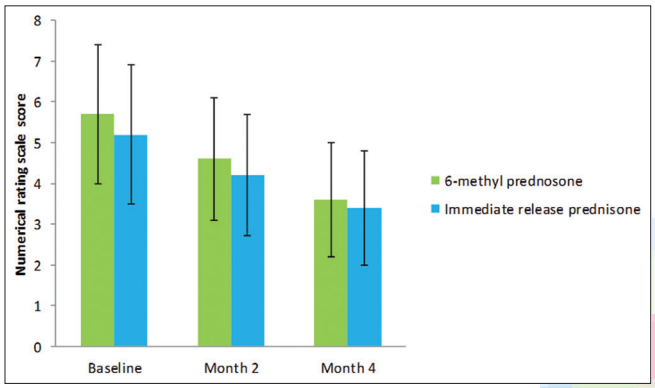

Figure 3: Switching over to modified-release prednisone from either 6-methyl prednisone or immediate-release prednisone significantly alleviated the intensity of pain after 4 months ($P < 0.001$) (drawn from data in reference 30)

Safety and tolerability of modified-release prednisone

Treatment-emergent adverse events (AEs) during the 12-week blinded period in CAPRA-1 were not different between MR and IR prednisone groups.[27,32] In the long-term extension of this study, the median duration of exposure to MR prednisone was 281 days and the mean dose was 6.8 mg/day.[29] In CAPRA-2 study, the overall incidence of AEs was slightly lower in patients receiving MR prednisone than in those receiving placebo, and none of the serious or severe AEs in the MR prednisone group was considered related to treatment.[28] In addition, there was no evidence for an increased risk of infection with active treatment.[28] On analyzing the results of aforementioned studies, overall, the safety and tolerability of MR prednisone appear similar to IR/conventional prednisone as reported in the literature.[2,4,33,34]

Effect of chronotherapy with modified-release prednisone on hypothalamic-pituitary-adrenal axis

Treatment with exogenous GCs affects the HPA; however, chronotherapy with MR prednisone had no AE on the HPA axis function.[27] In another study, over a period of 12 months, no deterioration or onset of adrenal insufficiency was reported.[34] There was no difference in the mean cortisol response between time points [Figure 4].[35] In

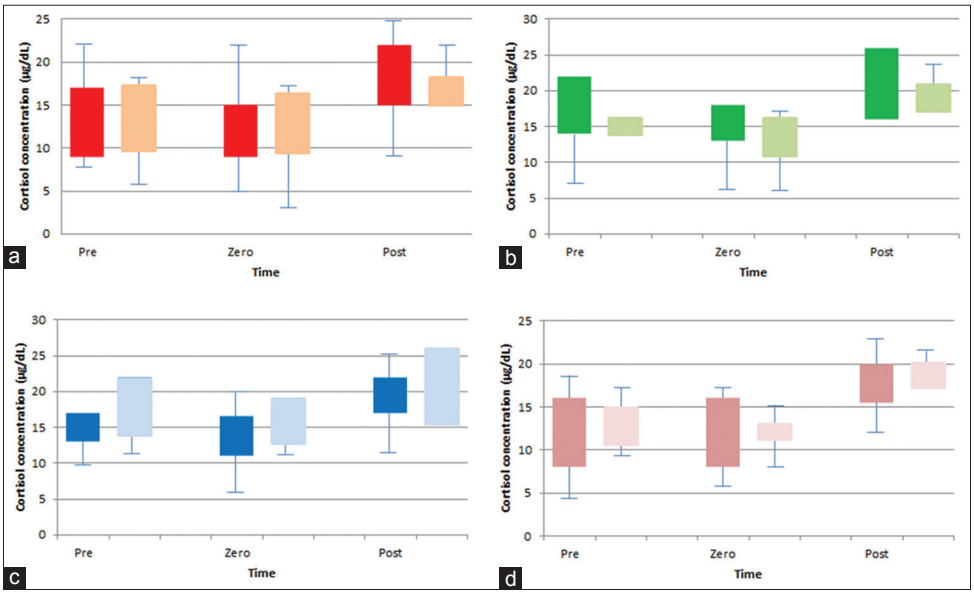

Figure 4: Maximum changes of cortisol after corticorelin injection in repeated tests of individual patients (modified from reference 35). Time points "pre" and "zero" are before corticorelin injection. "Post" denotes highest value of the two assessments at 30 or 60 min after injection. (a) Repeated tests on unchanged immediate-release prednisone. Pale orange indicates score after Test 1; dark orange after Test 2, $n = 11$. (b) Repeated tests on unchanged modified-release prednisone. Pale green indicates score after Test 2; dark green after Test 3, $n = 7$. (c) Results after the change of treatments from IR to MR prednisone after randomization. Pale blue: Test 1, MR/MR; dark 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. Pale brown: Test 2 after double-blind IR prednisone; dark brown: after 9 months of open MR prednisone, $n = 9$

the long-term extension of CAPRA-1, no signs or symptoms were noted that might indicate aggravation of suppression of the HPA axis.[29] Moreover, there was a 12% increase in maximum cortisol response (from 12 weeks to 9 months) in those who shifted to MR prednisone after being treated with IR prednisone for 12 weeks.[28,36] This suggests an improvement rather than deterioration in the responsiveness of HPA axis in patients with RA receiving chronotherapy with MR prednisone compared to conventional morning prednisone treatment.[36]

Conclusion

Awareness of the association between altered circadian pattern of cytokines and hormones, and disease activity in RA has resulted in a new treatment paradigm; the chronotherapy with MR prednisone. Synchronizing the timing of GC therapy with the nocturnal increase in blood IL-6 levels leads to alleviation of pain and stiffness far better that a morning dose of conventional prednisone. MR formulation of prednisone that is administered in the night at 10.00 pm is biologically available at 2.00 am, and this time of release is ideal to counter the circadian rise in pro-inflammatory cytokine levels. There is evidence from mechanistic studies that the increase in IL-6 was indeed almost completely suppressed and HPA axis responsiveness was not suppressed and may even be enhanced by 2.00 am prednisone. Toxicity of this timed release is similar to conventional IR prednisone. A switch from IR/conventional prednisone to MR prednisone can be made and leads to improvement in troublesome morning stiffness. MR prednisone therefore appears to be a useful addition to the armamentarium used in the treatment of RA along with therapy with DMARDs.

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Conflicts of interest

There are no conflicts of interest.

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