Rheumatoid arthritis (RA) is the most common chronic inflammatory joint disease, affecting approximately 2.8 million adults in the United States alone.1 The symptoms of RA include fatigue as well as swelling, pain, and stiffness of the joints2; these manifestations may vary in a predictable pattern throughout the day.3

This report will discuss the pathophysiology of the diurnal variations of the manifestations of RA along with the potential utility of a low-dose, delayed-release prednisone strategy to treat the symptoms of RA, including morning symptoms.

Diurnal Variations in Symptoms of Rheumatoid Arthritis

Physiologic and pathophysiologic biologic circadian rhythms can modulate the presentation and morbidity of various diseases. Similar diurnal variations have been observed in the clinical manifestations of RA.3 The early morning severity of RA symptoms coincides with the circadian rhythm of cytokine release.3 Specifically, plasma levels of proinflammatory mediators, such as interleukin (IL)-6 and tumor necrosis factor-α, peak during the middle of the night and early morning hours, resulting in pronounced early morning symptoms in patients with RA.3,4 which can impact patients’ ability to work or participate in normal activities.5

In patients without RA, an increase in inflammatory cytokine levels triggers a cascade of hypothalamic corticotropin-releasing hormone, pituitary production of adrenocorticotropic hormone, and glucocorticoid secretion by the adrenal cortex, which collectively inhibit the production of inflammatory cytokines.6 This represents normal physiologic feedback control. In patients with active RA, however, the cortisol response is impaired, which leads to a relative adrenal glucocorticoid insufficiency and unopposed cytokine-mediated inflammation during the early morning hours.3,4,6 These observations may support a role for appropriately timed exogenous glucocorticoid therapy to balance the pathologic circadian mismatch between cytokine and glucocorticoid production.4
Roles for Corticosteroids in Addressing Morning Symptoms

Tight control strategies for RA, defined as aggressive disease management and close monitoring to make adjustments using a predefined treatment outcome, have shown efficacy, but they can be improved with regard to both symptom control (ie, morning symptoms) and patient outcomes (ie, disease-modifying effects). Prednisone remains an essential tool in the clinician’s arsenal for the treatment of RA, but it has been associated with serious adverse events (AEs) when used in escalating doses (ie, >5 mg per day), including cataract formation, skin fragility and bruising, osteoporosis, diabetes, a higher risk for cardiovascular disease, and serious infections. Specifically, a retrospective, population-based cohort of 86,039 patients with RA (aged ≥66 years) with nested case–control analyses was performed to assess the risk for serious infections in this patient population. The results showed that seniors with RA experienced serious infections at a rate of 46.4 events per 1,000 patient-years, leading to significant morbidity. High-dose glucocorticoid use exhibited a clear relationship with patients’ risk for infections (odds ratio, 7.57; 95% confidence interval, 6.87-8.34). The severity of prednisone-related AEs is directly related to both the dose and the treatment duration. Data has shown that low-dose corticosteroids are utilized in approximately 50% of patients entering RA clinical trials, therefore it is essential that clinicians balance the risks versus benefits of these agents. Clinicians may want to consider using the lowest possible dose to achieve adequate clinical response.

Disease-modifying antirheumatic drugs (DMARDs) are the cornerstones of RA therapy. Clinical trial data showed that when low-dose, immediate-release (IR) prednisone was administered in combination with methotrexate (MTX), it reduced radiographic erosive joint damage 2 years after the initial diagnosis. Evidence from the CAMERA (Computer Assisted Management in Early Rheumatoid Arthritis)-II trial showed that this combination decreased disease activity and physical disability, improved sustained remission rates, and may have prevented or delayed the need for additional DMARDs. Furthermore, the rate of AEs with MTX-prednisone therapy was equivalent to or lower than that of therapy with MTX alone.

The advantages of prednisone therapy may further be improved through the use of precisely timed dosing strategies that address the circadian pathophysiology of RA. For example, the maximal activity of the adrenal cortex is between 4 and 8 AM; conversely, the minimal activity of the adrenal cortex is between 4 PM and midnight. When taken during times of maximal adrenocorticoid activity (ie, between 2 and 8 AM), exogenous corticosteroids offer less suppression of adrenocorticoid activity, so prednisone ideally should be administered before 9 AM.

A pilot study by Arvidson and colleagues examined the effect of timing on glucocorticoid administration. Twenty-six patients with RA were randomized to receive low doses of IR prednisolone (5 or 7.5 mg) at either 2:00 or 7:30 AM. The use of low dose-prednisolone at 2:00 AM was associated with improvements in the duration of morning stiffness (P<0.001), joint pain (P<0.001), Lansbury index—used for the assessment of RA, including the erythrocyte sedimentation rate, pain on motion, muscle weakness, and morning stiffness—(P<0.001), Ritchie index—used to measure joint tenderness for patients with RA—(P<0.001), and morning serum concentrations of IL-6 (P<0.01). Based on the results of the study, the authors wrote that timing may be an important aspect of glucocorticoid administration to control the acute inflammatory symptoms of RA.

However, it is impractical to expect patients to wake up every morning at 2 AM to engage in this therapeutic paradigm. Effective plasma concentrations for IR prednisone are sustained for less than 8 hours (half-life, 2-3 hours), and the time to peak plasma concentrations is 2 hours (Figure). Some clinicians may dose IR prednisone at night; however, this can lead to suppression of the adrenal cortex because of its minimal activity between 4 PM and midnight. As a result, the timing of prednisone therapy should take into account the condition being treated, its unique symptom patterns, and the pharmacokinetic properties of prednisone itself.

One strategy that has been proposed for patients with RA to experience the benefits of this timed therapeutic action and

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Figure. Mean plasma levels of prednisone after a single dose of 5-mg prednisone administered as a low-dose, delayed-release or IR tablet.

IR, immediate release
A) IR tablet under fasting conditions, administered at 2 AM.
B) Low-dose, delayed-release prednisone tablet administered 2.5 h after a light evening meal.
C) Low-dose, delayed-release prednisone tablet administered immediately after dinner.

a RAYOS (prednisone) delayed-release tablets.

From reference 20.
to alleviate the need for treatment administration during the middle of the night is a delayed-release formulation of prednisone. This would enable patients to administer therapy in the evening and, subsequently, to experience the onset of biologic action during the appropriate morning hours.

**Low-Dose, Delayed-Release Prednisone For Morning Symptoms of RA**

The FDA recently approved a delayed-release prednisone option (which previously was approved in parts of Europe) for the treatment of RA and several other disease states. The formulation consists of a tablet with a coating that dissolves approximately 4 hours after ingestion. Additionally, the absorption, distribution, and elimination of low-dose (5 mg), delayed-release prednisone are similar to those of conventional IR prednisone options.

The safety of low-dose, delayed-release prednisone tablets was assessed in the CAPRA (Circadian Administration of Prednisone in Rheumatoid Arthritis)-1 study, which included 288 patients with RA who were randomly assigned to either delayed-release prednisone (n=144) or IR prednisone (n=144). In this clinical trial, patients treated with delayed-release prednisone tablets ranged in age from 20 to 80 years (median age, 56 years); 99% Caucasian, 85% female (1% were African-American and <1% were Asian). Patients received a low-dose (3 to 10 mg) of delayed-release prednisone tablets once daily at 10 pm; 84% received doses of 5 mg or higher. The results from the CAPRA-1 trial did not raise any new safety concerns aside from those already reported with IR prednisone. Further results from the 12-week CAPRA-1 study and the 9-month open-label extension are published in *The Lancet* and *Annals of the Rheumatic Diseases*, respectively.

The FDA’s approval of delayed-release prednisone tablets was supported by data from the CAPRA-2 study. In this 12-week, double blind, placebo-controlled study, patients with active RA (N=350) were randomized to receive either 5 mg of delayed-release prednisone or placebo every evening in addition to their existing DMARD therapy. Response rates were measured using the American College of Rheumatology (ACR) criteria for 20%, 50%, or 70% improvements in the signs and symptoms of RA. The ACR20 was a primary end point and the ACR50 and ACR70 were secondary end points.

At week 12, patients in the delayed-release prednisone group experienced higher response rates compared with placebo (ACR20, 48% vs 29%, respectively; P<0.001; ACR50, 22% vs 10%, respectively; P<0.006; ACR70, 7% vs 3%, respectively; P=0.10). A key secondary end point in this study was the change in duration of morning stiffness between baseline and week 12. Specifically, patients in the delayed-release prednisone group experienced a greater reduction in morning stiffness compared with DMARD therapy. Furthermore, delayed-release prednisone was associated with greater reductions in fatigue and RA severity, along with better improvements in physical function compared with DMARD alone. The incidence of AEs was comparable between the delayed-release prednisone group and placebo group (median relative reduction of –55% vs –35%; P<0.002). Furthermore, delayed-release prednisone was associated with greater reductions in fatigue and RA severity, along with better improvements in physical function compared with DMARD alone. The incidence of AEs was comparable between the delayed-release prednisone group and placebo group (median relative reduction of –55% vs –35%; P<0.002).

The results from the CAPRA-1 trial did not raise any new safety concerns aside from those already reported with IR prednisone. Further results from the 12-week CAPRA-1 study and the 9-month open-label extension are published in *The Lancet* and *Annals of the Rheumatic Diseases*, respectively.

The relative efficacy of DR prednisone compared with IR prednisone has not been established. A summary of the CAPRA-2 study design did not include an IR prednisone arm. The relative efficacy of DR prednisone compared with IR prednisone to DMARD therapy caused no new AEs and its individual safety profile was similar to that observed in previous studies of IR prednisone. The CAPRA-2 study design did not include an IR prednisone arm. The relative efficacy of delayed-release prednisone compared with IR prednisone has not been established. A summary of the CAPRA-2 trial is presented in the Table.

### Table. CAPRA-2 Study

<table>
<thead>
<tr>
<th>Trial</th>
<th>Design</th>
<th>Number of Pts</th>
<th>Therapy</th>
<th>Primary Outcomes</th>
<th>Secondary Outcomes</th>
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<tr>
<td>CAPRA-2</td>
<td>12-wk, double-blind, placebo-controlled study</td>
<td>350 (323 completed the trial)</td>
<td>Pts were randomized to receive either DRa prednisone (5 mg) or placebo every evening in addition to their existing DMARD treatment.</td>
<td>At week 12, DRa prednisone plus DMARD therapy produced higher response rates than placebo plus DMARD therapy (ACR20, 48% vs 29%, respectively; P&lt;0.001)b.</td>
<td>At week 12, the DRa prednisone group had a greater median relative reduction in morning stiffness compared with DMARD therapy plus placebo (~55% vs ~35%; P&lt;0.002) as well as a greater reduction in fatigue and RA severity. The incidence of AEs was also comparable to placebo arm (43% vs 49%). ACR50 response rates were greater in DRa prednisone arm than placebo (ACR50, 22% vs 10%, respectively; P&lt;0.006). At week 12, few pts had an ACR70 response (ACR70, 7% vs 3%, respectively; P=0.10).</td>
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### Notes

1. The study authors used the term modified-release rather than delayed-release in this investigation.
2. Select secondary outcomes.
3. Adapted from reference 23.

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b RAYOS (prednisone) delayed-release tablets (1 mg, 2 mg, 5 mg).

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Acronyms:
- ACR, American College of Rheumatology
- AE, adverse event
- CAPRA, Circadian Administration of Prednisone in Rheumatoid Arthritis
- DR, delayed-release
- DMARD, disease-modifying antirheumatic drug
- pts, patients
- RA, rheumatoid arthritis
- yrs, years
Conclusion

Circadian patterns of inflammatory cytokine release and the insufficient secretion of endogenous cortisol contribute to peaks in the symptoms of RA, including joint stiffness during the early morning hours. Prednisone is an effective therapeutic agent for RA, especially when used in combination with DMARDs, and treatment with lower doses may reduce the incidence and severity of its treatment-related AEs. Clinical studies show that a novel, delayed-release formulation of prednisone can reduce the early morning peak in cytokine activity and may diminish the severity of morning RA symptoms.23

References