Rheumatoid Arthritis
Circadian Rhythms in Disease Activity, Signs and Symptoms, and Rationale for Chronotherapy with Corticosteroids and Other Medications

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Abstract

Biological processes and functions at all hierarchical levels are organized in time as biological rhythms of discrete periods. Circadian (24-hour) rhythms, which are of direct importance to clinical medicine, are orchestrated by a set of clock genes of the master brain clock situated in the suprachiasmatic nuclei of the hypothalamus plus numerous sub-servient peripheral cellular clocks of all tissues and organs. Circadian rhythms are kept in step with the surrounding physical and social milieu by periodic external time cues, the most important one being the 24-hour environmental light-dark cycle. The circadian time structure gives rise to predictable-in-time day-night patterns in morbidity and mortality events plus symptom occurrence and severity of common chronic conditions, including rheumatoid arthritis (RA). The circadian pattern of various cytokines and hormones in RA disease activity suggests a new treatment paradigm (i.e., chronotherapy — timing medications to 24-hour rhythms in disease pathophysiology) to improve desired outcomes. Since the 1950s, RA chronotherapy in the United States and Europe has involved several nonsteroid anti-inflammatory drugs (NSAIDs), certain disease modifying antirheumatic drugs (DMARDs), and various synthetic corticosteroid medications.

A major concept of clinical medicine is homeostasis (i.e., relative constancy of biological functions and processes). However, the concept of homeostasis is both incomplete and misrepresentative. In addition to an intricate structure in space, processes, and functions at all biological levels of organization exhibit an equally intricate structure in time revealed as: 1. ultradian rhythms that range in period from milliseconds to a few hours, 2. circadian rhythms that have a period of approximately 24 hours, and 3. infradian rhythms that range in period from several days, months, or years. This article focuses on the clinical relevance of endogenous circadian rhythms to understanding the pathophysiology and therapy of RA. The concept and mechanisms of biological timekeeping are first discussed as background for the content of subsequent sections that present 1. circadian rhythms in the signs and symptoms of RA and their underlying circadian chronopathology (predictable-in-time variation during the 24 hours in the mechanisms of disease activity) and 2. historical developments in RA chronotherapy (delivery of nonsteroid anti-inflammatory drugs [NSAIDs], synthetic glucocorticosteroids, and other medications with reference to the 24-hour pattern in cytokine biomarkers of RA disease activity and symptoms severity).

Biological Rhythms and Biological Timekeeping

The organization and communications of human biologic processes and functions entail a complex web, the components being the central nervous system with its sympathetic and parasympathetic branches, glandular endocrine system, peripheral endocrine tissues (e.g., adipose tissue and intestinal tract), and immune system. All components of this web are discretely organized in time in the form of a multifrequency time structure, with optimal functioning (i.e., “health”) being dependent on the well-adapted interactions of rhythmic variables. Less than optimal alignment of the
biological time structure—termed internal desynchronization—can lead to dysfunction and disease. Conversely, under certain circumstances, organic disease can cause rhythmic disturbances that further contribute to disease severity and disability. The body’s profound 24-hour rhythmic variation gives rise to highly predictable time-of-day differences in the susceptibility and occurrence of acute life-threatening medical events (e.g., stroke and myocardial infarction) and manifestation and severity of symptoms of most, if not all, chronic medical conditions (e.g., allergic rhinitis, asthma, RA, and osteoarthritis) that may be best mitigated by therapeutic interventions timed to specific circadian marker rhythms of disease activity.

Circadian rhythms, which are of great relevance to clinical medicine, are genetically determined and driven by a master molecular oscillator located in the suprachiasmatic nuclei (SCN) of the hypothalamus and also by peripheral cellular oscillators. The molecular mechanism of the cells of the master SCN clock, and also cellular oscillators in other nuclei in the brain and peripheral tissues and organs, consists of a discrete number of so-called clock genes—period (Per)1, Per2, Per3, Bmal, Clock, and Cryptochrome (Cry)—and their clock gene products organized as interacting positive and negative transcription and translation feedback loops, with several auxiliary mechanisms reinforcing their robustness and stability. The transcription factors CLOCK and BMAL1 drive the expression of Per1, Per2, Cry1, Cry2, plus a variety of other clock controlled genes. When CLOCK and BMAL1 accumulate to a critical concentration in the cytoplasm, PER and CRY proteins negatively feedback on the transcriptional activity of the CLOCK:BMAL heterodimer to inhibit transactivator function, and thus Per and Cry transcription, thereby creating the observed circadian rhythmic variation. The master brain SCN oscillator is kept in step (i.e., synchronized and entrained) to predictable-in-time environmental phenomena by the daily cycle of light and darkness. Information pertaining to environmental time, as conveyed by the 24-hour ambient light-dark cycle, is monitored by specialized retinal receptors and relayed via the retinohypothalamic neural tract to the SCN. Peripheral clocks of some cells, tissues, and organs may also respond and be synchronized by non-photic cyclic phenomena, such as the time of nutrient uptake, which under certain circumstances may uncouple their circadian rhythms from the central oscillator thereby altering the body’s internal time organization with potential loss of biological efficiency and even induction of disease.

The Hypothalamic-Pituitary-Adrenal Axis (HPA)

The HPA exhibits very prominent rhythmicity in all components—from the SCN to peripheral glucocorticoid receptors. SCN neurons rhythmically release the neuropeptide arginine vasopressin (AVP) into the rostral paraventricular nucleus where it inhibits production of corticotrophin releasing hormone (CRH) that controls ACTH release from the corticotrophic cells of the anterior pituitary. In diurnally

![Figure 1](https://example.com/figure1.png)
active persons, CRH is released into the hypophyseal portal vein in the form of pulsatile bursts but in a circadian fashion, resulting in ACTH being secreted in an identical temporal pattern, with the amplitude and frequency of ACTH pulses being highest during the late night and morning hours (Fig. 1). ACTH signals the synthesis and release of glucocorticoid (GC) secretion; however, GC secretion is further regulated by the intrinsic circadian clock of the adrenal cortex. Interplay between the circadian rhythm of ACTH stimulation and the intrinsic adrenal circadian clock determines in day-night synchronized subjects the 24-hour pattern of circulating cortisol characterized by a prominent early morning peak, declining concentrations during daytime activity, and daily “quiet period” of adrenal response during the evening and early night hours.

The overall activity of the HPA reflects interaction of hormone secretion and responsiveness of the target tissues. GC receptors are expressed in most peripheral tissues and brain, except the SCN. Accordingly, administration of synthetic GCs in pharmacologic doses will act as a time cue or suppress the circadian rhythm-dependent stimulation of the pituitary and adrenal; however, it will not interfere with the circadian periodic function of the SCN. GC receptors are rhythmically transcribed in various tissues leading to differences in GC response according to the circadian time of exogenous GC administration. Endogenous GC production, secretion signaling, and biological responses represent a complete integration of multiple biological clocks, including ultradian (pulsatile) variations organized as a hierarchical circadian system.

The highly organized time structure of the HPA leads to considerable differences as a function of time in its response to stimulation or to feedback effects by exogenous GC medication. Cortisol and its synthetic analogues inhibit ACTH secretion through negative feedback, the extent of which being both dose and circadian-time-dependent;

**Figure 2** Circadian rhythm-dependent differences in the induction of adrenal suppression (i.e., inhibition of cortisol synthesis and secretion) by methylprednisolone (MP) infused at a rate of 660 μg/hr. Urine samples were collected from the diurnally active young adult subjects at 2-hour intervals and analyzed for concentration of 17-OHCS, metabolite of cortisol, (solid circles = control, non-treatment placebo patterns; open squares = MP-affected cortisol patterns). Four-hour MP infusion (660 μg/hr) at the circadian times when endogenous cortisol synthesis and secretion are minimal or reduced in diurnally active persons, between midnight and 4 a.m. (upper left panel) or 4 and 8 a.m. (upper right panel) or 4 p.m. and 8 p.m. (lower right panel), induces severe and moderate adrenal suppression, respectively, while 8-hour infusion (twice the MP dose delivered in the other clock-hour trials) when endogenous secretion of cortisol is maximal, between 8 a.m. and 4 p.m. (lower left panel), exerts no adrenal suppression. Black and white shading along the bottom time axis indicates, respectively, the subjects’ nighttime sleep and daytime activity. (Figure drawn using data from Angeli, 1974.)
maximal suppression in normally diurnally active patients occurs when they are administered just before the nocturnal rise in ACTH production. In contrast, morning once-a-day administration of low or moderate GC doses results in least HPA suppression and lowest risk of side effects.2-8 Thus, the circadian organization of the HPA requires the time of dosing of synthetic GC analogues be chosen according to the effect desired; if suppression is desired (e.g., to manage congenital adrenal hyperplasia), administration has to take place in the evening or early night hours (Fig. 2).

**Circadian Variation of Cortisol and Other Hormones in RA**9-13

The cortisol circadian rhythm of RA patients with low or moderate activity remains normal. However, it can be disturbed—decrease of rhythm amplitude and elevated cortisol concentrations, often with double peaks in the morning and during the afternoon and evening daily “quiet period” of the adrenal—in RA patients with high disease activity. Cortisol concentrations in RA patients with high or advanced disease activity tend to be elevated but without sufficient effect to counter the pathological remodeling of affected tissues. The 24-hour variation in RA symptoms, such as joint pain, morning stiffness, and functional disability (Fig. 3), in large part is due to predictable-in-time differences during the 24 hours in the circulating concentration of the anti-inflammatory hormone cortisol relative to the circadian rhythm of key disease-exacerbating and pro-inflammatory cytokines. Plasma cortisol peaks early during the daytime activity span; however, during the late night and early morning, plasma cortisol level is markedly reduced and thus unable to counter the increased RA disease activity signaled nocturnally by IL-6, TNFα, and various other inflammatory cytokines (Fig. 4).

Melatonin and prolactin, produced primarily during the nighttime sleep span, up-regulate the immune system, resulting in increase of the Th1 inflammatory response and RA disease activation when cortisol values are lowest. In this regard, higher nighttime serum concentrations of melatonin and prolactin have been reported in patients with active RA. The analgesic β-endorphin exhibits circadian rhythmicity, with lowest concentrations during the nighttime—in phase with the nadir of the circadian rhythm of the anti-inflammatory hormone cortisol and peak concentration of the pro-inflammatory hormones prolactin and melatonin plus the pro-inflammatory cytokines TNFα, IL-6, and others. These rhythmic variations, in part, could explain the circadian rhythm in pain threshold of healthy subjects and also contribute to enhanced RA symptom severity, including morning pain, of patients with active RA disease.

**Chronobiology in Immunology**6,14,15

The interplay between the sleep-wakefulness 24-hour rhythm and circadian time organization of the nervous, endocrine, and immune systems exerts strong regulatory influence on immune function and circadian preponderance of pro- and anti-inflammatory cytokines. In animal experiments, the circadian clock protein cryptochrome (Cry) was recently shown to regulate the expression of pro-inflammatory cytokines, and it was demonstrated that the circadian clock controls the expression and function of Toll-like receptor 9 (TLR9), representing a direct molecular link between the circadian clock and immune system, with important implications for immunoprophylaxis and immunotherapy.

Circadian system-dependent immune processes interact with sleep-dependent biological functions, which are significantly altered by sleep deprivation. Pro-inflammatory cytokines—IL-6, IL-1, and TNFα, which are partially controlled

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**Figure 3** Previously unpublished data from a study conducted approximately 20 years ago using then popular Ritchie Index plus grip strength of right and left hand showing the prominent circadian variation in disease activity in 20 RA patients with active disease. Patients were sampled 14 or more days after cessation of therapy. Black and white shading along the bottom time axis indicates, respectively, the subjects’ nighttime sleep and daytime activity. (E. Haus, unpublished data.)
by sleep—themselves exert regulatory influences on both the immune system and sleep mechanisms. IL-6, a biomarker of RA disease activity, is circadian rhythmic; it attains peak plasma levels in the late night and early morning hours (Fig. 4). The actions of the pro-inflammatory cytokine TNFα are further amplified by the sleep-dependent, high-amplitude variation of soluble TNF receptors I and II (Fig. 4), thereby extending the trans-signaling effect of pro-inflammatory cytokines to a broader group of cells also outside the immune system. Production of pro-inflammatory cytokines is maximal during nocturnal sleep, whereas production of anti-inflammatory cytokines is maximal during diurnal wakefulness. In healthy subjects synchronized to daytime activity and nighttime sleep, peak plasma concentration of IL-6, which is induced by TNFα, follows peak plasma TNFα concentration by several hours. In RA patients, the peak time of both cytokines is shifted to the morning, with markedly elevated peak concentration of TNFα found at approximately 7 a.m., the result being markedly elevated amplitude of their circadian patterning with extension of their elevated levels later during the daytime wake span. The circadian periodic endocrine messengers of prolactin, growth hormone (GH), and melatonin, which show peak concentration during sleep, and cortisol and epinephrine, which show peak concentration during the early hours of daytime activity, control the rhythmic expression of the immune system, favoring production of pro-inflammatory Th1 cytokines during the nighttime and of anti-inflammatory Th2 cytokines during the daytime.

Among the pro-inflammatory cytokines, IL-2 and IFNγ peak earlier during the subjective night (between midnight to 2 a.m. in those adhering to a normal sleep-wake pattern), similar to TNFα-induced Th1 immune response. Prolactin and GH also favor Th1 immune response. In contrast, cortisol and norepinephrine, which support Th2 immune reactions, are at their nadir during this time. The morning rise and peak of cortisol follows the peak of IL-6 in clinically healthy
subjects and in RA patients with early stage disease by 1 to 2 hours, but lags behind peak TNFα levels by approximately 5 hours in healthy subjects and by approximately 2 hours in RA patients. Cortisol and β-endorphin inhibit secretion of IL-6, TNFα, and several other pro-inflammatory cytokines. Their decrease during the night, coupled with the rise in melatonin, GH, and prolactin, appear to drive the nocturnal and early morning increase of the TNFα, IFNγ, IL-2, IL-6, and IL-12 pro-inflammatory cytokines associated with the characteristic morning symptoms that coincide with elevated disease activity of RA.

**Historical Developments in the Chronotherapy of RA**

Chronotherapy is the timing of medical interventions according to biological rhythm determinants as a means to optimize treatment outcomes and minimize or avoid adverse effects. With reference to pharmaceutical agents, chronotherapy entails the delivery of medications, either by the judicious timing of conventional or special drug-release systems, with respect to 24-hour rhythms of disease activity and symptom intensity and patient tolerance. Chronotherapy is not at all a new concept in rheumatology. Over the past 60 years, several NSAIDs, GC, and disease-modifying antirheumatic drugs (DMARDs) have been trialed as chronotherapies in the USA and Europe.

**NSAIDs**

Commencing early in the 1980s, various controlled-release NSAIDs have been explored for administration-time differences in their palliative effects. Kowanko and associates, using a double-blind, crossover study design that included multiple (4 to 6 times per day) pain, stiffness, and hand strength self-assessments, reported that a twice-daily flurbiprofen schedule that lacked an evening dosing time (i.e., 200 mg in the morning and 200 mg at midday) was less effective in modulating morning RA signs and symptoms than ones that did (200 mg in the morning and 200 mg at bedtime or 200 mg at midday and 200 mg at bedtime). In addition, patient studies involving indomethacin and ketoprofen revealed significant reduction of gastrointestinal and neurological adverse effects when ingested once-daily in the evening rather than in the morning. In contrast, osteoarthritis patients derived enhanced benefit when ingested either before lunch, dinner, or bedtime.

**DMARDs**

These medications suppress the underlying pathological processes of RA. Some, such as cyclophosphamide and methotrexate, are known to induce adverse effects that are not only dose-dependent but also circadian time-dependent, thereby insinuating proper choice of treatment time of these and other such DMARDs can improve patient tolerance and also therapeutic outcome. Indeed, evening scheduling of methotrexate in synchrony with rise in the cytokine biomarker TNFα significantly enhances its effectiveness.

**Glucocorticosteroids (GC)**

In the 1950s, clinical appreciation of the circadian organization of the HPA began to influence the design of treatment schedules involving ACTH and GCs to minimize risk of adrenal suppression and improve outcomes. Indeed, one of the investigators (EH) established *morning* timing of synthetic ACTH administration, in combination with physical therapy, significantly lessened the intensity of morning-time RA symptoms, verified by patient self-assessments conducted at multiple time points daily during the wake span.

Pioneers like Ceresa and Angeli in Italy and Di Raimondo and Grant in the USA in the 1950s and 1960s established the risk of HPA suppression from GC infusion (e.g., methylprednisolone) (Fig. 2) or tablet (e.g., triamcinolone); treatment is dependent not only upon dosage but circadian timing. In all cases, morning GC dosing of diurnally active patients is associated with lowest risk of HPA disruption and other adverse effects. Thus, the initial chronotherapies involving GCs for inflammatory conditions, including RA, stressed the importance of their *morning* timing, at the commencement of diurnal activity. Accordingly, in the 1960s, Harter and coworkers introduced the concept of *morning* alternate-day, higher-dose tablet methylprednisolone chronotherapy for RA and other steroid-responsive medical conditions; shortly thereafter, it became the first chronotherapy widely accepted into routine clinical practice (Medrol™; Upjohn Pharmaceutical Company). During the 1980s, a unique twice-a-day GC combination chronotherapy (Dutimel 8-15™) was introduced by the Italian division of the Hoechst Pharmaceutical Company; the tablet designated for daily ingestion at 8 a.m. contained 7 mg prednisolone acetate plus 4 mg prednisolone alcohol, and the tablet designated for ingestion daily at 3 p.m. contained 3 mg prednisolone alcohol and 15 mg cortisone acetate. The plasma GC levels of this unique chronotherapy closely mimic the endogenous circadian cortisol rhythm. Although a number of small European trials showed it to be safe (i.e., without suppression of the HPA and other adverse effects) and effective for the management of early disease RA, it never achieved popularity with patients or doctors due to its difficult and atypical twice-daily dosing-time requirements that compromise compliance.

Prednisone and prednisolone are commonly used to manage RA, and most clinicians prescribe them for morning administration, primarily because RA symptom severity is greatest and HPA suppression risk is least at this time. Various investigators, commencing early in the 1980s, explored...
whether an evening or bedtime low-dose (typically < 6 mg) prednisolone schedule is more advantageous than a morning one. Kowanko and colleagues in 1982 using a double-blind within-patient designed trial found no difference in therapeutic effect or HPA suppression when dosed either once-daily at 8:00 a.m., 1:00 p.m., or 11:00 p.m. The study by De Silva and coworkers in 1984 produced different results, finding the duration of morning stiffness was significantly shortened by a nighttime versus morning-time once-daily low-dose (mean 5.8 mg) prednisolone treatment regimen. Later, in 1997, Arvidson and colleagues explored the hypothesis that administration of low-dose GCs prior to the exacerbation of disease and inflammatory activity, signaled by the circadian rise of IL-6 synthesis, results in improved clinical management of RA patients. Patients were randomized into two 4-day treatment groups—prednisolone (5 to 7.5 mg/d) either at 7:30 a.m. or 2:00 a.m. The 2:00 a.m. group showed more favorable responses to prednisolone than the 7:30 a.m. one, in terms of the duration of morning stiffness, severity of joint pain, and the formerly popular Landbury and Ritchie indices, plus greater reduction of morning circulating IL-6 concentration. These findings, particularly regarding suppression of the IL-6 biomarker, suggest proper circadian timing of GCs (i.e., at approximately the middle of the nocturnal sleep span) may exert chronovo-preventive, disease-altering effects. In recent years, a modified-release, low-dose prednisone chronotherapy was approved in Germany; it is especially formulated according to the findings of the Arvidson and coworkers study to ensure the release of medication commences at approximately 4 hours after bedtime ingestion, so sufficient drug level is achieved when IL-6 begins to rise to attain better control of the morning RA symptoms and without HPA and other adverse effects as verified by patient outcome studies. This low-dose prednisone chronotherapy, marketed as Rayos™ (Horizon Pharma) in the USA, for treatment of RA potentially represents a significant advance in the management of early stage RA.

**Discussion and Conclusion**

This article focuses on the circadian time structure and the role it plays upon day-night differences in RA disease activity and optimal management by medications. Circadian rhythms in pro-inflammatory cytokines, such as IL-6 and TNFα, are modulated by prominent ultradian and circadian rhythms in the neuroendocrine milieu, particularly involving cortisol, epinephrine, GH, melatonin, and prolactin. The circadian periodicity of IL-6 has been shown to be an important target for low-dose, modified-release prednisone chronotherapy; timing of GC therapy to its nocturnal rise better reduces morning RA symptoms and functional disability compared to either once-daily morning or bedtime conventional prednisone tablet therapy. An initial small-scale study also suggests methotrexate bedtime chronotherapy enhances treatment effect. In addition, studies with popular NSAIDs verify an evening or bedtime regimen is superior to either a morning (on awakening or with breakfast) or midday (lunch-time) one. Although research shows that the adverse effects of certain other DMARDs can be modulated by proper timing to circadian rhythms, the potential advantage of their delivery with respect to circadian criteria has yet to be sufficiently explored in RA patients.

**Disclosure Statement**

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