Advances in Rheumatoid Arthritis

TOP 10 THINGS

RHEUMATOLOGISTS WISH PCPS TREATING RHEUMATOID ARTHRITIS KNEW, WITH A FOCUS ON DISEASE CHRONOBIOLOGY AND CHRONOTHERAPY

Electronic CME Monograph

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Target Audience

- Primary audience
  - Primary care physicians (PCPs), nurse practitioners, and physician assistants
- Secondary audience
  - Rheumatologists who wish to learn about issues faced by PCPs who encounter patients with rheumatoid arthritis (RA)

Program Description

Rheumatoid arthritis (RA) is a chronic, inflammatory disease characterized by joint swelling, joint tenderness, and progressive destruction of synovial joints, which can lead to severe disability and premature mortality. Treat-to-target recommendations emphasize the need to commence therapeutic intervention early using disease-modifying antirheumatic drugs (DMARDs) with frequent reassessment and adjustment of treatment to ensure that patients have a chance to achieve the goal of disease remission. However, diagnosis and active therapy for early RA is often delayed, which can have long-term adverse consequences on disease progression.

By providing evidence-based "top 10" pearls to PCPs, rheumatologists can help PCPs to diagnose RA and to be familiar with the available treatment options for RA, as they have to decide whether to initiate treatment or refer the patient to a specialist—but also care for the patient while awaiting a specialist appointment. Chronotherapeutic advances in the treatment of RA can help PCPs to bridge* therapy and treat to target*. Chronotherapy—which is defined as the judicious timing of conventional or special drug-release therapeutic interventions in order to align drug peak and trough concentrations to specific circadian (~24-hour) rhythm markers of disease activity of medical conditions—is a means to optimize treatment outcomes and potentially minimize or avoid adverse effects (AEs).

Learning Objectives

- Develop strategies that reflect the importance of early initiation of RA treatment and "treating to target*"
- Describe chronotherapeutic* advances in the treatment of RA and how this may help to bridge therapy and treat to target
- Develop ways in which rheumatic disease specialists can work more closely with PCPs to treat RA by using a "team" approach

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- Michael H. Smolensky, PhD, has no conflicts of interest to disclose. He has disclosed that he has received honorarium from EHC Communications for participation on an advisory committee, honorarium from Science Branding for consulting, and honorarium from Informa Healthcare as co-editor of the academic journal *Chronobiology International.*
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*For definitions of these terms, please see the glossary on page 23.

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Introduction

RA is a chronic inflammatory disease characterized by joint swelling, joint tenderness, and destruction of synovial joints, which can lead to severe disability and premature mortality.[1-6] Indeed, the standardized mortality ratio* among persons with RA is 2.3 times higher than it is in the general population.[3]

Disease progression can vary among patients, but early therapeutic intervention leads to greater improvement in clinical outcomes and greater reduction in joint damage and disability.[1] Treat-to-target recommendations emphasize the need to commence therapeutic intervention early using disease-modifying antirheumatic drugs (DMARDs) with frequent reassessment and adjustment of treatment to ensure that patients have a chance to achieve the goal of disease remission.[7;8] Unfortunately, diagnosis and active therapy for early RA is often delayed, which can have long-term adverse consequences on disease progression.

By providing evidence-based "top 10" pearls to PCPs, rheumatologists can help PCPs to diagnose RA and to be familiar with the available treatment options for RA, as they have to decide whether to initiate treatment or refer the patient to a specialist—but also care for the patient while awaiting a specialist appointment.[7]

Certain terms and concepts that may be new to the reader are defined in the glossary on page 23.

Diagnosis of RA is within the scope of practice of the PCP

Early diagnosis and therapeutic intervention can improve clinical outcomes and reduce joint damage and disability.[1] Because PCPs are often the first and sometimes the only point of contact for patients with RA, they play a major role in the evaluation and management of the disease.[9;10]

In 2010, the American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) developed new classification criteria for RA, designed to be used in clinical trial enrollment and research.[1] In contrast to the previous 1987 ACR (formerly the American Rheumatism Association) classification criteria for RA, which focused exclusively on late-stage disease features to identify established disease, the new classification system focuses on features at earlier stages of disease that are associated with persistent and/or erosive disease.[1;11] In light of recent advances in patient management—with DMARDs and new biologic agents having dramatically improved the success of RA treatment—the new criteria are intended to refocus attention on the need for earlier diagnosis and institution of effective disease-modifying therapy to prevent or minimize disease progression and the occurrence of the sequelae of RA.[1]

The 2010 criteria can be applied to any patient who has currently active clinical synovitis (i.e., swelling) in at least 1 joint (**Table 1**), that is not better explained by another diagnosis, such as systemic lupus erythematosus (SLE), psoriatic arthritis, or gout, among others. The criteria require a medical history of symptom duration, a thorough joint evaluation, and at least one serologic test (rheumatoid factor [RF] or anti-citrullinated protein antibody [ACPA]) and one acute-phase response measure (erythrocyte sedimentation rate [ESR] or C-reactive protein [CRP]) (**Table 1**).[1] A patient who presents with at least one joint with definite clinical synovitis, that is not better explained by another disease, and achieves a score of ≥6/10 is classified as having definite RA.[1] A patient with a score <6 cannot be classified as having definite RA, but might fulfill the criteria at a later time.[1] Outside of clinical trial enrollment and research, an individual patient may meet the definition of RA without conducting the specified laboratory tests.[1] For example, a patient with multiple joint involvement (e.g., one swollen joint and ten tender joints) for 6 weeks will achieve a score of 6 independent of serologic or acute-phase response

*The Standardized Mortality Ratio (SMR) is a ratio between the observed number of deaths in a study population and the number of deaths that would be expected, based on the age- and sex-specific rates in a standard population and the age and sex distribution of the study population. If the ratio of observed:expected deaths is greater than 1.0, there is said to be "excess deaths" in the study population.

status, but other potential diagnoses must been ruled out.[1]

The ACR/EULAR authors state that the aim of their classification system is clinical research and trials of persons at earlier stages of RA, rather than to establish a diagnostic threshold or referral tool for PCPs.[1] They acknowledge that a separate body of work is needed to develop such tools, which may be informed by classification criteria.[1] Nonetheless, they can be used as a diagnostic aid, although clinicians may be able to diagnose an individual with RA who does not meet or display features specific to the classification criteria.[1] For example, despite not having been included in the criteria, significant erosive disease seen on radiographs that is typical of destructive RA can be used as evidence of RA, precluding the necessity to apply additional measures.[1] Although structural changes, which can be visualized by radiography or other imaging techniques, best distinguish RA from other arthritic disorders, joint damage is rarely apparent in the very early stages of disease, but accumulates over time.[1] Patients with longstanding disease, including those whose disease is inactive (with or without treatment) who, based on retrospectively available data, have previously fulfilled the 2010 criteria, should be classified as having RA.[1]

Diagnosis of RA is within the scope of practice of the PCP. When evaluating a patient presenting with peripheral joint manifestations suggestive of RA, PCPs should:

- Take a thorough medical history, asking the patient about the presence, intensity, location, and duration of joint pain, swelling, and stiffness, with particular attention to the time of day when symptoms occur or worsen. RA symptoms in normally diurnally active persons are typically worse in the morning and improve over the course of the day. PCPs should also gauge how the symptoms affect the patient's quality of life (QOL), particularly in the morning.
- Perform a physical examination of the feet and hands to assess for synovitis (presence

TABLE 1. The 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for rheumatoid arthritis

	Score
Target population (Who should be tested"): Patients who 1) have at least one joint with definite clinical synovitis (swelling)* 2) with the synovitis not better explained by another disease†	
Classification criteria for RA (score-based algorithm: add score of categories A-D; a score of ≥6/10 is needed for classification of a patient as having definite RA)‡	
A. Joint involvement§	
1 large joint	0
2-10 large joints¶	1
1-3 small joints (with or without involvement of large joints)#	2
4-10 small joints (with or without involvement of large joints)	3
>10 joints (at least one small joint)**	5
B. Serology (at least one test result is needed for classification)††	
Negative RF and negative ACPA	0
Low-positive RF *or* low-positive ACPA	2
High-positive RF *or* high-positive ACPA	3
C. Acute-phase reactants (at least one test result is needed for classification)‡‡	
Normal CRP *and* normal ESR	0
Abnormal CRP *or* abnormal ESR	1
D. Duration of symptoms§§	
<6 weeks	0
≥6 weeks	1

ACPA = anti-citrullinated protein antibody; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; RF = rheumatoid factor.

*The criteria are aimed at classification of newly presenting patients. In addition, patients with erosive disease typical of RA evidencing a history compatible with prior fulfillment of the 2010 criteria should be classified as having RA, as should patients with longstanding disease, including those whose disease is inactive (with or without treatment) who have previously fulfilled the 2010 criteria based on retrospectively available data.

†Differential diagnoses vary among patients with different presentations, but may include conditions such as systemic lupus erythematosus, psoriatic arthritis, and gout. If it is unclear about the relevant differential diagnoses to consider, an expert rheumatologist should be consulted.

‡Although patients with a score of <6/10 are not classifiable as having RA, their status can be reassessed and the criteria might be fulfilled cumulatively over time.

§Joint involvement refers to any swollen or tender joint on examination, which may be confirmed by imaging evidence of synovitis. Distal interphalangeal joints, first carpometacarpal joints, and first metatarsophalangeal joints are excluded from assessment. Categories of joint distribution are classified according to the location and number of involved joints, with placement into the highest category possible based on the pattern of joint involvement.

¶"Large joints" refers to shoulders, elbows, hips, knees, and ankles.

#"Small joints" refers to the metacarpophalangeal joints, proximal interphalangeal joints, second through fifth metatarsophalangeal joints, thumb interphalangeal joints, and wrists.

**In this category, at least one of the involved joints must be a small joint; the other joints can include any combination of large and additional small joints, as well as other joints not specifically listed elsewhere (e.g., temporomandibular, acromioclavicular, sternoclavicular, etc.).

††Negative refers to IU values that are less than or equal to the upper limit of normal (ULN) for the laboratory and assay; low-positive refers to IU values that are higher than the ULN but ≤3 times the ULN for the laboratory and assay; high-positive refers to IU values that are >3 times the ULN for the laboratory and assay. Where RF information is only available as positive or negative, a positive result should be scored as low-positive for RF.

‡‡Normal/abnormal is determined by local laboratory standards.

§§Duration of symptoms refers to patient self-report of the duration of signs or symptoms of synovitis (e.g., pain, swelling, tenderness) of joints that are clinically involved at the time of assessment, regardless of treatment status.

and pattern of swollen or tender joints and limited range of motion). Swelling suggests an inflammatory arthritis as opposed to arthralgia.

- Order laboratory tests:
  - Inflammatory markers—both ESR and serum CRP levels are typically elevated in RA.
  - Biologic markers—positive RF or ACPA test results suggest RA, with a greater specificity when both tests are positive.
  - Most laboratories offer a RA panel, which may be more cost-effective than ordering individual tests.
- Order radiographs of the hands, wrists, and feet—these may reveal erosions characteristic of RA, and are useful as a baseline to monitor disease progression. Radiographic changes may also suggest an alternative diagnosis. Radiographic findings indicating erosions suggest late-stage disease and mandate urgent evaluation and treatment initiation by a rheumatologist.

When referring a patient for specialist evaluation, all of the PCP-collected diagnostic information should be provided to the rheumatologist.

Differential diagnoses to consider in patients who present with joint pain include psoriatic arthritis, gout, SLE, osteoarthritis (OA) (particularly if joint pain tends to worsen towards the end of the day), fibromyalgia, parvovirus infection (or Fifth disease), and Lyme arthritis in endemic areas. Moreover, elderly patients may present with comorbid (i.e., mixed) RA and OA, which can complicate diagnosis. Another confounder is fibromyalgia, which frequently occurs with other painful conditions, including RA and OA. PCPs encountering such patients should obtain a rheumatology consult if feasible.

2 Delayed initiation of treatment for RA—a "wait and see" approach—can have long-term adverse consequences

Advances in the treatment of RA have made remission a realistic goal for patients; thus, treatment with DMARDs should ideally be started as soon as the diagnosis of RA is made.[10;12] However, a US survey found the majority (61%) of PCPs were only "somewhat" confident in their ability to diagnose RA.[9] Any delay in making the diagnosis of RA and commencement of DMARD treatment may compromise treatment outcomes and foster disease progression leading to irreversible joint destruction, compromised function, and disability.[10;12-16] In this regard, one study found that 40% of PCPs who prescribe DMARDs report that delayed initiation is appropriate.[9] This "wait and see" approach implies a lack of urgency toward aggressive treatment with potentially future unintended and possibly preventable, or at least attenuated, deleterious effects on patient well being and QOL.[9]

3 A number of factors are responsible for delays in treatment

PCPs often encounter patients presenting with multiple comorbidities within a 15-minute office visit. If joint symptoms are not the purpose for a medical appointment, it is important to reschedule the patient to assess him/her within a short time frame, because the 3-month span following symptom onset represents an important therapeutic window for RA.

Many PCPs will want to refer patients who they suspect have RA—based on the above described evaluation—to a rheumatologist to confirm the diagnosis and initiate DMARD therapy. However, there are too few rheumatologists to adequately care for the growing population in need of rheumatic disease expertise, particularly in rural areas.[7;9] The shortage of rheumatologists manifests as long wait times—with a delay from symptom onset to patient assessment by a

rheumatologist—or even an inability to refer.[9;17-22] One author described the wait time for an appointment to be typically 3 to 4 months or more in her area.[7] One study reported that 34% of patients were given an appointment within 3 months of referral, 32% waited longer than 3 months, and 34% were told that the rheumatologist was not accepting new referrals at the time the request was made.[23] Another study reported wait times to appointments averaged 48 days in "urgent" patients (as defined by the PCP), and even longer delays in non-urgent patients, such that the overall mean interval between a patient's onset of symptoms and appointment with a rheumatologist equaled 7 months.[24]

In addition, PCPs may not be providing rheumatologists with sufficient information when requesting a consult.[25] Investigators found that once a RA patient does present to their PCP, important additional delays in assessment can occur because referral letters sent to rheumatologists often lack key elements of the medical history, making triage of referrals by rheumatologists difficult.[25] Referral letters received over a one-year period by a rheumatologist practicing at a tertiary-care center demonstrated that only:[25]

- A small percentage of referral letters made mention of the pattern of joint involvement.
- 17% indicated symptom duration.
- 2% mentioned any time-of-day pattern of symptoms (such as morning stiffness).
- 6% provided information about functional status.
- 62% specified solely 'joint pain' in the referral letter.

RA can be missed in patients who present with late-onset disease, especially when both patient and physician expect joint pain to occur with increasing age and degeneration of joints. Late-onset RA (age ≥60 years) represents up to one-third of all RA cases, and may differ from the classical picture of RA.[26] There may be a more equal gender distribution, more elevated acute-phase reactants, and a higher frequency of abrupt onset of symptoms, of constitutional manifestations, and of a clinical presentation resembling polymyalgia rheumatica (PMR) with prominent shoulder involvement.[26;27] Conversely, erosive joint disease, RF positivity, and extra-articular manifestations, including subcutaneous nodules, are less frequent than in classical RA.[26]

4 The importance of treat-to-target recommendations

The goal of treat-to-target recommendations is low disease activity or remission in patients with early or established RA, which leads to better structural and functional outcomes than persisting residual disease activity.[7;8;12;28-31] The ACR treat-to-target recommendations emphasize the need to commence therapeutic intervention using DMARDs early, with frequent reassessment and adjustment of treatment to achieve tight disease control.[28] A description of the ACR recommendations for the use of DMARDs and biologic agents to treat RA can be found in the article by Singh et al.[28] However, because early diagnosis of RA by PCPs and subsequent referral to a rheumatologist remain a challenge, early and aggressive treatment often do not occur.[10] For example, one study that examined the proportion of patients with RA seen by a rheumatologist and treated with a DMARD found that only 22.6% received a DMARD immediately, i.e., within 3 months, and only 47.6% within 6 months.[22]

Not all PCPs are comfortable initiating DMARD treatment, and even those that are may not be comfortable adding on or switching therapy. A survey of US PCPs found that the majority reported some RA training after medical school (59%), but only one-third felt very confident managing RA.[9] Most (81%) reported prescribing DMARDs, but 37% did not initiate them, with only 9% being very confident starting a DMARD.[9] Common reasons for discomfort using DMARDs included their adverse effects (AEs)—toxicities and infections—and inconvenience of intravenous therapy.[9] Furthermore, when asked what factors make patients inappropriate candidates for DMARD therapy, approximately half of respondents reported that there was no need for a DMARD, one-third noted patients were too sick to receive a DMARD, and more than half felt that the AEs of DMARDs were too problematic.[9] The majority (71%) of the surveyed PCPs stated that they were very likely to

TABLE 2. Patient-driven RA disease activity measure

Measure	Number of items	Response format	Administration time	Measure output	Disease activity cutoffs
RAPID-3	3	MDHAQ: 0-3 Pain VAS: 0-10 Pt Global VAS: 0-10	Patient: ≈1.5 minutes Provider: <30 seconds	A single score on a continuous 0-10 scale	Remission: 0 to 1.0 Low/minimal: >1.0 to 2.0 Moderate: >2.0 to 4.0 High/severe: >4.0 to 10

HAQ = Health Assessment Questionnaire; MDHAQ = Multidimensional HAQ; Pt Global VAS = Patient global assessment of disease activity VAS; RAPID-3 = Routine Assessment of Patient Index Data with three measures; VAS = Visual analog scale

refer patients with RA to a specialist, but when asked "Under what situations would you refer your patients to a rheumatologist?", "advanced disease" was the most cited reason, followed by "patient desire" and "uncomfortable prescribing DMARDs."[9] However, almost half (44%) of the PCPs reported that patients had difficulty getting appointments with rheumatologists.[9] PCPs who did not refer cited "insurance problems," "too difficult to schedule a rheumatology appointment," and "no need" as their reasons for not referring.[9] Thus, poor access to rheumatologists and PCPs' discomfort in prescribing DMARDs constitute major barriers to optimal treatment for patients with RA.[9]

PCPs who are confident initiating DMARD therapy should systematically utilize a RA disease activity measure to facilitate clinical decision making in order to achieve treat-to-target goals and effectively implement the ACR recommendations.[32] Several validated RA disease activity measures have been recommended by the ACR for application in the clinical setting.[32] A commonly used patient-driven tool—Routine Assessment of Patient Index Data with three measures (RAPID-3) as outlined in **Table 2**—is advantageous because it does not require laboratory tests and is relatively easy to use, with the patient able to complete it in the waiting room.[32-34] Completion of this self-report questionnaire on standardized paper or electronic forms by a patient in the waiting area provides relevant information to the clinician before seeing the patient.[32;35;36] Patients' scores on a scale of 0 to 10 categorize their RA disease activity as in remission, low/minimal, moderate, or high/severe.[32] The RAPID-3 instrument, as well as instructions for how to calculate a patient's score, can be found at **http://echo.unm.edu/common/pdf/clinic-rheumatology-rapid3.pdf**.

Patient-driven tools such as RAPID-3 have been validated for use in clinical practice, but because they are subjective in nature, the results may be influenced by factors such as patients' cultural beliefs, self-efficacy, and mood.[32] Recently, novel multi-biomarker disease activity (MBDA) assays have been developed to quantitatively assess current clinical RA disease activity and show promise as an option to track changes in disease activity over time.[37-40] Such blood tests are simple to perform and interpret, and may become an important objective addition to disease activity measures in the clinic.[37]

5 PCPs should utilize bridging therapy

It is not appropriate for PCPs to do nothing and take a "wait and see" approach while awaiting a rheumatology consult or referral, or learning more about possibly initiating a DMARD.[7] Glucocorticoids (GCs) and nonsteroidal anti-inflammatory drugs (NSAIDs) are useful for bridging the interval before initiation of DMARDs, and between initiation of DMARDs and onset of their therapeutic effect by rapidly controlling inflammation while awaiting the benefits of slow-acting agents.[15;41]

In addition to anti-inflammatory properties, GCs have also demonstrated disease-modifying properties that have also made them useful beyond bridging therapy.[12;42] The addition of low-dose GCs, either to standard DMARD monotherapy or combinations of DMARDs, yields clinical benefits and inhibits radiographic progression compared with DMARDs alone, that may extend over many years.[12;15;41;43-45] "Low-dose" GCs have been variously described as doses that range from <5 mg/day to 7.5 mg/day, or even 10 mg/day of prednisone, but <5 mg/day appear effective for many patients with RA.[45]

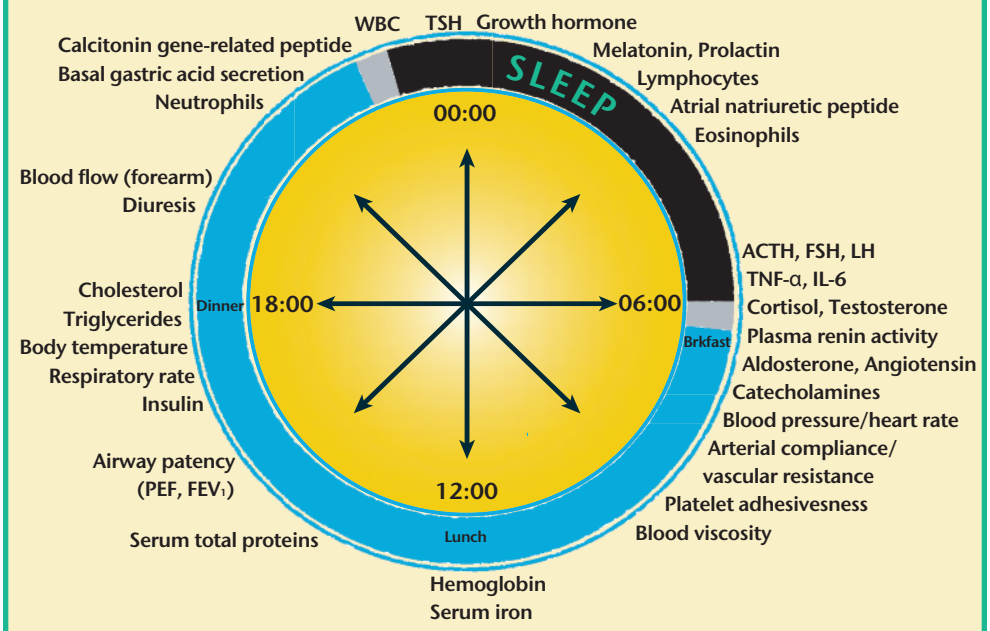
However, despite the use of GC therapy for more than 60 years to treat RA, some consider it controversial, mainly because of the potential for AEs, such as suppression of endogenous corticosteroid production, stomach ulcers, osteopenia, cataract formation, metabolic disturbances, and mood alterations.[46-48] Such AEs may be drug-, dose-, and administration-time (i.e., circadian [~24-hour] rhythm)-dependent and/or they may be an aspect of RA disease activity, cotherapies, or other comorbidities.[46] Thus, when the decision is made to institute GC therapy, it is important to monitor patient tolerance and complaints.[46]

The development of a novel, low-dose, delayed-release (DR) prednisone formulation that—when ingested at bedtime—synchronizes drug level to predictable-in-time innate circadian rhythms in RA disease biomarkers, may improve the benefit-risk ratio of low-dose GC treatment in patients with RA compared with immediate-release (IR) prednisone conventionally dosed in the morning and at other times during the daytime activity period.[47;49;50] The circadian rhythm basis and clinical trial evidence for such a therapeutic intervention is described in the next two sections.

6 RA has a circadian pattern of symptoms

A major concept of clinical medicine is homeostasis (i.e., the relative constancy of biologic functions and processes), but the concept of homeostasis is incomplete.[51] In addition to an intricate structure in space, expressed by the gross and microscopic anatomy, human processes and functions at all biologic levels exhibit an equally intricate structure in time manifested as innate biologic rhythms of discrete periods.[51] For example, ultradian rhythms range in period from milliseconds to a few hours, circadian rhythms have a period of approximately 24 hours, and infradian rhythms range in period from several days, months (e.g., menstrual cycle), or year.[51] The organization and communication of human biologic processes and functions entail a complex web.[51] The components of this web (central nervous system, glandular endocrine system, peripheral endocrine tissues, and immune system) 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

FIGURE 1. Peak time of selected human circadian rhythm variables of clinical relevance during 24 hours[55;56]

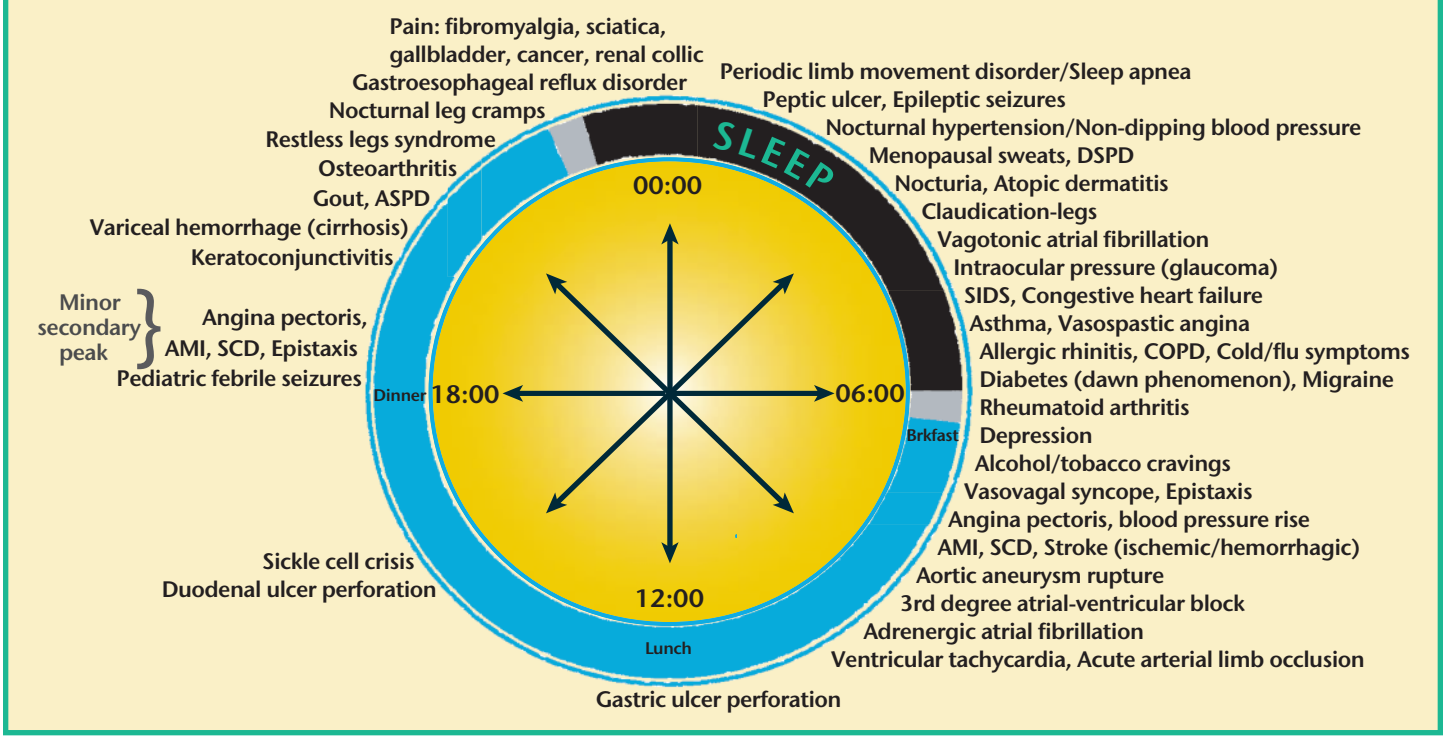


The entries around the 24-hour circular clock indicate the approximate peak time of selected biologic variables in individuals who ordinarily adhere to a routine of diurnal activity and nighttime sleep. The peak times are approximate, varying to some extent between morning and evening chronotypes, i.e., larks and owls. The circadian timing and dose strength of certain pharmacotherapies may alter the designated time patterns. Time is shown in military format (i.e., 00:00 = midnight; 06:00 = 6 AM; 12:00 = noon; 18:00 = 6 PM), and the sleep span (~22:30 to 06:30) and waking span (~06:30 to 22:30) are indicated by the darkened and blue bands of the circle, respectively, and the presumed approximate times of breakfast, lunch, and dinner of the subjects in the reported studies are depicted.

ACTH = Adrenocorticotropic hormone; FEV_1 = Forced expiratory volume in 1 second; FSH = Follicle stimulating hormone; IL-6 = Interleukin-6; PEF = Peak expiratory flow; TNF-α = Tumor necrosis factor-α; TSH = Thyroid stimulating hormone; WBC = White blood cells

Adapted from: Smolensky MH, et al. Biological Rhythms, Drug Delivery, and Chronotherapeutics. In: Siepmann J, Siegel RA, Rathbone MJ, eds. *The Fundamentals of Drug Delivery.* New York: Springer; 2012;359-444. Smolensky MH, Peppas NA. Chronobiology, drug delivery, and chronotherapeutics. *Adv Drug Deliv Rev* 2007;59:828-851.

FIGURE 2. Peak time occurrence during 24 hours of common acute life-threatening events or worst symptoms of prevalent chronic medical conditions[56]



The entries around the 24-hour circular clock indicate the approximate time of greater risk of occurrence of acute life-threatening (morbid and mortal) events, the most severe manifestation or exacerbation of signs and symptoms of various chronic medical conditions, and acute infectious and other nonserious medical ailments in individuals who ordinarily adhere to a routine of diurnal activity and nighttime sleep. The times of greatest risk are approximate, varying to some extent between morning and evening chronotypes, i.e., larks and owls. The circadian timing and dose strength of certain pharmacotherapies may alter the designated time patterns. Time is shown in military format (i.e., 00:00 = midnight; 06:00 = 6 AM; 12:00 = noon; 18:00 = 6 PM), and the sleep span (approximately 22:30 to 06:30) and waking span (approximately 06:30 to 22:30) are indicated by the darkened and blue bands of the circle, respectively, and the presumed approximate times of breakfast, lunch, and dinner of the subjects in the reported studies are depicted.

AMI = Acute myocardial infarction; ASPD/DSPD = Advanced/Delayed sleep phase disorder; COPD = Chronic obstructive pulmonary disease; SCD = Sudden cardiac death; SIDS = Sudden infant death syndrome

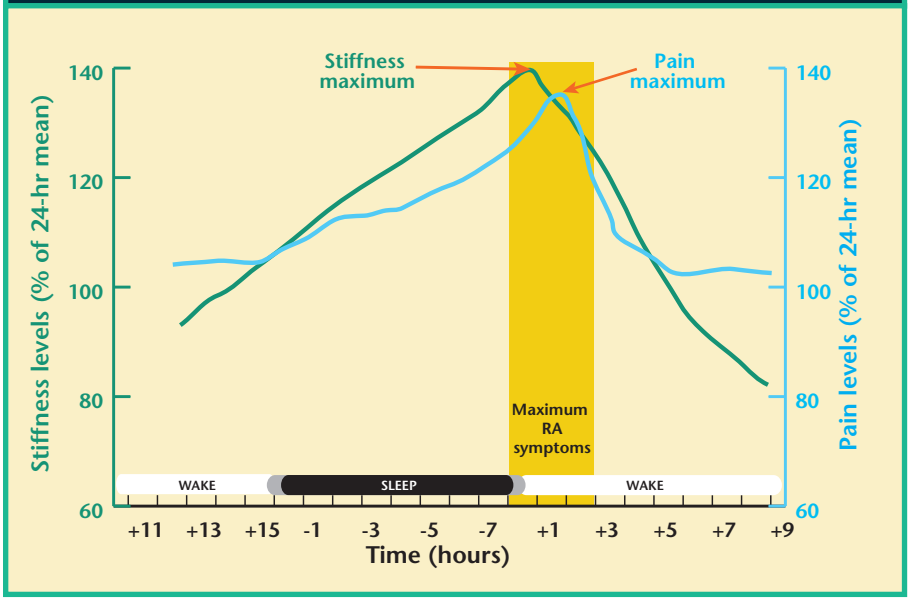
Adapted from Smolensky MH, Siegel RH, Haus E, Hermida R, Portaluppi F. Biological Rhythms, Drug Delivery, and Chronotherapeutics. In: Siepmann J, Siegel RA, Rathbone MJ, eds. *The Fundamentals of Drug Delivery.* New York: Springer; 2012;359-444.

interactions of the many rhythms extending from the molecular to organismic level.[51] Less than optimal alignment of the biologic time structure—termed "internal desynchronization"—can lead to dysfunction and disease.[51-53] Conversely, under certain circumstances, organic disease can cause rhythmic disturbances that further contribute to disease severity and disability.[51]

Circadian rhythms are widely studied and are critically significant to clinical medicine (**Figure 1**).[51-56] Circadian rhythms are kept in step ("synchronized") to periodic environmental phenomena by the 24-hour light-dark cycle, and less so by non-photic cyclic phenomena, such as the time of food uptake, social routine, and physical exercise.[51-53] In daily life, circadian rhythms determine the rhythmically varying degrees of cognitive function and physical strength and dexterity, resulting in predictable timing of best and worst work performance and efficiency.[52;53] Overall, the most important time cue that determines the staging of human circadian rhythms is the customary activity in light/sleep in darkness 24-hour routine. However, not all persons are diurnally active (e.g., those who work nights and rotating shifts), and the circadian rhythms of these individuals are differently staged and specific to the activity-sleep 24-hour pattern adopted. Thus, the physician's knowledge of the typical activity-rest 24-hour pattern of a given patient informs the staging of circadian rhythms of disease activity and the optimal timing of therapy. To help illustrate this, Figures 3-5 do not designate time-of-day clock hours, but instead designate time in terms of hours into the sleep and awake spans, which can be generalized to persons who keep relatively consistent schedules.

Of particular relevance to clinical medicine is the knowledge that the body's 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 exacerbation of chronic medical conditions (e.g., allergic rhinitis, asthma, OA, and RA, among many others) (**Figure 2**).[51;54;56;57] Body rhythms can also significantly affect responses

FIGURE 3. Circadian rhythm of symptoms of RA



The data, extrapolated from Straub et al and Kirwan et al[58;64], are expressed relative to the postulated sleep-wake routine of the RA subjects to emphasize that the 24-hour pattern of RA symptoms are circadian-rhythm dependent rather than time-of-day-dependent. The RA symptoms of pain and stiffness increase markedly in intensity during the latter half of the sleep span, and are worse upon awakening. Temporal changes in symptoms intensity self-scored by VAS are shown as percentages of the respective 24-hour group mean value.

The black bar along the horizontal axis represents the postulated approximate 8-hour sleep period, and the white bars represent the approximate 16-hour wake period. Time is shown as hours after waking (positive numbers) and hours after falling asleep (negative numbers). The yellow column represents the time of maximum RA symptoms.

VAS = Visual analog scale

of patients to diagnostic tests and medications.[54]

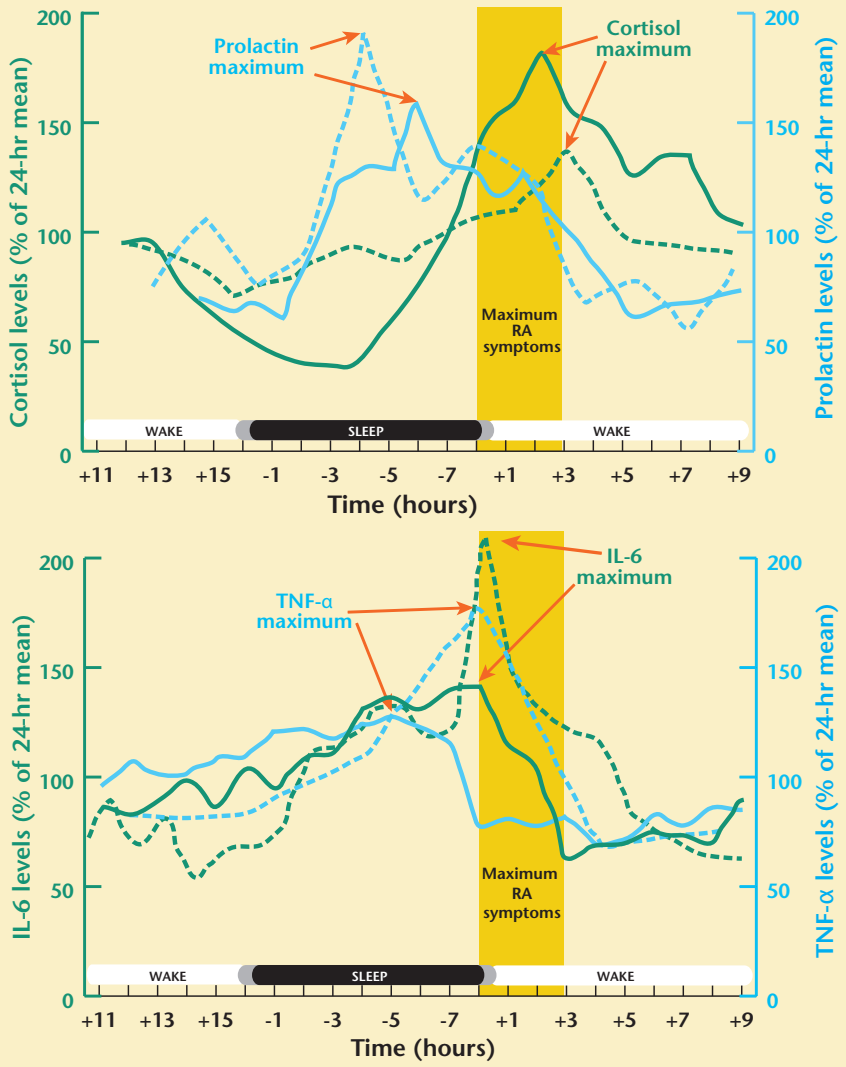
A circadian pattern of symptoms in typically day-active persons with RA—which include stiffness, joint swelling, and pain that are worse, or present only, in the morning than in the evening—is a well-known feature of RA (**Figure 3**).[51;58-62] Morning stiffness and pain can impair function and have considerable economic consequences in terms of employment and disability.[61;62] Most importantly, the morning symptoms—lasting for several hours in some patients—can severely affect patients' QOL. Understanding the underlying pathophysiology of the overt circadian patterning of symptoms has led to the development of chronotherapeutic* approaches of different classes of anti-inflammatory and pain medications, both to improve RA outcomes and to temper or even avert AEs.[51;59;60;63]

The circadian time structure plays a critical role in the pathologic mechanisms that give rise to the observed day-night differences in RA disease activity.[51;58-61] Circadian rhythms in pro-inflammatory cytokines, such as interleukin (IL)-6 and tumor necrosis factor (TNF)-α, are modulated by neuroendocrine rhythms, particularly those of cortisol, epinephrine, growth hormone (GH), melatonin, prolactin, and endorphin.[51;60;61] The pro-inflammatory hormones prolactin, GH, and melatonin peak during sleep and favor inflammatory immune responses and production of pro-inflammatory cytokines. In healthy subjects, production of pro-inflammatory cytokines is maximal during the middle of the sleep period.[51] However, in RA patients, the peak time of pro-inflammatory cytokines seems to shift somewhat toward the end of the sleep span, with markedly elevated peak concentration of TNF-α and IL-6 found in most studies at around wake-up time.[51;58;60]

In healthy diurnally-active subjects, the 24-hour pattern of circulating cortisol is characterized by a prominent early morning peak, which favors strong anti-inflammatory action by suppression of pro-inflammatory cytokines and their effects, declining concentrations during daytime activity, and a daily "quiet period" during the evening and early night (sleep) hours (**Figure 4**).[51;58;64] The cortisol circadian rhythm of RA patients with low or moderate disease activity remains normal; nonetheless, during sleep, levels of the anti-inflammatory endogenous cortisol and other anti-inflammatory mediators are insufficient to counteract the rise in inflammatory agonists at this time.[51;58;63-65] In diurnal RA patients with high disease activity, cortisol concentrations tend to be elevated, yet without sufficient effect to counter the pathologic remodeling of affected tissues.[51;58] This is particularly the case during the late night and early morning when plasma cortisol level, due to its circadian variation, is markedly reduced and RA disease activity is increased, largely attributable to circadian peaks in IL-6, TNF-α, and other inflammatory cytokines (**Figure 4**).[51;58] Thus, the temporal variation in RA symptoms, with the characteristic morning joint pain, stiffness, and functional disability that is typical for most patients who are ordinarily diurnally active, results in large part from the predictable-in-time (i.e., circadian rhythm-dependent) differences in the circulating concentration of the anti-inflammatory hormone cortisol relative to the predictable-in-time (i.e., circadian rhythm-dependent) differences in key disease-exacerbating and pro-inflammatory cytokines.[51;58;60]

*Chronotherapeutics = The judicious timing of conventional or special drug-release therapeutic interventions to align drug peak and trough concentrations to specific circadian rhythm markers in order to optimize the desired pharmacologic effects and/or minimize or avoid undesirable drug AEs.

FIGURE 4. Circadian variation of hormones (cortisol and prolactin) and pro-inflammatory cytokines (TNF-α and IL-6) in patients with active RA (broken lines) and clinically healthy adults (solid lines)



The data, extrapolated from Straub et al and Kirwan et al[58;64], are expressed relative to the postulated sleep-wake routine of the RA subjects to emphasize that the high amplitude 24-hour pattern of the depicted hormones and cytokines are circadian-rhythm dependent rather than time-of-day dependent. Temporal changes of each variable during the 24 hours are expressed as percentages of the respective 24-hour mean value.

Broken lines indicate patients with active RA; solid lines indicate healthy subjects.

The black bar along the horizontal axis represents the postulated approximate 8-hour sleep period, and the white bars represent the approximate 16-hour wake period. Time is shown as hours after waking (positive numbers) and hours after falling asleep (negative numbers).

The yellow column represents the time of maximum RA symptoms.

IL-6 = Interleukin-6; TNF-α = Tumor necrosis factor-α

7 Chronotherapy of RA is facilitated by the development of low-dose delayed-release (DR) prednisone

Chronotherapy is the timing of therapeutic interventions in order to align drug peak and trough concentrations to specific circadian rhythm markers as a means to optimize treatment outcomes and/or potentially minimize or avoid AEs.[51;54;63;66] It entails the delivery of medications, either by the judicious timing of conventional or special drug-release systems, with respect to circadian rhythms of disease activity, symptom intensity, and patient tolerance.[51] For RA, the circadian periodicity of IL-6 is an important target of low-dose GC chronotherapy to reduce morning RA symptoms, functional disability, and possibly slow the progression of disease.[51;58;60;64]

Chronotherapy is not a new concept in rheumatology—over the past 60 years, several NSAIDs, GCs, and DMARDs have been trialed as chronotherapies in the United States, Europe, and Asia.[51] In the 1950s, clinical appreciation of the circadian organization of the hypothalamic-pituitary adrenal (HPA) axis began to influence the design of treatment schedules involving GCs to minimize risk of adrenal suppression and improve outcomes.[48;51] In the 1960s, researchers established that the risk of HPA suppression from GC administration was lowest by an once-a-day morning dosing strategy.[48;51;67-69] However, this may not be the right time to take GCs to best control the symptoms and pathology of arthritic disease.[48] In the 1980s, researchers—now utilizing low-dose GCs—began to explore whether administration in the evening or at bedtime, before the peak of pro-inflammatory cytokines, such as IL-6, occurs is more effective than when administered in the morning upon waking in controlling morning pain and stiffness.[48;51;70;71] In one study, low-dose prednisolone* given at night resulted in a significantly shorter duration of morning stiffness than did an equivalent dose given in the morning.[71] In the other study, the morning and evening prednisolone treatment schedules were equally effective.[70]

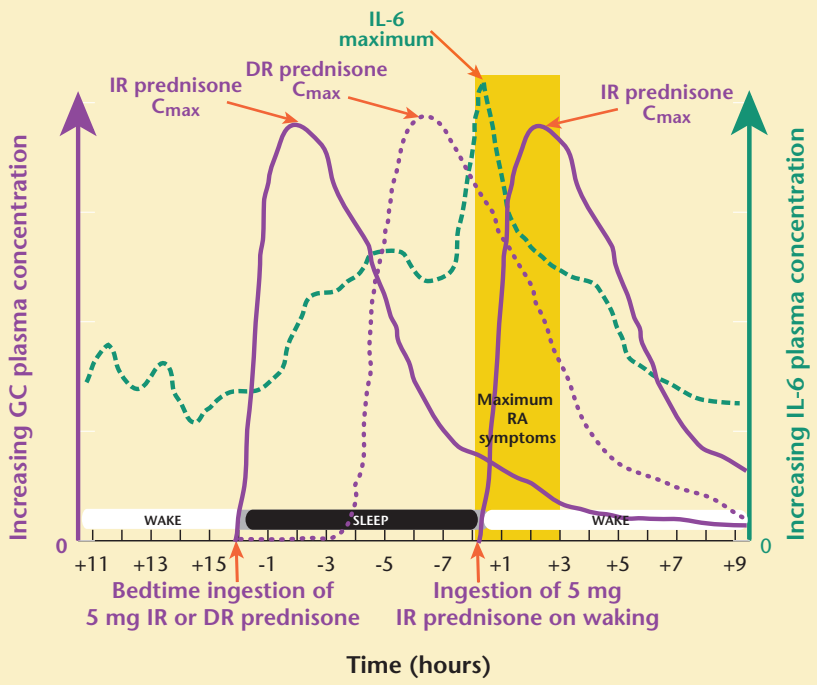
In 1997, researchers examined whether administration of low-dose GCs in the middle of the sleep span prior to the exacerbation of disease and inflammatory activity, signaled by the circadian rise of plasma IL-6 concentration, improves management of RA.[51;72] Groups of ordinarily diurnally active patients with RA were randomized to low-dose (5 or 7.5 mg) immediate-release (IR) prednisolone at either 2 AM (using alarm clocks to awaken participants from nighttime sleep) or 7:30 AM (after spontaneous awakening in the morning from nighttime sleep).[51;72] Peak plasma concentrations of IR prednisolone occur 1 to 3 hours after oral administration.[73] Administration of low-dose GCs at 2 AM exerted a significant beneficial effect on duration of morning stiffness, joint pain, and joint indices ($P<.001$ in all cases).[72] In contrast, administration at 7:30 AM produced no significant improvements in these variables, except for morning stiffness ($P<.05$).[72] Patients' self-assessment of the global effect of 5 days of the two different IR prednisolone treatment-time schedules, based upon a five-grade scale, was scored "good-excellent" (score 3.3) in the 2 AM group, but only "poor-fair" (score 1.6) in the 7.30 AM group ($P<.01$).[72] The morning serum concentrations of IL-6 decreased in both treatment-time groups, but to a greater extent in the 2 AM ($P<.01$) than in the 7.30 AM group ($P<.05$).[72] These results suggest that proper circadian timing of GCs, i.e., that result in peak drug concentrations at approximately the middle of the nocturnal sleep span, may exert preventive, disease-altering effects.[51;60;63;64;72;73] However, long-term adherence to a therapeutic regimen that entails patients to awaken every night at 2 AM is likely to be very poor since it is impractical and inconvenient.[60;61;63;64;73]

This chronotherapeutic approach has now been facilitated by the development of a novel low-dose DR prednisone tablet system.[47;58-61;63;64;74-77] An inactive tablet shell surrounding the IR prednisone medication delays its systemic release for approximately 4 hours after ingestion, which is triggered by penetration of water through this shell.[47;51;59;64] Taken at bedtime (approximately 10 PM) by normally diurnally active RA patients, this formulation delivers peak or near peak prednisone plasma concentrations at approximately 2 AM, so a sufficient drug level is achieved when IL-6 normally begins its rise (**Figure 5**); the end effect is reduction in IL-6 production and plasma and tissue concentrations, resulting in better control of morning RA symptoms and with low risk of HPA suppression and other AEs.[47;51;58-60;63;64;75] The pharmacokinetics of DR prednisone are unaffected once released, with absorption, distribution, and elimination comparable with IR prednisone.[47;78-80] There are no apparent detrimental consequences of the bedtime-dose of DR prednisone on sleep quality and quantity.[81] Data from two large clinical trials—Circadian Administration of Prednisone in Rheumatoid Arthritis (CAPRA)—confirmed that optimizing the timing of peak GC levels in relation to the circadian rhythm of provocative cytokine mediators, in particular IL-6, improves the benefit of long-term low-dose GC treatment, with a significant reduction in morning joint stiffness, in addition to other therapeutic effects described for conventional IR prednisone, without affecting HPA axis suppression.[47;49;50;63;74;75;82]

CAPRA-1 assessed the efficacy and safety of DR prednisone compared with IR prednisone.[49] In this 12-week, multicenter, randomized, double-blind trial, 288 diurnally-active patients with active RA were randomly assigned to either bedtime DR prednisone (n=144) or to morning-time IR prednisone tablet therapy (n=144).[49] Before study, patients were taking GCs for at least 3 months, with a stable daily dose of 2.5 to 10 mg prednisone for at least 1 month before randomization.[49] Patients also received DMARDs (unless not tolerated, in which case inclusion without a DMARD was allowed) for at least 3 months before the study, with a stable dose for at least 1 month before screening.[49] Biologic drugs were not allowed during the 4 months before inclusion.[49] DR prednisone taken at bedtime (approximately 10 PM), with prednisone release delayed roughly by 4 hours (at approximately 2 AM) following ingestion, was compared with morning, between 6 AM and 8 AM, administration of IR prednisone.[49] After randomization, patients continued with the study drug on the same prednisone dose that they had taken before study inclusion or received a prednisone dose that was equivalent to their previous GC dose, i.e., ranging from 3 to 10 mg prednisone daily.[49]

*Prednisolone is the biologically active metabolite of prednisone, the precursor medication.

FIGURE 5. Optimized pharmacokinetic drug profile of DR prednisone bedtime chronotherapy (dotted line) versus IR prednisone at bedtime or upon awakening (solid line) to improve RA symptoms



This simplified schematic is designed to illustrate how optimizing the pharmacokinetic profile of GCs by timing medication peak GC levels in relation to the circadian rhythm of the pro-inflammatory cytokine IL-6 can improve the ability of GCs to reduce RA symptoms.

The circadian variation of IL-6 plasma concentrations (broken green line) in patients with active RA (data are extrapolated from Kirwan et al and Straub et al[58;64]) represents the temporal relationship between elevated levels of pro-inflammatory cytokines and exacerbated disease symptoms upon awakening (pain and stiffness data are modified from Straub et al and Cutolo et al[58;60]) in RA patients without GC treatment. The rise during sleep of pro-inflammatory cytokines initiates an inflammatory cascade and pathophysiologic processes that lead to RA disease symptoms.

To simplify the comparison of the IR and DR GC pharmacokinetics, the precursor drug prednisone is illustrated, although the original studies from which IR pharmacokinetic data were extrapolated analyzed the active metabolite, prednisolone (English et al[78]). The pharmacokinetics of IR prednisone (solid purple line) show that the traditional approach of ingesting IR prednisone upon waking is too late to optimally prevent pain and stiffness—the peak concentration of IL-6 has already occurred and the signs and symptoms have already manifested. Ingesting IR prednisone at bedtime results in a C_{max} that occurs too early to optimally suppress the ascending curve of IL-6, and so is unable to appreciably attenuate the cascade of pro-inflammatory events that results in pain and stiffness upon awakening.

Ingesting DR prednisone (dotted purple line: pharmacokinetic values are extrapolated from the DR prednisone prescribing information[79]) at bedtime is followed by a 4-hour delay until the prednisone is released, with a subsequent pharmacokinetic profile and total drug exposure almost identical to IR prednisone. Because of the 4-hour delay, the prednisone levels are synchronized to reach C_{max} just prior to the increase of IL-6 production that occurs in the absence of GC bedtime chronotherapy, and so optimally inhibit the circadian increase in pro-inflammatory cytokines that occurs during sleep, thereby counteracting the inflammatory cascade and pathophysiologic processes that lead to the observed clinical signs and symptoms of RA. This chronotherapeutic approach of bedtime ingestion of DR prednisone targets known pathophysiologic rhythms to attain clinical improvement in the signs and symptoms of RA that is superior to ingesting IR prednisone at bedtime (too early to suppress IL-6) or upon waking (too late to suppress symptoms that are already established).

The dotted purple line indicates DR prednisone; solid purple lines indicate IR prednisone.

The black bar along the horizontal axis represents the postulated approximate 8-hour sleep period, and the white bars represent the approximate 16-hour wake period. Time is shown as hours after waking (positive numbers) and hours after falling asleep (negative numbers).

The yellow column represents the time of maximum RA symptoms.

C_{max} = Maximal drug concentration; DR = Delayed-release; GC = Glucocorticoid; IL-6 = Interleukin-6; IR = Immediate-release

After 12 weeks of treatment, the mean relative shortening in the duration of morning stiffness of the joints from baseline was significantly improved with bedtime chronotherapy of DR prednisone than with morning administration of conventional IR prednisone (-22.7% vs. -0.4%; P=.045).[49] Patients in the DR prednisone group experienced a mean reduction in the duration of morning stiffness of 44.0 minutes compared with baseline.[49] The absolute difference between the treatment groups was 29.2 minutes in favor of DR prednisone (P=.072).[49] Improvement in morning joint stiffness with DR prednisone was evident after 2 weeks of treatment, with a difference of 10% between the 2 treatment groups.[49] This difference increased with continued treatment and plateaued at 38% from week 7 until the end of the 12-week treatment period.[49] The safety profile of the DR prednisone and IR prednisone did not differ.[49] Occurrence of AEs that led to premature discontinuation of study treatments was similar between the two modes of therapy—12 patients receiving bedtime DR prednisone and 10 patients receiving morning-time IR prednisone.[49]

The long-term effects of low-dose bedtime chronotherapy with DR prednisone on the HPA axis were also assessed as part of the CAPRA-1 study.[82] Over 12 months (a 3-month double-blind, active-controlled phase and 9-month open-label extension when dose changes were allowed for DR prednisone), corticotrophin-releasing hormone tests were performed at baseline on prestudy morning-time IR prednisone, after the 3-month double-blind phase on either morning-time IR prednisone or bedtime DR prednisone, and after the 9-month open-label extension on bedtime DR prednisone.[82] There was no indication that changing treatment—from morning-time conventional IR prednisone to bedtime DR prednisone

chronotherapy—increased the risk of HPA axis insufficiency, or deterioration of preexisting adrenal suppression resulting from previous GC therapy.[82]

CAPRA-2 was a 12-week, double-blind, placebo-controlled study, with patients who had active RA randomized to receive 5 mg DR prednisone (n=231) or placebo (n=119) once daily in the evening (with or after the evening meal), in addition to their existing stable DMARD treatment.[50] The primary endpoint was the percentage of patients achieving a 20% improvement in RA signs and symptoms according to ACR criteria (an ACR20 response) at week 12.[50] Changes in morning pain, duration of morning stiffness, 28-joint Disease Activity Score (DAS28*), and health-related QOL were also assessed.[50] The addition of bedtime DR prednisone chronotherapy versus placebo at bedtime to the DMARD-treated patients produced higher ACR20 (48% vs. 29%, P<.001) and ACR50 (22% vs. 10%, P<.006) response rates, and greater median relative reduction from baseline in the duration of morning stiffness (55% vs. 35%, P<.002) at week 12.[50] In addition, significantly greater reductions in the severity of RA (DAS28) (P<.001) and fatigue (Functional Assessment of Chronic Illness Therapy-Fatigue Score) (P<.003), and greater improvement in physical function (36-item Short-Form Health Survey Score) (P<.001) were observed at week 12 for DR prednisone chronotherapy compared with placebo.[50;83] The incidence of treatment-related AEs was similar for DR prednisone (7.8%) and placebo (8.4%).[50] The authors concluded that: "The results of this study demonstrate that even at a dose considered to be below substitution levels, DR prednisone chronotherapy is highly effective and well tolerated in patients with RA, providing rapid relief of symptoms and, particularly, improving morning function. Further, longer-term studies are warranted to determine the dose and strategy that optimises the benefit-to-risk ratio for MR prednisone in the management of RA."[50]

A 9-month observational study conducted under conditions of normal clinical practice assessed the functional ability of patients with RA treated with bedtime DR prednisone chronotherapy without restrictions on the DR prednisone dose or use of concomitant therapy; it included a total of 1,733 patients, with baseline and study-end data derived from 1,185 patients.[84] The mean total Questionnaire on Activity Status (QAS) score (ranging from 0 [severely impaired] to 100 [completely unimpaired]) improved significantly after 9 months of treatment with bedtime DR prednisone chronotherapy, from 54.3 to 70.2 (P<.001).[84] There were also significant improvements in all three QAS dimensions— performance of occupational (66.6 to 78.9, P<.001) and household duties (55.6 to 70.9, P<.001), as well as leisure activities (51.6 to 69.4, P<.001).[84] Therefore, the functional ability of the patients with RA improved significantly from baseline after 9 months of treatment with bedtime DR prednisone chronotherapy in this observational study.[84]

Also relevant to normal clinical practice was another 4-month, open-label, observational study that included 950 patients with RA.[85] They had been treated with DMARDs and low-dose GCs, and were switched from morning-time IR prednisone or 6-methyl (6M)-prednisolone to bedtime DR prednisone chronotherapy—at a dose determined by the treating physician to be similar to that of their previous GC.[85] Dose adjustments of the bedtime DR-prednisone chronotherapy, analgesic medications, and DMARDs were allowed at any time-point during the study by the physician. A total of 30 patients withdrew from the study—24 switched back to their previous oral GC and six were unwilling to continue GC treatment.[85] Among the remaining 920 patients who completed the 4-month observation after switching to bedtime DR prednisone chronotherapy, the duration of morning stiffness, the maximal intensity of pain, the patient and physician global assessment of disease activity scores, and DAS28 scores all significantly decreased between the initial and final 4-month visits.[85]

These findings require further confirmation in long-term observational studies, but they do support the importance of the choice of GC administration time and pattern of release in relation to the circadian rhythm in disease activity in determining its long-term benefit in patients with RA.[47] Future trials should address lower doses of bedtime DR prednisone chronotherapy to determine if fewer or less severe AEs can be demonstrated in comparison to morning-time IR prednisone, while providing similar or superior efficacy. In recent years, the bedtime DR low-dose prednisone chronotherapy has been approved for use in 16 European countries, Australia, and Israel, and in 2012 was approved in the United States to treat RA.[47;51] DR low-dose prednisone was also approved in the United States to treat other rheumatologic conditions such as PMR and psoriatic arthritis, as well as certain allergic, dermatologic, endocrine, gastrointestinal (GI), hematologic, ophthalmologic, nervous system, renal, respiratory, specific infectious diseases or conditions, certain neoplastic conditions, and organ transplantation.

Other Examples of Chronotherapy in RA

Additional examples of the application of chronotherapies in clinical medicine can be found in Smolensky et al, 2012.[56] Two of these chronotherapies related to RA are described below.

*DAS28 is a composite score based on tender and swollen joint counts (28 joints), the patient's global assessment of disease activity (VAS: 0=not active, 100=extremely active), and erythrocyte sedimentation rate (ESR)

NSAID Chronotherapy of RA

Chronotherapy research on other drugs used to treat RA began in the 1980s, when researchers discovered that evening dosing of the NSAID flurbiprofen to patients with RA was more effective in alleviating morning pain and stiffness than morning or other dosing times.[86] In the years thereafter, various controlled-release NSAIDs were evaluated for administration-time differences in their palliative effects.[51;87;88] Investigators are currently testing the efficacy of bedtime chronotherapeutic delivery of DR indomethacin formulations, which have a lag time (4 to 6 hours) before drug release.[89;90]

DMARD Chronotherapy of RA and Cancer

Some DMARDs, such as cyclophosphamide and methotrexate that are also used as cancer therapies, are known to induce AEs that are not only dose-dependent, but also circadian time-dependent.[51;91-94] The tolerability of cancer chemotherapy varies up to several fold as a function of the circadian timing of drug administration. The greatest antitumor efficacy of single-agent or combination chemotherapy usually corresponds to the delivery of anticancer drugs near their respective biologic times of best tolerability.[91-94]

Selecting an appropriate treatment time of these and other DMARDs may improve patient tolerance and therapeutic outcome in RA.[51] An initial, small-scale RA study suggests evening scheduling of methotrexate immediately prior to the rise of the cytokine TNF-α significantly enhances drug effectiveness and patient tolerance.[51;95]

Safety issues associated with GCs, including bedtime DR prednisone chronotherapy

Low-dose bedtime DR prednisone chronotherapy had a similar safety profile as low-dose morning-time IR prednisone in the CAPRA clinical trials.[49] PCPs should be aware of important safety information for GCs, including DR prednisone:[79]

- Contraindications
  - Known hypersensitivity to prednisone or any excipients in the DR formulation
- Warnings and precautions
  - Prednisone can cause HPA axis suppression, Cushing's syndrome, and hyperglycemia. Monitor patients for these conditions with chronic use. Taper doses gradually for withdrawal after chronic use.
  - Prednisone may increase susceptibility to new infection and increase risk of exacerbation, dissemination, or reactivation of latent infection. Prednisone may mask signs and symptoms of infection. The rate of infectious complications increases with increasing doses of prednisone.
  - Prednisone can cause elevated blood pressure, salt and water retention, and hypokalemia. Monitor blood pressure and sodium and potassium serum levels. Prednisone should be used with caution in patients with a history of recent myocardial infarction, congestive heart failure, hypertension, or renal insufficiency.
  - There is an increased risk of GI perforation in patients with certain GI disorders. Prednisone may mask signs and symptoms of GI perforation.
  - Prednisone use may be associated with behavioral and mood disturbances, including euphoria, insomnia, mood swings, personality changes, severe depression, and psychosis. Existing conditions may be aggravated.
  - Prednisone use may lead to inhibition of bone growth in children and adolescents and the development of osteoporosis at any age. Give special consideration to patients at increased risk of osteoporosis (e.g., postmenopausal women) before initiating prednisone therapy, and bone density should be monitored in patients on long-term prednisone therapy.
  - Prolonged use of prednisone may result in cataracts, infections, and glaucoma. Monitor intraocular pressure if prednisone therapy is continued for more than 6 weeks.

- Do not administer live or attenuated vaccines to patients receiving immunosuppressive doses of prednisone.
- Long-term use of prednisone can have negative effects on growth and development in children. Monitor pediatric patients on long-term prednisone therapy.
- Fetal harm can occur with first trimester use of prednisone. Apprise women of potential harm to the fetus.

- Adverse reactions
  - Common adverse reactions for prednisone include fluid retention, alteration in glucose tolerance, elevation in blood pressure, behavioral and mood changes, increased appetite, and weight gain.
- Drug interactions
  - Anticoagulant agents: May enhance or diminish anticoagulant effects.
  - Antidiabetic agents: May increase blood glucose concentrations. Dose adjustments of antidiabetic agents may be required.
  - CYP 3A4 inducers and inhibitors: May, respectively, increase or decrease clearance of corticosteroids, necessitating dose adjustment.
  - Cyclosporine: Increase in activity of both cyclosporine and corticosteroid when administered concurrently. Convulsions have been reported with concurrent use.
  - NSAIDs, including aspirin and salicylates: Increased risk of GI side effects.

9 Patient education is an important component when managing patients with RA

Treatment of RA should be based on a shared decision between the patient and provider.[12] This requires discussion of the goals of treatment, management plans, and reasons for the recommended approaches.[12] The importance of early initiation of treatment to prevent disease progression and irreversible joint damage should be stressed.

In clinical practice, patients often voice concerns about initiating treatment with GCs, and many hold strong views about the use of these drugs.[96] Patient attitudes towards oral GC therapy in RA are therefore important and should be addressed.[96] One study found a significant portion of patients with RA (68%) were unwilling to consider treatment with oral GCs, although older, more disabled patients with more active disease, were more likely to accept it, which may have implications for GC use in early disease.[96] When asked about the benefits of GC treatment in RA, the majority of patients did not know whether they were helpful, but most patients were able to list several AEs of GC treatment, with weight gain and bloating most commonly cited.[96] It is important that patients' decisions regarding the acceptance of GC therapy be influenced by a balanced discussion with clinical staff, rather than preconceived ideas, which may be informed by experiences of individuals known to them who have received GCs (quite possibly high-dose GC therapy), or information gathered from the Internet or the lay press.[96;97]

Patients should be informed of the following information before initiating therapy with bedtime DR prednisone chronotherapy and periodically during the course of ongoing therapy:[79]

- Patients should be warned not to discontinue the use of DR prednisone abruptly or without medical supervision, to advise any medical attendants that they are taking it, and to seek medical advice at once should they develop fever or other signs of infection. Patients should be told to take DR prednisone exactly as prescribed, follow the instructions on the prescription label, and not stop taking DR prednisone without first checking with their healthcare providers, as there may be a need for gradual dose reduction.
- Patients should discuss with their physician if they have had recent or ongoing infections or if they have recently received a vaccine.
- Persons who are on immunosuppressant doses of GCs should be warned to avoid exposure to chickenpox or measles. Patients should also be advised that if they are exposed, medical advice should be sought without delay.

- A number of medicines can interact with DR prednisone. Patients should inform their healthcare provider of all the medicines they are taking, including over-the-counter and prescription medicines (such as phenytoin, diuretics, digitalis or digoxin, rifampin, amphotericin B, cyclosporine, insulin or diabetes medicines, ketoconazole, estrogens including birth control pills and hormone replacement therapy, blood thinners such as warfarin, aspirin or other NSAIDs, barbiturates), dietary supplements, and herbal products. If patients are taking any of these drugs, alternate therapy, dosage adjustment, and/or special tests may be needed during the treatment.
- Patients should take DR prednisone before bedtime with or following a light snack.
- Patients should be advised not to break, divide, or chew DR prednisone tablets.
- Patients should be advised of common adverse reactions that could occur with DR prednisone use to include fluid retention, alteration in glucose tolerance, elevation in blood pressure, behavioral and mood changes, increased appetite, and weight gain.

A team approach between PCP and rheumatologist can improve the care of patients with RA

Researchers who explored the factors that are related to PCPs' diagnosis and management of RA, and what may present barriers to recommended RA care, concluded that it is prudent to develop ways in which rheumatologists can work more closely with PCPs to manage RA using a "team" approach.[9] In areas with poor access to a rheumatologist, better communication can help shift some responsibility from the rheumatologist to the PCP, thus potentially reducing the number of office visits to the rheumatologist.[7] For patients with RA stabilized on DMARDs, who have well-controlled symptoms, long-term primary-care based supervision with annual specialist review combined with urgent specialist access when the need arises may be sufficient.[98]

In rural areas with a lack of access to rheumatologists, there may be potential to use telemedicine initiatives. For example, in New Mexico, Project Extension for Community Healthcare Outcomes is a program that is designed as a consultative link between specialists and community clinicians throughout the state in order to provide rheumatology consultations. It also provides training to family doctors, physician assistants, and nurse practitioners at distant sites to treat uncomplicated rheumatologic sequelae that do not require critical care, or to become experts in the care of these conditions and serve as a local resource for rheumatologic disease care.[99;100] Other telemedicine initiatives include the Georgia Telemedicine Network, which links rural patients with specialist physicians, including rheumatologists, while the Oregon Health & Science University Rheumatology Telemedicine Clinic uses computer technology to allow face-to-face evaluation and treatment of rheumatology patients attending the Wellness Center on the Warm Springs Reservation, located more than 100 miles from rheumatologist specialists in Portland. Such models of telemedicine improve access to healthcare and enable specialists to comanage patients with complex diseases.

While bridging therapy is valuable, it is by definition not designed to replace a rheumatology consult and treatment with a DMARD. PCPs should ensure that patients maintain their appointment for follow-up despite improved symptoms. The disconnect between improvement of symptoms and progression of structural damage is well-established; thus, treating to target goals with DMARDs remains the gold standard. When requesting a rheumatology consult, the PCP should provide complete details of the patient's history, physical examination, laboratory test results, scores using patient-report instruments, and any radiographs.

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Abbreviations

ACPA anti-citrullinated protein antibody

ACR American College of Rheumatology

ACR20 20% improvement in RA signs and symptoms according to ACR criteria

ACR50 50% improvement in RA signs and symptoms according to ACR criteria

ACTH adrenocorticotropic hormone

AE adverse effect

AMI acute myocardial infarction

ASPD advanced sleep phase disorder

CAPRA Circadian Administration of Prednisone in Rheumatoid Arthritis

C_{max} maximal drug concentration

COPD chronic obstructive pulmonary disease

CRP C-reactive protein

CYP cytochrome P450 enzyme

DAS28 28-joint Disease Activity Score

DMARD disease-modifying antirheumatic drug

DR delayed-release

DSPD delayed sleep phase disorder

ESR erythrocyte sedimentation rate

EULAR European League Against Rheumatism

FEV_1 forced expiratory volume in 1 second

FSH follicle stimulating hormone

GC glucocorticoid

GH growth hormone

GI gastrointestinal

HAQ Health Assessment Questionnaire

HF heart failure

HPA hypothalamic-pituitary adrenal

HTN hypertension

IL-6 interleukin-6

IR immediate-release

IU International Unit

LH luteinizing hormone

MBDA multi-biomarker disease activity

MDHAQ Multidimensional Health Assessment Questionnaire

NSAID nonsteroidal anti-inflammatory drug

OA osteoarthritis

PCP primary care physician

PEF peak expiratory flow

PMR polymyalgia rheumatica

Pt Global VAS patient global assessment of disease activity visual analog scale

QAS Questionnaire on Activity Status

QOL quality of life

RA rheumatoid arthritis

RAPID-3 Routine Assessment of Patient Index Data with three measures

RF rheumatoid factor

SCD sudden cardiac death

SIDS sudden infant death syndrome

SLE systemic lupus erythematosus

SMR standardized mortality ratio

TNF-α tumor necrosis factor-α

TSH thyroid stimulating hormone

ULN upper limit of normal

VAS visual analog scale

WBC white blood cells

Glossary

Bridging therapy Utilizing NSAIDs or GCs to bridge the interval before the initiation of DMARDs in patients with RA, and between the initiation of DMARDs and onset of their therapeutic effect, by rapidly controlling inflammation while awaiting the benefits of slow-acting agents.

Chronobiology The science of investigating and objectively quantifying phenomena and mechanisms of the biologic time structure, including the rhythmic manifestations of life. Term derived from: Chronos (time), bios (life), and logos (science).

Chronotherapy The judicious timing of conventional or special drug-release therapeutic interventions to align drug peak and trough concentrations to specific circadian rhythm markers in order to optimize the desired pharmacologic effects and/or minimize or avoid undesirable drug AEs.

Chronotypes Human preferences in the timing of sleep and wake (e.g., morning chronotypes or "larks" and evening chronotypes or "owls")

Circadian Relating to biologic rhythms that exhibit a period of oscillation of approximately 24 hours.

Delayed-release dosage forms A type of modified-release dosage form that is designed to delay the release of medication for a set period of time after its administration (i.e., these drug products exhibit a prolonged lag time in quantifiable plasma concentrations). Delayed-release dosage forms differ from extended-release, controlled-release, and sustained-release ones, which are other types of modified-release dosage forms that are formulated to discharge medication at a sustained and controlled rate over an extended period of time following ingestion to maintain a relatively constant drug level during the dosing interval and to enable a reduction in dosing frequency.

Immediate-release dosage forms Dosage forms that discharge medication without delay; quantifiable plasma concentrations occur within a short period of time after ingestion, typically less than 30 minutes.

Infradian Relating to biologic rhythms that exhibit a period of oscillation considerably greater than 24 hours (e.g., several days, months, or year).

Treat-to-target Targeting either low disease activity or remission (as defined by the ACR) in all patients with early RA and established RA by measuring disease activity and adjusting therapy accordingly to optimize outcomes in RA.

Ultradian Relating to biologic rhythms that exhibit a period of oscillation considerably less than 24 hours (e.g., milliseconds to a few hours).

TOP 10 THINGS

RHEUMATOLOGISTS WISH PCPS TREATING RHEUMATOID ARTHRITIS KNEW, WITH A FOCUS ON DISEASE CHRONOBIOLOGY AND CHRONOTHERAPY

PharmaCom Group, Inc ◉ 28 First Street, Stamford, CT 06905