# Prednisone chronotherapy

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**ABSTRACT**

*Glucocorticoids (GCs) are widely used in clinical medicine because of their anti-inflammatory and immunosuppressive effects. However, these agents have a considerable potential for adverse effects, especially if used in high doses. The currently most advanced approach to improve the risk-benefit ratio of GCs is low-dose prednisone chronotherapy with modified release (MR) prednisone timing drug release to chronobiological rhythms. In RA, the circadian rhythms of pain, stiffness and functional disability show maximum symptoms in the early morning hours, which is preceded by elevated levels of pro-inflammatory cytokines, in particular interleukin 6. It was hypothesised that preventing the nocturnal rise of pro-inflammatory cytokines by GC therapy is more effective than treating established symptoms in the morning. As waking in the night for tablet intake is impracticable, modified release (MR) prednisone was developed, which releases prednisone approximately four hours after ingestion (i.e. at approximately 2 am if taken at 10 pm bedtime). Data from two large-scale trials in rheumatoid arthritis (RA) (CAPRA-1 and 2) document that MR prednisone has greater efficacy for long-term, low-dose glucocorticoid treatment in patients with RA, with a significant reduction in morning joint stiffness, in addition to all known therapeutic effects with conventional prednisone and a similar safety profile without additional suppression of hypothalamic-pituitary-adrenal (HPA) axis. For patients with RA on low to medium doses of prednisone, especially those who continue to experience a long duration of morning stiffness, MR prednisone appears a valuable additional treatment option.*

## Introduction

Since the discovery of the anti-inflammatory and immunosuppressive effects of cortisone, glucocorticoids (GCs) have been widely used in the treatment of many diseases, including rheumatic diseases such as rheumatoid arthritis (RA), polymyalgia rheumatica and vasculitides, as well as allergic airway conditions, inflammatory bowel diseases, dermatological and other diseases. The overall prevalence of GC use over the past 20 years has been more or less stable (1, 2). As soon as mineralocorticoid-related and numerous other adverse effects (AEs) of GCs became apparent, such as osteoporosis, myopathy, skin atrophy, oedema and glaucoma, new drugs were synthesised with less mineralocorticoid activity but significant higher glucocorticoid potency (3).

In recent years our clinical view of GCs has changed considerably (3). First, low-dose GCs are no longer seen as providing "only" fast relief of inflammation, but also having the capacity to slow radiographic joint damage in early RA (4). Second, the toxicity profile of low-dose GCs was shown to be modest, in contrast to high-dose therapy in RA (5). Guidelines for safe use of GCs and monitoring of AEs have been developed (6, 7). Nevertheless, dose-related AEs of GCs and the risk-benefit ratio remain issues and driving forces for further research (8, 9).

The currently most advanced approach to improve the benefit of GCs is to use low-dose, taking advantage of knowing the chronotherapeutic strategy (3), in addition to possible selective glucocorticoid receptor agonists, nitroso-GCs, liposomal GCs and others. In prednisone chronotherapy, a new modified-release (MR) prednisone delivery system adapts the release of the administered GC to the circadian rhythms of the disease in order to improve efficacy (10). This review briefly summarises the development of chronotherapy with low-dose prednisone in RA and the current evidence for the efficacy and safety of MR prednisone.

## Chronotherapy and the "single morning dose" in GC therapy

The roots of clinical chronobiology date back to the 5th century when

the nocturnal occurrence of asthma was described (11, 12). The concept of chronotherapeutics – *i.e.* timing medication to biological need to optimise beneficial outcomes or to reduce or eliminate adverse effects (11, 13, 14) – was used by Thomas Sydenham [1624–1689], who recommended that opium (laudanum) be dosed late in the evening, rather than in the morning, for optimum narcotic effect (11, 12). Currently, emerging concepts are being explored to design chronotherapeuticals for major chronotherapeutic relevant diseases such as asthma, allergic rhinitis, cardiovascular disorders, rheumatoid arthritis and cancer, and many other conditions (15).

According to Smolensky *et al*. the first "chronotherapy" to be widely applied in clinical practice was the alternate-day morning schedule of glucocorticoids introduced in the 1960s (13, 16). At that time, the timing of GC administration was focused primarily on chronotoxicological aspects (*i.e.* rhythm-dependent differences in the manifestation and severity of adverse effects (17)) – rather than on chrono-effectiveness (*i.e.* rhythm-dependent differences in the magnitude of the desired therapeutic effects (17)).

Administration-time differences in adrenocortical suppression of GC medications have been described since 1956 (13, 18). A series of studies indicated that once-daily ingestion of small to moderate doses of GCs in the morning caused little or no adrenocortical suppression; however, when a part or all of a moderate daily dose of GC was administered later in the day, especially in the evening between dinner and bedtime, the risk of adrenocortical suppression was heightened (18-22). These findings significantly impacted the manner in which GC therapy was prescribed as single-daily or alternate-day morning doses in the following years (13, 16, 18).

## "The nightly dose" – effect on morning stiffness

Despite the practice of the single morning dose, some RA patients required a nocturnal glucocorticoid dose to control morning stiffness (23). Some studies, as early as in 1964, specifically found a nightly prednisolone dose more effective regarding morning stiffness than an equivalent morning dose (24-26). However, other studies described no differences in effectiveness between administration of prednisolone at three different times of day (27).

## Chronobiology of inflammation in RA

In RA, the circadian rhythms of pain, stiffness and functional disability as well as the underlying cyclic variations in hormone levels and cytokine concentrations are well-known phenomena (28). It was demonstrated that the major signs and symptoms in RA, such as pain, inflammation and stiffness, vary with the time of the day, usually with maximum severity in the early morning hours (29-34). Furthermore, it was shown that these clinical symptoms are preceded by elevated levels of pro-inflammatory cytokines, especially of interleukin 6 (IL-6) (28, 35-37), and a causal beyond a temporal relationship was suggested (3, 10, 38).

A hypothesis was generated, based on these considerations, that improved timing of GC administration may help to optimise RA therapy (3, 10), to target IL-6 and other humoral factors as well as cellular reactions involved in RA pathophysiology (39). The rationale for this hypothesis was provided by the following points (3, 10): (i) pain, fatigue, morning stiffness and immobility are important symptoms of RA which significantly affect the patient´s quality of life and the ability to remain gainfully employed (40); (ii) the nightly increase of IL-6 and other pro-inflammatory cytokines is thought to trigger a cascade of events promoting these symptoms (28, 41); (iii) preventing the nocturnal rise of pro-inflammatory cytokines should be more effective than treating established symptoms (28, 42, 43). From this point of view, administration of GCs between 6 am and 8 am was suggested to be suboptimal.

## MR prednisone – formulation

In 1997, Arvidson and co-workers demonstrated that low doses of prednisolone taken at 2 am had significantly better therapeutic effects on duration of morning stiffness, joint pain and morning serum concentrations of IL-6 than equivalent doses taken at 7:30 am after only 5 days of treatment (44). However, a regimen which requires regular waking of the patient at 2 am was considered to be impractical for the therapeutic routine, whereas evening treatment may not be optimal due to the short, 2 hour, half-life of prednisolone (28).

These considerations and observations led to the development of a new modified-release (MR) prednisone tablet formulation, which allows timed release of glucocorticoids 4 hours after oral administration at 2 am (10). The MR prednisone tablet is a "tablet-in-tablet dosage form", which consists of an immediate-release prednisone core tablet surrounded by an inactive outer tablet shell (10). MR prednisone releases prednisone approximately four hours after ingestion, (*i.e.* at approximately 2 am if taken at 10 pm bedtime). Prednisone release is triggered by penetration of gastrointestinal fluid into the tablet shell. The pharmacokinetic profile and total drug exposure (maximum concentration and area under the curve) of 5 mg MR prednisone have been shown to be very similar to those of 5 mg conventional immediate-release prednisone – of course apart from the 4-hour delay (10).

## Efficacy and safety of MR prednisone – the CAPRA-1 study

The efficacy and safety of MR prednisone was investigated in a 3-month, double-blind, double-dummy, controlled clinical study (Circadian Administration of Prednisone in Rheumatoid Arthritis (CAPRA-1)) (10). Altogether, 288 patients with active RA were randomised to receive their current prednisone dose (2.5–10 mg prednisone per day) either as MR prednisone administered at approximately 10 pm or as conventional immediate-release (IR) prednisone administered in the morning. MR prednisone was shown to be clinically superior to the conventional IR preparation with respect to reducing morning joint stiffness, the primary endpoint of this study. This beneficial effect was noted in addition to clinical

control of disease resulting from treatment with conventional prednisone. IL-6 serum concentrations were also significantly decreased by MR prednisone after 3 months of treatment but remained unchanged by IR prednisone. The safety profile did not differ between the two regimens (10).

The CAPRA-1 study was followed by a 9-month, open-label extension, during which all patients were treated with MR prednisone (45). Reduction in morning stiffness duration and IL-6 serum levels was sustained during 12 months of treatment with MR-prednisone, with a reduction from baseline by approximately 50% (45). Similar improvements were observed in patients who switched to MR prednisone in the open-label phase. Furthermore, 37% of all patients were improved according to ACR20 criteria (45). Adverse events did not differ from the known profile of low-dose prednisone.

## Effect of MR prednisone on HPA axis

The hypothalamic-pituitary-adrenal (HPA) axis plays an important role in regulating and controlling immune responses, and dysfunction of the axis has been implicated in the pathogenesis of RA and other rheumatic diseases (28, 36, 46, 47). The influence of prednisone therapy on the HPA axis function remains a matter of concern, particularly for longer treatment duration, as knowledge is rather limited.

In order to investigate the influence of long-term, low-dose chronotherapy with MR prednisone on the HPA axis, corticotrophin releasing-hormone (CRH) tests were performed in a subgroup of 28 patients of the CAPRA-1 study (48). The CRH tests were performed (i) at baseline, (ii) at the end of the double-blind phase, and (iii) at the end of the 9-month open-label extension. There was no indication that changing treatments from IR prednisone to MR prednisone increased the risk of HPA axis insufficiency, or resulted in deterioration of preexisting suppression. In addition, no adverse events that could be attributed to HPA axis insufficiency were observed during the treatment with low-dose MR prednisone for the entire treatment period of 12 months (48).

## MR prednisone *vs*. placebo – the CAPRA-2 study

A second, large-scale, double-blind, placebo-controlled multicentre study (CAPRA-2) was conducted in order to quantify the net effect of low-dose MR prednisone in patients with RA poorly controlled by disease-modifying antirheumatic drugs (DMARDs). In this 12-week study, 350 RA patients were randomised to 5 mg MR prednisone or placebo once daily in addition to their pre-existing DMARD treatment. The ACR20 response rate at 12 weeks was 48% for patients randomised to MR prednisone *versus* 29% for patients randomised to placebo ($p<0.001$). Significant improvements were evident within two weeks of therapy initiation. Improvements in health-related quality of life, in particular physical functioning and fatigue, were also noted, while the safety profile of low-dose prednisone chronotherapy was comparable to that of placebo (unpublished observations). These initial results were presented at the European League against Rheumatism (EULAR) meeting 2010.

## Prednisone chronotherapy in other diseases?

Indications of circadian rhythms are reported in some other rheumatic diseases such as polymyalgia rheumatica and ankylosing spondylitis (41). In asthma, several drugs have been developed based on chronopharmacology, primarily administered once at night, including systemic and local GC preparations (17, 49, 50). Some data for chronotherapeutical applications of GC in other diseases are reported, *e.g.* multiple sclerosis (51). Modified-release hydrocortisone (MR-HC) is currently being tested in substitution treatment of congenital adrenal hyperplasia (CAH) (52). However, available data are scarce and studies such as in RA are needed in other diseases.

The concept of chronotherapy for RA might also be extended to other drugs. For example, it has recently been reported that switching RA patients from a standard methotrexate (MTX) application three times/week to once-a-day at bedtime improves disease activity and functional capacity (53-55).

## Conclusions

GCs remain important anti-inflammatory and immunosuppressive drugs; however, the potential of these agents to produce adverse effects is notable. The currently most advanced approach to improve the risk-benefit ratio is chronotherapy with low-dose prednisone, in which the programmed delivery of MR prednisone is coordinated with chronobiological rhythms of RA to optimise treatment outcome. Two large-scale trials (CAPRA-1 and 2) in RA support the view that MR prednisone is superior to conventional prednisone for significant long-term reduction of morning stiffness in addition to the conventional GC effects. Furthermore, adverse effects of MR prednisone appear to be unchanged from conventional GCs and without additional suppression of HPA axis. Thus, MR-prednisone can improve the risk-benefit ratio of long-term low-dose GC treatment in patients with RA and provides an additional treatment option, in particular in RA patients with long-standing and disabling morning stiffness.

## References


1. FARDET L, PETERSEN I, NAZARETH I: Prevalence of long-term oral glucocorticoid prescriptions in UK over the past 20 years. *Rheumatology* (Oxford) 2011; [Epub ahead of print].
2. HOES JN, JACOBS JW, BIJLSMA JW: Glucocorticoids are forever? *Rheumatology* (Oxford) 2011; [Epub ahead of print].
3. BUTTGEREIT F, BURMESTER GR, STRAUB RH, SEIBEL MJ, ZHOU H: Exogenous and endogenous glucocorticoids in rheumatic diseases. *Arthritis Rheum* 2011; 63: 1-9.
4. KIRWAN JR, BIJLSMA JW, BOERS M, SHEA BJ: Effects of glucocorticoids on radiological progression in rheumatoid arthritis. *Cochrane Database Syst Rev* 2007: CD006356.
5. DA SILVA JA, JACOBS JW, KIRWAN JR *et al*.: Safety of low dose glucocorticoid treatment in rheumatoid arthritis: published evidence and prospective trial data. *Ann Rheum Dis* 2006; 65: 285-93.
6. HOES JN, JACOBS JW, BOERS M *et al*.: EULAR evidence-based recommendations on the management of systemic glucocorticoid therapy in rheumatic diseases. *Ann Rheum Dis* 2007; 66: 1560-7.
7. VAN DER GOES MC, JACOBS JW, BOERS M *et al*.: Monitoring adverse events of low-dose glucocorticoid therapy: EULAR recommen-

dations for clinical trials and daily practice. *Ann Rheum Dis* 2010; 69: 1913-9.
8. HUSCHER D, THIELE K, GROMNICA-IHLE E *et al*.: Dose-related patterns of glucocorticoid-induced side effects. *Ann Rheum Dis* 2009; 68: 1119-24.
9. SCHACKE H, DOCKE WD, ASADULLAH K: Mechanisms involved in the side effects of glucocorticoids. *Pharmacol Ther* 2002; 96: 23-43.
10. BUTTGEREIT F, DOERING G, SCHAEFFLER A *et al*.: Efficacy of modified-release versus standard prednisone to reduce duration of morning stiffness of the joints in rheumatoid arthritis (CAPRA-1): a double-blind, randomised controlled trial. *Lancet* 2008; 371: 205-14.
11. LEMMER B: Chronobiology, drug-delivery, and chronotherapeutics. *Adv Drug Deliv Rev* 2007; 59: 825-7.
12. LEMMER B: Discoveries of rhythms in human biological functions: a historical review. *Chronobiol Int* 2009; 26: 1019-68.
13. SMOLENSKY MH, PEPPAS NA: Chronobiology, drug delivery, and chronotherapeutics. *Adv Drug Deliv Rev* 2007; 59: 828-51.
14. SMOLENSKY MH, PEPPAS NA: Chronobiology, drug delivery, and chronotherapeutics. *Adv Drug Deliv Rev* 2007; 59: 823-4.
15. SEWLALL S, PILLAY V, DANCKWERTS MP, CHOONARA YE, NDESENDO VM, DU TOIT LC: A timely review of state-of-the-art chronopharmaceuticals synchronized with biological rhythms. *Curr Drug Deliv* 2010; 7: 370-88.
16. HARTER JG, REDDY WJ, THORN GW: Studies on an intermittent corticosteroid dosage regimen. *N Engl J Med* 1963; 269: 591-6.
17. SMOLENSKY MH, LEMMER B, REINBERG AE: Chronobiology and chronotherapy of allergic rhinitis and bronchial asthma. *Adv Drug Deliv Rev* 2007; 59: 852-82.
18. DI RAIMONDO VC, FORSHAM PH: Some clinical implications of the spontaneous diurnal variation in adrenal cortical secretory activity. *Am J Med* 1956; 21: 321-3.
19. ANGELI A: Circadian ACTH-adrenal rhythm in man. *Chronobiologia* 1974; 1 (Suppl. 1): 253-70.
20. CERESA F, ANGELI A, BOCCUZZI G, MOLINO G: Once-a-day neurally stimulated and basal ACTH secretion phases in man and their response to corticoid inhibition. *J Clin Endocrinol Metab* 1969; 29: 1074-82.
21. GRANT SD, FORSHAM PH, DIRAIMONDO VC: Suppression of 17-hydroxycorticosteroids in plasma and urine by single and divided doses of triamcinolone. *N Engl J Med* 1965; 273: 1115-8.
22. NICHOLS T, NUGENT CA, TYLER FH: Diurnal Variation in Suppression of Adrenal Function by Glucocorticoids. *J Clin Endocrinol Metab* 1965; 25: 343-9.
23. KLINEFELTER HF, WINKENWERDER WL, BLEDSOE T: Single daily dose prednisone therapy. *JAMA* 1979; 241: 2721-3.
24. DE SILVA M, BINDER A, HAZLEMAN BL: The timing of prednisolone dosage and its effect on morning stiffness in rheumatoid arthritis. *Ann Rheum Dis* 1984; 43: 790-3.
25. DEANDRADE JR, MCCORMICK JN, HILL AG: Small doses of prednisolone in the management of rheumatoid arthritis. *Ann Rheum Dis* 1964; 23: 158-62.
26. NUGENT CA, WARD J, MACDIARMID WD, MCCALL JC, BAUKOL J, TYLER FH: Glucocorticoid toxicity: single contrasted with divided daily doses of prednisolone. *J Chronic Dis* 1965; 18: 323-32.
27. KOWANKO IC, POWNALL R, KNAPP MS, SWANNELL AJ, MAHONEY PG: Time of day of prednisolone administration in rheumatoid arthritis. *Ann Rheum Dis* 1982; 41: 447-52.
28. STRAUB RH, CUTOLO M: Circadian rhythms in rheumatoid arthritis: implications for pathophysiology and therapeutic management. *Arthritis Rheum* 2007; 56: 399-408.
29. BELLAMY N, SOTHERN RB, CAMPBELL J, BUCHANAN WW: Circadian rhythm in pain, stiffness, and manual dexterity in rheumatoid arthritis: relation between discomfort and disability. *Ann Rheum Dis* 1991; 50: 243-8.
30. HARKNESS JA, RICHTER MB, PANAYI GS *et al*.: Circadian variation in disease activity in rheumatoid arthritis. *Br Med J* (Clin Res Ed) 1982; 284: 551-4.
31. INGPEN ML: The quantitative measurement of joint changes in rheumatoid arthritis. *Ann Phys Med* 1968; 9: 322-7.
32. KOWANKO IC, POWNALL R, KNAPP MS, SWANNELL AJ, MAHONEY PG: Circadian variations in the signs and symptoms of rheumatoid arthritis and in the therapeutic effectiveness of flurbiprofen at different times of day. *Br J Clin Pharmacol* 1981; 11: 477-84.
33. OLSEN NJ, BROOKS RH, FURST D: Variability of immunologic and clinical features in patients with rheumatoid arthritis studied over 24 hours. *J Rheumatol* 1993; 20: 940-3.
34. STONE AA, BRODERICK JE, PORTER LS, KAELL AT: The experience of rheumatoid arthritis pain and fatigue: examining momentary reports and correlates over one week. *Arthritis Care Res* 1997; 10: 185-93.
35. ARVIDSON NG, GUDBJORNSSON B, ELFMAN L, RYDEN AC, TOTTERMAN TH, HALLGREN R: Circadian rhythm of serum interleukin-6 in rheumatoid arthritis. *Ann Rheum Dis* 1994; 53: 521-4.
36. CROFFORD LJ, KALOGERAS KT, MASTORAKOS G *et al*.: Circadian relationships between interleukin (IL)-6 and hypothalamic-pituitary-adrenal axis hormones: failure of IL-6 to cause sustained hypercortisolism in patients with early untreated rheumatoid arthritis. *J Clin Endocrinol Metab* 1997; 82: 1279-83.
37. PERRY MG, KIRWAN JR, JESSOP DS, HUNT LP: Overnight variations in cortisol, interleukin 6, tumour necrosis factor alpha and other cytokines in people with rheumatoid arthritis. *Ann Rheum Dis* 2009; 68: 63-8.
38. DAYER JM, CHOY E: Therapeutic targets in rheumatoid arthritis: the interleukin-6 receptor. *Rheumatology* (Oxford) 2010; 49: 15-24.
39. BUTTGEREIT F, STRAUB RH, WEHLING M, BURMESTER GR: Glucocorticoids in the treatment of rheumatic diseases: an update on the mechanisms of action. *Arthritis Rheum* 2004; 50: 3408-17.
40. WESTHOFF G, BUTTGEREIT F, GROMNICA-IHLE E, ZINK A: Morning stiffness and its influence on early retirement in patients with recent onset rheumatoid arthritis. *Rheumatology* (Oxford) 2008; 47: 980-4.
41. SPIES CM, CUTOLO M, STRAUB RH, BURMESTER GR, BUTTGEREIT F: More night than day--circadian rhythms in polymyalgia rheumatica and ankylosing spondylitis. *J Rheumatol* 2010; 37: 894-9.
42. KEES MG, PONGRATZ G, KEES F, SCHOLMERICH J, STRAUB RH: Via beta-adrenoceptors, stimulation of extrasplenic sympathetic nerve fibers inhibits lipopolysaccharide-induced TNF secretion in perfused rat spleen. *J Neuroimmunol* 2003; 145: 77-85.
43. PETROVSKY N, MCNAIR P, HARRISON LC: Diurnal rhythms of pro-inflammatory cytokines: regulation by plasma cortisol and therapeutic implications. *Cytokine* 1998; 10: 307-12.
44. ARVIDSON NG, GUDBJORNSSON B, LARSSON A, HALLGREN R: The timing of glucocorticoid administration in rheumatoid arthritis. *Ann Rheum Dis* 1997; 56: 27-31.
45. BUTTGEREIT F, DOERING G, SCHAEFFLER A *et al*.: Targeting pathophysiological rhythms: prednisone chronotherapy shows sustained efficacy in rheumatoid arthritis. *Ann Rheum Dis* 2010; 69: 1275-80.
46. STRAUB RH, PAIMELA L, PELTOMAA R, SCHOLMERICH J, LEIRISALO-REPO M: Inadequately low serum levels of steroid hormones in relation to interleukin-6 and tumor necrosis factor in untreated patients with early rheumatoid arthritis and reactive arthritis. *Arthritis Rheum* 2002; 46: 654-62.
47. STRAUB RH, PONGRATZ G, CUTOLO M *et al*.: Increased cortisol relative to adrenocorticotropic hormone predicts improvement during anti-tumor necrosis factor therapy in rheumatoid arthritis. *Arthritis Rheum* 2008; 58: 976-84.
48. ALTEN R, DORING G, CUTOLO M *et al*.: Hypothalamus-pituitary-adrenal axis function in patients with rheumatoid arthritis treated with nighttime-release prednisone. *J Rheumatol* 2010; 37: 2025-31.
49. BURIOKA N, FUKUOKA Y, KOYANAGI S *et al*.: Asthma: Chronopharmacotherapy and the molecular clock. *Adv Drug Deliv Rev* 2010; 62: 946-55.
50. REINBERG A, HALBERG F, FALLIERS CJ: Circadian timing of methylprednisolone effects in asthmatic boys. *Chronobiologia* 1974; 1: 333-47.
51. GLASS-MARMOR L, PAPERNA T, GALBOIZ Y, MILLER A: Immunomodulation by chronobiologically-based glucocorticoids treatment for multiple sclerosis relapses. *J Neuroimmunol* 2009; 210: 124-7.
52. VERMA S, VANRYZIN C, SINAII N *et al*.: A pharmacokinetic and pharmacodynamic study of delayed- and extended-release hydrocortisone (Chronocort) vs. conventional hydrocortisone (Cortef) in the treatment of congenital adrenal hyperplasia. *Clin Endocrinol* (Oxf) 2010; 72: 441-7.
53. CUTOLO M, MASI AT: Circadian rhythms and arthritis. *Rheum Dis Clin North Am* 2005; 31: 115-29, ix-x.
54. CUTOLO M, STRAUB RH, BUTTGEREIT F: Circadian rhythms of nocturnal hormones in rheumatoid arthritis: translation from bench to bedside. *Ann Rheum Dis* 2008; 67: 905-8.
55. TO H, YOSHIMATSU H, TOMONARI M *et al*.: Methotrexate chronotherapy is effective against rheumatoid arthritis. *Chronobiol Int* 2011; 28: 267-74.