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CHRONOBIOLOGICAL APPROACH FOR TREATMENT OF RHEUMATOID ARTHRITIS

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Abstract

Arthritis is a disease state with pathological symptoms like joint stiffness, swelling and restricted movements. All these symptoms are at their prime in the morning hours. In diseased individuals higher concentration of pro-inflamatory mediators like Interlukin-6, nocturnal hormones like melatonin and lower concentration of glucocorticoids have been reported, thus pathological states of rheumatoid arthritis can be regulated by working on interactions between above listed mediators. Conventional treatment approaches use large dose of drugs and thus are not safe to the patients; moreover, their administration time leads to non-compliance of the patients. Novel approaches making use of chronotherapy have shown good results, as they not only reduce the risk of overdose but also improve the patient compliance. This review paper attempts to concisely explicate the role of circadian rhythms in pathogenesis of rheumatoid arthritis and further more describes various chronotherapeutic approaches that have been employed for the treatment of rheumatoid arthritis.

Key Words: Arthritis, Chronobiology, Chronotherapy, Glucocorticoids

Introduction to Chronobiology and Chronotherapeutics

Rhythmic variations govern almost every process in an organism's body. Animals, humans and plants show rhythmic variations at various levels, starting from cellular level to the organism level.[1-2] Rhythms with frequency of one in 24 h are referred as circadian rhythms; while those which occur more or less than once a day are refereed as ultradian and infradian rhythms respectively.[3-4] Many biological phenomena display cyclic variations and rhythmicity and tend to work according to biological time keeper. Biological rhythms are speculated as adaptive adjustment to cyclic changes in surrounding occurring over the course of the day, a month or a season and form the basis of chronobiology. Chronobiology is thus that discipline which deals with difference in physiology of an individual according to time of day, month or year or even period in one's life.[5] Endocrine system provides examples illustrating chronobiology, e.g., a range of hormones including cortisol, catecholamine's are secreted in morning, whereas hormones like melatonin (MLT), adrenocorticotropic hormone finds their maxima in the evening or during sleep. Priming of these hormones at various durations of the day leads to alteration in body's physiological functions at various times of the day.[6-9] Chronotherapeutics is a novel approach to produce effective results and safer medication regimen for pathophysiological states pertaining to chronobiology of various hormones. Chronotherapeutics may thus be defined as the science of designing and giving medications in synchrony with circadian rhythms, it is devoted to design and evaluation of drug delivery system releasing a bioactive agent at a rhythm that ideally

matches biological requirement of a disease therapy. Chronotherapy is so designed that it delivers drug at specific time, at specific rate and in specific amount thus avoiding problems pertaining to conventional modified drug delivery system. This technique is thus beneficial to treat diseases like asthma, Rheumatoid arthritis (RA), cardiovascular diseases since they show chronobiological behavior. This methodology also proves beneficial for pathophysiological states where night time dosing is required.[10-13]

Arthritis[14-19]

Arthritis (derived from Greek word artho: joint, itis: inflammation), is a condition involving damage to joints of the body. Arthritis may broadly be classified as under:

a) Rheumatoid arthritis (RA)
b) Septic arthritis
c) Juvenile arthritis
d) Ankylosing spondilytis

RA is a disease in which body's own immune system starts to attack body's tissue. Immune complex composed of Ig M (Ig: immunoglobulin) activate complement and release cytokines which are chemotactic for neutrophils. These inflammatory cells secrete lysosomal enzymes which damage cartilage and bones, while prostaglandins produced in the process cause vasodilatation and pain. Attack is directed not only to joints but also on different body parts. In RA damage mostly occurs to the joint lining and cartilage resulting in erosion of two opposing bones. Common symptoms includes varied level of pain, swelling, joint stiffness and sometimes a constant ache around the joints (Fig. 1). [19]

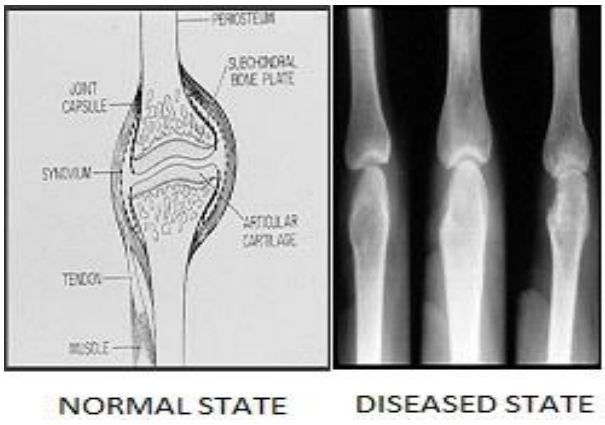

Fig. 1. Condition of joints state in normal and diseased individual

Theories regarding pathogenesis of RA

a) T-cell on interaction with unidentified antigen is responsible for initiating an inflammatory response. Origin of this theory lays in the thought that there is association of RA with class 2 Major Histocompatibility antigens (Fig. 2).[16,19]
b) According to another theory T-cells may be important in initiating the disease, but chronic inflammation is self perpetuated by macrophages and fibroblasts. Absence of activated T- phenotypes in chronic RA and presence of activated macrophage and fibroblast phenotypes lays substance to this theory. At site of inflammation fibroblast of affected cartilage secretes:
    i. Cytokines: IL-6, IL-8 (IL: Interleukin)
    ii. Prostaglandins
    iii. Protease enzyme

Protease and prostaglandins act directly to erode and destroy bones and cartilage thus producing inflammation and other symptoms of arthritis (Fig. 3).[18,19]

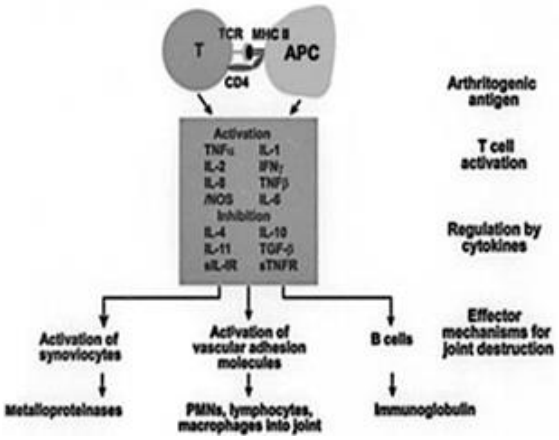

Fig. 2. T-cell model for synovitis in rheumatoid arthritis

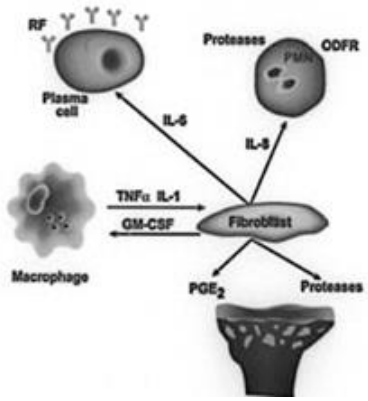

Fig. 3. Macrophage model for synovitis in rheumatoid arthritis

Conventional treatment approaches for arthritis

From past few decades scientists have been attempting to develop drugs (except corticosteroids), which can suppress the rheumatoid process and bring about a remission, but do not have nonspecific anti-inflammatory or analgesic action. Commonly used treatment approaches for RA includes use of:

Non Steroidal Anti-inflammatory Drugs (NSAID's)[4]**:** NSAID's blocks the cyclo-oxygenase thus inhibits the synthesis of prostaglandins which is a common inflammatory mediator, thus are used commonly to treat RA, e.g., Indomethacin, Ibuprofen, Diclofenac sodium.

Glucocorticoids[20,22,24]**:** Glucocorticoids are amongst the most prominent class of drugs used for treatment of RA glucocorticoids are immunosuppressant and have the anti-inflammatory potential; this proves glucocorticoids to be an important contender for RA therapy, e.g., Prednisolone.

Disease modifying antirheumatic drugs (DMARD)[7,8,24,25]**:** They are also known as slow acting anti-rheumatic drugs (SAARD). They possess the potential to reduce or prevent joint damage .These drugs are used in cases where inflammatory disease does not respond to cyclo-oxygenase inhibitors. Commonly used DMARD are Methotrexate, Leflunomide, Chloroquine, Penicillamine, Gold salts etc.

Anti-cytokine therapy[16, 18, 19]**:** It has been reported that interleukins and tumor necrosis factor- α are prominent cytokines in pathogenesis of RA. When secreted by synovial macrophages, IL-1b and tumor necrosis factor -α (TNF-α) stimulate synovial cell to proliferate and synthesize collagenase, thereby degrading cartilage, stimulating bone resorption and inhibiting proteoglycan synthesis. Thus drug which are antagonist to these cytokines have the potential to prove effective in treating rheumatoid arthritis. Etanercept, Infliximab, Adalimumab, Anikara are the commonly used cytokine inhibitors (Fig. 4).[19]

Circadian rhythm of nocturnal hormones in rheumatoid arthritis[1-3,6-9,26]

From decades it had been known that pathological symptoms in RA follow circadian rhythm, with priming of symptoms in early morning, abatement during the noon and then starts increasing from late evening. Researchers have reported temporal relationship between elevated levels of pro-inflammatory cytokine and symptoms of RA. Patients of RA report elevated cytokine level in early hours of day, which subsides till noon.[6]

Serum concentration and release cytokine is triggered by melatonin and other hormones from hypothalamus, and follow a strict 24 h cycle. IL-6 is the most important of all cytokines responsible for pathological symptoms pertaining to RA. Other pro-inflammatory hormones manifesting RA include TNF, IL-1, IL-8, IL-12 and IL-17.[20]

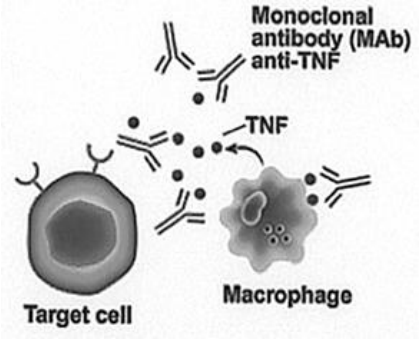

Fig. 4. Monoclonal antibodies directed against TNF or IL-1

Positive genetic relationship between melatonin and RA had been reported by the researchers. Survey in 2002 reported that serum MLT levels at 8 PM and 8 AM were significantly higher in patients suffering from RA, than in healthy controls. MLT levels increased progressively from 8 PM to early morning with a peak at midnight. From researches it had been concluded that MLT concentration stimulate the production of interferon γ, IL-1, IL-2, IL-6 etc. in mononuclear cells of blood, moreover MLT enhances production of inflammatory cytokine from human monocytes. Excess concentration of MLT had been reported in synovial fluids of patients having RA, moreover binding sites for MLT were also found to be present in synovial macrophage. It was found that concentration of various cytokine primes during night and early morning just after the stage when MLT serum levels are higher whereas plasma cortisol level the lowest, thus it is concluded that MLT up regulates cytokine production and immune functions, thus leading to joint inflammation, joint stiffness etc.[6,27-30]

Research conducted by Harkness et al[31], depicted circadian variations in common symptoms associated with arthritis further confirms the circadian variation in disease activity in rheumatoid

arthritis. Researchers selected 10 patients with definite RA having a mean age of 54.6 years (range 33-76) who were taking NSAID's like indomethacin (six), naproxen (one), ibuprofen (one), benorylate (one), flurbiprofen (one). Five of them were on Penicillamine therapy, and one was receiving weekly gold injections. None was taking corticosteroids or hypnotics. Patients were studied over 24 h. The results confirmed the circadian nature in disease activity.

Cortisol secretion and glucocorticoids receptor density has been reported to be altered in patients with RA[32]. It was found that increased cortisol synthesis inhibits the rise in concentration of IL-6 in RA patients. Moreover, circadian changes of peripheral metabolism of endogenous glucocorticoids had also been reported to contribute to the early morning manifestation of the disease symptoms in RA, thus this biorhythm had been tried to turn to an advantage by administering a low dose of glucocorticoids at around 2:00 h instead of administering the same dose at 7:00 h in morning, thus improving the state of RA patients to a considerable extent.[6, 7, 32]

Chronotherapeutics for treatment of rheumatoid arthritis

Chronotherapy of arthritic disease involves determining the best time to administer various types of medicines to enhance their desired effects and avoid or minimize unwanted ones. Various methodologies used are:

Use of glucocorticoids: Researchers have reported that in healthy controls, plasma cortisol level inhibit a circadian rhythm with priming at around 6:00 h – 8:00 h and nadirs at around 22:00 h -2:00 h. The earlier rise in RA patients is due to rise in IL-6 concentration which has a pleiotropic role in pathogenesis of RA. IL-6 stimulates the hypo physical axis (HPA) axis resulting in increased cortisol synthesis and suppression of arthritis.[20-25, 33] This bio-rhythm had been used to advantage for treatment of arthritis.[20-25] Through research scientists concluded that small amount of Prednisolone taken at 02:00 h improves the rheumatic arthritis but the problem which arose was that patient had to be woken up at night.[33] Newly developed modified release (MR) Prednisolone proved an answer to this, it releases drug four hours after ingestion thus by taking it in evening and adapting it's release to the circadian increase in pro-inflamatory cytokine concentration, the symptoms of RA were found to lessen in early morning.[34, 35]

Use of Methotrexate: French researcher Carpentier in his study to determine optimal time for administration of Methotrexate in RA therapy reported hardly any difference in pharmacokinetic study of Methotrexate except the cretenine clearance level in the subjects in whom the drug was administered at 10:00 h 18:00 h, hence concluded that Methotrexate can be administered either in the morning (10 A.M.) or evening (6 P.M.) in the treatment of RA.[36]

Use of NSAID's: Huskisson in 1976 reported that an evening once-a-day treatment with indomethacin was much more effective in controlling the prominent morning symptoms of rheumatoid arthritis than a morning one. Moreover, he reported people to be much better tolerant with less complaint of side effects when drug was administered as a single daily dose in the evening than morning.[37]

In another study examining the role of treatment schedule on the therapeutic effect of the NSAID's: flurbiprofen, it was found that to control the morning symptoms of RA, a daily NSAID's dose must be taken in the evening or at bedtime.[38]

Future prospective

Other treatment methodologies which are under investigation and can prove to be a boon in cure of RA are:

Delivering drugs which blocks the receptors for melatonin at the time when its concentration is maximum: It had been previously reported that MLT levels in subjects suffering from RA shows an excess as compared to normal individuals; increased MLT levels results in increased IL levels which further results in increased inflammatory responses and hence onset of RA, thus if receptors for MLT are blocked the disease state might not proliferate.

Blocking the action of cytokine at site of target cells: Increased cytokine and IL levels have been reported to be the prime cause of RA. Cytokines on attachment to target cells serve as inducers of chemotactic response for the neutrophils, which on proliferation lead to inflammatory response and hence onset of RA. Thus approaches preventing

attachment of cytokines to the target cells may prove beneficial to cure RA (Fig. 5).[19]

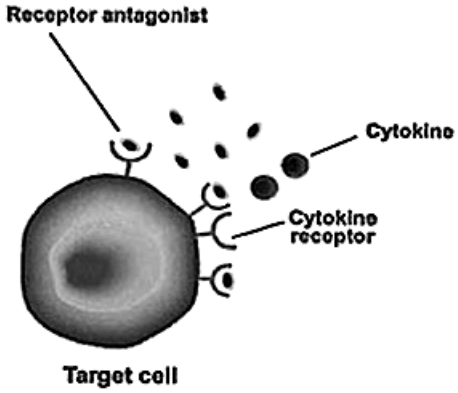

Fig. 7. Antagonists of the TNF or IL-1 receptors

Advantages of using chronotherapy

1. It is more effective and less toxic when drugs are administered at selected time of the day.
2. Chronotherapeutics aids in delivering drug in concentration that may vary according to the body's circadian rhythm.
3. It minimizes the side effect of glucocorticoids since the concentration of hormone used is very less.

Conclusion

First and foremost aim of this article had been to make clinicians, biologists and pharmacists realize the importance of chronobiology and chronotherapeutics for safer and effective treatment of pathological states like RA. The article also lays emphasis on the teamed effect as well as interdependence on each other of nocturnal hormones like MLT, inflammatory mediators like cytokine, glucocorticoids like cortisol which together leads to RA. Moreover the article also summarizes how by intelligently modifying the concentration of mediators, the diseased states can be modified /controlled. Thus the article tries to enlighten the path for new researchers and developers for developing a better, safer and therapeutically effective dosage form for treatment of RA.

In the era where big pharmaceutical giants strive to flood market with new solutions, use of these intelligent systems could not only offer better therapeutic results but also increases patient compliance in disease states like rheumatoid arthritis.

Declaration of Interest

It is hereby declared that this paper does not have any conflict of interest.

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