Air Travel, Circadian Rhythms/Hormones, and Autoimmunity

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Air Travel, Circadian Rhythms/Hormones, and Autoimmunity

J. Torres-Ruiz1 · A. Sulli2,3 · M. Cutolo2,3 · Y. Shoenfeld4

Abstract Biological rhythms are fundamental for homeostasis and have recently been involved in the regulatory processes of various organs and systems. Circadian cycle proteins and hormones have a direct effect on the inflammatory response and have shown pro- or anti-inflammatory effects in animal models of autoimmune diseases. The cells of the immune system have their own circadian rhythm, and the light-dark cycle directly influences the inflammatory response. On the other hand, patients with autoimmune diseases characteristically have sleep disorders and fatigue, and in certain disease, such as rheumatoid arthritis (RA), a frank periodicity in the signs and symptoms is recognized. The joint symptoms predominate in the morning, and apparently, subjects with RA have relative adrenal insufficiency, with a cortisol peak unable to control the late night load of pro-inflammatory cytokines. Transatlantic flights represent a challenge in the adjustment of biological rhythms, since they imply sleep deprivation, time zone changes, and potential difficulties for drug administration. In patients with autoimmune diseases, the use of DMARDs and prednisone at night is probably best suited to lessen morning symptoms. It is also essential to sleep during the trip to improve adaptation to the new time zone and to avoid, as far as possible, works involving flexible or nocturnal shifts. The study of proteins and hormones related to biological rhythms will demonstrate new pathophysiological pathways of autoimmune diseases, which will emphasize the use of general measures for sleep respect and methods for drug administration at key daily times to optimize their anti-inflammatory and immune modulatory effects.

Keywords Circadian · Flights · Autoimmunity · Biological rhythms

Introduction

The current lifestyle has made sleep restrictions more and more common. The variability in work schedules as well as flights across different time zones favor changes in the biological rhythms of humans. Such changes include the lack of sleep and exposure to new environmental factors such as cosmic radiation that could represent new risk factors for autoimmune diseases or exacerbate their symptoms. In this review, we analyze the possible connection between the transatlantic flights and the mechanisms of autoimmunity, and we conclude with specific recommendations for the control of the disease before and during the airplane trip.

Circadian Cycle

Generalities

Circadian rhythms involve physiological changes in gene expression with peaks every 12 h to complete a cycle of 24 h [1].
Cycles that last more than 24 h are known as infradians, while those that last less than 24 h are called ultradians [2]. Circadian cycles are adjusted daily using external stimuli; in humans, light is the most important [3].

In adult primates, the biological clock resides in the suprachiasmatic nucleus [1]; however, many peripheral tissues have their own circadian cycle [2]. The biological clock is autonomous and consists of a transcription-translation loop [1]. The proteins BMAL1 (ARNTL) and CLOCK are in the center of the pacemaker [1]. The latter protein induces the expression of period (PER) and cryptochrome (CRY). These proteins are repressors that translocate to the nucleus and inhibit its expression by interfering with the BMAL/CLOCK complex [1]. When PER and CRY are degraded, the repression of BMAL and CLOCK is released, and another cycle of 24 h is initiated [1].

The second loop consists of nuclear receptors ROR (αβγ) and REV-ERB (α, β) (also known as NR1D1 and 2). RORs activate, whereas REV-ERBs inhibit the expression of BMAL1 [1]. The third loop consists of transcriptional activator albumin D-box binding protein (DBP) and the nuclear repressor factor interleukin 3 (NFIL3 or E4BP4) that are regulated via ROR. These genes regulate the expression of PER [1].

The clinical variables that are used as markers of endogenous rhythms are the rest/activity cycles, body temperature, and the time of onset of melatonin secretion in dim light [2]. When these parameters are normal, it is said that an organism has a normal chronobiological configuration [2]. On the other hand, there is an external desynchronization when circadian cycles are not in accord with astronomical time (for example in people who are not able to perceive light [2]), while internal desynchronization occurs when there is no synchrony between two or more endogenous rhythms [2].

### Inflammation, Immunity, and Biological Rhythms

Table 1 shows the proteins related to the biological clock and some of their functions in inflammation.

<table>
<thead>
<tr>
<th>Protein</th>
<th>Relation with inflammation</th>
</tr>
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<tbody>
<tr>
<td>CLOCK</td>
<td>Acetylate-transferase of histones [1]. Acetylate the glucocorticoid receptor with the consequent inhibition of binding to its target genes [1]. Promotes phosphorylation and acetylation of p65, which increases the transcriptional activity of NF-κB [1].</td>
</tr>
<tr>
<td>PER</td>
<td>Promotes the rhythmicity of IFN-γ [1]. Increases TLR9 in macrophages [1, 4, 78].</td>
</tr>
<tr>
<td>BMAL1</td>
<td>In animal models conditional deficiency has been shown to inhibit the production of ccl2 and IL-6 [1]. Regulation of TLR9 expression along with CLOCK [1, 4]. Induce RORx [1]. Dim the effect of CLOCK [1].</td>
</tr>
<tr>
<td>REVERBα</td>
<td>It limits the release of IL-6 into macrophages and reduces the mRNA of Cccl11, Cccl2, Cccl6 and Il1β [1].</td>
</tr>
<tr>
<td>RORα</td>
<td>Induces 1αBx and regulates NF-κB [1].</td>
</tr>
<tr>
<td>PPARγ</td>
<td>Exerts an anti-inflammatory effect on the synovium [5].</td>
</tr>
<tr>
<td>CRY1 y 2</td>
<td>Decrease expression Il-6, Tnfsf, Cccl1 and Inos mRNA in fibroblasts and dendritic cells of bone marrow [1, 6, 79]. Their deletion increases the expression of IL-6 and TNF-α after stimulation with LPS in bone marrow dendritic cells [1, 6, 79].</td>
</tr>
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</table>

### The Sleep-Wake Cycle and Related Hormonal Changes

One of the most important endogenous biological rhythms and strongly related to inflammation and autoimmune diseases is the sleep-wake cycle. The sleep-wake cycle is regulated by a series of homeostatic mechanisms that increase during awake state and decrease during sleep as well as through the CLOCK pathway [6]. In adult primates, only visible light (400–700 nm) is received by the retina, and it promotes neuroendocrine changes through the pituitary and pineal glands [7]. The pineal gland transforms neuronal signals into endocrine secretion of indolamines such as melatonin and others such as serotonin, AVP, and oxytocin [8].

Mediators of the variations of inflammatory response through the circadian cycle include histamine, bradykinin, prostaglandins, and pro- and anti-inflammatory cytokines [7]; however, one of the most important mechanisms is hormonal and is related to the circadian variation in cortisol secretion [7]. Glucocorticoids suppress the production of
inflammatory perpetuating factors including IL-2 in T cells, IL-6 in glial cells, and β-endorphin in lymphocytes [8], while IL-1, IL-6, and TNF-α are considered to be factors that promote glucocorticoid secretion [8].

The rhythm of IFN-γ, IL-12, and TNF-α is contrary to the rhythm of cortisol, and that hormone favors a Th2 phenotype and related anti-inflammatory cytokines such as IL-10 [9]. Luminous stimuli cause increased secretion of cortisol, seroton, and dopamine, while suppressing that of melatonin, noradrenaline, and acetylcholine [3].

On the other hand, melatonin is a key regulator of the immune system, and its circadian release is stimulated by the darkness [7]. Therefore, melatonin is able to stimulate the secretion of reactive oxygen species and IL-1 by monocytes and promotes its cytotoxic activity against tumor cells in vitro in a basal and LPS-induced manner. In addition, melatonin is capable of stimulating the production of IL-1, IL-2, IFN-γ, and IL-12 in lymphocytes [10, 11], as well as the production of IL-6 in monocytes [11].

Lymphocytes are able to synthesize melatonin [10]; so apparently, melatonin and IL-12 function autocrine or paracrine to promote T cell-mediated immunity [10]. In addition, melatonin favors the production of antibodies against T-dependent antigens and NK cell activity [11]. IFN-γ, IL-1, and IL-6 are secreted by mononuclear cells in response to melatonin [3], and it increases the secretion of IL-1 and IFN-γ by monocytes [9].

During pro-inflammatory stimuli, such as infections or in autoimmune diseases, there is release of cytokines that reach the brain. Some of them, such as IL-1 and TNF, are proinflammatory, while counteracting factors such as IL-4, IL-10, CRH, and glucocorticoids have the opposite effect [6].

The need for sleep may be imperative to combat certain viral infections, as in the case of infectious mononucleosis or influenza [6]. During sleep, the levels of IL-2, IFN-γ, and IL-12 increase, which favors the appearance of a Th1 phenotype [12, 13] to combat viruses.

In conclusion, light-dark cycle is crucial in the regulation of inflammatory response. Most inflammatory stimuli predominate at night and they are possibly counteracted with the morning cortisol peak. Therefore, it is possible that DMARDs such as methotrexate are more effective if given at night in presence of active inflammatory-autoimmune diseases [14].

**Effects of Sleep Deprivation on Inflammation**

In animal models where light-dark cycles are manipulated, post-challenge with lipopolysaccharide (LPS), there is marked hypothermia and increased mortality [15]. Twenty-four hours after challenge with LPS, there is an increase in pro-inflammatory cytokines, including IL-1β, GM-CSF, IL-23, and IL-13 [15]. When a lower dose of LPS is used to prevent death by sepsis, the mice in which the light cycle was modified had higher IL-6, IL-18, MIP-2, and the IL-6 class cytokine LIF [15]. In mice in which the light-dark cycle was manipulated, there was a delay in Per2 peak in various tissues such as the suprachiasmatic nucleus, liver, and thymus and a higher synthesis of IL-6 in response to LPS by peritoneal macrophages [15].

Sleep-deprived animal models have demonstrated an increase in the genetic and protein expression of IL-1β, TNF-α, and IL-6 in endothelial cells, associated to a decrease in CRY1 protein expression in endothelial cells of the thoracic aorta [16].

The pro-inflammatory phenotype is given by increased cAMP which promotes the phosphorylation of the p65 subunit of NF-κB [16]. Expression of the CRY1 protein in endothelial cells was able to reverse the adhesion of monocytes, suggesting a reduction in the pro-inflammatory phenotype [16].

The results of sleep deprivation studies in humans have shown controversial results as they depend on the type of protocol used and the chronicity of sleep deprivation.

In healthy volunteers, a sleepless night increases cortisol levels and is associated with an increase in subjective perception of stress [17]. In healthy subjects with sleep deprivation, levels of IL-1β and IL-6 tend to increase and to recover after normalization of sleep [6]. Higher levels of immunoglobulins and complement have also been observed [18].

In healthy subjects, sleep deprivation for 40 h even decreases the levels of CRP and IL-6 [19] due to increased cortisol, while post-1-week sleep deprivation, there are increased levels of IL-6 in men and women and increased levels of TNF-α only in women. These changes are associated with a lower intensity cortisol peak and its availability [20].

Chronic sleep deprivation is associated with increased C-reactive protein [12, 21], IL-6 [12, 22], granulocytes, and monocytes [12, 23] and with a reduction in IL-2 secretion [24], decreased secretion of IL-12 by monocytes, and increased Th2 subpopulations by augmenting secretion of IL-10 [12, 25].

In subjects with chronic insomnia, there is a decrease in CD3+, CD4+, and CD8+ [12, 26]. Other studies have shown that sleep restriction induces increase in plasma concentrations of IL-6, TNF-α in men [27] and increase in IL-1β, IL-6, and IL-17 transcripts [12, 28], although these changes do not occur when the restriction is for a couple of nights [12]. Sleep deprivation decreases the activity of NK cells and their ability to be activated by IL-2 [12, 29].

The consequences of sleep deprivation include increased susceptibility to infections and decreased efficacy of certain vaccines such as hepatitis A [12, 30], hepatitis B [12], and influenza [12, 31].

Continuous flights represent a challenge for the adaptation of biological rhythms, especially in patients with autoimmune diseases. We then discuss the main risks to aircraft crews on transatlantic flights.
In Fig. 1, we summarize the main effects of circadian rhythms on inflammation.

**Flights and Autoimmunity**

**Cosmic Radiation**

Aircraft crews are exposed to cosmic radiation [32], and it interacts with atmospheric molecules and generates secondary and tertiary radiation at aircraft heights [33]. Although no relation has been described between cosmic radiation and autoimmunity, some studies have associated it with cognitive alterations [34]. Further studies are required to disclose the effects of cosmic radiation exposure in humans.

**Shift Changes**

Jobs related to changes in work shifts include night shifts, flexible shifts, extended shifts, rotations, or frequent trips such as airline crew [15]. Sleeping less than normal has been associated with obesity, cancer, diabetes, and cardiovascular disease, all of which are characterized by chronic inflammation as a common mechanism [35].

The misalignment of circadian rhythms occurs when sleep and awakening occur at inappropriate circadian moments [17]. Alterations to adjust body rhythms with respect to environmental stimuli (chronodisruption) or alterations in the function of the body cycles (internal desynchronization) cause at the end alterations in the immune system [13].

Among subjects with shift works, there are sleep disturbances including insomnia and hypersomnia, which are known as shift work disorder [36], while jet lag disorder includes insomnia or hypersomnia when traveling in at least two time zones [36] and people on aircrew are in risk for these disorders.

In rheumatic musculoskeletal diseases, it is known that the symptoms vary according to the hours of the day, and generally, they are more intense in the morning (6–9 am), in rheumatoid arthritis (RA), polymialgia rheumatica (PMR), and spondylarthritis (SPA) and in the evening-night in osteoarthritis (OA) and gout [37]. Therefore, in case of long distance air fights, it is reasonable to apply DMARDs and prednisone at night, before the trip initiates. On the other hand, there is the need to take the measures to favor the adaptation to the time zone. In flights, sleeping at night during the trip is a suitable measure to adjust to the time zone of arrival [38].

The role of cortisol/glucocorticoids as enhancers of the flight resistance and well-being at high altitudes, in any case, was discovered in a very interesting way. During World War II, a rumor reached the United States (US) and the United Kingdom (UK) that the Germans were successfully using an adrenal hormone product to protect Luftwaffe pilots from the adverse effects of high altitudes [39].

The product was said to be obtained from adrenal glands, collected in a huge amount in Argentina and transported by U-boats to Germany. The US and the UK exerted their war efforts by setting up urgent research projects to produce similar products. In 1942, a chemist from Merck and Company,
Rheumatoid Arthritis

Decreased sleep is associated with fatigue, depression, and increased pain in RA [41]. In women, shift work has been associated with a slight increase in the risk of developing RA [41].

The symptoms of patients with RA including stiffness and increased circumference of the fingers are more marked upon awakening [42], and variation in its symptoms follows a cycle of approximately 24 h [13].

In RA, symptoms of morning stiffness are associated with increased pro-inflammatory cytokines (including TNF-α and IL-6) at night and in the morning, which decrease after noon [43] favoring edema and accumulation of synovial fluid, with the consequent appearance of morning stiffness and swelling [43].

Cortisol levels are lower at night and higher in the morning in the normal way [43]. The increase in TNF-α levels promotes hepatic expression of 11β-hydroxysteroid dehydrogenase, which converts cortisol into inactive cortisone [43].

Therefore, patients with RA benefit from the availability of glucocorticoids at late night, since they can counteract the peak of inflammatory cytokines and prevent the morning symptoms [44].

Indeed, in patients with RA who were given modified-release prednisone at night (administration at 10 pm and release from the capsule after 4 h at 3–4 am), the IL-6 morning peak was abolished and this correlated with improvement in morning stiffness [45].

Although in normal subjects, ACTH levels increase with the administration of IL-6, over time, this response is abolished [43]. Indeed, in studies of patients with RA and PMR, ACTH and cortisol levels are identical in comparison to healthy subjects despite the fact that pro-inflammatory cytokine levels are 10 times higher, so that patients with this disease have an inadequate response of ACTH/cortisol in relation to the levels of pro-inflammatory cytokines [43] including IL-6, IL-1, and TNF-α [9].

In patients with long time RA, continuous nocturnal cortisol peaks (due to the presence of the chronic night inflammatory reaction) could inhibit the proliferation of cells in the adrenal cortex, leading to “relative adrenal insufficiency” [9].

The reason for long-term low doses of glucocorticoids (less 5 mg prednisone/day) in RA is fundamentally linked to a sort of “replacement” therapy to compensate for the before mentioned “relative adrenal insufficiency” [46].

In normal subjects, melatonin peak occurs around 2 am (in RA at least 2 h earlier), while cortisol at 4–5 am and inflammatory mediators such as IL-6, IL-12, and IL-1 have it between 1 and 4 am and remain low during the day [9]. Melatonin favors the synthesis of IL-12 and nitric oxide by synovial macrophages, increases IL-2, IL-6, and IFN-γ levels by CD4+, and potentiates the gene expression of TNF-α and M-CSF [9]. Melatonin levels in RA patients are higher compared to control subjects, especially in those over 60 years of age and in northern countries [9].

Several genes related to the circadian cycle are differentially expressed in fibroblasts of subjects with RA compared to OA [47]. REV-ERBa is over expressed in patients with RA [48]. In addition, there are alterations in the rates of expression PER1, CRY2, and TNF-α in fibroblasts of subjects with this disease [48]. Further, the stimulation of fibroblasts with TNF-α modifies the expression of ARNTL2 and NPAS2 [48].

In animal models of collagen-induced arthritis, many inflammatory markers within the synovium show circadian cycles including Cxcl5, ifn-γ, and il10 that with exposure to light while ifn-γ and il10 had their peak in the darkness and ifn-α and il10 remained stable in the light-dark cycle [4]. When mice were exposed to continuous light, pro-inflammatory cytokines had continuous elevation [4]. Loss of cry 1 and 2 expression resulted in a consistent increase in the levels of Cxcl5, il6, cxcl1, and il10β [4].

In animal models of collagen-induced arthritis, administration of melatonin decreased expression of Cry1 [49]. This was related to greater swelling of the legs and greater erosive changes [49], as well as with higher serum TNF-α and IL-6 concentrations compared to control [49].

Interestingly, a clinical study based on the assumption that melatonin administration could be beneficial in RA patients because of its antioxidant activity showed somewhat disappointing and “surprising” as the authors stated in the discussion [50].

The occasion, to underline that before being “one of the most powerful endogenous free radical scavengers” (in vitro) melatonin, as discussed, is a chronological pacemaker signaling the time of the day and of the year to the body. This activity is achieved by the circadian activation of specific high affinity melatonin receptors that expressed several cell types including immunocompetent cells [51]. Therefore, large majority of the studies addressing the effect of melatonin on the immune system report an immunoenhancing effect. In fact, as already discussed, melatonin is recognized to increase the production of Th1-type and inflammatory cytokines in RA and to enhance both cell mediated and humoral responses [52]. In regard to RA, melatonin has been shown to exacerbate collagen-induced arthritis, and we have suggested that it might exert a disease promoting role in patients [53, 54].

In addition, serum TNF-x was found to be higher in rheumatoid arthritis patients (Estonia) than in their controls and
was correlated with the increased latitude-related serum melatonin concentrations, at least in winter. For sure, altered serum concentrations (increased levels and longer serum plateau) and circadian rhythms of melatonin have been implicated in clinical RA symptoms [4]. For these reasons, we would have never dared to administer melatonin to RA patients. We are not surprised at all from the results obtained in the mentioned study; rather, we are amazed that melatonin did not worsen the clinical symptoms [54]. As consequence, flight travelers that use melatonin to induce sleep should avoid it especially if affected by inflammatory or autoimmune diseases.

Similarly, for autoimmune patients, having a long flight without sleep, the reduced increase on melatonin (linked to darkness) should be advantageous.

In conclusion, close relationship between circadian proteins and hormones and inflammation emphasizes the importance of maintaining internal and external rhythmicity during flights.

**Systemic Lupus Erythematosus**

In spontaneous systemic lupus erythematosus (SLE) animal models such as NZB/W (F1), alterations in sleep patterns have been found by polysomnography [55].

Animal models like MRL/lpr lose the circadian cycle of ACTH and melatonin [8]. The highest cortisol levels in these mice occur between 8 and 14 h, peak at 6:00 pm, and then fall to 6:00 am [8]. Likewise, higher concentrations of plasmatic ACTH and melatonin [8]. The highest cortisol levels in these patients with SLE have alterations in cortisol rhythmicity, especially during active disease.

Peptides derived from ACTH, such as the melanocyte-stimulating alpha-hormone, may have an anti-inflammatory effect; so, it was tested whether an analog of this hormone (NDP-MSH) could attenuate the phenotype of pristane-induced lupus [59]. Administration of such peptide decreased the incidence and severity of arthritis, as well as levels of IgG1 and IgG2a, IL-6 and IL-10, and the prevalence of antinuclear antibody positivity in the pristane-induced lupus model [59]. Mice with pristane-induced lupus that were treated with the peptide had a lower renal histological score [59].

On the other hand, in pristane-induced lupus, administration of melatonin decreased the amount of anti-single stranded DNA and histone antibodies [60]. Similarly, after stimulation with ConA, IL-2 levels increased to levels even higher than wild-type mice, whereas IL-6 and IL-13 levels were minor [60].

Interestingly, prolactin, another polypeptide hormone produced by the pituitary gland, is involved in the regulation of humoral and cell-mediated immune response, with peaking again at night and is increased also in men with RA [61].

A recent meta-analysis revealed that, compared with the control group, the SLE group had significantly higher plasma/serum PRL levels ($P < 0.001$) [62].

However, in the case of active autoimmune patients, having a long flight without sleep, the reduced increase of prolactin (that normally increase with the darkness) should be advantageous.

In summary, maintaining the light-dark cycle is important to prevent exacerbations of the disease in patients with SLE. Since patients with active disease have alterations in cortisol rhythmicity, it is reasonable to administer immunosuppressants and/or prednisone during night before the flight begins and possibly using modified release prednisone at least in rheumatoid arthritis (release after 3–4 h).

**Type 1 Diabetes Mellitus 1**

Partial sleep deprivation increases insulin resistance even in type 1 diabetes mellitus 1 (DM1) [63], and subjects with DM1 have insufficient sleep more frequently than age-matched controls [64].

Melatonin levels are elevated in rats with DM1 [65], and in animal models, it has been observed that sleep deprivation generates lymphopenia, especially in non-obese diabetic (NOD) mice [66].

**ARNTL2** is a protein similar to **ARNTL1** (BMAL1) and is fundamental in controlling obesity and type 2 diabetes mellitus [67]. The role of circadian cycle regulatory genes like **Arntl2** has been studied in congenic strains of NOD mice [68]. In CD4+ T cells transfected with **Arntl2** mRNA, there is decreased proliferation in effector cells [68]. The transfer of these cells was able to inhibit the disease in recipient mice although it was not related to changes in CD4+ subpopulations or decrease in insulitis [68]. To check the protective effect of **Arntl2** on DM1, shRNA vectors were injected to silence this gene [69]. This intervention was related to reversal of protection against the disease that was originally observed in the congenic mouse strain [69].

The effect of **Arntl2** is to inhibit the production of IL-21 in CD4+ cells [70], which decreases the expansion of T cells [70]. Therefore, in patients with DM1, it is fundamental to sleep during flights, to avoid external desynchrony and insulin resistance with related complications.

Interestingly, in a recent review looking at the outcomes of medical emergencies on commercial airline flights, most in-
flight medical emergencies were related to syncope, respiratory symptoms, or gastrointestinal symptoms [71].

However, DM complications all together, even if represented, only the 1.6% of the total, on the other hand, were found among the most frequent cause of aircraft diversion and transport to a hospital.

Multiple Sclerosis

Subjects starting shift work have a slightly increased risk of developing multiple sclerosis (MS), especially before age 20 [72, 73]. In animal models of MS (autoimmune encephalomyelitis), there is loss of the expression rate of Per2 and CLOCK in tissues outside the suprachiasmatic nucleus. There is also a higher peak of cortisol [74]. In women with relapsing-remitting MS, fatigue levels are increased and melatonin decreased compared to control subjects [75]. Melatonin levels rise after treatment with IFN-β [75]. In patients with MS, there is a higher morning cortisol peak compared to healthy subjects, and this alteration is more marked among subjects with MS and associated depression [76]. Although further studies are required, the data exposed above and before for other autoimmune diseases. Also, in this case remark, keeping the circadian rhythms as physiologic as possible is possible during flights in patients with MS. For sure, a case of prolonged postdural puncture headache in a patient with MS exacerbated by air travel was reported [77].

Conclusions and Final Recommendations

Sleep restriction has become a frequent practice nowadays. Transatlantic flights imply a challenge for patients with autoimmune diseases, since the lost of biologic rhythmicity may be related to exacerbation of disease symptoms. Therefore, the following measures may be taken to diminish this adverse outcome:

1. For patients with SLE, primary Sjögren syndrome and RA whom have severe articular symptoms during the morning, administration of DMARDs and make available exogenous prednisone during the night (obtainable by modified-release prednisone after 3–4 h from administration) may counteract the early night inflammatory cytokine peak and therefore lessen morning symptoms. No administration of melatonin is suggested (since it is a pro-inflammatory night hormone)
2. For patients with SLE, primary Sjögren syndrome, and RA but also for those with type 1 DM and MS, it is fundamental to maintain the biologic rhythmicity. Therefore, it is important to have a good night sleep during the flight and to keep the synchrony of the light-dark cycle in order to favor adaptation to the new time zone.
3. In particular, for all the mentioned patients, the administration of natural or artificial light at least 2 h before the landing is suggested, in order to facilitate the rise of the endogenous cortisol (anti-inflammatory action) when the local arrival is planned during the day light.

Compliance with Ethical Standards

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Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

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