Research Article

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Circadian variation in plasma IL-6 and the role of modified-release prednisone in polymyalgia rheumatica

Aims: To investigate the circadian variation in IL-6 and effects of morning and night time glucocorticoids in polymyalgia rheumatica. **Methods:** Cytokines were measured in newly diagnosed polymyalgia rheumatica over two 24-h periods, 2 weeks apart during which they received 7 mg/day of modified-release prednisone at night or morning prednisolone. All patients then received 15 mg/day morning prednisolone. Morning IL-6 concentrations were measured after 2 weeks. Morning stiffness, changes in peak IL-6 levels and area under the curve were compared. **Results:** IL-6 followed a circadian rhythm with a peak at 04h00. Modified-release prednisone caused greater reduction of IL-6 and area under the curve. **Conclusion:** IL-6 showed marked circadian variation. The possibility that modified-release prednisone offers a treatment advantage over standard therapy should be tested in a larger study.

Keywords: chronobiology • circadian variation cytokines • glucocorticoids • morning stiffness • polymyalgia rheumatica • treatment

Samy A Zakout*[,1], Lynsey L Clarke[1], David Jessop[2], Rainer H Straub[3] & John R Kirwan[1]

[1]University of Bristol, Academic Rheumatology Unit, Bristol Royal Infirmary, Bristol, UK

[2]Henry Wellcome Laboratories for Integrative Neuroscience & Endocrinology, University of Bristol, Bristol, UK

[3]Laboratories of Experimental Rheumatology & Neuroendocrine Immunology, University Hospital, Regensburg, Germany

*Author for correspondence:
Tel.: +44 117 342 2906
Fax: +44 117 342 3841
samy.zakout@bristol.ac.uk

Polymyalgia rheumatica (PMR), an inflammatory disease with a lifetime risk estimated at 2.4% for women and 1.7% for men, is the most common rheumatological disorder in people over 60 years [1–3]. The principal symptoms are pain and stiffness of the proximal muscle girdles, usually worse in the morning, with subsequent profound disability [4]. PMR is one of the commonest indications for long-term glucocorticoid (GC) therapy [5]. There are wide variations in clinical management in primary and secondary care [6], reflecting the dearth of strong evidence available on which to develop treatment policies. Although guidelines have been published [7], treatment recommendations are not based on the results of randomized controlled trials, and alternative interpretations of the available data have led others to recommend different regimens [8,9]. Nevertheless, all these treatment recommendations advocate the use of medium dose GC (e.g., 15 mg/day prednisone or prednisolone) as starting treatment with a reduction in the dose over 1–2 years [7–9]. While the majority of patients show a rapid clinical response [10–14], it is clear that, even with a rapid reduction in GC dose, there are substantial adverse effects [4]. In the absence of placebo-controlled trials, the frequency of adverse effects attributable to GC can only be estimated, but up to 85% of those treated with current protocols report GC-related adverse events [4]. There is a clear need to find ways of optimizing dosing of GC to maintain efficacy while minimizing the potential for adverse events.

Active PMR is characterized by increased serum levels of the pro-inflammatory cytokine IL-6, but not of other pro-inflammatory cytokines [15,16]. In rheumatoid arthritis (RA), where there is also an increase in IL-6 concentration, there is a circadian variation in levels of the cytokine that coincides with the circadian variation in symptoms, with plasma IL-6 concentrations at their peak at the time of waking [17–20]. However, as noted by Spies and colleagues [16], studies in PMR have collected blood samples at only one time point (mainly in the morning), without specifying the exact timing. They concluded that a more detailed analysis of the circadian variation

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in cytokines in patients with PMR was required. The primary aim of this study was therefore to determine for the first time the circadian variation in plasma IL-6 and other cytokines in patients with newly diagnosed untreated PMR.

In RA, the administration of GCs at night using a modified- (delayed-) release preparation of prednisone causes both a marked reduction in morning IL-6 [20] and a reduction in morning stiffness [21,22]. This modified- (delayed-) release preparation of prednisone is taken in the evening (approximately 22h00), but GC is released approximately 4 h later (approximately 02h00) with the same bioavailability profile as standard immediate-release prednisone tablets [23]. The impact of this treatment in patients with PMR has not been investigated. Therefore an exploratory study was under taken to compare the effect on plasma IL-6 concentration and duration of morning stiffness of modified- (delayed-) release prednisone and the same dose (7 mg/day) of standard prednisolone taken in the morning.

Method

Patients & procedure

The study was approved by the South West Research Ethics Committee UK and was registered with ClinicalTrials.gov number NCT00836810 [24].

Patients with newly diagnosed PMR fulfilling Bird criteria [25], having a raised acute phase response (CRP ≥10 mg/l, erythrocyte sedimentation rate ≥29 mm/h or plasma viscosity >1.72 mPa.s) and taking no or stable doses of NSAIDs or analgesic therapy for at least 7 days, were recruited within the University of Bristol Academic Rheumatology Unit at Bristol Royal Infirmary and gave informed written consent. Patients were excluded if they were on oral glucocorticoid treatment or had taken oral or parenteral GCs within the previous 2 months; had any clinical suggestion of coexistent giant cell arteritis, signs of peripheral synovitis, other autoimmune disease, malignancy or any infection within the preceding 6 weeks; were pregnant or lactating; were undertaking shift work or had jet lag.

Of note, plasma viscosity is the preferred used blood test over erythrocyte sedimentation rate at the University Hospitals Bristol, in line with CRP, to check on the acute phase response [26].

Patients stayed overnight in the Rheumatology Centre where a 24-h research facility was provided. On the first occasion (night A), an intravenous (iv.) cannula was inserted into the antecubital fossa and flushed with 0.9% saline. At least 1 h after the iv. cannula was placed, but usually at 16h00, a blood sample (2 ml) was taken through the iv. cannula and the cannula flushed with 0.9% saline. Further blood samples were taken at 18h00, 19h00, 21h00, 22h00, 23h00, 24h00, 01h00, 02h00, 03h00, 04h00, 05h00, 06h00, 07h00, 08h00, 09h00, 11h00, 13h00, 14h00 and 16h00. Samples after 22h00 and before 07h00 were taken with as little disturbance as possible using low level lighting. Dinner, breakfast and lunch were served to all patients at 18h00, 07h00 and 13h00, respectively.

After night A, each patient was randomized (by the hospital pharmacy) to take 7 mg/day prednisolone in the morning (on waking) or 7 mg/day modified- (delayed-) release prednisone (Lodotra®/RAYOS®, Horizon Pharma Inc., IL, USA) in the evening (22h00). Treatment was not blinded. Treatment continued until the day after the patient was admitted 14 days later for 24-h venous sampling (night B). All study medication was then discontinued and standard therapy commenced (15 mg/day prednisolone taken in the morning). Patients were reviewed at 10h00 after approximately 2 weeks to evaluate clinical response and to obtain a final blood sample (day C).

Laboratory measurements

Samples were collected into chilled ethylenediaminetetraacetic acid blood collection tubes and centrifuged at 5750 rpm for 7 min immediately after collection. Plasma was separated and stored at -20°C before transfer to -80°C within 25 h of collection. In addition to IL-6, other pro- and anti-inflammatory cytokines were measured including IL-4, IL-8, IL-10, TNF, IL-1ra and IL-1β. Cytokines were measured by Luminex Multiplex Detection technology using Beadlyte reagents (Lincoplex, MO, USA). The inter- and intra-assay coefficients of variation with this technique are below 10% for all cytokines measured. Lower limits of detection were 0.79 pg/ml for IL-6, 2.87 pg/ml for IL-4, 0.32 pg/ml for IL-8, 0.41 pg/ml for IL-10, 0.22 pg/ml for TNF, 7.47 pg/ml for IL-1ra and 0.19 pg/ml for IL-1β.

Clinical assessments

Clinical assessments were undertaken on arrival at the research unit and at each subsequent visit. Patients reported the duration of morning stiffness in minutes for the previous day. In addition, pain was assessed using a 100 mm visual analog scale for the question: 'How much pain have you had in the last 24 h?' using anchors of no pain to severe pain. Using a visual analog scale, patients were also asked: "Considering all the ways your pain and/or stiffness affect(s) you, please mark on the line how well you think you are doing," with anchors of very well to very badly.

During nights A and B fatigue was assessed using the Bristol Rheumatoid Arthritis Fatigue Multidimensional Questionnaire [27], and anxiety and depression were assessed using the Hospital Anxiety and Depression Scale [28].

Sample size

In the absence of numerical data about changes in IL-6 in PMR, sample size was based on biological considerations. Previous work in RA indicated that the pattern of variations in serum cytokines could be reasonably well captured with approximately 12 subjects [19,20]. Therefore the study ended when the target of 12 recruited patients was reached.

Statistical analysis

The mean and 95% CI were calculated for IL-6 and other cytokines for all patients taken together at each time point over 24 h on night A. For night B, the mean and 95% CI were calculated separately according to treatment and compared using the unpaired t-test. The changes between night A and night B were compared within patients using paired t-tests. Area under the curve was calculated for IL-6 for each patient on each occasion and the change in mean values compared between treatment groups. Percentage change in reported duration of morning stiffness between night A, night B and day C were compared within patients using paired t-tests and between groups with an unpaired t-test. Pearson correlation coefficient was used to compare duration of morning stiffness and peak plasma IL-6 concentration. All p-values were two-tailed and significance was defined as $p < 0.05$.

Results

Patients

Of 35 patients invited to take part in the study, 12 were recruited. All patients presented with a classical history of upper and lower limb girdle muscle pain and stiffness, with marked disability and a marked circadian variation in the severity of symptoms. Six patients were randomized to treatment with prednisolone and six to treatment with modified- (delayed-) release prednisone. Two patients were not included in the analysis because of technical difficulties with blood samples (one patient) and revision of the diagnosis (one patient). Characteristics of the ten patients included (seven females and three males; age range: 67–79 years) are shown in Table 1.

Table 1. Baseline characteristics of patients included in the study.

Patient	Age (years)	Gender	Past medical history	Trial treatment	Days between night B and day C†	Initial plasma viscosity (mPa.s)
A	70	Female	Unremarkable	P	15	2.13
B	67	Female	Epilepsy, hypothyroidism and aortic stenosis	P	15	1.75
C	79	Female	Type 2 DM, bilateral CTS, OA and depression	P	15	1.80
D	68	Female	Hypertension, IHD, hiatus hernia, asthma and hay fever	P	22	1.80
E	79	Male	Hypertension and IHD	P	16	1.96
F	75	Male	Hypertension, spinal stenosis, gout and OA	P	14	1.95
G	79	Female	IHD and trigeminal neuralgia	M	14	1.75
H	77	Female	Hypertension and atrial fibrillation	M	15	1.73
I	78	Female	Type 2 DM, hypertension, OA, IHD and cataract	M	15	1.90
J	67	Male	Hypertension, IHD and psoriasis	M	15	1.79

†Day C is following 15 mg/day prednisolone for 2 weeks.
CTS: Carpal tunnel syndrome; DM: Diabetes mellitus; IHD: Ischemic heart disease; M: Modified- (delayed-) release prednisone; OA: Osteoarthritis; P: Prednisolone.

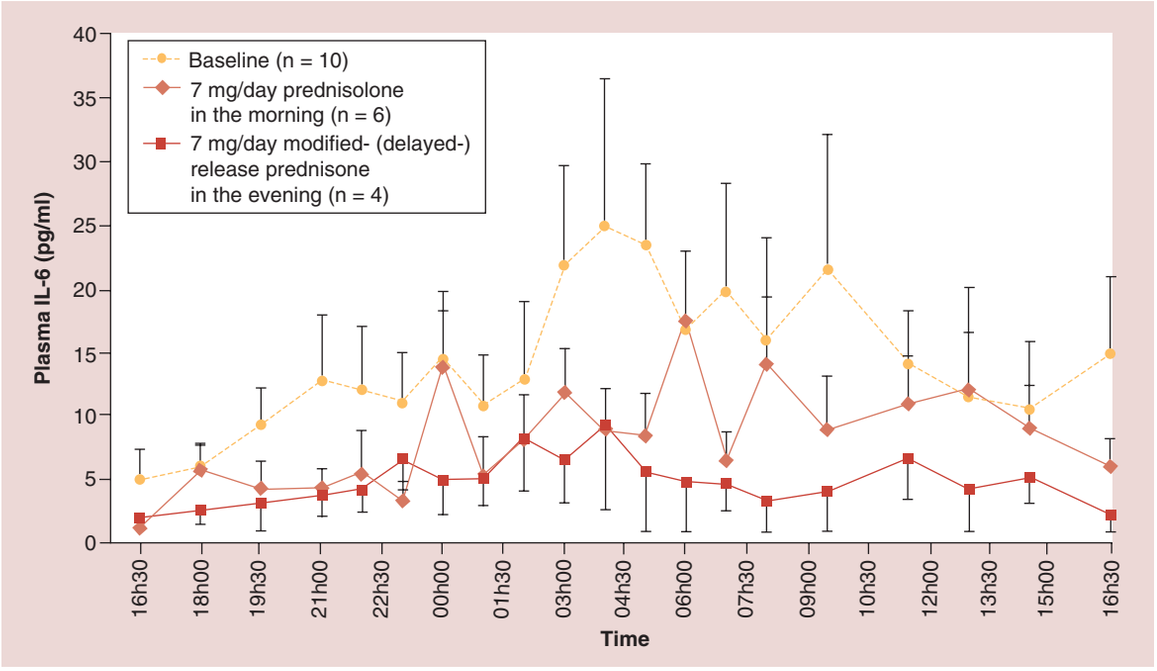

Figure 1. Mean (standard error of the mean) plasma IL-6 concentrations at baseline and after 2 weeks of glucocorticoid treatment. $p < 0.01$ for differences between all three curves.

Cytokines

In untreated patients, there was a marked circadian variation in plasma levels of IL-6 as shown in Figure 1, with a peak in IL-6 concentration occurring in the early hours of the morning. Also shown in Figure 1, the amplitude of circadian variation was reduced with GC treatment, particularly with modified- (delayed-) release prednisone.

Compared with untreated patients, peak plasma IL-6 concentration and total IL-6 area under the curve were significantly reduced with GC treatment (Table 2), by 15.8 and 39.6%, respectively, with morning prednisolone. However, there was a markedly greater reduction from baseline in peak plasma IL-6 (73.5%) and total IL-6 (62.2%) with modified- (delayed-) release prednisone taken in the evening, with a significant difference between treatments ($p = 0.0013$). This was reflected in the mean morning IL-6 plasma concentrations (measured at 09h00), which were reduced from baseline by 53.9% with 7 mg/day morning prednisolone and by 82.4% with 7 mg/day modified- (delayed-) release prednisone in the evening. This compared with an overall 80.6% reduction in all patients taken together at day C, achieved after 2 weeks of treatment with twice the dose (15 mg/day) of prednisolone in the morning.

The other cytokines measured (at 6-hourly intervals) showed no clear indication of circadian variation. Levels were above the lower limit of detection for TNF (ten patients), IL-8 (eight patients), IL-4 (three patients), IL-1ra (two patients), IL-1β (two patients) and IL-10 (two patients).

Clinical assessments

Mean duration of morning stiffness in untreated patients was 99 min (standard deviation 51) with a significant reduction from baseline with GC treatment (Table 3). Patients taking 7 mg/day prednisolone in the morning showed a non-significant 42.1% reduction in reported morning stiffness after 2 weeks ($p = 0.09$), compared with a 90.4% reduction in those taking modified- (delayed-) release prednisone ($p = 0.02$) (Figure 2). Treatment with 7 mg/day modified- (delayed-) release prednisone in the evening achieved similar percentage reduction in mean duration of morning stiffness as achieved at day C with twice the dose (15 mg/day) of prednisolone in the morning.

The other clinical variables assessed all showed improvements in all patients, but with the small numbers of patients involved, there were no clear or statistically significant distinctions between treatment groups. For all patients taken together on nights A and B, duration of morning stiffness correlated with peak plasma IL-6 concentration ($R = 0.464$; $p < 0.05$).

Discussion

The main and previously unreported findings from this study are the large circadian morning, the correlation between peak concentration of IL-6 and duration of morning stiffness, and the marked reduction in both IL-6 and duration of morning stiffness with modified- (delayed-) release prednisone.

Table 2. Changes in plasma IL-6 peak values (pg/ml) and area under curve.

	Prednisolone 7 mg in the morning			Modified- (delayed-) release prednisone 7 mg at night		
	Night A	Night B†	Percentage reduction	Night A	Night B†	Percentage reduction
Peak value	21.2	17.9	15.8‡§	38.1	10.1	73.5‡§
AUC	295.5	178.5	39.6‡	300.2	113.5	62.2‡§

†Night B is 14 days after night A. Patients were treated with study medication between night A and night B.
‡$p < 0.001$ for night A compared with night B.
§$p < 0.01$ for modified- (delayed-) release prednisone compared with prednisolone in the morning.
AUC: Area under the curve.

In untreated PMR, IL-6 concentrations were substantially elevated compared with those reported for normal volunteers [19], and were similar to those reported for RA [17–20]. The circadian variation in IL-6 seen in this study was also similar to that reported for RA [19,20], where there is evidence that IL-6 originates in the synovial fluid and concentrations may be 100-times greater than in plasma throughout the night [29]. The origin of IL-6 in PMR remains undetermined and, although some authors include peripheral synovitis within their definition of PMR, none of the patients in this study had any evidence of inflammatory arthritis. None of the other cytokines measured in this study showed consistently elevated concentrations or any evidence of circadian variation. It is possible that IL-6 is controlled by, or linked to, other cytokines not measured here (e.g., IL-17 [30]) and that these may show circadian variations.

The nature of circadian assessments, and the resultant demands on patients, limits the size of any such study. Consequently, the number of patients in this study was small and powered for the primary objective. Nevertheless, although not powered to draw definitive clinical conclusions, we took the opportunity to evaluate differential effects of GC treatment administered in the morning and evening. Despite the small number of patients, the difference between the effects of treatment with modified- (delayed-) release

Table 3. Patient reported duration of morning stiffness (min).

Patient	Night A	Night B†	Day C†	Change		Percentage reduction compared with night A	
				Night A to night B	Night B to day C	Night B	Day C
Prednisolone in the morning							
A	60	15	0	45	15	75	100
B	90	45	0	45	45	50	100
C	180	120	15	60	105	33	92
D	60	60	0	0	60	0	100
E	120	120	5	0	115	0	96
F	180	10	0	170	10	94	100
Mean	115	61.7	3.3	53.3	58.3	42.1	97.9*
SD	55	48.9	6.1	62.4	44.2	38.7	3.5
Modified- (delayed-) release prednisone at night							
G	60	0	0	60	0	100	100
H	120	30	0	90	30	75	100
I	90	3	0	87	3	97	100
J	30	3	5	27	-2	90	83
Mean	75	9	1.3	66	7.8	90.4*	95.8*
SD	38.7	14.1	2.5	29.3	15	11.1	8.3

†Night B is 14 days after night A; day C is 14 days after night B. Patients were treated with study medication between night A and night B, and with 15 mg/day prednisolone in the morning between night B and day C.
*$p < 0.05$.
SD: Standard deviation.

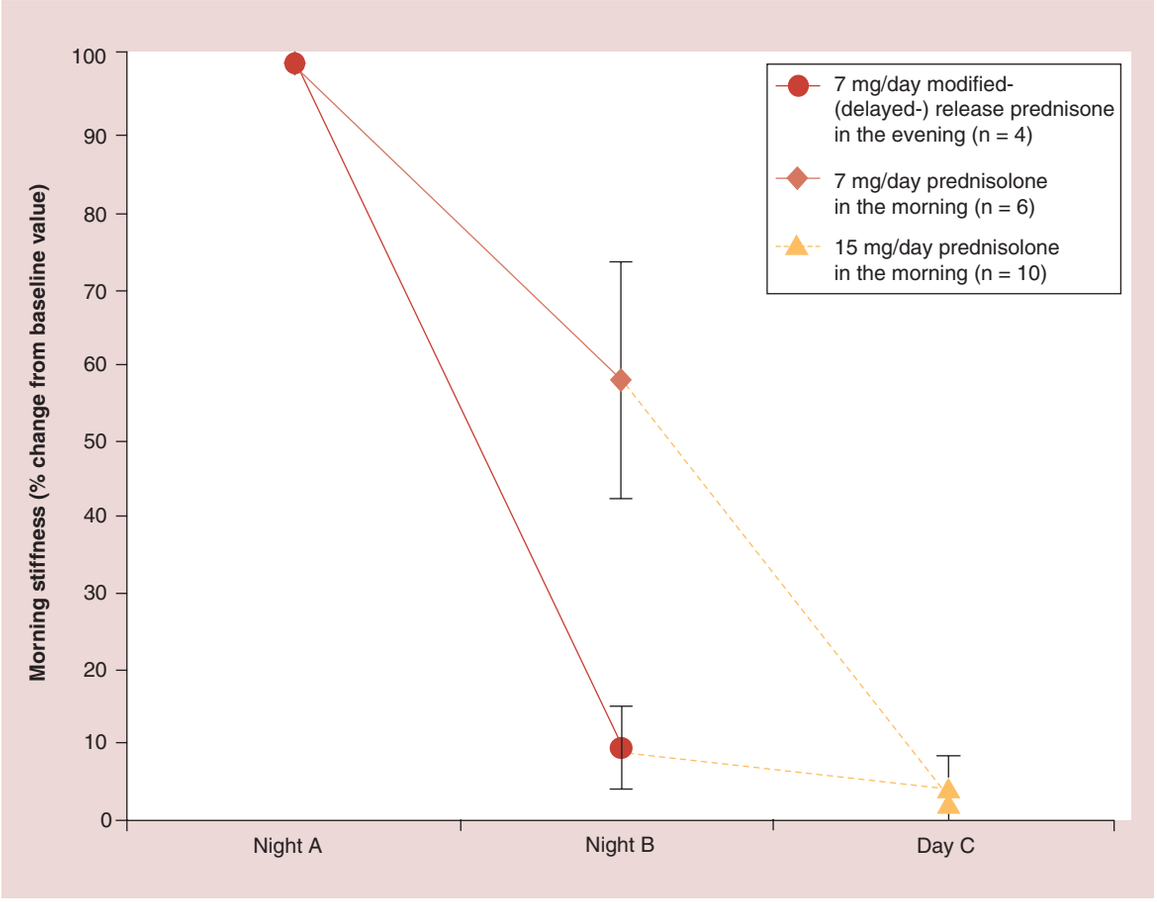

Figure 2. Mean (standard error of the mean) percentage change in morning stiffness. p = 0.044 for difference at night B.

prednisone and morning prednisolone was large and statistically significant. Modified- (delayed-) release prednisone reduced total and peak IL-6, and the duration of morning stiffness, significantly more than the same dose (7 mg/day) prednisolone administered at the conventional time in the morning. Similar results have been reported in patients with RA [20,21], which supports the hypothesis that there may be an enhanced effect of GC when administration is timed to coincide with the nocturnal rise in IL-6 [18].

The improvement in morning stiffness in patients with PMR taking 7 mg/day modified- (delayed-) release prednisone in the evening was almost as much as that obtained when patients took 15 mg/day prednisolone in the morning. This is the conventional GC dose for newly diagnosed patients, and generally results in rapid and complete suppression of symptoms, usually within 24–48 h [31]. Such doses of GC are associated with substantial adverse effects but lower doses have not proved sufficient to control PMR using traditional dosing regimens [2]. If the findings from this exploratory study are confirmed in a larger study, this would suggest that use of modified- (delayed-) release prednisone may lead to a reduction in GC dose with the potential to reduce GC-induced adverse effects. These results provide evidence to aid in the design of such a double-blind, randomized, controlled trial to compare the effectiveness of a reduced dose of modified- (delayed-) release prednisone and standard treatment of 15 mg/day prednisolone in the morning. The possibility that standard GC given at 22h00 might have greater efficacy has been considered in the past but there are good reasons to specifically target the early morning [32].

The study had a number of limitations. In addition to the small number of patients involved, participants were not blind to study treatment. This may have influenced patient reports of morning stiffness. However, there was a correlation between reported duration of morning stiffness and peak plasma IL-6 concentrations, suggesting that such a biasing effect, if present, was small. There was considerable difference between treatment groups in the mean duration of morning stiffness at baseline. The loss of two patients from the group treated with modified-

(delayed-) release prednisone may have contributed to variability between groups.

Conclusion

In conclusion, PMR shows marked circadian variation in plasma IL-6, and peak cytokine levels correlate with duration of morning stiffness. The possibility that IL-6 levels and morning stiffness are related was reinforced by their common response to GC treatment. Although this was a small short-term study, 7 mg/day modified- (delayed-) release prednisone taken in the evening reduced night time IL-6 and duration of morning stiffness significantly more than the same dose of prednisolone given in the morning, raising the possibility that it may be sufficiently effective to treat patients with a lower dose of GC and thereby reduce the potential for adverse effects. To be adequately established this will require a large scale, double-blind randomized controlled trial.

Future perspective

The potential for GC use at night is enhanced by the natural rhythm of cortisol production, which is at its lowest at approximately 02h00. We hypothesize that lower doses of GC will be needed to control PMR symptoms when modified- (delayed-) release prednisone is used, and that this will substantially reduce the occurrence of adverse effects and simplify and enhance the management of PMR. The next step will be to establish, with greater reliability than that reported here, the dose response relationship between modified- (delayed-) release prednisone and morning symptoms. With this information our hypothesis can undergo specific testing in a long-term randomized controlled trial.

The origin of IL-6 in PMR is unknown. In uncomplicated cases there is no evidence of synovitis. Circulating white blood cells, blood vessel endothelial cells, and noninflammatory cells such as hepatocytes can all produce IL-6. It is conceivable that there is no specific focus of inflammation, and that PMR is an 'IL-6 overproduction disease'.

Links between stiffness, fatigue and plasma IL-6 concentrations have been hinted at in RA and PMR. This study adds a further impetus to the exploration of these links, perhaps seeking occasions when stiffness or fatigue respond differently than other symptoms and measuring correlations between symptom changes and IL-6 changes.

Of one thing we are confident: the use of chronobiology in the management of diseases with circadian variation in symptoms will increase.

Author contribution

SA Zakout participated in study design, managed recruitment and sample collection, made substantial contributions to data analysis and interpretation, and wrote the first draft of the manuscript. LL Clarke conceived of the study, participated in study design, and made substantial contributions to data analysis and interpretation and critical revision of the manuscript. D Jessop participated in study design and data analysis, and made substantial contributions to data interpretation and critical revision of the manuscript. RH Straub performed the cytokine assays and made substantial contributions to data interpretation and critical revision of the manuscript. JR Kirwan conceived of the study, led the design of the study, participated in recruitment and sample collection, made substantial contributions to data analysis and interpretation and critical revision of the manuscript. All authors read and approved the final manuscript.

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Executive summary

Polymyalgia rheumatica is characterized by profound morning stiffness

- In rheumatoid arthritis, morning stiffness is associated with nocturnal IL-6 and significantly improved with modified- (delayed-) release prednisone (taken at 22h00 for release of glucocorticoid during the night).
- A similar pattern of the circadian variation in IL-6 and relationship with morning stiffness are anticipated to occur with polymyalgia rheumatica.
- Night time glucocorticoids would be superior to conventional standard morning preparations in alleviating morning stiffness in polymayalgia rheumatica.

Conclusion

- Plasma levels of IL-6 showed marked circadian variation.
- The possibility that modified- (delayed-) release prednisone offers a treatment advantage over standard therapy should be tested in in a large scale, double-blind, randomized controlled trial.

Future perspective

- The use of chronobiology in therapeutics will increase.

other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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