Editorial

Matching Therapy to Body Rhythms: An Endocrine Approach to Treating Rheumatoid Arthritis

The value and efficacy of corticosteroids in treatment of rheumatoid arthritis (RA) has been recognized ever since the Nobel Prize in Physiology and Medicine was awarded in 1950 for the astonishing discovery of Edward Kendall, Philip Hench, and Tadeus Reichstein[1]. The description of Hench's treatment of the first patient with Kendall's compound E (later known as cortisone) reads like a story out of the annals of the miracle cures at Lourdes[2]. The young woman, unable to walk and bedridden with severe debilitating RA for 4 years, gets up, walks and leaves hospital recovered, only 4 days after treatment with daily intramuscular injections of the drug. The Nobel Prize was awarded to this team only one year after this observation, and after treatment of another couple of dozen patients[3]. Prednisone has since been a mainstay of treatment of RA and other inflammatory/autoimmune conditions.

The major stumbling block for this otherwise miraculous drug has been its severe side effects when used in high doses and for prolonged periods of time. These include adrenal insufficiency; osteoporosis; metabolic syndrome, including diabetes; central fat deposition; skin atrophy; "moon" face; impaired resistance to infection, with increased severity and frequency of sometimes life-threatening infections; and the sometimes under-appreciated side-effect of severe mood disorders including hypomania, manic symptomatology, and severe depressive disorder, including suicidality[4,5]. These are not surprising in light of the similar symptoms seen in Cushing's disease patients with pituitary tumors and elevated levels of the endogenous hormone cortisol.

The challenge, then, for over half a century has been to capture the beneficial antiinflammatory/immunosuppressive therapeutic effects of corticosteroids while minimizing their deleterious side effects. Until recently, the only approach to achieve this was to use very low doses of 10 mg prednisone per day or lower. This has some effectiveness, especially in RA, as these patients seem to be particularly sensitive to small doses of the drug. However, symptoms, particularly morning joint stiffness, still break through on such low-dose treatment. Since, under normal circumstances, the endogenous hormone cortisol is released from the adrenal glands in a circadian fashion, it is logical to predict that administering the drug in a manner that mimics the physiological pattern of release should go a long way towards reducing many of the side effects. This principle has long been recognized in endocrinology in treatment of diabetes with insulin. In that condition, it is accepted practice that the hormone should be administered in as close to physiological patterns as possible, at doses and times that coincide with the expected or actual levels of blood glucose. Until recently, however, in the case of RA, rheumatologists have not had the luxury of having an easily measurable plasma or tissue biomarker comparable to blood glucose in diabetes, which can be measured, and against which dosing with corticosteroids could be matched. Nor have we had a preparation of corticosteroids that could be easily administered in the middle of the night, at a time when the blunted HPA axis in patients with RA needs an extra boost.

The current study by Alten and colleagues[6], coupled with 2 studies recently published by this group[7,8], does just that. In the initial studies, Buttgereit, *et al* showed improved effectiveness of a preparation of a novel modified-release (MR) prednisone formulation, which releases the drug at about 2:00 AM when administered at bedtime, relative to immediate-release (IR) prednisone administered in the morning (between 6:00 and 8:00 AM). This means, as the authors point out, that the MR prednisone is released during the rising phase of the circadian cycle, which begins around 2:00 AM, prior to the rise of early morning proinflammatory cytokines. In the first study, the authors monitored clinical symptoms (morning stiffness of the joints), and plasma interleukin 6 (IL-6), a biomarker of inflammation known to exhibit circadian fluctuations in RA, and found this chronotherapy treatment regimen to be more effective in reducing morning joint stiffness and IL-6 levels than the IR

See HPA axis function in RA patients taking night-release prednisone, *page 2025*

prednisone regimen over a 3-month time course. Their second article showed that the reduction in morning joint stiffness and IL-6 levels was sustained during treatment with MR prednisone up to 12 months. Moreover, prednisone chronotherapy was shown to be safe and well tolerated.

In the current study[6], the authors evaluate the effects of longterm treatment with low doses of the MR prednisone preparation on the activity of the HPA axis. The premise is that if this treatment regimen does indeed mimic the physiological pattern of release of corticosteroids, then HPA axis function should remain intact and will not be suppressed, as generally occurs during longterm treatment with corticosteroids. In the study, the authors evaluate HPA axis function with a corticotrophin-releasing hormone (CRH) stimulation test, in which exogenous human CRH (corticorelin) is administered. Lack of cortisol release in response to this stimulus (as well as low resting cortisol levels) indicates relative adrenal insufficiency.

One drawback of this study is the small 'n' (only 28 subjects). Nonetheless, no deterioration or onset of adrenal insufficiency was noted in the patients treated with the chronotherapy regimen for up to 12 months. This new and simple approach to administration of an old drug according to physiological parameters is logical and holds future promise for reducing side effects in therapy with corticosteroids. Additional studies with considerably larger numbers of subjects will be needed to verify these findings. Further, additional outcome measures will also be needed to evaluate whether this chronotherapy regimen also protects patients from other deleterious side effects of prednisone, while still effectively reducing inflammatory symptomatology. If these findings hold up, this highly effective and extensively used drug will be even more useful in the treatment armamentarium of RA and other inflammatory disorders. Finally, rheumatologists will be able to approach RA therapy much like endocrinologists approach diabetes therapy — replacing the missing hormone in the most physiological manner possible.

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