Morning Glucocorticoids Versus Night Glucocorticoids: How Chronotherapy May Optimize Long-Term Glucocorticoid Use in Rheumatoid Arthritis

Activity Director: Discussion

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Dr. Cutolo has given us an excellent review of the complexities and advances in the field of glucocorticoid therapy. If you think back it was the goal several decades to seize on the circadian rhythms of steroid production but then it was to give them every other day. Why? Because this would preserve the hypothalamic-pituitary-adrenal axis (HPA) and minimize side effects. Unfortunately we readily appreciated that when administered this way they were far less effective in relieving signs and symptoms of inflammatory diseases.

Today we have a new view and recognize that these agents are active via both classic genomic and non-genomic mechanisms of action. In addition, we now appreciate that there is a circadian rhythm of pain, stiffness, and disability in rheumatoid arthritis (RA) that is related to cyclic release of inflammatory mediators and counterbalancing regulators. It should be no surprise to we rheumatologists to learn that our patients’ early morning stiffness is preceded by surges of IL-6 and other pro-inflammatory cytokines. This should not be surprising given other well documented shifts in the neuroendocrine network including changes in melatonin and prolactin, both of which have been demonstrated to activate the immune system. Preventing the nocturnal rise in IL-6 and other pro-inflammatory mediators could enhance the effectiveness of glucocorticoids, specifically by dosing these drugs at strategic times during the day. Unfortunately given the absorption and pK/pD effects of short acting glucocorticoids this would require awakening in the night to take such medications thus disrupting sleep. Advances in delayed release glucocorticoids now offer an additional weapon in our armamentarium to treat inflammatory diseases, specifically by timing the delivery of the drug before the circadian surge in inflammatory activity caused by the elevated nocturnal levels of proinflammatory cytokines. Surprisingly while more effective than equivalent doses of glucocorticoid given early in the day (i.e. traditional time point) the delayed release glucocorticoids are not more suppressive to the HPA. While the EULAR guidelines acknowledge that glucocorticoids added at low to moderately high doses to synthetic DMARD monotherapy or combinations of synthetic DMARDs provide benefit as short-
term therapy, the guideline also acknowledges that the timing of glucocorticoid administration might influence its efficacy.

Therefore:

- In RA patients, stiffness and functional disability seen in the early morning hours is consistent with reduced night adrenal cortisol production, which under the chronic stress of the disease, becomes insufficient to inhibit the immune/inflammatory reaction.
- The concept of optimizing glucocorticoid therapy by following the chronobiology of RA may potentially be achieved by the use of delayed release glucocorticoids, which follow the circadian rhythm.

So the question now is whether chronotherapy with glucocorticoids will teach this old dog a new trick.

References