Timing Prednisone Release Eased Stiffness in RA

BY MICHELE G. SULLIVAN

A modified-release formulation of prednisone reduced morning stiffness duration in patients with rheumatoid arthritis, according to data presented at the annual European Congress of Rheumatology.

The new formulation is designed to be taken at bedtime. The medication is released about 4 hours after ingestion, with the goal of adapting glucocorticoid drug release to the circadian rhythms of endogenous cortisol and symptoms of the disease, both of which have their peaks during the early morning hours. It has been theorized that morning glucocorticoid dosing only inadequately controls the circadian rhythm of RA symptoms in these patients, Prof. Frank Buttgereit, of Charité Medical University of Berlin, said in an interview.

"It's well known that symptoms of rheumatoid arthritis follow circadian rhythms and are typically most promi-

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nent in the early morning hours," he said. "Therefore, the timing of systemic glucocorticoid therapy may be important with respect to the natural secretion of endogenous glucocorticoids as well as the control of symptoms."

Findings from earlier research conducted by Prof. Buttgereit and his associates involved a 3-month randomized, controlled trial of 288 patients with longstanding active rheumatoid arthritis (Lancet 2008;371:205-14).

The data he presented at EULAR concerned 219 patients who completed a new 9-month follow-on open-label trial of the same group, during which all patients took the modified-release formulation.

At baseline, the patients' mean age was 55 years; their mean duration of disease was 10 years. Patients who were randomized to the active group took a placebo tablet in the morning and the study drug in the evening. The comparator group took immediate-release prednisone in the morning and placebo in the evening. The prednisone dose was individually titrated (range, 3-10 mg/day).

The mean relative reduction of morning stiffness duration was significantly higher in the modified-release group than in the immediate-release group (23% vs. 0.4%). Patients taking the modified-release drug had a significantly greater decrease in duration of morning joint stiffness than did those taking the immediate-release tablet (44 vs. 23 fewer minutes of morning stiffness). Median levels of interleukin-6 were also reduced in the modified-release group compared with the immediate-release group (29% vs. 0%).

Adverse events led to premature discontinuation of the study drugs in 8% of patients in the modified-release group and 7% of those in the immediate-release group. The frequency of serious adverse events was low and similar in both groups (3% vs. 2%).

The combined results of the randomized and open-label trials, showed that in both groups, morning stiffness duration remained similarly low over the entire study duration, he said. At 12 months, the reduction was somewhat greater in the group that had taken the modified-release formulation during both trials (55%) than among those who took the immediate-release during the first trial and the modified-release during the follow-on study (45%).

Among his expected conclusions is that "bedtime administration of prednisone via the new modified-release tablet provides significantly greater efficacy for at least 12 months over conventional immediate-release prednisone, due to prednisone release which occurs prior to the circadian flare-up of IL-6 synthesis and inflammatory activity."

The study was sponsored by Merck Pharma GmbH and Nitec Pharma AG. Prof. Buttgereit and some of the coauthors said they had received consulting and grant funding from the companies. ■