Combination NSAID, Acid Suppressant Tablet May Avert Gastric Injury

BY BRUCE JANCIN
Denver Bureau

HONOLULU — A novel fixed-combination tablet comprising an immediate-release proton pump inhibitor plus an enteric-coated NSAID showed considerable promise for the prevention of upper GI mucosal injury in a pilot study, Dr. W. James Alexander reported at the annual meeting of the American College of Gastroenterology.

Large clinical trials are now being planned to evaluate the efficacy of the fixed-combination drug, which is designed to ensure adherence to gastroprotective therapy when recommended for NSAID users, explained Dr. Alexander, senior vice president of product development and chief medical officer at Pozen Inc., Chapel Hill, N.C.

Pozen has been issued a patent for the fixed-combination tablet, known for now as PN 100.

Each tablet contains 15 mg of immediate-release lansoprazole surrounding a core of 500 mg of naproxen, which has a pH-sensitive enteric coating.

Dr. Alexander reported on 60 healthy volunteers randomized to 14 days of one of three treatment regimens: PN 100, twice daily; 500 mg of enteric-coated naproxen, twice daily; or 15 mg of delayed-release lansoprazole in the morning plus naproxen 500 mg, twice daily, which is the type of gastroprotective regimen most often used in current clinical practice.

Endoscopy performed on day 14 by a gastroenterologist blinded to treatment status revealed 5 subjects in the PN 100 group had Lanza grade 3 or 4 mucosal lesions, compared with 15 subjects on twice-daily enteric naproxen and 14 on delayed-release lansoprazole plus naproxen twice daily. Two patients on enteric naproxen developed gastric ulcers, as did one on delayed-release lansoprazole plus naproxen. None of the PN 100–treated subjects developed gastric ulcers.

Large clinical trials are being planned to evaluate the combo agent's efficacy.

DR. ALEXANDER

The mean cumulative number of erosions found at endoscopy on days 8 and 14 was 10 in the PN 100 group, 26 with enteric naproxen alone, and 19 with delayed-release lansoprazole plus naproxen.

Findings from 24-hour gastric acid pH monitoring indicated nocturnal acid suppression was better in patients taking twice-daily PN 100 than in those using the once-daily delayed-release lansoprazole preparation plus twice-daily naproxen. ■

Early RA Treatment Forestalled the Need for Later Surgical Intervention

BY NANCY WALSH
New York Bureau

SAN DIEGO — Patients in the Utrecht Rheumatoid Arthritis Cohort who began treatment early in the course of disease were less likely to need joint surgery later on, Dr. Suzan M.M. Verstappen said at the annual meeting of the American College of Rheumatology.

In the ongoing Utrecht cohort study, begun in 1990, patients initially were randomized to early treatment with methotrexate, intramuscular gold, or hydroxychloroquine—or to a "pyramid" treatment approach, which was at that time the traditional paradigm.

In the pyramid strategy patients first take aspirin and other NSAIDs, delaying treatment with the DMARDs until later in the course of disease.

At the time of the first analysis, in 1994, it was apparent that patients in the early DMARD group were faring better, and henceforth, all patients were randomized to one of the three drugs, she said.

"In the present study we investigated the prevalence of joint surgery and looked at which clinical, radiographic, and demographic variables in the first 2 years of treatment—when we all know a lot of disease activity occurs—predicted later joint surgery," said Dr. Verstappen of University Medical Center Utrecht (the Netherlands).

The cohort included 482 patients, whose mean age was 56 years and mean disease duration was 7.2 years. A total of 70% of the patients were female, and 65% were rheumatoid factor positive.

Overall, 144 patients underwent a total of 256 surgeries. Of these interventions, 32% were major surgeries such as total joint replacement, 50% were intermediate procedures such as arthrodesis, and 18% were minor interventions such as arthroscopy.

By the end of the fifth year, approximately 18% of patients had required at least one type of surgical intervention, according to Kaplan-Meier survival analysis. Overall mean survival time until surgery was 10 years, and for the major surgical interventions, the mean survival time was 12 years.

With regard to the need for surgical intervention among patients who responded to drug therapy, compared with those who were nonresponders, at the end of the first year no significant difference was seen between the two groups.

But by the end of the second year patients who responded to drug therapy had fewer surgical interventions, she said.

Furthermore, surgical interventions were significantly more common in two patient subsets: those whose functional disability was worse at baseline and those who initially were randomized to NSAID therapy.

Multivariate Cox regression analyses of the 1-year data found that female gender, delayed start with DMARDs, and radiographic progression were predictive of later surgery.

Hazard ratios for these variables were 1.55, 1.68, and 1.016, respectively, Dr. Verstappen said.

At the end of the second year, only a delayed start of DMARD therapy and radiographic progression were predictors, with hazard ratios of 1.73 and 1.029, respectively, on the multivariate analysis.

The need for joint surgery can be considered an outcome measure reflecting an unfavorable course of rheumatoid arthritis, and a significant number of patients still require some type of surgical intervention, Dr. Verstappen said.

"This is the first study to demonstrate that early treatment prevents later surgical intervention, and we hope that with more early aggressive treatment the percentage of patients requiring surgery later on will decrease further," she said. ■

Repeat Courses of Rituximab Don't Seem to Trigger Toxicity

BY NANCY WALSH
New York Bureau

SAN DIEGO — A second or third course of treatment with rituximab was safe and effective in patients with active rheumatoid arthritis enrolled in an open-label extension study, according to two poster presentations at the annual meeting of the American College of Rheumatology.

The monoclonal antibody rituximab had previously been investigated in two phase II studies in rheumatoid arthritis, and patients who had demonstrated improvement in the first treatment course (C1) were eligible to enroll in the extension phase.

Thus far 192 have enrolled; 141 have received a second course (C2) of rituximab treatment, and 25 received a third course (C3), according to Dr. Paul Emery of the Leeds (England) General Infirmary.

During C1, patients received intravenous rituximab in a dosage of 500 mg or 1,000 mg on days 1 and 15, along with methotrexate, cyclophosphamide, or no disease-modifying antirheumatic drug. They also received corticosteroids or placebo.

During C2, patients received 1,000-mg rituximab on days 1 and 15, 10-25 mg/week of methotrexate, and intravenous glucocorticoid premedication; they also received oral glucocorticoids for two weeks. Responses at week 24 were compared with the C1 and C2 baselines.

There was no evidence of cumulative toxicity with repeated courses of rituximab.

DR. EMERY

In the poster that summarized the safety data from C2, Dr. Emery reported that the percentage of patients who experienced serious adverse events after C2 was similar to that after C1 (11% and 10%, respectively).

There was no evidence of cumulative toxicity with repeat courses of the drug, he noted.

Following C1, there was one serious infection (bacterial arthritis). Four patients experienced serious infections following C2—one each of appendicitis, otitis media, bronchopneumonia, and urinary tract infection.

There have been no reports of serious infections following C3, wrote Dr. Emery.

The majority of infusion-related adverse events were mild to moderate.

A separate poster presented efficacy data from the first 78 patients who have either been followed for 24 weeks following C2 or who withdrew from the trial.

"By all measures, rituximab retreatment following C2 was effective," wrote Dr. Roy M. Fleischmann of the University of Texas Southwestern Medical Center, Dallas.

Disease Activity Score (DAS)-28 fell from a mean of 6.95 at C1 baseline to 4.58 at week 24, and then from a mean of 6.43 at C2 baseline to 4.16.

A total of 47 patients achieved ACR20 responses from the C2 baseline, and 57 achieved good to moderate EULAR responses.

C-reactive protein levels and rheumatoid factor titers both were significantly reduced during the observation periods after C1 and C2.

Rituximab targets CD20-positive B cells, and by binding CD20 it depletes B cells. However, because CD20 is not expressed on stem or plasma cells, B-cell recovery subsequently occurs.

Both B-cell depleted and B-cell recovered patients responded following C2, Dr. Fleischmann wrote.

Dr. Fleischmann disclosed that he has received research grants and consulting fees and is on the speakers' bureau of Genentech Inc.

Dr. Emery disclosed that he has received research grants and consulting fees from Roche. ■