Mortality Easing in Pediatric Rheumatic Disease

BY ELIZABETH MECHCATIE

A study that analyzed data on almost 49,000 children and adolescents enrolled in a U.S. pediatric rheumatology registry found that the overall mortality for pediatric rheumatic diseases was not increased when compared to the general population, results that require further follow-up but were described as "encouraging" by the authors.

"Even for those diseases and conditions associated with increased mortality, the rates were significantly lower than those reported in previous studies," especially for systemic juvenile rheumatoid arthritis (JRA), childhood systemic lupus erythematosus (SLE), dermatomyositis (DM), and vasculitis, reported Dr. Philip J. Hashkes of the Cleveland Clinic and his associates.

The study, which they said was "the largest systematic mortality outcome study in pediatric rheumatology published to date," analyzed mortality outcomes among the 48,885 children newly diagnosed with a rheumatic disease between 1992 and 2001 and enrolled in the Indianapolis PRDR (Pediatric Rheumatology Disease Registry), involving patients from 62 centers in the United States. Children with a malignancy were excluded. Patients were followed for a mean of 8 years.

Almost 64% had an inflammatory diagnosis, of which the majority (almost 40%) was JRA, followed by SLE in almost 6% and Raynaud's phenomenon in almost 5%. Arthralgia was the most common noninflammatory diagnosis, affecting 36% of those with a noninflammatory rheumatic disease. Almost 7,000 patients had more than one rheumatic diagnosis.

To compare the observed survival rates to the expected survival rates, the authors calculated the SMR (standardized mortality ratio, defined as the number of observed deaths divided by the number of expected deaths).

The mortality of the patients in the registry was significantly lower than was the expected mortality of the U.S. population, adjusted for age and sex. Overall, there were 110 deaths (0.23%) among the nearly 48,000 patients for whom complete data were available, for an SMR of 0.65.

Put another way: The 5-year survival rate was 99.77% for the entire group, and was slightly lower for those with connective tissue disease, systemic JRA, and those with primary vasculitis other than Kawasaki disease.

There were significant differences in the SMR for several diagnostic categories and specific diseases. SMR was significantly increased for the categories of connective tissue diseases and primary vasculitis, with the exception of Kawasaki disease and Henoch-Schönlein purpura (HSP). The SMR was significantly greater for SLE (3.06) and DM (2.64), but not for systemic JRA (1.8). The SMR was significantly decreased for pain syndromes (0.41) and arthralgia (0.23). The SMR did not differ significantly for other specific diseases, including all subtypes of JRA, Kawasaki disease, and HSP.

The SMRs in the group of patients with noninflammatory diseases (0.58) and those with inflammatory diseases (0.76) were significantly lower than in the general population; the difference was more significant in the noninflammatory group.

Of all the 110 deaths, 64 (58%) were in patients with an inflammatory disease. The rest, with the exception of one patient whose primary diagnosis was not known, were in patients with a noninflammatory disease.

In 39 cases (35%), the cause of death was related to the rheumatic diagnosis. Other causes of death included treatment complications in 11 patients (10%), nonnatural causes in 25 (23%), and background disease in 23 (21%). In 12 (11%) patients, the cause of death was unknown or not clear.

The investigators found a significant correlation between the rheumatic diagnosis and cause of death: Among the 64 patients who had been diagnosed with an inflammatory disease before their death, 28 (44%) deaths were related to the diagnosis, for which they were being treated by a rheumatologist, compared with 11 (24%) of the 45 patients diagnosed with a noninflammatory disease.

The cause of death among the patients with SLE included renal disease in six cases, pancreatitis in two patients, pulmonary hemorrhage in one patient, and intracranial hemorrhage in one patient. Four died of an infection, including two who had had a bone marrow transplant. Of the patients with JRA who died, two died of macrophage activation syndrome, which the authors said is "probably currently the most common cause of death" in patients with systemic JRA. Two patients died of heart disease, one died of an infection, and one died of a secondary malignancy.

Significant predictors of mortality identified in the study included the age at the first visit. Being older than 14.5 years was associated with a 2.3-fold greater risk of mortality. Other factors that included sex, ethnicity, time from onset of the disease to diagnosis, and initial medication use were not associated with increased mortality.

Any connective tissue diseases, SLE, DM, primary vasculitis (except for Kawasaki disease and HSP), systemic JRA, and a genetic/chromosomal/metabolic disease were also significant predictors of increased mortality, whereas an arthralgia diagnosis was significantly predictive of better survival.

Morality was higher for systemic JRA, SLE, DM, and vasculitis. But the rates were still significantly lower than in previous studies, they said (Arthritis Rheum. 2010;62:599-608). ■

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Major Finding: Overall mortality among children with rheumatic diseases was lower than expected; and although SLE and some other rheumatic conditions were associated with higher mortality, the rates were lower than previously reported for those diseases in this age group.

Data Source: Data from the Indianapolis Pediatric Rheumatology Disease Registry on nearly 49,000 children who were followed for about 8 years.

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Ped Rheumatologists Most Likely to Give COX-2s to Kids

BY AMY ROTHMAN SCHONFELD

Many physicians who care for children feel that selective cyclooxygenase-2 nonsteroidal anti-inflammatory agents have equivalent or greater safety, efficacy, or tolerability and fewer side effects than do coventional NSAIDs. However, in the years since the voluntary withdrawal of rofecoxib and valdecoxib from the market, few practitioners aside from rheumatologists prescribe selective COX-2 NSAIDs for children, according to a report of survey results published in Pediatric Rheumatology.

Investigators e-mailed a link to a 22-question survey to 1,289 pediatricians, pediatric rheumatologists, sports medicine physicians, pediatric surgeons, and pediatric orthopedic surgeons. In all, 84 e-mails were returned as "undeliverable." Despite reminders and incentives, only 338 (28%) of the 1,205 e-mail recipients completed the surveys. Response rate varied by specialty, with the highest response rates from pediatric rheumatologists (100 of 247, 40%) and the lowest for sports medicine specialists (12 of 106, 11%).

Indeed, one limitation of the study was that it was skewed to include a large percentage of pediatric rheumatologists, since investigators were particularly interested in hearing from those who often prescribe NSAIDs, according to Dr. Deborah M. Levy, a pediatric rheumatologist at the Hospital for Sick Children in Toronto, and Dr. Lisa F. Imundo, a pediatric rheumatologist at the Morgan Stanley Children's Hospital of New York–Presbyterian, Columbia University.

Nonrheumatologists frequently (more than once a week) prescribed ibuprofen, naproxen, and ketorolac, but they rarely prescribed any other NSAID. Rheumatologists used a wider variety of medications, most notably ibuprofen, diclofenac, indomethacin, naproxen, celecoxib, and rofecoxib.

About half of the respondents (164 of 330) had never prescribed a selective COX-2 NSAID. By specialty, 72% of pediatricians, 52% of orthopedic surgeons, 79% of pediatric surgeons, and 4% of rheumatologists had never prescribed a selective COX-2 NSAID. The most common reasons for prescribing a selective COX-2 NSAID were for arthritis, musculoskeletal pain, soft-tissue injury, and fracture. Use of these agents was more likely after failure of an NSAID.

Pediatric rheumatologists reported that certain adverse events were more common with conventional NSAIDs than with selective COX-2 agents. Abdominal pain (81% vs. 23%), epistaxis (13% vs. 2%), easy bruising (64% vs. 8%), headaches (21% vs. 1%), and fatigue (12% vs. 1%) were more common with conventional NSAIDs (n = 99), compared with the selective COX-2 medications (n = 95).

COX-2 NSAIDs were rated as equivalent or superior to conventional NSAIDs for safety (66%), pain relief (72%), relief of inflammation (74%), and tolerability (83%) in the opinion of physicians who had prescribed the agents.

Eleven physicians reported that one or more patients had a cardiovascular event while taking an NSAID, all of which were attributed to the patients' underlying diseases, and not to the use of either a conventional or selective COX-2 NSAID, according to the investigators.

Rofecoxib was voluntarily withdrawn from the market in September 2004, and valdecoxib was withdrawn in April 2005, and these events affected physician prescribing habits. For pediatric rheumatologists, 57% said they prescribed selective COX-2 NSAIDs less frequently and 26% said they no longer prescribed them. Consequently, 44% increased their prescriptions of conventional NSAIDs.

Nine conventional NSAIDS (aspirin, etodolac, ibuprofen, indomethacin, ketorolac, meloxicam, naproxen, oxaprozin, and tolmetin) and one selective COX-2 NSAID (celecoxib) currently have Food and Drug Administration–approved pediatric indications. At the time of the survey, no COX-2 NSAID had a pediatric indication. The authors suggest that phase IV, open-label postmarketing studies of conventional and selective COX-2 NSAIDs in children are needed to more accurately assess the risks and benefits of these medications (Pediatr. Rheumatol. Online J. 2010 Feb. 4 [doi:10.1186/1546-0096-8-7]). ■

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