Questions Remain About RA Treatment’s Link to Lymphoma

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New York — Data from large registries ultimately should provide answers about the long-term lymphoma risk associated with the tumor necrosis factor-α (TNF)-blocking drugs, but for now, questions and contradictions remain.

Patients with rheumatoid arthritis (RA) have an elevated risk of lymphoma that has been estimated to be between two- and eightfold. How much of the risk relates to disease activity and how much relates to immunosuppressive treatment is not yet clear. Dr. Jeffrey Greenberg said in reviewing recent studies during a rheumatology meeting sponsored by New York University.

The mortality background excess from the overall risk of lymphoma has emerged from a large Swedish registry that included 74,651 patients who received a diagnosis of RA between 1964 and 1995. Within this cohort, there were 378 cases of lymphoma; these patients were matched with 378 controls from the cohort where the cancer free when the lymphoma patients were diagnosed.

The cases were then analyzed for factors that might influence the development of lymphoma. The investigators also sought to determine whether RA-associated malignancy is disease- and inflammation-driven and could be associated with inadequate immunosuppression, or whether it results directly from immunosuppression.

Level of disease activity strongly predicted risk in this study. Medium overall disease activity was associated with an 8-fold increase in risk, while in lymphoma risk, a high disease activity was linked to a 70-fold increase. There also was a threefold increase in risk among patients with the highest erythrocyte sedimentation rates (Arthritis Rheum. 2006;54:692-701).

The investigators reported that having ever been treated with a traditional disease-modifying antirheumatic drug (DMARD) was not associated with an increased risk. Although increases in risk were seen with some individual drugs such as azathioprine, other drugs such as corticosteroids were associated with relative risk estimates of less than 1, reflecting a reduction in risk. Immunosuppression is the driving force in inflammation-associated lymphomas.

In a separate study, a different group of Swedish investigators looked at the risk of hematopoietic malignancies among RA patients being treated with TNF antagonists. The lymphoma risk was tripled in those being treated with these drugs compared with the general population, but the risk was no different from that in other patients (Ann. Rheum. Dis. 2005;64:1414-20).

Overall, in clinical trials thus far, the standardized incidence ratios for lymphomas were 1.8, but this could be an underestimate because clinical trials are not powered to detect rare events such as malignancies, Dr. Greenberg said. To overcome this lack of power, another group of researchers undertook a meta-analysis of nine randomized trials of patients undergoing anti-TNF therapy, with 3,493 receiving active treatment and 1,512 receiving placebo. In this analysis, the pooled odds ratio for malignancy was 3.3, a finding that was “somewhat inconsistent” with the results seen in the Swedish studies (JAMA 2006;295:2277-85).

The mortality background excess from the overall risk of lymphoma, according to Dr. Greenberg, for example, it included only studies with infliximab and adalimumab, etanercept was omitted. The study also did not account for length of time on the drug. “They simply counted the number of people exposed to the drug versus placebo,” he said. This was in contrast to the method the Food and Drug Administration used in its analysis of the safety of all three TNF blockers, which found no elevations in malignancy rates in patients on these drugs (JAMA 2006;295:1012-21).

As to the method of analyzing drug exposure and risk, “There’s an argument to be made on either side—it’s not black and white—but the results of the meta-analysis have to be taken with a grain of salt,” Dr. Greenberg said.

The opposite approach, of analyzing risk according to time of exposure, had quite different results in another recent report. In an abstract presented at the 2006 meeting of the European League Against Rheumatism, a total of 124 lymphomas were seen during 109,884 patient-years of follow-up. There were 79 observed cases of lymphoma, compared with 45 expected cases, giving a standardized incidence rate of 1.8, which does not differ from background risk in RA.

There were also no statistically significant increases in risk associated with any specific treatments, including DMARDs and biologics (Ann. Rheum. Dis. 2006;65[suppl 2]:S12-3).

With regard to the effects of biologic treatment on lymphoma risk, there are still more questions than answers, Dr. Greenberg said. The way risk is determined also needs to change. “As we move toward personalized medicine, we need to move from population-based risk estimates, where we tell a patient, ‘You have a 1.5-fold risk of developing a malignancy in the next 10 years,’ to a position where we can look at your genetic profile, you have a 10-fold risk of malignancy but an extremely high likelihood of benefiting from this drug,” he said. Then we can balance the risk with the benefit on a personal level rather than relying on overall population-based estimates,” Dr. Greenberg said.

Revised BMI Cut-Offs Reflect Risk in Arthritis

BY LUANN DALLOJAcono  
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Patients with rheumatoid arthritis exhibited increased body fat for a given body mass index when compared with healthy controls in a recent study. This suggests that standard BMI cut-offs in those patients with rheumatoid arthritis should be reduced to more accurately reflect risk for cardiovascular disease, according to Dr. Antonios Stavropoulos-Kalinoglou of the University of Wolverhampton’s Research Institute in Healthcare Science, England, and his associates.

BMI does not distinguish between fat and lean body mass when it uses height and weight to measure body mass. As a result, individuals with the same height and weight, but different muscle content, may have the same BMI but different levels of body fat. This shortcoming should be taken into consideration when determining risk for cardiovascular disease, especially with rheumatoid arthritis (RA) patients, who often experience involuntary loss of lean body mass and an increase of fat mass, according to the researchers (Ann Rheum Dis. 2007 Feb. 8 [Epub doi:10.1136/ard.2006.003019]).

The study included 299 individuals: 174 with RA, 43 with osteoarthritis of the hip or knee, and 82 healthy, medication-free controls by self-report. Body fat was assessed in all participants by bioelectrical impedance using a body analyzer. BMI was calculated based on measured height and weight.

Body fat and BMI differed significantly between those with RA and healthy controls, judging from analyses of covariance findings. For a given BMI, patients with RA showed significantly increased levels of body fat percentage compared with the healthy participants. Patients with RA also showed BMI levels reduced by 1.83 kg/m² compared with the healthy controls for a given body fat.

The study also found that when the widely accepted BMI cut-offs of 25 kg/m² for overweight and 30 kg/m² for obesity were used to classify the subjects in each group, 9% of male and 11% of female RA patients were misclassified as being of normal weight. These misclassifications were corrected when the proposed rheumatoid arthritis-specific BMI cut-offs of 23 kg/m² and 28 kg/m² were used. However, body fat percentage is a better way to assess fat measurement and risk for cardiovascular disease, according to the investigators. They developed a predictive model as part of the study to calculate body fat of RA patients without relying on the sophisticated equipment often needed to measure body fat.

The model, which uses BMI, age, gender, and disease status to determine body fat, was validated using Limits of Agreement Analysis against measured body fat in a group of 342 patients with RA. In that validation group, the model predicted body fat to be 0.4% higher than actual levels, but results were within suitable limits and the cross-validation was “reassuring,” according to the investigators.

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Land Clinic during January 2000 to July 2006, a total of 2,428 patients. Patients were identified as having peripheral artery disease (PAD) from a large Swedish registry that included 74,651 patients who received a diagnosis of RA between 1964 and 1995. Among the 2,116 patients without peripheral atherosclerotic disease (3%), there were 378 deaths, which was “somewhat inconsistent” with the results seen in the Swedish studies (JAMA 2006;295:2277-85).

The meta-analysis of nine randomized trials of patients undergoing anti-TNF therapy, with 3,493 receiving active treatment and 1,512 receiving placebo. In this analysis, the pooled odds ratio for malignancy was 3.3, a finding that was “somewhat inconsistent” with the results seen in the Swedish studies (JAMA 2006;295:2277-85).