TNF Blockers Up Lymphoma Risk

Experts say the study was too small to reach a 'robust conclusion' about such drug-related risks.

BY PATRICE WENDLING
Chicago Bureau

Tumor necrosis factor agents do not increase the overall risk of cancer in patients with rheumatoid arthritis but may be associated with an increased risk of lymphomas, an analysis of data from the South Swedish Arthritis Treatment Group register suggests.

The study is the first to question whether use of anti-TNF-α agents increases the risk of lymphoma independently of disease severity.

Pierre Geborek, M.D., and colleagues at Lund (Sweden) University Hospital, identified 757 patients treated with etanercept (Enbrel) or infliximab (Remicade) from the register and 800 conservatively treated patients recruited from an outpatient clinic and private practices (Ann. Rheum. Dis. 2005;64:699-703).

Patients were followed from initiation of anti-TNF treatment (or July 1, 1997, for the comparison group) until death or Dec. 31, 2002.

In the anti-TNF group, there were 16 tumors (5 lymphomas) in 1,603 person-years at risk, compared with 69 tumors (2 lymphomas) in 3,948 person-years in the control group.

The standardized incidence ratios in the anti-TNF group and the control group were 1.1 and 1.4 for all tumors and 11.5 and 1.3 for lymphomas, respectively.

The increased overall tumor incidence in the control group was mainly due to smoking-related lesions, according to the investigators.

The total cancer risk excluding lymphomas was 0.79 among patients treated with anti-TNF agents and 1.39 in the comparison group.

The unadjusted hazard ratio for lymphoma was 4.9 in anti-TNF–treated patients relative to the conventionally treated patients. The hazard ratio was 5.0 after adjusting for differences in baseline Health Assessment Questionnaire scores, which were used as a marker of severity.

The results for overall tumor standardized incidence ratios in the anti-TNF–treated patients, compared with controls, must be interpreted with caution because of the limited number of observations and the relatively short follow-up period, the investigators wrote.

The withholding of anti-TNF treatment in patients with a known previous cancer also may have contributed to the lower incidence of cancer in this group.

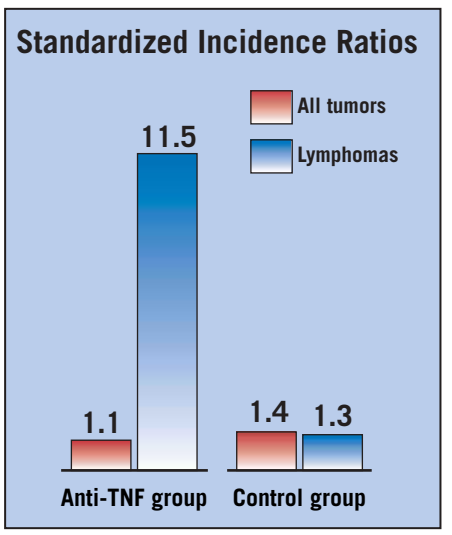
In an accompanying editorial, Jarrod Franklin and colleagues at Manchester (England) University noted the study failed to detect a raised incidence of lymphoma in the control group, despite detecting an increased risk of all-site cancers in this population.

This is surprising, they said; given that the results of several studies would suggest such patients would be at an increased risk of lymphoma.

They welcomed the investigation but agreed it is difficult to reach a "robust conclusion" on the question of anti-TNF-α agents, disease severity, and lymphoma risk.

"With increasing recruitment and follow-up of such cohorts, a more definitive answer should be available in the not too distant future," they wrote.

Eric Ruderman, M.D., a rheumatologist with Northwestern University, Chicago, concurred. "It's important information, but the issue you have to take into consideration is that their denominators were fairly small to look at such a rare event," he said in an interview. "One or two patients one way or the other may have made a significant difference." ■



Effects Sustained At 4 Years

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a disease activity score (DAS)-28 below 2.6 for 6 consecutive months. The mean time to remission was 10 months, and the mean duration of remission was 25 months, said Dr. Emery, who heads the academic unit of musculoskeletal disease at the University of Leeds (England).

'More than half of patients are achieving an ACR 50 response, and increasingly that is what we are aiming at.'

DR. EMERY

"More than half of patients are achieving an ACR 50 response, and increasingly that is what we are aiming at," he said. Responses usually occur within the first year, and clinical improvements are being sustained for up to 4 years, he said.

Methotrexate doses were reduced from baseline in 176 patients, and of 294 patients initially receiving corticosteroids, the dose was decreased or the drug discontinued in 158 (54%).

The rate of serious adverse events was 0.01 events per patient-year, while the rates of serious infections and malignancies each were 0.03 per patient-year.

The regimen is well tolerated and has shown a very acceptable risk-benefit ratio over time, he said. ■

Out of Africa: Retrovirus Connected to Autoimmune Diseases

BY NANCY WALSH
New York Bureau

Birmingham, England — A newly identified human endogenous retrovirus that is much more prevalent in Africa than in other parts of the world may place its carriers at risk for certain autoimmune diseases, David Moyes, Ph.D., said at the joint meeting of the British Society for Rheumatology and the German Society for Rheumatology.

Patients with autoimmune diseases often have elevated antibody levels to certain structural proteins of human endogenous retroviruses (HERVs), suggesting a possible role for these viruses in autoimmune disease, Dr. Moyes said.

Until recently it was thought that HERVs were ubiquitous and fixed in the population, having been incorporated into the genome before the initial wave of human migration out of Africa some 200,000 years ago. But two of these viruses, HERV-K113 and HERV-K115 are now known to vary widely in prevalence across different populations. "This means that both viruses are likely to have been incorporated into the genome during more recent human evolution and that both could potentially induce an autoimmune response," he said.

The mean prevalence of HERV-K113 identified by polymerase chain reaction testing in a sample of 174 subjects from Kenya, Malawi, and Côte d'Ivoire was 21.8%, compared with 4.2% in a sample of 96 subjects from the United Kingdom, said Dr. Moyes of the Kennedy Institute of Rheumatology, Imperial College, London.

Similarly, HERV-K115 was present in 34% of subjects from Africa and in only 1% of those in the United Kingdom.

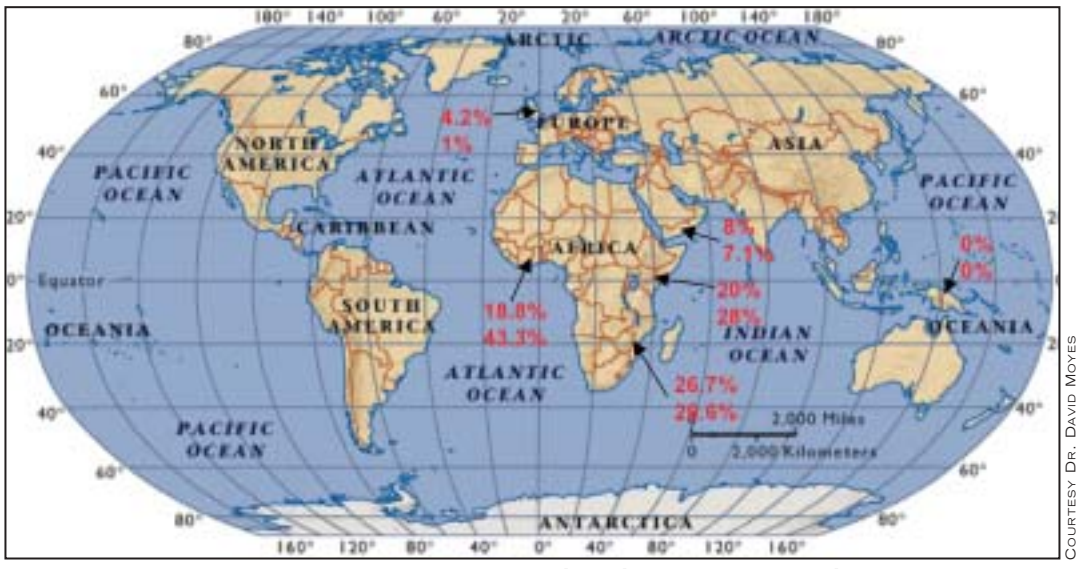
"When you move off the African continent to the Arabian peninsula the prevalence drops off markedly. Neither virus was detected in any of 54 samples from Papua New Guinea," he said.

"Because of the possibility that one or both of these retroviruses could be involved in autoimmune disease, we went on to analyze their prevalence in two U.K. disease cohorts," he said. Among 96 patients with Sjögren's syndrome, the prevalence of the K113 allele was significantly increased, at 15.6%, compared with 4.2% among 96 normal controls. The allele also was more prevalent among 100 patients with multiple sclerosis, at 11.6%, he said.

Increases in these diseases were not associated with K115, however, which is a defective virus. "Both are full length proviruses, but HERV-K113 is a complete virus that has open reading frames and can fully express all its genes. HERV-K115 has a single deletion that prevents the expression of the *Pro/Pol* genes," he said.

An audience member asked if there was any evidence that these viruses were pathogenic, and whether there was an association with the autoantibodies Ro and La that are present in many autoimmune diseases. Dr. Moyes replied that there does not appear to be an association with Ro and La specifically, but that there is an increase in many other autoantibodies seen in patients with scleroderma, rheumatoid arthritis, and Sjögren's syndrome.

"The exact relevance of those increases is open to question, but there is also a degree of evidence suggesting that proteins from these viruses can induce inflammation," he said. ■



Courtesy Dr. David Moyes

The prevalence of HERV-K113 and HERV-K115 varies widely across countries. The top number is the prevalence of HERV-K113 in each country. Underneath is the prevalence of HERV-K115.

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