JOINT VENTURES

Safety Update From the European Biologics Registries

From the outset, there has been concern that anti–tumor necrosis factor agents that manipulate the immune system through cytokine blockade could have unforeseen negative consequences. To address this, registries were established around Europe to identify rare adverse events that would not show up in short-term clinical trials or even open-label extension studies.

Currently, there are eight large European registries in the U.K., Sweden, Germany, Spain, Norway, Denmark, the Netherlands, and Switzerland. Each was established by the respective national rheumatology society. They are funded jointly by all companies that manufacture biologic drugs. The registries function independently, however. Standardized reporting systems of serious adverse events are used; and, once enrolled, patients continue to be followed even if treatment is withdrawn.

BY LORETO CARMONA, M.D.

Different types of comparator cohorts are followed in conjunction with the biologic treatment groups, depending on national policies for the provision of anti-tumor necrosis factor (TNF) drugs and other biologics. For example, the Spanish registry uses a historical cohort, because almost all patients in Spain who need biologics are provided with them at government cost. In contrast, in countries with more stringent requirements for the administration of biologic agents, such as prior failure of multiple conventional disease-modifying antirheumatic drugs (DMARDs), comparator controls are patients on conventional drugs. While longer follow-up is needed, patterns and signals have been identified.

TNF Blockade and Infections

Data on infections associated with anti-TNF therapy have thus far been published by several registries. In Germany, which enrolled 1,529 RA patients between May 2001 and September 2003, 512 patients began treatment with etanercept and 346 with infliximab, while 601 had a change in their conventional DMARD therapy and served as controls. The relative risk of serious infections, versus controls, in this cohort was 2.2 for etanercept and 2.1 for infliximab (Arthritis Rheum. 2005;52:3403-12).

In Sweden, where there are several registries, crosslinking data found 367 hospitalizations from infections in 4,167 patients during 7,776 person-years. The Swedish investigators analyzed the data according to time on treatment, reporting that the relative risk for serious infection with TNF antagonists was 1.43 during the first year of treatment, 1.15 during the second year, and 0.82 thereafter (Ann. Rheum. Dis. 2007;66:1339-44).

In an analysis from the British Society for Rheumatology (BSR) Biologics Register, which included 3,596 patients on etanercept, 2,878 on infliximab, 1,190 on adalimumab, and 1,354 controls being treated with DMARDs, there were 525 serious infections among patients receiving TNF blockers and 56 among the controls during median follow-up periods of 1.26 and 0.94 years, respectively. Adjustment for age and sex resulted in a significantly increased incidence rate ratio (IRR) of 1.47, but further adjustment for multiple other factors including disease severity and comorbidities lowered the IRR to 1.03 (Arthritis Rheum. 2006;54:2368-76).

Of particular interest in the BSR report was an increase in infections of skin and soft tissue. The British investigators reported that anti-TNF treated patients had 118 skin and soft-tissue infections, while the DMARD-treated patients had only 4, for an adjusted IRR of 4.28. They suggested that this increase may relate to the important role TNF plays in cutaneous immunity, with this cytokine being central to endothelial activation, recruitment of inflammatory cells, and mobilization of Langerhans cells from the epidermis to the lymph nodes.

Reactivation of latent tuberculosis continues to be an issue. The screening programs instituted after the initial reports of tuberculosis in patients treated with biologics have significantly reduced the number of cases, but the risk has not been entirely eliminated. In the BSR report, there were 19 bacterial intracellular infections, all in anti-TNF patients. Ten were *Mycobacterium tuberculosis*, and seven were extrapulmonary.

The Spanish investigators analyzed how adherence to recommendations for the prevention of reactivation of latent tuberculosis infection had affected the rate of new cases and found that the probability of developing active tuberculosis was seven times higher when recommendations were not fully followed. Two-step tuberculin skin testing "appeared to be the major barrier to complying with recommendations that have been shown to be effective," they wrote (Arthritis Rheum. 2007;57:756-61).

BY DEBORAH P.M. SYMMONS, M.D.

The Cancer Question

An early report of an elevated 11.5-fold increase in the incidence of lymphoma among patients being treated with anti-TNF drugs sparked concern about hematopoietic and other malignancies in RA patients. This has been explored in some detail in the Swedish registries and was presented in abstract form by Dr. Johan Askling of the Karolinska Institute, Stockholm, at the 2008 meeting of the European League Against Rheumatism.

The Swedish national cohort includes nearly 67,000 RA patients enrolled between 1998 and 2006, 6,403 of whom received anti-TNF therapy. Cancer was identified through the Swedish Cancer Registry.

There were 169 new cases of cancer following initiation of treatment with anti-TNF drugs, and 3,746 new cancers among the national RA cohort who were not receiving anti-TNF, for an overall relative risk of 0.94. For cumulative exposure the relative risk was 0.96 before 1 year, 0.77 for 1-2 years, 1.09 for 2-3 years, 1.02 for 3-4 years, 0.92 for 4-5 years, and 0.88 for 5+ years.

"The results of our study do not indicate any increase in the overall risk of cancer following anti-TNF therapy. Specifically, these data do not suggest any trend in risk with increasing time since treatment start or duration of therapy during the first five years. Nor do they suggest any markedly different occurrence of cancer compared to the general population," Dr. Askling wrote.

New Signals and Beyond

A recent unexpected development is the occurrence of new-onset psoriasis in RA patients being treated with anti-TNF agents. Among 9,826 patients with severe RA in the British registry, 25 incident cases of psoriasis were reported between 2001 and 2007, while none were found in the comparator DMARD-treated group. The risk of developing psoriasis was highest in patients treated with adalimumab, with an IRR of 4.6, compared with etanercept, and an IRR of 3.5 compared with infliximab. The researchers wrote, "In the subset of patients who develop psoriasis, TNF-α has an entirely different role than in the majority of patients" (Ann. Rheum. Dis. [doi 10.1136/ard.2007.087288]).

Future challenges these registries face include the fact that patients increasingly are being treated with multiple biologics. We don't know if a patient who has already had five biologics is the same as one on a first biologic and what will be the result of cumulative immune suppression and the different molecular targets. However, the registries show that rheumatologists can join efforts to quickly provide information about safety that would otherwise have taken a long time to accumulate. And the data we have are reassuring. Had there been an important adverse signal, we would have picked it up. ■

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Colorful Dual-Energy CT May Have Role in Gout Diagnosis

BY SHERRY BOSCHERT
San Francisco Bureau

SAN FRANCISCO — Dual-energy computed tomography scans showed red-colored uric acid deposits in 20 consecutive patients with clinically obvious tophaceous gout but not in 10 controls with other nongout joint conditions.

The 100% sensitivity and specificity of dual-energy computed tomography (DECT) to identify uric acid deposits could provide a needed imaging tool to aid in gout diagnosis and treatment, Dr. Abdullatif M. Alarfaj said at the annual meeting of the American College of Rheumatology.

DECT assesses chemical composition and provides specific color-coded displays to differentiate between uric acid (which shows red), calcium (blue), and other renal calculi, previous investigators have shown.

The current proof-of-concept study, in addition to assessing the accuracy of DECT in gout patients, also measured the uric acid burden in peripheral joints and performed a computerized quantification of tophus volume. The volume of uric acid in each anatomic area was measured by automated volume estimation software. The sum of tophus volume in the hands, wrists, elbows, feet, ankles, and knees comprised the total uric acid volume of peripheral joints.

DECT scans identified 440 areas of urate deposition, compared with 111 areas identified on clinical examination, reported Dr. Alarfaj of the University of British Columbia, Vancouver, and his associates. The investigators have no conflicts of interest related to this study.

DECT could be used to detect subclinical tophus deposits and the extent of intra- and extra-articular gout, he said, adding it could be used to measure individual tophus volume and total burden.

The relatively new technology also may be used in evaluating nodular lesions, diagnosing concurrent gout in patients with other arthropathies, and identifying urate deposits in body areas atypical for gout. An individual DECT scan can cost about one-sixth of the amount for an MRI, Dr. Alarfaj's senior investigator, Dr. Hyon Choi, said. The DECT hardware equipment is very expensive but is used for a variety of purposes, such as imaging coronary artery calcifications and renal calculi. The technology provides dramatic color displays and can be used to create impressive three-dimensional images of uric acid deposits that could aid clinicians in communicating about the disease to patients with gout, he added. The patients in the gout group had an average 12-year history of gout and nine painful joints in the previous year. Mean serum uric acid level was 492 micromol/L; mean age was 63; 75% were male; and 12 were white. Comorbidities were present in 17 patients. ■

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