

5-Year Data Support Rituximab for Pemphigus

BY BRUCE JANCIN

BUDAPEST — Rituximab for the treatment of severe pemphigus continued to demonstrate positive results in the 2-year extension of a landmark 3-year multicenter trial.

After 5 years of follow-up, 19 of 22 rituximab-treated patients (86%) were in complete or near-complete remission, including 8 who were off all therapies,

Dr. Pascal Joly reported at the annual congress of the European Society for Dermatological Research.

Also noteworthy was the finding that no new rituximab-related side effects emerged during years 4 and 5. The only serious side effects over the course of 5 years were a case of pyelonephritis 12 months after a single cycle of rituximab (Rituxan) and a fatal septicemia at 18 months in a patient taking etanercept for

comorbid rheumatoid arthritis, both of which were detailed in the initial 3-year report (N. Engl. J. Med. 2007;357:545-52), said Dr. Joly of Rouen (France) University Hospital.

Five of the eight patients in complete remission off all treatment at 5 years achieved their remission several months after their first and only cycle of rituximab and never experienced a relapse in the intervening years, he said.

Based upon these encouraging results, a new randomized trial is underway to evaluate an expanded use of rituximab in treating pemphigus.

Instead of reserving the biologic therapy for patients with severe pemphigus who are corticosteroid refractory or have contraindications to high-dose steroids, as was the case in the original 5-year French study, the new multicenter study is testing rituximab as first-line treatment. The investigators also are enrolling patients with moderate as well as severe pemphigus vulgaris or foliaceus, he added.

Fourteen patients in the 5-year trial had pemphigus vulgaris, seven had pemphigus foliaceus, and one had paraneoplastic pemphigus.

Thirteen of the 22 patients experienced relapse after a mean delay of 28.2 months. The 2-, 3-, and 5-year relapse rates were 33%, 43%, and 59%, respectively.

Relapse in six patients was treated with a second cycle of rituximab; five of the six achieved complete remission once again. The other seven patients had their relapse treated with stepped-up doses of corticosteroids.

The mean dose of prednisone used by participants dropped from 55 mg/day at baseline to 6 mg/day after 5 years. The decrease was even more impressive in the five patients who entered the trial with steroid-refractory disease; their corticosteroid use went from a mean of 94 mg/day at baseline to 6 mg/day 5 years later, Dr. Joly continued.

The rituximab regimen consisted of four weekly infusions at 375 mg/m² of body surface area.

Rituximab is a monoclonal antibody directed against the CD20 antigen of B lymphocytes. Beginning 3 weeks after rituximab administration, peripheral B cells became undetectable. B cells remained suppressed for 6 months to 2 years. When they reappeared they displayed a naive phenotype similar to that found in neonatal cord blood.

No changes were detected in levels of T cells, total IgG, or titers of antibodies against tetanus toxoid or pneumococcal capsule polysaccharide in response to rituximab. The pathogenic autoantibodies anti-desmoglein-1 and -3, which are produced by activated B cells, responded to rituximab differentially. Anti-desmoglein-1 titers dropped steeply in all patients with a complete response and increased when patients experienced relapse. In contrast, five patients in prolonged remission maintained high titers of anti-desmoglein-3 throughout and four other patients relapsed despite persistently low anti-desmoglein-3.

In the new randomized trial of rituximab as first-line therapy in moderate to severe pemphigus, the rituximab group receives low-dose prednisone at 0.5-0.75 mg/kg per day for the first 2-3 months of the study.

"Of course, the absence of corticosteroids would make for more spectacular results. However, rituximab typi-

Continued on following page



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More Research Is Warranted

Psoriasis from page 1

tal and pharmacy linked databases covering 2.5 million Dutch patients. The 15,820 psoriasis patients and 27,577 non-psoriatic controls (mean age 48 years) were followed for a mean of 6 years.

The IHD hospitalization rate was 611 cases per 100,000 person-years in psoriasis patients and 599 in controls. MI hospitalization rates were also similar: 234 per 100,000 person-years in psoriasis patients and 235 in controls.

At study entry, the psoriasis patients had slightly, but statistically significant-

from statistical significance, she said.

Dr. Wakkee noted that her study findings are at odds with those of a much-publicized analysis of the U.K. General Practice Research Database (JAMA 2006;296:1735-41), which concluded that psoriasis patients had a small but significantly increased risk of MI.

It is possible, she said, that the earlier finding was due to detection bias. This potential confounder could occur because

psoriasis patients have greater consumption of health care.

Further muddying the waters, investigators at the University of Basel in Switzerland recently analyzed the U.K. General Practice Research Database and found no overall increased risk of MI, stroke, or transient ischemic attack (TIA) in patients with recently diagnosed psoriasis, although there was a suggestion of a possible small absolute increase in MI risk in patients younger than age 60 with severe psoriasis (Br. J. Dermatol. 2009;160:1048-56).

So the question remains: Is psoriasis as

a systemic inflammatory state an independent risk factor for cardiovascular events, or does the increased risk, if present, result from psoriasis patients' increased prevalence of obesity, smoking, metabolic syndrome, and other cardiovascular risk factors?

Dr. Wakkee said the only way to resolve the controversy is to conduct a large, detailed, long-term prospective study. Whether that is realistic is unclear, she said. In the absence of definitive data, physicians will have to help their psoriasis patients work hard to optimize their cardiovascular risk factor profile. ■



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DR. WAKKEE

ly, higher rates of antihypertensive drug therapy, compared with controls (19.4% vs. 16.4%, respectively), lipid-lowering drugs (7.0% vs. 6.2%, respectively), and antidiabetic medications (4.4% vs. 3.6%, respectively). This wasn't surprising, said Dr. Wakkee, given that prior studies have shown the prevalence of metabolic syndrome to be elevated in psoriasis patients. Psoriasis patients also had more hospitalizations for reasons other than psoriasis in the prior 6 months.

In a multivariate analysis adjusted for age, gender, medications, and hospitalizations in the prior 6 months, the relative risk of IHD hospitalization during 6 years of follow-up was 5% higher in psoriasis patients, and the MI hospitalization risk was 6% lower than in controls. These differences were far

Continued from previous page

cally has a 2- to 3-month delay in action, and it's difficult not to treat patients during this delay. This is why we're using low-dose corticosteroids, especially to treat the pain in our patients with mucosal lesions. A dose of 0.5 mg/kg per day of prednisone is not sufficient to lead to clearance in these patients, but it's a dose that has an anti-inflammatory effect and will decrease their pain," Dr. Joly explained.

In light of the timing of relapses in the original 5-year study, the new trial incorporates maintenance rituximab at 500 mg given at 12 months and again at 18 months in an effort to avoid relapses in the second and third year. The dose and timing of the maintenance therapy were chosen in consultation with rheumatologists, who have the most experience with rituximab. The biologic agent's approved indications are for treatment of rheumatoid arthritis unresponsive to anti-tumor necrosis factor therapy and in B-cell lymphomas.

The study was supported by the French Society of Dermatology and Roche. ■

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