Bullous Pemphigoid Managed With Methotrexate

BY NANCY WALSH
New York Bureau

Low-dose methotrexate combined with topical betamethasone dipropionate was a safe and effective treatment for bullous pemphigoid in a retrospective study conducted by Dr. Petra Kjellman and colleagues.

For the past 50 years, glucocorticoids have been the mainstay of treatment for bullous pemphigoid (BP), but the high doses of these drugs that are typically needed to control inflammation are poorly tolerated, particularly among the elderly, who are most commonly affected, according to the researchers.

To minimize the adverse effects of glucocorticoids, which include sepsis, pneumonia, gastrointestinal tract bleeding, diabetes, and osteoporosis, other immunosuppressants also have been tried as steroid-sparing agents in BP, but few controlled trials have been done, they noted.

For the past decade, Dr. Kjellman and colleagues from the department of dermatology and venereology, Karolinska University Hospital, Stockholm, have preferentially used methotrexate for BP patients, with prednisone if needed or if methotrexate could not be given or tolerated.

The usual regimen involved an initial dosage of 5 mg/week of methotrexate, with topical betamethasone dipropionate applied twice daily until the disease was controlled. If necessary, methotrexate dosage was increased by 2.5 mg/week.

If symptoms persisted despite methotrexate treatment, prednisone was added in doses of 10-20 mg/day, and if methotrexate could not be given because of anemia, liver disease, or renal failure, prednisone was given alone.

Between 1999 and 2003, 138 patients whose mean age was 81 years were diagnosed with BP. Of these, 57% were women, 51% had mild disease, 38% had moderate disease, and 11% had severe disease.

Methotrexate treatment was initiated in 98 (71%), with a median weekly dosage of 5 mg. Among these patients, 61 continued on methotrexate monotherapy (group 1) and had a mean cumulative dose of 280 mg.

Among patients who received methotrexate, 37 also were treated with prednisone (group 2). The median weekly dosage of methotrexate in this group was 6 mg, and the median cumulative dose was 440 mg.

Forty patients did not receive methotrexate, with 15 receiving high-dose prednisone alone at a median daily dosage of 12 mg and with a median cumulative dose of 4,000 mg (group 3). The other 25 patients who did not receive methotrexate (group 4) had mild disease and were managed with topical betamethasone gel alone.

Median follow-up was 26 months. At 24 months, the remission rates were 43% in group 1, 35% in group 2, 0% in group 3, and 83% in group 4 (Arch. Dermatol. 2008;144:612-16).

Mortality in BP is considerable, with previous reports finding 1-year mortality ranging from 10% to 41%, according to the researchers. In this series, 2-year survival was 65%, 67%, 47%, and 52% in the four groups, respectively, and there was a tendency toward better survival for the methotrexate-treated patients, with median survival times of 38 and 24 months in groups 1 and 2, respectively.

Only one patient in this series developed anemia, and although elevated liver enzymes were seen on occasion during the first weeks of therapy, normalization usually followed within 4-6 weeks. They did not perform pretreatment liver biopsies.

They researchers noted that they are also developing a BP quality register and biobank to enable further follow-up of these patients, and they plan a prospective study to provide further information. They had no conflicts of interest to disclose. ■

Bullous Pemphigoid and Pemphigus Vulgaris Rates Climbing in U.K.

BY BRUCE JANCIN
Denver Bureau

KYOTO, JAPAN — The annual incidence of both bullous pemphigoid and pemphigus vulgaris has climbed steadily over the past decade in the United Kingdom for reasons unknown, according to a study of more than 1,000 patients.

The mortality associated with these autoimmune diseases may have been underestimated in the past, based upon the results of Dr. Sinéad Langan's large, population-based study presented at an international investigative dermatology meeting.

"People with bullous pemphigoid are twice as likely to die and those with pemphigus vulgaris are three times as likely to die as [are] matched controls," said Dr. Langan of the University of Nottingham (England).

Her study of The Health Improvement Network (THIN)—a large, population-based database of computerized primary care medical records—identified 868 patients diagnosed with bullous pemphigoid (BP) and 139 diagnosed with pemphigus vulgaris (PV) during 1996-2006. Each patient was matched by age and gender with four controls from the same general practice.

She undertook the study because, despite the substantial morbidity and mortality associated with these autoimmune diseases, little is known about their epidemiology. For example, there are only two published studies addressing PV mortality; one, from the Middle East, reported a 1-year mortality of 5%, while a 1975 U.S. study found a 50% 1-year mortality, she said. The reported BP mortality has cut a similarly wide swath.

The incidence of BP in the new U.K. study climbed with advancing age, peaking in a group aged 80-84 years. The median age at presentation was 80 years, and 62% of affected patients were women.

PV incidence showed a bimodal distribution, with a peak at ages 45-49 years and a second, larger one at 80-84 years. Median age at presentation was 71 years, and two-thirds of patients were women.

The incidence of BP was 4.3 cases/100,000 person-years; for PV it was 0.7/100,000 person-years. The incidence of BP showed a "dramatic" average yearly increase of 17% during the study period, while PV incidence increased by 11% each year, according to Dr. Langan. The 1-year mortality rate among patients with BP was 19%, resulting in an estimated 70 excess deaths/1,000 person-years. After adjustment for age and gender as potential confounders, BP patients had a 2.3-fold greater risk of mortality than did controls. The adjusted mortality risk in PV patients was 3.4-fold greater than in controls; PV resulted in 62 excess deaths/100,000 person-years.

Dr. Joel M. Gelfand commented that he doesn't believe the rising annual incidence rates of BP and PV observed in the U.K. study are real, and suspects that more sophisticated statistical analyses would show as much.

'People with bullous pemphigoid are twice as likely to die and those with pemphigus vulgaris are three times as likely.'

DR. LANGAN

"If you look at these kinds of data sets across almost all diseases, the incidence seems to increase over time. It's probably an issue of chronic diseases being picked up over time," according to Dr. Gelfand, who has led several landmark studies carefully documenting increased cardiovascular and cerebrovascular risks in psoriasis patients using the U.K. General Practice Research Database. He is medical director of the clinical studies unit in the department of dermatology at the University of Pennsylvania, Philadelphia.

Dr. John R. Stanley, professor and chair of dermatology at the University of Pennsylvania, said Dr. Langan's study left him uncertain about how to apply the findings in clinical practice. "We don't know [from the U.K. study] whether to treat more aggressively or less," Dr. Stanley observed at a meeting of the European Society for Dermatological Research, the Japanese Society for Investigative Dermatology, and the Society for Investigative Dermatology.

Dr. Langan agreed these data are not illuminating on that score. However, the database also contains information on medications, and she is planning a study she hopes will help guide treatment decisions. ■

Autoantibodies for Bullous Pemphigoid Found in Unaffected

KYOTO, JAPAN — More than 7% of individuals without any form of autoimmune disease possess elevated serum bullous pemphigoid 180 and/or BP230 autoantibodies on the commercially available enzyme-linked immunosorbent assay, according to testing of stored serum from 370 people.

These autoantibodies have been considered diagnostic for bullous pemphigoid, the most common cutaneous autoimmune bullous disorder, but that is clearly not the case, Dr. Nneka I. Comfrere of the Mayo Clinic in Rochester, Minn., reported at an international investigative dermatology meeting.

"I think there's not one test we can clearly rely on to make the diagnosis. What we've concluded at the Mayo Clinic is disease confirmation requires a correlation of multiple measures, including the clinical pattern, the presentation of disease, routine histopathology, and both direct and indirect immunofluorescence studies, as well as the ELISA [enzyme-linked immunosorbent assay], in order to ensure the highest diagnostic accuracy. Clearly, one cannot rely solely on the ELISA," she said.

Dr. Comfrere and her associates examined the prevalence of circulating BP180 and BP230 autoantibodies across the age spectrum of individuals who did not have bullous pemphigoid or any other autoimmune disease. They tested stored serum from patients aged 20 years to more than 90 years.

A positive test for one or both autoantibodies, defined by the manufacturer as a level of nine units or more, was detected in 7.4% of subjects. The prevalence did not vary by decade of life or by gender. Moreover, the geometric mean titer also remained similar across the decades, she said at a meeting of the European Society for Dermatological Research, the Japanese Society for Investigative Dermatology, and the Society for Investigative Dermatology.

Audience members raised the possibility that the presence of circulating autoantibodies in asymptomatic individuals might precede clinical manifestations of the disease, but the finding that prevalence of the autoantibodies was similar across the decades rather than peaking in the elderly argues against this, Dr. Comfrere noted.

The role of these autoantibodies in initiating and perpetuating the disease process remains unclear, she added. It's possible that the development of clinical bullous pemphigoid requires exogenous factors in susceptible individuals.

—Bruce Jancin