Small-Vessel Vasculitis: Tx-Related Cancers Falling

The use of cyclophosphamide-sparing regimens 'might have started to show a benefit.'

BY PATRICE WENDLING

FROM ANNALS OF THE RHEUMATIC DISEASES

An extensive range of cancers was found in long-term follow-up of patients with antineutrophil cytoplasm antibody–associated vasculitis, although the findings also suggest that the use of cyclophosphamide-sparing regimens could be paying off.

Among 493 evaluable patients in four randomized clinical trials, the standardized incidence ratio for all cancers indicated a 58% increased risk, compared with the general population (standardized incidence ratio, 1.58; *P* value = .003).

The only site-specific cancer that was significantly increased, however, was nonmelanoma skin cancer (NMSC), with an SIR of 2.78 (*P* = .001), reported Dr. Caroline Heijl on behalf of the European Vasculitis Study Group (EUVAS).

The SIR was 1.30 for cancers at all sites, excluding NMSC (*P* = .16), 2.41 for bladder cancer (*P* = .17), 3.25 for leukemia (*P* = .26), and 1.11 for non-Hodgkin's lymphoma (*P* = 1.0).

For the past 2 decades, researchers have been working to limit the use of cyclophosphamide in the treatment of patients with antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis (AAV) because of the increased incidence of cancer in AAV patients, reported to be 1.6-2.4 times higher than that of the general public.

Particularly worrisome have been cancer type–specific analyses showing an increased risk of bladder cancer and leukemia in AAV patients because of the known urothelial and hematologic toxicities of cyclophosphamide, and higher incidence of lymphoma and NMSC, Dr. Heijl wrote.

Three of the four trials that formed the basis of the analysis helped to advance cyclophosphamide-sparing regimens, demonstrating that cyclophosphamide use could be limited to the remission-induction phase, given as periodic intravenous pulses, or replaced by methotrexate.

"Although the lower cyclophosphamide exposure achieved by these treatment regimens remains difficult to quantify, the lower standardized incidence ratios for cancers in any site, particularly for bladder cancer and leukemia in our study population as compared with findings obtained earlier, could indicate that the more contained use of this drug might have started to show a benefit," Dr. Heijl wrote (Ann. Rheum. Dis. 2011;70:1415-21).

VITALS

Major Finding: The standardized incidence ratio for cancers at all sites indicated a 58% increased risk, compared with the general population (SIR 1.58; *P* = .003).

Data Source: Long-term follow-up of 493 patients with ANCA-associated vasculitis.

Disclosures: Dr. Heijl and her coauthors report no conflicts of interest.

The researchers analyzed long-term data from 535 patients with newly diagnosed AAV who had been enrolled in four trials organized by the EUVAS between March 1995 and September 2002. Follow-up ran from 2004 to 2007, with a mean of 4.85 years.

Among the 493 patients with detailed treatment data available, 53 definitive cancers were identified. They included 13 basal and 5 squamous cell carcinomas in 15 patients, and 35 non-NMSCs in 34 patients.

All 15 patients with NMSC had received cyclophosphamide, and 13 of those had also taken azathioprine. All four patients identified with bladder cancer had received cyclophosphamide for 6-36 months, with 2.1 to 6.6 years elapsing from the time of trial enrollment to bladder cancer diagnosis.

Three of the bladder cancers were observed in patients with granulomatosis with polyangiitis (GPA) and one in a patient with microscopic polyangiitis (MPA). Higher SIR was observed for cancers at all sites in GPA vs. MPA patients (SIR, 1.92 vs. 1.20), but their 95% confidence intervals overlapped. The corresponding relative risk was 1.60, reported Dr. Heijl of the nephrology department at Skåne University Hospital in Lund, Sweden.

A further analysis of three follow-up periods (less than 3 years, 3-5 years, and longer than 5 years) did not indicate a clear cancer incidence trend over time. Nevertheless, longer follow-up data are warranted to appraise the risk of developing cancers later during the course of AAV, the authors noted. ■

Vitamin D Insufficiency May Trigger Inflammation in Lupus

BY DIANA MAHONEY

The science supporting vitamin D supplementation in lupus patients is catching up to the recommendation that all patients with the autoimmune disease increase their intake of the fat-soluble secosteroids.

Findings from a new study by Dr. Suzan Abou-Raya, professor of geriatric medicine at the University of Alexandria (Egypt), and her associates demonstrate that there is a high prevalence of vitamin D deficiency associated with an increased inflammatory burden and thrombophilic state in patients with systemic lupus erythematosus (SLE).

'We've learned that [vitamin D] has potent immunomodulatory properties that have promoted its potential use in the treatment of autoimmune conditions.'

The findings also suggest that oral vitamin D supplementation ameliorates chronic inflammatory and hemostatic markers in this patient group.

The use of supplementary calcium and vitamin D is routinely recommended for SLE patients to help minimize the bone loss and increased risk of developing osteoporosis associated with the disease and its treatment. Beyond supporting bone and mineral hemostasis, "vitamin D is now recognized as having additional pleiotropic roles," according to Dr. Abou-Raya.

"We've learned that it has potent immunomodulatory properties that have promoted its potential use in the treatment of autoimmune conditions, including lupus," she said.

The study was designed to evaluate vitamin D status in lupus patients and to assess alterations in disease-related inflammatory and hemostatic markers before and after vitamin D supplementation.

To do this, Dr. Abou-Raya and her fellow researchers conducted a randomized, placebo-controlled trial comprising 148 males and premenopausal females who fulfilled the ACR (American College of Rheumatology) classification criteria for SLE. Also enrolled in the study were 75 lupus-free adults who served as controls and who matched the cases in age, sex, ethnicity, and body mass index. Individuals with other inflammatory disorders and those taking supplemental vitamin D at the time of the study were excluded, she noted.

Study patients were randomized in a 1:1 fashion to receive either 2,000 IU per day of oral cholecalciferol (vitamin D_3) or placebo for 6 months together with standard SLE treatment, Dr. Abou-Raya explained.

Before and after 6 months of vitamin D supplementation, the investigators evaluated disease activity using the SLE disease activity index (SLEDAI), levels of serum 25-hydroxyvitamin D (25[OH]D) via DiaSorin's Liaison immunoassay, levels of proinflammatory cytokines interleukin-1 (IL-1), IL-6, IL-18, tumor necrosis factor (TNF)–alpha, C-reactive protein (CRP), and the hemostatic markers fibrinogen and von Willebrand factor (vWF). Individuals with 25(OH)D levels of 10-30 ng/mL were classified as having vitamin D insufficiency; those with levels lower than 10 ng/mL were considered vitamin D deficient, she noted.

The mean age of the SLE patients was 38.8 years and the mean disease duration was 5.2 years. The mean baseline vitamin D level in the SLE patients, 19.8 ng/mL, was significantly lower than the mean 28.7 ng/mL in the control group. The baseline levels of the inflammatory and hemostatic markers were significantly higher in the SLE patients. "The overall prevalence of vitamin D insufficiency and deficiency, respectively, was 69% and 39%," she said.

At 6 months, "there was a significant decrease in levels of inflammatory and hemostatic makers in lupus patients who were supplemented with vitamin D" compared with patients who were given placebo together with ongoing therapy, Dr. Abou-Raya reported at the annual European Congress of Rheumatology in London. After multivariate adjustment, there was a negative correlation between vitamin D levels and IL-1, IL-6, IL-18, TNF-alpha, CRP, fibrinogen, and vWF, "and lower vitamin D levels were associated with significantly higher SLEDAI scores," she said.

The results suggest that hypovitaminosis D contributes to a chronic inflammatory and thrombophilic state in SLE patients, said Dr. Abou-Raya. "The findings support the routine recommendation for oral vitamin D supplementation," she said.

Dr. Abou-Raya disclosed having no financial conflicts of interest related to her presentation. ■