Specifically, the median duration of follow-up was 30 weeks for placebo and 31 weeks for REMICADE.), 17% of patients receiving REMICADE experienced elevations in ALT at >1 to <3 times the ULN compared to 12% of patients treated with placebo. ALT elevations ≥3 times the ULN were observed in 2% of patients who received REMICADE compared with 1% of patients who received placebo. ALT elevations ≥5 times ULN were observed in <1% of patients in both REMICADE and placebo groups. In an AS clinical trial (median follow up 24 weeks) 40% of patients receiving REMICADE experienced elevations in ALT at >1 to <3 times the ULN compared to 13% of patients treated with placebo. ALT elevations ≥3 times the ULN were observed in 6% of patients who received REMICADE compared to none in patients who received placebo. ALT elevations ≥5 times ULN were observed in 2% of patients who received REMICADE compared to none in patients treated with placebo. In a PsA clinical trial (median follow up 24 weeks for REMICADE group and 18 weeks in placebo group) 42% of patients receiving REMICADE experienced elevations in ALT at >1 to <3 times the ULN compared to 16% of patients treated with placebo. ALT elevations ≥3 times the ULN were observed in 5% of patients who received REMICADE compared to none in patients who received placebo. ALT elevations ≥5 times ULN were observed in 2% of patients who received REMICADE compared to none in patients treated with placebo. In PsO clinical trials, (ALT values are obtained in 2 phase 3 psoriasis studies with median follow-up of 50 weeks for REMICADE and 16 weeks for placebo). 49% of patients receiving REMICADE experienced elevations in ALT at >1 to <3 times the ULN compared to 24% of patients treated with placebo. ALT ≥3 x ULN were observed in 8% of patients who received REMICADE compared to <1 % who received placebo. ALT elevations ≥5 x ULN were observed in 3% of patients who received REMICADE compared to none in patients treated with placebo. **Adverse Reactions in Pediatric Crohn's Disease** There were some differences observed in the adverse reactions observed in the pediatric patients receiving REMICADE compared to those observed in adults with CD. The following adverse events were reported more commonly in 103 randomized pediatric CD patients administered 5 mg/kg REMICADE through 54 weeks than in 385 adult CD patients receiving a similar treatment regimen: anemia (11%), blood in stool (10%), leukopenia (9%), flushing (9%), viral infection (8%), neutropenia (7%), bone fracture (7%), bacterial infection (6%), and respiratory tract allergic reaction (6%). Infections were reported in 56% of randomized pediatric patients in Study Peds Crohn's and in 50% of adult patients in Study Crohn's I. In Study Peds Crohn's, infections were reported more frequently for patients who received every 8 week as opposed to every 12 week infusions (74% and 38%, respectively), while serious infections were reported for 3 patients in the every 8 week and 4 patients in the every 12 week maintenance treatment group. The most commonly reported infections were upper respiratory tract infection and pharyngitis, and the most commonly reported serious infection was abscess. Pneumonia was reported for 3 patients, (2 in the every 8 week and 1 in the every 12 week maintenance treatment groups). Herpes zoster was reported for 2 patients in the every 8 week maintenance treatment group. In Study Peds Crohn's, 18% of randomized patients experienced one or more infusion reactions, with no notable difference between treatment groups. Of the 112 patients in Study Peds Crohn's, there were no serious infusion reactions, and 2 patients had non-serious anaphylactoid reactions. Antibodies to REMICADE developed in 3% of pediatric patients in Study Peds Crohn's. Elevations of ALT up to 3 times the upper limit of normal (ULN) were seen in 18% of pediatric patients in CD clinical trials; 4% had ALT elevations ≥3 x ULN, and 1% had elevations ≥5 x ULN. (Median follow-up was 53 weeks.) The most common serious adverse events reported in the post-marketing experience in children were infections (some fatal) including opportunistic infections and tuberculosis, infusion reactions, and hypersensitivity reactions. Serious adverse events in the post-marketing experience with REMICADE in the pediatric population have also included malignancies, including hepatosplenic T-cell lymphomas (see *Boxed WARNINGS* and *WARNINGS*), transient hepatic enzyme abnormalities, lupus-like syndromes, and the development of autoantibodies. **Adverse Reactions in Psoriasis Studies** During the placebo-controlled portion across the three clinical trials up to Week 16, the proportion of patients who experienced at least 1 SAE (defined as resulting in death, life threatening, requires hospitalization, or persistent or significant disability/incapacity) was 1.7% in the 3 mg/kg REMICADE group, 3.2% in the placebo group, and 3.9% in the 5 mg/kg REMICADE group. Among patients in the 2 Phase 3 studies, 12.4% of patients receiving REMICADE 5 mg/kg every 8 weeks through one year of maintenance treatment experienced at least 1 SAE in Study I. In Study II, 4.1% and 4.7% of patients receiving REMICADE 3 mg/kg and 5 mg/kg every 8 weeks, respectively, through one year of maintenance treatment experienced at least 1 SAE. One death due to bacterial sepsis occurred 25 days after the second infusion of 5 mg/kg REMICADE. Serious infections included sepsis, and abscesses. In Study I, 2.7% of patients receiving REMICADE 5 mg/kg every 8 weeks through 1 year of maintenance treatment experienced at least 1 serious infection. In Study II, 1.0% and 1.3% of patients receiving REMICADE 3 mg/kg and 5 mg/kg, respectively, through 1 year of treatment experienced at least 1 serious infection. The most common serious infections (requiring hospitalization) were abscesses (skin, throat, and peri-rectal) reported by 5 (0.7%) patients in the 5 mg/kg REMICADE group. Two active cases of tuberculosis were reported: 6 weeks and 34 weeks after starting REMICADE. In placebo-controlled portion of the psoriasis studies, 7 of 1123 patients who received REMICADE at any dose were diagnosed with at least one NMSC compared to 0 of 334 patients who received placebo. In the psoriasis studies, 1% (15/1373) of patients experienced serum sickness or a combination of arthralgia and/or myalgia with fever, and/or rash, usually early in the treatment course. Of these patients, 6 required hospitalization due to fever, severe myalgia, arthralgia, swollen joints, and immobility. **Other Adverse Reactions** Safety data are available from 4779 REMICADE-treated adult patients, including 1304 with RA, 1106 with CD, 484 with UC, 202 with AS, 293 with PsA, 1373 with plaque PsO and 17 with other conditions. (For information on other adverse reactions in pediatric patients, see *ADVERSE REACTIONS, Adverse Reactions in Pediatric Crohn's Disease*.) Adverse events reported in ≥5% of all patients with RA receiving 4 or more infusions are listed below. The types and frequencies of adverse reactions observed were similar in REMICADE-treated RA, AS, PsA, plaque PsO and CD patients except for abdominal pain, which occurred in 26% of REMICADE-treated patients with CD. In the CD studies, there were insufficient numbers and duration of follow-up for patients who never received REMICADE to provide meaningful comparisons. The percentages of adverse events for placebo-treated patients (n=350; average weeks of follow-up 59) and REMICADE-treated patients (n=1129; average weeks of follow-up 66), respectively, are: *Gastrointestinal:* Nausea: 20, 21; Abdominal pain: 8, 12; Diarrhea: 12, 12; Dyspepsia: 7, 10; *Respiratory:* Upper respiratory tract infection: 25, 32; Sinusitis: 8, 14; Pharyngitis: 8, 12; Coughing: 8, 12; Bronchitis: 9, 10; Rhinitis: 5, 8; *Skin and appendages disorders:* Rash: 5, 10; Pruritis: 2, 7; *Body as a whole—general disorders:* Fatigue: 7, 9; Pain: 7, 8; *Resistance mechanism disorders:* Fever: 4, 7; Moniliasis: 3, 5; *Central and peripheral nervous system disorders:* Headache: 14, 18; *Musculoskeletal system disorders:* Back pain: 5, 8; Arthralgia: 7, 8; *Urinary system disorders:* Urinary tract infection: 6, 8; *Cardiovascular disorders, general:* Hypertension: 5, 7. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in clinical trials of another drug and may not predict the rates observed in broader patient populations in clinical practice. The most common serious adverse events observed in clinical trials were infections (see *ADVERSE REACTIONS, Infections*). Other serious, medically relevant adverse events ≥0.2% or clinically significant adverse events by body system were as follows: *Body as a whole:* allergic reaction, diaphragmatic hernia, edema, surgical/procedural sequela; *Blood:* pancytopenia; *Cardiovascular:* circulatory failure, hypotension, syncope; *Gastrointestinal:* constipation, gastrointestinal hemorrhage, ileus, intestinal obstruction, intestinal perforation, intestinal stenosis, pancreatitis, peritonitis, proctalgia; *Central & Peripheral Nervous:* meningitis, neuritis, peripheral neuropathy, dizziness; *Heart Rate and Rhythm:* arrhythmia, bradycardia, cardiac arrest, tachycardia; *Liver and Biliary:* biliary pain, cholecystitis, cholelithiasis, hepatitis; *Metabolic and Nutritional:* dehydration; *Musculoskeletal:* intervertebral disk herniation, tendon disorder; *Myo-, Endo-, Pericardial, and Coronary Valve:* myocardial infarction; *Platelet, Bleeding, and Clotting:* thrombocytopenia; *Neoplasms:* basal cell, breast, lymphoma; *Psychiatric:* confusion, suicide attempt; *Red Blood Cell:* anemia, hemolytic anemia; *Reproductive:* menstrual irregularity; *Resistance Mechanism:* cellulitis, sepsis, serum sickness; *Respiratory:* adult respiratory distress syndrome, lower respiratory tract infection (including pneumonia), pleural effusion, pleurisy, pulmonary edema, respiratory insufficiency; *Skin and Appendages:* increased sweating, ulceration; *Urinary:* renal calculus, renal failure; *Vascular (Extracardiac):* brain infarction, pulmonary embolism, thrombophlebitis; *White Cell and Reticuloendothelial:* leukopenia, lymphadenopathy. **Post-marketing Adverse Events** The following adverse events have been reported during post-approval use of REMICADE: neutropenia (see *WARNINGS, Hematologic Events*), interstitial pneumonitis/fibrosis, idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura, pericardial effusion, systemic and cutaneous vasculitis, erythema multiforme, Stevens-Johnson Syndrome, toxic epidermal necrolysis, Guillain-Barré syndrome, transverse myelitis, and neuropathies (additional neurologic events have also been observed, see *WARNINGS, Neurologic Events*) and acute liver failure, jaundice, hepatitis, and cholestasis (see *WARNINGS, Hepatotoxicity*). Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to REMICADE exposure. **OVERDOSAGE:** Single doses up to 20 mg/kg have been administered without any direct toxic effect. In case of overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions or effects and appropriate symptomatic treatment instituted immediately. **Administration Instructions Regarding Infusion Reactions** Adverse effects during administration of REMICADE have included flu-like symptoms, headache, dyspnea, hypotension, transient fever, chills, gastrointestinal symptoms, and skin rashes. Anaphylaxis might occur at any time during REMICADE infusion. Approximately 20% of REMICADE-treated patients in all clinical trials experienced an infusion reaction compared with 10% of placebo-treated patients (see *ADVERSE REACTIONS, Infusion-related Reactions*). Prior to infusion with REMICADE, premedication may be administered at the physician's discretion. Premedication could include antihistamines (anti-H1 +/- anti-H2), acetaminophen and/or corticosteroids. During infusion, mild to moderate infusion reactions may improve following slowing or suspension of the infusion, and upon resolution of the reaction, reinitiation at a lower infusion rate and/or therapeutic administration of antihistamines, acetaminophen, and/or corticosteroids. For patients that do not tolerate the infusion following these interventions, REMICADE should be discontinued. During or following infusion, patients that have severe infusion-related hypersensitivity reactions should be discontinued from further REMICADE treatment. The management of severe infusion reactions should be dictated by the signs and symptoms of the reaction. Appropriate personnel and medication should be available to treat anaphylaxis if it occurs.

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Antimalarials May Lower Risk for Cancer in Lupus

BY DIANA MAHONEY
New England Bureau

Antimalarial drugs may confer some protection against cancer in lupus patients, according to the results of a prospective cohort study that linked treatment with antimalarials to improved cancer-free survival.

In a study of 235 patients with systemic lupus erythematosus (SLE) from an ongoing, prospective observational study, those who had been treated with antimalarials were significantly less likely to develop cancer over a median 10-year follow-up than those who had never been treated with the drugs, according to Dr. Guillermo Ruiz-Irastorza of the Hospital de Cruces in Bizkaia, Spain, and colleagues.

Previous studies have suggested that individuals with SLE are at increased risk for developing certain types of malignancies, although the causes for this increased susceptibility remain unknown. The possibility that antimalarial agents may have an anticarcinogenic effect might impact treatment decisions in this patient population, the authors wrote (Ann. Rheum. Dis. 2007 Jan. 4 [Epub doi:10.1136/ard.2006.067777]).

Antimalarials such as hydroxychloroquine (Plaquenil), chloroquine, and quinacrine are frequently used to treat both the skin and systemic symptoms of mild to moderate lupus. Recent studies have demonstrated important long-term effects of the drugs in lupus patients, including a reduction in the accrual of disease-related damage and a reduction in long-term mortality, the authors wrote. Antimalarials have also demonstrated potential antineoplastic properties in investigations looking at their use as adjuvant cancer therapy agents.

Based on these collective findings, Dr. Ruiz-Irastorza and colleagues sought to determine the impact of antimalarials on cancer risk in lupus. Of the 235 patients included in the investigation, 156 had ever received antimalarial treatment and 79 had not. Only 2 of the patients in the antimalarial-treated group had developed a radiologically or histologically confirmed neoplasm during the study follow-up, compared with 11 of the 79 patients who had never been treated, the authors reported.

All of the patients in the study fulfilled the updated American College of Rheumatology criteria for the classification of SLE and were included in the cohort at the time of lupus diagnosis. Pediatric lupus patients (younger than 14 years) enrolled in the larger observational study were excluded from the current investigation.

As per study protocol, most of the patients in the cohort underwent clinical and immunologic assessment every 3 months. Patients with long-standing inactive disease required fewer visits, while those with active disease required more frequent visits.

The study criteria for antimalarial exposure included treatment with the agents for any period of 6 months or longer. The median time on antimalarial drugs was 56 months.

To compare the frequencies of cancer in the patients ever treated with antimalarials and those who were never treated with the drugs, the investigators used a chi-square test and created Kaplan-Meier free-of-cancer survival curves. They used a COX proportional hazards model to adjust for variables that could potentially influence the development of neoplasms: age at diagnosis; year of diagnosis; gender; treatment with azathioprine, cyclophosphamide, and methotrexate; smoking history; and SDI at 6 months after lupus diagnosis. "Treatment variables were only counted if patients received the [antimalarial] drug prior to the time of diagnosis of cancer," the authors wrote.

The COX model showed that, compared with patients who had never received antimalarials, the patients who received them were younger, more likely to have received methotrexate, and less likely to have severe organ damage at 6 months. In addition, patients diagnosed with lupus between 1996 and 2005 were more likely to receive antimalarials than those diagnosed prior to 1996.

With a total observation time of 2,620 patient-years, the incidence of cancer in the full cohort was 4.9/1,000 patient-years, according to the authors. The specific neoplasms observed in the cohort included basal cell carcinoma in three patients and glioblastoma in two, and in one patient each hepatocarcinoma, renal cell carcinoma, endometrial carcinoma, cervical carcinoma, breast cancer, sarcoma, urothelial carcinoma, and Hodgkin's lymphoma. The median time to cancer diagnosis from the time of lupus diagnosis was 3 years.

The cumulative cancer-free survival rates for patients ever treated with antimalarials compared with the never-treated group was 0.98 vs. 0.73, respectively. "The adjusted [hazards ratio] of patients treated with antimalarials was 0.15," the authors wrote. The only additional variables that showed independent associations with cancer were age at diagnosis and male gender, Dr. Ruiz-Irastorza and colleagues reported.

The limitations of the current investigation included the fact that patients in the cohort who were ever treated with antimalarials were younger and had less severe organ damage at the time of diagnosis, although severity of damage was not associated with cancer in the analysis, the authors stressed. In addition, some patients in the antimalarial group spent some time at risk for malignancy before receiving the drugs, although "a significant association with a lower frequency of cancer is unlikely to be explained by this fact," they wrote.

Larger, more ethnically diverse cohorts (99% of the current cohort was white) are needed to confirm the hypothesis that antimalarials exert some favorable action against some of the predisposing factors in patients with SLE, according to the authors. Such confirmation "would reinforce the recommendation of universal use of hydroxychloroquine in all patients with SLE," they concluded. ■