

Inflammatory Myopathies Linked to Thrombi

BY DAMIAN McNAMARA

Patients with dermatomyositis or polymyositis are at increased risk for arterial thrombotic events that immunosuppressant use may lessen, according to a case-control study.

These autoimmune diseases are known to cause muscle inflammation, weakness, and significant morbidity. However, there are fewer data on the risk

for arterial events in affected patients.

So Dr. Christian A. Pineau and colleagues assessed 607 people with dermatomyositis (DM) or polymyositis (PM). The researchers measured events such as acute myocardial infarction, stroke, and ischemic heart disease in this cohort during 1994-2003.

Patients were identified from the province of Quebec's physician billing, hospitalization, and pharmacy databases.

Their average age was 62 years, and women accounted for 70% of the cohort. All patients were beneficiaries of the public drug insurance plan, which covers approximately 42% of the residents of Quebec. The investigators reported their findings in the *Journal of Rheumatology* (2009 July 31 [doi: 10.3899/jrheum.090061]).

Results suggest a high incidence of arterial events in DM and PM. There were

124 arterial events experienced by 80 patients during the study period. Events included 34 incident cases of acute MI (equivalent to 13.8 per 1,000 person-years). The investigators estimated that they would expect about 17 acute MIs during this time in the same number of people in the general population, so the study cohort's relative risk was 1.95.

There were 13 strokes during the study (a rate of 5.2 per 1,000 person-years), similar to the rate of 5.1 per 1,000 person-years reported in rheumatoid arthritis (*Ann. Rheum. Dis.* 2006;65:1608-12). Stroke incidence in the general Canadian population is estimated at 3.1 per 1,000 person-years, suggesting a near doubling of risk for people with one of these inflammatory myopathies.

"As rheumatologists, we should be sensitive to the fact that comorbidities such as coronary artery disease represent a high burden for our patients," said Dr. Pineau, a rheumatologist at McGill University Health Centre in Montreal.

Nonatherosclerotic heart disease, hypertension, and lipid disorders were important determinants of arterial events in the study. For example, risk for an event in someone with a lipid disorder carried an adjusted rate ratio of 4.9; heart failure or valve disease, 3.0; and hypertension, 2.5, according to a multivariate analysis.

In contrast, exposure to nonsteroidal immunomodulators was associated with a significantly lower arterial event rate (adjusted RR, 0.5). "The use of immunosuppressants, which improve disease control and minimize the need for steroids, could in theory have the potential to lower the risk of coronary artery disease," Dr. Pineau said.

A majority (85% of the cohort) was exposed to systemic glucocorticoids; 26% to methotrexate; 21% to azathioprine; 14% to antimalarial drugs; and 6% to cyclophosphamide.

An unanswered question is why the researchers found a higher rate of arterial thrombotic events for people with DM or PM, compared with the general population. "I would like rheumatologists to see all rheumatic diseases in the same light as they see rheumatoid arthritis," Dr. Pineau said.

Although the use of disease-modifying antirheumatic drugs is the cornerstone of therapy in rheumatoid arthritis, many rheumatic diseases such as PM and DM are primarily—and often exclusively—treated with steroids, he said. At the same time, other immunosuppressants take only a secondary role. "As exemplified in this study, this strategy could potentially lead to increased morbidity, either through the toxicity associated with the use of higher steroid doses, or because of a higher inflammatory burden brought upon by a suboptimal control of the disease."

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comparison of the incidence of antibodies to infliximab with the incidence of antibodies to other products may be misleading. **Hepatotoxicity** Severe liver injury, including acute liver failure and autoimmune hepatitis, has been reported rarely in patients receiving REMICADE (see **WARNINGS, Hepatotoxicity**). Reactivation of hepatitis B virus has occurred in patients receiving TNF-blocking agents, including REMICADE who are chronic carriers of this virus (see **WARNINGS, Hepatitis B Virus Reactivation**). In clinical trials in RA, CD, UC, AS, PsO and PsA, elevations of aminotransferases were observed (ALT more common than AST) in a greater proportion of patients receiving REMICADE than in controls, both when REMICADE was given as monotherapy and when it was used in combination with other immunosuppressive agents. In general, patients who developed ALT and AST elevations were asymptomatic, and the abnormalities decreased or resolved with either continuation or discontinuation of REMICADE, or modification of concomitant medications. In RA clinical trials (median follow-up 58 weeks), 34% of patients who received REMICADE + MTX experienced elevations in ALT at >1 to <3 times the upper limit of normal (ULN) compared to 24% of patients treated with placebo + MTX. ALT elevations ≥ 3 times ULN were observed in 4% of patients who received REMICADE + MTX compared with 3% of patients who received MTX alone. ALT elevations ≥ 5 times ULN were observed in <1% of patients in both REMICADE + MTX and MTX alone groups. In CD clinical trials (median follow up 54 weeks), 39% of patients receiving REMICADE-maintenance experienced elevations in ALT at >1 to <3 times the ULN compared to 34% of patients treated with placebo-maintenance. ALT elevations ≥ 3 times the ULN were observed in 5% of patients who received REMICADE-maintenance compared with 4% of patients who received placebo-maintenance. ALT elevations ≥ 5 times ULN were observed in 2% of patients who received REMICADE-maintenance compared to none in patients treated with placebo-maintenance. In UC clinical trials (median follow up 30 weeks). 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 for placebo group and 102 weeks for REMICADE group) 51% of patients receiving REMICADE experienced elevations in ALT at >1 to <3 times the ULN compared to 15% of patients treated with placebo. ALT elevations ≥ 3 times the ULN were observed in 10% of patients who received REMICADE compared to none in patients who received placebo. ALT elevations ≥ 5 times ULN were observed in 4% of patients who received REMICADE compared to none in patients treated with placebo. In a PsA clinical trial (median follow up 39 weeks for REMICADE group and 18 weeks in placebo group) 50% 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 7% 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 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.) **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 perirectal) 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 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 $\geq 5\%$ 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, 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; Pruritus: 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 $\geq 0.2\%$ or clinically significant adverse events by body system were as follows: **Body as a whole:** allergic reaction, diaphragmatic hernia, edema, surgical/procedural sequelae; **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, some with fatal outcome, have been reported during post-approval use of REMICADE: neutropenia (see **WARNINGS, Hematologic Events**), interstitial lung disease (including pulmonary fibrosis/interstitial pneumonitis and very rare rapidly progressive disease), idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura, pericardial effusion, systemic and cutaneous vasculitis, erythema multiforme, Stevens-Johnson Syndrome, toxic epidermal necrolysis, peripheral demyelinating disorders (such as Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, and multifocal motor neuropathy), psoriasis (including new onset and pustular, primarily palmar/plantar), 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. The following serious adverse events have been reported in the post-marketing experience in children: 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. **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, reinstitution 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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