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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Meningococcal Vaccine Is Safe, Effective in JIA

BY BARBARA J. RUTLEDGE
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The meningococcal C conjugate vaccine can be safely and effectively administered to children with juvenile idiopathic arthritis, without aggravating disease activity or increasing relapse frequency, according to study results.

In 2002, Dutch health authorities initiated a national campaign to promote vaccination of all children aged 1-19 years against meningococcal serogroup C disease, but guideline recommendations were nonspecific regarding exclusion of patients with autoimmune diseases and patients on immunosuppressive therapy.

The MenC vaccine 'does not aggravate JIA … and results in adequate antibody levels, even in patients receiving highly immunosuppressive therapy.'

Therefore, Dr. Evelien Zonneveld-Huijssoon, of Wilhelmina Children's Hospital at University Medical Center Utrecht (the Netherlands), and colleagues undertook a study to determine whether vaccination exacerbates disease activity in patients with autoimmune disease and to assess the effect of immunosuppressive medication on vaccine efficacy.

Children with juvenile idiopathic arthritis (JIA) were selected as the study population. Investigators monitored JIA disease activity and immune responses before and after inoculation with a meningococcal C (MenC) conjugate vaccine (Arthritis Rheum. 2007;56:639-46).

A total of 234 JIA patients enrolled in the study. All patients were aged 1-19 years and attended one of the five pediatric rheumatology outpatient clinics participating in the study. The majority of the patients were female (65%), and mean disease duration was 5.9 years.

Patients were followed clinically for 6 months before and after vaccination. The primary outcome measure was disease relapse. Regardless of JIA disease activity, each patient received a single intramuscular dose of the vaccine during the national vaccination campaign and reported the vaccination date on a study questionnaire. Patients provided blood samples for serologic analysis before vaccination and within 12 weeks after vaccination.

Disease activity was measured using six core set criteria for juvenile arthritis disease activity: physician global assessment, the well-being and disability scales of the Childhood Health Assessment Questionnaire, active joints, limited range of motion, and erythrocyte sedimentation rate. Relapse was considered most likely to occur in the month immediately after vaccination, which was defined as the period of vaccine exposure.

For data analysis, the remaining 11 months of the study period were considered the unexposed period.

Patients for which postvaccination blood samples were available were classified into four groups based on medication use. Patients in group 1 used no medication (47); group 2 used NSAID monotherapy (41); and group 3 used low-dose methotrexate (36) or sulfasalazine (7), with or without NSAIDs. Group 4 consisted of patients receiving high-dose methotrexate (15), methotrexate and sulfasalazine combination therapy (2), infliximab (2), etanercept (6), or cyclosporin A (1), with or without NSAIDs.

Disease activity did not worsen following vaccination, and vaccination did not increase the frequency of disease relapse. Over the 12-month study period, 158 relapses occurred in 97 patients, with 10 patients experiencing disease relapse in the month following vaccination. Risk of relapse in the month following vaccination (exposed period) was 6%, compared with an 8% risk of relapse in the remaining 11 months. Comparable results were seen when the exposed period was defined as 2, 3, or 6 months following vaccination.

Serologic analysis was performed on 141 prevaccination samples and 157 postvaccination samples, including 133 paired samples. Anti-MenC total IgG antibodies in serum were measured by an enzyme-linked immunosorbent assay with a lower limit of detection of 0.24 mcg/mL.

Anti–tetanus toxin antibodies were measured using a tetanus toxin–binding inhibition assay with a lower limit of detection of 0.01 IU/mL. Patients were classified as low responders if postvaccination anti-MenC IgG levels were not greater than 2 mcg/ml.

In the overall study population, anti-MenC IgG geometric mean concentrations increased significantly from 0.4 mcg/mL to 28.9 mcg/mL following vaccination. As expected, postvaccination concentrations were lower in medication groups 3 and 4 (18 and 16, respectively), compared with groups 1 and 2 (41 and 47, respectively).

Four patients were considered low responders. Further testing using serum bactericidal assays (SBA) against serogroup C strain was performed using sera from the 4 low responders and 10 randomly selected serum samples from high responders. The four low responders had postvaccination bactericidal titers within the range indicating an effective bactericidal response, and there were no significant difference in SBA titers in the low responders, compared with the high responders.

"The MenC conjugate vaccine does not aggravate JIA disease activity or increase relapse frequency and results in adequate antibody levels, even in patients receiving highly immunosuppressive therapy," wrote Dr. Zonneveld-Huijssoon and colleagues. Study results showed the MenC conjugate vaccine to be safe and effective for use in children with JIA. ■