efficacy and to experience an infusion reaction (see *ADVERSE REACTIONS, Infusion-related Reactions*) than were patients who were antibody negative. Antibody development was lower among RA and CD patients receiving immunosuppressant therapies such as 6-MP/AZA or MTX. In the psoriasis Study II, which included both the 5 mg/kg and 3 mg/kg doses, antibodies were observed in 36% of patients treated with 5 mg/kg every 8 weeks for 1 year, and in 51% of patients treated with 3 mg/kg every 8 weeks for 1 year. In the psoriasis Study III, which also included both the 5 mg/kg and 3 mg/kg doses, antibodies were observed in 20% of patients treated with 5 mg/kg induction (Weeks 0, 2 and 6), and in 27% of patients treated with 3 mg/kg induction. Despite the increase in antibody formation, the infusion reaction rates in Studies I and II in patients treated with 5 mg/kg induction followed by every 8 week maintenance for one year and in Study III in patients treated with 5 mg/kg induction (14.1%-23.0%) and serious infusion reaction rates (<1%) were similar to those observed in other study populations. The clinical significance of apparent increased immunogenicity on efficacy and infusion reactions in psoriasis patients as compared to patients with other diseases treated with REMICADE over the long term is not known. The data reflect the percentage of patients whose test results were positive for antibodies to infliximab in an ELISA assay, and are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors including sample handling, timing of sample collection, concomitant medication, and underlying disease. For these reasons, 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 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 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, 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, 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), new-onset and worsening psoriasis (all sub-types including pustular, primarily palmoplantar), 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, 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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RA Patients on the Frontier Of Joint Replacement

BY RICHARD HYER

EXPERT ANALYSIS FROM A SYMPOSIUM SPONSORED BY THE AMERICAN COLLEGE OF RHEUMATOLOGY

CHICAGO — On balance, the news about joint replacement innovations for people with rheumatoid arthritis is good.

New lumbar artificial disks, new ankle implants, customized patient instrumentation, and computer-assisted surgical planning offer options that patients with RA-destroyed joints lacked even a decade ago. The unfortunate flip sides of these advances are aggressive and sometimes misleading direct-to-consumer marketing, and occasional unfavorable biological responses to even the newest implant materials.

The field of orthopedic surgery has benefited from "a lot of great science," said presenter Dr. William Bugbee, an orthopedic surgeon with the Scripps Institute in La Jolla, Calif. Robust innovation has lead to "constant introduction of new technology."

In the half century since British orthopedic surgeon Sir John Charnley pioneered modern total hip replacement, joint replacement has become one of the most common and successful interventions for arthritis, said Dr. Bugbee. Joint-specific arthroplasty is now available for hips, knees, shoulders, ankles, elbows, the small joints of the feet and hands, and the lumbar and cervical spines.

Spinal disk replacement is now an alternative to spinal fusion, although its efficacy is unproven, said Dr. Bugbee. The objective is to preserve motion, particularly in the cervical spine; for every level that is fused, the patient loses about 15% of motion. The levels above and below also come under greater stress and tend to degenerate.

Shoulder arthroplasties are often performed on patients with RA. The functional outcomes are acceptable and provide pain relief, but fall short of restoring normal shoulder function, said Dr. Bugbee. "Few people can play tennis" following shoulder arthroplasty, he said. The results depend on the integrity of the rotator cuff. A recent innovation is the reverse shoulder arthroplasty, which accommodates a deficient rotator cuff to allow better function of the shoulder after replacement.

Ankle arthroplasty remains the most common operation for arthritis, and is another area of new design. It presents a particular design challenge because the biological ankle has only 9 cm^2 of joint surface and the cartilage is 1 mm thick. The joint requires congruity and endures high contact stress. There are multiple new implant designs.

Arthroplasties of the hip and/or knee have become common and successful surgical interventions for arthritis, and the need for them is growing with the population. It has been estimated that by 2030, the U.S. population will need 2.3 million knee replacements per year. "There's not enough manpower to do all that work," said Dr. Bugbee. Technical skill is the single most important factor in success.

The appropriate patient age for joint replacement now ranges from the 40s through the 90s said Dr. Bugbee. Although the intervention was originally conceived to relieve pain for elderly, low-demand patients, it is now expected to bring both pain relief and functional improvement. But it is not without risk: Dr. Bugbee estimated that 90-day mortality after surgery is less than 1%, but deep vein thrombosis occurs in 10%-40% of cases. Dislocation rates are 0%-10% because of larger ball and socket joints. Dr. Bugbee estimated that infection occurs in 0.3%-3% of operations.

There are also functional limitations after joint replacement. "A good hip replacement is tantamount to a normal joint," said Dr. Bugbee. "Unfortunately, the knee is not the same. It is a much more complex joint."

One area of concern is biological response to implant materials. Microscopic wear debris can be shed by the articulating surfaces. The polyethylene plastic in some implants can cause a granulomatous response, and an osteolytic response in the bone. In metal-on-metal joints, a tiny amount of wear debris may cause severe early osteoarthritis. Ceramic-to-ceramic hip joints have a wear rate about 50 times less than that of conventional polyethylene joints, but they may squeak.

Direct-to-consumer advertising campaigns have promoted minimally invasive surgery, but smaller incisions are not correlated with better outcome, said Dr. Bugbee. They may even have a higher complication rate.

"The next innovation is so-called customized patient instrumentation," said Dr. Bugbee. The surgery can actually be computer modeled in advance, and can incorporate instruments that are custom built to fit the individual patient's joints. The surgery is then more accelerated and more precise.

Moderator Dr. John J. Cush of Baylor University Medical Center in Dallas, asked, "When patients have bilateral knees, or right and left knees, one of the things I've noticed over the years [is that] they'll always say, 'My right (or my left) is the best one.' They always have an ipsilateral evaluation and a preference. Is there a good reason for that?"

"No. I've seen the same thing. I cannot for the life of me figure it out," said Dr. Bugbee. ■

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