

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 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 $\geq 5\%$ 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, 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; 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 $\geq 2\%$ 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, Guillain-Barré syndrome, 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, 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.

REFERENCES: 1. *Am J Respir Crit Care Med*. 2000;161:S221-S247. 2. See latest Centers for Disease Control guidelines and recommendations for tuberculosis testing in immunocompromised patients. 3. Gardam MA, Keystone EC, Menzies R, et al. Anti-tumor necrosis factor agents and tuberculosis risk: mechanisms of action and clinical management. *Lancet Infect Dis*. 2003;3:148-155. 4. Belhadj K, Reyes F, Farceat JP, et al. Hepatosplenic $\gamma 6$ T-cell lymphoma is a rare clinicopathologic entity with poor outcome: report on a series of 21 patients. *Blood*. 2003;102(13):4261-4269.

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Study Highlights Lack Of On-Call Specialists

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Emergency on-call coverage from specialist physicians, including dermatologists, is "unraveling" at hospitals across the country, resulting in delayed treatment, patient transfers, permanent injuries, and even death, according to a study from the Center for Studying Health System Change, a nonpartisan policy research group in Washington.

While the problem is predominantly an issue for hospital emergency departments, it also is becoming increasingly problematic for inpatients who need urgent specialty care, according to the report. The findings are based on 2007 data from 12 nationally representative communities: Boston; Cleveland; Greenville, S.C.; Indianapolis; Lansing, Mich.; Little Rock, Ark.; Miami; Northern New Jersey; Orange County, Calif; Phoenix; Seattle; and Syracuse, N.Y.

The picture is particularly grim given the fact that overall ED utilization rates have risen by 7% in the past 7 years, from 36.9 to 39.6 visits per 100 people, according to the report. While insured people account for the vast majority of ED visits, "the proportion of visits by uninsured people is rising at a relatively higher rate," the study's authors wrote.

Citing a 2006 paper from the American College of Emergency Physicians, the study reported that 73% of emergency departments in the United States report inadequate on-call coverage by specialist physicians. In particularly short supply are plastic surgeons, ophthalmologists, dermatologists, orthopedic surgeons, neurosurgeons, trauma surgeons, hand surgeons, obstetrician-gynecologists, and neurologists. While an actual shortage of such physicians may sometimes be to blame, "physician unwillingness to take call appears to be a more pressing issue for many hospitals," the study authors stated.

Although unwillingness to accept on-call duty is largely influenced by quality of life issues, the requirement to provide on-call coverage has traditionally been mandated by hospitals under the Emergency Medical Treatment and Labor Act. However, many specialists are now shifting their practices away from the hospital setting, and are no longer obligated by medical staff privileges, noted the report's authors.

Many physicians also believe payment for on-call care is inadequate, especially when they are caring for uninsured patients. Specialists are also concerned that providing emergency care may increase their exposure to medical liability and drive up the cost of their malpractice premiums, according to the report.

As a result, adverse patient outcomes are reported. One study found that 21% of patient deaths or permanent injuries related to ED treatment delays are attributed to lack of specialists' availability, noted the report. Complete lack of access to specialty care in some EDs is forcing either travel or

transfer of patients. And for the physicians who continue to provide on-call coverage, increasing workload and decreasing morale may put patients further at risk.

Crisis May Drive Docs Away

"It's not a surprise that we're having this problem—it's a surprise to me that we have any on-call specialists at all," Dr. Todd Taylor, previously an emergency physician and speaker for the ACEP Council, said in an interview. Dr. Taylor left clinical medicine last summer to work in the computer industry, he said, because the risks of liability were more than he could justify.

For Dr. Taylor, it is these very liability risks that are at the root of the current on-call crisis. "The liability issue has become the overriding barrier to physicians being willing to put themselves at risk," he said. "Until and unless you solve the liability crisis in emergency care and health care in general, nothing else you do matters."

Most on-call specialists have a private practice outside of the emergency department—they don't need the ED—so it's not a big surprise they were the first to leave, he explained. "But now that core emergency physicians, who were trained to practice only emergency medicine, are making the same choices, that should be a wake-up call," Dr. Taylor said. "That's what's different now compared to 2 or 3 years ago."

On-Call Shortage Cripples Trauma Care

Lack of optimal on-call coverage is what will ultimately "cripple" trauma and emergency care, agreed Dr. L. D. Britt, professor of surgery at the Eastern Virginia Medical School in Norfolk. "Some of the specialists are asking for unbelievably exorbitant fees to provide coverage, and hospitals are being held hostage," he said in an interview.

While Dr. Britt sympathizes with physicians' struggles with payment and liability issues, he believes the true bottom line is simply that obligations are being overlooked. "It cannot be everyone saying, 'I can't do this.' Something has to give," Dr. Britt said. "Speaking for myself, I consider it my obligation to provide emergency coverage if I am on call. I know that's my responsibility—and I'm a chairman of a department. Some people can find ways out of it, but I'm saying we cannot have all those options out there."

In addition, high fees charged by specialists and paid by hospitals for on-call coverage are not justified based on the premise that on-call coverage increases a physician's liability exposure, he said. "Being on call doesn't give you more litigation than being in general surgery—that's well documented," he said.

Dr. Taylor disagreed. "The literature is very clear that emergency care is one of the highest liability environments in health care," he said. "You only have to look at what's happened to emergency physician malpractice premiums relative to others not involved in emergency care. Mine almost doubled the last 3 years I worked." ■