

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.

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Mixed Results for Limb Infusion in Melanoma

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CHICAGO — Isolated limb infusion, a minimally invasive technique to deliver regional chemotherapy, was useful but not optimal in two melanoma studies presented at a symposium sponsored by the Society of Surgical Oncology.

In the largest isolated limb infusion (ILI) series conducted to date, involving 185 patients with advanced metastatic melanoma confined to the limb, the overall survival rate was 84% at a median follow-up of 20 months, said lead investigator Dr. Hidde Kroon, a fellow at the Sydney Melanoma Unit in Australia, where the study was performed and the technique was developed.

He reported the highest rates to date for complete response (38%) and for partial response (46%) to chemotherapy. Stable disease was seen in 10% of patients and progressive disease in 6%.

In the largest study outside Australia, however, U.S. and Taiwanese investigators concluded that isolated limb infusion was an effective way to regionally administer the cytotoxic agent melphalan, but that its efficacy fell short of isolated limb perfusion (ILP).

Sydney Melanoma Unit Experience

Dr. Kroon said that the duration of response was significantly longer in patients achieving a complete response (median 22 months) than was observed overall (median 13 months) in the Australian study.

"Response rates and duration of response after isolated limb infusion are at the lower end of those reported after conventional isolated limb perfusion," Dr. Kroon acknowledged.

"However, ILI was performed in patients with [higher stages] of disease and more comorbidities, which might explain the lower response rates, since stage of disease is a significant risk factor for responses," he said.

Most patients in the study (134, or 72%) had M.D. Anderson stage IIIA or IIIAB disease, with 3% having stage I, 8% stage II, and 16% stage IV disease.

Isolated limb infusion is essentially a low-flow ILP performed without oxygenation via percutaneous catheters. It is a minimally invasive alternative to the more labor-intensive ILP, requires no routine blood transfusion, and can be easily repeated if necessary, Dr. Kroon explained. Results have been promising, but it has not been established whether it is equally effective as isolated limb perfusion.

Patients in the Australian series were treated from 1992 to 2006 with a single isolated limb infusion of melphalan and actinomycin D for 20-30 minutes under

mild hyperthermic conditions. Their mean age was 74 years (range, 29-93 years), and the majority (62%) were female. Disease was present in the lower limb in 172 patients, and in the upper limb in 13.

The response rate significantly decreased with increasing stage of disease, Dr. Kroon said.

Response rates were 83% in stage I patients, 53% in stage II, 43% in stage IIIA, 33% in stage IIIAB, and 23% in stage IV.

Median overall survival was 38 months, but increased significantly to 53 months in patients achieving a complete response, he reported.

In a multivariate analysis, independent prognostic factors for complete response were lower disease stage (hazard ratio, 1.69) and greater increase in CO₂ level during the procedure (HR, 1.65).

The procedure was well tolerated, with only five patients developing grade 4 toxicity, and there were no amputations, said Dr. Kroon, who reported no conflicts of interest.

"We conclude that isolated limb infusion is a safe and effective alternative to conventional isolated limb perfusion to treat advanced metastatic melanoma in a limb," he said.

U.S./Taiwanese Experience

Lead investigator Dr. Georgia Beasley of the Duke University Medical Center in Durham, N.C., and associates compared outcomes after 59 ILP treatments in 54 patients against outcomes after 61 ILI treatments in 58 patients, all with in-transit malignant melanoma of the extremity.

Among 50 evaluable ILI patients, complete response was reported in 15 (30%), partial response in 7 (14%), stable disease in 5 (10%), and progressive disease in 23 (46%). The median duration of complete response was 12 months.

Isolated limb perfusion was associated with significantly better response at 3 months (complete response, 57%; partial response, 31%; and no response, 12%); however, significantly more ILP patients had grade 3 or greater toxicity, Dr. Beasley said.

There were nine compartment syndromes and two amputations among ILP patients, versus four compartment syndromes and no amputations among ILI patients.

"In our experience, limb infusion using melphalan did not appear to be as effective as limb perfusion, although the toxicity appears less," Dr. Beasley said.

The investigators noted that correcting the melphalan dose for ideal body weight appeared to minimize toxicity without altering response rates; 66% of ILI patients had their dose corrected, versus only 22% of ILP patients. ■

One group of investigators called isolated limb infusion a 'safe and effective alternative,' but another said it 'did not appear to be as effective as limb perfusion.'