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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Phototherapy May Alleviate Allergic Rhinitis

BY SHARON WORCESTER
Southeast Bureau

RHODES, GREECE — Targeted ultraviolet B phototherapy—the use of fiberoptic light delivery systems—allows treatment of previously inaccessible body sites such as the scalp and the oral and intranasal mucosa, Dr. Lajos Kemeny said at the 15th Congress of the European Academy of Dermatology and Venereology.

The fiber optics guide delivery of incoherent ultraviolet light to small areas while protecting nonlesional skin from excessive UV exposure. This has further enhanced phototherapy, improving delivery to areas like the scalp and nasal mucosa, and has led to investigation of its use for new applications, namely intranasal treatment for allergic rhinitis, said Dr. Kemeny of the University of Szeged (Hungary).

In a randomized double-blind clinical trial using a novel device for intranasal phototherapy, "rhinophototherapy" significantly reduced the symptoms of hay fever, reported Dr. Kemeny, who is a cofounder of the Rhinolight company, maker of the Rhinolight device used in the study.

In 49 patients, each intranasal cavity was illuminated three times weekly for 3 weeks with 5% UVB, 25% UVA, and 70% visible light (an approach known as mUV/VIS), or with just low-intensity visible light. Scores for sneezing, rhinorrhea, and nasal itching improved significantly in the treated patients but not in the control patients, he said.

Furthermore, scores for nasal obstruction improved slightly in the treated patients and increased significantly in control patients (J. Allergy Clin. Immunol. 2005;115:541-7).

In an open-label follow-up study using a similar protocol but with gradual increases in doses of mUV/VIS light, rhinophototherapy significantly inhibited allergic rhinitis symptoms in 90% of 70 treated patients. Significant improvements were seen in sneezing, rhinorrhea, nasal itching, nasal obstruction, and total nasal scores in this study.

Evaluation of nasal lavage in treated patients suggests that the mechanism of action can be at least partially attributed to apoptosis induction of cells that play an important role in the pathogenesis of allergic rhinitis: The mUV/VIS irradiation induces a dose-dependent increase in apoptosis of memory T cells, naive T cells, and eosinophils, Dr. Kemeny noted.

Intranasal phototherapy may represent a novel treatment for allergic rhinitis as well as other inflammatory and immune-mediated mucosal diseases, he said.

The Rhinolight device is available in Europe but has not yet been approved in the United States. ■

MAL-PDT Offers Better Cosmesis After Excision Than Cryotherapy

BY SHARON WORCESTER
Southeast Bureau

RHODES, GREECE — Photodynamic therapy using topical methyl aminolevulinate has efficacy comparable to cryotherapy for the treatment of basal cell carcinoma and actinic keratoses but provides substantially better cosmetic outcomes, according to data presented at the 15th Congress of the European Academy of Dermatology and Venereology.

In a multicenter study of 120 patients with superficial basal cell carcinoma who were randomized to photodynamic therapy with methyl aminolevulinate (MAL-PDT) or cryotherapy, complete responses were seen in 97% of those in the MAL-PDT group and 95% of those in the cryotherapy group at 3 months, Dr. Nicole Basset-Seguin reported in a poster.

The recurrence rate at 60 months also was similar in the two groups: 22% in the MAL-PDT group and 20% for cryotherapy patients, reported Dr. Basset-Seguin of Hôpital Saint Louis, Paris.

The investigators, however, rated cosmetic outcomes as excellent far more frequently in the MAL-PDT group (56%) than in the cryotherapy group (14%) at the 60-month follow-up.

In this study, MAL-PDT was provided as a single treatment. Patients who failed to respond at 3 months were retreated with an additional two consecutive MAL-PDT sessions 7 days apart. Cryotherapy was applied in two freeze-thaw cycles using liquid nitrogen spray. Patients who failed to respond were retreated with double freeze-thaw cryotherapy.

In another study presented at the meeting, MAL-PDT was superior to cryotherapy for treatment of actinic keratoses.

A total of 119 subjects with 1,501 cumulative lesions were treated on one side of the face or scalp with MAL-PDT and on the other side with double freeze-thaw cryotherapy. The treatments were randomly allocated to the sides of the face/scalp and were repeated at 12 weeks in those with incomplete response, Dr. Colin Morton of the Falkirk (Scotland) Royal Infirmary, reported in a poster.

At 12 weeks, significantly more patients in the MAL-PDT group had a reduction from baseline in the number of lesions, compared with cryotherapy (84% vs. 75%, respectively), and at 24 weeks, both groups showed similar reductions in the number of lesions from baseline (89% and 88%).

Both treatments were safe and well tolerated, and subject and investigator ratings of cosmetic outcome "clearly favored MAL-PDT," Dr. Morton wrote.

Both studies were sponsored by Galderma, maker of the PDT devices used. ■