Phase III: Reloxin Shows Rapid Onset, Lasting Effect

BY SHARON WORCESTER
Southeast Bureau

ATLANTA — Recently completed phase III data on Reloxin, a botulinum toxin type A formulation known as Dysport in Europe, may hasten the product's availability in the United States, Gary Monheit, M.D., said at the annual meeting of the American Society for Dermatologic Surgery and the American College of Mohs Micrographic Surgery and Cutaneous Oncology.

The new data on this "other Botox" have not been released, but Dr. Monheit described his experience with patients involved in the trial.

In a phase II trial in the United States, Reloxin was shown to be safe and effective at 30 days' follow-up. The phase III trial included 300 patients and tracked safety and efficacy for at least 5 months, he said.

The product had an excellent safety profile in both trials, and in some patients has an early onset of action, compared with Botox (Allergan Inc.), he said, noting that results were often seen in his patients in days rather than weeks.

"There was a very smooth, natural elimination of frown lines, a significant number of responders at 4 months, and action was still noted in a significant number of patients at up to 6 months," explained Dr. Monheit, an investigator for Ipsen Pharmaceuticals Ltd., the product's manufacturer, and Inamed Corp., which will develop and market the product in the United States.

Younger patients with significant frown lines had excellent results with full correction, and with very early onset—many within 24 hours. Furthermore, some had full response well beyond 4 months, he reported. Likewise, forehead and brow response was good at 4 months—and often well beyond that.

Older patients tended to take longer to respond, and some did not achieve the response that was expected. This might have been because of redundant skin, photodamage, or delayed or incomplete muscle response, Dr. Monheit speculated.

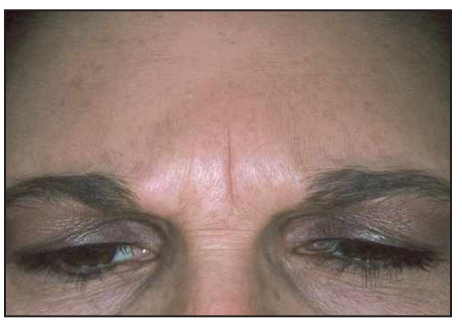
Forehead and brow response was good at 4 months—and often well beyond that.

DR. MONHEIT

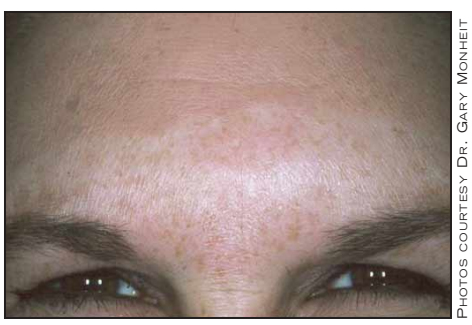
In a repeat-dose study that is now underway, investigators are evaluating whether repeat doses are as potent as the initial dose. A total of 1,200 patients are enrolled in the study and will be followed for 1 year, he said, noting that this will be the largest trial to date for the botulinum toxin.

Reloxin is identical to Botox except in its preparation. For example, Reloxin is provided in 500-unit vials, and Botox is provided in 100-unit vials; moreover, Reloxin is suspended in lactose, whereas Botox is suspended is sodium chloride, explained Dr. Monheit, of the department of dermatology at the University of Alabama at Birmingham, and president of the American Association for Dermatologic Surgery.

Given the differences in how Reloxin is prepared and in its onset and duration, it will likely require unique and individualized dosing and injection techniques, Dr. Monheit said. ■



Patient is shown at baseline in a "maximal frown" pose.



Smoothing is evident after treatment with Reloxin.

PHOTOS COURTESY DR. GARY MONHEIT

RAPTIVA® efalizumab

Brief Summary of Prescribing Information

Please see full Prescribing Information.

INDICATIONS AND USAGE RAPTIVA® [efalizumab] is indicated for the treatment of adult patients (18 years or older) with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

CONTRAINDICATIONS RAPTIVA should not be administered to patients with known hypersensitivity to RAPTIVA or any of its components.

WARNINGS **Serious Infections:** RAPTIVA is an immunosuppressive agent and has the potential to increase the risk of infection and reactivate latent, chronic infections. RAPTIVA should not be administered to patients with clinically important infections. Caution should be exercised when considering the use of RAPTIVA in patients with a chronic infection or history of recurrent infections. If a patient develops a serious infection, RAPTIVA should be discontinued. New infections developing during RAPTIVA treatment should be monitored. During the first 12 weeks of controlled trials, serious infections occurred in 7 of 1620 (0.4%) RAPTIVA-treated patients compared with 1 of 715 (0.1%) placebo-treated patients (see **ADVERSE REACTIONS, Infections**). Serious infections requiring hospitalization included cellulitis, pneumonia, abscess, sepsis, bronchitis, gastroenteritis, aseptic meningitis, Legionnaire's disease, and vertebral osteomyelitis (note some patients had more than one infection). Postmarketing reports of serious infections include necrotizing fasciitis and tuberculous pneumonia. Bacterial sepsis with seeding of distant sites, severe pneumonia with neutropenia (ANC 60/mm³), and worsening of infection (e.g. cellulitis, pneumonia) despite antimicrobial treatment have been observed.

Malignancies: RAPTIVA is an immunosuppressive agent. Many immunosuppressive agents have the potential to increase the risk of malignancy. The role of RAPTIVA in the development of malignancies is not known. Caution should be exercised when considering the use of RAPTIVA in patients at high risk for malignancy or with a history of malignancy. If a patient develops a malignancy, RAPTIVA should be discontinued (see **ADVERSE REACTIONS, Malignancy**).

Immune-Mediated Thrombocytopenia: Platelet counts at or below 52,000 cells per µL were observed in 8 (0.3%) RAPTIVA-treated patients during clinical trials compared with none among the placebo-treated patients (see **ADVERSE REACTIONS, Immune-Mediated Thrombocytopenia**). Five of the 8 patients received a course of systemic steroids for thrombocytopenia. Thrombocytopenia resolved in the 7 patients receiving adequate follow-up (1 patient was lost to follow-up). Reports of severe thrombocytopenia have also been received postmarketing. Physicians should follow patients closely for signs and symptoms of thrombocytopenia. Assessment of platelet counts is recommended during treatment with RAPTIVA (see **PRECAUTIONS, Laboratory Tests**) and RAPTIVA should be discontinued if thrombocytopenia develops.

Immune-Mediated Hemolytic Anemia: Reports of hemolytic anemia, some serious, diagnosed 4-6 months after the start of RAPTIVA treatment have been received. RAPTIVA should be discontinued if hemolytic anemia occurs.

Psoriasis Worsening and Variants: Worsening of psoriasis can occur during or after discontinuation of RAPTIVA. During clinical studies, 19 of 2589 (0.7%) of RAPTIVA-treated patients had serious worsening of psoriasis during treatment (n = 5) or worsening past baseline after discontinuation of RAPTIVA (n = 14) (see **ADVERSE REACTIONS, Adverse Events of Psoriasis**). In some patients these events took the form of psoriatic erythroderma, pustular psoriasis, or development of new plaque lesions. Some patients required hospitalization and alternative antipsoriatic therapy to manage the psoriasis worsening. Patients, including those not responding to RAPTIVA treatment, should be closely observed following discontinuation of RAPTIVA, and appropriate psoriasis treatment instituted as necessary.

PRECAUTIONS **Arthritis Events:** Infrequent new onset or recurrent severe arthritis events, including psoriatic arthritis events, have been reported in clinical trials and postmarketing. These arthritis events began while on treatment or following discontinuation of RAPTIVA and were uncommonly associated with flare of psoriasis. Patients improved after discontinuation of RAPTIVA with or without anti-arthritis therapy.

Immunosuppression: The safety and efficacy of RAPTIVA in combination with other immunosuppressive agents or phototherapy have not been evaluated. Patients receiving other immunosuppressive agents should not receive concurrent therapy with RAPTIVA because of the possibility of increased risk of infections and malignancies.

Immunizations: The safety and efficacy of vaccines administered to patients being treated with RAPTIVA have not been studied. In a small clinical study with IV administered RAPTIVA, a single dose of 0.3 mg/kg given before primary immunization with a neoantigen decreased the secondary immune response, and a dose of 1 mg/kg almost completely ablated it. A dose of 0.3 mg/kg IV has comparable pharmacodynamic effects to the recommended dose of 1 mg/kg SC. In chimpanzees exposed to RAPTIVA at ≥10 times the clinical exposure level (based on mean peak plasma levels) antibody responses were decreased following immunization with tetanus toxoid compared with untreated control animals. Acellular, live and live-attenuated vaccines should not be administered during RAPTIVA treatment.

First Dose Reactions: First dose reactions including headache, fever, nausea, and vomiting are associated with RAPTIVA treatment and are dose-level related in incidence and severity (see **ADVERSE REACTIONS**). Therefore, a conditioning dose of 0.7 mg/kg is recommended to reduce the incidence and severity of reactions associated with initial dosing (see **DOSAGE AND ADMINISTRATION**). Cases of aseptic meningitis resulting in hospitalization have been observed in association with initial dosing (see **ADVERSE REACTIONS, Inflammatory/Immune-Mediated Reactions**).

Information for Patients: Patients should be informed that their physician may monitor platelet counts during therapy. Patients should be advised to seek immediate medical attention if they develop any of the signs and symptoms associated with severe thrombocytopenia (such as easy bleeding from the gums, bruising, or petechiae) or with severe hemolytic anemia (such as weakness, orthostatic light-headedness, hemoglobinuria or jaundice), or with worsening of psoriasis or arthritis. Patients should also be informed that RAPTIVA is an immunosuppressant, and could increase their chances of developing an infection or a malignancy. Patients should be advised to promptly call the prescribing doctor's office if they develop any new signs of, or receive a new diagnosis of infection or malignancy while undergoing treatment with RAPTIVA.

Female patients should also be advised to notify their physicians if they become pregnant while taking RAPTIVA (or within 6 weeks of discontinuing RAPTIVA) and be advised of the existence of and encouraged to enroll in the RAPTIVA Pregnancy Registry. Call 1-877-RAPTIVA (1-877-727-8482) to enroll in the Registry.

If a patient or caregiver is to administer RAPTIVA, he/she should be instructed regarding injection techniques and how to measure the correct dose to ensure proper administration of RAPTIVA. Patients should be also referred to the RAPTIVA Patient Package Insert. In addition, patients should have available materials for and be instructed in the proper disposal of needles and syringes to comply with state and local laws. Patients should also be cautioned against reuse of syringes and needles.

Laboratory Tests: Assessment of platelet counts is recommended upon initiating and periodically while receiving RAPTIVA treatment. It is recommended that assessments be more frequent when initiating therapy (e.g., monthly) and may decrease in frequency with continued treatment (e.g., every 3 months). Severe thrombocytopenia has been observed (see **WARNINGS, Immune-Mediated Thrombocytopenia**).

Drug Interactions: No formal drug interaction studies have been performed with RAPTIVA. RAPTIVA should not be used with other immunosuppressive drugs (see **PRECAUTIONS, Immunosuppression**).

Acellular, live and live-attenuated vaccines should not be administered during RAPTIVA treatment (see **PRECAUTIONS, Immunizations**).

Drug/Laboratory Test Interactions: Increases in lymphocyte counts related to the pharmacologic mechanism of action are frequently observed during RAPTIVA treatment (see **CLINICAL PHARMACOLOGY, Pharmacodynamics**).

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term animal studies have not been conducted to evaluate the carcinogenic potential of RAPTIVA.

Subcutaneous injections of male and female mice with an anti-mouse CD11a antibody at up to 30 times the equivalent of the 1 mg/kg clinical dose of RAPTIVA had no adverse effects on mating, fertility, or reproduction parameters. The clinical significance of this observation is uncertain.

Genotoxicity studies were not conducted.

Pregnancy (Category C): Animal reproduction studies have not been conducted with RAPTIVA. It is also not known whether RAPTIVA can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. RAPTIVA should be given to a pregnant woman only if clearly needed.

In a developmental toxicity study conducted in mice using an anti-mouse CD11a antibody at up to 30 times the equivalent of the recommended clinical dose of RAPTIVA, no evidence of maternal toxicity, embryotoxicity, or teratogenicity was observed when administered during organogenesis. No adverse effects on behavioral, reproductive, or growth parameters were observed in offspring of female mice subcutaneously treated with an anti-mouse CD11a antibody during gestation and lactation using doses 3- to 30-times the equivalent of the recommended clinical dose of RAPTIVA. At 11 weeks of age, the offspring of these females exhibited a significant reduction in their ability to mount an antibody response, which showed evidence of partial reversibility by 25 weeks of age. Animal studies, however, are not always predictive of human response, and there are no adequate and well-controlled studies in pregnant women.

Since the effects of RAPTIVA on pregnant women and fetal development, including immune system development are not known, healthcare providers are encouraged to enroll patients who become pregnant while taking RAPTIVA (or within 6 weeks of discontinuing RAPTIVA) in the RAPTIVA Pregnancy Registry by calling 1-877-RAPTIVA (1-877-727-8482).

Nursing Mothers: It is not known whether RAPTIVA is excreted in human milk. An anti-mouse CD11a antibody was detected in milk samples of lactating mice exposed to anti-mouse CD11a antibody and the offspring of the exposed females exhibited significant reduction in antibody responses (see **PRECAUTIONS, Pregnancy**). Since maternal immunoglobulins are known to be present in the milk of lactating mothers, and animal data suggest the potential for adverse effects in nursing infants from RAPTIVA, a decision should be made whether to discontinue nursing while taking the drug or to discontinue the use of the drug, taking into account the importance of the drug to the mother.

RAPTIVA® [efalizumab]

Pediatric Use: The safety and efficacy of RAPTIVA® [efalizumab] in pediatric patients have not been studied.

Geriatric Use: Of the 1620 patients who received RAPTIVA in controlled trials, 128 were ≥65 years of age, and 2 were ≥75 years of age. Although no differences in safety or efficacy were observed between older and younger patients, the number of patients aged 65 and over is not sufficient to determine whether they respond differently from younger patients. Because the incidence of infections is higher in the elderly population, in general, caution should be used in treating the elderly.

ADVERSE REACTIONS The most serious adverse reactions observed during treatment with RAPTIVA were serious infections, malignancies, thrombocytopenia, hemolytic anemia, arthritis events, and psoriasis worsening and variants (see **WARNINGS**).

The most common adverse reactions associated with RAPTIVA were a first dose reaction complex that included headache, chills, fever, nausea, and myalgia within two days following the first two injections. These reactions are dose-level related in incidence and severity and were largely mild to moderate in severity when a conditioning dose of 0.7 mg/kg was used as the first dose. In placebo-controlled trials, 29% of patients treated with RAPTIVA 1 mg/kg developed one or more of these symptoms following the first dose compared with 15% of patients receiving placebo. After the third dose, 4% and 3% of patients receiving RAPTIVA 1 mg/kg and placebo, respectively, experienced these symptoms. Less than 1% of patients discontinued RAPTIVA treatment because of these adverse events.

Other adverse events resulting in discontinuation of RAPTIVA treatment were psoriasis (0.6%), pain (0.4%), arthritis (0.4%), and arthralgia (0.3%).

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of one drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described below reflect RAPTIVA exposure for 2762 adult psoriasis patients (age range 18 to 75 years), including 2400 patients exposed for three months, 904 for six months, and 218 exposed for one year or more, in all controlled and uncontrolled studies. The median age of patients receiving RAPTIVA was 44 years, with 189 patients above the age of 65; 67% were men, and 89% were Caucasian. These data include patients treated at doses higher than the recommended dose of 1 mg/kg weekly.

In placebo-controlled study periods, commonly observed adverse events reported at a ≥2% higher rate in RAPTIVA-treated patients than in placebo-treated patients were headache, infection (includes diagnosed infections and other non-specific infections), chills, nausea, pain, myalgia, flu syndrome, fever, back pain, and acne. Adverse events occurring at a rate between 1 and 2% greater in the RAPTIVA group compared to placebo were arthralgia, asthenia, peripheral edema, and psoriasis.

The following serious adverse reactions were observed in RAPTIVA-treated patients.

Infections: In the first 12 weeks of placebo-controlled studies, the proportion of patients with serious infection was 0.4% (7/1620) in the RAPTIVA-treated group (5 of these were hospitalized, 0.3%) and 0.1% (1/715) in the placebo group (see **WARNINGS, Serious Infections**). In the complete safety data from both controlled and uncontrolled studies, the overall incidence of hospitalization for infections was 1.6 per 100 patient-years for RAPTIVA-treated patients compared with 1.2 per 100 patient-years for placebo-treated patients. Including both controlled, uncontrolled, and follow-up study treatment periods there were 27 serious infections in 2475 RAPTIVA-treated patients. These infections included cellulitis, pneumonia, abscess, sepsis, sinusitis, bronchitis, gastroenteritis, aseptic meningitis, Legionnaire's disease, septic arthritis, and vertebral osteomyelitis. In controlled trials, the overall rate of infections in RAPTIVA-treated patients was 3% higher than in placebo-treated patients.

Malignancies: Among the 2762 psoriasis patients who received RAPTIVA at any dose (median duration 8 months), 31 patients were diagnosed with 37 malignancies (see **WARNINGS, Malignancies**). The overall incidence of malignancies of any kind was 1.8 per 100 patient-years for RAPTIVA-treated patients compared with 1.6 per 100 patient-years for placebo-treated patients. Malignancies observed in the RAPTIVA-treated patients included non-melanoma skin cancer, non-cutaneous solid tumors, Hodgkin's lymphoma and non-Hodgkin's lymphoma, and malignant melanoma. The incidence of non-cutaneous solid tumors (8 in 1790 patient-years) and malignant melanoma were within the range expected for the general population.

The majority of the malignancies were non-melanoma skin cancers; 26 cases (13 basal, 13 squamous) in 20 patients (0.7% of 2762 RAPTIVA-treated patients). The incidence was comparable for RAPTIVA-treated and placebo-treated patients. However, the size of the placebo group and duration of follow-up were limited and a difference in rates of non-melanoma skin cancers cannot be excluded.

Immune-Mediated Thrombocytopenia: In the combined safety database of 2762 RAPTIVA-treated patients, there were eight occurrences (0.3%) of thrombocytopenia of <52,000 cells per µL reported (see **WARNINGS, Immune-Mediated Thrombocytopenia**). Three of the eight patients were hospitalized for thrombocytopenia, including one patient with heavy uterine bleeding; all cases were consistent with an immune mediated thrombocytopenia. Antiplatelet antibody was evaluated in one patient and was found to be positive. Each case resulted in discontinuation of RAPTIVA. Based on available platelet count measurements, the onset of platelet decline was between 8 and 12 weeks after the first dose of RAPTIVA in 5 of the patients. Onset was more delayed in 3 patients, occurring as late as one year in 1 patient. In these cases, the platelet count nadirs occurred between 12 and 72 weeks after the first dose of RAPTIVA.

Immune-Mediated Hemolytic Anemia: Two reports of hemolytic anemia were observed in clinical trials. Additional cases were reported in the postmarketing setting. The anemia was diagnosed 4-6 months after the start of RAPTIVA and in two serious cases the hemoglobin level decreased to 6 and 7 g/dl. RAPTIVA treatment was discontinued, erythrocyte transfusions and other therapies were administered (see **WARNINGS, Immune-Mediated Hemolytic Anemia**).

Adverse Events of Psoriasis: In the combined safety database from all studies, serious psoriasis adverse events occurred in 19 RAPTIVA-treated patients (0.7%) including hospitalization in 17 patients (see **WARNINGS, Psoriasis Worsening/Variants**). Most of these events (14/19) occurred after discontinuation of study drug and occurred in both patients responding and not responding to RAPTIVA treatment. Serious adverse events of psoriasis included pustular, erythrodermic, and guttate subtypes. During the first 12 weeks of treatment within placebo-controlled studies, the rate of psoriasis adverse events (serious and non-serious) was 3.2% (52/1620) in the RAPTIVA-treated patients and 1.4% (10/715) in the placebo-treated patients.

Arthritis Events: Infrequent new onset or recurrent severe arthritis events, including psoriatic arthritis events, have been reported in clinical trials and postmarketing (see **PRECAUTIONS, Arthritis Events**).

Hypersensitivity Reactions: Symptoms associated with a hypersensitivity reaction (e.g., dyspnea, asthma, urticaria, angioedema, maculopapular rash) were evaluated by treatment group. In the first 12 weeks of the controlled clinical studies, the proportion of patients reporting at least one hypersensitivity reaction was 8% (95/1213) in the 1 mg/kg/wk group and 7% (49/715) of patients in the placebo group. Urticaria was observed in 1% of patients (16/1213) receiving RAPTIVA and 0.4% of patients (3/715) receiving placebo during the initial 12-week treatment period. Other observed adverse events in patients receiving RAPTIVA that may be indicative of hypersensitivity included: laryngospasm, angioedema, erythema multiforme, asthma, and allergic drug eruption. One patient was hospitalized with a serum sickness-like reaction.

Inflammatory/Immune-Mediated Reactions: In the entire RAPTIVA clinical development program of 2762 RAPTIVA-treated patients, inflammatory, potentially immune-mediated adverse events resulting in hospitalization included inflammatory arthritis (12 cases, 0.4% of patients) and interstitial pneumonitis (2 cases). One case each of the following serious adverse reactions was observed: transverse myelitis, bronchiolitis obliterans, aseptic meningitis, idiopathic hepatitis, sialadenitis, and sensorineural hearing loss. Myositis, eosinophilic pneumonitis, resolving after discontinuation of RAPTIVA have been reported postmarketing.

Postmarketing Experience: In postmarketing experience, other reported adverse events included toxic epidermal necrolysis and photosensitivity reactions.

Laboratory Values: In RAPTIVA-treated patients, a mean elevation in alkaline phosphatase (5 Units/L) was observed; 4% of RAPTIVA-treated patients experienced a shift to above normal values compared with 0.6% of placebo-treated patients. The clinical significance of this change is unknown. Higher numbers of RAPTIVA-treated patients experienced elevations above normal in two or more liver function tests than placebo (3.1% vs. 1.5%).

Other laboratory adverse reactions that were observed included thrombocytopenia, (see **WARNINGS,** and **ADVERSE REACTIONS, Immune-Mediated Thrombocytopenia**), lymphocytosis (40%) (including three cases of transient atypical lymphocytosis), and leukocytosis (26%).

Immunogenicity: In patients evaluated for antibodies to RAPTIVA after RAPTIVA treatment ended, predominantly low-titer antibodies to RAPTIVA or other protein components of the RAPTIVA drug product were detected in 6.3% (67/1063) of patients. The long-term immunogenicity of RAPTIVA is unknown.

The data reflect the percentage of patients whose test results were considered positive for antibodies to RAPTIVA in the 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 medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to RAPTIVA with the incidence of antibodies to other products may be misleading.

OVERDOSAGE Doses up to 4 mg/kg/wk SC for 10 weeks following a conditioning (0.7 mg/kg) first dose have been administered without an observed increase in acute toxicity. The maximum administered single dose was 10 mg/kg IV. This was administered to one patient, who subsequently was admitted to the hospital for severe vomiting. In case of overdose, it is recommended that the patient be monitored for 24–48 hours for any acute signs or symptoms of adverse reactions or effects and appropriate treatment instituted.

HOW SUPPLIED RAPTIVA® [efalizumab] is supplied as a lyophilized, sterile powder to deliver 125 mg of efalizumab per single-use vial.

Each RAPTIVA carton contains four trays. Each tray contains one single-use vial designed to deliver 125 mg of efalizumab, one single-use prefilled diluent syringe containing 1.3 mL sterile water for injection (non-USP), two 25 gauge × 5/8 inch needles, two alcohol prep pads, and a package insert with an accompanying patient information insert. The NDC number for the four administration dose pack carton is 50242-058-04.

RAPTIVA® [efalizumab] Manufactured by: **Genentech** 1 DNA Way, South San Francisco, CA 94080-4990 4826402 7421902 FDA Approval Date: June 2005 ©2005 Genentech, Inc.