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R E S I D E N T



**Management Series:
Porocarcinoma and
Sebaceous Carcinoma**

**Raptiva® (efalizumab)
Treatment of Patients Who
Respond Inadequately to
Anti-Tumor Necrosis
Factor Therapy**

Genentech

Welcome Residents!

We're pleased to bring you the latest issue of **Derm Resident**, a quarterly newsletter created to help answer your questions as you move toward full-time practice.

We hope the articles help you address the challenges you'll face. These articles provide you with easy-to-follow advice to ease your transition from resident to practicing dermatologist.

In this issue's cover story, Dr. Phillip M. Williford, Associate Professor of Dermatology at Wake Forest University School of Medicine, Winston-Salem, NC, discusses diagnosis and therapeutic options for porocarcinoma and sebaceous carcinoma, with attention to avoiding snares that may inhibit appropriate patient care. This is the first of several articles in our new Management Series focusing on cutaneous cancers.

In addition, Leon Kircik, MD, Associate Clinical Professor of Dermatology, Indiana University Medical Center, Louisville, KY, describes the use of Raptiva® (efalizumab) for treatment of patients with chronic, moderate-to-severe plaque psoriasis who respond inadequately to anti-tumor necrosis factor therapy.

We hope you'll find information in this newsletter that you can use in your everyday practice now, and in the future.

If you know of any of your colleagues who are not receiving **Derm Resident** and would like to receive it for free, please call the Publisher, Joe Morris, at (800) 237-7285, ext. 204, or e-mail him at jmorris@hmpcommunications.com.

Best regards,



Ivor Caro, MD
Fellow of the American Academy of Dermatology
Medical Director, Dermatology, Genentech

Raptiva[®] (efalizumab) Treatment of Patients Who Respond Inadequately to Anti-Tumor Necrosis Factor Therapy

By Leon Kircik, MD

Patients with psoriasis now have hope: Several biologic therapies are either currently approved or are being developed for the management of chronic, moderate-to-severe psoriasis. Clinical studies have demonstrated the overall safety and efficacy of three therapies—efalizumab (Raptiva[®]), alefacept (Amevive[®]), and etanercept (Enbrel[®])—all of which have received FDA approval for the treatment of patients with chronic, moderate-to-severe plaque psoriasis. In addition, Enbrel is FDA-approved for the treatment of patients with psoriatic arthritis. Two other agents, infliximab (Remicade[®]) and adalimumab (Humira[®]), are in late-stage clinical studies for chronic, moderate-to-severe plaque psoriasis; however, these agents are currently FDA-approved for use in patients with psoriatic arthritis.

TWO CLASSES

These five therapies can be divided into two classes according to their mechanism of action. Raptiva and Amevive are called *T-cell modulators* because they affect the activity of T cells, which are key components in the pathogenesis of psoriasis. Raptiva binds to the CD11a subunit of lymphocyte function-associated antigen (LFA)-1 and inhibits binding to intercellular adhesion molecule (ICAM)-1, blocking activation, reactivation, and trafficking of T cells. Amevive prevents the interaction between LFA-3 and the memory effector T-cell antigen CD2, thereby inhibiting T-cell



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Management Series:

Porocarcinoma and Sebaceous Carcinoma

By Phillip M. Williford, MD

One of the intriguing aspects of dermatology is the frequency of patients arriving in our waiting rooms with rare disease. The canvas of practice is highlighted with common disease presenting in uncommon ways, and rare disease presenting without warning. It is important for dermatologists to welcome the opportunity to enjoy the intellectual challenge of offering expert advice to those patients who can most benefit from knowledgeable and caring physicians possessing familiarity with unusual presentations of disease. In the next couple of issues, we will focus on cutaneous cancers that are not the focus of weekend media reports or late-night television. They are all tumors, however, that the average dermatologist will see during his or her practice career, so understanding the current state of knowledge—and in some cases the absence of knowledge—limiting our informed therapies is important. In this issue, a review of salient data driving diagnosis and therapeutic options for porocarcinoma and sebaceous carcinoma will be shared, with attention to avoiding snares that sometimes entrap us in our efforts to care for our patients.

POROCARCINOMA

Porocarcinoma, also known as *malignant eccrine poroma*, *malignant hidroacanthoma simplex*, *poroepithelioma*, and *eccrine porocarcinoma*, is a malignant adnexal neoplasm arising out of the intraepidermal portion of the eccrine duct coil (acrosyringium). It tends to be seen in patients older than 50 years of age, with the average patient age of 68 and the youngest reported patient, 12. Despite the eccrine derivation, few cases have been reported on plantar or palmar surfaces, where eccrine glands achieve their highest density. The majority of tumors arise on the lower extremity, with approximately 50% of cases

on the foot, leg, or thigh, followed in frequency by the head and face. Caucasians represent most of the world's cases, though this may simply reflect publication bias. Males and females are equally affected. No precipitating exposures, including radiation exposure, are known to increase incidence. Controversy exists regarding the likelihood of evolution from benign poromas, with some experts predicting a significant number of cancers arising from nonmalignant poromas, and others noting an infrequent conversion from benign sources.

Clinically, they present in a nondescript fashion with single keratotic, erythematous, or amelanotic papules. The broad clinical differential generated by this presentation makes primary clinical diagnosis uncommon, with diagnosis generally made after biopsy. Most tumors are present a number of years before diagnosis due to the nondescript and often benign clinical presentation. The histology is generally diagnostic by hematoxylin and eosin-stained sections, and accurately implies biology. Microscopically, the tumor demonstrates poromatous and basaloid cells in nests with cytologic atypia, small clefts, and ductal differentiation. Tumors extending greater than 7 mm into the dermis and demonstrating more than 14 mitotic figures per high-power field are more likely to recur and result in nodal or widespread invasion. Epidermotrophism also has been associated with poor prognosis. Immunohistochemistry can be useful. Tumors generally stain positive for carcinoembryonic antigen (CEA), epithelial membrane antigen (EMA), and cytokeratin 7, and negative for S-100 protein. A particularly virulent presentation with epidermotrophism and multiple widespread nodules representing in-transit metastases exists, with mortality in that presentation approaching 68%. Most English-language reports suggest mortality in the 20% range, although

Japanese literature reports mortality in the range of 50% for all cases.

Treatment of porocarcinoma has not been subjected to well-designed clinical trials. The literature reports treatments including electrocautery, radiation, excisional surgery, and Mohs micrographic surgery. Wide excision of well-defined tumors without negative histologic parameters have cures in the 85% range. Some authors report that Mohs micrographic surgery gives better control of local disease, with recurrent tumors and tumors presenting with epidermotrophic histology.



Despite claims for efficacy, the literature does not support radiation as a single therapeutic modality, and the role of adjuvant radiation is anecdotal only. Chemotherapeutic trials for metastatic disease demonstrate limited success, with porocarcinoma reported to be refractory to 5-fluorouracil, cytarabine, cisplatin, and leucovorin. Other studies report palliation of disease



or complete responses with continuous infusion 5-fluorouracil or interleukin-2 and interferon alpha. Small studies support the use of isotretinoin at 1-2 mg/kg over prolonged periods as a modifying influence.

SEBACEOUS CARCINOMA

Sebaceous carcinoma is a rare tumor arising in ocular and extraocular sites from sebaceous glands. Ocular adnexal structures have five types of sebaceous glands, including glands of Zeis that lubricate eyelid cilia, meibomian

glands that lack follicular association, and glands associated with the caruncle, eyebrow, and fine eyelash follicles. Despite the propensity of these tumors to arise on the head and neck, there is no causative association with ultraviolet light. Ionizing radiation has been associated with increased risk in the Japanese literature and in case series of survivors of retinoblastoma treated with radiation therapy. An intriguing causative association with thiazide diuretics has been suggested in some case series, with the mechanism suggesting that ingested thiazide diuretics exposed to gastric secretions produce carcinogenic nitrosamines. Muir-Torre syndrome has been associated with sebaceous carcinoma, and each patient diagnosed with this neoplasm needs to be referred for an appropriate evaluation to include surveillance for breast, prostate, testicular, uterine, and colon cancers. Imaging studies need to include chest radiograph and mammography; colonoscopy should be encouraged, as well as potential endometrial biopsies. Urinary tract tumors may also occur, but less frequently.

The clinical presentation is often banal with chalazion-like features. The clinical separation of the malignant neoplasm from a chalazion may be impossible, though chalazia are more likely to be painful and well defined. Any persistent and atypical chalazion raises the specter of sebaceous carcinoma, and biopsy should be considered. While shave biopsies can be diagnostic, persistent lesions should undergo full thickness biopsy to better ascertain pathology. The literature suggests that delay in diagnosis is common due to lack of clinical suspicion and due to initial incorrect pathology, with biopsies interpreted as basal cell carcinomas or squamous cell carcinomas.

The utility of special stains such as Oil red O and Sudan IV is controversial. Best performed on fresh tissue, these can be useful in differentiating those tumors with poorly differentiated features by routine hematoxylin and eosin. Immunohistochemistry generally shows EMA positivity and human milk fat globule-1 positivity, and negative cytokeratins and S-100 protein.

Once diagnosed, work-up should include a complete history and physical exam to include the screening concerns noted above for Muir-Torre syndrome, as well as targeted studies prior to surgery that may include sentinel node biopsies (though data for this are limited), and orbital imaging if concern for extension into the orbit

exists. Controversy exists as to whether routine frozen margin control or Mohs micrographic surgery are adequate means of removal compared to permanent sections. There is literature documenting efficacy with both routine frozen sections and Mohs micrographic surgery, although others note a 25% positivity on subsequent permanent sections with routine frozen sections. The tumor is noted to have a potential for epidermotropism, best termed *pagetoid spread*, that can make margin control difficult. While there is debate as to whether conjunctival involvement with pagetoid spread demands orbital exenteration for cure, most experts would suggest exenteration for disease that involves the orbit. The role of conjunctival biopsies for mapping is supported by some advocates, but well-designed studies assessing the importance of this technique are lacking. Historical mortality figures for ocular disease are in the 24% range; however, recent series are in the 10% range. Extraocular disease is believed to carry less mortality risk, but that assertion is questioned by some authors. The role of adjuvant radiation has advocates and is believed to be helpful, but is unsupported by good, well-designed studies. Topical chemotherapy for conjunctival disease with mitomycin-C may spare orbital exenteration but it is ineffective if there is stromal invasion. Early diagnosis and aggressive surgical extirpation remain the most effective therapeutic interventions.

CONCLUSION

Porocarcinoma is an adnexal neoplasm, generally presenting on the lower leg of middle-aged to elderly patients as nondescript keratotic papules. Management includes wide excision versus Mohs micrographic surgery, with limited data to support radiation therapy except as adjuvant modality. The management of sebaceous carcinoma requires a high index of suspicion in patients presenting with what clinically appears to be banal eyelid lesions. A multispecialty, coordinated approach involving a dermatopathologist, Mohs micrographic surgeon, and oculoplastic surgeon may lend itself to optimum case management. ●●●



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The opinions expressed in this article are those of the author and are not necessarily those of Genentech, Inc.

activation. Enbrel, Remicade, and Humira work through a different mechanism of action: They target the cytokine tumor necrosis factor-alpha (TNF- α), which triggers the inflammatory response and cell-mediated immune responses key to the pathogenesis of psoriasis. Because these agents inhibit TNF- α activity, they are called *TNF antagonists*.

INADEQUATE RESPONSE

Although a significant percentage of patients respond well to each of these agents, the response of individual patients will vary, and no patient is guaranteed to respond to any specific agent. Some patients respond well when first treated with biologics, but then they reach a plateau and do not achieve complete clearance. Other patients cannot maintain clearing over time while receiving a biologic. Under such circumstances, it might be necessary to switch patients from one type of therapy to another because of lack of response, change in response, disease progression, or contraindications.

Up to 25% of patients using a TNF antagonist do not achieve a clinical response (measured by a 50% improvement from baseline on the Psoriasis Area and Severity Index [PASI 50]) in 12 or 24 weeks of treatment.^{1,2} In addition, recent data indicate that an initial treatment response to the TNF antagonists may erode with long-term use.³⁻⁵ For example, at 10 weeks 80% of patients treated with Remicade in a phase 3 trial achieved a 75% improvement from baseline in PASI (PASI 75), but only 61% of patients showed this response by 50 weeks.¹ A similar reduction in efficacy was observed in patients receiving weekly treatment with Humira in a phase 3 trial: 80% and 64% of patients had achieved PASI 75 at 12 weeks and 60 weeks, respectively.⁴ Recent presentations of Enbrel data at the 2006 meeting of the American Academy of Dermatology showed a similar trend: 63% and 51% of patients receiving Enbrel 50 mg twice weekly in a phase 3 trial achieved PASI 75 at 48 weeks and 96 weeks, respectively.^{5,6}

When patients with psoriasis do not respond adequately to TNF antagonist activity, it is important to consider switching to a treatment with a different mechanism of action, such as Raptiva. A recent presentation of six case reports illustrates the efficacy of Raptiva in patients who

responded inadequately to anti-TNF therapy.⁷ These inadequate responders, whose responses plateaued at 8% affected body surface area or worsened despite treatment with Enbrel, were switched to treatment with Raptiva. These patients had histories of psoriasis ranging from 5 to 41 years and achieved clearance of their disease after switching to Raptiva.

SAFETY CONSIDERATIONS

Safety considerations may restrict the treatment choices available to patients with psoriasis. Raptiva has been shown to be safe and effective for up to 3 years in patients with chronic, moderate-to-severe plaque psoriasis.⁸ The most serious adverse reactions observed during treatment with Raptiva were serious infections, malignancies, immune-mediated thrombocytopenia, immune-mediated hemolytic anemia, arthritis events, and psoriasis worsening and variants. Serious infections and immune-mediated thrombocytopenia have been reported during postmarketing surveillance. Physicians should follow patients for signs and symptoms of thrombocytopenia; platelet monitoring is recommended. Acellular, live, and live-attenuated vaccines should not be administered during Raptiva treatment. The most common adverse reactions associated with Raptiva were a symptom complex that included headache, chills, fever, nausea, and myalgia within 48 hours following the first two injections. These events were largely mild to moderate when a first dose of 0.7 mg/kg was given. Less than 1% of patients discontinued Raptiva treatment because of these adverse events.⁹

The use of TNF antagonists is contraindicated for patients with congestive heart failure. TNF antagonists are not recommended when a patient has a positive tuberculosis test. These and other warnings are listed in the prescribing information for these agents.¹⁰⁻¹² Use of TNF antagonists has been associated with rare cases of demyelinating disease¹³ and induction of anti-nuclear antibodies; discontinuation of use is recommended in such cases.^{11,12} These safety issues may preclude the use of the TNF antagonists in certain patients. Raptiva can be considered as a therapeutic option for these patients.

Because Raptiva's mechanism of action differs from that of the TNF antagonists, patients who are refractory to or ineligible for treatment with the TNF antagonists may

benefit from switching to a psoriasis therapy that acts through T-cell modulation. Raptiva may be an effective alternative for patients who inadequately respond to treatment with TNF antagonist therapies. ●●●



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Please see www.raptiva.com or call 1-877-RAPTIVA for full prescribing information.



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 reoccur 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 1626 (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, Legionnaires' disease, and vertebral osteomyelitis (none of these patients had more than one infection). Postmarketing reports of serious infections include necrotizing fasciitis and tuberculous pneumonia. Bacteroides species with seeding of distant sites, severe pneumonia with neutropenia (ANC <50/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 rate 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 (0.5%) 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 = 9) or worsening post baseline after discontinuation of RAPTIVA (n = 10) (see **ADVERSE REACTIONS**, Adverse Events of Psoriasis). In some patients these events took the form of pustular psoriasis, psoriasis pustulosa, 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 exposed 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 nonadjuvanted tetanus toxoid vaccine resulted in a decreased 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 200 times the clinical exposure level (based on mean peak plasma level) antibody responses were decreased following immunization with tetanus toxoid compared with untreated control animals. Acetabular live and live-attenuated vaccines should not be administered during RAPTIVA treatment.

First Dose Reactions: First dose reactions, including headache, fever, nausea, and sore throat 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 **DOSEAGE AND ADMINISTRATION**). Cases of aseptic meningitis resulting in hospitalization have been observed in association with initial dosing (see **ADVERSE REACTIONS**, Inflammation/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 bruising 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).

Acetabular 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 CD11c antibody at up to 38 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 CD11c antibody at up to 38 times the equivalent of the recommended clinical dose of RAPTIVA, no evidence of maternal toxicity, embryotoxicity, or fetotoxicity 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 CD11c 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 those 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, breastfeeding women are encouraged to enroll patients who become pregnant while taking RAPTIVA for 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 CD11c antibody was detected in milk samples of lactating mice exposed to anti-mouse CD11c 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 1626 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 than 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 protein (0.6%), pain (0.4%), arthritis (0.4%), and asthenia (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 asthenia, edema, 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% (0.1626) in the RAPTIVA-treated group (5 of these were hospitalized, 0.29% and 0.1% (0.0715) 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, Legionnaires' disease, septic arthritis, and vertebral osteomyelitis. In controlled trials, the overall rate of infections in RAPTIVA-treated patients was 2% 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 melanoma. The incidence of non-cutaneous solid tumors (6 in 1790 patient-years) and melanoma (1 in 1000 patient-years) were within the range expected for the general population. The majority of the malignancies were non-melanoma skin cancer, 20 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 sternal bleeding; all cases were consistent with an immune-mediated thrombocytopenia. Antiprotein 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. Death was more delayed in 3 patients, occurring as late as one year in 1 patient. In these cases, the platelet count nadir occurred between 12 and 32 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 patients cause the hemoglobin level decreased to 6 and 1 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 39 RAPTIVA-treated patients (0.7%) including hospitalization in 17 patients (see **WARNINGS**, Psoriasis Worsening/Variants). Most of these events (24/39) 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 psoriasis. During the first 12 weeks of treatment with placebo-controlled studies, the rate of psoriasis adverse events serious and non-serious was 3.2% (52/1626) in the RAPTIVA-treated patients and 1.4% (0.0715) 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, edema, 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% (85/1213) in the 1 mg/kg/week group and 7% (48/715) of patients in the placebo group. Urticaria was observed in 1% of patients (51/1213) receiving RAPTIVA and 0.4% of patients (2/515) receiving placebo during the first 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 reactions. One patient was hospitalized with a serum sickness-like reaction.

Inflammation/Immune-Mediated Reactions: In the entire RAPTIVA clinical development program of 2762 RAPTIVA-treated patients, inflammation, 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: toxicosepsis, bronchitis/obstructive, aseptic meningitis, idiopathic hepatitis, disseminated, and serous/mucosal healing loss. Myelitis, eosinophilic pneumonitis, resulting 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 (U/ml) 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 uncertain; higher numbers of RAPTIVA-treated patients experienced elevations above normal in two or more liver function tests than placebo (5.1% vs. 1.5%).

Other laboratory adverse reactions that were observed included thrombocytopenia (see **WARNINGS**, and **ADVERSE REACTIONS**, Immune-Mediated Thrombocytopenia), lymphocytosis (0.6%) including three cases of transient atypical lymphocytosis, and leukocytosis (0.6%).

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% (63/1003) 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.

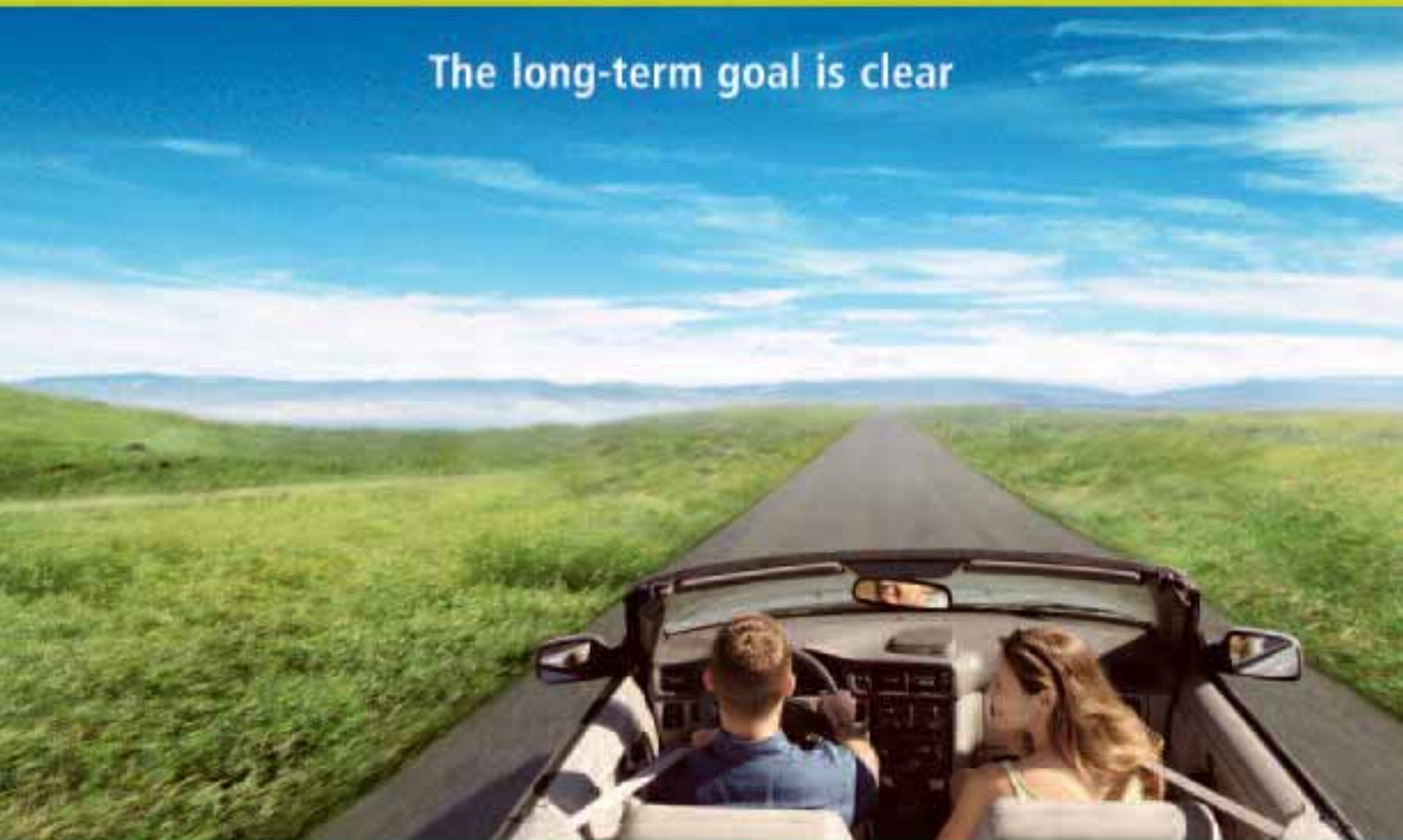
OVERDOSAGE Doses up to 4 mg/kg/week SC for 10 weeks following a conditioning (0.7 mg/kg) first dose have been administered without an observed increase in acute toxicity. The maximum administered single dose was 10 mg/kg SC. This was administered to one patient, who subsequently was admitted to the hospital 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 is 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 x 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 50242-098-04.

FOR MODERATE TO SEVERE PLAQUE PSORIASIS INVOLVING THE HANDS AND FEET

The long-term goal is clear



Prescribe RAPTIVA as a first-line biologic therapy for moderate to severe plaque psoriasis involving the hands and feet

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.

IMPORTANT TREATMENT CONSIDERATIONS

The most serious adverse reactions observed during treatment with RAPTIVA were serious infections, malignancies, immune-mediated thrombocytopenia, immune-mediated hemolytic anemia, arthritis events, and psoriasis worsening and variants. Serious infections and immune-mediated thrombocytopenia have been reported during post-marketing surveillance. Physicians should follow patients for signs and symptoms of thrombocytopenia; platelet monitoring is recommended. Acellular, live, and live-attenuated vaccines should not be administered during RAPTIVA treatment. The most common adverse reactions associated with RAPTIVA were a symptom complex that included headache, chills, fever, nausea, and myalgia within 48 hours following the first 2 injections.

Please see Brief Summary of Prescribing Information on the reverse side.

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