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UNDER MY SKIN

Negotiating the Alternative

∽ say, Holmes," said, "how did you deduce that my last patient was a devotee of Alternative Medicine?'

"Elementary,

my dear Rocky," he replied. Even Holmes grows informal with the times. "First, I observed that she'd brought a bottle of calendula, an emollient with cachet among those who prefer their remedies natural.

"Second. I observed that her address was in the vicinity of Harvard Square, a district rife with holistic clinics, purveyors of supplements, and establishments where cleansing detoxification may be procured.

'More important," he continued, "take note of her historical narrative. Attributing a similar rash last year to the water in her Cape Cod cape, she had showered exclusively at her health club. What disturbed her was that the affliction returned despite continued remote bathing. Blaming disease on diet and environment is a staple of Alternative thinking.

"What clinched the matter," Holmes continued, warming to his subject, "was her opening challenge to you. 'Don't just treat the symptoms,' she said, 'Get to the root cause!' The term, 'root cause,' capsulizes Alternative healing's central critique of Western medicine—that you paper over symptoms and fail to address the true source, which must come from the approved list of usual suspects: diet, water, atmosphere, hygiene, allergy. Demanding a 'root cause,' Rocky-et voilà!"

'Capital, Holmes!" I enthused.

He ignored me, as usual. "You physicians," Holmes continued, "often discuss Alternative therapies as though all that matters is whether they 'work.' This question is far too narrow, and misses the point that the Alternative world is in fact a subculture with a package of ideas linked as much by sociology as logic."

"Such as?" I inquired.

"Such as preferring nature to artifice. Such as rejecting analysis—the body as an aggregate of specific organs and systems-in favor of synthesis-the body as a whole. When you allopathic physicians diagnose a condition eczema and call it a 'skin disease,' Alternatives bristle, insisting as an article of faith that what appears on the skin must be 'systemic,' that is, must reflect what goes on within.

"This is a very old notion. Consider the word, 'eruption.' What do you think is erupting and where is it erupting from? An abnormal surface is assumed to reflect what the body has extruded in an effort to balance the humors roiling within. One stuffs it back down through the pores at peril. Hence the often-heard question, 'If you clear up the rash here, won't it just pop out somewhere else?' "

"Holmes!" I exclaimed. "Could your discussion be an instance of what has been called 'Cultural Competence' by the New England Journal of Medicine (N. Engl. J. Med. 2004;351:953-5)?

"My subscription lapsed," Holmes sniffed. "In any case, people may express alien cultural ideas in perfect English. One ought to address members of the Alternative culture, as those of any tradition, with care and forethought.'

"Have you any suggestions?" I ventured. "Four," came his crisp retort. "First, candidly admit that you often don't know root causes. Suggest instead alleviating symptoms as a limited yet worthwhile goal.

'Second, use steroids, the Alternative's archnemesis, with discretion. If you must prescribe them, explain that circulating adrenal steroid hormones are natural, with any increment from percutaneous absorption all but imperceptible to the

"Third, concede the role of diet and environment, adding that this role is often erratic and individual. Advise patients to avoid what they themselves observe to consistently reproduce symptoms (shower water, for instance).

"Finally, endorse lay therapies when you have no reason not to. Aver that echinacea may be just the thing, that tea tree oil makes a lovely shampoo."

'Will this approach work?" I inquired.

"Usually," said Holmes. "Few people are doctrinally consistent about anything. Besides, a pure Alternative would not be in your office.

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 seve plaque psoriasis who are candidates for systemic therapy or phototherapy. CONTRAINDICATIONS RAPTIVA should not be administered to patients with known hyper

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 administed to patients with dinically 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 updates [ATIVA] treatment should be monitored. During the first 12 weeks of controlled trials, serious infections occurred in 7 of 1620 (0.45) RAPTIVA-treated patients compared with 1 of 715 (0.1%) placebo-treated patients (see ADVERSE RACE/TIONs), infections, Serious infections requiring hospitalization included cellulitis, pneumonal, aboses, spais, bronchitis, guistionerlentis, asepten meningtis, Legionnaire's deese, and vertebral octemplies (new some patients that more than one infection).

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

If a patient develops a malignancy, RAPTINA should be discontinued (see ADVERSE REACTIONS, Malignancy).

Thrombocytopenia Platelet counts to a below 52,000 colls per µ were observed in 8 (a) 38, RAPTIVA-freated patients during clinical trials compared with none among the placebo-treated patients (see ADVERSE REACTIONS, Thrombocytopenia). Five of the 8 patients received a course of systemic steroids for frumthocytopenia. Thrombocytopenia resolved in the 1 patients received a course of systemic steroids for frumthocytopenia. Thrombocytopenia resolved in the 1 patients receiving adequate follow-up (1 patient was lost to follow-up). Physicians should follow patients (seek) for sigms and symptoms of thrombocytopenia Assessment of platelet counts is recommended during treatment with RAPTIVA (see PRECAUTIONS, Laboratory Tests) and RAPTIVA building for the store of the st

PRECAUTIONS Immunosuppression: The safety and efficacy of RAPTIVA in combination with other immunosuppressive agents or phototherapy have not been evaluated. Patients receiving other immunosuppressive agents on thorough the product of the possibility of increased risk of infections and malignancies.

and malignances. Immunizations: The safety and efficacy of vaccines administered to patients being treated with RAPTIVA have not been studied, in a small clinical study with N administered RAPTIVA, a single dose of 0.3 mg/kg given before primary immunization with a neontigen decreased the secondary immune response, and a dose of 1 mg/kg afmost completed ablated it. A dose of 0.3 mg/kg almost completed ablated it. A dose of 0.3 mg/kg have been primary and a dose of 1 mg/kg commended dose of 1 mg/kg. Sc in chimpanerse exposed to RAPTIAN at 2.10 times the clinical exposure level dosed on men pesh glasmal levels artibody responses were decreased following immunization with telanus toxical compared with unterested control animals. Acaditud, the and five attenuated vaccines should not be administered during RAPTIVA treatment.

animals. Acellular, live and live-attenuated vaccines should not be administered during RAPTIVA treatment. IFSI Dove Reactions: First doer reactions including headache, fever, nausea, and vornining 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 DSAGE AND ADMINISTRATION). One case of aseptic meningits resulting in hospitalization has been observed in association with initial dosing (see ADVERSE REACTIONS), filantimatory/immune-Mediated Reactions). Information for Patients: Should be ADVERSE REACTIONS, filantimatory/immune-Mediated Reactions, Information for Patients: Should be advised to seek immediate medical attention of they develop any of the signs and symptoms associated with severe thrombotytopenia, such as easy bleeding from the quinty brushing, or peterbiae. Patients should be advised to seek immediate medical attention of they develop any of the signs and symptoms associated with severe thrombotytopenia, such as easy bleeding from the quinty. Studies, or peterbiae, Patients is should also be informed that APITVA is an immunosyppressart, and could increase their chances of developing any new signs of, or creave in ever degradors of infection or maligrancy. Platients should be advised to promptly call the prescribing doctor's office if they develop any new signs of, or creave in ever disposors of infection or maligrancy with undergoing returners with APITVA. Grandle 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.

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 Should he also referred to the RAPTIVA Patient Should he also referred to the proper disposal of needles and syringes to comply with state and local laws. Patients should also be cautioned again reuse of syringes and needles.

Laboratory Tests. Assessment of platelet counts is recommended upon initiating and periodically while receiving RAPTINA 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, 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).

Aceillula, live and live-attenuated vaccines should not be administered during RAPTIVA treatment (see PRECAUTIONS, Immunosuppression).

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.

Pregnany (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.

RAPTIMA should be given to a pregnant woman only if clearly needed.

In a developmental bruckly study conducted in mice using an anti-mouse CD11a antibody at up to 30 times the equivalent of the recommended dinical dose of RAPTIMA, no evidence of maternal toxicity, embryotoxicity, or testopenicly 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 location is major disease. In a 30-limes the equivalent of the recommended dinical dose of RAPTIMA 11 weeks of age, the offspring of these females exhibited a significant reduction in their ability to mount an antibod response, which showed evidence of partial reversibility by 52 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 (APTIVA on pregnant women and fetal development, including immune system development are not known, healthcare provides are encouraged to enrol patients who become pregnant while taking RAPTIVA (or within 6 weeks of discontinuing RAPTIVA) in the RAPTIVA Pregnancy Reprint (Prognancy Raptiva).

Nursing Mothers: It is not known whether RAPTINA is excreted in human milk. An anti-mouse CD11a antibody was detected in milk samples of lectating mice exposed to anti-mouse CD11a antibody and the offspring of the exposed the males oblibited significant reduction in antibody responses (see PRECAUTIONS, Rengarway, Succe maternal of the proposed to the proposed to anti-mouse CD11a antibody and the offspring of the exposed the males oblibited significant for adverse fellows: The proposed to anti-mouse CD11a antibody was considered for adverse effects in nursing infants from RAPTINA, a decision should be made whether to discontinue nursing while taking the during to discontinue the use of the drug taking into account the importance of the drug to the mother. Pediatric Use: The safety and efficacy of RAPTINA in pediatric patients have not been studied.

Gerlatic User Of the 1620 patients who received RAPTIVA northrold trials, 128 were 265 years of age, and 2 were 275 years of age. Although no differences in safety or efficacy were observed between older and young patients, the number of patients aged 65 and over is not sufficient to determine whether they respond different from younger patients. Because the incidence of infections is higher in the elderly population, in general, caution should be used in treating the delder.

RAPTIVA® [efalizumab]

ADVERSE REACTIONS The most serious adverse reactions observed during treatment with RAPTIVA® [efalizumab] were serious infections, malignancies, thrombocytopenia and psoriasis worsening and variants see WARNINGS)

(see WAKNINGS).

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 of 0.7 mg/kg was used as the first dose in placebo-controlled trials, 29% of patients treated with RAPTIVA 1 mg/kg and placetos. After the child dose, 4% and 3% of patients receiving placetos. After the third dose, 4% and 3% of patients receiving hardrink 1 mg/kg and placetos, 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.

rates ubserted in justices.

The data described below reflect RAPTIVA exposure for 2762 adult psoriasis patients (age range 18 to 75 years), all controlled and patients exposed for three months, 904 for six months, and 218 exposed for one year or more, in including 2400 patients exposed for the patients receiving RAPTIVA was 44 years, with 189 patients above the age of 55, 67% were men, and 59% were Caucasian. These data include patients treated at doses higher than the recommended dose of 1 mg/dg weekly.

In placebo-controlled study periods, commonly observed adverse events reported at a 22% higher rate in RAPTIVA-treated patients than in placebo-treated patients were headable, infection (includes diagnosed infections and other non-specific infections), chills, susee, pain, myadig, flux 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, asthenic earthral advans and rocrisis: peripheral edema, and psoriasis.

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

The following serious adverse reactions were observed in RAPTIVA-treated patients. In Infections In the first 12 veeks of packed-controlled studies, the proportion of patients with serious infection was 0.4% 071620) in the RAPTIVA-treated group (5 of these were hospitalized, 0.3%) and 0.1% (1/715) in the placeborgroup (see WARRINGS, Serious Infections), in the complete safery 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 placebor-breated patients. Including both controlled, uncontrolled, and follow-up study treatment periods there were 27 serious infections in 2475 RAPTIVA-treated patients. These infections included cellulists, pneumonia, abscess, spesis, sinsusits, bronchtis, gastorenteitis, aseptic meningits, Legionnaire's disease, septic arthritis, and vertebral osteomyellis. In controlled triad, the overall rate of infections in RAPTIVA-treated patients was 3% higher than in placebor-treated patients. Malignancies: A mong the 2762 positiasis patients who received RAPTIVA at any dose (median duration 8 months). 31 patients were dagnosed with 37 malignancies (see MARNINGS, Malignancies). The overall incidence of malignancies of any kind was 1.8 per 100 patient-years for RAPTIVA-treated patients incidence non-melanoma skin cancer, ono-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 patient (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.

non-melanoma són cancers cannot be excluded.

Thrombocytopenia in the combined safety database of 2762 RAPTINA-treated patients, there were eight occurrences (0.3%) of thrombocytopenia of <52,000 cells per jul. reported (see WARNINGS, Thrombocytopenia). Three of the eight patients were hospitalized for thrombocytopenia, of the condition 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. Earl. access resulted in discontinuation of RAPTINA. Based on available platelet count measurements, the onset of platelet decline was between 8 and 12 weeks after the first dose of RAPTINA in 5 of the patients. One was more dislayed in 3 patients, occurring as late as one year in 1 patient. In these cases, the platelet count nadis occurred between 12 and 72 weeks after the first dose of RAPTINA.

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 clinica angioedema, maculopapular rash) were evaluated by treatment group. In the first 1,2 weeks of the controlled clinic studies, the proportion of patients reporting at least one hypersensitivity reaction was 8% (95/123) in the 1 mg/kg/wk group and 7% (49/15) of patients in the placebo group. Urkicaria was observed in 1% of patients (16/123) received patients of the placebo group. Urkicaria was observed in 12-week treatment period. Other observed adverse events in patients receiving RAPTIVA and to APTIVA that may be indicative of hypersensitivity included: lanyngospasm, angioedema, erythema multiforme, asthma, and allergic drug eruption. One patient was hospitalized with a serum sickness-like reaction.

nospitatized with a setum sistones-wise reaction. Inflammatoryfimmum-Mediated Reactions: In the entire RAPTIVA clinical development program of 2762 RAPTIVA-treated patients, inflammatory, potentially immum-emediated adverse events resulting in hospitalization included inflammatory artificis (12 cases, 0.4% of patients) and intestitatial preumonitis (2 cases). One see each of the following serious adverse reactions was observed: transverse myellib, bronchiolitis obliterans, aseptic meningitis, idiopathi petapora, siabilearitis, and sersorineural heraing loss.

Laboratory Values: In RAPTINA-treated patients, a mean elevation in alkaline phosphatase (5 Units/L) was observed; 4% of RAPTINA-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 RAPTINA-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 thrombooytopenia, (see WARNINGS, and ADVERSE REACTIONS Thrombooytopenia), lymphocytosis (40%) (including three cases of transient atypical lymphocytosis), and leukooytosis (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% (6/7/1063) of patients. The long-term immunogenicity of RAPTIVA is unknown.

(67106.3) of patients. The long-term immunogenicity of RAPTIVA is unknown.

The data reflort the precentage of patients whose test results were considered positive for antibodies to RAPTIVA in the ELSA assay, and are highly dependent on the sensitivity and specificity of the assay, Additionally, the observed incidence of antibodies positivity in an assay may be influenced by several factors including sample heading, 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 the productive and antibodies of the incidence of antibodies to RAPTIVA with the incidence of antibodies to the productive and antibodies of antibodies of the RAPTIVA with the incidence of APTIVA with the I

HOW SUPPLIED RAPTIVA is supplied as a lyophilized, sterile powder to deliver 125 mg of efalizumab Each RAPTIVA carton contains four trays. Each tray contains one single-use vial designed to deliver 125 mg of efalizumah one single-use prefilled diluent syringe containing 1.3 mL sterile water for injection (non-USP), two

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, a package insert with an accompanying patient information insert. The NDC number for the four administration dose pack carton is 50242-058-04. 7421900 FDA Approval Date: October 2003 ©2004 Genentech, Inc

RAPTIVA® [efalizumab] Manufactured by: Genentech 1 DNA Way, South San Francisco, CA 94080-4990

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Continued on following page

BY ROBERT S. JANSSEN, M.D.

GUEST EDITORIAL

The Ongoing Challenge of HIV

with patients about HIV testing and pos-

sible risk factors—something we are not

doing frequently enough. Research pub-

lished in 2002 showed that 41% of peo-

ple who get tested do so because of ill-

ness. Only 10% of men and 17% of

women get tested because the test is of-

fered or recommended by a health care

Health care providers should offer the

test to all patients in high-HIV-prevalence

provider.

Thanks to the advent of effective antiretroviral treatments, patients living with the human immuno-deficiency virus

in the United States can now expect to live nearly 2 decades from the day of becoming infected, and perhaps even to have a normal lifespan.

But there's some bad news about AIDS in America: The downward trend in the rate of new HIV infections leveled off several years ago at about 40,000 per year. Perhaps most alarming, of the 850,000-950,000 Americans living with HIV today—the largest number since the epidemic began more than 20 years ago—one-fourth do not know they are infected.

Recognizing the urgent need to ensure that infected individuals know their serostatus and are linked to care and prevention services, the Centers for Disease Control and Prevention launched the Advancing HIV Prevention initiative in 2003. A major component of this effort is to make HIV antibody testing a routine part of patient care.

Our work is cut out for us. CDC estimates show that fewer than half of all U.S. adults between the ages of 18 and 64 years have ever been tested for HIV, and only 28% have been tested within the past 12 months. Of the individuals who do get tested, too many do not keep the appointment to learn their result. As a result, many people with HIV go undiagnosed, untreated, and unconnected to prevention services.

In one CDC study, about 40% of AIDS patients developed the disease within 1 year of being diagnosed with HIV. The average time between infection and the appearance of symptoms (without treatment) is 10 years, so these individuals will start treatment late in the course of disease, when antiretroviral options are fewer and potentially less effective.

How can we ensure that a greater number of at-risk individuals are tested, get their results, and act upon them quickly? One way is to take time to talk regularly

Continued from previous page

"As they say in the garment trade," he concluded with a flourish, "you gotta know your customers."

"Gadzooks, Holmes!" I expostulated. "This barbarous colloquialism has gone too far!"

Alas, too late. I gaped as Holmes exchanged his deerstalker for a Red Sox World Series cap, which he pulled on backwards.

"Chill, Rocky," said Holmes, with a thin smile. Turning to leave, he flipped me a small phial. "Have some of this chamomile. Calm you right down."

DR. ROCKOFF practices dermatology in Brookline, Mass. To respond to this column, write Dr. Rockoff at our editorial offices or e-mail him at sknews@elsevier.com.

areas, as well as to patients in low–HIV-prevalence settings who have risk factors. In order to lower the barrier to testing imposed by physicians' time constraints, providers can use streamlined pretest counseling to help them perform more HIV tests. Patients should be provided information about HIV disease and give consent to be tested, but they can be referred for risk-reduction counseling.

We've learned a lot about AIDS over the

past 2 decades, but the development of a cure or a vaccine remains a hope for the future. And even though HIV infection is preventable, we are still falling far short when it comes to stopping transmission from one person to another.

DR. JANSSEN is director of the division of HIV/AIDS prevention at the CDC's National Center for HIV, STD, and TB Prevention in Atlanta.

