

Maggots Clear Necrosis From Purpura Fulminans

BY SHERRY BOSCHERT

SAN FRANCISCO — Maggot debridement therapy helped clear necrotic tissue from purpura fulminans in a 9-month-old boy who was not responding to standard wound care, according to Dr. Xuan Nguyen.

Reports of maggot debridement therapy in children are scarce. This appears to be the first case of using the therapy

in a child with purpura fulminans, Dr. Nguyen said at a meeting of the Society for Pediatric Dermatology.

Maggot debridement therapy—also called biosurgery—was used in the United States in the 1930s and 1940s and reintroduced into medical practice in the 1980s and 1990s. In 2004, the Food and Drug Administration approved the production and marketing of medical maggots for debridement of nonhealing

necrotic skin and soft tissue wounds, pressure ulcers, venous stasis ulcers, neuropathic foot ulcers, and nonhealing traumatic or postsurgical wounds.

Although purpura fulminans is not a specific indication, it is a chronic wound infection that seems amenable to maggot debridement therapy, she said.

The previously healthy boy presented to the Phoenix Children's Hospital with mottled skin 24 hours after receiving

immunizations. He developed *Staphylococcus aureus* septicemia that led to extensive purpura fulminans, a diffuse necrosis of the skin and subcutaneous tissue secondary to microvascular thrombosis from transient protein C deficiency. All four extremities and some other areas became necrotic.

Conventional wound management using Dakin's solution, Vaseline petroleum gauze dressing over the ecchymotic wounds, Kerlix wraps, and daily wound dressing changes was applied as some of the wounds and mummified regions started to demarcate. Wounds on the face healed relatively well, but the lower extremities of the patient, in particu-

The maggots ingest nothing but necrotic tissue, and 200 maggots can consume up to 15 g/day. Mouth hooks on their front ends make them remarkable eating machines.

lar, had trouble healing. One patella was exposed after the rotting lower leg slid off, said Dr. Nguyen, a pediatric dermatologist at the hospital.

Dr. Nguyen and her associates applied five rounds (lasting 4-5 days each) of maggot debridement therapy combined with adjunctive daily whirlpool baths to which bleach was added. After five rounds of maggot treatment, whirlpool baths were scheduled three times per week as maintenance.

Maggot therapy serves three functions: It debrides necrotic tissue, acts as an antimicrobial therapy, and stimulates wound healing. Maggots like a moist environment and are relatively contraindicated in dry wounds. "We try not to use them in open wounds of body cavities, because the maggots get lost" when it is time to remove them, she said.

The maggots, which are larvae of the greenbottle blowfly (*Lucilia sericata*), are applied when 1-2 mm in size and grow to 10 mm after 4-5 days, when they are removed from the wound. The maggots ingest nothing but necrotic tissue, and 200 maggots can consume up to 15 g/day. Mouth hooks on their front ends rake in decaying flesh, making them remarkable eating machines.

The maggots secrete proteolytic enzymes including collagenase, trypsinlike enzymes, and chymotrypsinlike enzymes that facilitate wound healing. Their activity disrupts tissue planes only minimally, and some of their secretions inhibit gram-positive and gram-negative bacteria.

Sterile maggots on gauze were tied over the boy's leg wounds and covered with a Kerlix wrap, netting, and a stocking to keep the maggots in the wound. The boy is healing after amputation of his hands and feet, maggot debridement therapy, and use of maintenance baths, Dr. Nguyen said.

Information about conflicts of interest could not be obtained by press time. ■



BRIEF SUMMARY

For Dermatologic Use Only—Not for Ophthalmic, Oral, or Intravaginal Use Rx only

CONTRAINDICATIONS

FINACEA® Gel, 15%, is contraindicated in individuals with a history of hypersensitivity to propylene glycol or any other component of the formulation.

WARNINGS

FINACEA® Gel, 15%, is for dermatologic use only, and not for ophthalmic, oral, or intravaginal use.

There have been isolated reports of hypopigmentation after use of azelaic acid. Since azelaic acid has not been well studied in patients with dark complexion, these patients should be monitored for early signs of hypopigmentation.

PRECAUTIONS

General: Contact with the eyes should be avoided. If sensitivity or severe irritation develops with the use of FINACEA® Gel, 15%, treatment should be discontinued and appropriate therapy instituted. The safety and efficacy of FINACEA® Gel, 15%, has not been studied beyond 12 weeks.

Information for Patients: Patients using FINACEA® Gel, 15%, should receive the following information and instructions:

- FINACEA® Gel, 15%, is to be used only as directed by the physician.
- FINACEA® Gel, 15%, is for external use only. It is not to be used orally, intravaginally, or for the eyes.
- Cleanse affected area(s) with a very mild soap or a soapless cleansing lotion and pat dry with a soft towel before applying FINACEA® Gel, 15%. Avoid alcoholic cleansers, tinctures, and astringents, abrasives, and peeling agents.
- Avoid contact of FINACEA® Gel, 15%, with the mouth, eyes and other mucous membranes. If it does come in contact with the eyes, wash the eyes with large amounts of water and consult a physician if eye irritation persists.
- The hands should be washed following application of FINACEA® Gel, 15%.
- Cosmetics may be applied after FINACEA® Gel, 15%, has dried.
- Skin irritation (e.g., pruritus, burning, or stinging) may occur during use of FINACEA® Gel, 15%, usually during the first few weeks of treatment. If irritation is excessive or persists, use of FINACEA® Gel, 15%, should be discontinued, and patients should consult their physician (See ADVERSE REACTIONS).
- Avoid any foods and beverages that might provoke erythema, flushing, and blushing (including spicy food, alcoholic beverages, and thermally hot drinks, including hot coffee and tea).
- Patients should report abnormal changes in skin color to their physician.
- Avoid the use of occlusive dressings or wrappings.

Drug Interactions: There have been no formal studies of the interaction of FINACEA® Gel, 15%, with other drugs.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term animal studies have not been performed to evaluate the carcinogenic potential of FINACEA® Gel, 15%. Azelaic acid was not mutagenic or clastogenic in a battery of *in vitro* (Ames assay, HGPRT in V79 cells [Chinese hamster lung cells], and chromosomal aberration assay in human lymphocytes) and *in vivo* (dominant lethal assay in mice and mouse micronucleus assay) genotoxicity tests.

Oral administration of azelaic acid at dose levels up to 2500 mg/kg/day (162 times the maximum recommended human dose based on body surface area) did not affect fertility or reproductive performance in male or female rats.

Pregnancy: Teratogenic Effects: Pregnancy Category B

There are no adequate and well-controlled studies of topically administered azelaic acid in pregnant women. The experience with FINACEA® Gel, 15%, when used by pregnant women is too limited to permit assessment of the safety of its use during pregnancy.

Dermal embryofetal developmental toxicology studies have not been performed with azelaic acid, 15%, gel. Oral embryofetal developmental studies were conducted with azelaic acid in rats, rabbits, and cynomolgus monkeys. Azelaic acid was administered during the period of organogenesis in all three animal species. Embryotoxicity was observed in rats, rabbits, and monkeys at oral doses of azelaic acid that generated some maternal toxicity. Embryotoxicity was observed in rats given 2500 mg/kg/day (162 times the maximum recommended human dose based on body surface area), rabbits given 150 or 500 mg/kg/day (19 or 65 times the maximum recommended human dose based on body surface area) and cynomolgus monkeys given 500 mg/kg/day (65 times the maximum recommended human dose based on body surface area) azelaic acid. No teratogenic effects were observed in the oral embryofetal developmental studies conducted in rats, rabbits, and cynomolgus monkeys.

An oral peri- and postnatal developmental study was conducted in rats. Azelaic acid was administered from gestational day 15 through day 21 postpartum up to a dose level of 2500 mg/kg/day. Embryotoxicity was observed in rats at an oral dose that generated some maternal toxicity (2500 mg/kg/day; 162 times the maximum recommended human dose based on body surface area). In addition, slight disturbances in the postnatal development of fetuses was noted in rats at oral doses that generated some maternal toxicity (500 and 2500 mg/kg/day; 32 and 162 times the maximum recommended human dose based on body surface area). No effects on sexual maturation of the fetuses were noted in this study. Because animal reproduction studies are not always predictive of human response, this drug should be used only if clearly needed during pregnancy.

Nursing Mothers:

Equilibrium dialysis was used to assess human milk partitioning *in vitro*. At an azelaic acid concentration of 25 µg/mL, the milk/plasma distribution coefficient was 0.7 and the milk/buffer distribution was 1.0, indicating that passage of drug into maternal milk may occur. Since less than 4% of a topically applied dose of azelaic acid cream, 20%, is systemically absorbed, the uptake of azelaic acid into maternal milk is not expected to cause a significant change from baseline azelaic acid levels in the milk. However, caution should be exercised when FINACEA® Gel, 15%, is administered to a nursing mother.

Pediatric Use: Safety and effectiveness of FINACEA® Gel, 15%, in pediatric patients have not been established.

Geriatric: Clinical studies of FINACEA® Gel, 15%, did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

ADVERSE REACTIONS

Overall, treatment related adverse events, including burning, stinging/tingling, dryness/tightness/scaling, itching, and erythema/irritation/redness, were 19.4% (24/124) for FINACEA® Gel, 15%, and 7.1% (9/127) for the active comparator gel at 15 weeks.

In two vehicle controlled, and one active controlled U.S. clinical studies, treatment safety was monitored in 788 patients who used twice daily FINACEA® Gel, 15%, for 12 weeks (N=333) or for 15 weeks (N=124), or the gel vehicle (N=331) for 12 weeks.

Table 3. Cutaneous Adverse Events Occurring in ≥1% of Subjects in the Rosacea Trials by Treatment Group and Maximum Intensity*

| | FINACEA® Gel, 15% N=457 (100%) | | | Vehicle N=331 (100%) | | |
|-----------------------------------|-----------------------------------|---------------------------|------------------------|-------------------------|--------------------------|-----------------------|
| | Mild n=99 (22%) | Moderate n=61 (13%) | Severe n=27 (6%) | Mild n=46 (14%) | Moderate n=30 (9%) | Severe n=5 (2%) |
| Burning/ stinging/ tingling | 71 (16%) | 42 (9%) | 17 (4%) | 8 (2%) | 6 (2%) | 2 (1%) |
| Pruritus | 29 (6%) | 18 (4%) | 5 (1%) | 9 (3%) | 6 (2%) | 0 (0%) |
| Scaling/dry skin/xerosis | 21 (5%) | 10 (2%) | 5 (1%) | 31 (9%) | 14 (4%) | 1 (<1%) |
| Erythema/ irritation | 6 (1%) | 7 (2%) | 2 (<1%) | 8 (2%) | 4 (1%) | 2 (1%) |
| Contact dermatitis | 2 (<1%) | 3 (1%) | 0 (0%) | 1 (<1%) | 0 (0%) | 0 (0%) |
| Edema | 3 (1%) | 2 (<1%) | 0 (0%) | 3 (1%) | 0 (0%) | 0 (0%) |
| Acne | 3 (1%) | 1 (<1%) | 0 (0%) | 1 (<1%) | 0 (0%) | 0 (0%) |

*Subjects may have >1 cutaneous adverse event; thus, the sum of the frequencies of preferred terms may exceed the number of subjects with at least 1 cutaneous adverse event.

FINACEA® Gel, 15%, and its vehicle caused irritant reactions at the application site in human dermal safety studies. FINACEA® Gel, 15%, caused significantly more irritation than its vehicle in a cumulative irritation study. Some improvement in irritation was demonstrated over the course of the clinical studies, but this improvement might be attributed to subject dropouts. No phototoxicity or photoallergenicity were reported in human dermal safety studies.

In patients using azelaic acid formulations, the following additional adverse experiences have been reported rarely: worsening of asthma, vitiligo depigmentation, small depigmented spots, hypertrichosis, reddening (signs of keratosis pilaris), and exacerbation of recurrent herpes labialis.

Post-marketing safety—Skin: facial burning and irritation; Eyes: iridocyclitis on accidental exposure with FINACEA® Gel, 15%, to the eye (see PRECAUTIONS).

OVERDOSAGE

FINACEA® Gel, 15%, is intended for cutaneous use only. If pronounced local irritation occurs, patients should be directed to discontinue use and appropriate therapy should be instituted (See PRECAUTIONS).

December 2007

Distributed under license; U.S. Patent No 4,713,394

Manufactured by Intendis Manufacturing S.p.A., Segrate, Milan, Italy
Distributed by:

INTENDIS Pine Brook, NJ 07058
6706800 80660910



Intendis is part of the Bayer Group

FINACEA is a registered trademark of Intendis, Inc.
CeraVe is a registered trademark of CORIA Laboratories, Ltd.

© 2009 Intendis, Inc. All rights reserved. 09-JA-003 February 2009