SUBCHRONIC AND CHRONIC TOXICITY OF TAZAROTENE GEL FOLLOWING TOPICAL APPLICATION IN HANFORD MINISWINE

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Tazarotene, a member of a novel class of synthetic acetylenic retinoids, is the first topical retinoid to demonstrate both efficacy and an acceptable patient tolerability profile in the treatment of psoriasis. The subchronic and chronic toxicity of topically applied tazarotene gel (0.025–0.1%; 0.05–0.5 mg/kg/d) was evaluated in Hanford miniswine in two separate, prospective, randomized, vehicle-controlled studies of 3 months' and 12 months' duration. Although tazarotenic acid, the active metabolite of tazarotene, was detected in the blood of animals in both studies, no signs of systemic toxicity could be detected in hematology, blood chemistry, posttreatment physical examination, necropsy, or histopathological examination of organ tissues. In both studies, the reversible signs and symptoms of cutaneous irritation caused by topical application of tazarotene gel were consistent with those effects commonly produced by other topical and oral retinoids.

Keywords psoriasis, retinoid, tazarotene, toxicity

Tazarotene, a member of a novel class of synthetic acetylenic retinoids, is the first topical retinoid to demonstrate both efficacy and an acceptable patient tolerability profile in the treatment of psoriasis (Lew-Kaya et al., 1992; Sefton et al., 1993; Esgleyes-Ribot et al., 1994). Other topical retinoids, such as retinoic acid, either have proved ineffective in the treatment of psoriasis or have been found to be excessively irritating (Fredriksson, 1971; Gunther, 1973).

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Oral retinoids, such as etretinate, are very effective in the treatment of psoriasis and other disorders of keratinization (Bollag, 1983; Kingston et al., 1987). However, their usefulness has been limited by a range of adverse systemic events associated with their use, including alterations in lipid metabolism, liver toxicity, photosensitivity, and (with chronic use) effects on the skeletal system that simulate diffuse idiopathic hyperostosis syndrome (David et al., 1988; Armstrong et al., 1994). These drugs also have a significant teratogenic potential that limits their use in premenopausal women (Armstrong et al., 1994; Pinnock and Alderman, 1992; Teelmann, 1989).

In the present reports, the subchronic and chronic toxicity of topically applied tazarotene gel (0.025–0.1%; 0.05–0.5 mg tazarotene/kg/d) was evaluated in Hanford miniswine in two separate, prospective, randomized, vehicle-controlled studies of 3 months' and 12 months' duration. The 12-month study was followed by a 2-month recovery period during which the health of the animals was monitored. Hanford miniswine were chosen because the percutaneous absorption of many topically applied substances through the skin of miniature swine is very similar to that of human skin (Maibach and Wester, 1989). In order to maximize the potential for toxicity, the maximum dose used was equivalent to the maximum tolerated dose (MTD), based on the severity of topical irritation observed following drug application. Although tazarotenic acid, the active metabolite of tazarotene, was detected in the blood of animals in both studies, no signs of systemic toxicity could be detected in hematology, blood chemistry, posttreatment physical examination, necropsy, or histopathological examination of organ tissues. In both studies, the reversible signs and symptoms of cutaneous irritation caused by topical application of tazarotene gel were consistent with those effects commonly produced by other topical and oral retinoids (Armstrong et al., 1994).

MATERIALS AND METHODS

All procedures in the present report were conducted by Toxicology and Pathology Services, Inc. (Mt. Vernon, IN) under the sponsorship of Allergan, Inc. (Irvine, CA).

Test Animals

Twenty healthy, 5- to 12-month-old Hanford miniswine (Charles River Laboratories, Pittsfield, NH) were used in the subchronic toxicity study (initial weights: females 18.4–37.3 kg; males 14.5–39.3 kg), and 48 miniswine were used in the chronic toxicity study (initial weights: females 26.6–34.1 kg; males 25.9–34.3 kg). Each animal was identified by an

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ear notch and tag. They were housed individually in temperature- and humidity-controlled rooms with a filtered air supply and cycled lighting (12 h of light daily). Approximately 1 lb of Prolab minipig diet (Agway) was provided each morning and evening. Tap water was available ad libitum. All animals were housed and treated according to the institutional guidelines for the care and use of laboratory animals.

Test Substances

Tazarotene gel (0.025%, 0.05%, 0.1%) was provided by Allergan, Inc., (Irvine, CA), as was tazarotene vehicle gel. Tazarotene is a yellow powder or crystals with a melting range of 102–107°C. It is insoluble in water (pH 5), sparingly soluble in ethanol, slightly soluble in mineral oil, and freely soluble in benzyl alcohol.

Tazarotene gel contains tazarotene (0.025%, 0.05%, or 0.1%), ascorbic acid (0.05%), butylated hydroxyanisole (0.05%), butylated hydroxytoluene (0.05%), edetate disodium (0.05%), purified water (49.25%), polyethylene glycol 100 (45.0%), hexylene glycol (2.0%), polysorbate 40 (0.2%), poloxamer 407 (0.2%), benzyl alcohol (1.0%), carbomer 934P (1.25%), and tromethamine (0.8%).

Study Design

The numbers of miniswine in each treatment group in the subchronic and chronic toxicity studies are shown in Table 1. Test animals were randomly assigned to one of five treatment groups in the subchronic study (two male and two female) and one of four treatment groups in the chronic study (six male and six female). Prior to study initiation and at weekly intervals thereafter, the back of each miniswine was closely clipped to expose an area equal to approximately 10% of the total surface area of the animal in the subchronic study, or approximately 46 × 36 cm (1656 cm^2) in the chronic study.

Tazarotene gel (0.025%, 0.05%, 0.1%) or vehicle gel was applied topically once daily to the closely clipped intact skin on the dorsum of each miniswine for at least 92 consecutive days in the subchronic study and twice daily for 365 consecutive days in the chronic study. If an eschar was present, some gel was applied directly to the eschar as well as the adjacent skin. Any residual gel was removed prior to each dose by gently wiping the test area with a towel moistened with tap water and then blotting the area dry. After week 52 of the chronic toxicity study, two miniswine per sex per group were observed for an additional 2 months without treatment (recovery period).

The tazarotene doses administered in the five groups in the subchronic study and the four groups in the chronic study are listed in

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Table 1. Treatment groups

Treatment group	*n* (m/f)	Amount of gel (g/kg)	Drug dose	
			mg/kg/d	mg/m²/d
Subchronic toxicity study (3-month duration)				
Placebo	2/2	0.50	0	0
0.025% Tazarotene	2/2	0.20	0.050	0.90
0.05% Tazarotene	2/2	0.25	0.125	2.22
0.1% Tazarotene	2/2	0.25	0.250	4.43
0.1% Tazarotene	2/2	0.50	0.500	8.85
Chronic toxicity study (12-month duration)[a]				
Placebo	6/6	0.25	0	0
0.025% Tazarotene	6/6	0.20	0.050	0.92
0.05% Tazarotene	6/6	0.25	0.125	2.30
0.1% Tazarotene	6/6	0.25	0.250	4.60

[a]Two miniswine/sex/group were observed for an additional 2 months without treatment (recovery period).

Table 1. The doses are described in milligrams per kilogram per day and milligrams per meter squared per day (calculated from the dose in milligrams per kilogram per day, the mean body weight, and a conversion factor published by Freireich et al., 1996). The maximum daily tazarotene dose in the minipigs used in the present study was 0.5 mg/kg/d or 8.9 mg/m²/d. This greatly exceeds the maximum daily dose used in human clinical studies (0.1 mg/kg/d or 4.1 mg/m²/d).

In order to prevent oral ingestion of the test substances, all animals were individually housed throughout the course of both studies, so that no animal could ingest the test material by licking it off of another animal. In addition, the location of the treatment site (upper back) prevented animals from ingesting the test material by licking themselves.

Physical and Ophthalmic Examinations

Treatment sites were scored daily for the severity of dermal irritation (Draize procedure), which included an evaluation of the presence of erythema and edema, prior to the morning application of each test substance.

Physical examinations, including slit-lamp biomicroscopy and ophthalmic examinations, were conducted by a veterinarian and veterinary ophthalmologist at baseline in both studies. Physical and ophthalmic examinations were also conducted just prior to the termination of the subchronic study and during study weeks 13, 26, 39, 52 (treatment period), and 60 (posttreatment period) in the chronic study. During the

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ophthalmic examination, the animals were anesthetized with an intramuscular injection of ketamine hydrochloride (Aveco, Fort Dodge, IA; 20–26 mg/kg) to reduce movement, and their eyes were dilated with tropicamide ophthalmic solution, USP 1% (Schein, Port Washington, NY). Body weight was obtained at baseline and at weekly intervals thereafter, and drug dosages were calculated after each weighing. Food consumption was estimated by visual inspection twice daily.

Laboratory Tests

Blood samples for evaluation of hematologic and clinical chemistry parameters were collected from the anterior vena carva of all animals at baseline and during weeks 4 and 13 of the subchronic study and during weeks 13, 19, 26, 39, 52, and 60 of the chronic study. Animals were fasted the night before blood collection for these tests. Additional whole-blood samples (2–3 mL) for the measurement of drug blood concentrations were collected from each animal just prior to dosing and 4, 8, 12, 16, 20, and 24 h following dosage administration on days 1 and 91 of the subchronic study. In the chronic study, the additional blood samples were collected just prior to the morning dose and 4 h after the evening dose on treatment days 1, 91, 182, and 364. During the recovery period of the chronic study (weeks 52–60), blood samples for drug concentration determination were collected in the morning on study day 399 (week 57) and study day 420 (week 60). Blood collection tubes containing ethylene diamine tetraacetic acid (EDTA) and extraction tubes containing 3 mL of acetonitrile:1-butanol (1:1) were used. Solvent-extracted blood from each sample was sent frozen, packed on dry ice, for drug analysis by a validated gas chromatography/mass spectrometry (GC/MS) method (Oneida Research Services, Whitesboro, NY).

Hematological evaluation included leukocyte count with differential (percentage and absolute), erythrocyte count, hemoglobin, hematocrit, platelet, mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration. Clinical chemistry evaluation included serum albumin, glucose, urea nitrogen, creatinine, total bilirubin, calcium, inorganic phosphorus, total cholesterol, alkaline phosphatase, sodium, chloride, potassium, alanine aminotransferase, aspartate aminotransferase, creatine kinase, triglycerides, total protein, globulin, and albumin–globulin ratio (calculated).

Necropsy

At the conclusion of the subchronic toxicity study, all of the animals were subjected to a complete necropsy. In the chronic toxicity study, four miniswine/sex/group were subjected to a complete necropsy after

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at least 365 days of treatment. The remaining 2 miniswine/sex/group were necropsied 2 months later (after the recovery period).

Following sedation with ketamine hydrochloride, the animals were euthanized by intravenous injection of sodium pentobarbital (Anthony Products Co., Arcadia, CA). During prosection, gross examination was conducted of the skin; the thoracic, abdominal, and pelvic cavities with enclosed organs and tissues; and the head and cervical organs and tissues. Representative specimens of the following organs and tissues were removed and examined: skin, including treated skin at the application site and untreated skin anterior to the application site; brain; pituitary gland; eyes, including optic nerve and eyelids; salivary glands; submaxillary lymph nodes; thyroid; trachea; lungs; heart; aorta; thymus; mammary gland; esophagus; stomach; duodenum; jejunum; ileum; colon; cecum; rectum; gallbladder; liver; spleen; pancreas; mesenteric lymph nodes; adrenal glands; kidneys; urinary bladder; uterus; prostate gland; gonads (ovaries or testes with epididymides); skeletal muscle; bone and marrow (rib including costochondral junction); spinal cord; peripheral nerve; and other tissues containing any gross lesions. The brain, pituitary gland, thyroid, heart, liver, spleen, kidneys, and gonads (ovaries and testes/epididymides) were removed and weighed.

Histopathology

In both studies, representative specimens of the protocol-designated organs and tissues already noted were fixed in 10% neutral buffered formalin, followed by routine embedding, sectioning, and staining with hematoxylin and eosin for histologic examination by a veterinary pathologist.

Statistical Analysis

Statistical evaluation was performed using the methods of Dunnett (1955, 1964), which incorporate a one-way analysis of variance to compare one or more treatment groups to a control group (Brownlee, 1965; Dunnett, 1955, 1964). Statistical analysis was performed on body weights, organ weights, hematologic data, and serum chemistry data. In the 12-month study, data from male and female miniswine were combined in the analysis of the recovery groups in order to obtain an adequately large sample size for statistical analysis (Brownlee, 1965; Dunnett, 1955, 1964).

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RESULTS

Physical and Ophthalmic Examinations

No treatment-related mortality occurred during either study. Physical examinations indicated that all the miniswine remained systemically healthy for the duration of each study. Additionally, except for select laboratory changes (see Clinical Chemistry), no treatment-related adverse systemic events were noted (Table 2). No consistent or distinct systemic treatment-related adverse pharmacological, toxicological, hematologic, or behavioral effects were observed. No significant changes in food consumption were observed. Animals in each of the different treatment groups experienced some weight gain. However, there

Table 2. Physical and laboratory results after 12 months

Parameter	Vehicle	0.05	0.125	0.25
Clinical chemistry				
Serum albumin	4.0	3.8	3.5	3.8[a]
Glucose	81.8	79.5	71.8	77.7
Urea nitrogen	14.0	13.7	13.0	13.3
Creatinine	1.46	1.33	1.24	1.42
Total bilirubin	0.12	0.14	0.15	0.12
Calcium	10.9	10.8	10.5	10.9
Inorganic phosphorus	6.4	6.2	6.2	6.2
Total cholesterol	68.2	74.2	66.8	77.9
Alkaline phosphatase	46.4	47.7	44.2	46.4
Sodium	141.2	139.6	141.2	139.5
Chloride	106.9	105.6	103.8	103.6
Potassium	4.78	4.05	4.23	4.17
Alanine aminotransferase	51.8	60.2	50.4	61.1
Aspartate aminotransferase	31.4	60.0	47.7	42.0
Creatine kinase	1122[a]	7636[a]	3379[a]	1851[a]
Triglycerides	34.6	30.6	20.3	42.0
Total protein	7.1	7.5[a]	7.9[a]	7.8[a]
Globulin	3.2	3.8[a]	4.4[a]	4.0[a]
Albumin–globulin ratio	1.3	1.0	0.8	1.0
Hematology	NTE	NTE	NTE	NTE
Necrospsy	NTE	NTE	NTE	NTE
Physical examination	NTE	NTE	NTE	NTE
Ophthalmic examination	NTE	NTE	NTE	NTE

Note. Values for males and females combined; determined after recovery period. NTE, no treatment effect (see text).

[a]Significantly different from vehicle ($p < .05$).

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was no statistically significant difference in the amount of weight gained by animals in the different treatment groups. Ophthalmologic examinations revealed no significant ocular abnormalities during the course of either study.

Primary Dermal Irritation Scores (Draize Scores)

In both studies, tazarotene produced dermal irritation that was typified by erythema followed by eschar formation in many animals.

In the subchronic toxicity study, black eschars began to develop at the treatment sites by the end of week 1 in all four active-treatment groups, precluding further dermal scoring of the sites. A black eschar was present in one animal in the 0.125 mg/kg/d group and two animals in the 0.500 mg/kg/d group during week 2. Eight animals from the 0.125 mg/kg/d, 0.250 mg/kg/d, and 0.500 mg/kg/d groups developed black eschars during week 5, and one animal from the 0.125 mg/kg/d group developed an eschar during week 12. No eschars formed in the treated areas of the 0.050 mg/kg/d group or the vehicle group.

In the chronic toxicity study, multiple focal papules were observed throughout the treated skin area during week 2, and by week 4 or 5, black eschars had developed at the majority of treatment sites, precluding further dermal scoring. Papules were also noted at the treatment sites in the vehicle group beginning between weeks 7 and 12. Most of the papules had disappeared by week 53 (end of treatment period), and they had completely disappeared by week 61 (end of recovery period).

The size and severity of the eschars were greater in animals receiving larger drug doses. The eschars cracked secondary to movement of the animals, and the underlying skin was erythematous. With the exception of a single animal from the 0.250 mg/kg/day group in the subchronic study, which exhibited slight edema on day 20, none of the animals developed edema at the treatment site. The vehicle group did not develop eschars, erythema, or edema during either study.

By the end of the 2-month recovery period following the chronic toxicity study (week 60), the eschars had fallen off all but one female miniswine (0.250 mg/kg/d), and the eschars on the male miniswine had decreased in severity in a dose-related manner.

Gross Necropsy/Histopathology

Gross necropsy and histologic examination were conducted on all animals at the conclusion of the 3-month study and, in the 12-month study, after at least 365 days of treatment or 53 days of recovery. No distinct or consistent treatment-related systemic toxicity was found

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(Table 2). Statistical evaluation of relative and absolute organ weights did not demonstrate any treatment-related effects.

A dose-related increase in the severity of eschar formation at the treatment sites was observed as the concentration of tazarotene in the test material increased. The eschars were characterized by accumulations of coagulated serum, test material, dust, and/or bedding materials in areas of hair regrowth.

Microscopic evaluation of treated areas of skin indicated a dose-response relationship in both studies. These changes were slight to minimal in the group receiving 0.050 mg/kg/d, slight to moderate in the groups receiving 0.125 mg/kg/d and 0.250 mg/kg/d, and marked in the 0.500 mg/kg/d group. The following pathologic changes were described: acanthosis, hyperkeratosis, focal dermal fibrosis, dermal inflammatory cellular infiltration, neutrophilic cellular infiltration, focal erosion, and/or focal ulceration. No other distinct or consistent compound-related microscopic changes were found. Additionally, there was no evidence of systemic toxicity on microscopic examination. The treated areas of skin in the vehicle group were within normal limits.

At the end of the 2-month recovery period, the skin of the animals that had received 0.050 mg/kg/d was histologically comparable to the control group; the animals that had received 0.125 mg/kg/d and 0.250 mg/kg/d exhibited slight to minimal irritation with acanthosis, hyperkeratosis, dermal inflammatory cellular infiltration, moderate neutrophilic cellular infiltration, focal dermal fibrosis, and cellular debris on the surface. This sequence suggested a dose-response recovery relationship. One miniswine from the 0.125 mg/kg/d group had a grossly raised circular area in the treatment area that on microscopic examination was consistent with healing of a chronic focal ulceration.

Clinical Chemistry/Hematology

In both studies, the results of hematology and clinical chemistry evaluations made at baseline were within the expected range for untreated animals and internal historical controls. During treatment, the hematology data did not show any consistent or distinct drug-related effects (Table 2).

Serum levels of creatine kinase were elevated in several animals in both the tazarotene and vehicle treatment groups during both studies (Table 2). The elevations were thought to be related to stress and increased muscle activity when the miniswine were restrained for blood collection.

The only other treatment-related systemic effects were significant increases in total protein and globulin in animals given 0.05 mg/kg/d, 0.125 mg/kg/d, and 0.250 mg/kg/d and a significant decrease in albumin

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in animals given 0.250 mg/kg/d in the 12-month study (Table 2). There was a significant increase in total protein and globulin serum concentrations in animals in all three active treatment groups ($p < .05$), except for the group of female miniswine that received 0.050 mg/kg/d. A significant decrease in serum albumin occurred in the group receiving 0.250 mg/kg/d at week 19, 26, and 52 (males: $p < .05$; females: $p < .01$). The albumin values at week 52 were also significantly decreased in the female animals dosed at 0.050 mg/kg/d ($p < .05$) and 0.125 mg/kg/d ($p < .01$). At the end of week 59 (7 weeks into the recovery period), a decrease in total protein and globulin concentrations and an increase in serum albumin were observed, indicating reversibility of the drug effect. Due to the small number of animals in the recovery portion of the study, data from male and female miniswine were combined for statistical analysis.

Drug Blood Concentrations

Tazarotene was not detected in the blood of animals at any time during the treatment periods (quantification level: $\geq$0.05 ng/mL), although tazarotenic acid was detected. This indicates that virtually all absorbed tazarotene was converted to tazarotenic acid. Mean blood tazarotenic acid concentrations in the miniswine ranged from 0.49 to 2.5 ng/mL, demonstrating low systemic drug exposure following topical administration (Figure 1). The blood concentrations during the subchronic (3-month) study were very similar to the blood concentrations measured during the first 3 month of the chronic (12-month) study. The blood concentration after 52 weeks of treatment was less than that at 26 weeks and, in some animals, lower than the blood concentration measured at 13 weeks. The reason for this is unknown. No tazarotenic acid was detected in the blood at the end of the 2-month recovery period. Neither tazarotene nor tazarotenic acid was detected in animals treated with the vehicle control. Concentrations of tazarotenic acid in the blood of male animals were slightly but significantly greater than those seen in female animals.

DISCUSSION

The most significant finding in the present report is that topical administration of tazarotene gel was associated with limited systemic absorption and minimal or no systemic toxicity in Hanford miniswine. The maximum daily dose used in this study (0.5 mg/kg/d or 8.9 mg/m^2/d) was much greater than the maximum daily dose used in humans (0.1 mg/kg/d or 4.1 mg/m^2/d). Nonetheless, no adverse effects were seen on hematology, clinical chemistry, physical examination, gross necropsy, or

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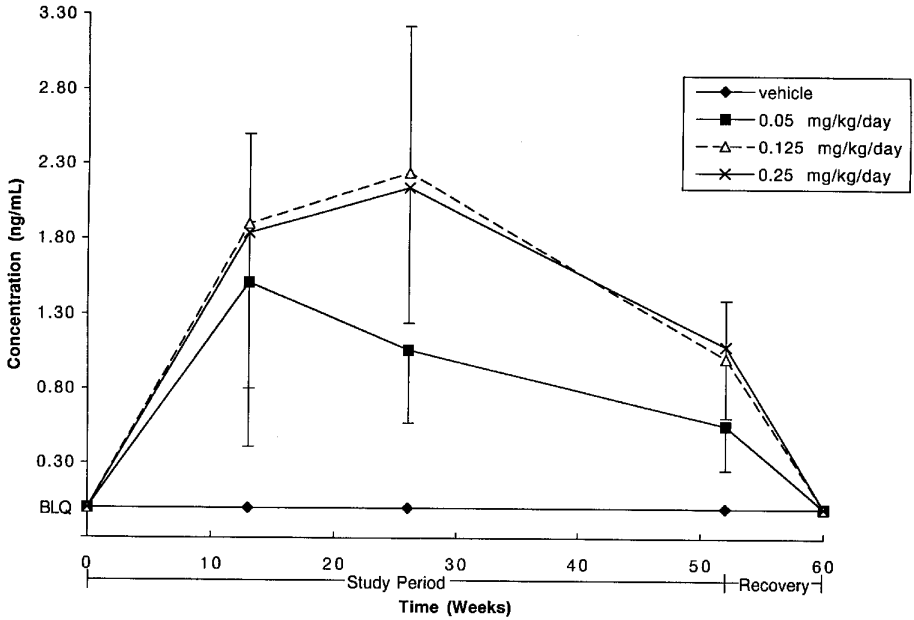


Figure 1. Blood tazarotenic acid concentration during the 12-month chronic toxicity study. Each data point represents the mean value for four animals. The error bars represent the standard deviation from the mean. BLQ, below the lower limit of quantification. Study period: drug treatment period. Recovery: no drug applied.

histopathology at any dose of tazarotene. This is marked contrast with the significant toxic effects produced by oral retinoids (Armstrong et al., 1994). The cutaneous effects associated with tazarotene use in these studies were very similar in type and severity to those effects commonly reported for other topical retinoids (Armstrong et al., 1994).

Tazarotene was not detected in the blood following topical administration, and the mean blood concentrations of tazarotenic acid, the major circulating metabolite of tazarotene, were low, demonstrating low systemic drug exposure. The tazarotenic acid blood concentration was actually lower at the end of the 12-month study than at its midpoint. This could be due to either decreased drug absorption, increased drug elimination, or increased volume of distribution as the study progressed. The fact that the blood tazarotenic acid concentration dropped below the level of quantification after the 2-month recovery period suggests that the drug was eventually eliminated. An earlier pharmacokinetic study (Hsyu et al., 1990) also reported low mean blood concentrations of tazarotenic acid following topical administration and failed to detect any tazarotene in the blood. In an unpublished clinical study (in

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preparation) of 112 psoriasis patients treated with either 0.1% or 0.05% tazarotene for up to 1 year, only 3 patients had detectable tazarotene plasma concentrations ($\leq$0.79 ng/mL). Plasma tazarotenic acid was detected in 32 of the 112 patients, but only four patients had tazarotenic acid concentrations greater than 1 ng/mL.

The only distinct systemic findings attributable to tazarotene were a dose-dependent increase in total protein and globulin serum concentrations, a decrease in serum albumin, and a decrease in the calculated albumin–globulin ratio. These changes are probably due to the effects of the skin irritation and injury that occurred at the treatment sites as a result of the high drug concentrations used. If the changes in protein had been the result of a true systemic effect, the changes in protein, globulin, and albumin would have all been in the same direction. These treatment-related effects resolved upon discontinuation of the drug.

Tazarotene caused a dose-dependent cutaneous irritation that is typical of retinoids in general (Armstrong et al., 1994). On physical examination, this irritation manifested as erythema, but not edema, at the treatment site. By treatment week 4 or 5, a hard, black eschar developed at the treatment site in all of the active treatment groups, with the exception of the 0.050 mg/kg/d group from the 3-month study, and precluded scoring dermal irritation through the end of the study.

In the chronic toxicity study, both tazarotene and vehicle produced multiple focal papules at the treatment sites. This suggests that these papules were due to the effect of some component of the vehicle formulation rather than tazarotene.

Histologically, the treated skin exhibited slight to minimal irritation in the animals treated with tazarotene at 0.050 mg/kg/d, slight to moderate irritation in animals treated with tazarotene at 0.125 mg/kg/d and 0.250 mg/kg/d, and marked irritation in the group treated with 0.500 mg/kg/d. Dermal irritation was accompanied by acanthosis, hyperkeratosis, cellular infiltration, and focal dermal fibrosis, all cutaneous changes that are commonly seen with retinoid use (Armstrong et al., 1994).

During the 2-month recovery period following the chronic (12-month) toxicity study, the cutaneous irritation subsided in a dose-dependent manner. At the end of this period, the treated areas of skin from the 0.050 mg/kg/d group were comparable to the treated areas in the vehicle group. In the animals from the 0.125 mg/kg/d and 0.250 mg/kg/d groups, slight to minimal irritation was present. Eschars decreased in severity in a dose-related manner and in some cases had fallen off.

Cutaneous drug absorption was not evaluated in the present study, but previous studies have demonstrated that tazarotene gel provides relatively high cutaneous concentrations (Matsumoto et al., 1992) with low systemic absorption (Schaefer, 1993). In humans, percutaneous absorption of tazarotene in vivo is low, and its metabolites are rapidly

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eliminated in the urine and feces (Hsyu et al., 1990; Franz et al., 1992). The apparent lack of systemic toxicity associated with topically applied tazarotene distinguishes it from oral retinoids (Armstrong et al., 1994). In patients treated with oral retinoids, careful consideration must be given to the risk–benefit ratio of treatment for any individual patient. Particular care is required when using oral retinoids in patients with risk factors such as liver disease, alcoholism, diabetes mellitus, cardiovascular disease, obesity, or concomitant treatment with hepatotoxic agents. Additionally, the long half-life of drugs such as etretinate requires that special precautions be taken in women of childbearing potential (David et al., 1988).

Tazarotene gel is currently being evaluated in the treatment of psoriasis and acne vulgaris (Sefton et al., 1993; Esgleyes-Ribot et al., 1994). The low systemic toxicity and apparent clinical efficacy of tazarotene in the treatment of psoriasis and acne vulgaris suggest that it may be a very promising new therapy for a wide range of disorders of keratinization.

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