

BRAF, KIT–Mutation Targeters Offer Hope

BY PATRICE WENDLING

ORLANDO — The concept of targeted therapies in melanoma took a step closer to reality with two early trials reporting positive responses to agents that specifically target BRAF or KIT mutations.

In a phase I study of 55 patients with a variety of cancers, 21 metastatic melanoma patients were treated twice daily with at least 240 mg PLX4032, an

investigational oral, small-molecule inhibitor that selectively targets the BRAF V600E kinase mutation occurring in most melanomas.

Partial responses by RECIST (Response Evaluation Criteria in Solid Tumors) were confirmed in 9 of 16 BRAF V600E mutation-positive patients. Five of the nine responders had M1c disease, the highest “M” stage, Dr. Keith Flaherty and his associates reported at the annual

meeting of the American Society of Clinical Oncology.

Seven patients developed disease progression at 3-14 months while still on therapy. A preliminary analysis suggests a progression-free survival of about 6 months, but the data are very immature and that estimate is likely to change with longer follow-up, said Dr. Flaherty of the University of Pennsylvania, Philadelphia.

In contrast, no tumor regression was

observed in the five melanoma patients lacking the BRAF mutation, and all developed progressive disease within the first 3 months.

Interim results from a second phase II study of imatinib in inoperable melanoma showed that a KIT mutation or amplification was present in 21% (31 of 146 tumors) screened. Thus far, 15 of the 31 patients, median age 71 years, have been treated with 400 mg imatinib twice daily on a continuous basis.

Of the 12 patients evaluable for response, the overall rate was 33% by RECIST and included two complete responses and two partial responses, said Dr. Richard Carvajal, an oncologist with Memorial Sloan-Kettering Cancer Center in New York. Stable disease was reported in six patients and disease progression in two. The responses have been durable, lasting 40 weeks in some patients.



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DR. FLAHERTY

Dr. Carvajal noted that only one response by RECIST was reported in three prior phase II studies of imatinib in a total of 62 nonselected patients with advanced melanoma.

The findings are proof of concept that targeted therapies work in melanoma, a heterogeneous group of diseases, said Dr. Boris Bastian of the University of California, San Francisco, who was invited to discuss the studies. He acknowledged that it is obviously early and few patients were treated, but that “it’s a decisive step toward personalized medicine for our melanoma patients.”

In the dose-escalation PLX4032 trial, sponsored by Plexxikon Inc. and Hoffman-La Roche Inc., dose-limiting toxicities developed in four of six patients who received 1,120 mg twice daily, the highest dose evaluated. A 960-mg twice-daily dosage is being evaluated as the maximum tolerated dose in an expanded cohort of mutation-positive melanoma patients, Dr. Flaherty said.

Adverse events with PLX4032 were clearly dose related, but even at higher doses, they tended to be mild, he said. Of note, 11% (six patients) were diagnosed while on study with cutaneous squamous cell carcinoma. Grade 3 or higher rash, fatigue, and pruritus were each reported in 2% of patients.

The PLX4032 study investigators disclosed financial ties with Plexxikon and Hoffman-La Roche. Dr. Carvajal and associates disclosed no personal conflicts of interest, but the study was supported by a Food and Drug Administration grant, an ASCO Young Investigator Award, and the Live4Life Foundation. Dr. Bastian disclosed consulting for Novartis and Exelixis Inc.

VECTICAL™ (calcitriol) OINTMENT, 3 mcg/g

For topical use only.

Not for oral, ophthalmic, or intravaginal use.

Not to be applied to the eyes, lips, or facial skin.

BRIEF SUMMARY

INDICATIONS AND USAGE:

VECTICAL Ointment is a vitamin D analog indicated for the topical treatment of mild to moderate plaque psoriasis in adults 18 years and older.

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

Effects on Calcium Metabolism

In controlled clinical trials with VECTICAL Ointment, among subjects having laboratory monitoring, hypercalcemia was observed in 24% (18/74) of subjects exposed to active drug and in 16% (13/79) of subjects exposed to vehicle. However, the increases in calcium and albumin-adjusted calcium levels were less than 10% above the upper limit of normal.

If aberrations in parameters of calcium metabolism occur, treatment should be discontinued until these parameters have normalized. The effects of VECTICAL Ointment on calcium metabolism following treatment durations greater than 52 weeks have not been evaluated. Increased absorption may occur with occlusive use.

Ultraviolet Light Exposure

Animal data suggest that the vehicle of VECTICAL Ointment may enhance the ability of ultraviolet radiation (UVR) to induce skin tumors.

Subjects who apply VECTICAL Ointment to exposed skin should avoid excessive exposure of the treated areas to either natural or artificial sunlight, including tanning booths and sun lamps. Physicians may wish to limit or avoid use of phototherapy in patients who use VECTICAL Ointment.

Unevaluated Uses

The safety and effectiveness of VECTICAL Ointment in patients with known or suspected disorders of calcium metabolism have not been evaluated. The safety and effectiveness of VECTICAL Ointment in patients with erythrodermic, exfoliative, or pustular psoriasis have not been evaluated.

ADVERSE REACTIONS

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

Clinical Studies Experience

VECTICAL Ointment was studied in two vehicle-controlled studies (419 subjects), and in one open label study (324 subjects). The table below describes exposure to VECTICAL Ointment in 743 subjects, including 239 exposed for 6 months and 116 exposed for one year.

Four hundred and nineteen subjects were treated with VECTICAL Ointment twice daily for 8 weeks. The population included subjects ages 13 to 87, males (284) and females (135), Caucasians (372) and non-Caucasians (47); with mild (105) to moderate (313) chronic plaque psoriasis.

Selected Adverse Events Occurring in at least 1% of Subjects in the Two Pooled Vehicle-Controlled Studies

	VECTICAL Ointment (n=419)	Vehicle Ointment (n=420)
Discomfort skin	3%	2%
Pruritus	1%	1%

Among subjects having laboratory monitoring, hypercalcemia was observed in 24% (18/74) of subjects exposed to active drug and in 16% (13/79) of subjects exposed to vehicle, however the elevations were less than 10% above the upper limit of normal. The open label study enrolled 324 subjects with psoriasis who were then treated for up to 52 weeks. Adverse events reported at a rate of greater than or equal to 3% of subjects treated with VECTICAL Ointment were lab test abnormality (8%), urine abnormality (4%), psoriasis (4%), hypercalciuria (3%), and pruritus (3%). Kidney stones were reported in 3 subjects and confirmed in two.

Postmarketing Experience

The following adverse reactions have been identified during worldwide post-approval use of VECTICAL Ointment: acute blistering dermatitis, erythema, pruritus, skin burning sensation, and skin discomfort. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

DRUG INTERACTIONS

VECTICAL Ointment should be used with caution in patients receiving medications known to increase the serum calcium level, such as thiazide diuretics. Caution should also be exercised in patients receiving calcium supplements or high doses of vitamin D.

USE IN SPECIFIC POPULATIONS

Pregnancy

Teratogenic Effects: Pregnancy Category C.

VECTICAL Ointment contains calcitriol which has been shown to be fetotoxic. There are no adequate and well-controlled studies for VECTICAL Ointment in pregnant women. VECTICAL Ointment should be used during pregnancy only if the potential benefit to the patient justifies the potential risk to the fetus.

Teratogenicity studies with calcitriol were performed in which rats were treated orally at dosages up to 0.9 mcg/kg/day (5.4 mcg/m²/day) and in which rabbits received topical application of calcitriol ointment (3 ppm) to 6.4% of the body surface area. No effects on reproductive or fetal parameters were observed in rats. In rabbits, topically applied calcitriol induced a significantly elevated mean post-implantation loss and an increased incidence of minor skeletal abnormalities due to retarded ossification of the pubic bones. A slightly increased incidence of skeletal variation (extra 13th rib, reduced ossification of epiphyses) was also observed. These effects may have been secondary to maternal toxicity. Based on the recommended human dose and instructions for use, it is not possible to calculate human dose equivalents for animal exposures in these studies.

Nursing Mothers

It is not known whether calcitriol is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when VECTICAL Ointment is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Clinical studies of VECTICAL Ointment did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported experience has not identified differences in responses between the elderly and younger patients.

OVERDOSAGE

Topically applied calcitriol can be absorbed in sufficient amounts to produce systemic effects.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

When calcitriol was applied topically to mice for up to 24 months, no significant changes in tumor incidence were observed. Concentrations of calcitriol in ointment base of 0 (vehicle control), 0.3, 0.6 and 1.0 ppm were evaluated.

A two-year carcinogenicity study was conducted in which calcitriol was orally administered to rats at dosages of approximately 0.005, 0.03, and 0.1 mcg/kg/day (0.03, 0.18, and 0.6 mcg/m²/day, respectively). The incidence of benign pheochromocytomas was significantly increased in female rats. No other significant differences in tumor incidence data were observed.

In a study in which albino hairless mice were exposed to both ultra-violet radiation (UVR) and topically applied calcitriol ointment, a reduction in the time required for UVR to induce the formation of skin tumors was observed in all groups that received the ointment base, including the vehicle-treated control group, relative to animals that received no ointment but which were exposed to UVR. The time required for UVR to induce the formation of skin tumors did not differ between animals that received plain vehicle and those that received vehicle that contained calcitriol. Concentrations of calcitriol in ointment base of 0 (vehicle control), 0.3, 0.6 and 1.0 ppm were evaluated. These data suggest that the vehicle of VECTICAL Ointment may enhance the ability of UVR to induce skin tumors.

Calcitriol did not elicit genotoxic effects in the mouse lymphoma TK locus assay. Studies in which male and female rats received oral doses of calcitriol of up to 0.6 mcg/kg/day (3.6 mcg/m²/day) indicated no impairment of fertility or general reproductive performance.

Based upon the recommended human dose and instructions for use, it is not possible to calculate human dose equivalents for animal exposure in these studies.

PATIENT COUNSELING INFORMATION

This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects. Patients using VECTICAL Ointment should receive the following information:

Instructions for Use

This medication is to be used as directed by the physician. It is for external use only. This medication is to be applied only to areas of the skin affected by psoriasis, as directed. It should be gently rubbed into the skin so that no medication remains visible.

Adverse Reactions

Patients should report any signs of adverse reactions to their physician.

Marketed by:

GALDERMA LABORATORIES, L.P.
Fort Worth, Texas 76177 USA

Manufactured by:

Galderma Production Canada Inc.
Baie d'Urfé, QC, H9X 3S4 Canada
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References: 1. Data on file. Galderma Laboratories. 2. Leibold M, Menter A, Weiss J, et al. Calcitriol 3 µg/g ointment in the management of mild to moderate plaque type psoriasis: results from 2 placebo-controlled, multicenter, randomized double-blind, clinical studies. *J Drugs Dermatol.* 2007;6:428-435. 3. Ortonne JP, Humbert P, Nicolas JF, et al. Intra-individual comparison of the cutaneous safety and efficacy of calcitriol 3 µg g⁻¹ ointment and calcipotriol 50 µg g⁻¹ ointment on chronic plaque psoriasis localized in facial, hairline, retroauricular or flexural areas. *Br J Dermatol.* 2003;148:326-333. 4. Vectical™ Prescribing Information. Fort Worth, TX: Galderma Laboratories, L.P.; 2009.