

Laser Treatment Didn't Make Nevi More Malignant

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BOSTON — Irradiation of benign pigmented nevi with Q-switched laser does not induce malignant transformation of the lesions, said Dr. David J. Goldberg at the annual meeting of the American Society for Laser Medicine and Surgery.

While the use of lasers to treat melanocytic nevi has been the subject of much debate because of concerns about

malignant transformation, “to date there has been no study to fully evaluate this theoretical concern,” said Dr. Goldberg of the department of dermatology at Mount Sinai School of Medicine, New York.

Toward this end, Dr. Goldberg and colleagues undertook a preliminary study to determine if irradiation with Q-switched laser increases the malignant potential of benign nevi. The investigators analyzed biopsy samples from 10 individuals with laser-treated nevi looking for changes

suggestive of malignant transformation.

All participants had multiple benign nevi, one of which was laser irradiated with a Q-switched Nd:Yag laser. “In each patient, the treated nevus was matched with a paired control nevus that was not irradiated,” said Dr. Goldberg, who is also in private practice in New York and New Jersey. Twenty-four hours after the laser treatment, both the treated and untreated nevi were excised and biopsy samples were analyzed for three instantaneous markers

of malignant transformation: proliferating cell nuclear antigen, pyrimidine dimers, and 8-hydroxydeoxyguanosine. The specimens also were analyzed for p53.

“We didn't find any significant markers for malignant transformation in the laser-treated nevi,” said Dr. Goldberg, suggesting not only that Q-switched laser irradiation is a safe option for biopsy-confirmed benign nevi, but also that “any future malignant transformation of such nevi is not the result of the laser treatments.” ■



ALDARA™

[al dar' a]
(imiquimod)
Cream, 5%

Brief Summary of prescribing information

For Dermatologic Use Only Not for Ophthalmic Use

INDICATIONS AND USAGE Aldara Cream is indicated for the topical treatment of clinically typical, nonhyperkeratotic, nonhypertrophic actinic keratoses on the face or scalp in immunocompetent adults. Aldara Cream is indicated for the topical treatment of biopsy-confirmed, primary superficial basal cell carcinoma (sBCC) in immunocompetent adults, with a maximum tumor diameter of 2.0 cm, located on the trunk (excluding anogenital skin), neck, or extremities (excluding hands and feet), only when surgical methods are medically less appropriate and patient follow-up can be reasonably assured. The histological diagnosis of superficial basal cell carcinoma should be established prior to treatment, since safety and effectiveness of Aldara Cream have not been established for other types of basal cell carcinomas, including nodular, morpheiform (fibrosing or sclerosing) types. Aldara Cream is indicated for the treatment of external genital and perianal warts/condyloma acuminata in individuals 12 years old and above. **CONTRAINDICATIONS** This drug is contraindicated in individuals with a history of sensitivity reactions to any of its components. It should be discontinued if hypersensitivity to any of its ingredients is noted. **WARNINGS** The diagnosis of sBCC should be confirmed prior to treatment, since safety and effectiveness of Aldara Cream have not been established for other types of basal cell carcinomas, including nodular, morpheiform (fibrosing or sclerosing) types and is not recommended for treatment of BCC subtypes other than the superficial variant (i.e., sBCC). Patients with sBCC treated with Aldara Cream are recommended to have regular follow-up of the treatment site. Aldara Cream has not been evaluated for the treatment of urethral, intra-vaginal, cervical, rectal, or intra-anal human papilloma viral disease and is not recommended for these conditions. **PRECAUTIONS General** The safety and efficacy of Aldara Cream in immunosuppressed patients have not been established. Aldara Cream administration is not recommended until the skin is completely healed from any previous drug or surgical treatment. Aldara Cream has the potential to exacerbate inflammatory conditions of the skin, including chronic graft versus host disease. Aldara Cream should be used with caution in patients with pre-existing autoimmune conditions. Intense local inflammatory reactions including skin weeping or erosion can occur after only a few applications of Aldara Cream. Local inflammatory reactions may be accompanied, or even preceded, by flu-like systemic signs and symptoms including malaise, fever, nausea, myalgias, and rigors. An interruption of dosing should be considered. Exposure to sunlight (including sunlamps) should be avoided or minimized during use of Aldara Cream because of concern for heightened sunburn susceptibility. Patients should be warned to use protective clothing (hat) when using Aldara Cream. Patients with sunburn should be advised not to use Aldara Cream until fully recovered. Patients who may have considerable sun exposure, e.g., due to their occupation, and those patients with inherent sensitivity to sunlight should exercise caution when using Aldara Cream. Phototoxicity has not been adequately assessed for Aldara Cream. The enhancement of ultraviolet carcinogenicity is not necessarily dependent on phototoxic mechanisms. Despite the absence of observed phototoxicity in humans (see *ADVERSE REACTIONS*), Aldara Cream shortened the time to skin tumor formation in an animal photocarcinogenicity study (see *Carcinogenesis, Mutagenesis, Impairment of Fertility*). Therefore, it is prudent for patients to minimize or avoid natural or artificial sunlight exposure. **Actinic Keratosis** Safety and efficacy have not been established for Aldara Cream in the treatment of actinic keratosis with repeated use, i.e. more than one treatment course, in the same 25 cm² area. The safety of Aldara Cream applied to areas of skin greater than 25 cm² (e.g. 5 cm X 5 cm) for the treatment of actinic keratosis has not been established. **Superficial Basal Cell Carcinoma** The safety and efficacy of treating superficial basal cell carcinoma (sBCC) lesions on the face, head and anogenital area have not been established. The efficacy and safety of Aldara Cream have not been established for patients with Basal Cell Nevus Syndrome or Xeroderma Pigmentosum. **Information for Patients General Information** Patients using Aldara Cream should receive the following information and instructions: 1. This medication is to be used as directed by a physician. It is for external use only. Eye contact should be avoided. 2. The treatment area should not be bandaged or otherwise covered or wrapped as to be occlusive. 3. Some reports have been received of localized hypopigmentation and hyperpigmentation following Aldara Cream use. Follow-up information suggests that these skin color changes may be permanent in some patients. **Patients Being Treated for Actinic Keratosis (AK)** 1. It is recommended that the treatment area be washed with mild soap and water 8 hours following Aldara Cream application. 2. It is common for patients to experience local skin reactions (can range from mild to severe in intensity) during treatment with Aldara Cream, and these reactions may extend beyond the application site onto the surrounding skin. Skin reactions generally decrease in intensity or resolve after cessation of Aldara Cream therapy. Potential local skin reactions include erythema, edema, vesicles, erosion/ulceration, weeping/exudate, flaking/scaling/dryness, and scabbing/crusting. Most patients using Aldara Cream for the treatment of AK experience erythema, flaking/scaling/dryness and scabbing/crusting at the application site with normal dosing. Patients may also experience application site reactions such as itching and/or burning. Local skin reactions may be of such an intensity that patients may require rest periods from treatment. Treatment with Aldara Cream can be resumed after the skin reaction has subsided, as determined by the physician. Patients should contact their physician promptly if they experience any sign or symptom at the application site that restricts or prohibits their daily activity or makes continued application of the cream difficult. 3. Because of local skin reactions, during treatment and until healed, the treatment area is likely to appear noticeably different from normal skin. The skin surrounding the treatment area may also be affected, but less intensely so. 4. Contact with the eyes, lips and nostrils should be avoided. 5. Use of sunscreen is encouraged, and patients should minimize or avoid exposure to natural or artificial sunlight (tanning beds or UVA/B treatment) while using Aldara Cream. 6. During treatment, sub-clinical AK lesions may become apparent in the treatment area and may subsequently resolve. 7. Partially-used packets should be discarded and not reused. 8. Dosing is twice weekly for the full 16 weeks, unless otherwise directed by the physician. However, the treatment period should not be extended beyond 16 weeks due to missed doses or rest periods. **Patients Being Treated for Superficial Basal Cell Carcinoma (sBCC)** 1. It is recommended that the treatment area be washed with mild soap and water 8 hours following Aldara Cream application. 2. Most patients using Aldara Cream for the treatment of sBCC experience erythema, edema, induration, erosion, scabbing/crusting and flaking/scaling at the application site with normal dosing. These local skin reactions generally decrease in intensity or resolve after cessation of Aldara Cream therapy. Patients may also experience application site reactions such as itching and/or burning. Local skin reactions may be of such an intensity that patients may require rest periods from treatment. Treatment with Aldara Cream can be resumed after the skin reaction has subsided, as determined by the physician. 3. During treatment and until healed, affected skin is likely to appear noticeably different from normal skin. 4. It is prudent for patients to minimize or avoid exposure to natural or artificial sunlight. 5. The clinical outcome of therapy can be determined after regeneration of the treated skin, approximately 12 weeks after the end of treatment. 6. Patients should contact their physician if they experience any sign or symptom at the application site that restricts or prohibits their daily activity or makes continued application of the cream difficult. 7. Patients with sBCC treated with Aldara Cream are recommended to have regular follow-up to re-evaluate the treatment site. **Patients Being Treated for External Genital Warts** 1. It is recommended that the treatment area be washed with mild soap and water 6-10 hours following Aldara Cream application. 2. It is common for patients to experience local skin reactions such as erythema, erosion, excoriation/flaking, and edema at the site of application or surrounding areas. Most skin reactions are mild to moderate. Severe skin reactions can occur and should be promptly reported to the prescribing physician. Should severe local skin reaction occur, the cream should be removed by washing the treatment area with mild soap and water. Treatment with Aldara Cream can be resumed after the skin reaction has subsided. 3. Sexual (genital, anal, oral) contact should be avoided while the cream is on the skin. 4. Application of Aldara Cream in the vagina is considered internal and should be avoided. Female patients should take special care if applying the cream at the opening of the vagina because local skin reactions on the delicate moist surfaces can result in pain or swelling, and may cause difficulty in passing urine. 5. Uncircumcised males treating warts under the foreskin should retract the foreskin and clean the area daily. 6. Patients should be aware that new warts may develop during therapy, as Aldara Cream is not a cure. 7. The effect of Aldara Cream on the transmission of genital/perianal warts is unknown. 8. Aldara Cream may weaken condoms and vaginal diaphragms, therefore concurrent use is not recommended. **Carcinogenesis, Mutagenesis, and Impairment of Fertility** Note: The Maximum Recommended Human Dose (MRHD) was set at 2 packets per treatment of Aldara Cream (25 mg imiquimod) for the animal multiple of human exposure ratios presented in this label. If higher doses than 2 packets of Aldara Cream are used clinically, then the animal multiple of human exposure would be reduced for that dose. A non-proportional increase in systemic exposure with increased dose of Aldara Cream was noted in the clinical pharmacokinetic study conducted in actinic keratosis subjects. The AUC after topical application of 6 packets of Aldara Cream was 8 fold greater than the AUC after topical application of 2 packets of Aldara Cream in actinic keratosis subjects. Therefore, if a dose of 6 packets per treatment of Aldara Cream was topically administered to an individual, then the animal multiple of human exposure would be either 1/3 of the value provided in the label (based on body surface area comparisons) or 1/8 of the value provided in the label (based on AUC comparisons). The animal multiples of human exposure calculations were based on weekly dose comparisons for the carcinogenicity studies described in this label. The animal multiples of human exposure calculations were based on daily dose comparisons for the reproductive toxicology studies described in this label. In an oral (gavage) rat carcinogenicity study, imiquimod was administered to Wistar rats on a 2X/week (up to 6 mg/kg/day) or daily (3 mg/kg/day) dosing schedule for 24 months. No treatment related tumors were noted in the oral rat carcinogenicity study up to the highest doses tested in this study of 6 mg/kg administered 2X/week in female rats (87X MRHD based on weekly AUC comparisons), 4 mg/kg administered 2X/week in male rats (75X MRHD based on weekly AUC comparisons) or 3 mg/kg administered 7X/week to male and female rats (153X MRHD based on weekly AUC comparisons). In a dermal mouse carcinogenicity study, imiquimod cream (up to 5 mg/kg/application imiquimod or 0.3% imiquimod cream) was applied to the backs of mice 3X/week for 24 months. A statistically significant increase in the incidence of liver adenomas and carcinomas was noted in high dose male mice compared to control male mice (251X MRHD based on weekly AUC comparisons). An increased number of skin papillomas was observed in vehicle cream control group animals at the treated site only. The quantitative composition of the vehicle cream used in the dermal mouse carcinogenicity study is the same as the vehicle cream used for Aldara Cream, minus the active moiety (imiquimod). In a 52-week dermal photocarcinogenicity study, the median time to onset of skin tumor formation was decreased in hairless mice following chronic topical dosing (3X/week; 40 weeks of treatment followed by 12 weeks of observation) with concurrent exposure to UV radiation (5 days per week) with the Aldara Cream vehicle alone. No additional effect on tumor development beyond the vehicle effect was noted with the addition of the active ingredient, imiquimod, to the vehicle cream. Imiquimod revealed no evidence of mutagenic or clastogenic potential based on the results of five in vitro genotoxicity tests (Ames assay, mouse lymphoma L5178Y assay, Chinese hamster ovary cell chromosome aberration assay, human lymphocyte chromosome aberration assay and SHE cell transformation assay) and three in vivo genotoxicity tests (rat and hamster bone marrow cytogenetics assay and a mouse dominant lethal test). Daily oral administration of imiquimod to rats, throughout mating, gestation, parturition and lactation, demonstrated no effects on growth, fertility or reproduction, at doses up to 87X MRHD based on AUC comparisons. **Pregnancy** Pregnancy Category C: Systemic embryofetal development studies were conducted in rats and rabbits. Oral doses of 1, 5 and 20 mg/kg/day imiquimod were administered during the period of organogenesis (gestational days 6 – 15) to pregnant female rats. In the presence of maternal toxicity, fetal effects noted at 20 mg/kg/day [577X MRHD based on AUC comparisons] included increased resorptions, decreased fetal body weights, delays in skeletal ossification, bent limb bones, and two fetuses in one litter (2 of 1567 fetuses) demonstrated exencephaly, protruding tongues and low set ears. No treatment related effects on embryofetal toxicity or teratogenicity were noted at 5 mg/kg/day (98X MRHD based on AUC comparisons). Intravenous doses of 0.5, 1 and 2 mg/kg/day imiquimod were administered during the period of organogenesis (gestational days 6 – 18) to pregnant female rabbits. No treatment related effects on embryofetal toxicity or teratogenicity were noted at 2 mg/kg/day (1.5X MRHD based on BSA comparisons), the highest dose evaluated in this study, or 1 mg/kg/day (407X MRHD based on AUC comparisons). A combined fertility and peri- and post-natal development study was conducted in rats. Oral doses of 1, 1.5, 3 and 6 mg/kg/day imiquimod were administered to male rats from 70 days prior to mating through the mating period and to female rats from 14 days prior to mating through parturition and lactation. No effects on growth, fertility, reproduction or post-natal development were noted at doses up to 6 mg/kg/day (87X MRHD based on AUC comparisons), the highest dose evaluated in this study. In the absence of maternal toxicity, bent limb bones were noted in the F1 fetuses at a dose of 6 mg/kg/day (87X MRHD based on AUC comparisons). This fetal effect was also noted in the oral rat embryofetal development study conducted with imiquimod. No treatment related effects on teratogenicity were noted at 3 mg/kg/day (41X MRHD based on AUC comparisons). There are no adequate and well-controlled studies in pregnant women. Aldara Cream should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Nursing Mothers** It is not known whether topically applied imiquimod is excreted in breast milk. **Pediatric Use** Safety and efficacy in patients with external genital/perianal warts below the age of 12 years have not been established. AK and sBCC are not conditions generally seen within the pediatric population. The safety and efficacy of Aldara