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5-Fluorouracil 0.5% Cream for Multiple Actinic or Solar Keratoses of the Face and Anterior Scalp

New Drug Spotlight

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ABSTRACT

Carac® (5-fluorouracil 0.5% cream, Aventis Pharma) was approved by the US FDA in October 2000, for the treatment of multiple actinic or solar keratoses involving the face and anterior scalp. The cream should be applied in a thin film once daily to the skin where actinic keratoses (AKs) are present. When it is applied for 1, 2 or 4 weeks, it is significantly more effective than a vehicle in the management of patients with five or more AKs at pretherapy. Pooled data from the two pivotal trials (n=384) indicate that following 4 weeks of therapy the number of subjects with total AK clearance in the Carac® and vehicle groups was 52.9% and 1.6%, respectively ($p<0.001$). Furthermore, the corresponding reduction of AK lesion counts in the Carac® and vehicle groups was 82.5% and 19.3%, respectively ($p<0.001$). Treatment should be continued for up to 4 weeks as tolerated by the patient. The most common adverse-effect is facial irritation.

KEY WORDS: *actinic keratosis, actinic keratoses, solar keratosis, 5-fluorouracil*

Actinic keratoses (AKs) can be described as cutaneous neoplasms that display chromosomal abnormalities and occur primarily on sun-exposed skin surfaces.[1] They may develop as a result of long-term exposure to the sun's ultraviolet light in susceptible individuals.[2–4] Other risk factors include increasing age, male gender and increased susceptibility to ultraviolet radiation.[5] We may be in the midst of an ongoing skin cancer epidemic since the development of AKs, and basal cell and squamous cell carcinomas is a growing health issue especially for individuals who have a fair-skinned complexion.[2,6] In a survey of outpatient visits to dermatologists in the US between 1990–1994, the most common reasons given for office visits were acne, dermatitis, actinic dermatoses and skin cancer.[7]

AKs may be a sensitive indicator of an individual's exposure to sunlight over the years, and a predictive factor of that person's potential for the development of both basal cell and squamous cell carcinomas.[10] The average number of AKs per individual is reported to be 6–8.[8,9] The natural history of AKs in the community may be one of high turnover with a small percentage of susceptible individuals carrying the major burden. Marks, et al[10] estimated that the risk of malignant transformation of an average AK into a squamous cell carcinoma (SCC) in one year is 0.0075%. Dodson, et al[11] demonstrated that over a 10-year period, a person with an average of 7.7 AKs has a 6.1–10.2% chance of developing an SCC. Therefore, a low yearly rate of transformation of a single AK lesion into an SCC can translate into an increased risk in patients with multiple AKs, especially when considered over a long period of time.[11]

The treatment modalities approved by the US FDA for the treatment of AKs include topical 5-fluorouracil (5-FU) (Carac®, Efudex®, Fluoroplex®) and photodynamic therapy (Levulan® Kerastick™, Solaraze®).[12,15,16] Another option is local excision or destruction of the lesion, including liquid nitrogen cryotherapy.[15]

Mechanism of Action

Pyrimidine analogs can be subdivided into fluoropyrimidine and cytidine analogs, with 5-FU being an example of the former.[13] Biochemically, 5-FU may mimic uracil, interact with enzymes of pyrimidine metabolism, and interfere with other aspects of pyrimidine action. Fluorouracil may prevent DNA synthesis by inhibiting thymidylate synthetase. It may be incorporated into RNA resulting in an aberrant form of one or more types of RNA, and interfere with the incorporation of uracil into RNA.[14] It is possible that the inhibition of thymidylate synthetase and the consequent interruption of DNA synthesis may distort the metabolism of the DNA-synthesizing cell to the extent that they are unable to reproduce normally, thereby leading to cell death.[14] The effects of DNA and RNA deprivation may be most marked in those cells that grow more rapidly and take up fluorouracil at a relatively faster rate.

Pharmacokinetics

In a multiple-dose, randomized, open-label, parallel study, patients with AKs were treated with Carac® (0.5% cream) in a once daily 1gm application, or with Efudex® (5% cream) 1gm in two divided daily doses, for a maximum of 28 days. Data from plasma and urine samples were available from 20 patients. Only 3 of 10 patients applying the 0.5% cream had measurable 5-FU plasma concentrations, with only one patient having enough data points to determine systemic pharmacokinetics. Five of 10 patients applying the 0.5% cream had measurable urine concentrations. The data showed that both formulations demonstrated low plasma concentrations of fluorouracil when administered under steady-state concentrations. Cumulative urinary excretion was low for both the 0.5% and 5% cream formulations: 0.055% and 0.24% of the applied doses, respectively.

Clinical Trials

Three concentrations of Carac®, 0.5%, 2.5% and 5%, as well as 5% Efudex®, and a vehicle (placebo) cream were evaluated for the treatment of AKs in a double-blinded, parallel group, multicenter study.[17] All patients were randomly assigned a treatment cream to be applied twice daily for 4 weeks. Although there were no statistically significant differences between the three concentrations of the Carac® and the 5% Efudex®, patients in the 0.5% and 2.5% groups demonstrated a greater reduction in AK lesions. There was a greater proportion of patients with 100% improvement in the evaluations of overall AK severity when compared to the two 5% creams. Furthermore, the 0.5% cream had the best irritation/tolerability profile of all the concentrations tested. As a result, the 5-FU 0.5% cream was chosen for further studies in a Phase III program.

Two phase III multicenter, vehicle-controlled, double-blinded, parallel group trials were performed with three different treatment arms and three matching vehicle arms.[17] The treatment arms consisted of 0.5% 5-FU cream and vehicle being applied in a 1:1:1 ratio for 1, 2 and 4 weeks. All patients had five or more AKs on the face or anterior bald scalp, and were randomly allocated to active or vehicle treatment in a 2:1 ratio. Each treatment was applied once daily to the affected area. The clinical response was evaluated 4 weeks after the last scheduled application of the study cream. The clinical efficacy outcome from the use of the vehicle cream for 1, 2 and 4 weeks was pooled because duration of treatment with vehicle had no substantive effect on clearance of AKs. The clinical efficacy of the 0.5% 5-FU cream in the treatment of AKs on the ears and other sun exposed areas was not evaluated in these studies. The 0.5% 5-FU cream, when applied once daily for 1, 2 or 4 weeks was significantly more effective than the vehicle control group, both in the reduction and in the number of AKs, and in the proportion of patients experiencing total clearance.

The perception of many physicians is that the clinical efficacy of 5-FU is associated with the severity of skin irritation induced following its application. In fact, the data indicate that there was a statistically significant correlation between a reduction in the severity of AK lesions and the severity of facial irritation, or the presence of symptoms/signs of facial irritation (e.g., erythema, dryness, edema, erosion, pain and burning) evaluated at the final visit in the treatment phase, or at 1-week posttreatment.

In general, patients with a greater number of lesions, or more severe actinic damage at pretherapy, were observed to have a greater absolute reduction in the number of lesions from pretherapy to the final evaluation, when compared to those with less actinic damage at pretherapy.

Improved efficacy was observed with increased treatment duration. The course of treatment should be continued for as long as possible, up to a maximum of 4 weeks, depending upon the tolerance of the patient to treatment.

There were no significant differences in efficacy and safety parameters in patients aged 65 years and older when compared to all other patients.

The data show that the 0.5% 5-FU cream in a Microsponge® formulation applied once daily for 1, 2 or 4 weeks is effective in the treatment of patients with five or more AKs.

Study	Characteristics	Number of subjects with total AK clearance	Proportional reduction of AK lesion counts
US 1 study	N=207 Age (mean ± SD): 65.0 ± 10.1 years Male/Female: 166/41 Skin Type (1/ II/ III/ IV): 80:99:27:1	Active 4 week: 26/45 (57.8%) Vehicle: 0/69 (0%) P<0.001	Active 4 week: 15.4 ± 8.0 (baseline) to 2.2 ± 4.2 (91.7% reduction) Vehicle: 15.6 ± 12.0 (baseline) to 12.4 ± 12.5 (21.6% reduction) P<0.001
US II Study	N=177 Age (mean ± SD): 63.2 ± 11.1 years Male/ Female: 152/ 25 Skin Type (1/ II/ III/ IV): 69:81:27:0	Active 4 week: 19/40 (47.5%) Vehicle: 2/58 (3.4%) P<0.001	Active 4 week: 14.1 ± 8.2 (baseline) to 3.0 ± 5.7 (88.7% reduction) Vehicle: 16.4 ± 11.1 (baseline) to 13.7 ± 12.3 (34.4% reduction) P<0.001
Pooled studies	N=384 Age (mean ± SD): 64.2 ± 10.6 years Male/ Female: 318/66 Skin Type (1/ II/ III/ IV): 149:180:54:1	Active 4 week: 45/85 (52.9%) Vehicle: 2/127 (1.6%) P<0.001	Active 4 week: 14.8 ± 8.1 (baseline) to 2.5 ± 5.0 (82.5 % reduction) Vehicle: 5.9 ± 11.6 (baseline) to 13.0 ± 12.4 (19.3 % reduction) P<0.001

Table 1: Efficacy of 0.5% 5-Fluorouracil cream in the two Phase III studies

Adverse-effects

In the phase III studies, the adverse-effects that occurred in at least 1% of all patients were application site reaction (facial irritation), eye irritation, headache, common cold, sinusitis, allergy, and skin irritation.

There was no evidence of a duration response effect for the incidence of any adverse event, including application site reaction. The 0.5% 5-FU cream demonstrated excellent systemic tolerance with few reported non-facial irritation adverse effects. No serious adverse events were thought to be related to the study medication.

In the Phase III studies, application of the 0.5% 5-FU cream in each of the 1, 2, 4 week and vehicle groups resulted in facial irritation, probably due to the study drug, in 87.1%, 95.4%, 95.3% and 48.0%, of patients respectively. The most common symptoms and signs of facial irritation were dryness, burning and erythema. Only facial irritation demonstrated a dose-response and dose-duration relationship. Patients with the greatest amount of actinic damage, and those with the highest number of AKs at pretherapy were more likely to experience moderate or severe facial irritation.

The median day of onset of facial irritation for all groups was 4 days after therapy began. Severity increased with treatment duration, generally increasing during the first 2 weeks of treatment using a once daily application. There was little increase in severity beyond the second week of therapy. The number of patients who discontinued treatment due to facial irritation also increased as the treatment duration became longer: 1-week active therapy (0 patients), 2-week group (7 patients, 8.0%), 4-week group (20 patients, 23.5%), and vehicle group (1 patient, 0.8%). The median duration of facial irritation following completion of 0.5% 5-FU cream therapy was 16 days and this was similar for the three active treatment groups (compared to 4 days for the placebo group).

Following the completion of therapy, facial irritation decreased rapidly and the incidence of each symptom and sign was below pretherapy levels by 2 weeks after treatment was stopped.

In phase I dermal safety tests the 0.5% 5-FU cream demonstrated no phototoxicity, photoallergy, little irritation potential and no contact sensitization.

Drug interactions

No formal drug-drug or drug-food interaction studies have been conducted with the 0.5% 5-FU cream. However, pharmacokinetic studies confirm that there is very limited systemic absorption, making it unlikely that there would be any important interactions with oral or systemic products, which could have an effect on efficacy.

Dosage and cost

Carac® is indicated for once daily application for up to 4 weeks by adults to treat AKs on the face and the anterior portion of the scalp. Enough cream should be used to cover the entire area with a thin film 10 minutes after thoroughly washing, rinsing, and drying the sites where the cream is to be applied. It should not be applied under occlusion or in close proximity to certain anatomic sites such as the eyes, nostrils or mouth. The patient should be counseled that in many instances skin reaction may develop at the application site, including redness, dryness, burning, pain, erosion, and edema. The user should also be informed that the treated area may become somewhat unsightly during therapy and for >2 weeks following the end of therapy. The once daily application and relatively short duration of application may help with compliance.

While using the 5-FU the patient should be encouraged to avoid sunlight or other ultraviolet light sources (e.g., tanning beds). When out in the sun during a treatment course, sun protection measures are recommended.

The 0.5% 5-FU cream is contraindicated in women who are or may become pregnant (US FDA category X), in patients with dihydropyrimidine dehydrogenase (DPD) enzyme deficiency, and in those with known hypersensitivity to any of the components of the cream. This product is not recommended for use when patients are breast-feeding, or in individuals under 18 years of age. Carac® is available in a 30gm tube in the US; it is currently unavailable in Canada. The average wholesale price in the US is $95.00 USD (January 2001 price).

Conclusion

The US FDA recently approved 0.5% 5-FU cream (Carac®) for the topical treatment of multiple actinic or solar keratoses on the face and anterior scalp. The cream should be applied once daily to the actinic keratoses for up to 4 weeks as tolerated by the patient. The most common adverse-effect is facial irritation.

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The manuscript should be 1200–1500 words in length with an abstract (not to exceed 175 words), conclusion and a limited list of references. If the paper discusses a new drug, then it should include information about its indications, regulatory agency approval, mechanism of action, adverse effects, and clinical trial data. If the manuscript discusses a dermatologic disease, then it should include background information about the disease, past and current therapies, under what conditions those treatments are most effective, and any adverse effects. We do not publish color pictures but welcome tables that briefly outline the information included in the manuscript.

The paper should be double-spaced and must conform to acceptable English usage. Submit the original (via fax is acceptable) and an electronic version of the manuscript (on computer disk or as an e-mail attachment) to the Publishing Editor, Penelope Gray-Allan, Ste. 450 – 633 West Hastings, Vancouver, BC, Canada V6B 1P1; telephone 604-633-1926; fax: 604-633-1921; e-mail: grayallan@skincareguide.com.

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Update on Drugs

Class	Name/Company	Approval Dates and Comments
Antihistamine	**Desloratidine** *Claritin®* Scherin-Plough	The Committee for Proprietary Medicinal Products (CPMP) of the European Agency for the Evaluation of Medicinal Products (EMEA) recommended approval in May 2001, of the 5mg tablets of this nonsedating antihistamine for the treatment of the symptoms of chronic idiopathic urticaria.
Anit-Acne Agent	**Azelaic Acid Cream 20%** *Finevin®* Berlex Laboratories	The US FDA granted marketing approval in May 2001, for the topical treatment of mild to moderate inflammatory acne. Finevin® will be the second azelaic acid product available on the US market.
HIV/AIDS	**Valganciclovir** *Valcyte®* Hoffmann-La Roche	The US FDA approved this drug in May 2001, for the treatment of cytomegalovirus (CMV) retinitis in AIDS patients.
Antibacterial Agent	**Dapsone** *Atrisone®/SMP®* Atrix Laboratories	An NDA was submitted to the US FDA in May 2001, for this potent antibiotic that is coupled with Atrix's proprietary drug delivery system, SMP®. This special system allows water insoluble drugs to be applied topically. Atrisone® is currently in a pivotal Phase III clinical trial for treatment of moderate to severe acne, and in Phase I proof of concept trials for treatment of itch associated with healing severe burn wounds.
Drug News		
Drug Warning	The US FDA issued a Public Health Advisory in May 2001, to announce labeling changes for Sporanox® (Itraconazole, Janssen Phramaceutica). These changes include a warning to physicians not to prescribe Sporanox® capsules to treat onychomycosis in patients who have a history of heart failure, including congestive heart failure (CHF). It further states that Tikosyn® (Dofetilide, Pfizer) an antiarrhythmic agent should not be taken in conjunction with itraconazole, and caution should be used when co-administering Sporanox® with calcium channel blockers. The antibiotic erythromycin was also added to the list of drugs that interact with Sporanox®.	
Drug Warning	The US FDA issued a Public Health Advisory in May 2001, to alert healthcare professionals that rare cases of serious liver problems have been associated with Sporanox® capsules (Itraconazole, Janssen Phramaceutica) and Lamisil® tablets (Terbinafine HCl, Novartis Pharmaceuticals). The new labeling recommends that that clinicians should obtain nail specimens for laboratory testing prior to prescribing either of these drugs for fungal nail infections. FDA concerns do not apply to topical Lamisil® products.	
Drug Recall	Two lots (#0000067143 and 0000067144) of a collegenase product (Santyl® Ointment, Abbott Laboratories) were recalled because these lots were found to exceed potency limits. This ointment is indicated for the treatment of debriding chronic dermal ulcers and severely burned areas.	
Leprosy	The World Health Organization (WHO) announced in May 2001, that the global prevalence of leprosy has been reduced by over 90% over the past 10 years. However, six countries, including Brazil, India, Madagascar, Mozambique, Myanmar, and Nepal still report elevated rates of this disease because leprosy services were not available in the more remote areas.	

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