Skin Therapy Letter ©

Volume 3 · Number 1 · 1997

EDITOR: STUART MADDIN

The Skin-Cap® Story

In a matter of months, consumer's word of mouth, presentations at scientific meetings and Internet hype result in spectacular sales for an unlabelled use of Skin-Cap®. This OTC product is eventually banned after the presence of a potent corticosteroid is suggested by the private sector and later confirmed by drug agencies.

Nothing quite like this has taken place in the modern era of dermatology. With all-powerful drug regulatory agencies, evidence based medicine and sophisticated, accurate drug assays, how could this saga take place?

Dr. Stuart Maddin, Editor

A Chronology of Events

Manufacture

Early 1980s

- Skin-Cap® developed by Cheminova Internacional S.A., Spain.
- Active ingredient is listed as zinc pyrithione and the labelled indication is *seborrheic dermatitis (dandruff).*

Marketing

- Marketed as an OTC in many countries. Patients treating their own psoriasis spread the word about good results and usage increases.

Mid 1990's

- In the USA, available from distributors through mail-order with *dandruff* as the labelled indication.

Early 1997

- ***Rumors of unlabelled corticosteroid present in Skin-Cap.®***

March, 1997

- **Preliminary results from a clinical trial** in progress at the University of Minnesota, presented at the AAD by Dr CE Crutchfield III, are reported widely generating much interest.
- Patient psoriasis self-help groups and discussion on the Internet fuel further interest in the product.

Mid 1997

- Skin-Cap is widely endorsed by some dermatologists after they witness improvement in patients' psoriasis.
- ***World-wide demand for Skin-Cap® reaches 1,000,000 units per month.***

Regulatory concerns

- Regulatory agencies in Spain, Austria, Belgium and the Netherlands express concern about the possibility that Skin-Cap® contains corticosteroids.

- Acting on concerns expressed by the National Psoriasis Foundation and others, the FDA in the USA and the HPB in Canada decide to investigate the formulation.

1st August, 1997

- At the AAD Summer meeting, Professor Mark Lebwohl, Mt. Sinai School of Medicine, announces that clobetasol proprionate was present in several units of Skin-Cap® tested.

- FDA detects "prescription" levels of clobetasol proprionate.

- Analysis at the Mayo Clinic and assays conducted independently in several other laboratories in North America detect the presence of corticosteroids in Skin-Cap®

4th August, 1997

- *Cheminova repeatedly deny that the US product contains steroid.* Most recent denial dated 4th August in a letter to the National Psoriasis Foundation.

Warnings and regulatory action

8th August, 1997

- FDA issues a warning about Skin-Cap® containing steroids and orders detention of shipments at all border entries.

- National Psoriasis Foundation issues a warning.

- AP, Reuters and other news agencies circulate the warnings and mentions appear in daily newspapers.

12th August, 1997

- AAD president circulates an alert to all members.

13th August, 1997

- Health Canada issues a warning and states that the Canadian distributor has voluntarily stopped sale of Skin-Cap® in Canada.

26th August, 1997

- Withdrawn in Belgium

September, 1997

- It is rumored that the 7-8 American distributors of Skin-Cap® are meeting to consider whether or not to start a class-action against Cheminova.

- Manufacturers of DermaZinc®, through a Florida distributor, are attempting to meet the needs of psoriatics unable to obtain Skin-Cap®.

Counter-claims

- Cheminova, still claiming that appropriate assay procedures will show that corticosteroids are not present, submits samples to an assay using a MALDI-TOF mass spectrophotometer located in Vancouver, Canada.
This test was positive for the presence of corticosteroid.

September 5th, 1997

- An independent laboratory (Michigan State University, Dept. of Biochemistry), using specified extraction techniques and Fast Atom Bombardment Mass Spectroscopy, is unable to detect clobetasol.

Continued on page 5

Photodynamic Therapy (PDT) in Dermatology: Sooner or Later?

Dr. Harvey Lui, Vancouver

Although PDT remains an investigational treatment modality in dermatology, several important areas of development may ultimately lead to official and practical acceptance of PDT for the skin. Indeed the skin is usually the first organ in which many of the newer second generation photosensitizers are evaluated.

The modern era of PDT began in the 1970s with the pioneering work by Dougherty et al at the Roswell Park Memorial Cancer Institute in Buffalo using hematoporphyrin derivative.[1] It is perhaps somewhat ironic that although the skin was the first organ in which PDT was systematically evaluated, as of mid 1997 the only official regulatory approvals for PDT are for the treatment of internal malignancies involving the lung, genitourinary system, and gastrointestinal tract using porfimer sodium (Photofrin®), the first generation photosensitizer.

For treating diseased tissue, PDT, like PUVA, involves the sequential administration of drug followed by light. However, PDT involves the photochemical generation of reactive singlet oxygen that interacts with tissue components, whereas PUVA's effects appear to depend more on reactions independent of O_2.

New photosensitizers

Persistent generalized cutaneous photosensitivity due to photosensitizer retention in the skin has been the main limitation of porfimer sodium, which is administered parenterally. This has led to the development of second generation photosensitizers, some of which appear to be cleared far more rapidly from the skin than porfimer sodium (Table). With topically active agents such as 5-aminolevulinic acid (5-ALA) and ATMPn, skin photosensitivity is restricted to areas of direct drug application. 5-ALA is unique in that it is actually a low molecular weight porphyrin precursor that is metabolized *in situ* within the skin to protoporphyrin IX, which possesses significant PDT activity.

Are lasers essential for PDT?

PDT has become synonymous with the use of porphyrins and lasers for treating skin cancer. While lasers are indispensable for delivering light to internal organs via fiberoptic endoscopy, they are relatively expensive and inefficient light sources for photosensitizer activation in the skin. The critical property for any PDT light source is that its spectral output provides sufficient power at an activation wavelength that is appropriate for the photosensitizer being used. *In the future, non-coherent, broad or narrow band light sources such as incandescent bulbs, arc lamps, fluorescent tubes, and light-emitting diodes may prove to be the light sources of choice for dermatologic PDT. These latter devices are usually cheaper to operate, more compact, and more effective for irradiating large surfaces than lasers.*

Does PDT work?

- *Skin cancer* Although the literature documents an extensive collective experience for PDT of skin cancer (reviewed in Reference 2) there is a dearth of either long term follow-up data (i.e. more than 2-5 years of reported follow up) or histologic evaluation of treated sites. Moreover, in dermatology, there is only one published, controlled trial of PDT. In treating Bowen's disease, the combination of ALA and a broad band lamp was felt to be as effective as cryotherapy, but with fewer adverse effects.[3] More studies such as this will be needed in order to more precisely define the role of PDT for skin cancer management.

Novel indications for PDT

- *Non-hypertrophic actinic keratoses of the face and scalp* In a vehicle-controlled study, topical ALA and red laser light have recently been shown to clear up to 91% of these keratoses.[4] Multicenter phase III studies of topical ALA for this indication are currently underway in the US.
- *Psoriasis* PDT has been shown to demonstrate significant immunomodulatory effects in animal models of arthritis.[5] Thus there is a rationale for using PDT in treating inflammatory disorders such as psoriasis. *One potential advantage of PDT over PUVA is that PDT may not be intrinsically carcinogenic.* Pilot studies have demonstrated clearing of psoriasis using topical[6] and systemic photosensitizers.[7]

- *Removal of unwanted terminal hair* Topical ALA selectively photosensitizes pilosebaceous structures and Grossman et al have used ALA-PDT to remove unwanted terminal hair with some degree of success.[8] How this modality will compare to the current generation of hair removal lasers will await controlled clinical studies.

If the potential therapeutic advantages of using PDT to treat actinic keratoses, non-melanoma skin cancers, psoriasis and hair removal continue to be demonstrated in clinical trials, Dermatologists would welcome PDT as an effective, safe and cheaper treatment alternative to current therapy, including lasers. Photodynamic therapy should no longer be looked upon as a procedure looking for a disease to treat.

Dr. Stuart Maddin, Editor

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Table: Photosensitizers for PDT

Photosensitizer	Status	Dermatologic Indications and Comments	Manufacturer
First generation			
Porfimer sodium (Photofrin)	Approved: *US, Canada, Netherlands, Japan, France, Germany*	• Approved for lung, bladder, esophageal and cervical cancer.	QLT Phototherapeutics
	Investigational	• In dermatology, porfimer sodium has been investigated for non-melanoma skin cancer, Kaposi's sarcoma, psoriasis and vascular malformations.	
Second generation			
BPD verteporfin (benzoporphyrin)	Investigational	Non-melanoma skin cancer, cutaneous metastases, psoriasis	QLT Phototherapeutics
SnET2	Investigational	Non-melanoma skin cancer, Kaposi's sarcoma, cutaneous metastases	PDT Inc.
NPe6	Investigational	Non-melanoma skin cancer, cutaneous metastases	Nippon Pharmaceuticals
mTHPC	Investigational	Clinical trials are ongoing.	Scotia Pharmaceuticals
Lutetium texaphyrin	Investigational	Melanoma and non-melanoma skin cancer	Pharmacyclics Inc.
ATMPn (porphycene)	Investigational	May possess significant topical activity	Glaxo-Wellcome
Photosensitizer precursor			
5-Aminolevulinic acid (Levulan)	Investigational	Actinic keratosis, non-melanoma skin cancer, mycosis fungoides, psoriasis, acne, hypertrichosis. Topical, oral, and parenteral activity.	DUSA Pharmaceuticals

Skin-Cap® *(continued from page 2)*

September 9th, 1997

- Cheminova International states that Skin-Cap® is once again allowed to be marketed in the Netherlands, that new batches have been dispatched to Germany, Holland, France and Italy, and the product is legal in all these markets.

With regard to the reintroduction of Skin-Cap® into the Netherlands, it should be understood that tests conducted at four different laboratories in the Netherlands DID show the presence of prescription amounts of steroids and the original formulation is not allowed to be marketed and sold there. A REFORMULATED product can be marketed if it does not contain steroids, and if the accompanying patient information leaflets make no medical claims about psoriasis. The reformulated product will be subjected to random testing for the presence of steroids.

Future

After reviewing the events that have unfolded, it is quite likely that in the future Skin-Cap® reformulated without corticosteroids, or similar products containing zinc pyrithione, will continue to be promoted for dandruff and/or psoriasis.

Dr. Stuart Maddin

The Internet Angle

Dermatology feels the influence of the Internet

Physicians treating AIDS patients are no strangers to the power of the Internet, but this is the first time that dermatologists have experienced such pressures.

1. A quick surf demonstrates intense interest and lively debate about Skin-Cap®.
2. A web-site (http://members.tripod.com/~saveskincap/) is spreading the message – *Save Skin-Cap®*! Psoriatic patients find the product effective and don't want any interruption in the availability of Skin-Cap®, regardless of whether steroids are present.
3. Advice is given on obtaining "cross border" supplies from Mexico.
4. As one would expect, rumours of a conspiracy between regulatory agencies, drug companies and the dermatologic establishment abound. The National Psoriasis Foundation is said to be influenced by heavy sponsorship from drug companies. Dermatologists are said to be trying to protect their income.

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Update on Drugs

Class	Name/Company	Approval Dates and Comments
Antipsoriatic	**Cyclosporine solution & capsules** Neoral® *Novartis*	Approved by the FDA June 19, 1997 for the treatment of severe recalcitrant psoriasis. Already approved in Canada and Europe. The previous formulation is being withdrawn.
Actinic keratosis	**Diclofenac gel 3%** Solarase® *Hyal*	British regulatory authorities have given conditional acceptance for the treatment of actinic keratosis. Hyal is presently awaiting approval for this indication in a number of other countries.
Artificial skin	Dermagraft® *Smith & Nephew*	Approved by the HPB in Canada August, 1997 as a human dermal replacement for the treatment of diabetic foot ulcers.
Laser system	**Er,Cr:Y laser system** Dermalase system® *Biolase Technology*	Approved by the FDA July, 1997. This laser system utilizes an air-water spray to cool the tissues during dermatologic and general surgical procedures.
Scars	**Silicon based device** SKAR CARE *Life Medical Sciences*	Approved by the FDA August, 1997 as an externally worn device for the management of hypertrophic & keloid scars.
Class	**Name/Company**	**Clinical Trial Outcome**
Male hair loss	**Finasteride 1 mg** Propecia® *Merck*	Results from an international Phase III, double-blind, placebo controlled trial found that finasteride stopped hair loss in 86% of the men treated and led to hair growth in half those treated. Loss of libido was reported in 1.8% of men.
Class	**Name/Company**	**New Formulation**
Anti-acne	**Adapalene cream 0.1%** Differin® *Galderma Canada*	This cream formulation was recently approved by the Canadian HPB for the topical treatment of acne. Gel and solution (both 0.1%) were approved by the FDA April, 1996. Adapalene is also approved in many other countries.
Class	**Name/Company**	**Drug Warning**
Antiseborrheic	**Zinc pyrithione** Skin-Cap® *Cheminova*	Some assays detect potent steroids (see Page 1). The FDA have issued a Stop & Detain order on all shipments and have been warning users, including psoriatics, of potential side effects.

Published six times yearly by International Skin Therapy Newsletter Inc., 835 West Tenth Avenue, Vancouver, British Columbia, Canada V5Z 4E8. Tel: (604) 874-6112. Fax: (604) 873-9919.
Annual subscription: Canadian $85 individual; $155 institutional (GST included). US $60 individual; $110 institutional. Outside North America: US$80 individual; $130 institutional. Quotes on multiple subscriptions and student rates supplied upon request.

Printed in Canada