Dermatological radiotherapy.
From the Florentine pioneers to an urbi et orbi message

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In this issue of the Giornale Italiano di Dermatologia e Venereologia you will find an interesting paper by Serena Percivalle et al. “Radiotherapy of cutaneous carcinomas of the eyelids: results in 88 lesions”.

Positive risk/benefit ratios of radiotherapy for skin tumours have been repeatedly reported by several authors 1-9 and by our group,10,11 by showing the high cure rates, the excellent safety profile and the outstanding cosmetic results mainly in areas (nose, eyelids, lips etc…) of relevant cosmetic concern.

Unfortunately, today cutaneous epithelial malignancies can be successfully treated with radiotherapy only in a very few of Italian dermatological departments, always with excellent results and at extremely low cost. This situation prompted us to give a contribution through some comments and reflections.

The first is: why is dermatologic radiotherapy disappearing and being often forgotten by dermatologists? Looking into the past, we will try to find interesting suggestions for the future of this branch of dermatology.

Historical reminiscence of the Florentine pioneers and their successors

In 1905 Celso Pellizzari, Professor of Dermatology, goes from Florence to London where he acquires 10 mg of Radium from W. Martindale and personally carries it back to Florence “enclosed in an ebanite box”. This radium is stored in the Istituto Fototerapico at the Orbatello Hospital which had been officially inaugurated on May 11, 1905 by Celso Pellizzari himself in the presence of the Town Council representatives and members of the Italian Royal Family (Figure 1). The official speech of Pellizzari, reported in extenso by the newspaper il Fieramosca of May 15, 1905 is touching: “Allorchè nei primi dell’anno decorso manifestammo l’idea di creare in Firenze un Istituto Fototerapico, poco mancò che fossimo tacciati di sognatori. E quando cominciai a darmi attorno per raccogliere le prime offerte, io sorpresi il sorriso del dubbio sulla riuscita del mio tentativo….[…]. Sembrava quasi che volessero dirmi: “O non riuscirai a costruirlo questo famoso stabilimento; o creerai un organismo embrionale, incapace di vita”. Gli argomenti detti o fatti capire erano sempre i medesimi. Come sperare di riuscire in una città piccola, povera, scettica come Firenze? Eppure non mi detti per vinto, perché io la conosco e la sento la mia Firenze!”.

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Professor Pellizzari in his inspired talk describes Florence with its virtues and vicious attitudes and focuses on the energy of light which means creation to him, healing and God. His enthusiasm is clear, and contagious!

In 1907 under his direction the Florence Istituto Fototerapico becomes the first in Italy to employ radium in contact therapy regularly.

In 1911 a revolutionary technique is used for the first time: the introduction of radium needles directly into the neoplastic tissue (interstitial therapy).

When in 1923 the stock of radium in the Istituto is more than 1 g, divided into 88 preparations, a second floor of the Istituto Fotoradioterapico entirely devoted to roentgenterapy and equipped with seven units for superficial and deep therapy and one diagnostic unit, is inaugurated.
We still work there, where a picture of Celso Pellizzari looks at us (Figures 2, 3).

On Christmas, December 25, 1925, Prof Celso Pellizzari dies. He had treated more than 4000 cases of malignant tumours with a sufficient follow-up to define the results as “positive”, according to the report of one of his late successors, Professor Carlo Vallecchi.12

Thus, Professor Jader Cappelli and Dr. Mario Scopesi carries on the activity of the Istituto amid the many difficulties of the World War II. When in 1950 Professor Scolari takes over the responsibility from Jader Cappelli, the stock of radium in the Istituto is 4 g.

On November 4, 1966 the Istituto is water-flooded by the river Arno with devastating effects: several hundreds of precious slides pertaining to clinical cases are lost, together with the historical documents originally signed by Marie Curie.

But the radium is safe!

In 1973 Professor Scolari dies and Professor Emiliano Panconesi starts a new fight, for dermatological radiotherapy which he would eventually win.

The Florence University School of Medicine, first in Italy, in fact introduces Dermatological Physiotherapy as an official part of the curriculum.

Professor Carlo Vallecchi takes over the responsibility of the Istituto Fotoradioterapico, which after some years, would change its name in Unità Operativa di Fisioterapia Dermatologica and would be directed by Professor Pietro Cappugi and, after a while, by one of us, Torello Lotti who is still, like all his predecessors, responsible for the section of Radiotherapy Unit directed by Dr. Piero Campolmi with the assistance of Cristina Izzap and Susanna Lombardi.

All activities are still carried out in that second floor of the Istituto proudly inaugurated in 1923 by Celso Pellizzari, and currently more than 1000 treatments per year are given with roentgentherapy.

A lesson from the past

The enthusiasm of the pioneers declined probably under the harsh criticisms of the International (and, less of the National) Scientific Communities which did not encourage enough the use of dermatological radiotherapy after evaluation of side effects related to its irrational use.

In 1989 the Italian General Review of Dermatology, edited by Emiliano Panconesi published a special issue entitled “Radiotherapy in Dermatology” guest edited by Carlo Vallecchi. The illuminating presentation written by Emiliano Panconesi 17 years ago is evocative of the declining interest of the Scientific Community toward dermatological radiotherapy.

“The science of radiation is a century old. Since the end of the 1960’s there has been an extreme paucity of serious incentives for researchers, who often were denied access to scientific data. Thus, this science has not yet answered many questions vital for radiotherapy. For example, we are still not able to establish exactly the acceptable thresholds and distance efforts of radiation and we are obliged to follow criteria of extreme caution, in all likelihood usually excessive, but in some cases insufficient. This state of relative ignorance leads in part to that particular psychological attitude of diffidence or distrust, and even fear, regarding radiotherapy. This attitude does not spare doctors, including dermatologists, and it leads to a condition of unjustified emargination and underestimation of this precious technique that is all too often used only as the last resort therapy of inoperable malignant tumors”.

A further comment by Emiliano Panconesi is even more explicit and bitter: “Unfortunately, the status of near emargination that has lasted for decades has taken its toll. Properly functioning centres for dermatological radiotherapy with modern, up-to-date equipment are few, and often only limited use is made of available structures because of diffidence and/or inadequately informed and trained doctors. In fact, even the teaching of the theoretical and practical aspects of this specific field is undermined by various lacunae, also in the field of dermatology”.

The future of dermatological radiotherapy. It is not dark yet ...

What is the situation, today? Was the enthusiasm of the pioneers misplaced? We can all agree that radiotherapy is painless, does not cause loss of blood and can be done in an office or out-patient clinic. Remarkable scientific advances have been made, and major technical improvements are evident in:

a) the use of strict dosimetric criteria, where the dosimetric reference is now the absorbed depth dose, expressed in Gy;

b) the abandoning of radium needles and contact radium in favour of artificial isotopes, dosimetrically reliable;

c) the use of radiotherapy after histological diagnosis, and for strictly selected cases.

Today dermatological radiotherapy can be and is a valid alternative to surgery mainly for subjects with
poor health or on anticoagulant therapy, and, generally, for those who refuse surgery but accept radiotherapy as a less stressful and invasive procedure. Age is also a critical parameter because of the potential carcinogenic effect of radiotherapy. Thus, it is inadvisable in subjects under 50 years of age. Definition of the histological type of the tumour is important, as well as tumour vascularity and oxygen supply (which can influence the response to radiotherapy).

After considering this, we all must agree that highly positive risk/benefit ratios of radiotherapy for skin tumours have been reported from all over the world, and therefore we all should continue to develop this branch of dermatology without prejudices or diffidence. Some practical suggestions from our group are listed here:

1) Radiotherapy can be chosen as treatment and offers advantages over other treatments.
2) Community fears regarding adverse effects need a special communication strategy.
3) Decommissioning or not replacing radiotherapy machines in departments needs a clear strategy.
4) Electron beam therapy is expanding while superficial radiotherapy has declined. We need a strategy for financing.
5) Excellent cosmetic outcome should to be outlined.
6) Reconsidering all previous statements after having evaluated the photodynamic therapy options (definition of the X-ray niche is mandatory) is necessary.
7) Discussing openly with general practitioners and other specialists the possible advantages of radiotherapy is mandatory.
8) Discussing within National and International Scientific Societies the current place and role of this treatment modality is necessary.
9) When appropriate principles are followed and precautions are taken, X-ray treatment is still a safe and most effective method.

In conclusion, we are thankful to Serena Percivalle et al. for their interesting report published in this issue of the Giornale Italiano di Dermatologia e Venereologia, not only for giving us the chance to indulge on our local Florentine Institute which would need better tools, but, mainly, for showing the world that the enthusiasm of the Florentine pioneers is not lost, and that our Italian Community, as stated by Serena Percivalle et al., is leading the scientific development in the field. An urbi et orbi message, which, we hope, will be of help to our discipline and to our patients.

References

Coelenterates (Cnidaria), also known as “sea nettles”, are marine invertebrates characterized by a symmetrical radial structure, a mouth that opens out of a single cavity (coelenteron) and a body membrane consisting of 2 layers of cells separated by an amorphous jelly-like substance. Despite the elegant and apparently inoffensive aspect, they hide microscopic weapons all over the body surface. The Coelenterate phylum predominates in tropical and subtropical seas and comprises at least 9000 species, with about 100 harmful to man. The species that are relevant in human pathology belong to the Scyphozoa, Anthozoa and Hydrozoa classes and share common mechanisms of offense against the prey.1-3 The body surface and tentacles of Coelenterates have thousands of microscopic organs, called cnidocytes or cnidoblasts, which contain venom-filled corpuscles called nematocysts. The contact with a foreign body, including human skin, stimulates an external receptor which causes the violent and prompt release of nematocysts from the cnidocyst. Nematocysts penetrate the skin and inject their toxins. This mechanism is used by Coelenterates not only for offensive purposes but also to ensure their nourishment, immobilizing their preys (e.g., fishes, crustaceans, molluscs). In fact, they are not capable of capturing the prey by means of mechanical devices, as they live either attached to the sea-bed (anemones) or free-floating in the sea (jellyfish).

Nematocysts vary greatly in size, shape of the corpuscle and length and morphology of the filament contained into the corpuscle, according to the different species. The process of penetration into the victim’s body has been studied with electron microscopy, although the precise mechanisms responsible for the release of nematocysts and invagination of the filament are still obscure. It has been hypothesized that the toxins present into the nematocysts are injected through the filament or alternatively that the filament itself contains the toxins. The study of nematocysts of Coelenterates is particularly complex and represents a fundamental step for the analysis of jellyfish toxins. The meticulous study of Kokelj et al., published in this issue, provides important findings about the identification of nematocysts of Rhizostoma pulmo by means of optic and scanning electron microscopy. It is worthy to mention that this study...
led to the discovery of 2 novel types of nematocysts never described so far.

In addition to mechanical stimuli, specific chemical stimuli are also needed for the expulsion of nematocysts. Several types of biologically active toxic substances are contained in the nematocysts and only few of these have been identified. Various substances with a low molecular weight have been isolated in the nematocysts of Coelenterates, including tetramethylammonium, adenine, γ-butyrobetaine, histamine and its releasers, imidazol-acetic acid and 5-hydroxytryptamine. The substances with a low molecular weight have pharmacological properties but are not harmful in the concentrations usually present in the organules. Tetramine, histamine and 5-hydroxytryptamine contribute to the development of skin burning, erythema and oedema. Particular species of venomous Coelenterates may also contain peptides and proteins with haemolytic, myotoxic, cardiotoxic, neurotoxic or dermonecrotic properties.

Some of the cytotoxic and cytolytic effects are mediated by damage to the cell membranes, secondary to mitochondrial alterations. Some species contain protease inhibitors or exhibit phospholipase activity. Highly poisonous Coelenterates live among the coral barriers of the Pacific and the Caribbean and belong to the Zoantharia family and the genus Palythoa. Palytoxin is the most poisonous biotoxin in the animal world, consisting of a very long carbon chain with no repetitive units, and a high content of methyl and hydroxyl groups. The toxin exerts its action on the cardiovascular system and especially on the coronary arteries: at the cellular level it increases permeability to sodium and hence induces depolymerization of the cytoplasmic membrane.

Skin reactions due to contact with nematocysts are of variable type and severity, depending on the surface of the area stung and the toxicity of the poison. Symptoms vary from a slight pricking sensation to pain, itching and intense burning. Objective signs are generally of erythematous-oedematous type and present with more or less bizarre appearance.

Diffuse urticarial reactions up to anaphylaxis can also develop; the risk of shock and fatal outcome is increased in children and extremely sensitive subjects.

**Reactions to jellyfish**

Jellyfish species are widespread in all the seas and are the most common cause of diseases induced by marine animals. In the Mediterranean sea, there are 11 species of jellyfish, 6 of which are harmful to man. Among these, *Pelagia noctiluca*, well known to be toxic to the skin, is a phosphorescent Coelenterate that lives in deep waters and is very common in the Mediterranean sea, especially in the eastern areas. The skin symptoms induced by this Coelenterate are urticarial, painful local lesions that usually last 1-2 weeks. Extensive local reactions and systemic symptoms, up to anaphylactic shock, are possible but appear to be exceptional. Other Mediterranean jellyfishes which were previously considered harmless have been found to be responsible for contact dermatitis. This is the case of *Rhizostoma pulmo*, which was investigated in the paper of Kokelj et al. presented in this issue. In comparison with jellyfish coming from the Atlantic, the Pacific and those along the Australian coasts, the Mediterranean jellyfish are in any case less toxic and only exceptionally induce severe or fatal reactions. The migration of jellyfishes from the oceans into the Mediterranean sea, especially the west coasts, is, however, a possible event. Jellyfish poison consists of polypeptides and enzymes with toxic and antigenic properties so that both toxic and immunological mechanisms have been implicated in the clinical manifestations caused by jellyfish. Immune mechanisms include either umoral or cellular responses. Toxic reactions are observed in all subjects after any exposure, and are dose-dependent. Instead, allergic reactions develop only in sensitized subjects, in a dose-independent manner, with possible cross-reactions to jellyfish of different species.

The toxins include various enzymes, compounds of quaternary ammonium, catecholamines, proteins, 5-hydroxytryptamine, histamine, histamine-releasing substances, serotonin and quinine-like products. These substances cause erythema and oedema in acute reactions and contribute to the onset of pain and itching.

**Local reactions**

Contact of the skin or mucosa with a jellyfish induces immediate local pain, lasting 30 min to 24 h, which is immediately followed by linear skin eruptions of variable shape. These are urticarial lesions whose colour turns rapidly from pale to red. The lesions have a variable duration, usually of minutes or hours, but sometimes persist much longer according to the intensity of the skin damage. Lesions can also be vesicular, blistering, intensely oedematous, haemorrhagic and necrotizing and may be associated with local asymmetri-
cal excessive sweating or local lymphadenopathy. Contact with the eyes can induce an array of ophtalmological signs, that are usually transient. However, persistent mydriasis (with duration of several months) and permanent sequelae (anterior synechiae, unilateral glaucoma) have been described.

IgE-mediated angioedema, diffuse urticaria, persistent delayed granulomatous reaction and reactions at distant sites have been sporadically observed. Delayed recurrences are possible at time intervals ranging from a few days to several months without additional causal contact with the jellyfish. These recurrent eruptions are considered to be of an allergic nature in view of the increase in specific immunoglobulins which can persist for many years. Contact dermatitis to the tentacles or nematocysts of Coelenterates is an infrequent but possible observation, that can be confirmed by patch test.

Indirect source of jellyfish-induced dermatitis is the release of nematocysts into the aquatic environment or the release of antigenic substances which can induce sensitisation in swimmers even without any contact with the nematocysts.

The local outcome of jellyfish-provoked dermatitis may be represented by cheloids, postinflammatory dyschromia, scarring, subcutaneous atrophy, gangrene, contracture, impairment of peripheral nerves.

Systemic reactions

Skin reactions are sometimes accompanied by toxic systemic symptoms such as malaise, weakness, ataxia, vertigo, cramps and muscular spasm, paraesthesia, nausea and vomiting, slight hyperpyrexia.

Fatal reactions may be caused by anaphylaxis and especially toxicity and are mostly reported in the South-East Pacific area, where highly poisonous jellyfishes live. Causes of death are cardiac arrest, respiratory failure or more rarely renal failure.² ⁴

Irukandji syndrome,⁵ originally described in Australia and caused by Carukia barnesi, is characterized by generalised pain, nausea, vomiting, distress, hypertension and may lead to cardiac arrhythmia and other signs related to catecholamine excess.

Reactions to sea anemones

The Actiniariae (sea anemones) belong the Anthozoa class and all species have nematocysts.¹ The most frequent species in our seas is Anemonia sulcata, common in shallow waters and up to depths of 10 m; younger examples can frequently be found in pools and under the tide-line where they cover the submerged rocks. Studies of the tentacles of sea anemones have led to the discovery of anaphylaxis and the identification of the active pharmacological substances hypotoxin (responsible for somnolence followed by respiratory paralysis), thalaxin (a substance capable of causing skin wheals and cardiac arrest) and congestin (with anaphylactic properties and apt to induce vomiting, diarrhoea and gastrointestinal bleeding). Polypeptides with paralysing properties have also been isolated from various species.

Although well recognised, dermatitis caused by sea anemones have been reported less frequently than those due to jellyfish.² ³ Local reactions are most commonly toxic, and generally characterized by more marked symptoms than those due to local reactions to jellyfish. Lesions are much more extensive, assuming very bizarre arabesque-like pictures. Morphologically, in addition to the erythematous-oedematous aspect, the lesions are more often vesicular or blistering and sometimes necrotizing. The oedema is often very pronounced. Lesions last from 15 days to 20-30 days and are accompanied by local pain and burning and sometimes intolerable and systemic reactions, such as malaise, weakness and muscular cramps. Dyschromic or scarring sequelae are frequent. Fatal reactions have never been reported.

One of the most common reactions to sea anemones is dermatitis from Sagartia elegans, also known as sponge fishermen’s disease.³ Sagartidae are very common Coelenterates that live symbiotically at the base of sponges, and can be found from Iceland right down to the southern Mediterranean. During the manipulation of sponges and the subsequent contact with Sagartia’s tentacles, immediate burning and itching sensations develop, which are followed by intense erythema and blisters. Multiple abscesses and ulcers may complicate the clinical picture. Systemic symptoms are possible and comprise headache, nausea, vomiting, fever, shivering, muscular spasm and collapse.

Sea bather’s eruption

This eruption has been attributed to the exposition to the larvae of Cnidaria (jellyfish, Portuguese Man-of-
war, sea anemones, hydroids and corals).6, 7 It is thought
that nematocysts discharge toxins as the larvae get
trapped in the swimsuit. Further toxins can be released
when the bather rinses in fresh water. It has periodically
been reported in Florida, Cuba, the Caribbean and
Mexico.

The activities preceding the sea bather’s eruption
include swimming and less frequently underwater div-
ing, surfing and boating. Clinical signs may be imme-
diate but usually have a latency of some hours (mean,
12 h). Itching is generally intense and is sometimes
associated with malaise, fatigue, fever, shivering,
headache, nausea, coughing, abdominal pain and diar-
rhoea.

Skin manifestations consist of multiple erythema-
tous papules, that sometimes evolved into pustules
or blisters, predominant in covered skin areas, espe-
cially under the swimming costume and in the skin
folds. A few patients present with urticarial lesions or
regional adenopathy. The eruption last from 1 to 4
weeks.

Reactions to Physaliae

Physaliae are floating bluish-purple jellyfish that
belong to the Hydrozoa class and usually live in the
tropical regions of the Pacific, Atlantic and Indian
Ocean. In recent years, a large number of Physaliae
have been seen on the Mediterranean coasts due to
the changes of environmental conditions which have
favoured their migration and development. The most
representative species is Physalia physalis (present in
the tropical Atlantic and the Mediterranean), com-
monly known as the sea caravel or Portuguese Man-o’-
war.1, 8 Physalia cnidocysts can penetrate the skin of the
palms even through rubber gloves. The venom they
contain is a protein complex which is very labile and
has weak antigenic properties, a slight necrotizing
action, cardiotoxic activity and a fatal neuromyotox-
ic activity. After contact, the poison is rapidly inject-
ed into the tissues and provokes what is commonly
called the “physalic syndrome”.2, 3

Subjective symptoms are an extremely violent pain
and intense burning sensation. The objective picture
is characterized by erythematous-oedematous linear
lesions; vesicles and blisters can develop. An urticar-
ial eruption can sometimes follow. Other signs include
anxiety, lipothymia, muscle pain, breathlessness, nau-
sea, vomiting, weakness, bradycardia and hypothermia,
ocular problems. In our latitudes, coma is a rare late
complication but it is common in the tropical zones. In
benign cases the skin lesions resolve after a few hours
leaving hyperpigmented or scarred areas.

Reactions to hydroids

Hydroids (Hydrozoa class) form colonies on many
rocks and on the tips of corals and resemble other ani-
mal and plants attached to hard surfaces. They live in
tropical and subtropical waters and, after contact, may
induce immediate urticarial eruption or haemorrhag-
ic, papulous or zoster-like reaction after some hours,
associated with systemic symptoms.3

Reactions to corals

The order of corals (Scleractinia) belongs to the
Anthozoa class. Corals can provoke skin lesions of
various types. Because of the variety of plant and ani-
mal species found on coral reefs, envenomation usu-
ally involves toxins from multiple sources. Toxic con-
tact reaction are relatively infrequent and generally
fairly mild, although the frequency of irritant contact
reactions can be underestimated.

In comparison with the toxins in coral nematocysts
that are not very harmful to man, those of “stinging or
fire corals” of the Millepora genus (Milleporina order
of the Hydrozoa class) are much more serious. The
main clinical manifestations attributed to their nema-
tocysts are: erythema with associated itching, contact
urticaria, eczema, vesiculo-bullous eruptions and lichenoid
and granulomatous lesions. Sometimes several differ-
ent clinical pictures can be observed in succession in the
same patient. In exceptional cases, generalized symp-
toms such as fever and nausea can be observed.

Instead, lacerations from corals are very frequent:
despite their fragile appearance, hard corals have very
sharp, cutting surfaces. These wounds rapidly evolve
into painful ulcers and unless they are promptly and
appropriately treated, into cellulitis. These wounds
heal very slowly.9

Diagnosis, prognosis and treatment

The correct management of Coelenterate enveno-
mation begins with a correct clinical diagnosis and
the identification of the etiologic agent. Overall, the clinical diagnosis is not particularly difficult, although the possible onset of cutaneous and/or systemic symptoms, even without direct contact with a Coelenterate, should be consider.

To identify subjects at high risk, tests apt to detect specific IgE against Coelenterate toxins have been developed. Specific IgE can be formed after repeated exposure to these animals; significant levels of circulating antibodies can persist for several years and immunoglobulins directed to antigens of one species can cross-react with those from other species.3

In serum of affected patients, specific IgG blocking antibodies with putative protective properties have also been documented. The presence of increased levels of specific IgE in the absence of IgG blocking antibodies may be a marker of an extremely high susceptibility.

There are no definitive and safe preventive measures against Coelenterate poisoning. In Australia and the USA, where the risk of severe and fatal reactions is a real problem, special protective wetsuits are produced in order to minimize the severity of the damage. Instead, the use of barrier creams and mechanical barriers have not been found to be effective.4

The development of specific antiserum implies the identification of all the toxins of the various Coelenterate species, but unfortunately this preventive tool is available only for sporadic species.3

Therefore, treatment of reactions is mainly symptomatic. To alleviate the symptoms of Coelenterate stings, old remedies are still useful, such as vinegar (5% acetic acid in water), ammonia, urine, formaldehyde, potassium permanganate crystals, warm water, Coca-Cola and ice.2, 3, 10

The following recommendations should be kept in mind when treating these conditions. It is absolutely essential to avoid using freshwater as this is hypotonic and can cause the nematocysts to burst. For the same reason, the subject must not shower until the toxins have been completely neutralized. Instead, the affected skin areas can be gently washed with sea water without any risk.

The use of alcohol is still controversial, considering that in vitro evidences showed an enhanced nematocyst bursting, whereas some experiences have described its use as useful. Anyway, perfumes, after-shave lotions and ethanol must not be used, as in some cases they prolong the agony. As an alternative to vinegar and ammonia, the proteolytic enzymes of meat (papain) can be used. The use of a formalin solution stop the nematocysts from bursting more effectively than ammonia and vinegar. Salt water heated to the limit of the patient’s tolerance contributes to neutralize the poison. Even sodium bicarbonate and alkaline solutions can neutralize the toxins; in some cases sun lotions have been found to help.

The skin must not be rubbed to remove sand, again to prevent the nematocysts from bursting.

To remove the tentacles, thick gloves must be used, or a paste made with salt water and sodium bicarbonate left on for a few minutes. The use of talcum powder of flour or of dry sand can have the same effect, causing agglomeration of the tentacles that can then be removed with sharp tool. Afterwards, the affected skin area can be carefully washed with sea water.

Topical treatment is based on topical corticosteroids and anaesthetics (e.g., 5% lidocaine) to relieve itching and burning sensations. Instead, in case of eye involvement, only topical steroids should be used.

In particularly severe cases, especially in children, a haemostatic rubber tourniquet can be used if a limb has been affected.3 For systemic treatment, antihistamines and corticosteroids are very useful, as well as cardiotonics. States of shock must be treated with epinephrine, together with systemic corticosteroids. Cramps can be treated by intravenous calcium gluconate, while a combination of aspirin, codeine and phenacetin help to alleviate acute pain.

Necrotic and ulcerative lesions must be cleansed 3 times a day and treated with topical antibiotics (erythromycin, tetracycline). These antibiotics can also be used systemically in cases of secondary infections or involvement of vast skin areas.

The doctor and first aid workers must be aware that nematocysts that have been detached from the tentacles can maintain their toxic action for several months. For this reason, bathers must avoid areas infested with Coelenterates, especially after a storm.

References

Radiotherapy of cutaneous carcinomas of the eyelids: results in 88 lesions

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Aim. The treatment of skin carcinomas of the eyelids is still an open question: the objective is to link radical therapy to the conservation of the physiological functions and an adequate esthetic result. To prove the consistency with this objective, we performed a retrospective study on a series of cases enrolled during the period 1976-2004 and treated with radiotherapy.

Methods. A total of 85 patients suffering from 88 epithelial neoplastic lesions of the eyelids were treated with radiotherapy: 48 patients were females, 37 males, aged 38 to 89 years (mean age 71.07). The 88 lesions treated were 86 basal cell carcinomas, 1 squamous cell carcinoma e 1 metatypic carcinoma. Radiotherapy was delivered by contact X-ray therapy (CXRT) according to Chaoul, using a cup-shaped internal eye shield made of an alloy of lead, zinc and nickel to avoid lens damage. The total doses administered ranged from 40 to 65 Gy.

Results. Complete remission was achieved in 86 lesions (97.72%), and 2 basal cell carcinomas relapsed marginally (2.28%). The 5-year cure-rate from the end of radiotherapy (evaluated according to the life-table method) was 96.72%. So far, neither complications nor sequelae to the radiological treatment have been observed.

Conclusions. The excellent therapeutic and esthetic results obtained in this series of patients treated with radiotherapy confirm the reports of the literature and support the choice of dermatological radiotherapy in the treatment of cutaneous carcinomas of the eyelids.

Key Words: Radiotherapy - Eyelids - Basal cell carcinoma - Squamous cell carcinoma.

Most of primary malignant neoplasms of the eyelids are epithelial forms (basal and squamous cell carcinomas). Roughly 10% of basal-cell carcinomas of the face involve the palpebral region,1 most often the lower lid. Squamous cell carcinomas, on the other hand, are much less common and generally affect the upper lid. The eyelids represents, for their anatomical constitution, a difficult area to treat: in fact, the objectives of the treatment are not only to obtain radical results, but also the preservation of the physiological functions and a satisfying esthetic result. The therapeutical management of the epithelial neoplasms is multi-disciplinary, involving the ability of different specialists (dermatologist, plastic surgeon, oculist, radiotherapist). For all these reasons, the therapeutical
approach to epithelial neoplasms of the eyelids represents an open question and the results of further case series can be useful to underline the real efficacy of the various available treatments. Therefore, we think to be interesting to report our nearly thirty-year experience about radiotherapy of these neoplasms.

Materials and methods

A retrospective study was performed on a series of 85 patients affected by 88 carcinomas of the eyelids, treated by radiotherapy in the period 1976-2004 (Table I). They represent 1.66% of 5124 patients affected by primitive skin carcinomas irradiated in the same period. All patients underwent a biopsy for histopathological investigation or a scraping for cytologic assessment, when the clinical type of the lesion made it possible (Tables II, III). Furthermore, the lesions were classified according to TNM classification (Table IV). The location of the irradiated lesions is reported in Table V. Sixteen cases were relapsing after other treatments: 13 after surgery (12 central relapses, 1 marginal); 1 lesion underwent 11 operations, another lesion 3, 3 lesions underwent 2 operations and 8 lesions 1 operation. One lesion relapsed centrally after laser therapy, another lesion relapsed centrally after laser therapy and surgery and another after electrodessication. In 4 cases there was an incomplete surgical removal. Radiotherapy was delivered in all cases by means of contact X-ray therapy (CXRT) according to Chaoul. The technical data of radiotherapy are indicated in Table VI. The quality of the radiation and the size of irradiation fields were chosen on the basis of size and degree of infiltration of the neoplasm. The size of irradiation fields was always wide enough to include an adequate skin margin (0.5 cm) around the neoplastic lesion. The total doses administered ranged from 40 to 65 Gy (40 Gy in 3 lesions, 45 Gy in 3 lesions, 50 Gy in 16 lesions, 55 Gy in 52 lesions, 60 Gy in 13 lesions, 65 Gy in 1 lesion). Because of the voltage used in CXRT, a single dose of 2 Gy or doses of 4

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<td>Sex</td>
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<td>Age</td>
<td>Years</td>
</tr>
<tr>
<td>Mean age</td>
<td>71.07</td>
</tr>
<tr>
<td>Range</td>
<td>38-89</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Table II.—Histotype.</th>
<th></th>
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<tbody>
<tr>
<td>Histotype</td>
<td>No. of lesions</td>
</tr>
<tr>
<td>Basal cell carcinoma</td>
<td>86</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>1</td>
</tr>
<tr>
<td>Metatypic carcinoma</td>
<td>1</td>
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<table>
<thead>
<tr>
<th>Table III.—Clinical characteristics.</th>
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<tbody>
<tr>
<td>Clinical characteristics</td>
<td>No. of lesions</td>
</tr>
<tr>
<td>Nodulo-ulcerative</td>
<td>35</td>
</tr>
<tr>
<td>Nodular</td>
<td>32</td>
</tr>
<tr>
<td>Ulcerative</td>
<td>8</td>
</tr>
<tr>
<td>Papulo-nodular</td>
<td>7</td>
</tr>
<tr>
<td>Flat</td>
<td>6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table IV.—TNM classification.</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>TNM classification</td>
<td>No. of lesions</td>
</tr>
<tr>
<td>T1N0M0</td>
<td>62</td>
</tr>
<tr>
<td>T2N0M0</td>
<td>17</td>
</tr>
<tr>
<td>T3N0M0</td>
<td>9</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table V.—Site of irradiated lesions.</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Site</td>
<td>No. of lesions</td>
</tr>
<tr>
<td>Right eye</td>
<td>48</td>
</tr>
<tr>
<td>Left eye</td>
<td>40</td>
</tr>
<tr>
<td>Lower lid</td>
<td>64</td>
</tr>
<tr>
<td>Upper lid</td>
<td>18</td>
</tr>
<tr>
<td>Medial canthus (upper and lower eyelids)</td>
<td>4 (2)</td>
</tr>
<tr>
<td>Lateral canthus (upper and lower eyelids)</td>
<td>2 (1)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table VI.—Technical data of radiotherapy.</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Technical data</td>
<td>Voltage</td>
</tr>
<tr>
<td>Amperage</td>
<td>4-6 mA</td>
</tr>
<tr>
<td>Focus-skin distance</td>
<td>1.5-3 cm</td>
</tr>
<tr>
<td>Half-value-depth</td>
<td>2-12 mm</td>
</tr>
<tr>
<td>Size of irradiation fields</td>
<td>1-4.5 cm</td>
</tr>
<tr>
<td>Dose per fraction</td>
<td>5 Gy</td>
</tr>
<tr>
<td>Fractionation</td>
<td>Twice a week</td>
</tr>
<tr>
<td>Total dose</td>
<td>40-65 Gy</td>
</tr>
<tr>
<td>Shielding</td>
<td>Cup-shaped internal eye shield</td>
</tr>
</tbody>
</table>

kV=kilovolt. mA=milliampère. Gy=Gray.
Gy, fractionated over a period of 1-3 months, invariably cause the lens to cloud.\textsuperscript{3, 4} Since a cancericidal dose administered to a neoplastic lesion of the eyelid necessarily delivers enough radiation to the lens to cause radiation cataract, the use of an internal eye shield is indispensable. Using such shields, we first carried out a series of dosimetric tests utilizing a tissue-equivalent phantom and LIF thermoluminescence microdetectors.\textsuperscript{5} The results of this study demonstrated that the doses delivered in correspondence to the lens with eye shields are appreciably lower than the doses capable of inducing cataract. In all the patients of this series we used cup-shaped eye shields made of an alloy of lead, zinc and nickel. They are easily inserted in the conjunctival sac following instillation of a few drops of anesthetic solution and are removed at the end of radiotherapy session. The smooth surface of the shields precludes any possibility of corneal abrasion. The follow-up was planned so as to perform 2 clinical examinations in a year (one every 6 months) for 5 years after the end of radiotherapy and once a year after the first 5 years. Furthermore, annual ocular examinations were performed. Data were processed by means of Microsoft Excel 2003. Cure-rate was evaluated according to the life-table method.\textsuperscript{6}

**Results**

The mean follow-up time of the whole series of patients was 44.26 months (range 1-372 months). The percentage of relapse-free patients is reported in Figure 1. In particular, the cure-rate 60 months after the end of radiotherapy was 96.72%. Eighty-six lesions out of 88 (97.72%) got complete remission; 2 basal-cell carcinomas relapsed marginally (2.28%), respectively 8 and 12 months after the end of therapy. Both the lesions relapsed marginally, so that it was possible to perform CXRT again, shielding the area corresponding to the previous irradiation; we obtained a complete remission lasting for 24 and 72 months, respectively. The cosmetic results, with the exclusion of the relapsed 2 lesions, were considered as good in 70 lesions (79.54%), acceptable in 17 lesions (19.32%) and not acceptable in the remaining lesion (1.14%).

We considered as good the cases characterized by no visible radiation injury, as acceptable those characterized by mild dystrophy and/or mild dyschromia, and as not acceptable those with severe skin dystrophy and/or marked dyschromia and presence of numerous telangectasias. Obviously, in all cases there was a permanent loss of eyelashes of the irradiated area. The functional result was excellent in all the patients of the series (cases of entropion, ectropion or obliteration of lacrimal duct never occurred). As yet, neither complications nor sequelae to the radiotherapy have been observed (Table VII, Figures 2, 3).

**Discussion and conclusions**

In the treatment of skin carcinomas of the eyelids the choice among the available therapeutic possibilities (surgical excision, electrodessication, cryosurgery, chemosurgery, radiotherapy) must be carried out attentively evaluating the neoplasm location and size, the age of the patient and his general condition and previous possible treatments. Radiotherapy has some very advantageous characteristics for the patient: it is a non-aggressive and painless method, that can be performed in an outpatient practice, also on patients with

![Figure 1.—Cure-rate of 88 cutaneous carcinomas of eyelids after contact X-ray therapy.](image-url)
Radiotherapy of cutaneous carcinomas of the eyelids: different contraindications to surgery. This supports the choice of this method especially in the treatment of elderly patients. As for its costs, if equipment of dermatological radiotherapy is used, they are very limited. The excellent results obtained in this series of patients, due to a long experience on this subject, 2 (5-year cure-rate from the end of radiotherapy 96.72%), successful results in the 2 relapsed lesions obtained with a new course of radiotherapy, functional results good in 100% of the lesions, cosmetic results good or acceptable in 98.86% of the lesions, lack of complications and/or sequelae) are in the mean of the data published in the literature 8-11 and confirm that radiotherapy is a very effective and sure therapeutical option in the treatment of cutaneous carcinomas of the eyelids. In our opinion, and in that of other authors, 12 there is a particular indication to prefer the use of radiotherapy (that doesn’t cause a loss of tissue) in lesions over the lacrimal duct, at the internal canthus and at the eyelid margins, in order to prevent the possible damages of a surgical excision. Furthermore, kilovoltage X-rays and in particular CXRT, that is very suitable to perform, are in our experience and in that of other authors 13 to prefer to electrons in the treatment of these neoplasms: this for the easiness of shielding, for the unnecessary complicated working to make the ionizing radiation beam superficial and for the lower cost of treatments.

Another important fact emerged from the study is the lack of damages (leukoplakia) 14 to the palpebral and tarsal conjunctiva induced by the use of internal eye shields; in fact, as we demonstrated during the execution of experimental dosimetry, 5 back-scattering from the eye shields was found to be lower than 10%.

In conclusion, the results of our experience support the use of dermatological radiotherapy in the treatment of cutaneous carcinomas of the eyelids, conducted utilizing machines dedicated to skin diseases and using the appropriate eye shields to protect crystalline lens.

Riassunto

Radioterapia dei carcinomi cutanei palpebrali: risultati in 88 lesioni


Metodi. Sono stati sottoposti a radioterapia 85 pazienti portatori di 88 lesioni neoplastiche epiteliali delle palpebre; 48 pazienti erano di sesso femminile, 37 di sesso maschile, con un’età media di 71.07 anni (range 38-89 anni). Le 88 lesioni trattate comprendevano 86 carcinomi a cellule basali, 1 carcinoma a cellule squamose e 1 carcinoma metatipico. La radioterapia è stata effettuata mediante plesiorontgentherapia (Chaoul), utilizzando uno schermo sottopalpebrale “a conchiglia” costituito di piombo, zinco e nichel al fine di evitare danni al cristallino. La dose totale somministrata è stata compresa tra 40 e 65 Gy.
Risultati. Si è ottenuta remissione completa in 86 lesioni (97,72%), mentre in 2 si è avuta recidiva marginale (2,28%). Il cure-rate a 5 anni dal termine della radioterapia (calcolato con il metodo delle tabelle di sopravvivenza) è stato del 96,72%. Non sono state finora osservate complicazioni e sequelle dovute al trattamento radiologico.

Conclusioni. Gli eccellenti risultati terapeutici ed estetici ottenuti nella serie di pazienti irradiati confermano i dati della letteratura e supportano la scelta della radioterapia dermatologica nel trattamento dei carcinomi cutanei palpebrali.

Parole chiave: Radioterapia - Palpebre - Carcinoma basocellulare - Carcinoma squamocellulare.

References

Adverse drug reactions: dermatological experience

F. AYALA, G. FABBROCINI, F. BARTIROMO, E. BARBERIO, O. RESCIGNO, L. DI SIMONE, C. CAPASSO

**Aim.** Adverse drug reaction (ADR) monitoring is useful tool for the determination of the negative side effects of drugs from the ethical and practical points of view. It is also a guide to their safest and most efficient use with the aim of improving the quality of healthcare. In addition to their effect on human health, ADRs also impact significantly on healthcare costs. Since ADRs present most frequently with cutaneous signs and symptoms, patients are often referred to dermatologists, who thus come to play a fundamental role in the detection and diagnosis of these reactions, as well as in patient management.

**Methods.** Epidemiological data of 649 patients admitted to the Department of Dermatology of University of Naples Federico II for suspect ADRs were examined.

**Results.** Amongst the ADR identified in our cases, the most frequently observed cutaneous and extracutaneous manifestations were urticaria-angioedema (62%), maculopapular rash (21.4%), loss of consciousness (4.2%), dyspnea (3.7%), anaphylactic shock (2.5%), nausea (1.8%), itching (1.5%), stomatitis (1.1%), Stevens-Johnson’s syndrome (0.6%), epistaxis (0.3%), erythema nodosum (0.3%), fixed eruption (0.3%), paraesthesia (0.3%), Stevens-Johnson’s syndrome (0.6%), paraesthesia (0.3%), epistaxis (0.3%). ADRs were more often triggered by the following therapeutic categories: antibiotic agents (45%), antipyretic and analgesic drugs (23%), non steroidal anti-inflammatory drugs (23%).

**Conclusion.** The widespread use of these drugs justifies the importance of drug-surveillance activity, aimed at decreasing the negative effects of liberal drug use and at increasing their safety.

**Key words:** Pharmaceutical Preparations, adverse effects - Skin - Drug response.

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within 2–8 weeks after drug administration. Serum sickness-like reaction, which is most frequently seen after 7–14 days of drug exposure, is characterized by fever, cutaneous eruption and arthralgias. Delayed reactions (such as drug induced lupus) can occur 1–2 years after the onset of administration of medication.

Anticonvulsants, sulphonamides, antibiotics, allopurinol, and dapsone are the most frequent causative drugs.2 Among hospitalized patients, the incidence of these reactions ranges from 1% through 3%, but the frequency of cutaneous reactions to specific drugs may exceed 10%.3 Australia’s current ADRs reporting rate of over 12 000 reports per year places it in the top few nations in terms of per capita reports.4

Different symptoms and time of eruption can characterize ADRs to other drugs, such as Stevens-Johnson’s syndrome and toxic epidermal necrolysis associated with the use of antiretroviral medication in AIDS patients.5 Drug response is best understood as a complex interplay between pharmacokinetics, pharmacodynamics, and other disease-associated factors. ADRs are common, but only 6% through 10% are immunologically mediated. Allergic drug reactions are often unpredictable. Whereas some drug-induced allergic reactions may be easily classified into one of the four classical Gell and Coombs’ hypersensitivity categories, many others appearing to have an immunologic component cannot be classified because there is lack of evidence 5 of their actions mechanism.6 There is a large number of genetic variants in the enzymes of phase I and phase II drug metabolism, in drug transporters, and drug targets, all of which account for differences in drug response. The polymorphisms in the cytochrome P450 enzyme system have been investigated most extensively. Genotype-based dose adjustment, which should ensure “bioequivalent” drug concentrations in all patients, has been derived from pharmacokinetic parameters, but this approach will be validated in prospective studies. Drug transport has recently been recognized as a further crucial determinant in pharmacokinetics.7

In addition to their impact on human health, ADRs have a significant impact on healthcare costs, too. These costs are essentially hospital costs, due to a longer hospitalization time caused by ADRs. It has been recently estimated that the occurrence of an ADR during hospitalization or leading to hospitalization costs approximately € 2 800. Because of the substantial annual estimated cost of ADRs in industrialized countries, it is necessary to implement preventive programs. Different strategies have been proposed: educational programs, identification of risk groups, implementation of good drug practice, and clinical and laboratory moni-
ADVERSE DRUG REACTIONS: DERMATOLOGICAL EXPERIENCE

AYALA

Monitoring of ADRs. Promotion of pharmacoeconomic studies and cooperation between clinicians, medical pharmacologists and pharmacists seem to be key factors for preventing ADRs and decreasing their costs.8

As ADRs are most frequently associated with cutaneous signs and symptoms, patients often refer to a dermatologist, whose crucial role in diagnosis, treatment and subsequent patient management is widely recognized.

The aim of our study was to review patients hospitalized in the Department of Dermatology of University of Naples Federico II for suspected ADRs from an epidemiological point of view.

Materials and methods

The study was performed on 649 patients, who came for drug eruption consultation at the Department of Dermatology, University of Naples Federico II, from January 2001 through May 2002. Medical histories and physical examinations were always performed by a dermatologist.

In any case where a definitive diagnosis could not be made on the basis of history and clinical signs and symptoms, histopathological examination of a skin biopsy was performed to confirm the diagnosis. Patch tests were done in some patients with maculopapular rash, fixed drug eruption and acute generalized exanthematous pustulosis. Informed consent was obtained.

All patients with a history of cutaneous ADRs were included. All reports of interactions were evaluated for clinical effect, clinical significance, and quality of evidence.

Statistical analysis

Both a descriptive analysis and an association study carried out by means of a two statistical software package (SPAD and SPSS) were done on this group. (χ² test was performed first; it was followed by multiple correspondence analysis, in order to identify a possible statistically significant association between variables considered in patients.

Variables considered in the multiple correspondence analysis were sex, age-range (0-15; 16-35; 36-55), therapeutic agent involved in ADR and ADR typologies, paying particular attention to cutaneous signs.

Data were analysed through bivariated analysis and multiple correspondence analysis, which is at present the best known method of multidimensional treatment of qualitative data. Multiple correspondences analysis is a multivariate statistical method that relates subjects manifesting conformity, presenting a reference plan through proximity measures. All analyses were elaborated by Windows SPSS.10 and SPAD.3 statistical programs.

Results

ADRs account for between 2% and 6% of hospital admissions and may limit the physicians in the administration of some necessary therapeutic agents. Among our patients 424 out of 649 were female (65.3%) and 225 (34.7%) were male. Regarding ADR distribution, with respect to age range and sex, females were more numerous in all age groups except for the first group (0-15).

Amongst ADRs identified in our cases, the most frequently observed cutaneous and extracutaneous manifestations were urticaria-angioedema (62%), maculopapular rash (21.4%), loss of consciousness (4.2%), dyspnea (3.7%), anaphylactic shock (2.5%), nausea (1.8%), itching (1.5%), stomatitis (1.1%), Stevens-Johnson’s syndrome (0.6%), paraesthesia (0.3%), erythema nodosum (0.3%), fixed eruption (0.3%), epistaxis (0.3%) (Figure 1).
Discussion

Exanthema and urticaria are the most common cutaneous reactions observed and the eruptions were most frequent in women and in patients in their forties or older generations. In our study the agents most responsible for ADR were antimicrobial agents (45%), non steroidal anti-inflammatory drugs (NSAID) (28%) and antipyretic and analgesic drugs (23%) (Figure 2).

The \( \chi^2 \) test did not show any statistically significant relationship between sex and the kind of adverse reaction, nor between sex and class of drug suspected to be involved.

On the contrary, multiple correspondence analysis (MCA) showed significant differences between the kind of drug and kind of ADR. Urticaria-anigoedema, the most frequent cutaneous manifestation, was equally distributed between the two sexes and more specifically involved some therapeutic categories (general antimicrobials for systemic use and anaesthetics).

Naldi et al., in a study conducted in 4 Italian regions, showed that there is a female/male ratio of 1.58, the female group, compared to males, showed higher frequency for severe drug reactions such as anaphylactic shock and lipothymia; the male group showed a major prevalence of itching, skin rash and gastroenteric disorders without severe consequences. Therefore, females seemed to be particularly affected by severe adverse reactions, although, few cases of severe reactions were registered in our study.

In this study, the drugs most frequently responsible for ADR were those most widely used in clinical practice (antibiotics, NSAID, antipyretics and analgesics). This, once again, confirms the importance of drug-surveillance, aimed at decreasing the negative side effects of liberal drugs use and increasing their safety.

Riassunto

Reazioni avverse a farmaci: esperienza dermatologica

Obiettivo. Il monitoraggio delle reazioni avverse ai farmaci (ADRs) è abitualmente effettuato per determinare l’entità degli effetti collaterali di alcuni farmaci sia dal punto di vista etico che pratico. Tale monitoraggio risulta essere poi una guida per un utilizzo più sicuro ed efficiente dei farmaci con lo scopo di migliorarne la qualità terapeutica. Oltre alle considerazioni medico-legali di tali reazioni avverse, non è da trascurare l’impatto significativo sulla spesa sanitaria. Poiché le ADRs si manifestano frequentemente con segni e sintomi cutanei, i pazienti si rivolgono spesso ai dermatologi, che rivestono perciò un ruolo fondamentale nell’identificazione e nella diagnosi di queste reazioni, così come nella gestione di tale paziente.

Metodi. Sono stati analizzati i dati epidemiologici di 649 pazienti afferenti al Dipartimento di Dermatologia dell’Università di Napoli Federico II, con sospetta diagnosi di ADRs.

Risultati. Tra le ADRs identificate nella nostra casistica, le manifestazioni cutanee ed extracutanee più frequentemente osservate sono state orticaria-anigoedema (62%), rash maculopapuloso (21,4%), perdità di coscienza (4,2%), dispnea (3,7%), shock anafilattico (2,5%), nausea (1,8%), stomatite (1,1%), sindrome di Stevens-Johnson (0,6%), parestesia (0,35%), eritema nodoso (0,3%), eritema fissare (0,3%), epistassi (0,3%).

Le ADRs sono più spesso causate dalle seguenti categorie terapeutiche: agenti antibiotici (45%), farmaci antipiretici ed analgesici (23%), farmaci antinfiammatori non steroidei (28%).

Conclusioni. Il largo utilizzo di questi farmaci giustifica l’importanza dell’attività di farmaco-vigilanza, finalizzata alla diminuzione degli effetti negativi dovuti all’ampio utilizzo di questi farmaci e all’aumento della loro sicurezza.

Parole chiave: Reazione avversa al farmaco - Eruzione cutanea - Risposta al farmaco.

References

Video-capillaroscopic aspect in different sites and types of psoriasis

P. ROSINA, A. GIOVANNINI, M. R. ZAMPERETTI, C. CHIREGATO, A. BARBA

Aim. Video-capillaroscopy is a non invasive technique used for the direct observation of the cutaneous superficial capillary microcirculation. In psoriasis this method shows specific capillary alterations (pattern) comparable to histopathologic modifications.

Methods. We performed optical probe capillaroscopy (VIDEOCAP), at 100× and 200× magnification, on 40 patients affected by different types of psoriasis (guttate, nummular, patchy, palm-plantar and inverted) and we analyzed lesions in different cutaneous sites (scalp, trunk, limbs, palm, sole, folds).

Results. All lesions show a typical pattern with altered dilated and tortuous capillary-loops that appear with a characteristic clew form. In addition, the mean number of capillaries per mm² is 22,7 (16-32) and the mean diameter of the clew is 76 µm (45-140). These aspects are the same in every type and site of psoriasis.

Conclusion. In conclusion, psoriasis has a constant capillaroscopic pattern in all its types and cutaneous sites.

Key Words: Capillaroscopy - Psoriasis, diagnosis - Psoriasis, therapy.

In 1992 optical probe videocapillaroscopy was introduced. This is an instrumental, non invasive method to analyze all cutaneous peripheral microcirculation morpho-functionally, using an optical fiber probe connected to a microvideotelecamera.1

Psoriasis is a chronic relapsing inflammatory disease that involves the cutaneous microcirculation. Histological examination shows thickened epidermal strata and the papillary dermis shows elongated (extended) papillae with very broad, dilated capillaries.2

Recent studies have shown that immunological, inflammatory and microcirculatory alterations in psoriasis, are present in genetically predisposed patients.3 In the pathogenesis of psoriasis, endothelial cells show specific receptors for the adhesion of lymphocytes. This mechanism produces T lymphocytes and macrophage infiltration through the endothelia, and keratinocyte hyperproliferation.3

Some authors have already described a specific video-capillaroscopic pattern of psoriasis in plaques as bush or clew capillaries.2,3

The aim of our study is to use video-capillaroscopy to evaluate if all clinical types and sites of psoriasis show a different or identical capillaroscopic pattern.
Materials and methods

Patients

In our study, 40 patients affected by different types and cutaneous sites of psoriasis were examined (27 male, 13 female). Mean age was 49 years (range 16-80); 38 were European, 1 Indian and 1 Nigerian. All patients received an accurate dermatological examination and a capillaroscopic evaluation of the psoriatic lesions with video-capillaroscopy. All capillaroscopic images of each district explored were analyzed measuring capillary bush diameter and number of capillary loops per square millimeter (loop density) with differing type and site of psoriasis.

Videocapillaroscopy was performed in patients without any specific topical therapy for 1 month. Beside these patients were not affected by collagenopathy, diabetes and were not treated with vasodilatory drugs.

Optical probe videocapillaroscopy (VPC)

We used an optical probe videocapillaroscopy (Videocap 200) that consists of a main unit, an optical fiber probe with video-optical terminal, contact and no-contact lenses, and a high resolution color TV microcamera.

The main unit consists of a cold quartz-iodine light source, emitted by a 150 watt lamp equipped with a device controlling light intensity both automatically and manually (according to the magnification used); a video signal processing unit, equipped with an automatic/manual blank tuning device on a standard reference blank.

The optical fiber probe with video-optical terminal consists of a 1.5 m long flexible cable containing the flexible type of light (wavelengths); a cable connecting the video signal processing unit, contained in the main unit, and the CCD high resolution color TV microcamera.

The main unit consists of a cold quartz-iodine light source, emitted by a 150 watt lamp equipped with a device controlling light intensity both automatically and manually (according to the magnification used); a video signal processing unit, equipped with an automatic/manual blank tuning device on a standard reference blank.

The optical fiber probe with video-optical terminal consists of a 1.5 m long flexible cable containing the flexible type of light (wavelengths); a cable connecting the video signal processing unit, contained in the main unit, and the CCD high resolution color TV microcamera.

The video-optical terminal, there is a micro focusing system. (The need for focusing is reduced).

Each objective is equipped with a series of devices such as sterilizable plexiglas dome shaped.

Video-capillaroscopic probe was performed applying a drop of cedar oil to improve skin translucency and so capillary visibility.

We first removed the psoriatic scales with a lancet or with topic salicylic vaseline 5% for 5-7 days. Disinfectants were not used, respecting functional alterations of the microcirculation.

Patients rested in a supine position during examination and they didn’t smoke in the last hour before, so as not to cause microcirculatory alterations.

Results

At capillaroscopic examination, all analyzed psoriatic lesions, independently of the type of psoriasis (patchy, nummular, guttate, inverted and palm-plantar) and of the localization (trunk, arms, scalp, palms, soles, flexures), present a homogeneous pattern with tortuous and dilated capillaries (appearing as a bush or a clew) and a completely disarranged microangiarchitecture. The capillary loops have the same morphology in all lesion extension.

The mean density of capillaries per mm² was 22.7 (range: 16-32, Standard Deviation [DS]=4) with no differences between male and female (M=23, F=22) and the mean diameter of the capillary bush was 76 µm (range: 45-110, DS=18) with slight differences depending on sex (M=79, F=70). Both the mean density and capillary diameter show some differences according to sites and types of psoriasis (Tables I, II).

Discussion

Optical probe capillaroscopy (VCSO) is a recent and improved technique compared with classical capillaroscopy and permits evaluation of every affected cutaneous microcirculation site. For example, psoriasis can be evaluated with this technique because in it the microcirculation is modified.

Until a few years ago, only nailfold capillaroscopy studies were performed in arthropathic psoriasis. In the literature, there are contrasting opinions about the results: Bushan nail-fold capillaroscopic study showed that in arthropathic psoriasis, there is a reduction in capillary density and in capillary dimensions, but it is not confirmed if this result is compared with the control group. In other studies periungueal capillaroscopy showed a specific pattern with smaller capillary loops and with tortuosity (clew appearance). Many authors with this technique looked for a particular periungueal pattern in psoriasis, particularly in arthropatic psoriasis, but they did not succeed in finding a specific pat-
tern, giving us contrasting data where the existence of this one is confirmed and denied by different authors.4

The activation of T lymphocytes plays an important role in triggering and/or perpetuating the disease which is believed to be autoimmune.10, 11

Microcirculation involvement is important in the pathogenesis of psoriasis and for capillaroscopy utilization.

Controversies still exist about the role of angiogenesis in the development of psoriatic lesions.

Bacharach-Blues showed that loop capillary elongation is not due to neoangiogenesis, but to a capillary alteration.12

Bull showed that capillary density (number of capillaries) in psoriatic plaque is not increased compared with normal surrounding skin,13 at least up to 2 cm around.

Other authors formerly stated that there was neoangiogenesis.14

The clinical forms of psoriasis that have been examined are absolutely typical. The usefulness of the observation may therefore appear limited. Our aim, before any possible use of differential diagnosis, has been to evaluate the reproducibility of the capillaroscopic pattern in different types and localizations of psoriasis.

In our study, we analyzed 40 patients with different types (guttate, nummular, patchy, palm-plantar and inverted) and sites (trunk, arms, scalp, palms, soles, flexures) of psoriasis and the results showed that capillaroscopic modifications are equivalent and homogeneous in different type and localizations of this disease: the capillary lesions are always like a clew. The pericapillar area shows a “flou” area due to an increase of interstitial capillary permeability (oedema).

For the parameters evaluated (mean diameter of clew and capillary density), differentiated by types and sites of psoriasis, no differences were seen. Only the sole and fold sites showed differences perhaps due to a higher or lower epidermal thickness that probably modifies the vision of the capillary loops falsifying the data of capillary diameters.

**Conclusions**

In conclusion, we observed that in psoriasis there is always a specific videocapillaroscopic pattern and a complete disarranged microangiarchitecture present in all clinically analyzed types and sites.

Videocapillaroscopy is a useful, easily executable, non-invasive technique, which makes it possible to diagnose the disease and follow-up psoriasis during treatment.

**Table I.—Sites and types of psoriasis.**

<table>
<thead>
<tr>
<th>Psoriasis</th>
<th>Type</th>
<th>Scalp</th>
<th>Trunk</th>
<th>Arms</th>
<th>Palms</th>
<th>Soles</th>
<th>Inverted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guttate</td>
<td>12</td>
<td>2</td>
<td>4</td>
<td>6</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Patchy</td>
<td>29</td>
<td>12</td>
<td>5</td>
<td>12</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Nummular</td>
<td>8</td>
<td>5</td>
<td>1</td>
<td>2</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Palm-plantar</td>
<td>8</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>5</td>
<td>3</td>
<td>—</td>
</tr>
<tr>
<td>Inverted</td>
<td>9</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>9</td>
</tr>
<tr>
<td><strong>Tot</strong></td>
<td>40</td>
<td>66</td>
<td>19</td>
<td>10</td>
<td>20</td>
<td>5</td>
<td>3</td>
</tr>
</tbody>
</table>

**Table II.—Capillary clew’s diameter and capillary density differing by types and sites of psoriasis.**

<table>
<thead>
<tr>
<th>Types and sites</th>
<th>Diameter (µm)</th>
<th>Density (mm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guttate</td>
<td>81.4</td>
<td>21.1</td>
</tr>
<tr>
<td>Nummular</td>
<td>75.3</td>
<td>22.1</td>
</tr>
<tr>
<td>Patchy</td>
<td>74.5</td>
<td>23.8</td>
</tr>
<tr>
<td>Palm-plantar</td>
<td>69.7</td>
<td>23.2</td>
</tr>
<tr>
<td>Inverted</td>
<td>87.7</td>
<td>24</td>
</tr>
<tr>
<td>Scalp</td>
<td>73.7</td>
<td>24.4</td>
</tr>
<tr>
<td>Trunk</td>
<td>80.1</td>
<td>22.3</td>
</tr>
<tr>
<td>Arms</td>
<td>75.3</td>
<td>22.9</td>
</tr>
<tr>
<td>Palmar</td>
<td>73.6</td>
<td>22.2</td>
</tr>
<tr>
<td>Plantar</td>
<td>63.3</td>
<td>24</td>
</tr>
<tr>
<td>Flexures</td>
<td>87.7</td>
<td>24</td>
</tr>
<tr>
<td><strong>Total mean</strong></td>
<td>76</td>
<td>22.7</td>
</tr>
</tbody>
</table>

**Riassunto**

Aspetti video-capillaroscopici nelle diverse sedi e tipologie di psoriasi

Obiettivo. La capillaroscopia è una metodica strumentale non invasiva con cui è possibile valutare il microcircolo...
cutaneo che nella psoriasi presenta notevoli alterazioni già evidenziate da altri autori a livello istopatologico.

**Metodi.** Abbiamo eseguito la videocapillaroscopia a sonda ottica (VIDEOCAP), con ingrandimenti 100X e 200X, su 40 pazienti affetti da diversi tipi di psoriasi (guttata, nummulare, in chiazze, palmo-plantare ed invertita), ed abbiamo analizzato lesioni in diverse sedi cutanee (capillizio, tronco, arti, palmare e plantare, pieghe).

**Risultati.** Tutte le lesioni considerate presentano sempre un pattern omogeneo, con morfologia costante delle anse capillari tortuose e dilatate (con aspetto a gomitolo o a cespu- glio) e con sconvolgimento della microangiotettonica regionale indipendentemente dalla sede e dal tipo di psoriasi. Inoltre il numero medio dei capillari per mm$^2$ è 22,7 (range: 16-32) ed il diametro medio del gomitolo è 76 µm (range: 45-110); entrambi questi aspetti risultano sostanzialmente indipendenti dalla variante clinica della psoriasi e dalla sede della lesione.

**Conclusioni.** In conclusione la psoriasi, nelle sue diverse sedi e tipologie, presenta un pattern capillaroscopico costante.

**PAROLE CHIAVE:** Capillaroscopia - Psoriasi, diagnosi - Psoriasi, terapia.

**References**


An analysis of the different nematocysts of the jellyfish *Rhizostoma pulmo* by means of scanning electron microscopy

F. KOKELJ 1, M. AVIAN 2, E. MARTINELLI 1, S. SARTINI 2, G. TREVISAN 1

Aim. *Rhizostoma pulmo* is a jellyfish very common along the Mediterranean Sea coasts, that can cause mild dermatitis to bathers. It has a simple structure with a dome-shaped umbrella and 8 oral arms. The tentacles contain the nematocysts in which the toxins are present. Till now the toxins of this jellyfish have not been completely identified but their hemolytic and cytotoxic activity has been reported.

Methods. In the present study we analyzed, by means of optic and scanning electron microscope, the nematocysts of some specimens of *Rhizostoma pulmo* from the Gulf of Trieste. Pieces of marginal lappets and mouth-arms were excised from freshly caught specimens and immersed, separately, in cold distilled water, left to macerate and then homogenized; the resulting suspension was filtered and centrifuged and then frozen.

Results. We identified 3 different types of nematocysts, isolated from *Rhizostoma pulmo*’s marginal lobes and oral arms: olotrichous isorhiza haploneme, eterotrichous microbasic eurytele, atrichous isorhiza haploneme; the last two types are described for the first time in this paper. The microscopic analysis has made it possible to prove the presence of different concentrations of toxins in these 3 types.

Conclusion. These data will allow more focused chemical and toxicological studies in the future in order to improve our knowledge in this field.

Key Words: Jellifish - Nematocyst - *Rhizostoma pulmo* - Toxin.

Dermotoxicity from jellyfish is a world-wide problem that affects in particular fishermen and bathers. *Rhizostoma pulmo* is often found in the Mediterranean Sea and, to a lesser extent, along the Atlantic coast, in the Black Sea and the North Sea. It belongs to the Cnidaria phylum, Scyphozoa class.

It has a simple structure, with a dome-shaped umbrella with different colours and 8 oral arms with tentacle-like projections. The diameter ranges from 20-40 mm in the smaller specimens to 50-60 mm in the larger ones.

The possibility that *Rhizostoma pulmo* causes contact dermatitis has been discovered only in the last few years; since then several studies have been undertaken to investigate its toxicity: these studies, based on cells cultivated in vitro, demonstrated a hemolytic and cytotoxic activity of the *R. pulmo* toxins. The aim of this study is to identify the morphology and the distribution of the different types of the nematocysts of this jellyfish as a first step for a better knowledge of the toxicological properties of this marine animal.

Materials and methods

Freshly caught specimens of *Rhizostoma pulmo* from the Gulf of Trieste, Italy, were used for the mor-
phological examination of the nematocysts (Figure 1). Pieces of marginal lappets and mouth-arms were excised from freshly caught specimens and immersed, separately, in cold distilled water (0-4 °C). The samples were left to macerate for 2 h, then homogenized in the distilled water for 30 min at 0-4 °C with a magnetic stirrer. The resulting suspension was filtered through a plankton net of 0.5 mm mesh in order to discard their mesogleal component, and then it was centrifuged at 1 100 rpm for 15 min in a Sorvall RC5C refrigerated centrifuge set at 0 °C. The supernatant was discarded and the pellet was resuspended in seawater sterilized by filtering through a 0.42 µm filter. Centrifugation and resuspension were repeated twice. The final suspension was stored in Eppendorf vials and frozen. The discharge of nematocysts was obtained by the addition of 1.0 M potassium iodide, 1.0 M sodium citrate or 1.0 M sodium isothiocyanate. Unfixed nematocysts were photomicrographed using a microscope supplied with Nomarski interference contrast optics (Olympus BX50 photomicroscope), before and after discharge. Samples examined with the scanning electron microscope were fixed for 2 h 30 min at 0-4 °C in 2.5% w/v glutaraldehyde buffered with 0.1 M cacodylate buffer at pH 7.2, with 0.36 M NaCl and 3 mM CaCl\_2 added for osmotic balance, then washed 3 times for 15 min at 0-4 °C in a washing solution containing 0.1 M cacodylate buffer at pH 7.2, with 0.5 M NaCl and 3 mM CaCl\_2. Samples were then postfixed for 1 h at 0-4 °C in 1% w/v OsO\_4 in 0.1 M cacodylate buffer at pH 7.2, with 0.49 M NaCl and 3 mM CaCl\_2. After 2 washes in the washing solution and one in distilled water, the samples were dehydrated in an ascending series of ethanol solutions, then critical-point dried with CO\_2, mounted on stubs, coated with a gold-palladium film, and observed under a LEICA Cambridge Stereoscan 430i scanning electron microscope.

**Results**

The study of the nematocysts, isolated from *Rhizostoma pulmo*’s marginal lobes and oral arms, has lead to the identification of 3 types of nematocysts: holotrichous isorhiza haploneme, euterotrichous microbasic eurytele, atrichous isorhiza haploneme, the last 2 types are described here for the first time.

**Holotrichous isorhiza haploneme**

The loaded nematocyst has an oval shape, 3-4×2-2.5 µ long. The everted tubule has a short proximal shaft, 1.6-1.8 µ long, without spines; the remaining part is loaded with 3 series of elliptical small spines (Figure 2).

**Euterotrichus microbasic eurytele**

The loaded nematocyst has an elliptical capsule, 4-5 µ long with a percolate opening, disk shaped in apical position. The in-turned tubule is well visible at the optical microscope; it surrounds the shaft, situated along the capsule’s major axis, with numerous spirals. The unloaded nematocyst has a slightly enlarged distal shaft; it has 3 series of elliptical spines, 1-1.6 µ
long, and the remaining tubule is armed with 3 series of smaller spines. During the preparation for SEM we observed that most of the unloaded nematocysts have partially or totally lost their spines (Figure 3).

*Attrichous isorhiza haploneme*

This is a new type of nematocyst that has never been recognized till now.

The loaded capsule has an oval-spherical variable shape, 3-3.5×2-3 µ long.

The unloaded capsule has an isodiametric tubule, totally spineless (Figure 4).

**Discussion and conclusions**

*Rhizostoma pulmo* is a very common jellyfish found along the coasts of the Mediterranean Sea, where it usually appears in small groups in Spring and Summer.

In the past, *Rhizostoma pulmo* was not included in the toxic Coelenterate phylum: it was considered harmless so as to be handled without risk while observation by fishermen and bathers reported its offensive nature. In the last years we observed and reported several toxic reactions due to this common jellyfish. The more frequent clinical picture, especially in adults, is characterized by a burning sensation on the areas of contact. Contact dermatitis can occasionally occur, with a slight erythema that spontaneously disappears. More seldom, urticaria-like reactions occur with reddening and swelling.

In the past Cleland et al. described a burning feeling in the waters where these jellyfish were found, that seems to be caused by the release of thousands of nematocysts in the adjacent area. This phenomenon is also well known in the Adriatic Sea.

There is also another clinical aspect related to the presence of *Rhizostoma pulmo*. Von Zeyneck describes “rinorrea” reactions after manipulation of dried jellyfish. Similarly, Krumbach states that sensitive subjects cannot stay in a room where *Rhizostoma pulmo* is dissectioned (this occurred also to Avian; personal communication, 1984).

The toxic properties of *Rhizostoma pulmo* are not entirely known. Like other classes of dermotoxic Coelenterate, *Rhizostoma pulmo* has microscopic organelles called nematocysts in which toxins are contained. The contact of the jellyfish with a foreign surface, like human skin, determines the stimulus of a specific external receptor, with a consequent violent release of nematocysts. After penetrating the skin, the nematocysts pour their toxins in it.

The data in the literature show that toxins in *Rhizostoma pulmo* present a fraction with cytotoxic and emolistic activities.

The chemical profile of only one toxin is known, corresponding to a protein, called “rhizolisina”, with a molecular weight of 260 000 Da, probably composed of 3 subunits and an overall structure stretched over an axial ratio of 1:5.

Given these considerations, the aim of our study has been to improve the “toxicological” knowledge
of this jellyfish, very popular in our sea. The purification of nematocysts, a difficult and laborious procedure, has allowed us to identify 3 distinct types of nematocysts, 2 of which, the eterotrichus microbasic eurytele and the holotrichous isorhiza haploneme have been isolated for the first time.

The microscopic analysis has made it possible to define the morphometric parameters and the precise collocation of the 3 types of nematocysts and to prove the presence of a different concentration of toxins within them.

These data, and particularly those on the *Rhizostoma pulmo*’s components in which the toxins are best represented, will allow more focused, future “chemical and toxicological studies”, thus expanding the knowledge of this jellyfish, once thought to be harmless.

Riassunto

Analisi al microscopio elettronico a scansione delle nematocisti della medusa *Rhizostoma pulmo*

**Obiettivo.** *Rhizostoma pulmo* è una medusa molto comune lungo le coste del Mar Mediterraneo, che può causare dermatiti di moderata entità ai bagnanti. Questa medusa ha una struttura semplice caratterizzata da un corpo a forma di ombrello e 8 braccia oralì; all’interno dei tentacoli sono contenute le nematocisti e le rispettive tossine. Benchè le tossine di questa medusa non siano ancora state completamente caratterizzate, è stata dimostrata la loro attività emolitica e citotossica.

**Metodi.** In questo studio presentiamo l’analisi effettuata con il microscopio elettronico a scansione delle nematocisti ottenute da alcuni esemplari di *Rhizostoma pulmo*, raccolti nel Golfo di Trieste. I tentacoli e le braccia oralì sono stati recisi e poi immersi, separatamente, in acqua distillata, lasciati a macerare e quindi omogeneizzati; la sospensione ottenuta è stata filtrata e centrifugata e quindi congelata.

**Risultati.** Abbiamo identificato 3 diversi tipi di nematocisti, isolati dai lobi marginali e dalle braccia oralì di *Rhizostoma pulmo*: olotrichous isoriza haploneme, eterotrichous microbasic eurytele, atrichous isoriza haploneme (gli ultimi 2 sono descritti per la prima volta). L’analisi microscopica ha reso possibile dimostrare la presenza di differenti concentrazioni di tossine al loro interno.

**Conclusioni.** Questi dati possono rappresentare la base per ulteriori studi chimici e tossicologici delle diverse tossine e approfondire le nostre conoscenze in questo campo.

**Parole chiave:** Medusa - Nematocisti - *Rhizostoma pulmo* - Tossina.

**References**

Efficacy and tolerability of terbinafine in children

M. PAU, N. ASTE, N. ASTE

**Aim.** Dermatomycoses in children are very frequent and often require systemic treatment. We report our experience on the efficacy and tolerability of terbinafine in a group of children.

**Methods.** Fifty children between 2 and 14 years of age, 22 of whom suffering from *tinea capitis* and 28 from *tinea corporis*, widespread and/or with hair involvement, were treated with terbinafine. Doses employed were 62.5 mg/day in patients weighing less than 20 kg, 125 mg/day between 20 and 40 kg, 250 mg/day in patients weighing more than 40 kg. Treatment periods ranged between 2 and 12 weeks based on clinical symptoms. Clinical and mycological tests were performed at weekly intervals in children affected by *tinea corporis* and every 2 weeks in those with *tinea capitis* for the whole period of treatment and 4 weeks after the end of treatment.

**Results.** Overall clinical and mycological recovery was achieved in 45 children (or 90% of cases): 18 cases of *tinea capitis* and 27 of *tinea corporis*. In patients affected by tinea capitis from *Microsporum canis* treatment duration was 12 weeks and healing was achieved in 16 cases out of 20. In the 2 children with *tinea capitis* from *Tricophyton mentagrophytes*, healing was achieved after 6 weeks’ treatment.

**Conclusion.** Terbinafine is a highly effective drug for the treatment of skin fungal infections in children. As regards *tinea capitis* from *Microsporum canis* additional studies are needed to better standardize dosage and treatment cycles.

**KEY WORDS:** Dermatomycosis - Child - Terbinafine - *Tinea capitis* - *Tinea corporis*.

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Terbinafine is an allylamine antifungal compound. For many years it has been used, with excellent results, to treat adult dermatomycoses. On the other hand, data on its use in pediatric age fungal infections of the skin are somewhat scarce, also as a result of the fact that authorization of its use with children is relatively recent. The majority of studies concerned cases of *tinea capitis* and showed that forms caused by *Tricophyton* respond better to treatment compared to *Microsporum* cases.

The purpose of this study was to verify the efficacy and tolerability of terbinafine in dermatophyte infections in children.

**Materials and methods**

We used terbinafine to treat 50 children suffering from dermatomycosis, 28 males and 22 females, aged between 2 and 14 years. Twenty-two children were suffering from *tinea capitis*, 26 from *tinea corporis* and/or faciei with hair involvement, 2 from widespread *tinea corporis*. Duration of the complaint varied from 15 days to 6 months. Clinical diagnosis was confirmed by direct microscopic examination and by cultures on Sabouraud medium. Identification of the fungi was based on the macro- and micromorphology of the cul-
tures. None of the patients had taken any topical and/or systemic treatment for at least 1 month. Terbinafine was administered at daily doses of 62.5 mg in children weighing less than 20 kg, 125 mg in those weighing between 20 and 40 kg and 250 mg in patients weighing more than 40 kg, for a period ranging from 2 to 12 weeks, according to clinical form and mycological diagnosis. No local treatment was applied. Clinical and mycological checks were performed at weekly intervals on children affected by *tinea corporis* and every 2 weeks on those with *tinea capitis* for the whole period of treatment, and for 4 weeks afterwards. Blood chemistry text and urinalysis were performed at the start and at the end of the treatment cycle. All patients were followed-up at 3 and 6 months.

### Results

Results are shown in Table I. In the 20 children suffering from *tinea capitis* caused by *Microsporum canis*, terbinafine was administered for a maximum period of 12 weeks and the fungal infection was cured in 16 (80%) patients after 10-16 weeks. In 2 children with *tinea capitis* caused by *Tricophyton mentagrophytes* healing was achieved after 6 weeks’ treatment. In the group of children suffering from *tinea corporis* and/or faciei with hair involvement we isolated *Microsporum canis* in 23 cases and *Tricophyton mentagrophytes* in 3. Treatment with terbinafine was carried out for 4 weeks and clinical and mycological healing was achieved in 25 (96%) patients. The single case in which healing was not achieved belonged to the group infected by *Microsporum canis*.

In 2 children with widespread *tinea corporis* we isolated *Microsporum canis* and cure was achieved after 2 weeks’ treatment.

Overall, clinical and mycological cure was achieved in 45 (90%) patients: 18 cases of *tinea capitis* and 27 of *tinea corporis* and/or faciei. In no cases did we observe relapses. Tolerability in all cases was excellent. Only 2 (4%) children complained of gastrointestinal problems, which did not however warrant suspension of the therapy.

### Discussion and conclusions

In our study, terbinafine proved to be an extremely effective drug in the treatment of *tinea capitis* and *tinea corporis* in a pediatric population. *Tinea capitis* caused by *Microsporum canis* can be challenging to cure since data available in the literature show that often the healing rate is not high. Dragos et al. reported that in a group of 22 children affected by *tinea capitis* due to *Microsporum canis*, treated with terbinafine for 6 weeks, none was cured at the end of the treatment cycle. Baleviciene et al. reported that they treated 36 children with *tinea capitis* due to *Microsporum canis* with terbinafine, for 4-8 weeks and at the 12th week 44% of patients had not healed. On the contrary, numerous studies on the use of terbinafine to treat *tinea capitis* caused by *Tricophyton* showed that 4-6 weeks are sufficient to achieve clinical and mycological cure. Although Nejjam et al. maintained that infantile *tinea capitis* caused by *Tricophyton* can be cured in 56 days of treatment with terbinafine, it is now acknowledged that the forms caused by *Microsporum canis* require longer treatment and results are often unsatisfactory. Indeed treatment failure might be linked to the length of the treatment cycle rather than to dosage. Dosages adopted today are standardized and based on body weight: 62.5 mg/day up to 20 kg, 125 mg/day from 20 to 40 kg and 250 mg/day above 40 kg, whereas there are no established guidelines as to length of treatment. We administered conventional dosages of terbinafine to our cohort of patients affected by *tinea capitis* from *Microsporum canis*, but we extended the treatment for 12 weeks, since the aim was to eradicate the fungal infection at the end of treatment.

### Table I.—Results.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Organism</th>
<th>N. cases</th>
<th>Treatment periods (weeks)</th>
<th>N. cases cured</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Tinea capitis</em></td>
<td><em>M. canis</em></td>
<td>20</td>
<td>12</td>
<td>16 (80%)</td>
</tr>
<tr>
<td></td>
<td><em>T. mentagrophytes</em></td>
<td>2</td>
<td>6</td>
<td>2 (100%)</td>
</tr>
<tr>
<td><em>Tinea corporis</em> with hair involvement</td>
<td><em>M. canis</em></td>
<td>12</td>
<td>4</td>
<td>12 (100%)</td>
</tr>
<tr>
<td><em>Tinea faciei</em> with hair involvement</td>
<td><em>M. canis</em></td>
<td>6</td>
<td>4</td>
<td>12 (100%)</td>
</tr>
<tr>
<td><em>Tinea corporis</em> e faciei with hair involvement</td>
<td><em>M. canis</em></td>
<td>5</td>
<td>4</td>
<td>4 (80%)</td>
</tr>
<tr>
<td></td>
<td><em>T. mentagrophytes</em></td>
<td>3</td>
<td>4</td>
<td>3 (100%)</td>
</tr>
<tr>
<td>Widespread <em>tinea corporis</em></td>
<td><em>M. canis</em></td>
<td>2</td>
<td>2</td>
<td>2 (100%)</td>
</tr>
</tbody>
</table>
Mycological cure was achieved in 80% of patients with no relapses. Undoubtedly, the treatment period we adopted is relatively long, but considering the low recovery rates reported by other authors after 4-6 weeks’ treatment, we can conclude that a longer treatment period is clearly more effective.

Several authors reported that by increasing dosage to 7-9 mg/kg/day high cure rates can be obtained with treatment cycles between 6 and 8 weeks. We feel that further studies are necessary to standardize these high dosages which, in the absence of side effects, could be extremely useful in the treatment of tinea capitis caused by Microsporum canis. For the time being, using the currently accepted dosages it is necessary to opt for treatment cycles between 8 and 12 weeks to obtain high recovery rates, absence of relapses and no side effects. The 2 cases of tinea capitis caused by Tricophyton mentagrophytes were cured after 6 weeks’ treatment. While the small number of patients involved does not enable us to draw definite conclusions, in agreement with data in the literature it would seem that tinea capitis caused by Tricophyton requires shorter treatment cycles as compared to Microsporum.

Of the 26 children suffering from tinea corporis and/or faciei with hair involvement 25 (96%) were cured after 4 weeks’ treatment regardless of the type of fungus: indeed both Microsporum canis and Tricophyton mentagrophytes infections healed successfully over the same period of time. We must however stress the fact that the only case not cured belonged to the Microsporum canis group. The remaining 2 cases of widespread tinea corporis caused by Microsporum canis were cured after 2 weeks’ treatment.

In no cases did relapses occur and only 2 (4%) patients reported minor side effects consisting of nausea and abdominal pain which did not however warrant suspension of treatment. On the basis of the results obtained we feel that terbinafine is a drug to be highly recommended in the treatment of dermatomycoses in children.

Riassunto

Efficacia e tollerabilità della terbinafina nei bambini

Obiettivo. Le dermatomicosi infantili sono molto frequenti e spesso necessitano di trattamento sistematico. In questo lavoro è stata studiata l’efficacia e la tollerabilità della terbinafina in una popolazione infantile.

Metodi. Cinquanta bambini di età compresa tra 2 e 14 anni, affetti da tinea capitis (22 casi) e da tinea corporis difusa e/o con interessamento pilare (28 casi), sono stati trattati con terbinafina. I dosaggi impiegati sono stati 62.5 mg/die nei pazienti che pesavano meno di 20 kg, 125 mg/die in quelli con peso tra 20 e 40 kg, 250 mg/die nei pazienti con peso superiore ai 40 kg. I tempi di trattamento variavano da 2 a 12 settimane a seconda della forma clinica. Controlli clinici e micologici sono stati effettuati settimanalmente nei bambini affetti da tinea corporis e ogni 2 settimane in quelli con tinea capitis per tutta la durata del trattamento e dopo 4 settimane dalla fine della terapia.

Risultati. Complessivamente la guarigione clinica e micologica è stata ottenuta in 45 (90%) bambini: 18 casi di tinea capitis e 27 di tinea corporis. Nei pazienti affetti da tinea capitis da Microsporum canis il trattamento è stato effettuato per 12 settimane e la guarigione è avvenuta in 16 casi su 20 mentre nei 2 bambini con tinea capitis da Tricophyton mentagrophytes la guarigione è stata registrata dopo 6 settimane di terapia.

Conclusioni. La terbinafina è un farmaco da tenere in alta considerazione nel trattamento delle micosi superficiali nei bambini. Per quanto riguarda la tinea capitis da Microsporum canis sono necessari ulteriori studi per standardizzare meglio i dosaggi e i tempi di trattamento.

PAROLE CHIAVE: Dermatomicosi - Età pediatrica - Terbinafina - Tinea capitis - Tinea corporis

References

There is no effective treatment other than surgery for patients with all types of melanoma. Patients' survival depends on the stage of the disease. Once the disease has spread, there is no cure. Melanoma patients die of systemic metastases and, therefore, systemic therapy is to be administered early in the course of the disease, after potentially curative surgery, to prevent or at least delay disease recurrence. This is known as adjuvant therapy. Chemotherapy and hormonal therapy failed to show any survival benefits. Therefore, major emphasis has been placed on immunotherapy, which includes biotherapy and vaccines. These are intended to stimulate the immune system of the patient against the micrometastases, which were not eliminated by surgery. In this review, several types of melanoma vaccines are presented. These include the whole cell melanoma vaccines (allogenic or autologous), melanoma cell lysates, melanoma cell shed antigens, peptide vaccines and others. There are advantages and disadvantages to each vaccine. While the ideal vaccine may be constituted of melanoma specific antigens, unfortunately the exact number of these antigens needed to stimulate an antitumor response remains unknown. In conclusion, autologous whole cell melanoma vaccines seem to be the most beneficial when administered to high-risk patients. The role of adding biotherapy to a vaccine is being investigated.

**Keywords:** Melanoma - Skin - Vaccines.

There are 4 types of primary melanomas, namely: 1) cutaneous melanoma, which is the most common and most studied; 2) mucosal melanoma, that arises in the oral cavity, oropharynx, larynx, sinuses, anal canal, vulva and vagina; 3) uveal melanoma which originates in the iris, ciliary body or choroids plexus of the eye; 4) the rarest of all, leptomeningeal melanoma that arises in the meninges of the brain in the posterior fossa. All these sites share ectodermal origin, and melanocytes that may have been arrested there can undergo malignant transformation.

Tumor immunotherapy consists of 2 components, namely biotherapy and vaccines. Biotherapy, in the form of cytokines are nonspecific immune modulators, while the vaccines are tumor-specific immune stimulators. Cancer vaccines are based on the success established in the vaccines of infectious diseases which are also specific for each disease. However, there are major differences between infectious diseases and cancer. While the vaccines for infectious diseases are directed against foreign pathogens, cancer vaccines are directed against autologous antigens derived from patient's own body. Another difference is that vaccines for infectious diseases are administered prior to the infection for prevention, while cancer vaccines are administered to patients who have had cancer.

Surgery remains the most effective initial therapeutic modality in patients with all types of melanoma.
Restricting my review to cutaneous melanoma, and as it can be seen in Figure 1, the effect of surgery has reached a plateau and the survival of the patients depends on the stage of the disease at the time of diagnosis. Another fact about melanoma is once it spreads, there is potentially no cure except on rare occasions and the patients rarely survive more than one year. Therefore, every effort should be made to control the disease early in its course at the time of potentially curative surgery by the addition of some sort of therapy, in the high-risk group. We have to keep in mind that patients who die of melanoma succumb to distant metastases. Thus after potentially curative surgery, some type of systemic therapy is needed to prevent or at least delay recurrence and metastases. Such an approach is called adjuvant therapy. Adjuvant chemotherapy and hormonal therapy failed to show survival benefits.

Justification for the use of immunotherapy

Immunotherapy has shown some positive role in the management of high-risk patients. These patients are rendered grossly disease-free by surgery, but have guarded prognosis with tendency for developing metastases. Adjuvant immunotherapy is supported by several factors: 1) the biology of melanoma, where regression of normal skin pigment in the form of vitiligo has been noted in patients with melanoma as well as in some patients receiving immunotherapy; 2) clinical responses are noted in melanotic lesions injected with microbial immune stimulators (Figure 2), monoclonal antibodies, and systemic immune modulators and vaccines; 3) the presence of mononucleated cell infiltrates at the primary and metastatic lesions, indicating the presence of some cellular immune response; 4) spontaneous tumor regression has been reported in
patients with wide spread metastases on very rare occasion.10

There are several factors that may interfere in patients' response to a given vaccine. While some of these factors may be vaccine related, others can be due to defects in the recipient host. The vaccine may not cause enough immune stimulation as it is constituted of weak antigens. On the other hand, the recipient may be immune suppressed and cannot mount a response due to several factors that may include; lack of antigen presenting cells (APC), failure of APC in processing the antigen and to produce m-RNA to activate T-lymphocytes to become killer cells, lack of costimulatory factors B7-1 and B7-2 which are needed for the process of recognition and stimulation, or defects in the lymphocytes which cannot be stimulated. Such defects are common in patients with immune deficiency disorders, those receiving steroids, and in patients with advanced metastases. It seems that the ideal recipient of a vaccine should be patients who had potentially curative surgery and are not immune suppressed by a concurrent disease or medications. The patients should be tested for immune competence prior to vaccination to insure that they can mount an immune response. In addition, the vaccine should be combined, at least initially, with a stimulatory agent (as adjuvant) such as bacillus Calmette-Guerin (BCG), haptens such as dinitrophenyl (DNP), alum or other similar compounds to insure immune stimulation. Such agents are stronger than any melanoma antigen, and should be added to the vaccine with careful concentration to avoid immune deviation.

The ideal melanoma vaccines may be constituted from antigens expressed by melanoma cells but not by normal cells. Unfortunately, most of the tumor antigens are shared by normal cells and are referred to as melanoma associated antigens. Another important fact is that the presence of in vitro or in vivo cellular or humeral response does not usually translate to clinical responses and survival in human. Only survival data are the indicators for benefit of a given vaccine.

Melanoma vaccines

The are 2 types of melanoma vaccines:

1. Nonspecific immune stimulators such as BCG and corynebacterium parvum.

2. Melanoma-specific vaccines: these include the whole cell (autologous or allogenic), or acellular such tumor-cell lysates, peptides, epitopes or other melanoma associated antigens. Each has its advantages and disadvantages which are summarized in Table I.

Who are the ideal candidates for vaccination?

a. Patients who are at high-risk of recurrence, metastases and death from melanoma. They include patients with deeply invasive primary melanoma, those with ulcerated primary lesions, patients with regional lymph node (LN) metastases and those with resected distant metastases.

b. Patients who postoperatively have no residual disease clinically or radiologically and have normal blood chemistries including liver function tests and lactic dehydrogenase (LDH).

c. The vaccine is to be administered as adjuvant therapy after eliminating the disease surgically, in patients who are immunocompetent. These patients are then monitored for disease-free survival (DFS), and overall survival (OS).

**non specific immune stimulator**

**Bacillus Calmette-Guerin**

An editorial report in 1991, found no established or convincing evidence that immunotherapy plays a major role in cancer.11 However, intrasional injection of primary or metastatic melanoma of the skin (but not in subcutaneous metastases) with BCG showed limited local control, but no systemic benefit.12 Such an approach yielded 74% response rate which was transient.13 Since then, several conflicting reports followed. Some investigators reported systemic benefit and raised the question of possible shared antigens between BCG and

### Table I. — Advantages and disadvantages of different vaccines.

<table>
<thead>
<tr>
<th>Types of vaccine</th>
<th>Advantages</th>
<th>Disadvantages</th>
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<tbody>
<tr>
<td>Autologous whole cell</td>
<td>No histoincompatibility</td>
<td>Limited availability Available to patients with large tumors Needs special laboratory to prepare</td>
</tr>
<tr>
<td>Allogenic whole cell</td>
<td>Made of banked cells Always available</td>
<td>Histoincompatibility</td>
</tr>
<tr>
<td>Allogenic cell lysates</td>
<td>Always available</td>
<td></td>
</tr>
<tr>
<td>Shed antigens</td>
<td>Contains no cellular material (nuclei or cytoplasm) Always available</td>
<td></td>
</tr>
<tr>
<td>Melanoma associated antigens</td>
<td>Always available</td>
<td>Not all melanoma antigens have been identified</td>
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</table>
Melanoma. The possibility exists that BCG injection at a melanoma site may convert a nonspecific approach into a tumor-specific one by exposing immune cells recruited by BCG to melanoma cells. Furthermore, BCG was utilized as adjuvant systemic therapy and some studies showed beneficial results, while others showed no benefit regardless to the type of BCG preparation. Overall, BCG injections have no systemic effect on melanoma, and can be associated with some complications with the most serious of all, the development of BCGosis. The patient shown in Figure 2 was one whom I treated with BCG followed by repeated intralesional injections with PPD (250 TU) eliminating all his scalp lesions. Unfortunately, he died of cold abscess (tubercolic abscess) that eroded his aorta.

Corynebacterium parvum

It is similar to BCG as a nonspecific stimulator, but differs in that it can stimulate cellular and humeral immunity. Some investigators reported slightly better DFS and OS than BCG. However, the systemic side effects in the form of fever, chills and headache can be severe and require the use of systemic steroids which could defeat the objective of immune stimulation.

Melanoma specific vaccines

Most of the tumor antigens recognized by T-cells are still unknown, and, therefore, tumor-cell itself is the best source for immunization.

Allogenic cell vaccines

These are constituted of banked tumor cells or cell cultures and used for active immunotherapy. In 1992, we reported on a new approach utilizing allogenic melanoma cells as adjuvant therapy in melanoma. Patients with metastatic cutaneous melanoma to regional LN have poor prognosis despite radical resection of the LN. In an attempt to improve the survival and to determine the safety of a new method of tumor-specific adjuvant immunotherapy in such high-risk group of patients, 9 patients with matted metastases regional LN were studied. Three to 4 weeks after complete regional LN dissection, each patient received a single intradermal (ID) injection of BCG for sensitization. Three weeks later, the patient was immunized with allogenic melanoma cells obtained under sterile condition from live donor with distant metastases. Each patient received 3 vaccinations, each from a different donor, to avoid development response against HLA antigens while maintaining exposure to melanoma antigens. No cultured melanoma cells were used. Each vaccine consisted of mitomycin-C treated melanoma cells mixed with PPD (250 TU) administered ID once per month for 3 months. In spite of the short duration of the vaccination, 5 of the 9 treated patients (55%) were alive free of the disease at five-years, compared to 10% to 20% in historical controls. No autoimmune diseases were encountered in any of the patients. Such short duration of 3 months of vaccination seemed to be insufficient and at least 8 vaccinations are needed to
show more significant effect. However, with the increase in the incidence of hepatitis and HIV in the general population, this program was discontinued.

In the meantime, it was reported that active specific immunotherapy with a polyvalent vaccine that consisted of 3 cultured melanoma cell lines and 18 melanoma-associated antigens resulted in delayed type hypersensitivity skin reaction and in vitro cellular immune response.\(^{19}\) Furthermore, it has been reported that it improves the survival compared to historical controls.\(^{20,21}\) In addition, the polyvalent vaccine "CancerVax" showed benefit in patients who developed delayed hypersensitivity skin reactions to melanoma-associated antigens and had a rise in IgM (TA90). Based on these reports and other similar ones, 2 prospective randomized adjuvant studies were initiated in late 1997 with CancerVax: (1) one study dealt with patients with regional LN metastases (stage III disease) who underwent complete lymphadenectomy and had no evidence of residual disease, and (2) the second study was in patients with completely resected distant metastases (stage IV disease). Both of these studies were initiated with BCG adjuvant agent to the vaccine and to the placebo, with repeated injections for a five-year period. In case the patient develops metastases, these were resected and the vaccination was reinitiated in the same fashion. However, both studies were terminated after an interim analysis revealed lack of evidence for any benefit. These 2 studies were so well planned and well monitored. However, there may be 2 possibilities for the failure of such vaccine. First, the vaccine is made of allogenic cells and transplanted antigens may play a major role in its rejection rather than sensitization. Second, this vaccine consisted of long cultured melanoma cell lines which may result in partial loss of melanoma-specific antigens. However, further analysis of the results may identify a subset of patients who benefited from CancerVax.

**Autologous Cell Vaccine**

Patients who present with enlarged regional LN have poor prognosis despite undergoing lymphadenectomy, with a five-year survival ranging from 10% to 25%. In an attempt to improve such survival, we initiated a feasibility study.\(^{22}\) Twenty-two patients with large regional LN metastases were studied. They underwent therapeutic lymphadenectomy creating a disease-free status in the patient. These LN were large enough to allow for pathological examination and to obtain over 100 million melanoma cells for the vaccination, i.e., these patients had advanced stage III disease. One month after their surgery, each patient signed the consent form for such experimental approach, and received 5 autologous melanoma vaccines. Each vaccine consisted of 20 million irradiated (20 000 cGy) autologous melanoma cells and administered ID. The first 2 vaccines contained BCG and were given one week apart. The other 3 vaccines consisted of irradiated melanoma cells without BCG, administered over 2, 4, and 8 weeks interval. Low dose cyclophosphamide, as recommended by Berd et al., was administered intravenously as 300 \(\mu\)g/m\(^2\) 3 days prior to vaccine number 1, 4, and 5 to reduce the population of T-suppressor lymphocytes. The patients were then observed with no further therapy. Three patients developed metastases that were resected, and were revaccinated in the same fashion utilizing autologous melanoma cells from the newly resected metastases. We felt that such metastases may contain different clones of melanoma cells that were not represented in the initial vaccination. After 4 to 6 years of follow-up, 15 patients (including the 3 patients who were revaccinated) of the initial 22 patients (68%) were alive free of disease compared to the historical controls of 10% to 25%. As a general rule, patients who develop recurrences or metastases while receiving chemotherapy are considered as a failure to such agent(s). On the other hand, those receiving immunotherapy and develop recurrence should not be considered as failure, and every effort must be made to eliminate such recurrence surgically and continue the immunotherapy. Only patients with wide spread or unresectable metastases are considered failure to the immunotherapy.

At the same time, Berd et al. reported on the use of autologous melanoma vaccine modified by a hapten (DNP) used as adjuvant therapy after resection of nodal metastases. In addition, the vaccine was mixed with BCG and given once per month for 8 doses, and compared to a weekly program. These investigators introduced the use of 8 vaccinations and the administration of low dose cyclophosphamide prior to the vaccination. Their projected five-year DFS was 45%, with an OS of 58%.\(^{23}\) More recently, they reported on their results of treating 214 patients with an OS of 44%.\(^{24}\) They had also pointed out that patients who expressed delayed hypersensitivity skin reaction to their irradiated autologous melanoma cells had better survival.
than those who did not. However, a critical review expressed concern over such results and suggested that the delayed hypersensitivity skin reaction could be directed at the hapten rather than an antitumor response. While this is doubtful, the reviewers pointed out to another concern, patients who expressed the skin reaction could be patients with less aggressive, more differentiated and more immunogenic tumors and, therefore, the delayed hypersensitivity skin reaction correlated to the outcome. While this may true I do believe that immunogenicity varies in potency and some people are more immune competent than others.

Autologous melanoma cells are the best source for tumor antigens. However, it was suggested that antigens shared by tumors of the same histology may not make effective vaccine. Melanoma cells are weak antigenically, and the use of adjuvants agents such as BCG or DNP is needed to induce antigenicity. However, the use of such strong adjuvants with weak tumor antigens may cause immune deviation if not given in carefully and adjusted concentration.

**ALLOGENC MELANOMA LYSATES**

There are 3 types of allogenic melanoma lysates: 1. Viral melanoma oncolysate (VMO) by Wallack. 2. Vaccinia melanoma cell lysate (VMCL) by Hersey. 3. Melacine by Sondak and Sosman. Several melanoma cell lysates, prepared by mechanical or viral lyses, were evaluated as adjuvant therapy with the hope of initiating an immune response.

**Viral melanoma oncolysate.**—Wallack introduced vaccinia melanoma oncolysate prepared from allogenic melanoma cells, as adjuvant therapy. However, in a randomized controlled trial, it failed to show any benefit in DFS or OS.

**Vaccinia melanoma cell lysate.**—Another melanoma cell lysate by Hersey, prepared by a single allogenic melanoma cell line and infected with vaccinia virus was tried in a prospective controlled randomized study. It failed to yield any survival benefits. However, during this trial, the investigators found that their melanoma cell line contained several melanoma antigens including tyrosinase, gp100, MART-1 and others. In spite of that, such vaccines failed to show any benefit. The probability exist that the virus was a strong antigen that may created immune deviation, i.e., the immune response could be directed to the virus.

**Melacine.**—Melacine is made of mechanically lysed 2 allogenic melanoma cell lines and combined with monophosphoryl lipid A and Detox which is a purified mycobacterial cell wall (Ribi vaccine). In a prospective randomized adjuvant therapy trial, melacine failed to show survival benefits in stage II melanoma. However, in a retrospective analysis based on human leukocyte antigen (HLA) showed a potential benefit in DFS in a subset of patients with HLA-2A and HLA-C3 types with melanoma of 3 mm or less depth of invasion. This is being further evaluated. However, melacine was approved in Canada as adjuvant therapy.

**GANGLIOside VACCINES**

Gangliosides are carbohydrate antigens formed of sialic acid containing glycolipid molecules and have increased surface membrane expression on cancers of neuroectodermal origin, including melanoma. Melanoma cells are rich in gangliosides; the most prominent are GD3 and GM3 followed by GD2 and GM2, which are expressed on melanoma cells surface. These stimulate humoral response rather than cytotoxic T-lymphocytes, producing IgM antibody response, which is short-lived without IgG response. To increase the immunogenicity, GM2 was conjugated with keyhole limpet hemocyanin (KLH) and QS-21, which produced higher titer of IgM antibody response and a consistent IgM response. However, a randomized trial comparing high-dose interferon alfa-2b for 1 year to GM2-KLH/QS-21 was terminated after an interim analysis indicated the inferiority of the ganglioside vaccine to the interferon.

**PEPTIDE VACCINES**

The best way to create an immune response in theory is to induce tumor antigens onto APC to process it and present it to cytotoxic T-lymphocytes. Tumor derived proteins, RNA or synthetically generated peptides, epitopes and DNA are being used as antigenspecific immunization. Epitopes are found on the melanoma cell surface which are antigenic determinant of known structure such as MAGE-1, MART-1 (Melan-A), gp100 (Pmel 17). Purified peptides are recognized by cytotoxic T-cells that are bound to class I MHC
MELANOMA VACCINES

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related to survival. Intranodal administration of mature DCs may result in superior T-cells stimulation. Such vaccines are in very early stages of evaluation.

**DNA vaccine.**—Cytosine-based DNA of a specific antigen introduced in a bacterial cytoplasm (plasmid), injected in the recipient can be picked-up by APCs such as DCs or non-APCs such as keratinocytes or myocytes. Clinical trials utilizing DNA-encoding antigens such as tyrosinase, MART-1 and gp100 are under investigation.

**Viral vaccines.**—Recombinant poxvirus, adenovirus and other viruses encoding melanoma-associated antigens are being investigated as potential vaccines.

**Allogenic polyvalent shed-antigens vaccine.**—Bystryn et al. introduced a polyvalent vaccine, prepared from 3 allogenic melanoma cell lines and 1 xenogenic line; shed antigens in culture medium. In a prospective controlled study, 38 patients with regional LN metastases were randomized after their lymphadenectomy to receive the vaccine versus placebo (2:1 ratio). The results revealed DFS advantage for those who received the vaccine, but not in OS. Furthermore, it was shown that this vaccine induced CD8+ T-cell responses to gp100, MART-1, MAGE-3 and tyrosinase in 56% of HLA-A01 and HLA-A02 patients.

**Biotherapy**

Several cytokines have been utilized as adjuvant therapy for their immune modulation. Interferon alfa-2b was shown to be of modest benefit as adjuvant therapy in high-risk patients. This was approved for its use as adjuvant therapy. Interleukin-2 has shown some beneficial effects in patients with metastatic melanoma and renal cell carcinoma, and it was approved for that use. Other cytokines have been reported to be beneficial as biotherapy for cancer. Granulocyte-macrophage colony stimulating factor (GM-CSF) has been shown to have some activity as adjuvant therapy in patients with resected stage III and IV melanoma. IL-12 was administered with 2 melanoma peptides as adjuvant therapy in patients with resected disease. The results suggested that some of these patients mounted antigen-specific immune response against the peptides used and it seems to indicate that IL-12 may increase the immune response. Melanoma peptides administered in GM-CSF or pulsed on DCs are being tested. These 2 agents namely GM-CSF and IL-12, are being evaluated with a variety of vaccines. In the meantime, it has been reported that vaccination with autologous melanoma cells retrovirally transduced with GM-CSF gene has been studied in 64 patients with metastatic melanoma. Such vaccination has low toxicity, and 6 patients are alive for over 5 years. This vaccine induced also vitiligo at multiple sites in 2 patients with MART-1 or gp100-specific T-cells infiltrating the vitiligo.

Table II.—Overall 5-year survival of the patients who received perioperative bio-immunotherapy (IL-2 and interferon α-2b and autologous vaccine) as adjuvant therapy compared to historical controls.

<table>
<thead>
<tr>
<th>Stage of the disease</th>
<th>Study patients</th>
<th>Historical controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIIB</td>
<td>65%</td>
<td>47-59%</td>
</tr>
<tr>
<td>IIIC</td>
<td>57%</td>
<td>24-29%</td>
</tr>
<tr>
<td>IV (resected)</td>
<td>40%</td>
<td>&lt;5%</td>
</tr>
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</table>

Figure 3.—Photograph of delayed hypersensitivity skin reaction to irradiated autologous melanoma cells only in a patient treated with postoperative autologous melanoma vaccine. Note the erythema and induration of over 1 cm of most of the injection sites on the patient's back.

At the Maryland Melanoma Center, we combined biotherapy and autologous tumor vaccines for many years. In one of our early trials, 30 patients with resected regional LN and distant metastases were studied. Every patient received IL-2: 11 million IU per day for 2 consecutive days, 1 week before surgery. This theoretically may induce lymphokine activated killer cells (LAK), and tumor infiltrating lymphocytes (TIL) in
vivo with no or minimal toxicity. This was repeated in the same fashion 1 week after surgery. The patient then received interferon alfa-2b as 10 million IU 3 times per week for 4 weeks. This was followed a week later by autologous melanoma vaccine. Each vaccine consisted of 20 million autologous melanoma cells, irradiate: 20 000 cGy, and administered ID at several sites at 1, 2, 4 and 8 weeks apart. The first 2 vaccines contained BCG. Figure 3 shows delayed hypersensitivity skin reactions to the irradiated autologous melanoma vaccine without BCG. Table II compares the survival of the study patients to the historical controls and it is interesting to note such potential benefits with a very low toxicity program administered over a very short period. Figure 4 shows the survival curves of the patients with resected stage III and IV who received adjuvant perioperative biotherapy followed by autologous vaccine.

Our present study employs bioimmunotherapy administered postoperatively in high-risk patients. It consists of the administration of GM-CSF at a dose of 125 µgm/m² per day for 14 consecutive days, followed by IL-2 at a dose of 9 million IU/m² per day over 4 consecutive days. This is followed by 10 to 12 days of rest. This cycle is repeated every month for 1 year. At the beginning of the second cycle, autologous melanoma vaccine is initiated and administered over GM-CSF sites of injection to expose the irradiated autologous tumor cells to the macrophages/DCs created by GM-CSF. This study has been opened for 2 years, and no results are available.

In conclusion, it is clear that several vaccines are in experimental phases. The autologous whole cell melanoma vaccines seem to be the most effective in improving the survival. Such vaccines have to be administered as adjuvant therapy, i.e., early in the course of the disease, after potentially curative surgery to the high-risk patients. Furthermore, in case of recurrence, these can be resected and the patients are revaccinated by tumor cells from the newly resected metastases as these may contain new clones of cells that were not represented in the first vaccination. The role of adding biotherapy, specifically GM-CSF, to a variety of vaccines may prove beneficial and is under investigation.

Acknowledgments.—The author would like to thank Ms. Jessica McGeeney for her librarian help.

Riassunto

Vaccini per il melanoma

Oltre all’intervento chirurgico, non esiste un trattamento efficace per i pazienti affetti da melanoma, indipendentemente dal tipo. La loro sopravvivenza dipende dallo studio della malattia. Dal momento in cui la malattia si è disseminata non esiste alcuna cura. I pazienti con melanoma decedono a causa delle metastasi sistemiche e di conseguenza la terapia sistemica deve essere somministrata precocemente nel corso della malattia, dopo l’intervento chirurgico potenzialmente risolutivo, per prevenire o almeno ritardarne la recidiva. Tutto ciò è noto come terapia adiuvante. Per quanto riguarda la sopravvivenza, la chemioterapia e la terapia ormonale non si sono dimostrate efficaci. Di conseguenza, l’immunoterapia, che comprende la bioterapia e i vaccini, ha destato sempre più interesse. L’immunoterapia ha quale obiettivo di stimolare il sistema immunitario del paziente nei confronti delle micrometastasi che non sono eliminabili con l’intervento chirurgico. In questa revisione vengono presi in considerazione i diversi tipi di vaccino per il melanoma. Essi comprendono i vaccini a cellule intere (allo-genico o autologo), i lisati di cellule di melanoma, gli antigeni presenti sulle cellule del melanoma, i vaccini peptidici e altri. Ogni tipo di vaccino presenta vantaggi e svantaggi. Il vaccino ideale può essere composto da antigeni specifici del melanoma ma sfortunatamente il numero esatto di questi antigeni, necessari per stimolare una risposta anti-tumorale, resta ignoto. In conclusione, i vaccini anti-melanoma composti da cellule intere sembrano essere quelli più efficaci quando somministrati a pazienti ad alto rischio. Attualmente è in fase di studio il ruolo della bioterapia aggiuntiva al vaccino.

Parole chiave: Melanoma - Cuto - Vaccini.
References


Recent advances in laser dermatology

D. J. GOLDBERG, H. A. ALOKAILY

Laser physics, safety and a greater understanding of the concept of selective photothermolysis has led to a proliferation of lasers and laser like devices over the last 20 years. The treatment of vascular lesions was followed by the development of pigment specific lasers in the 1980s. In the 1990s ablative laser resurfacing (and non-ablative dermal remodeling) and the laser and light source treatment of unwanted hair became very popular techniques. This article will present 4 of the most recently developed techniques in the laser and laser like arena. Topics to be addressed are fractional resurfacing as an alternative for ablative and non-ablative resurfacing; cosmetic photodynamic therapy; radiofrequency for skin tightening; and the treatment of unwanted hair in darker skin types. It is recognized that all 4 areas are controversial. However, 20 years ago the treatment of children's port-wine stains was also controversial. There will continue to advances in laser dermatology.

KEY WORDS: Skin - Lasers - Dermatology.

In 1983 Anderson and Parrish postulated their newly developed concept of selective photothermolysis (SPTL). SPTL revolutionized laser medicine and dermatology. This original concept explained how laser physicians could safely and effectively treat children with port wine stains using laser light. SPTL also led to the development of a specific laser, the pulsed dye laser, to treat a specific condition, port wine stains in children. This concept has now also been used to develop more effective treatments of many other cutaneous problems including the treatment of tattoos, benign pigmented lesions, and the removal of unwanted or excessive hair. Our understanding of SPTL defined a way to localize thermal injury to the tissue being treated while minimizing collateral thermal damage to the surrounding non-targeted tissue. This is accomplished by choosing the proper wavelength of light that will be absorbed by the specific targeted chromophore and delivering the right amount of energy with the proper pulse duration, known as the thermal relaxation time (TRT). The TRT is based on the physical size of the target. It is these basic concepts of laser physics that have led in the short period of 2 decades to the transformation of laser skin treatments.

This article looks at the most recent advances in laser dermatology. Although there are many changes that occur continuously in this field, the most recent advances will be discussed below. These include 1) fractional resurfacing; 2) cosmetic photodynamic therapy; 3) non-surgical skin tightening and 4) removal of unwanted hair in darker skin types.

Fractional resurfacing

Over last decade the treatment of photoaged skin has dramatically changed. Traditionally available laser
treatment modalities for skin rejuvenation have been either fully ablative techniques or approaches that utilize non ablative dermal remodeling. Many laser and light system have been developed for the treatment of photoaging.\textsuperscript{1-6} CO\textsubscript{2} and Er:YAG lasers have traditionally been considered the most effective laser technologies for the treatment of photodamaged skin.\textsuperscript{4, 5} However adverse postoperative sequela such as extended recovery times, potential infection, possible scarring and persistent pigmentary changes have led many clinicians and patients to shy away from this treatment approach. In addition many have been wary of using ablative lasers off the face.

For all the aforementioned reasons, ablative laser resurfacing has become significantly less popular with the advent of non-ablative epidermal sparing technology. Nonablative laser technology offers the advantage of skin rejuvenation without the risks associated with ablative lasers. Non-ablative lasers induce dermal collagen remodeling by selective dermal thermal wound without epidermal damage.\textsuperscript{6} Some of the systems require proper epidermal cooling so as to lessen the risk of thermally induced epidermal and dermal blisters.

Although nonablative laser treatments do satisfy patients who are unwilling to undergo ablative treatment with its postoperative sequelae, the post-treatment efficacy clearly does not approximate that of ablative laser treatments.

In the end, both patients and physicians are seeking the dramatic results of an ablative laser procedure with the minimal down time of a non-invasive laser treatment.

Recently, a treatment concept called fractional photothermolysis (Fraxel\textsuperscript{TM} Reliant, Technologies, San Diego,CA), has been developed in an attempt to address the problems seen with both ablative and nonablative treatments. This technology depends on treating skin fractionally with a near infrared laser (1550 nm diode pumped erbium fiber laser) that delivers a highly collimated column of tissue damage that has been termed a microthermal zone (MTZ). Each MTZ is surrounded by an island zone of spared tissue. Because of this spared viable tissue there is rapid re-epithelialization of microscopic treatment zones with minimal or no downtime except for mild post-treatment erythema or bronzing that can last for about 24 hours (Figure 1). The laser uses water as its absorbing chromophore; the epidermis is relatively protected because of its low water content. Currently most physicians use an associated cooling system at the time of laser treatments. This allows pain to be minimized while at the same a greater more efficacious amount of energy can be delivered.

With fractional resurfacing, the skin is fractionally resurfaced with each visit. Because of this each treatment lasers about 15-20% of the skin area, while 80% of the viable tissue is left behind as a reservoir to enhance rapid healing. It is because of this that one can treat depths up to 400-700 micron of skin with minimal risk of scarring as compared to a CO\textsubscript{2} laser and without associated down time. However it also must be recognized that the tissue remodeling effect of this laser for very deep rhytides will never match the capacity of the more aggressive CO\textsubscript{2} laser.
Fractional resurfacing is highly effective in the treatment of fine lines, dyschromias, as well as for improving the texture of skin (Figures 2, 3). The Fraxel™ laser has also just received Food and Drug Administration clearance for the treatment of melasma. Multiple treatment sessions are generally required (4-5 sessions in many patients) spaced at 1-2 week intervals. Final collagen remodeling occurs 3 months after treatment.

In an early clinical study by Manstien, fractional resurfacing led to significant improvement of periorbital wrinkles (P<0.001), with a wrinkle score improvement of 18% 3 months after the last treatment. In the same study different MTZ densities were tested on the forearm of a variety of different skin types (II-VI) in 15 subjects. The results of the study suggested that it might be possible to perform fractional resurfacing even on darker skin types.7

Fractionated resurfacing is a new treatment modality developed from our continuing understanding of laser physics and laser-tissue interaction. Future studies are required to establish and refine treatment parameters.

Photodynamic therapy for photorejuvenation and acne

Photodynamic therapy (PDT) is defined as the use of light to activate a chemical photosensitizer to induce a specific tissue effect. At the beginning of the 20th century Hereon Hermann von Tappeiner, director of the Institute of Pharmacology at the University of Munich, described the term ‘photodynamic reaction’ as an oxygen-dependent tissue reaction that occurs following photosensitization and irradiation with light. PDT requires the simultaneous presence of a photosensitizer, light and oxygen inside the target tissue. The photosensitizer is accumulated in the target cells and absorbs light of a certain wavelength. The sensitizer will then produce highly reactive oxygen species (ROS), or singlet oxygen, which can destroy the cells containing the photosensitizer. According to the dose of light used one can induce damage of the target tissue, necrosis and apoptosis (e.g. treating cutaneous malignancy), or immunomodulatory effect at lower light dose (e.g. treating inflammatory dermatosis).

In the past most experience with PDT has been in the treatment of cutaneous non-melanoma neoplasms using intravenous injected porphyrins. However, due to the prolonged phototoxic effect of systemic photosensitizers, topical photosensitizers are now preferred for use in dermatology.8

In 1990, Kennedy et al. introduced 5-aminoluvulinic acid (ALA) as a new photosensitizing agent. ALA is a precursor of the potent photosensitizer protoporphyrin IX (PpIX) in the biosynthetic pathway for heme. Certain types of cells have the capacity to produce PpIX when exposed to an adequate concentration of exogenous ALA.3 When PpIX is activated either by red
or blue light sources, cytotoxic reactive oxygen species and free radicals are generated. This phototoxic effect destroys the target cells through an effect on mitochondria, nuclei and cell membranes. Of note, PpIX topical photosensitization can be induced in the epidermis and its appendages but not in dermis. It is this effect that explains the role of PDT in photorejuvenation and the treatment of acne vulgaris.

The pathogenesis of acne vulgaris involves 4 factors: 1) hypercornification of pilosebaceous duct; 2) increased sebum production; 3) propionibacterium acne colonization and 4) inflammation.

It is known that *P. acnes* produces porphyrins, particularly coproporphyrin III. Various light sources activate these porphyrins to produce a photodynamic reaction, even without the use of a topical photosensitizing agent, which has the potential to destroy the bacteria.

Topical ALA is known to be preferentially taken up by the pilosebaceous unit. Therefore, ALA-PDT shows its potential usefulness in the treatment of acne. The mode of action of PDT-ALA in the treatment of acne is thought to through its direct photodynamic destruction of sebaceous glands, photodynamic killing of *P. acnes* or reduction of follicular obstruction by keratinocyte shedding and hyperkeratosis.9,10

Several studies have been performed to evaluate the efficacy of PDT for treatment of acne vulgaris over the past several years. Hongcharu et al., studied ALA-PDT therapy for acne vulgaris of the back in 22 patients utilizing a broadband light after a 3 hour topical drug incubation. Significant clinical clearance in acne was noted after 4 weekly treatments in all patients compared to control non-treated areas. This improvement persisted up to 20 weeks. Rare complications included an acniform folliculitis, postinflammatory hyperpigmentation, superficial peeling and crusting.11

Itoh et al. treated one facial acne patient with a single treatment of 5-ALA PDT after 4 hours drug incubation and 635 nm laser light at 5 J cm². They reported an improvement lasting 8 months following the treatment. Erythema and edema were seen followed by crusting and healed after 10 days.12 Gold evaluated 10 patients with moderate to severe acne vulgaris utilizing short contact (30-60 minutes) ALA-PDT and a blue light system. Four weekly sessions showed a response of approximately 60% which persisted 3 months after treatment. No side effects were noted.13

The most effective treatment regimen for ALA-PDT in acne is not yet established. Multiple treatment sessions are required and a variety of lasers and light sources have been used. These include blue light (405-420 nm), red light (635 nm), pulsed dye lasers (585 nm), and the intense pulsed light source (500-1200 nm). All are safe and effective in photodynamic therapy and can be utilized for both acne treatment and photorejuvenation (Figures 4, 5).

Photorejuvenation of facial skin has been reported after intense pulsed light treatments. Several studies have reported on the enhancement of photorejuvenation by photodynamic therapy with combination of topical 5-ALA and IPL treatments. Gold13 has studied short contact (30-60 min) full-face 20% 5-ALA treatments with an IPL. Ten patients received 3 treatments at 1 month intervals; follow-up evaluations occurred at 1 and 3 month post treatment. More than 85% of the treated actinic keratoses responded to this therapy. Ninety percent of patients showed improvement in mottled hyperpigmentation; 50% had less facial erythema.

Alster et al. evaluated the safety and efficacy of 5-ALA plus IPL compared to IPL alone in a split face comparison study. They found higher clinical improvement scores on the combination ALA plus IPL treated areas. Mild erythema and desquamation were observed on the areas where ALA was applied.14 Goldman et al.15 also studied 32 patients with actinic keratoses moderate photodamage, utilizing topical 5-ALA for 60 minutes prior to blue light therapy. Their study showed a 90% clearance of actinic keratoses, improvement in skin texture in 72% and skin pigmentation in 59% of treated individuals.

In a recently published study comparing ultrastructural changes after treatment of facial skin with either an IPL or IPL pretreated with topical ALA (PDT), we showed an increase in new collagen formation on the PDT side as compared to the solely IPL treated side. In this study, 7 adult subjects (6 women, 1 man) with minimal photodamage were treated with full face IPL treatment. Half of the face was pretreated with topical ALA. Pre- and post treatment biopsies were analyzed for changes in collagen by electron microscopic ultrastructural analysis.

An increase in Type I collagen fibers was seen after treatment in all subjects. There was a greater increase in Type I collagen formation in those subjects who were pretreated with topical ALA.16

These studies all document the potential usefulness of photodynamic therapy utilizing a variety of lasers.
Recent Advances in Laser Dermatology

Goldberg

Topical photodynamic therapy, using 5-ALA, is a practical and safe treatment without significant adverse effects. Cosmetic improvements have been shown in photorejuvenation and acne vulgaris. This is a promising modality of treatment that may have a variety of uses in the near future.

Radiofrequency for skin tightening

Skin laxity is one of the most common cosmetic complaints. Traditional surgical treatments, although dramatic provide the patient with down time, the risk of postoperative complications and scars as a result of healing of the surgical wounds. Most lasers and light systems do not improve skin laxity without postoperative risks and down time.

Monopolar radiofrequency (RF) tissue tightening (Thermacool TC™; Thermage, Inc., Hayward, CA) was designed and developed in an attempt to meet this demand. This radiofrequency device delivers RF energy deep into dermal tissues leading to volumetric uniform heating of dermal tissues. Unlike a laser, RF devices depend on tissue’s natural resistance to produce heat. The higher the tissue resistance, the greater is the actual resultant heat. The greater the resultant heat, the greater is the degree of new collagen formation.

The depth and the degree of thermal injury also depend on the size of the RF contact tip, delivered energy treatment levels and the conductive properties of the treated tissue.

With the ThermaCool™ device, a cryogen spray is contained within the contact cooling device to protect the epidermal tissue before, during and after RF tissue heating.

Despite the initial enthusiasm for this non-surgical skin tightening device, intraoperative pain was a major of early RF treatments. This was alleviated with topical anesthetic creams applied under occlusion for 1 hour before the procedure, the use of oral analgesics and low dose of valium. Recently, the use of much lower energy, multiple pass techniques has markedly decreased procedure associated discomfort, while at the same time increasing efficacy and safety. In fact, older utilized higher treatment energies have led to mixed results. The degree of response often did not correlate with degree of improvement and potentially could lead to a higher incidence of burns and resultant scarring. Although today’s low to medium energy settings may stimulate the fibroblasts to produce collagen, older utilized very high energies may actually melt down the contractile proteins. In that situation, there will be no tissue contraction except by tissue necrosis and subsequent scarring.

Ruiz-Esparza, in one of the first monopolar RF studies, evaluated treatment results in 15 subjects ages 41 to 68. He noted 50% improvement in the nasolabial folds of 50% of treated subjects. In addition, he saw 50% improvement in the cheek rhytides of more than
60% of the subjects. Finally, marionette lines improved 50% or more in 65% of the subjects.22

The best candidates for monopolar RF skin tightening patients with mild to moderate skin laxity. Treatment induced thermal damage causes immediate collagen contraction. Then dermal remodeling begins with the resultant wound-healing response which ultimately produces additional skin tightening during the 5-6 months after treatment.

Zelickson studied the histological and ultrastructural effects of monopolar radiofrequency-based nonablative dermal remodeling both bovine tendon and human abdominal skin. Ultrastructural analysis of the human skin disclosed isolated scattered areas of collagen fibrils with increased diameter and loss of distinct borders.23

Most of the studies have been performed on either lax facial and neck skin 24-26 (Figures 6, 7). However, this procedure can be used on different part of body and on areas where surgical lifting is major operation and thus undesirable, such as arms, thighs and buttocks. In a multicenter study evaluating the use of RF for periorbital tissue tightening 86 subjects received a single monopolar RF treatment and were evaluated at 6 months for subjective and objective improvement. Improvement was noted in size of periorbital wrinkles, a measurable change in brow position was also noted.27 Other studies support these findings. Alster studied the effect of monopolar RF treatment on check and neck laxity in 50 treated subjects. She found significant improvement in both cheek and neck laxity 6 months after a single treatment.28

It should be noted that this modality does not replace current surgical procedures but is an excellent complement to them and is a considerable treatment option for patients with mild to moderate skin laxity who do not want to undergo surgical treatments. Non-ablative RF treatments appear to be safe and effective in producing acceptable tissue tightening. However the longevity of clinical result has yet to be determined. Further refinement of the technology and techniques for its use will lead to further benefit of this therapy. Finally the non-surgical skin tightening results of newer more superficial bipolar RF devices and/or other heat based light devices will need to be evaluated and/or compared to the treatment results after monopolar RF treatment.

Laser hair removal of darker skin types

Excessive hair growth on undesirable sites is a very common cosmetic complaint. The growth may be due to a variety of causes such as genetic, iatrogenic or hormonal factors. However, in the majority of patients the aim is to simply normal body hair. Until recently electrolysis was the only long lasting hair removal method. However, electrolysis is painful, time consuming and has known and defined risk of scarring and treatment induced pigmentary changes.

In 1996 the US Food and Drug Administration approved the first laser hair removal laser system. Since that time the greatest advances in laser technol-
ogy have been in area of laser assisted hair removal. Lasers and other light based sources have been developed for hair removal based on the principle of selective photothermolysis. Selective photothermolysis, as it applies to laser hair removal, involves targeting melanin both within the hair shaft and matrix. This melanin chromophore is the primary light absorber in the optical window between the 600 and 1100 nm red or near-infrared wavelengths. The absorption of these wavelengths depend on the amount and type of melanin in the hair follicle. Darker hair is more susceptible to laser-induced thermal damage. In order to confine thermal damage to the hair follicle, the pulse duration must not exceed the thermal relaxation time of the hair follicle, which is estimated to be 10 to 100 ms for terminal hair follicles.

Melanin within the overlying epidermis functions as a competing absorber for laser light. The greater the amount of melanin within the epidermis, the greater is the risk of epidermal injury (blistering, hypopigmentation, hyperpigmentation and scarring). This risk further increases with increasing skin pigmentation, whether constitutive or tanned. For this reason hair removal in darker skin types (IV-VI) has been more difficult. In addition, the absorption of laser by greater amounts of epidermal melanin will also decrease the amounts of light reaching the intended target (hair follicle). Various methods can be used to protect the epidermis from thermal damage, including, longer pulse durations, longer wavelengths, and adjunctive epidermal cooling.

Longer pulse duration tend to limit the thermal damage of the epidermis based on the principle of thermo-kinetic selectivity. This concept states that smaller structures e.g. epidermal melanin will lose heat quicker than larger structures e.g. hair follicle. The epidermis will cool by heat dissipation quicker than the larger hair follicle if the pulse duration exceeds the thermal relaxation time of epidermis which is 1-2 ms. The ideal pulse duration for hair removal is in the range of 3 to 50 ms, between the thermal relaxation time of epidermis and the hair follicle.

In addition to longer pulse durations being a protective factor for dark skin, longer wave lengths (within the optical absorbing window of melanin) will provide deeper penetration into skin and more effective targeting of the hair bulb which is located deep within the dermis.29,30

Myriad lasers and light source are highly successful for the treatment of unwanted hair. However, the 2 commonly available safest wavelengths for darker skin appear to be 810 (diode) and 1064 nm (Nd:YAG).31,32

Both lasers have been Food and Drug Administration cleared in the US for laser-assisted hair removal in darker skin phototypes and are highly popular throughout the world. In terms of efficacy the shorter wavelength lasers (810 nm) are probably more effective because of their wavelengths higher absorption by melanin. This wavelength can be safely used for laser-assisted hair removal in skin types (I-V). However caution should be used when treating skin types V and VI. To treat skin type VI, very long pulse durations (400 ms and longer) as well as aggressive skin cooling should be used.31,35

The 1064 nm Nd:YAG wavelength is safer than the 810 nm wavelength for the treatment of darker skin types.36 This is due to low melanin absorption at 1064 nm which does not generally lead to significant epidermal thermal damage. However the wavelength does lead to sufficient follicular damage because it is long 1064 nm wavelength leads to deeper penetration (5-7 mm) into the dermis to reach the whole length of the hair follicle.37-39

Long pulsed Nd:YAG lasers shows little or no risk of laser induced hypo- and hyperpigmentation, 32,37,40-43 making it suitable for darker skin type.

Despite the safety threshold associated with 1064 nm laser systems, conservative appropriate fluences are crucial in the first treatment of very dark skinned individuals. Lower fluences and longer pulse width is recommended for the first treatment of darker skinned individuals. One study suggested that relatively high fluences (50-80 J/cm²) could be used with longer pulse durations (50 ms) as long as an appropriate safe and effective cooling device was utilized.40

Another Nd:YAG laser hair removal study, using different pulse durations, fluences and spot sizes, reported that the largest utilized spot sizes and longest pulse durations led to the best results at a 12 month follow-up.

As is generally true for all laser hair removal systems, multiple treatment session are required when using longer wavelengths. There is anecdotal evidence that more laser hair removal systems are required with longer wavelength systems than those utilizing shorter wavelengths (694-755 nm). Nevertheless, long-term efficacy up to 1 yr after the last treatment session has
been reported.\textsuperscript{36, 37, 44} With each treatment one can expect to see 10\% to 20\% reduction in hair count, color and diameter. Nd:YAG 1064 nm lasers represent the safest laser systems for hair removal in very dark skin types (IV-VI). Conservative fluences with longer pulse durations and multiple treatments are required for effective and safe treatments.\textsuperscript{45}

In addition to the difficulties in treating darker skin types, clinicians have been frustrated in their attempt to treat non-pigmented hairs. Such hairs lack significant amounts of the requisite melanin absorbing chromophore. We, and others, have attempted to treat such non-pigmented hairs with a combined IPL/bipolar radiofrequency source after pretreatment with topical ALA. This represents a variation on the cosmetic PDT described above.\textsuperscript{46}

In this study, 15 adult females, skin phenotypes II-IV were entered into the study. Ten subjects were determined to have white terminal hairs; an additional 5 females presented with fine facial vellus hairs. Unwanted facial hair was treated twice at 4-6 week intervals with a combined optical bipolar radiofrequency source. At each treatment half of the treatment area was pretreated with topical aminolevulinic acid; the other half was not. Follow-up visits were undertaken at 6 months after the 2\textsuperscript{nd} treatment. Hair counts were obtained before treatment and 6 months after the final treatment.

An average terminal white hair removal of 35\% was observed at 6 months after treatment with the combined pulsed light bipolar radiofrequency device. When pretreatment with topical aminolevulinic acid was provided the average hair removal of terminal white hairs was found to be 48\%. None of the 5 subjects with vellus hair were noted to respond to either treatment (Figures 8, 9).

This study suggested that eventually all skin types and hair color will respond to treatment.

\textbf{Riassunto}

Recenti scoperte riguardo l’utilizzo dei laser in dermatologia

L’utilizzo dei laser, la sicurezza ed la migliore conoscenza del principio della fototermodolisi selettiva ha determinato un proliferazione dei laser e dei dispositivi che utilizzano il laser negli ultimi 20 anni. Il trattamento delle lesioni vascolari è stato seguito dallo sviluppo di specifici laser per pigmenti negli anni ’80. Negli anni 90 l’ablazione laser di superficie (e il rimodellamento dermico non ablativo) e il trattamento mediante sorgente luminosa o laser di capelli o peli indesiderati sono divenute delle tecniche molto utilizzate.

L’articolo descrive 4 delle più recenti tecniche sviluppate riguardo la tecnologia laser. Gli argomenti trattati sono il rimodellamento frazionario come alternativa del rimodellamento ablativo e non ablativo; la terapia cosmetica fotografica; la radiofrequenza per il fissaggio cutaneo ed il trattamento dei capelli indesiderati nelle cuti più scure. È risaputo che si tratta di 4 argomenti che tuttogi sono ampiamente dibattuti. In ogni caso 20 anni fa anche il trattamento delle macchie cutanee rosso-vino dei bambini era un argomento dibattuto. Sarà presente una continua evoluzione nel trattamento delle patologie dermatologiche mediante laser.

\textbf{Parole chiave:} Cute - Laser - Dermatologia.
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Psoriasis is a common complex disease that has many different manifestations. The many treatments for psoriasis magnify the complexity of managing the disease. An overall structure can help guide appropriate, comprehensive psoriasis treatment. Psychosocial issues need to be addressed for all patients with psoriasis. Then, for treatment purposes, most psoriasis patients can be classified as having either localized disease which is amenable to topical treatment or more generalized disease that requires photo or systemic treatment. The key to success in topical psoriasis treatment is good compliance. Phototherapy - with or without an oral retinoid - is the first line option for patients with extensive psoriasis. If that is not effective, the patient should be counseled about their systemic treatment options and should be involved in the decision of what is the most appropriate treatment. Support groups, such as the National Psoriasis Foundation, are helpful for both managing patients' psychosocial issues and educating them about their treatment options.

**KEY WORDS:** Psoriasis - Phototherapy - Biologics.

Psoriasis is a common, complex condition that can be frustrating for both patients and their physicians. There can be manifestations on any part of the skin or nail, and the extent can vary from quite localized involvement to profoundly extensive disease. The complications inherent in this variability are magnified by the variability in the impact disease has on patients and their idiosyncratic feelings about how they want their disease managed.1, 2

To help a relative neophyte like myself approach this complex condition, a structured approach may be helpful. Step 1 in the treatment of psoriasis for all patients is to address their psychosocial issues. Step 2 is to decide if they have relatively localized psoriasis to which they feel they can apply topical therapy or if they have more generalized disease which will require phototherapy or systemic treatment. Of course there are special localized areas such as scalp and palm and sole involvement (as well as psoriatic arthritis) that need to be considered separately.

In this article, 10 treatment tips are presented to help manage psoriasis patients. This begins with addressing psychosocial issues and moves on towards the importance of compliance and the effective use of topical therapy. We, then, will discuss tips for addressing patients who have more extensive involvement. These include the value of phototherapy with or without topical therapies and oral retinoid as the first line
Tip 1: Establishing the physician-patient relationship

The foundation of effective psoriasis treatment is to establish a strong physician-patient relationship. Many patients with psoriasis are frustrated with their disease and frustrated with the care they have received in the past. It is important to establish oneself as an empathetic physician who will work with the patient to effectively manage their disease. To begin with, the physician should sit within touching distance of the patient. As part of the physical examination the physician should palpate the lesions, commenting on how thick they are (Figure 1). Of course, the dermatologist can tell from across the room that the lesions are thick. Commenting on thickness, however, justifies the contact with the patient. Some physicians may choose to place their hand on the lesion and then touch it to one’s own face commenting, “of course this is nothing contagious.”

This form of human contact has dramatic impact on the relationship between the patient and physician. The patient with psoriasis, especially new patients who just developed psoriasis, have serious concerns about how the disease will affect social interactions. This is also true for the parent of a child with psoriasis. The casual contact that a physician makes with the lesions reassures the patient and the family that the disease does not have to inhibit human contact.

The second part of establishing a relationship with the patient involves asking the patient a few questions about their psoriasis. A question or two should be asked about the character of the lesions, how itchy they are, how past treatments were probably messy and frustrating and how psychosocial issues are important. These questions probably will not have a great impact on what treatment will be prescribed. Indeed, most dermatologists can probably tell from across the room, without asking questions, what treatment might be appropriate. Instead these questions are asked so the patient realizes the physician is caring and understanding with respect to psoriasis. Establishing this bond and trust between patient and physician will encourage patients to be more adherent to their physician’s recommendations concerning treatment and likely will improve treatment compliance and outcomes.3,4

Tip 2: Addressing the psychosocial issues

Patients have endless questions about their psoriasis, what causes it, and what they can do about it. They question how to handle social situations, for example, what to do when a lifeguard tells them they cannot go in the pool or what to do when children in the grocery store are pointing at them. Patients feel an intense sense of isolation because of their disease. Often this results in psychiatric morbidity.

No physician has the time to answer all these questions and probably few dermatologists even have the answers to all the questions patients may raise. Nevertheless it is critically important to address these issues. Dermatologists can do this easily by encouraging patients to join a psoriasis support group. In the United States, we use the National Psoriasis Foundation (www.psoriasis.org). This is a fabulous organization devoted to educating patients about psoriasis and empowering them to work toward the development of new treatments.5 By joining this organization, patients lose their sense of isolation, realizing that other patients are in the same boat they are. Through the organization they can share their questions and answers.
about their psoriasis. They also can work together to ensure themselves access to appropriate treatment options.

Accessing Psoriasis Foundation resources is easy, as the website, www.psoriasis.org, is available to people worldwide. I like to encourage patients to join by telling them, “The Psoriasis Foundation is an organization of people just like you who have psoriasis. You can join for a donation of any size. I think you will find it very helpful.”

**Tip 3: Topical treatments work better when patients apply them**

Now that we have addressed psychosocial issues we can move on to tips related to treatment of relatively localized psoriasis, in other words the use of topical therapy.

The critical element in topical therapy of psoriasis is getting patients to apply the medication. In research studies 40% of patients with psoriasis report non-compliance. I suspect the other 60% are probably lying. To encourage patients to be compliant, it is helpful to establish a strong physician-patient relationship and involve the patient in treatment planning. Often it is very helpful to involve them in the choice of treatments, particularly choosing a vehicle that they feel they can reasonably use.

Compliance research studies using electronic monitors reveal that psoriasis patients regularly do not apply their medication even while telling their physician that they do use it. There tends to be a rapid initial decrease in compliance when a treatment is started with a subsequent slow decrease over time. At the rate of decline observed in clinical trials it can be expected that patients probably stop using their topical therapy completely by the end of 6 months. This drop in compliance may explain most if not all of the “tachyphylaxis” phenomenon that is observed with the chronic use of topical steroids in psoriasis patients. Adherence studies also reveal that adherence increases right around the time of study visits. Clinicians can use this effect to improve patients’ compliance by giving them a return appointment within 1-2 weeks after initiating a new treatment. This will help encourage initial use of the medication; when patients see that the medication works they will be more likely to use it long term. If there is no visit shortly after starting therapy, patients may be less compliant with the medication, they may not see that it works, and they will assume it is not helpful for long term use.

Poor compliance is probably most influential in the treatment of scalp psoriasis. Scalp psoriasis is extremely frustrating for both patients and their dermatologist. The failure of scalp psoriasis to improve is not due to poor penetration; penetration through the normal scalp is similar to axilla. Penetration through a diseased scalp is undoubtedly even higher. The reason scalp psoriasis does not improve is usually because patients do not apply the prescribed medication to the scalp. I think this would be obvious to us if only we took the time to visualize how difficult it would be for us to comply if a physician asked us to apply a medication to our scalp daily and to return in 8 weeks for follow up. Instead, by giving patients a relatively non-messy topical therapy and having them patient return in just 3 to 7 days, one can maximize compliance over that time. Scalp psoriasis will actually improve dramatically even over such a short interval.

**Tip 4: You do not have to use ointments to treat psoriasis**

Many of us were taught that ointments are more potent than nonointment vehicles. We are taught that you have to moisturize psoriasis to make it well. We may have been taught that patients do not like ointments but they will tolerate them at night. I believe that these are all myths. Patients who dislike ointments and prefer a less preparation do so both day and night.

Moisturizing psoriasis may be helpful but certainly is not necessary; highly effective treatments such as methotrexate and cyclosporine do not moisturize the plaques. Most importantly, modern, less messy, nonointment vehicle delivery systems can be very potent.

For example with the superpotent topical corticosteroid clobetasol propionate, ointment, cream, gel, solution, foam, shampoo, lotion, and spray vehicles are all capable of delivering the active molecule through the skin. The vasoconstrictor assay - which measures the ability of the active drug to activate corticosteroids and the ability of the vehicle to deliver the drug through the skin - demonstrates the high potency of all these clobetasol propionate preparations. Unfortunately, the vasoconstrictor assay does not measure the third factor that determines the potency of topical corticos-
teroids in real life use - whether patients actually apply the medication. Messy ointment preparations may have good vasoconstrictor scores but patients may not like to use them; such products may not be as effective in real life use as less messy products. This is particularly a problem for treatment of diseases that require chronic use over long periods of time as patients quickly tire of the hassle of treatment.

The ultimate proof that an ointment vehicle is not necessary was the success seen with the over-the-counter product “Skin Cap”. This product was said to contain zinc pyrithione but was then reported to contain clobetasol propionate. Many dermatologists found that it was far more effective than clobetasol ointments they had prescribed. The 3 reasons that Skin Cap was more effective probably was 1) compliance; 2) compliance; and 3) compliance. Physicians prescribing clobetasol might scare patients with risks of the drug: there were no apparent risks from using Skin Cap as neither the patient nor physicians believed that it contained clobetasol. Patients also may have been more invested in using Skin Cap having paid for it out-of-pocket themselves. Most importantly, Skin Cap was not a messy ointment. It was a spray that dried right out. This drying spray clobetasol product appeared to be more effective than clobetasol ointment ever was. I believe the perceived effectiveness was purely because of the patients’ willingness to use the product; it was not due to either greater absorption of clobetasol or to an interaction with the zinc pyrithione. If one applies clobetasol propionate to the plaques one can expect the inflammation to resolve and the psoriasis to clear whether one uses a moisturizing ointment vehicle or not.

Tip 5: Combining topical calcipotriol with topical corticosteroids

When topical calcipotriol was first approved in the United States there was tremendous excitement: here was a drug that could be used as monotherapy, and in 8 weeks 70% of patients would clear or almost clear. When it was used in this manner rarely did it work, however. Patients would not continue to use it, as it did not work rapidly enough for them to see an effect. Also some patients developed an irritation and felt they could not continue using it. These treatment characteristics were not apparent from the clinical trials. The clinical trials were somewhat misleading. In clinical trials, patients returned for frequent return visits, likely increasing patients’ compliance with the drug. They are also paid to apply the drug and are probably more tolerant of irritation. Quickly dermatologists realized that for this drug to be effective it needs to be used in combination with a topical corticosteroid. The combination provides much faster relief, and the corticosteroid prevents the irritation that is sometimes seen with the topical calcipotriene. A 2 week study was done showing that the combination of calcipotriene and halobetasol was more effective than calcipotriene or halobetasol used alone. This study showed a very high response rate. I suspect the main reason the response rate was so high was that it was a short 2 week study. Patients are probably far more compliant when they are only being asked to apply the medicine for a short period of time (2 weeks in this clinical trial) compared to a clinical practice setting where they are told to try the drug for 8 weeks.

Tip 6: For patients with severe psoriasis, start with something safe and move on from there

We now consider tips for treatment of more generalized psoriasis. There are some advantages to starting with rapid acting treatments and switching to things that are safer for the long run. In general, however, I think phototherapy should be the first choice for patients with extensive skin involvement without severe joint involvement (Figure 2). UVB phototherapy is extremely safe and very effective for psoriasis. It is also quite cost effective. Topical agents can be used to augment the effect on resistant plaques to help speed clearing. Oral retinoid therapy can be used with UVB phototherapy to make UVB much more effective. While retinoid PUVA regimens perhaps have more visibility, retinoid plus UVB helps obviate the need for PUVA in the first place. For patients who do not respond to UVB phototherapy, one can consider biologics (such as tumor necrosis factor [TNF] inhibitors, alefacept, and efalizumab), methotrexate and PUVA. If those don’t work even more toxic long term therapies such as cyclosporine or hydroxyurea can be considered. Often some patients do require combinations of these.

UVB phototherapy appears to have very little risk. Surely there is some increase of skin cancer, but this risk appears to be so small that long term studies have trouble detecting an increased risk. Perhaps the great-
est limitations to UVB phototherapy are inaccessibility and disruption to daily life. In many areas office phototherapy is not available, and even when it is available patients may have trouble leaving work for 3 to 5 treatments per week.

**Tip 7: UVB phototherapy is always accessible**

While office UVB treatment may not be available to patients, some form of phototherapy is available to almost everyone. In regions where there is sufficient sun exposure, patients can get heliotherapy from the sun. Home UVB phototherapy units, either broadband or narrowband, are relatively inexpensive and allow patients to have phototherapy in the convenience of their own homes at a time that is most suitable for them.23-25 A 6 bulb single panel home UVB unit can provide a lifetime of phototherapy at a cost of less than 1 month of an injectable biologic treatment. I typically prescribe only home light units that have a built-in prescription timer that provides patients a limited number of treatments. Patients must then return to my office for follow-up in order to assess potential safety issues; at that time I can give them a new prescription allowing them to use the unit for additional treatments.

For those patients who cannot have office light treatment or home UVB phototherapy, use of a tanning bed may an appropriate treatment for their disease.26 The risk/benefit ratio of tanning beds is certainly not as well characterized as office phototherapy. Thus office phototherapy is preferred. But for those patients who cannot access phototherapy by other means, tanning may be an appropriate choice and, I believe (although there are not a lot of data on which to base this belief), a choice probably safer than systemic treatment options.

When recommending a tanning bed, I recommend the patient to go to the same tanning salon for each visit and to use the same bed within that tanning salon at each visit. I encourage patients to check with the operator of the tanning bed to find out what the appropriate starting dose is and then I encourage the patient to start by using at time of one half of whatever they are told. They can then increase their exposure by 15 s each day, going 5-7 days a week if possible. I do not use tanning beds in conjunction with psoralen; there is a risk of death with such an approach.

**Tip 8: Oral retinoid treatment can be very safe, effective and easy to use**

Oral retinoid treatment is not a particularly helpful monotherapy for plaque type psoriasis. Nevertheless it is very helpful for making UVB phototherapy more effective.28 It is also very helpful for pustular psoriasis including palmoplantar pustular psoriasis.29 Low dose oral retinoid therapy helps dry up the pustules and helps make the thick scale fall off. It makes both UVB and PUVA more effective 21 and probably makes topical therapies more effective as well.

I typically prescribe very low doses of oral retinoids, 25 mg every day or every other day of acitretin. This is usually sufficient for improving the effectiveness of other treatments. The low dose also helps minimize side effects. When describing these potential side effects to patients I prefer to list them in order starting with the head and working my way down (Figure 3). Thus there is the potential for depression, headaches, hair loss, dry eyes, trouble with night vision, dry nose and nose bleeds, dry lips and dry mouth, dry itch skin, joint pains, potential liver toxicity and effects on triglycerides. Patients should be told that if they are a regular blood donor that blood donor organizations probably will not want their blood because of the teratogenicity of oral retinoids.
Because of teratogenicity I (almost) never use acitretin for women of child bearing potential.

Monitoring of oral retinoid therapy is rather straightforward. This includes complete blood count, liver function tests and triglycerides at baseline and repeating these 2 to 4 weeks after the initiation of therapy and then every 4 to 6 months thereafter. Of these tests, it is not clear that a complete blood count is required. I do not believe there are any long term side effects with the doses used for patients with psoriasis, and therefore X-ray monitoring does not appear needed.

**Tip 9: What to do for patients who have extensive psoriasis and a little bit of joint pain**

When patients have modest joint pain it probably does represent psoriatic arthritis. Perhaps some of the patients have osteoarthritis. In either case my approach to treatment of extensive psoriasis remains to try phototherapy first and to try to control the joint disease with a nonsteroidal anti-inflammatory drug. I will also refer the patient to a rheumatologist for evaluation of their joints. I do not have skill in range of motion testing nor in choice and interpretation of X-rays to assess joint involvement, so I utilize my rheumatology colleagues. If patients do have severe psoriatic arthritis that will definitely require methotrexate or a biologic treatment, then I will start those drugs in place of phototherapy.

**Tip 10: Methotrexate or a biologic, which is best?**

Methotrexate and new biologics are all excellent, helpful options for the treatment of patients with severe psoriasis. Each has its own advantages and disadvantages. Methotrexate is very effective for the skin and the joints. Yet there is a risk of death with the drug along with a host of other toxicities. New agents such as alefacept and efaluzimab do not appear to have the same serious risks of methotrexate, but the long term risks are not yet as well understood. We do have more long term experience with TNF inhibitors, but even with these we do not have the 50 years of experience that we have with methotrexate. TNF inhibitors are probably as effective as methotrexate for both the skin and joints, perhaps more so, and while we have more safety information on them, we still do not know what happens with 10 to 20 years of use. Side effects such as multiple sclerosis, opportunistic infections and the development of antinuclear antibodies are probably real, though such serious side effects are rare.

Which of these is the best drug? I like to discuss all of them with the patient and involve them in the choice. Patients vary considerably in their preferences, and some may choose a lower cost drug that has been around a long time while others may choose something newer without all the known risks of methotrexate. In any event, I think it is helpful to give patients the risks and benefits of all these drugs in writing. This helps them to make a well educated decision, and it also helps them remember all the potential risks that may come up. An easy way to do this is to give them a systemic treatment brochure from the National Psoriasis Foundation. This brochure is available freely through the Psoriasis Foundation website (www.psoriasis.org).

**Conclusions**

The first step in managing patients with psoriasis is to address their psychosocial needs. Start by estab-
lishing a strong physician/patient relationship by sitting close to the patient, touching them and asking them a few questions about their disease, showing that you are understanding and knowledgeable. Encourage patients to educate themselves and address the psychosocial questions they have.

For patients who have relatively localized psoriasis, use topical treatments. You will find that topical therapies will be more effective when patients actually apply them. Don’t overly scare patients with the side effects of medications, especially not at the first visit. Involve them with the treatment and choose a vehicle they find appropriate to both their skin and their lifestyle. Bring them back for a return visit within 1-2 weeks of initiating therapy in order to maximize their initial compliance to the drug; long term side effects can be discussed in more detail at that visit.

For patients with more extensive psoriasis, UVB phototherapy is almost always available and feasible. It works especially well in combination with topical therapy and oral retinoids. Oral retinoids with a long half life (acitretin) should not be used, however, in women of child-bearing potential. For those patients who fail phototherapy or who have severe psoriatic arthritis, methotrexate and biologicals are valuable options. I encourage you to involve patients in the choice of which of these are best for them.

**Riassunto**

I 10 punti fondamentali del trattamento della psoriasi

La psoriasi è una malattia complessa e comune che ha varie manifestazioni. I molti trattamenti per la psoriasi sottolineano la complessità gestionale della malattia. Una visione strutturale, complessa e orientata al paziente può aiutare a scegliere il trattamento appropriato, globale, della psoriasi. In tutti i pazienti con psoriasi devono essere presi in considerazione aspetti psicosociali. Inoltre, ai fini del trattamento, la maggior parte dei pazienti con psoriasi può essere diversificata in base alla forma localizzata, per la quale è possibile un trattamento topico, o più generalizzato della malattia, che richiede un fototrattemento o un trattamento sistemico. La base del successo del trattamento topico è rappresentata dalla buona compliance del paziente. La fototerapia, con o senza retinoidi per os, rappresenta la prima scelta per i pazienti con psoriasi estesa. Se questa non è efficace, si dovrebbe informare il paziente sulle opzioni terapeutiche sistemiche e lo si dovrebbe coinvolgere nella scelta del trattamento più adeguato. I gruppi di supporto, quali il National Psoriasis Foundation, sono utili sia per gestire gli aspetti psicosociali dei pazienti, sia per informarli sulle opzioni terapeutiche per loro possibili.

**Parole chiave:** Psoriasi - Fototerapia - Farmaci biologici.

**Rivista**

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What to do when acne treatments fail?

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Acne is a very common disease affecting both sexes from adolescence until their 4th decade. This extremely common condition has a major impact on the quality of life of patients, with significant physical, psychological and economical aspects. It is caused by increased sebum production, ductal cornification, bacterial colonization of the pilosebaceous ducts and inflammation. Topical and systemic treatment modalities aim against the various aetiological factors, and maintenance therapy is required in order to avoid relapses. Despite proper management and good patient compliance, there are cases of treatment failures. This article offers an overview of the guidelines on the treatment of acne, and highlights the aetiology and management in cases of poor response.

KEY WORDS: Acne, drug therapy - Acne, diagnosis - Acne, drug therapy, side effects.

Acne is the most common cutaneous disorder of multifactorial origin with a prevalence of 70-85% in adolescents. Typically, lesions are pleomorphic and range from open and closed comedones to inflammatory papules, pustules, cysts, and nodules, which may lead to scarring and disfigurement. It causes considerable morbidity through soreness, social handicap due to inflammatory lesions, and has a considerable psychologic impact including anxiety and depression. The effective treatment of acne remains a challenge, achieving an optimal response whilst minimizing side effects is often difficult. Topical therapy is employed as first-line treatment in mild acne, whereas for moderate and severe acne, administration of systemic therapy is required, often in combination with topical therapy. Suboptimal medication adherence is one of the major reasons for treatment failure among patients with acne. Motivating patients to adhere to treatment, especially during the maintenance phase, remains a challenge.

Of those patients who do not respond despite proper management and patient compliance, there are genuine poor responders, cases with serious side effects, patients with acne variants and patients with scars. When acne develops in individuals outside the usual susceptible age group, precipitating causes such as exposure to comedogenic substances or drugs must be excluded. Additionally, endocrine causes and the administration of anabolic steroids should be considered.

Pathophysiology of acne

The etiology of acne vulgaris is multifactorial and complex. The 4 key factors involved in the development of acne include abnormal desquamation of the follicular epithelium in the duct of the sebaceous gland,
inflammation, the presence and activity of *Propionibacterium acnes*, and excessive sebum production. Androgen hormones stimulate the sebaceous gland and promote sebum excretion.

The primary lesion in acne is the microcomedo. Histological examination reveals hyperkeratosis of the intrafollicular sebaceous ducts and dilatation of the sebaceous glands, in about 30% of facial follicles of a patient with acne. Interleukin-1α, an inflammatory cytokine, plays a major role in inducing inflammation in the microcomedo, with resultant activation of the entire acne process. *Propionibacterium acnes* is a Gram-positive anaerobic rod. There is a strong correlation between the number of these bacteria and the level of sebum production and inflammation in acne cysts. Humoral and cellular immune responses induced *Propionibacterium acnes*, such as the generation of enzymes, the production of interleukin-1α, the generation of heat-shock proteins and a mitogenic effect on T-cells, modulate acne severity. A positive chemotactic effect on neutrophils is a consequence of the breakdown of sebum into free fatty acids by bacterial lipase.

**Topical therapy**

Topical antibacterials are indicated for mild-to-moderate acne, and are a useful alternative for patients who cannot take systemic antibacterials. They act both as antibacterial agents suppressing *Propionibacterium acnes* in the sebaceous follicle and as anti-inflammatory agents inhibiting the production of free fatty acids. Selection of a topical antibacterial agent should be tailored for specific patients by choosing an agent that matches the patient’s skin characteristics and acne type. The extensive use of topical formulations of erythromycin and clindamycin has been complicated by the development of *Propionibacterium acnes* resistance to these antibiotics. In order to avoid *Propionibacterium acnes* resistance, topical antibiotics should not be used as monotherapy but can be used in combination with other agents. Topical antibiotic therapy has to be discontinued once improvement is seen (and not exceed 3 months of continuous use), and should be discontinued if no response is observed within 6-8 weeks of treatment.

Benzoyl peroxide is a non antibiotic antibacterial agent that is bactericidal against *Propionibacterium acnes* and has the advantage that so far, no resistance has been detected against it. The primary limitation of benzoyl peroxide in some acne vulgaris patients is cutaneous irritation or dryness. Combination products containing benzoyl peroxide and the topical antibiotics have been shown to prevent the development of antibiotic resistance in acne patients, and confer significant clinical improvement to patients who have already developed antibiotic resistance.

Adapalene, tazarotene, tretinoin and isotretinoin are topical retinoids that normalize desquamation of the follicular epithelium, and have overall favourable safety profiles. Local adverse events, seen especially during the early course of treatment, include peeling, erythema, dryness, burning, itching, and, in some cases, temporary exacerbation of acne. The degree of local skin intolerance varies among patients and may relate to the vehicle formulation used. These local effects can be minimized by applying on alternate evenings, decreasing exposure to sunlight, avoiding extreme temperatures, and using moisturizers in the morning. Adapalene formulations 0.1% are equally effective and significantly better tolerated than the other retinoids of similar concentration, so they can be used in cases of irritant dermatitis caused by other topical retinoids. The patient should be informed of these adverse events, in order to adhere to therapy. Combining topical antibiotics and topical retinoids may enhance the efficacy, since the retinoid will improve the penetration of the antibiotic.

Azelaic acid 20% cream and salicylic acid 3-5% have mild comedolytic and antimicrobial effects, and can be used as second-line treatment, complementary to topical retinoids.

**Oral antibiotics**

Oral antibiotics are used in cases of moderate to severe acne, in acne that is resistant to topical treatment and in acne covering a large part of the body surface. Most frequently used are the tetracyclines, especially oxytetracycline, lymecycline, minocycline and the older first generation tetracyclines. Erythromycin and trimethoprim are also frequently used. They are bacteriostatic for *Propionibacterium acnes*, and have also been demonstrated to have anti-inflammatory activities through inhibition of lipase production by *Propionibacterium acnes*, as well as inhibition of leukocyte chemotaxis. The selection of the proper antibiotic is based on *Propionibacterium acnes* sensitivity or
resistance to the drug, the ability of the antimicrobial to reach the lipid-rich environment of sebaceous follicles, its cost and availability. The recommended daily doses are 50-200 mg for doxycycline or minocycline, 500-1000 mg for tetracycline or erythromycin, 300 mg for lymecycline, and 200-300 mg twice daily for trimethoprim. Treatment failures can be attributed to poor patient compliance, resistant strains of *Propionibacterium acnes*, development of gram-negative folliculitis and a very high sebum excretion rate.

Over the past 20 years, major concerns have been repeatedly expressed over antibiotic-resistant acne in Europe and in the USA. The rise in antibiotic resistance threatens to reduce the future usefulness of the current mainstay of therapy. The prescription of prolonged courses of antibiotics or multiple courses of antibiotics, and the extensive use of topical formulations of erythromycin and clindamycin are the main reasons for increased *Propionibacterium acnes* resistance. Resistance is highest with erythromycin and clindamycin, medium with tetracycline, doxycycline and trimethoprim, and rare with minocycline. In order to avoid *Propionibacterium acnes* resistance, one should limit the use of antibiotics to a short period (4 months) with minimum duration 6 weeks, avoid concomitant use of oral and topical dissimilar antibiotics, use topical retinoids and/or benzoyl peroxide to accelerate improvement and to maintain the good result, and use the same antibiotic (if it was effective) when retreatment with antibacterials is necessary. Cases of *Propionibacterium acnes* resistance can be treated with minocycline or isotretinoin.

Gram-negative folliculitis is caused by overgrowth of gram-negative species like Klebsiella, Pseudomonas, Proteus and Enterobacter, and manifests as a sudden onset of numerous pustules or sudden deterioration of acne in patients that were responding to therapy. It can be managed with administration of ampicillin or isotretinoin.

A high sebum excretion rate also reduces response to antibiotics, since the excess of sebum dilutes the drug and produces lower and sub-therapeutic concentration of the antibiotic in the pilosebaceous unit. This can be controlled by doubling the dose of the antibiotic or by administering isotretinoin or hormonal therapy with cyproterone plus estrogen.

Minocycline is the more frequently used oral antibiotic for acne, as it combines low *Propionibacterium acnes* resistance with rapid clinical improvement. The dermatologist should, however, be prepared to manage the possible adverse events. In case of hyperpigmentation of skin and mucosa, the drug should be stopped and treatment change to doxycycline. Minocycline occasionally causes headaches; if they are persistent and accompanied by dizziness, the suspicion of intracranial hypertension should rise, and the dose should be lowered, or the therapy change to doxycycline. It has rarely been linked with drug-induced lupus erythematosus, and can impair liver function. Laboratory testing of antinuclear factor and liver enzymes should be performed every 3 months while on therapy. All cyclines can cause photosensitivity, mucosal candidiasis and pseudomembranous colitis, and should be discontinued in that event.

### Isotretinoin

Oral isotretinoin has been used for decades in the treatment of acne vulgaris. It is the only agent that addresses all the pathophysiological factors involved in acne, since it reduces sebum production, normalizes follicular desquamation, and reduces inflammation and skin colonization by *Propionibacterium acnes*, even by antibiotic-resistant strains. It is considered the most efficacious therapeutic option for severe acne, but is currently being used with increasing frequency for the treatment of moderate acne that has failed to respond to other modalities. More specifically, oral isotretinoin is indicated in severe nodulocystic acne and its variants (pyoderma faciale and acne fulminans), inflammatory acne with scarring, moderate to severe acne unresponsive to treatment with three months of combination treatment including oral tetracyclines and contraceptives, acne with severe psychological distress, Gram-negative folliculitis, and frequently relapsing acne where repeated courses of systemic antibiotics are needed.

Large inflammatory cysts are managed with isotretinoin at 1 mg/kg, intralésional injection of triamcinolone acetate, drainage or spraying with liquid nitrogen. Pyoderma faciale was originally described by O’Leary and Kierland in 1940. It is an inflammatory disease that occurs in females 25-40 years, as a rapid development of devastating acne. This explosive onset of fluctuant facial papulonodules and confluent draining sinuses confined to the face is not a true pyoderma and it is not infectious. Seborrhoea prior to onset is typical. It is treated with isotretinoin at 1 mg/kg in
combination with topical and systemic corticosteroids. Scarring is often minimal when the lesions clear. Acne fulminans manifests as severe truncal acne in male patients, accompanied by fever, polyarthropathy and leucosytosis. It is managed with isotretinoin 1 mg/kg, oral erythromycin at 1 g/day and prednisone 0.5-1 mg/kg.

Isotretinoin has several side effects, which are usually manageable and outweighed by its benefits. It is, however, of critical importance to inform the patients about these side effects. Teratogenicity is a major concern but is preventable if the patient adheres to strict contraception starting a month before initiation of treatment, undergoes a negative pregnancy test thereafter and continuing contraception for another month after stopping the drug. Consensus has not been reached on the issue of depression and suicide resulting from the use of isotretinoin. Although case reports suggest an association between isotretinoin and depression and suicide, more rigorous observational and epidemiologic studies have shown a lower incidence of suicide in patients who are on treatment with this drug, compared with a similar population not exposed to it. However, the potential psychiatric side events should be discussed; the drug should be discontinued and the patient referred to a psychiatrist if any symptoms of depression occur while on treatment. Laboratory monitoring, involving total blood counts, liver enzymes, triglycerides, total cholesterol, low-density and high-density lipoproteins, is imperative in order to assess hematologic and metabolic deviations caused by the drug. It should be performed as baseline before treatment, and should be repeated at the end of the first and second month of therapy. If normal, further blood testing is unnecessary. Other side effects include dryness of the skin and mucosae that usually respond to topical moisturizers, initial temporary worsening of acne lesions that resolves after two months of treatment, photosensitivity that occurs in 5% of cases, arthralgia and myalgia that are treated with lowering the dose of isotretinoin or prescription of non steroidal anti-inflammatory drugs, severe night blindness that can hamper driving at night, and possibility of mild hair loss.

The dosage used for a full course of treatment is very important. This should not be below 0.5 mg/kg per day and should not exceed 1 mg/kg per day, in order to limit side effects. The duration of treatment is determined by the body weight of the patient and the daily dose taken. One should aim for a minimum target of 120 mg per kg as a total cumulative dose but this can be increased to 150 mg per kg if a satisfactory result has not been achieved once 120 mg/kg has been reached. The chances for a permanent cure are reduced if treatment is discontinued before the threshold of 120 mg/kg has been reached, even if the acne has cleared before then. In case of a severe acne flare-up during therapy, administration of 0.5-1 mg/kg of prednisone for 15-10 days with tapering of dose thereafter, usually improves the condition. In more severe cases, lowering of isotretinoin dosage or even discontinuation may be needed. If restarted, it should be administered initially at low dose (0.1 mg/kg) and gradually increased to 0.5 mg/kg.

Rates of recurrence vary (14-45%), but can be managed with oral antibiotics or additional course of isotretinoin. Low-dose treatment (10 mg daily or 10 mg 3 times a week) or pulse-dose regimen (e.g., 20 mg daily for 1 week every month), are quite effective as maintenance in patients with very severe chronic comedonal acne and greasy skin, who relapse after discontinuation of a full course of the drug. However, teratogenicity remains a significant issue for these patients.

Poor response to isotretinoin can be seen in patients with many macrocomedones and/or microcysts, young patients, patients who have received total cumulative dose less than 120 mg/kg, and women with endocrine problems. Macrocomedones and microcysts require excision or cautery under topical anaesthesia before treatment with isotretinoin. Patients who have received sub-optimal isotretinoin dose should repeat the regimen with the proper dose.

Hormonal treatment

Chronic, persistent acne in females that relapses after isotretinoin treatment, late onset of acne, and SAHA syndrome (Seborrhoea, Acne, Hirsutism, Androgenic alopecia) should rise suspicion for hyperandrogenism. Cutaneous manifestations of hyperandrogenic disorders can be caused by elevated levels of free testosterone or androgen precursors, due to polycystic ovarian syndrome (PCOS) or late onset adrenal hyperplasia. The main hormone responsible for increasing sebum production is dihydrotestosterone, converted from testosterone in the sebaceous glands by the enzyme 5-alpha-reductase. In women with normal serum levels of testosterone or androgen precur-
sors, enhanced local conversion to testosterone, or to the more potent androgen dihydrotestosterone, may lead to increased androgen activity in the pilosebaceous unit. Large individual variations in the response to normal or elevated androgens suggests considerable differences in local androgen metabolism and androgen receptor-mediated activities, which may partly be related to genetic disposition. PCOS is a syndrome of variable combinations of menstrual irregularity, hirsutism or acne, and obesity. These symptoms are often attributed to normal pubertal events, which can lead to a delay in diagnosis. PCOS is also associated with metabolic disturbances, such as obesity and insulin resistance with hyperinsulinemia. Treatment should be instituted early to decrease symptoms and long-term sequelae of PCOS, and includes weight loss, oral contraceptives and antiandrogens.

Oral contraceptives (OC) with a predominant estrogen effect may improve mild to moderate forms of acne and seborrhea, hirsutism and androgenetic alopecia, in a time-dependent manner. In women who do not respond satisfactorily, treatment with contraceptives containing a progestogen with antiandrogenic activity is recommended. In many women with severe acne or hirsutism, a considerable increase in the local concentration of the antiandrogenic progestogen is required to reduce the androgenic interaction with the androgen receptor. For this therapy, an OC containing cyproterone acetate can be used. Possible treatments include ethinylestradiol (EE) 35 mg and cyproterone acetate (CPA) 2 mg (Dianette), EE 25 mg and CPA 50 mg, EE 25 mg and levonogestrel 100 mg. Hormonal therapy should last at least 4-6 months, and relapses are common after discontinuation. In these cases, it is advisable to repeat the course or administer suitable low-dose formulations for a prolonged period of time. Adverse events include weight gain, headaches, melasma, thrombosis and depression. OC can be used in combination with topical retinoids or oral isotretinoin, speeding up and maintaining the response to treatment.

Spironolactone can be administered as an effective androgen receptor blocker at 25-200 mg taken with meals. Side effects include elevation in serum potassium, breast tenderness and disturbances in menstruation. Contraception should be used throughout therapy, due to the possible abnormalities in fetal male genitalia. Low-dose systemic corticosteroids are useful in treating patients with late-onset congenital adrenal hyperplasia, an inherited defect in 21- or 11-hydroxylase enzyme. Prednisone 2.5-5 mg/day, or dexamethasone 0.125-0.5 mg/day can be used, with dexamethasone having a greater risk for adrenal suppression. For this reason, an ACTH simulation test should be performed.

Conclusions

During the last 20 years, the number of topical and systemic drugs for the treatment of acne vulgaris has been enriched. However, the need for alternative therapies remains important. The use of laser and light-based modalities, such as aminolevulinic-photonodynamic therapy (ALA-PDT), which are currently being tested in combination therapy, may provide an additional safe and effective treatment for acne vulgaris. Office procedures such as comedo extraction, chemical peels and intralesional corticosteroids may be useful in selected cases but cannot replace medical treatment. Rational use of available modalities according to the type and severity of acne is a key component of successful therapy and allows the physician to provide optimum help. Clinical experience has shown that combination therapies, which affect various aspects of pathophysiology, are most likely to achieve this goal and help in its long-term management and resolution by individualizing treatment. It should be stressed out that all acne cases can be adequately controlled, if the doctor-patient relationship has been built on trust and confidence.

Riassunto

Che fare quando il trattamento per l’acne fallisce?

L’acne è una malattia molto comune, che colpisce entrambi i sessi dall’adolescenza sino alla quarta decade di vita. Questa condizione estremamente comune ha un impatto notevole sulla qualità di vita dei pazienti, con significativi aspetti fisici, psicologici ed economici. L’acne è provocata da un aumentata produzione di sebo, dalla cornificazione duttale, dalla colonizzazione batterica dei dotti pilosebacei e dall’inflammazione. I diversi trattamenti topici e sistemi- cici hanno quale obiettivo di contrastare i diversi fattori eziologici e la terapia di mantenimento è necessaria per evitare le recidive. Nonostante una gestione appropriata e una buona compliance da parte del paziente, vi sono casi nei quali il trattamento fallisce. Questo articolo offre una panoramica sulle linee guida di
trattamento dell’acne e focalizza l’eziologia e la gestione dei casi con scarsa risposta al trattamento.

PAROLE CHIAVE: Acne, terapia farmacologica - Acne diagnosi - Acne, terapia, effetti collaterali.

References

The case of a patient showing a typical nevus anemicus in close proximity of a port-wine stain is reported. Both nevi are functional anomalies, the difference between them being the tone of the cutaneous vessels. This case is a good example of vascular twin nevus. The mechanism of twin spotting offers a suitable explanation for the possible co-occurrence of the 2 nevi.

**KEY WORDS:** Nevus - Vascular nevus - Skin.

Vascular birthmarks are congenital anomalies of the cutaneous vessels that are frequently encountered in dermatological clinical practice. At times, these anomalies are found in association with other tissutal abnormalities forming complex syndromes, such as the Klippel-Trenaunay syndrome and the pigmento-vascular phacomatosis. Rarely, different cutaneous vascular anomalies may be found in a single patient. This may occur by mere chance or it may not. The unusual but non fortuitous association of 2 different vascular nevi in a single patient is the object this brief case report.

**Case report**

A 24-year-old patient was observed for possible laser therapy of a port-wine stain localised around his left eye, in the area of the first and second left trigeminal branches (Figure 1). The port-wine stain consisted of telangiectatic vessels and was said to have been present since birth. Ophthalmologic examination and MRI had been previously performed excluding Sturge-Weber syndrome. During dermatological examination a large pale macule with punched-out irregular borders, occupying the left upper part of the neck and chest was seen (Figure 1). This pale area had been noted after the first few years of life and was formed by the coalescence of smaller macules. The patient reported that when exposed to the sun, the pale area became tanned but to a lighter degree than the surrounding skin. Diascopy of the adjacent normal skin caused the whitish pale area to extend. Rubbing the pale area caused reddening of the normal surrounding skin but not of the pale skin itself (Figure 2). The patient was otherwise healthy and his family history was negative for similar cutaneous disorders. The diagnosis of vascular twin nevus was made because of the presence of a nevus anemicus and a port-wine stain in close proximity.

**Discussion and conclusions**

Nevus anemicus is a circumscribed vascular anomaly, characterised by the presence since birth of a pale macule with irregular geographic margins, most often
observed on the upper trunk.1, 2 The macule scarcely reddens after friction, is not enhanced by observation with Wood’s light, contains normally pigmented hair, and is not distinguishable from the surrounding skin when the latter is blanched by diascopy. Histological examination shows normal skin with normal vessels. The absence of anatomic abnormalities reflects the pharmacological or functional nature of nevus anemicus. The pale macule is due to sympathetic vasoconstriction as a result of an increased local hypersensitivity of the α-adrenergic receptor of cutaneous blood vessels.3, 4

Port-wine stain (nevus flammeus) is a congenital malformation characterised by a red vascular macule of variable dimension and clear-cut margins. It is most often observed on the face and head but can occur anywhere on the body surface.1 Histological examination shows the presence of dilated thin-walled capillaries and venules in the dermis. The permanent vascular ectasia of port-wine stain results from a functional alteration, most probably from a neural deficiency of the autonomic sympathetic innervation of the cutaneous blood vessels.5 Thus, both nevus anemicus and port-wine stain are functional anomalies. The difference between them lies in their vascular tone, namely in the former there is a sustained vasoconstriction, whereas in the latter there is a permanent vasodilatation. The 2 vascular nevi are complementary abnormalities.

The reported patient shows the combination of a nevus anemicus and a port-wine stain. This event is not uncommon. Hamm et al. reviewed 28 previously reported cases and added the description of 4 new ones, showing that the 2 different nevi were situated directly adjacent to each other.6 The frequent co-occurrence of the 2 nevi, their simultaneous appearance, and their close spatial proximity provide evidence that their association is not coincidental. Hence, the combination of the 2 nevi has been considered a distinct entity, originally called naevus vascularis mixtus6 and more recently called “vascular twin nevus”.7

An excellent explanation for the phenomenon of vascular twin nevus is provided by the theory of twin spotting, which has been mutated from genetic recombination studies in animals and plants.8, 9 A single autosomal gene locus controlling the balance between...
VASCULAR TWIN NEVUS

Figure 3.—Mechanism of twin spotting. A) A single autosomal gene locus controls the vascular tone. In the case of a somatic recombination occurring during the mitotic process, a cell being heterozygous for this locus could give rise to 2 different homozygous daughter cells. B) Two autosomal genes control the vascular tone and are localised at different loci of a homologous pair of chromosomes. Both genes are heterozygous for a given mutation. During the mitotic process a somatic recombination could lead to the formation of 2 different daughter cells, each one being homozygous for the given mutation. Modified from Happle.10

Vasoconstriction and vasodilatation would exist with different alleles. In the heterozygous state the vascular tone would be normal. In the case of somatic recombination occurring during the mitotic process, a cell heterozygous for this locus could give rise to 2 homozygous daughter cells (Figure 3A). One of these 2 daughter cells would be homozygous for vasoconstriction while the other would be homozygous for vasodilatation. If this process took place during the embryonal period, the 2 daughter cells could represent the stem
cells of 2 different vascular nevi (nevus anemicus and port-wine stain), which will both appear in close proximity to each other, thus giving rise to a vascular twin nevus.

The same mechanism could act in the case of 2 autosomal genes controlling the vascular tone (vasoconstriction/vasodilatation) localised in different regions of 2 chromosomes forming a homologous pair (non-allelic twin-spotting phenomenon). Two independent heterozygous mutations at these loci would become visible only in the rare event of somatic recombination occurring during the mitotic process. The pairing and recombination of the 2 homologous chromosomes could lead to an exchange of the 2 segments bearing the mutations, resulting in 2 different daughter cells, each one homozygous for either mutation (Figure 3B).10

**Riassunto**

**Nevi vascolari gemelli**

Viene riportato il caso di un paziente che presentava un ampio nevo anemico in prossimità di una chiazza di tipo «vino Porto». Entrambi questi nevi vascolari rappresentano anomalie funzionali, la differenza tra loro essendo costituita unicamente dal tono vascolare cutaneo. Il caso costituisce un buon esempio di nevo vascolare gemello e il meccanismo del cosiddetto «twin spotting» offre un’adeguata spiegazione alla possibile associazione delle 2 lesioni neviche.

**PAROLE CHIAVE:** Nevi - Nevi vascolari - Cute.

**References**

Efficacy and safety of long-term infliximab therapy in moderate to severe psoriasis and psoriatic arthritis

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Aim. Psoriasis is a genetically determined, chronic inflammatory skin disease affecting approximately 2% of the general population; it may cause physical discomfort and emotional psychological effects which may interfere with the quality of life. Patients with psoriatic arthritis show greater impairment of their quality of life and longer disease duration. The aim of this study was to evaluate the efficacy and safety of long-term infliximab therapy in psoriasis.

Methods. Efficacy and safety of long-term (week-102) infliximab therapy were evaluated in 34 plaque-type and 34 psoriatic arthritis patients, all not responsive or with contraindications to conventional therapies. Infusions, 5 mg/kg, were at week-0, 2, 6, followed by maintenance every 8 weeks.

Results. Improvement in Psoriasis Area and Severity Index (>75%) was in 85.3% of plaque-type patients at week-6, in 92.3% at week-22, in 94.1% at week-46, in 77.7% at week-102. Improvement in Health Assessment Questionnaire Disability Index (>75%) was in 88.8% of arthropathic patients at week-6, in 92.3% at week-22, in 94.1% at week-46, in 77.7% at week-102. Improvement in Pain Scale (>75%) was in 100% of arthropathic patients at week-6, in 92.3% at week-22, in 100% at week-46, in 100% at week-102. No serious adverse events were noted.

Conclusion. Infliximab appears to be an effective long-term therapy for psoriasis and may have a lower incidence of side effects than traditional systemic therapies.

KEY WORDS: Biologic therapy - Tumor necrosis factor alpha - Monoclonal antibodies.

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agents, was recently tested on long-standing inflammatory diseases. Infliximab is a chimeric anti-tumor necrosis factor (TNF-α) monoclonal IgG1 antibody, with high affinity and avidity for soluble and cell-surface transmembrane forms of TNF-α one of the major cytokines involved in cutaneous inflammatory diseases. In recent clinical studies in patients with moderate to severe psoriasis or psoriatic arthritis, infliximab infusions given at variable dosages of 3-10 mg/kg of body weight was effective and generally well-tolerated, with clinical benefit after the induction period, namely the first 3 infusions at week-0, 2 and 6. It has usually been prescribed in multiple administrations (rarely single) as monotherapy or with low-dose of immunosuppressants added to reduce the risk of side effects and the formation of antibodies to infliximab, human antichimeric antibodies (HACA).

We performed an open-label, compassionate-use, clinical trial to evaluate efficacy and safety of long-term infliximab (5 mg/kg) therapy in patients affected by moderate to severe psoriasis or psoriatic arthritis who were non-responders or ineligibles to conventional systemic therapies. Efficacy was evaluated using the Psoriasis Area and Severity Index (PASI) for plaque-type psoriatic patients and the Health Assessment Questionnaire (HAQ) Disability Index and Pain Scale measures for the arthropathic patients.

Materials and methods

To participate in the study, patients had to meet the following eligibility criteria: >18 years of age, moderate to severe plaque-type psoriasis with PASI score >20 or psoriatic arthritis with any PASI score, no response or ineligibility to conventional systemic treatments (cyclosporin-A, methotrexate, acitretin, etretinate, phototherapy, NSAID, steroids). Exclusion criteria were the following: drug-induced psoriasis, use of any systemic treatments affecting PASI score, live vaccinations during the trial, routine haematological laboratory screening test results > 2 times the normal range, history of latent or current active tuberculosis (TB), history of chronic or recurrent serious infectious disease (human immunodeficiency virus, hepatitis B, hepatitis C) or opportunistic infection, evidence of internal malignancies or serious infections within 3 months prior to the first infusion, signs or symptoms of systemic lupus erythematosus, demyelinating diseases, lymphoproliferative diseases or non-cutaneous malignancies within the previous 5 years, and congestive heart failure, even if medically-controlled and asymptomatic. All patients were screened for TB prior to study entry. Patients with a positive TB test but negative chest X-ray were permitted to enter the study after a period of 3 weeks on specific anti-tubercular treatment (isoniazid 200 mg/day) prescribed for up to 6-9 months. The wash-out period for systemic medications prior to study entry was 3 months, for topical treatments was 2 weeks. All patients provided written informed consent. The local ethical committee allowed the study.

Patients received intravenous drip treatment with infliximab at 5 mg/kg of body weight. The regimen consisted of an induction period, with infusions at week-0, 2 and 6, and a maintenance period, with booster infusions at the same dosage every 8 weeks. Patients were monitored for the occurrence of adverse events during the infusion and for 2 hours afterwards. Clinical and routine laboratory evaluations, including detection of antinuclear antibodies, thyroglobulin antibodies and thyroperoxidase antibodies, TB test, chest and articular X-rays, were performed at baseline, week-6, week-22, week-46 and week-102. Clinical assessment included physical examinations, photographic documentations, monitoring for adverse events, and PASI and HAQ evaluation. The reference time frame for HAQ was the past week. All patients were carefully instructed to avoid common risks of viral and/or bacterial infections and to immediately report these. Primary efficacy endpoints were >75% improvement of PASI (PASI75) in the plaque-type patients and >75% improvement of HAQ (HAQ75) Disability Index and Pain Scale measures in the arthropathic patients.

We enrolled 2 groups of subjects: 34 patients (20 male and 14 female, aged from 27 to 77, mean age 44.8) affected by plaque-type psoriasis, and 34 patients (23 male and 11 female, aged from 28 to 68, mean age 48.35) suffering from psoriatic arthritis with any PASI score. For patients with plaque-type psoriasis, PASI scores ranged from 20.4 to 48.6, mean PASI=28.4 (SD=6.7909). For patients with psoriatic arthritis, the mean baseline HAQ Disability Index score was 2.1 (range 0.3-2.7). SD for HAQ was not calculated because of its short range of values. All patients previously received systemic treatments (Figure 1). They
entered the study because of side effects, contraindications, unresponsiveness.

**Results**

All patients from both groups completed the induction period. Eight of the 34 plaque-type psoriatic patients are now at week-6, 10 at week-22, 8 at week-46, and 8 at week-102. Nine of the 34 patients with psoriatic arthritis are now at week-6, 8 at week-22, 8 at week-46 and 9 at week-102. At week-6, 29/34 (85.3%) plaque-type psoriatic patients achieved PASI75, with a mean PASI score of 4.6 (range 0.2-12.1 - SD 3.7364) and a mean PASI improvement of 70.7%. Two patients withdrew from the study because of antinuclear antibodies development (titers 1:320 and 1:160), at week-5 and 7, respectively. Concerning arthropathic patients, 19/34 of them (55.88%) experienced >75% improvement in HAQ Disability Index scores at week-6, 24/26 (92.3%) at week-22, 16/17 (94.11%) at week-46 and 7/9 (77.7%) at week-102. All the patients (100%) with arthritis referred >75% improvement in scores of the HAQ Pain Scale at week-6, 24/26 (92.3%) at week-22, 17/17 (100%) at week-46 and 9/9 (100%) at week-102. These data are summarized in Table I. There were no reports of severe adverse events during the treatment period or reports of delayed hypersensitivity reactions, occurring 1 to 14 days after the infusion. Among the non-specific adverse events, defined as infusion-related during or 2 h after infliximab administration of the agent, only mild headache was described by most of the subjects (49/68; 70%). One patient had an episode of mild hypertension at week-6, which was considered unlikely to be related to infliximab treatment, and a case of mild superficial folliculitis of the back was reported. No serious infectious or lymphoproliferative disorders were reported during the induction phase or during the long-term regimen.

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>Methotrexate</th>
<th>Acitretin</th>
<th>Etretinate</th>
<th>Ciclosporin A</th>
<th>Phototherapy</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>35</td>
<td>30</td>
<td>25</td>
<td>10</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>B</td>
<td>22</td>
<td>11</td>
<td>16</td>
<td>10</td>
<td>7</td>
<td>0</td>
</tr>
</tbody>
</table>

**Table I.—Percentages of patients achieving PASI75 and HAQ75 during infliximab therapy.**

<table>
<thead>
<tr>
<th>Week-6</th>
<th>Week-22</th>
<th>Week-46</th>
<th>Week-102</th>
</tr>
</thead>
<tbody>
<tr>
<td>PASI75</td>
<td>29/34 (85.3%)</td>
<td>24/26 (92.3%)</td>
<td>10/16 (62.5%)</td>
</tr>
<tr>
<td>HAQ75</td>
<td>19/34 (55.9%)</td>
<td>22/26 (92.3%)</td>
<td>16/17 (94.1%)</td>
</tr>
<tr>
<td>Disability Index Score</td>
<td>34/34 (100%)</td>
<td>24/26 (92.3%)</td>
<td>17/17 (100%)</td>
</tr>
<tr>
<td>HAQ Pain Scale</td>
<td>34/34 (100%)</td>
<td>24/26 (92.3%)</td>
<td>17/17 (100%)</td>
</tr>
</tbody>
</table>
Discussion

The rationale of using infliximab for treating psoriasis has been previously described.16-19 TNF-α increases the synthesis of proinflammatory cytokines (IL-1, IL-6, IL-8, IFNγ, colony stimulating factors), activates nuclear transcription factors (NFκB) and regulates expression of adhesion molecules.17 Detection of increased levels of TNF-α in psoriatic plaque, but not in normal skin, confirms the pivotal role of this factor on keratinocyte proliferation, expression of adhesion molecules on keratinocytes and endothelial cells, cell trafficking and enhancement of neutrophil functions.18 In addition, increased serum TNF-α levels are correlated with a higher disease activity and reduced by effective therapies.19 By blocking both soluble and cell-surface transmembrane forms of TNF-α infliximab induces rapid decrease of epidermal T-cell infiltration, down-regulates adhesion molecules expression and normalizes keratinocyte proliferation.

In our study of 68 psoriatic patients, we were able to confirm and validate the efficacy and safety of 2-year infliximab therapy on moderate to severe psoriasis and psoriatic arthritis. The choice of a dosage of 5 mg per kilogram instead of 3 mg was in accordance with previously reported protocols and personal observation.9, 10 The majority of plaque-type psoriatic patients obtained and maintained PASI75 during the course of treatment being the best results achieved along the first year of therapy. Degree of efficacy was observed from week-22 to week-102, in particular the percentages of patients showing PASI75 accounted for 92.5%, 62.5% and 50% at week-22, 46 and 102, respectively. However, all patients who reached 2-year observation maintained PASI50 with a mean PASI improvement of 70.7%. Cutaneous relapses observed during the treatment always showed a lower PASI than baseline score and they were mostly observed during the second month before the subsequent infusion. It could be hypothesized that reduction of efficacy, along the course of therapy, may be somehow related to the onset of immune tolerance to the antigenic structure of the drug, not necessarily linked to HACA formation. In another series of patients, we experienced that shortened of free-intervals between 2 infusions or combined therapy with topical antipsoriatic drugs can overcome this event, while increased dosages of infliximab did not correlate with better results (data not shown).

The reduction of arthritis-related symptoms was the most remarkable outcome in our study. The improvement of HAQ Disability score was substantial at week-22, more impressive at week-46 and still maintained at 2 years by most of the patients. Arthritis-related pain improved in almost all subjects during the whole course of therapy. The reduction of pain preceded the recovery of functional abilities. As expected, patients who entered the study already suffering from permanent ankyloses did not achieve a reversal of long-standing functional disabilities.

A high incidence of adverse events (76%) is reported in patients treated with infliximab for non-dermatologic indications.20 Patients who produce autoantibodies are more likely to develop infusion reactions than those who remain autoantibodies-negative, and the use of concomitant immunosuppressant agents reduces the frequency of sudden or delayed infusion reactions. In the overall safety analysis of infliximab, the comparison between patients treated with infliximab for other disease indications, e.g., Crohn’s disease (CD) and rheumatoid arthritis (RA),20 and psoriatic patients suggests a substantially lower incidence of side effects in dermatological patients (data not shown). We may assume that the difference could be in part related to the general better health conditions of the psoriatic patients in our study. RA patients show a higher incidence of lymphoproliferative diseases, autoimmune disorders (e.g. Sjogren’s syndrome),21 or specific pulmonary involvement (rheumatoid vasculitis, rheumatoid nodules). CD patients may develop several immune dysfunctions and are reported to have increase risk of neoplasms.22, 23 These observations could be related to the increased incidence of adverse events, such as secondary infections, autoimmune alterations or lymphomas, reported in infliximab-treated RA and CD patients,20 compared to the low incidence of side effects observed in infliximab-treated psoriatic patients. In our study, 17 patients are now at 2-year observation: none of them developed serious adverse events during the infusions or delayed hypersensitivity reactions following treatment. Headache, reported by the patients during the infusion, was easily resolved with paracetamol. During the long-term treatment, no serious signs of immunosuppression, onset of skin neoplasms or TB reactivation were observed. Although development of auto-antibodies during infliximab therapy is only rarely associated with symptoms suggestive of an autoimmune disease such as LES-like syndrome, the 2 patients with plaque-type psoriasis who discontinued...
the treatment because of positive antinuclear antibodies titers, did not, so far, present any clinical signs of autoimmune disorder.

**Conclusions**

In conclusion, our results show that, among the new biologic therapies, infliximab, at the dosage of 5 mg/kg, can be considered a valid alternative therapy for long-term inflammatory cutaneous diseases, such as psoriasis. The clearing of psoriatic plaques that was observed at week-6 has been maintained in most of the patients who have reached the 2-year observation period. In patients with psoriatic arthritis, infliximab treatment has resulted in significant improvements in reductions of pain and functional disability. Considering the chronic not-remitting course of the articular involvement in psoriatic arthritis, we propose that starting therapy at the first diagnosed signs of the arthropathy might prevent further damage. The absence of significant adverse events in the observation period suggests that infliximab therapy has a lower incidence of side-effects than traditional long-term systemic anti-psoriatic therapies.

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**Riassunto**

**Efficacia e sicurezza della terapia a lungo termine con infliximab nella psoriasi moderata-severa e nell’artrosi psoriasica.**

**Obiettivo.** La psoriasi è una patologia infiammatoria cronica cutanea geneticamente determinata che interessa circa il 2% della popolazione generale e può causare disagio fisico e potenziali conseguenze psicologiche che interferiscono con la qualità di vita. I pazienti con psoriasi artropatica presentano una notevole compromissione della qualità di vita e una più lunga durata della malattia. Lo scopo dello studio è stato valutare l’efficacia della terapia a lungo termine con infliximab nellapsoriasi.

**Metodi.** È stata valutata l’efficacia e la sicurezza a lungo termine (102 settimane) della terapia con infliximab in 34 pazienti affetti da psoriasi volgare e in 34 pazienti affetti da psoriasi artropatica, tutti non rispondenti o con controindicazioni alle terapie convenzionali. Le infusioni, alla dose di 5 mg/kg, sono state effettuate al tempo 0, dopo 2 e dopo 6 settimane, seguite da infusioni di mantimento ogni 8 settimane.

**Risultati.** Un miglioramento del Psoriasis Area and Severity Index (>75%) è stato osservato nell’85.3% dei pazienti affetti da psoriasi volgare alla settimana 6, nel 92.3% alla settimana 22, nel 62.5% alla settimana 46, nel 50% alla settimana 102.

Un miglioramento dell’Health Assessment Questionnaire Disability Index (>75%) è stato osservato nel 55.88% dei pazienti artropatici alla settimana 6, nel 92.3% alla settimana 22, nel 94.11% alla settimana 46, nel 77.7% alla settimana 102.

Un miglioramento della Pain Scale (>75%) è stato osservato nel 100% dei pazienti artropatici alla settimana 6, nel 92.3% alla settimana 22, nel 100% alla settimana 46, nel 100% alla settimana 102.

**Conclusioni.** Non sono stati osservati effetti collaterali gravi. L’infliximab si conferma quale terapia a lungo termine efficace e con minore incidenza di effetti collaterali rispetto alle terapie tradizionali.

**PAROLE DI CHIAVE:** Terapia biologica - TNF-α - Anticorpo monoclonale.

**Riferimenti**