LEADING ARTICLE

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Risk of Melanoma with Psoralen/Ultraviolet A Therapy for Psoriasis

Do the Known Risks Now Outweigh the Benefits?

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Abstract

Since the introduction in the 1970s of treatment with oral psoralens with long-wave ultraviolet radiation in the A range (PUVA), there has been an increasing concern about the long term carcinogenic effect of the therapy. The main indication for PUVA is psoriasis, a common, chronic and intractable skin disease that affects 1 to 3% of the world's population. The effectiveness of PUVA in inducing and maintaining the remission of severe psoriasis has been amply documented. Although psoriasis is not a life-threatening disorder, it may be associated with restriction of activities and days lost to hospitalisation. Therefore, a number of systemic treatments such as methotrexate and cyclosporin have been used. None of these treatments has been as carefully studied for long term adverse effects as PUVA.

The short-term adverse effects of PUVA are generally well known and tolerated. The major mid-term adverse effect, squamous cell carcinoma of the skin, has been well documented in a number of large-scale epidemiological studies that have led to recommendations such as to restrict the lifetime number of treatments. Although squamous cell carcinoma is potentially life-threatening, it is usually slow growing and can be adequately managed by proper surveillance, treatment and follow-up.

The situation is quite different for malignant melanoma, which is often fast growing and fatal. Except for anecdotal reports, malignant melanoma has not been observed in PUVA patients until recently. However, a report of a cohort of 1380 patients with psoriasis has concluded that about 15 years after the first treatment the risk of melanoma is increased approximately 5-fold in patients treated with high doses. Although this report needs to be confirmed by other multicentre trials, it is alarming since the association between exposure to ultraviolet light and development of melanoma is well established both in humans and in experimental animals. Until this study is validated, it is recommended that the guidelines for PUVA therapy should be rigorously followed and that the contraindications should be extended to include history or family history of melanoma and patients who have already received >200 treatments.

It has recently been reported in a cohort study of patients with psoriasis that therapy with oral methoxsalen (8-methoxypsoralen) and long-wave ultraviolet radiation in the A range (PUVA) is associated with an increased risk of developing malignant melanoma.[1] Previously, only sporadic cases of melanoma have been reported among treated patients, but it has been difficult to determine whether these melanomas were induced by PUVA or were coincidental.[2-10]

Since PUVA is an extremely valuable type of treatment for a great number of patients with severe psoriasis, we must ask what other options we have for dealing with the severe forms of this disease and examine carefully the data that have been presented on the risk of melanoma development. This must be done before abandoning PUVA as a treatment for psoriasis. Therefore, the aim of this review is to discuss safety issues associated with the use of PUVA therapy and to weigh the risks and benefits of PUVA in comparison with the other options currently available for psoriasis.

1. General Aspects of the Treatment of Psoriasis

Psoriasis is a common, chronic and intractable skin disease that affects 1 to 3% of the population,[11] i.e. at least 55 million people worldwide. It is as common as diabetes mellitus. The disease was already known in antiquity.

The evidence that psoriasis may be inherited is beyond doubt, and its relationship to the human leucocyte antigen (HLA) system has been well documented. The risk of those bearing the HLA-CW6 phenotype to develop psoriasis has been reported as 9 to 15 times normal.[12] It is believed that psoriasis is a polygenetic disease that is triggered by environmental factors. Many exogenous or endogenous stimuli can be recognised, e.g. friction, pressure, infectious diseases, drugs and stress. At present there is no evidence for a single aetiology for psoriasis.

The pathogenesis of psoriasis involves not only the epidermis, where mitotic activity and DNA synthesis in the basal cells are increased by a factor of 8, but also other skin compartments. Immunological changes are also of importance. It has been suggested that autoimmune reactions are involved.

The clinical picture of psoriatic skin changes and their response to treatment can be extremely variable from patient to patient and, therefore prescriptions of treatments are based on a number of circumstances, such as: type, extent or severity of psoriasis, the patient's age, gender, past medical history, lifestyle and availability to attend treatment. Physicians and psoriasis patients often picture treatments in relationship to a ladder. Treatments with little or no toxicity, e.g. topical medications used for mild psoriasis, are the bottom rungs, and treatments with significant adverse effects, e.g. systemic medications used for severe psoriasis, are at the top of the ladder.

2. General Aspects of Treatment with Psoralens/Ultraviolet A (PUVA)

In December 1974, the first report was published on the use of oral methoxsalen followed by high intensity long wave ultraviolet A (UVA) radiation (wavelength 320 to 400nm) for the treatment of psoriasis.[13] The treatment became known as PUVA or photochemotherapy. Multiple studies soon confirmed the efficacy of oral[14-22] and topical[17,23-25] PUVA therapy in various patterns of psoriasis.

Psoralen compounds are naturally occurring furocoumarin derivatives. They are phytoalexins, which means they are used by plants in a defensive response to attacks by fungi and insects.[26] Both naturally occurring and synthetic derivatives have photosensitising and phototoxic effects in humans and animals.[27-29] The therapeutic properties of PUVA treatment have been explained by photochemical reactions with DNA and RNA. The photosensitising property is related to the ability of the photoexcited psoralen molecules (triplet state) to transfer the absorbed ultraviolet energy to DNA. In this photochemical reaction, psoralen covalently binds to DNA, forming monofunctional single-strand photoadducts with thymine bases and inter-strand cross-links between opposite pyrimidine

base pairs.[27-29] The formation of these C_4-cyclobutane photo-adducts of psoralen and pyrimidines presumably leads to an inhibition of DNA synthesis, and thus cell division, within the rapidly dividing psoriatic epidermis. Damage to nucleic acid and membrane lipid components may also be of some importance.[30] Whether there are any other processes triggered by the photochemical reaction is unknown. For a review of psoralen photobiology, see Gasparro et al.[31]

The dose of methoxsalen is arbitrary, as is the interval before radiation. The standard oral dose using methoxsalen tablets is 0.6 mg/kg given 2 hours before radiation. The initial UVA dose is based on skin type. Treatment is given 2 to 4 times weekly and the UVA dose is increased by increments of 0.5 J/cm^2 according to response. Detailed guidelines have been prepared and have been followed in most cases.[32] Maintenance schedules varies between different centres as do combination therapies. Etretinate, dithranol and even cytotoxic drugs have been given concurrently.

Apart from the carcinogenic hazard of PUVA, a number of adverse effects have been reported. Erythema, pigmentation, nausea and pruritus are common problems. Various abnormalities of immune function have also been recorded.[33-43] For example, a reduction in the number and function of circulating T lymphocytes has been reported, and these alterations might be of importance for the oncological hazards of PUVA.[33]

As a substitute for the standard oral methoxsalen in PUVA therapy, 5-methoxypsoralen has been tested and it has been reported that it is as effective as methoxsalen in the same dose.[44-47] The main advantage of 5-methoxypsoralen lies in its better gastrointestinal tolerability.[44,45] 3-Carbethoxypsoralen has also been advocated.[48]

Topically applied psoralens have been used, especially in patients with localised forms of psoriasis, with the advantage that some of the adverse effects of oral treatment have been avoided.[17,23-25,49] Preparations containing 0.1 to 1% methoxsalen have been used. For obvious reasons, palmoplantar pustular psoriasis has been treated in this way.[17,25,50] Trioxsalen (trimethylpsoralen) may be applied topically to the whole body in a bath. Such 'bath-PUVA' is used mainly in Finland and Sweden, with good results.[24,51,52] The main advantage of bath-PUVA is the avoidance of nausea. Furthermore, the doses of UVA are 15 to 20 times lower than with oral PUVA. For a review of bath-PUVA, see Lüftl et al.[53]

It must be pointed out that PUVA treatment is not only used for psoriasis. In a large epidemiological study in Sweden of 4945 patients receiving PUVA, the most common indications were: psoriasis, 64%; pustulosis palmoplantaris, 10.5%; eczema, 9.4%. A total of 55 different diagnoses were reported.[54]

3. PUVA and Non-Melanoma Skin Tumours

Mutagenicity and carcinogenicity are well established effects of exposure to PUVA *in vitro* and in animal models.[55-58] Since 1979, numerous clinical trials have shown an increased incidence of non-melanoma skin cancers in patients receiving PUVA.[59-74] Most authors in these studies seem to agree that PUVA patients with >200 treatments have an increased risk of non-melanoma skin cancer.

Furthermore, only a small fraction of patients with psoriasis who are receiving long term PUVA have never received any other carcinogenic treatments,[74] e.g. arsenic, tar, x-rays, ultraviolet radiation B, methotrexate or other cytotoxic drugs. Squamous cell carcinomas of the skin have mainly been reported, but also basal cell carcinomas. It has been claimed that PUVA treatment causes a linear increase in tumour risk for squamous cell carcinoma, but not for basal cell carcinoma.[75]

In a detailed case-control study of 24 PUVA-treated patients with squamous cell carcinoma of the skin with regard to possible co-carcinogens, the only statistically significant association to emerge was that of prior therapy with methotrexate (relative risk 3.5).[76] There is no evidence that 5-methoxypsoralen is less carcinogenic than methoxsalen,[47] but the use of 3-carbethoxypsoralen

has been advocated because it is noncarcinogenic in mice.[48]

Trioxsalen has been used with good effect in PUVA baths, and promising data have been published on its carcinogenicity.[77-80] In a preliminary report, bath-PUVA with trioxsalen seemed to be less carcinogenic than oral administration.[79] Although promising, the study does not explain the surprisingly low frequency of skin cancers. The reason could be the bath delivery of psoralens, the use of trioxsalen, the high efficacy and low number of treatments as well as the reduced cumulative UVA dose required compared with oral PUVA therapy.[53]

4. PUVA and Malignant Melanoma

Although squamous cell carcinoma is well documented in patients with psoriasis who receive long term treatment with PUVA,[59-75] only anecdotal reports have so far been published concerning malignant melanoma.[2-10] However, in a recent report, Stern et al.[1] have reported 11 melanomas in 9 patients in a cohort of 1380 patients with psoriasis who had been treated with PUVA since 1975. They conclude that about 15 years must pass before the effect of PUVA on the risk of melanoma becomes clinically apparent. During 1975 to 1990, 4 melanomas were found in this cohort, an incidence nearly identical to that expected, whereas 7 were found from 1991 to 1996 [relative risk 5.4, 95% confidence interval (CI) 2.2 to 11.1]. Of these melanomas, 8 appeared >13 years after the first PUVA treatment and patients who had received ≥250 treatments had the greatest increased risk of melanoma.

This study is alarming, first because melanoma is a highly fatal form of cancer in comparison with squamous cell carcinoma, and secondly because of earlier findings that have suggested a relationship between PUVA treatment and melanoma. For example, patients receiving PUVA therapy often develop lentigines,[81] PUVA has been shown to induce cutaneous melanoma in mice,[82] and PUVA stimulates the growth of melanoma cells *in vivo*.[83]

Although the study of Stern et al.[1] is convincing, some authors have claimed that the findings might be due to inaccurate statistics on melanoma, confounding variables and surveillance bias.[84] The calculation of relative risks has been based on cancer statistics in the US [Surveillance, Epidemiology and End Results (SEER) data] which provide a sample of only 9.6% of the population.[85] Although the SEER data on the incidence of cancers in the US are the national standard, they are an approximation and might underestimate the true incidence of melanoma. A survey of the membership of the American Academy of Dermatology estimated that in 1992 the incidence of melanoma and melanoma *in situ* was double the incidence of invasive melanoma estimated by the SEER programme.[86] However, this survey could also be questioned because of, for example, low response rate.[87] The above illustrates some of the problems with epidemiological studies in the US.

Confounding factors might also be of importance. Is there a higher risk of melanoma in patients with psoriasis regardless of the treatment they receive? The study of Stern et al.[1] lacked a control group, and many other treatments for psoriasis may increase the risk of melanoma. However, 2 large epidemiological studies have not found any association between psoriasis and melanoma,[88,89] and without careful case-control studies it cannot be determined whether 1 or more confounding variables, including exposure to sun or UVB, a history of sunburn, coal tar therapy, methotrexate or other unknown factors, may partly or completely account for the association found.

It is also possible that some of the patients in the Stern et al.[1] report were at greater risk for melanoma because of, for example, a family history of melanoma. Of the 9 patients, 1 had 3 primary melanomas and if he had been excluded from the cohort the result of the study would have looked less significant.

5. Adverse Effects of Other Treatments Available for Severe Psoriasis

Apart from PUVA therapy for widespread severe psoriasis, there are a few well-documented alternative treatments, but these also have potentially

severe adverse effects. These treatments are methotrexate, retinoids and cyclosporin.

5.1 Methotrexate

The beneficial effect of methotrexate on psoriasis has been known since the beginning of the 1950s.[90,91] Methotrexate inhibits DNA synthesis, exerting a strong antimitotic action on the epidermis.[92] The main severe adverse effects are toxic myelosuppression and liver cirrhosis.[93] Patients must be monitored by serial liver biopsies. Generally, the clinical course of cirrhosis is an indolent, slowly developing process but sometimes it demands withdrawal of the drug. In a comprehensive review of the literature over a century, only 72 fatal cases of psoriasis were reported; the fatal complications of methotrexate therapy accounted for 38 of these cases.[94] Furthermore, in view of possible cancer induction, care should be exercised in using PUVA and methotrexate concomitantly.[76,95,96]

5.2 Retinoids

Vitamin A has long been recognised to have profound effects on epithelial differentiation. However, not until 1975 was its analogue, etretinate, reported to have antipsoriatic efficacy[97] and many subsequent reports have confirmed this.[98-100] The adverse effects of etretinate are usually inevitable, but are often nuisances rather than a real danger. The principal severe adverse effects are a potential skeletal toxicity[101,102] and teratogenicity.[103] The manufacturer recommends avoidance of pregnancy for 2 years after cessation of treatment. Fatal complications of etretinate treatment have been reported.[104]

5.3 Cyclosporin

The ability of cyclosporin to clear psoriasis was first reported in 1979,[105] but not until the mid-1980s did controlled trials appear[106-109] and not until the early 1990s were guidelines for the use of cyclosporin in psoriasis published.[110] The most important adverse effects are nephrotoxity and hypertension. Renal biopsy findings during long-term cyclosporin treatment of psoriasis reveal structural changes, leading to the recommendation that after 2 years of therapy with cyclosporin patients with psoriasis should be rotated to other treatments or be monitored carefully by renal function and sequential renal biopsies.[111] Furthermore, there is concern about the immunosuppressive effect of cyclosporin, which in the long term might increase the risk of malignancy.[112]

5.4 Rotational Therapy

Since methotrexate, retinoids and cyclosporin all have long-term adverse effects, they are used for shorter periods of time in order to minimise the adverse effects. This is called rotational therapy,[113] in which a treatment is used for 12 to 24 months and then the patient is rotated to another of these therapies. Once the patient clears the disease, therapy is discontinued until the psoriasis reoccurs. The same cycle can then be repeated.

6. Discussion and Conclusions

To balance the risks and benefits of a given treatment is a complex exercise.[114] The beneficial effects in terms of magnitude, duration and incidence must be evaluated. Furthermore, the risks must be decided in the same way, taking into account the seriousness and severity of an adverse effect and its frequency and duration. The benefit to patients must be assessed by asking questions such as:

- How serious is the disease being treated versus the expected extent of improvement?
- What is the expected time course of the disease and how much will the course be reduced by the treatment?
- What is the incidence of the disease compared with the incidence of improvement owing to treatment?

There is no doubt that PUVA treatment has a very pronounced effect, most patients with psoriasis experiencing complete remission for a fairly long duration. Bearing in mind that psoriasis is a very common disease and that many patients are treated with PUVA, serious adverse effects, e.g.

development of cancer, have so far been rare. The long-term effects of PUVA are not known. However, all existing treatments for severe psoriasis also have a potential for serious, even fatal, adverse effects.

There is no question that any risk of patients treated with PUVA developing malignant melanoma must be taken very seriously. However, this risk has so far been demonstrated in only 1 study.[1] Furthermore, a number of questions need to be answered, such as:

- Can we trust the results of this study?
- Did confounding factors have an important impact on the study?
- What other options do we have for dealing with severe psoriasis and what are the magnitudes of their adverse effects?
- Are different types of psoralen regimens of importance?
- Is it possible to limit the carcinogenic effect of PUVA treatment through extended guidelines?

Weighing the risks and benefits, these questions must be elucidated as much as possible in the light of present knowledge.[115] Although squamous cell carcinomas in PUVA-treated patients are potentially life-threatening, they are usually slow growing and can be removed in time by proper management and follow-up. In the case of malignant melanoma the situation is quite different. This form of cancer is often fast growing and fatal, and even close monitoring might not be sufficient to prevent death.

As the study of Stern et al.[1] is the only epidemiological study relating PUVA and risk of melanoma, the risk must be re-evaluated in other multicentre trials and case-control studies must be performed to evaluate possible cofactors. Furthermore, studies should evaluate whether different PUVA regimens have the same carcinogenic potential, for example whether bath-PUVA is less carcinogenic?

When comparing PUVA and methotrexate, there is no question that methotrexate appears to have the more serious adverse effects; a larger number of fatal cases have been reported than with PUVA at present. On the basis of present evidence, etretinate appears to be safer than PUVA. Cyclosporin is difficult to evaluate, but its long-term immunosuppressive effects are disquieting.

It is also quite possible that the risk of melanoma after PUVA treatment could be limited by guidelines. However, the present stage of knowledge indicates that patients receiving long-term PUVA treatment should be rigorously followed for the development both of melanoma and of non-melanoma skin cancer. In order to minimise the risks of PUVA treatment, a history or family history of melanoma, or a history of >200 PUVA treatments, should be considered as contraindications.

In conclusion, further epidemiological studies are necessary to ascertain the risk of melanoma after PUVA treatment. Patients should be carefully selected for PUVA and rigorously followed. Patients who have already received extensive PUVA treatment, and those with a history or family history of melanoma, should not be treated with PUVA.

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