Current Best Evidence

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Menon K, Voorhees A S V, Bebo B F, Gladman D D, Hsu S, Kalb R E, *et al*. For the National Psoriasis Foundation. Psoriasis in patients with HIV infection: From the Medical Board of the National Psoriasis Foundation. J Am Acad Dermatol 2010;62:291-9.

Psoriasis in human immunodeficiency virus (HIV)-infected patients is a challenging condition to treat as the systemic treatments for psoriasis are immunosuppressive and can potentially lead to severe complications in the setting of HIV infection. A task force of the National Psoriasis Foundation Medical Board was convened to evaluate the treatment options with the aim to arrive at a consensus on therapy for psoriasis in patients with HIV infection. A MEDLINE search of the terms "psoriasis," "psoriatic arthritis," "human immunodeficiency virus (HIV)" and "HIV skin diseases" was performed and the literature relevant to HIV-associated psoriasis was reviewed. Based on the review of 29 reports, a consensus was formed and the National Psoriasis Foundation Medical Board endorsed the recommendations in this article. The evidence consisted mainly of case reports or case series and randomized placebo-controlled trials. The recommended first-line therapy for mild to moderate HIV-associated psoriasis is topical preparations, which include calcipotriol (calcipotriene), corticosteroids, tazarotene and the two-compound formulation of calcipotriol and betamethasone dipropionate. For moderate to severe disease, phototherapy (UVB or psoralen plus UVA) and antiretrovirals are the recommended first-line therapeutic agents. Oral retinoids may be used as second-line treatment. In cases of severe refractory psoriasis, systemic agents such as cyclosporine (CSA), methotrexate (MTX) and tumor necrosis factor (TNF)-α inhibitors (etanercept, infliximab) may be considered in limited circumstances. However, evidence for the use of these agents is limited and consists of only anecdotal and case reports. Because immunosuppressants have been associated with the development of opportunistic infections, a cautious use of these agents is recommended.

Comments: The association between psoriasis and HIV infection is now well recognized. Pre-existing psoriasis may flare up or it may appear *de novo* in severe forms in HIV-infected individuals. The consensus recommendations of this article are a welcome addition to the evidence-based therapy for HIV-associated psoriasis. Psoriasis is known to present more often with advanced HIV infection when the CD4 counts are usually lower than 350 cells/mm3. Initiation of antiretroviral therapy leads to the control of both HIV and psoriasis. PUVA and UVB (both broad-band and narrow-band), despite their possible immunosuppressive and carcinogenic potential, have been reported to be beneficial and safe for HIV-associated psoriasis. Systemic agents evaluated are acitretin, CSA, MTX, and TNF-α, with acitretin being the safest, although a little slow-acting. In HIV infection, the risks of TNF-α inhibitors (reactivation of tuberculosis, infection, malignancy and demyelinating disease) may be potentiated. Their use should be restricted to rare refractory cases. Cost is another limiting factor for their use in our scenario. Two potential systemic modalities that this article failed to evaluate are systemic corticosteroids and the combination therapy. Although systemic steroids should not be used in routine care of these patients, they have a role in recalcitrant psoriatic erythroderma with metabolic complications, fulminant generalized pustular psoriasis of von Zumbusch type and pregnancy. A combination and cyclic therapy in psoriasis helps in reducing the toxicity by reducing the dosage and duration of therapy. The use of systemic drugs in these patients is further complicated by various drug interactions, additive adverse effects and worsening of immunosuppression. Therefore, close monitoring of patients for the detection of opportunistic infections and regular CD4 counts, viral load and other systemic parameters should be performed.

Chiang C, Sah D, Cho B K, Ochoa B E, Price V H. Hydroxychloroquine and lichen planopilaris: Efficacy and introduction of Lichen Planopilaris Activity Index scoring system. J Am Acad Dermatol 2010;62:387-92.

Lichen planopilaris (LPP) is a primary cicatricial alopecia caused by chronic lymphocytic inflammation

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around the upper portion of the hair follicle, and frontal fibrosing alopecia (FFA) is considered to be its variant. In this retrospective study at the University of California, San Francisco (UCSF), experience with hydroxychloroquine (HCQ) in 40 patients with LPP and FFA seen between October 2004 and October 2007 has been reported. The authors are also introducing the LPP Activity Index (LPPAI), which allows numeric scoring of the symptoms, signs, activity and spreading of the condition for statistical comparison. A chart review of 40 adult patients with LPP, FFA or both, who were treated with HCQ for up to 12 months, was carried out. The standardized cicatricial alopecia flow chart recorded symptoms (pruritus, pain, burning) and signs (erythema, perifollicular erythema, perifollicular scale), a measure of activity (the anagen pull test) and spreading of the condition. Numeric values to these subjective and objective surrogate markers of LPP were assigned to establish a numeric summary of disease activity, the LPPAI. The weights given to the symptoms (30%), signs (30%), anagen pull test (25%) and presence of spreading (15%) led to the equation: LPPAI (0–10) = (pruritus + pain + burning)/3 + (scalp erythema + perifollicular erythema + perifollicular scale)/3 + 2.5 (pull test) + 1.5 (spreading/2). Symptoms and signs were recorded on a 4-point scale: 0 = absent, 1 = mild, 2 = moderate and 3 = severe. The anagen pull test, when present, is a reliable measure of local disease activity. The outcome was recorded both as a binary value (0 for no anagen hairs and 1 for the presence of anagen hairs). Lastly, the assessment of spreading was recorded as 0 (no spreading) versus 1 (indeterminate) versus 2 (spreading). When the hair loss was difficult to judge, the issue of spreading was recorded as indeterminate. The LPPAI was calculated at baseline and at 6 and 12 months using the standardized flow chart. Patients with an LPPAI reduction >85% over the pre-treatment values were considered responders, with 25%–85% reduction were considered as partial responders and with <25% reduction were considered non-responders. The treatment with HCQ was found to be effective, with a significant reduction ($P < 0.001$) in the LPPAI at both 6 and 12 months. After 6 months, 69% of the patients (26 of 38) were full or partial responders, and this figure reached 83% at 12 months.

Comments: LPP is a challenging condition to treat. This is because of the chronic nature of the disease, irreversible loss of hair and consequent adverse impact on quality of life of the patients. This is further compounded by the lack of safe and unquestionably effective treatments. There is inadequate good-quality evidence in the literature for the current modalities of therapy for LPP. This article is a welcome addition to the literature on LPP. The strengths of this study override the fact that it is a retrospective case series. This, till date, is the largest case series on the efficacy of HCQ in this condition. For the first time, a numeric scale (LPPAI) has been used to assess the pre-treatment and post-treatment disease activity, which, to some extent, gives objectivity to the results. As this score has been devised and used by the authors for the first time only, there are many arbitrary values in it. For example, the weightage given to the spread of the disease is 15% only while that to the symptoms is 30%. The presence of symptoms in LPP may not really correlate with the disease activity. A relatively asymptomatic patient may have a fast-spreading disease, indicating higher severity. Further, the measure of response is based on arbitrarily chosen cut-offs, i.e. complete responders with LPPAI reduction >85% over the pre-treatment values, partial responders with a 25–85% reduction and non-responders with <25% reduction. Whether these values correlate with the objective assessment of improvement by the physician and subjective assessment of the patient remains to be seen. Notwithstanding these drawbacks, and considering that it is still in its infancy, LPPAI is a valuable addition to research. Further testing and validation of this score should be carried out in future clinical trials of LPP.

The armamentarium for the treatment of LPP includes topical and intralesional steroids. For rapidly progressive disease, systemic agents like oral corticosteroids, HCQ, tetracyclines, dapsone, systemic retinoids, cyclosporine, mycophenolate mofetil, thalidomide and methotrexate are used. With this current evidence added to the good safety and cost-profile of HCQ, it is on more firm footing for the treatment of LPP.

Piraccini B M, Sisti A, Tosti A. Long-term follow-up of toenail onychomycosis caused by dermatophytes after successful treatment with systemic antifungal agents. J Am Acad Dermatol 2010;62:411-4.

Recurrences (relapse or re-infection) of onychomycosis are not uncommon, with percentages reported in various studies ranging from 10% to 53%. This 7-year prospective study was designed to determine the prevalence of the long-term recurrences and identify the factors related to it in patients of toenail onychomycosis caused by dermatophytes who had been successfully treated with systemic antifungal

agents. This study included 73 patients (41 male and 32 female) who had been effectively cured from dermatophyte distal subungual onychomycosis involving more than one-third of the nail plate by systemic terbinafine (T) or itraconazole (I). These patients had complete clinical cure and negative cultures 12 months after the end of treatment. The 73 patients were divided into two groups depending on the therapy taken for onychomycosis: (1) pulsed I at 400 mg/d for 1 week every month, for 3 months (14 patients); and (2) continuous T at 250 mg/d, for 3 months (59 patients). Patients were evaluated every 6 months, with clinical and mycological evaluations being performed during these evaluations. The primary end point of the study was to assess the proportion of patients who remained mycologically and clinically cured. The secondary end point was to determine whether there were differences between the patients who remained cured and those who relapsed. The following parameters: age at onset, risk factors for onychomycosis (genetic susceptibility; concomitant diseases, including diabetes, rheumatoid arthritis and peripheral vascular disease; chronic trauma), responsible fungus, systemic antifungal used and use of nail lacquer as a preventive measure, were also considered. Twelve of the 73 patients (16.4%) were found to develop a recurrence of onychomycosis after a mean time of 36 months post successful treatment. These included five of the 14 patients (35.7%) who had taken I and seven of the 59 patients (11.9%) who had taken T ($P = 0.046$). This study suggested that the type of systemic drug used to treat the first episode of onychomycosis may be related to the risk of relapse. The administration of systemic T to treat the first episode of onychomycosis may provide better long-term success than I in those patients with a complete response. Other factors including the presence of predisposing factors, use of nail lacquer as a prophylactic treatment and the dermatophyte strain isolated were not significantly related to relapse.

Comments: Onychomycosis is a difficult condition to treat. Clinical cure does not always imply the mycological cure and vice versa. More advanced disease with a high degree of nail dystrophy may not return to normal appearance even after adequate antifungal therapy and negative mycological cultures. The management is further compounded by the high-recurrence rate. Autosomal-dominant susceptibility to *Trichophyton rubrum* infection has now been suggested. In this study also, the responsible fungus in recurrence was always the same as the first episode. The cause of recurrence as relapse or re-infection may have become clear if strain identification could have been performed by polymerase chain reaction.

The ideal treatment for onychomycosis caused by dermatophytes has for long been a topic of debate. Recent literature reviews put continuous therapy with terbinafine as the best bet for the cure for this condition. The majority of this data is industry sponsored, with a bias toward terbinafine. This independent study suggests that the use of systemic terbinafine to treat the first episode of onychomycosis may provide better long-term success than itraconazole. Both terbinafine and itraconazole persist in the nail tissue for a long time after stopping the drug. Terbinafine, being fungicidal and given in a continuous form, may be more effective than itraconazole, a fungistatic drug and given in episodic form. Episodic treatment, as a rule, is usually less efficacious than continuous therapy. These reasons could explain the results of this study. But, this study has a major limitation as there were only 14 patients in the itraconazole group and 59 in the terbinafine group. Therefore, the statistical significance of the result cannot be assessed correctly. More independent studies, preferably randomized comparative trials, are needed to confirm the findings.

Borska L, Andrys C, Krejsek J, Hamakova K, Kremlacek J, Palicka V, *et al*. Genotoxic and apoptotic effects of Goeckerman therapy for psoriasis. International Journal of Dermatology 2010;49:289-94.

Goeckerman therapy (GT) for psoriasis involves daily topical application of crude coal tar, a polycyclic aromatic hydrocarbon (PAH), and exposure to ultraviolet radiation (UVR). Both PAH and UVR have been incriminated for tumor induction due to their mutagenic, carcinogenic and immunotoxic properties. This study was carried out to measure the dermal absorption of PAH and to determine the genotoxic and apoptotic effects of GT in 20 patients with psoriasis. This was done by determining the numbers of chromosomal abnormalities (CA) in peripheral lymphocytes and the levels of 1-hydroxypyrene (1-OHP), p53 protein and soluble FasL (sFasL) in urine and/or blood before and after GT. Psoriasis Area and Severity Index (PASI) score was used to evaluate the clinical efficacy of GT. Apoptosis is thought to play a key role in the carcinogenesis of p53 proteins, while extrinsic induction of apoptosis is initiated by death ligands such as FasL. Therefore, increased p53 protein and sFasL, which control intrinsic and extrinsic pro-

apoptotic pathways, respectively, are considered to be markers of cell damage and cancer in occupational exposure to PAH. 1-OHP is another marker for exposure to PAH, mainly in occupational settings. A high degree of CA is the internationally standardized and validated biomarker of genotoxicity. The results showed a significant increase in urine 1-OHP after treatment, indicating a high degree of dermal absorption of PAH ($P < 0.01$). When compared with the pre-treatment levels, the study found a significant increase in the number of chromosomal abnormalities in peripheral blood lymphocytes ($P < 0.001$), suggesting that GT is genotoxic; significant increase in plasma p53 protein ($P < 0.05$), an indicator of cell response to DNA damage; and significant increase in sFasL ($P < 0.01$), an indicator of apoptosis. The clinical efficacy of this treatment was confirmed as the PASI score was significantly decreased after GT ($P < 0.001$). This study concluded that there is high dermal absorption of PAH during GT and that GT promotes genotoxicity and apoptosis.

Comments: Modified GT, as followed in most centers now, involves application of crude coal tar (2–5%) and exposure to UVR. UVB radiation has been found to be more effective when compared with UVA. The carcinogenic potential of PAH, like benz(o)pyrene and benzanthracene, has been evident in various occupational settings. Coal tar is a product of distillation of bituminous coal. About 48% of it is comprised of PAHs. Coal tar has been found to possess mutagenic and tumor-induction properties in experimental animal studies. But, whether these findings are confirmed in humans has been a topic of debate. Multiple experimental and epidemiological studies have been performed to find a satisfactory answer. This is one such experimental study in which the authors came up with the alarming result that coal tar gets absorbed systemically in significant amounts and found an increase in the markers of genotoxic and carcinogenic potential, like chromosomal abnormalities, p53 and FasL. So, what should we do? Stop using coal tar and shift to other therapies? Before we abandon this efficacious low-cost therapeutic modality for psoriasis, we have to analyze this study critically. This study has a few limitations, like it is not controlled. The use of 1-OHP as a marker of systemic absorption has been criticized as its levels fluctuate and show significant individual variation. The genotoxic effect, as evident from increased chromosomal abnormalities, has been found to be only short term, with studies showing no chromosomal abnormalities 78 days after GT. Whether the short-term effects of coal tar, as seen in this study, culminate in increased cancer incidence in the patients is a question that can only be answered by long-term epidemiological studies.

Roelofzen J H J, Aben K K H, Oldenhof U T H, Coenraads P J, Alkemade H A, van de Kerkhof P C M, *et al*. No increased risk of cancer after coal tar treatment in patients with psoriasis or eczema. Journal of Investigative Dermatology 2010;130:953-61.

Chronic exposure to coal tar, a complex mixture of polycyclic aromatic hydrocarbons (PAHs), has been linked with increased risks of lung and non-melanoma skin cancer in various animal and occupational studies. The risk of cancer after coal tar treatment in dermatological practice is still unclear because of the lack of large-scale observational studies. To assess this risk in patients with psoriasis or eczema, a large historical cohort study was performed: the late effects of coal tar treatment in eczema and psoriasis, the Radboud study (LATER study). The LATER study was initiated in 2003. The cohort comprised of 13,200 patients diagnosed with psoriasis (comprising one-third) or eczema (comprising two-third) between 1960 and 1990 in three large hospitals in the Netherlands. Detailed information on the medical history was collected from the medical files. Information on therapies that patients received was collected. This information was supplemented by questionnaires and linkages to the NCR, population-based cancer registry and Causes of Death Registry to assess cancer risk and death due to cancer. A detailed questionnaire concerning demographic factors, use of alcohol, smoking habits, skin type, history of sunlight exposure and residence in tropical areas, occupational history, detailed information on the skin disease and history of other (skin) diseases and cancer was also completed in 61% of the subjects. The median duration of follow-up was 21 years. The median exposure to coal tar ointments was 6 months (range, 1–300 months). No increased risk of skin cancer and non-skin cancer was found after coal tar treatment.

Comments: Coal tar is one of the first-line topical agents for the treatment of psoriasis because of its low cost and good efficacy. Its efficacy is further enhanced by combining with ultraviolet light. Concerns about its carcinogenic potential have been raised since ages because of the well known carcinogenic potential of PAHs, first noticed in chimney sweepers with increased incidence of scrotal cancer. This

carcinogenic potential is yet to be confirmed in any of the epidemiological studies of clinical usage of coal tar in eczema and psoriasis. By far, this is the largest study with a long follow-up, having sufficient power to pick up any evidence of the increased incidence of cancers after coal tar therapy. The low exposure to coal tar, of a median of 6 months, and the composition of the patient cohort, with two-third comprised of eczema patients, are the limitations of the study. Coal tar usage for eczema is only of historical relevance, after the advent of more efficacious corticosteroids. Notwithstanding these limitations, this study confirms the safety of this simple, time-tested treatment modality for psoriasis.

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