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Comparative Tolerability of Systemic Treatments for Plaque-Type Psoriasis

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Contents

Abstract

Psoriasis is a chronic, debilitating skin condition that affects millions of people and is attributed to both genetic and environmental factors. Topical therapy is generally considered to be the first-line treatment of psoriasis. However, many patients do not respond to topical therapy or have disease so extensive that topical therapy is not practical. For these patients, systemic therapy is indicated. Presently, there are four available systemic treatments, psoralen with ultraviolet A (PUVA), methotrexate, oral retinoids (acitretin), and cyclosporin. Unfortunately, all of these treatments have significant potential adverse effects. PUVA may acutely cause nausea, pruritis and sunburn. More chronic and concerning is the development of PUVA lentigines, ocular complications and skin cancer. Nonmelanoma skin cancer has been directly linked to PUVA; however, the association with melonoma is more elusive. Methotrexate use most notably carries the risk of hepatic fibrosis and cirrhosis, which is not always evident on liver function tests. Other more rare, but potentially life-threatening adverse effects include pancytopenia, lymphoproliferative disorders and acute pneumonitis. The addition of folic acid may help to reduce the risk of increasing liver enzymes and haematological toxicity seen in those taking methotrexate. Both methotrexate and oral retinoids are teratogenic and should never be used in pregnancy. Oral retinoids are probably the least effective available systemic medication for the treatment of plaque psoriasis. The effects are improved with the addition of other systemic therapies. Acitretin has replaced the formerly used etretinate primarily because of the significantly shorter half-life. The adverse effects are generally mild and reversible, making the drug fairly safe for long-term use. The most commonly seen adverse effects include elevated serum lipids, generalised xerosis and alopecia. Bony abnormalities, while somewhat controversial, have also been described and include diffuse idiopathic skeletal hyperostosis, skeletal calcifications and osteoporosis. Cyclosporin is the most recently approved systemic med-

ication for plaque psoriasis. The nephrotoxicity associated with the use of cyclosporin can be minimised when used in lower doses and for a limited duration. Hypertension is usually mild and can be seen in up to about one-third of patients receiving long-term therapy. Cutaneous and internal malignancies have also been reported with cyclosporin and tend to be correlated with duration of treatment. In this review, we will examine the potential adverse effects with these US Food and Drug Administration-approved treatments in adults, with specific emphasis on the controversies that surround long-term therapy with these agents and their cumulative adverse effects.

Psoriasis is a chronic condition that affects 1 to 3% of the US population.[5] Approximately 20% of patients with psoriasis have extensive disease that is unresponsive to topical therapy.[6] For these individuals, phototherapy or systemic medications are indicated. These systemic agents may be used alone or in combination with other treatment modalities. However, when approaching systemic treatments for psoriasis, it is important to understand the potential adverse effects of these therapies along with careful laboratory monitoring and patient selection. These are summarised in tables I and II. There are four widely accepted systemic treatments for psoriasis today, psoralen with ultraviolet A treatment (PUVA), systemic retinoids (acitretin), methotrexate, and cyclosporin. There are other systemic therapies for the treatment of plaque psoriasis including mycophenolate mofetil, hydroxycarbamide (hydroxyurea) and fumaric acid esters; however, these are not commonly used and there is a lack of data regarding their tolerability and safety. Children who require systemic therapy represent a minority and systemic therapy should only be used in extreme circumstances and with caution. Cyclosporin and methotrexate can be used in children, but little data exists in this age group.[7] In the elderly, most systemic therapies can be used relatively safely as long as there is not significant hepatic or renal impairment. Because of a decreased glomerular filtration rate in the elderly, cyclosporin should probably be avoided.

One concept critical to the understanding of the toxicities of the various systemic treatments for psoriasis is the use of rotational therapy. Many authors have pointed to the evidence that many of the most important toxicities of systemic drugs for psoriasis are related to cumulative exposure to the therapy. Thus, it has been suggested that medications be rotated when a patient requires long-term treatment. In other words, a patient might be started on phototherapy, but then changed to treatment with an oral agent even though the patient might still be responding to the initial treatment in order to lessen the potential exposure risk of the phototherapy. This strategy will be central to our understanding of the clinically significant toxicities reviewed in this paper.

1. Psoralen with Ultraviolet A

PUVA was reported for the treatment of psoriasis back in 1951 but was not approved by the US Food and Drug Administration (FDA) until 1982.[8] PUVA therapy consists of a psoralen, a photosensitising agent, being delivered to the skin and is then being activated by exposure to ultraviolet light. The psoralen most commonly used in the US is methoxsalen (methoxypsoralen) that intercalates into the DNA double helix and forms permanent cross-links within nucleotide pairs when exposed to the appropriate wavelength of ultraviolet light (UVA, wavelength 320 to 335nm). This interaction causes disruption of DNA and an inhibition of cell proliferation and apoptosis in many cell lines, including the type I activated T cells that drive the immune response in psoriasis.[9] While neither methoxsalen nor UVA light alone have a significant benefit in the treatment of psoriasis, the combination shows significant improvement in psoriasis in about 90% of patients with plaque psoriasis in 20 to 30 treatments.[10] Other forms of phototherapy such as UVB, and bath PUVA may be used, but do not require patients to take oral or

Table I. Laboratory monitoring for systemic psoriasis therapies

	Psoralen with ultraviolet A[1]	Methotrexate[2]	Retinoids (acitretin)[3]	Cyclosporin[4]
Baseline	Complete skin assessment Slit-lamp exam of lens and cornea Fundoscopic exam Visual acuity ± LFTs, renal function tests, lupus panel	LFTs Hepatitis panel for HAV, HBV, HCV CBC, platelets Chemical panel Serum creatinine, BUN, potassium Pretreatment liver biopsy in high-risk patients	βHCG CBC, platelets LFTs Fasting lipid profile Renal function tests Urinalysis ± X-ray of wrists, ankles or thoracic spine in long-term treatment ± Ophthalmology	Serum creatinine × 2 BUN, urinalysis Urinary protein Blood pressure × 2 GFR CBC LFTs, bilirubin Fasting lipid panel
Monitoring	Periodic complete skin assessments	LFTs, CBC, platelets qw × 2w, also 5-6d after dose escalation, then q3-4mo	Laboratory tests qmo × 3mo then q3mo	Laboratory tests as above
	Ophthalmology yearly or as needed	Delayed liver biopsy after 3-6mo in low-risk patients Liver biopsy q1.5-2.0g total dose in low-risk patients Liver biopsy q1.0g total dose in high-risk patients	CBC, platelets LFTs Fasting lipid profile Renal function tests ± Urinalysis ± βHCG ± Annual x-rays ± Ophthalmology	Serum creatinine and blood pressure at day 0,15,30, then if stable, monthly GFR at 6mo

βHCG = beta human chorionic gonadotropin; **BUN** = blood-urea nitrogen; **CBC** = complete blood count; **GFR** = glomerular filtration rate; **HAV** = hepatitis A virus infection; **HBV** = hepatitis B virus infection; **HCV** = hepatitis C virus infection; **LFTs** = liver function tests; **mo** = month(s); **qxmo** = every x month(s); **qw** = every week; **w** = weeks.

injectable medications and are therefore beyond the scope of this article.

The acute adverse effects of PUVA therapy are related to the ingestion of the methoxsalen and local cutaneous effects of the methoxsalen combined with the ultraviolet light exposure. About 10% of patients experience adverse gastrointestinal effects, particularly nausea, after psoralen ingestion.[11] This effect can be reduced by decreasing the dose and/or taking it with food.[11] If necessary, an antiemetic therapy can be added.[12] If these efforts fail to eliminate the nausea, topical or bath PUVA can be substituted or other systemic therapies considered. Other reported adverse gastrointestinal effects include diarrhoea, constipation, and liver function test (LFT) abnormalities, though these effects rarely require the cessation of therapy. Likewise, adverse CNS effects such as headache, insomnia, hyperactivity and depression are usually mild and do not adversely effect treatment outcome.

As would be expected from treatment with a photosensitising agent, acute adverse cutaneous effects are quite common. Most frequently, patients will experience an exaggerated sunburn-like response 48 to 72 hours after a treatment that can last for a number of days.[13] Many factors can influence the likelihood of a PUVA phototoxic reaction including irregular output from the UVA light source and inconsistent intestinal absorption of methoxsalen. When severe phototoxic reactions occur, phototherapy must be discontinued until the erythema subsides.[8] PUVA is relatively contraindicated in patients with photosensitive diseases like lupus erythematosus and should be used with special care in individuals who are receiving photosensitising drugs.[14,15] One phototoxic effect is the potential for a PUVA burn to worsen psoriasis. Patients with psoriasis may develop new and severe

Table II. Contraindications for systemic therapy

PUVA[1]	Methotrexate[2]	Retinoids[3]	Cyclosporin[4]
Absolute			
Light sensitising disorders	Pregnancy	Pregnancy	Uncontrolled hypertension
Lactation	Lactation	Lactation	Abnormal renal function
			History/current malignancy
			Hypersensitivity to cyclosporin
Relative			
Pregnancy	Liver dysfunction	Hypercholesterolaemia	Age <18 or >64
Photosensitising medications	Hepatitis	Alcohol abuse	Controlled hypertension
Melanoma	Renal insufficiency	Osteoporosis	Pregnancy
Non-melanoma skin cancers	Severe heme abnormalities	Bony abnormalities	Lactation
Severe organ dysfunction	Immunodeficiencies	Leukopenia	Active infection
	Active serious infection		Immunodeficiencies
	Alcohol abuse		Drug/alcohol abuse
	Hepatotoxic medications		Epilepsy
	History of arsenic therapy		Organ dysfunction
	Diabetes mellitus		Nephrotoxic or cytotoxic medications
	Obesity		Immunosuppressants
	Elderly		Current radiation therapy
			Live attenuated vaccine during therapy

plaques of their disease when the skin is injured, an element of the disease called the Koebner phenomena.[16] Thus, patients with a skin injury from a PUVA burn can have an acute and severe worsening of their psoriasis.

Pruritus can be either generalised or localised. The generalised form is secondary to xerosis and is easily treated with emollients. The localised form, referred to as 'PUVA itch' usually occurs in the mid-upper back, is much more intense and is unresponsive to treatment of any kind other than temporarily discontinuing phototherapy. Once the pruritus resolves, PUVA can be restarted at a slightly lower UVA dose.[8] Pruritus is a significant cause for non-compliance with therapy and can lead to discontinuation.[8]

The long-term adverse effects of PUVA therapy are more concerning and include ocular abnormalities and skin cancer.[17] Patients receiving long-term PUVA therapy are at risk for developing cataracts due to the ocular phototoxic effects of the psoralen. However, the relative risk can be reduced to near zero if patients use UV protective wrap-around eyeglasses immediately after taking psoralen during the daylight hours.[18] Patients are then required to wear opaque occlusive eyewear during UVA exposure for at least 24 hours. In addition, it is probably advisable that patients should have an ophthalmological assessment both prior to and during therapy.[17]

The most significant risk of PUVA therapy is skin cancer. The association of non-melanoma skin cancer (NMSC), mainly squamous cell carcinoma (SCC), with PUVA has been firmly established. The incidence of squamous cell carcinoma in patients treated with PUVA is related to the cumulative dose.[19-21] In some studies, the incidence of SCC in PUVA-treated patients who have had more than 1000 J/cm^2.[22,23] Lindelof et al.[23] found the relative risk of SCC in PUVA-treated patients to be 5.6 for men and 3.6 for women. Other studies have found the number of treatments to be of primary importance, with the incidence dramatically increasing with more than 160 to 260 treatments.[24-26] Stern and Lange[27] found an 11-fold increase risk in the incidence of SCC in patients receiving more than 250 treatments in comparison with those who received less than 160 treatments.

The association of NMSC in PUVA-treated patients and Fitzpatrick skin type has not been firmly established. One study by Stern and Momtaz[28] found that there was an increased risk of NMSC in patients with Fitzpatrick skin types I and II.[29] In contrast, there have been several studies that have shown no increased risk associated with skin type.[19,30] Importantly, genital skin has a greater susceptibility and should not be exposed during therapy.[17,31] Basal cell carcinomas and keratoacanthomas are also reported in conjunction with PUVA therapy, but this association is not as clear as with SCC.[32,33] Additional risk factors include patients who have inadequate responses to PUVA and those that have been treated with prior carcinogenic therapy.[11,34] Therefore, it is important to try to minimise the cumulative dose of PUVA therapy by finding ways to reduce the exposure of the patient including combination therapy with topical treatments and systemic retinoids.[11] Moreover, avoidance of excess sun exposure along with the use of sunscreens may be of benefit in these patients.

One of the most controversial issues with PUVA therapy is the possibility of an association with malignant melanoma, the most lethal form of skin cancer. It has long been suspected that UVB exposure (280 to 320nm) is a major risk factor for the development of melanoma, as a result of chromosomal damage.[35] However, data on the carcinogenic effects of UVA have been less obvious. DNA damage as a result of UVA radiation has been conclusively demonstrated in mammalian cell culture models by many investigators.[29,36-41] Moreover, the ability to induce melanoma through UVA exposure has been demonstrated in both the Xiphophorus hybrid fish[42] and *Monodelphis domestica* (opossums).[30] Several studies have demonstrated an association between the use of UVA tanning beds and the subsequent development of melanoma.[43,44] PUVA lentigines, normally occurring 6 to 15 months after the initiation of PUVA and lasting up to 7 years, are dose-dependent and often feature histologically atypical lymphocytes which could suggest a potential to develop into malignant melanoma.[45]

In 1997, Stern et al.[46] reported an increase in the incidence of melanoma identifiable 15 years after the first exposure to PUVA in patients in the US, most notably in those patients who had received more than 250 treatments. In an update to this study, they reported a doubling of diagnosed melanomas, giving a 20-fold increase in the incidence of malignant melanoma from 1990.[47] Concerns about this association have been expressed. Specifically, this study did not include a history of childhood sun exposure, previous history of phototherapy, and exposure to arsenic or methotrexate. There has also been criticism regarding the lack of a control group of patients with psoriasis who did not receive PUVA.[34,48] In support of melanomas occurring after long-term follow-up, Rahman et al.[49] found that those patients who developed melanoma had not received PUVA in the preceding 5 years. In opposition to this, Lindelof et al.[23] evaluated the long-term follow up of 4799 patients in Scandinavia after they received high doses of PUVA and found no increased risk for the development of malignant melanoma. These authors felt that the discrepancies might, perhaps, be explained by the differences in PUVA administration between the US and Europe.

Clearly, these epidemiological studies are far from conclusive and warrant the continued search for a possible relationship between UVA and the development of melanoma. We believe it is critical to continue to follow patients who have had more than 200 treatments or greater than 1500J of PUVA therapy. These patients should be followed up every 6 months, for life, with full body skin examination for the possible development of melanoma.

2. Methotrexate

Methotrexate, which was approved by the US FDA for severe psoriasis in 1971 is prescribed predominantly for the treatment of moderate to severe disease.[50] Methotrexate is a synthetic folate analogue that competitively and irreversibly binds to the enzyme dihydrofolate reductase, thus disrupting DNA synthesis and ultimately causing cell death during the S phase of the cell cycle.[51] The

exact mechanism of action has not been fully elaborated but is theorised to act as an immunosuppressant by inhibiting the inflammatory response rather than acting as an antiproliferative agent as previously thought.[52] Up to 80% of patients with psoriasis will respond to therapy with methotrexate.[2] Methotrexate can affect multiple different organ systems. It is also efficacious in the treatment of psoriatic arthropathy.

By far the most feared adverse effect of methotrexate is hepatic fibrosis and cirrhosis. Estimates of the frequency of these outcomes vary greatly. The rate of fibrosis is estimated at a rate of 1 to 50% and cirrhosis from 0 to 25%.[53-59] The highest estimates were given by Danish authors who may have reported complications in an older population and those with a greater history of exposure to hepatotoxins, mainly alcohol.[53] The incidence of hepatotoxicity associated with methotrexate is increased with advanced age, alcohol consumption, diabetes mellitus, obesity and pre-existing liver damage.[54,60] Recent studies done excluding these high-risk patients have found a much lower incidence of liver toxicity.[58,61,62] For those patients who do get cirrhosis, it tends to be relatively non-aggressive.[53,63] Unfortunately, there is no significant correlation between blood chemistries and liver histological evidence of hepatic fibrosis, thereby requiring periodic liver biopsies to evaluate potential disease.[64] Guidelines for monitoring methotrexate include a baseline liver biopsy either prior to treatment for high-risk patients or, in low-risk patients, a biopsy can be performed after 2 to 4 months of treatment or after a cumulative dose of 1.5g.[57] A delay in the initial liver biopsy is likely justified because it is important to establish effectiveness and tolerability of methotrexate in low risk patients. Repeat liver biopsies should be performed with each additional 1 to 1.5g cumulative dose depending on individual patient risk factors.[53,57] Some authors have suggested the measurement of serum type III procollagen peptide to detect ongoing fibrosis.[65-67] This test is not organ specific and requires serial monitoring, but if it remains normal, can help to decrease the number of liver biopsies required during treatment with methotrexate. More studies are needed, as this test may eventually greatly reduce the need for liver biopsies.

Of all the adverse effects associated with methotrexate, pancytopenia presents the greatest potential for a fatal outcome. Anaemia, thrombocytopenia and leucopenia can also occur in isolation. It has been estimated that the incidence of haematological toxicity in those patients receiving low-dose methotrexate varies from 3 to 9%.[68] Agranulocytosis and pancytopenia are generally reversible upon cessation of the drug.[69] Folinic acid (leucovorin) in high doses can reverse the acute haematological toxicity seen with methotrexate.[57] Possible risk factors for haematological toxicity include increased methotrexate levels due to drug interactions or to renal failure, or a functional folate deficiency.[68] Supplementing patients with folic acid 1 to 5 mg/day during therapy may be important in limiting haematological toxicity.[57,70] One antirheumatic study demonstrated a reduction in elevated liver enzymes levels with the use of folic acid.[57,71] Importantly, in order to minimise haematological toxicity, it is crucial to avoid potential drug-drug interactions with other drugs that inhibit folate metabolism, particularly sulphonamides, trimethoprim and dapsone.[72,73] Drugs that increase methotrexate levels by competing for secretion by the proximal tubules should also be avoided, including nonsteroidal anti-inflammatory agents, salicylates, colchicine, probenecid, cephalothin, sulphonamides and penicillin.[68]

Since the primary mechanism of action of methotrexate is the inhibition of lymphocyte function, it is no surprise that adverse effects related to immunosuppression, while rare, have been reported in the form of malignancy and infection.[74] Although there has been an association of lymphoproliferative disorders (LPD) with methotrexate, there is no reported increased risk of LPD in patients with psoriasis treated with methotrexate, despite a few documented case reports in patients treated for rheumatoid arthritis.[75-84] Only rarely has lymphoma been associated with methotrexate use in patients with psoriasis.[85] It has been pos-

tulated that long-term treatment with methotrexate may impair the immune control of Epstein-Barr virus-induced B-cell proliferation and potentially result in LPD. If this is suspected, it is essential to withdraw methotrexate therapy immediately to decrease further risk of immunosuppression. A spontaneous regression of LPD in approximately 50% is expected after withdrawal of the drug.[85] In addition, there have been some studies that have demonstrated an association of methotrexate use and the increased incidence of skin cancer.[19,20]

Acute pneumonitis is rare in patients with psoriasis receiving methotrexate but can occur even at minimal doses and can be fatal.[86] A prevalence of about 5% has been noted for those patients receiving methotrexate for rheumatoid arthritis.[7,86,87] The pathogenesis of methotrexate-induced acute pneumonitis is currently unknown, and there does not seem to be any specific population at risk for this adverse effect.[86] Chest x-rays and pulmonary function tests have not been useful in screening or diagnosis of this condition.[88] Therefore, a chest x-ray should not be routinely ordered unless a patient has developed symptoms suggestive of pneumonitis.[69] The withdrawal of methotrexate therapy is imperative if this diagnosis is suspected. In addition, starting systemic corticosteroids may be beneficial as long as a bacterial infection has been ruled out.[86]

Both men and women should practice adequate contraception while taking methotrexate, which has been shown to be a potent teratogen and abortifacient. In males it is known to cause reversible oligospermia and defective sperm.[17] Women should avoid pregnancy for 1 month and men should avoid fathering children for 3 months following cessation of therapy.[50,69]

3. Acitretin

Oral retinoids have been in use for the treatment of psoriasis since the 1980s. Etretinate was the first of the retinoids introduced for the treatment of severe psoriasis, but was removed from the US market in 1998. Acitretin, the active metabolite of etretinate, was developed in order to minimise toxicity.[89] Retinoids tend to have a slower onset of action when compared with other systemic therapies like methotrexate and cyclosporin. The retinoids tend to be more effective in inflammatory forms of psoriasis and typically produce only a partial improvement in plaque psoriasis.[90] Because of this lesser efficacy, they tend to work best when combined with UVB, PUVA or other systemic therapies or when used in rotational or sequential regimens.[25,91]

The reason for the adoption of acitretin rather than etretinate was that etretinate has an elimination half-life of about 100 days, compared with approximately 2 days for acitretin. Moreover, etretinate is a much more lipophilic compound and is stored in fat tissue to a much greater degree than acitretin.[92-94] Etretinate can be identified in the blood for years after discontinuation, prolonging the potential adverse effects and interactions.[92,95] Thus, the assumption was that with decreased exposure to the medication, long-term safety issues, primarily teratogenicity, may be reduced. However, acitretin has been shown to be reverse metabolised by endogenous esterases back to etretinate.[96-98] This conversion is potentiated by alcohol consumption. So, while there could be a decrease in the amount of stored retinoid, complete clearance of acitretin is not certain. The adverse effects of retinoids are multiple. However, with the significant exception of teratogenicity, the adverse effects tend to be mild or reversible upon discontinuation of the medication. Importantly, as opposed to other therapies for psoriasis, there are few adverse effects that worsen with cumulative dose making acitretin relatively safe for long-term therapy. Interestingly, retinoids have been used as chemoprevention for premalignant cutaneous diseases including actinic keratoses, arsenical keratoses, oral leucoplakia, Bowen's disease, and in some PUVA induced keratoses.[99-101]

Teratogenicity is probably the most serious adverse effect associated with the use of retinoids. Acitretin is US FDA pregnancy category X (i.e. highly unsafe during pregnancy, and the risk of use outweighs any possible benefit) and has no minimum safe dose for those who are pregnant. It has been shown to produce CNS, bone, craniofacial,

cardiovascular, ocular and auditory abnormalities, with the greatest risk between the third and sixth weeks of gestation.[102] These abnormalities are as a result of the toxic effect of retinoids on the cephalic neural crest development.[102] There is also an increased incidence of spontaneous abortions and stillbirths. It is imperative that women of childbearing potential adhere to some acceptable form of birth control during the course of acitretin therapy. Because of the known conversion of acitretin to etretinate that is significantly increased by alcohol consumption, it is advisable for these young women to continue with adequate contraception for 2 to 3 years. The minimum alcohol consumption for this conversion is unknown and inadvertent exposure to alcohol containing products may be unforeseeable. Women of child-bearing potential should also be advised not to consume alcohol for 2 months following cessation of therapy as well.[103] Authors have suggested that, due to the teratogenic risk and the difficulty in monitoring patients post-therapy, acitretin should probably not be used in women of child-bearing age.[13,92,95,104] Retinoids do not appear to affect spermatogenesis or sperm morphology, but it remains unclear as to whether the presence of retinoids in seminal fluids might be harmful to a fetus. Therefore, it is has been suggested that men on retinoids use condoms during drug therapy and for at least 1 month following cessation of therapy.[3] In addition, premature epiphyseal closure in children has been reported with etretinate.[105]

Up to one-third of individuals treated with retinoids will develop elevation in their LFTs[103,106,107] within about 8 weeks after starting therapy.[3] Though LFT abnormalities are common, severe hepatic toxicity is rare[103] and no specific pattern of liver damage has been identified.[106,108,109] Hepatitis, with increases in AST and ALT occur more frequently than do elevations of lactate dehydrogenase (LDH), alkaline phosphatase, and bilirubin. Cases of hepatic fibrosis and cirrhosis have been reported with the use of oral retinoids but are very rare.[110] Unlike methotrexate, LFTs tend to correlate with findings on liver biopsy.[106] Thus, hepatic toxicity may be monitored with blood tests rather than liver biopsy.[111] Patients with pre-existing liver damage from hepatitis, concurrent or prior use of methotrexate, diabetes mellitus, alcohol abuse, and obesity are at greater risk with the use of retinoids.[103,108] Withdrawal of therapy should be considered when LFTs are greater than three times the upper limit of normal and a decrease in the dose should be considered for those with mild elevations of liver enzymes. Once LFTs return to normal, retinoid therapy may be restarted at lower doses and with frequent laboratory checks.

Increased serum lipids are the most common of the laboratory value abnormalities observed in those receiving systemic retinoid therapy and are generally seen later in therapy.[112] Hypertriglyceridaemia and hypercholesterolaemia have been widely reported with the use of both etretinate and acitretin. Serum triglycerides are reported to be elevated in approximately 30 to 50% of patients, while serum cholesterol is elevated in up to 30% of those taking retinoids.[3,102,110,113] Those patients at greatest risk for these laboratory abnormalities include those with pre-existing hyperlipidaemia, high saturated fat and high cholesterol diets, obesity, diabetes mellitus, heavy smokers and those with alcohol abuse.[102,104] In patients with extremely high triglyceride levels, in the range of 800 to 1000 mg/dl, there is a risk of haemorrhagic pancreatitis.[114] Elevated lipids from retinoid use could also contribute to coronary artery disease if they are allowed to persist over prolonged periods of time.[115] It therefore is important to monitor serum lipids in addition to a baseline check for lipid abnormalities. Lipid control through bodyweight loss, cessation of smoking and alcohol, and a reduction of the dose, or lipid-lowering agents may all be attempted. However, once triglycerides exceed 400 mg/dl, withdrawal of therapy is indicated.[95] Upon discontinuing therapy, the hyperlipidaemia will usually resolve.[104]

Of the adverse effects of retinoids, mucocutaneous adverse effects probably are the most bothersome to patients and are nearly universal. The most common of the mucocutaneous adverse effects is chelitis, which is dose dependent and occurs in al-

most all individuals.[92,95] While it is a nuisance to patients, a mild chelitis is the goal of therapy. Generalised xerosis, dry eyes, dry nose, desquamation of the palms and soles, and a sensation of sticky skin have been reported.[10,32,40,116] These adverse effects are generally seen within the first couple of weeks after initiation of therapy, and can be disconcerting for patients.[112] These adverse effects are rarely serious and, in many cases, do not necessitate the withdrawal of therapy. Symptomatic treatment with the use of emollients, topical corticosteroids, and artificial tears in addition to education and reassurance are important factors in patient management.

Ophthalmological referrals become necessary when artificial tears do not correct dry eyes.[3] Pseudotumour cerebri is a rare, but potentially devastating, adverse effect of retinoids which might be associated with a drug interaction with tetracyclines.[117,118] Patients reporting visual changes in addition to nausea, vomiting, and headaches should be referred for neurological evaluation immediately. A majority of patients, up to 75%, will experience some degree of diffuse hair loss usually occurring in the third month of therapy.[104] This hair loss is dose-dependant and reversible with either discontinuation of therapy or a decrease in the dose.[104]

The only cumulative toxicity thought to occur with oral retinoid therapy is hyperostosis, though the causal relationship between these bony abnormalities and oral retinoid use is controversial. The aetiology of the associated bony effects caused by systemic retinoids remains unclear. The bony abnormalities seen with retinoid use include: progressive calcification of tendons and ligaments, periosteal thickening, seronegative spondyloarthropathies, sacroiliitis, premature epiphyseal plate closure in children and probably osteoporosis.[95,119] The occurrence of osteoporosis with long-term retinoid therapy, however, is controversial.

The individuals at greatest risk of osteoporotic changes are those receiving high dose retinoids for long periods of time.[119] The elderly and those with pre-existing arthritis and bony abnormalities may also be at increased risk.[3] Skeletal calcifications in the hips and forearms and osteoarticular aberrations at the level of the thoracic spine have been reported with long-term use of acitretin.[110] Earlier retrospective studies found an increased risk of diffuse idiopathic skeletal hyperostosis in those receiving long-term retinoids.[120-125] However, more recent prospective studies have shown this risk to be much less than previously reported and may largely involve a worsening of pre-existing abnormalities.[126] A prospective study published by Dooren-Greebe et al.[126] found that there was no statistically significant relationship between prolonged oral retinoid therapy and spinal abnormalities. Baseline x-rays and subsequent follow-up x-rays may be warranted, especially if patients become symptomatic or for those patients receiving long-term therapy.[103]

4. Cyclosporin

Cyclosporin was approved for the treatment of psoriasis by the US FDA in 1997 and is thought to be the most effective form of anti-psoriatic therapy with up to 90% of patients responding to the drug.[127] Though cyclosporin is well tolerated by patients, the safety profile of this medication have led most authors to agree that cyclosporin should only be considered in patients who have not responded to topical therapy and are either not candidates for or have not responded to other systemic therapy. Absolute contraindications to the use of cyclosporin include significant renal insufficiency, uncontrolled hypertension, history of malignancy current or cured with the exception of NMSC, and a prior history of any adverse reaction to cyclosporin.[128] In general, the adverse effects associated with the use of cyclosporin are dose-dependent and are reversible upon discontinuation.[129]

The most concerning toxicities include renal toxicity, hypertension, and malignancy. Other adverse effects include gastrointestinal upset, flu-like symptoms, upper respiratory tract infections, paresthesias, headaches, gingival hyperplasia, hypertrichosis and electrolyte abnormalities.

The rate at which psoriatic lesions clear with cyclosporin and remain in remission can be related to the severity of disease, the completion of clearance, and maintenance dosages.[130] Cyclosporin has been shown to induce remission in about 90% of patients within 7 to 10 weeks of therapy.[9] Longer remission times have been shown in patients who undergo maintenance dose therapy, as opposed to those who discontinue cyclosporin immediately after their psoriasis clears. Subsequent withdrawal of drug therapy rapidly leads to the reappearance of lesions to the same extent as before treatment.[131] Patients with more severe psoriasis may take longer to clear, may have shorter remission times, and may never achieve complete clearance. The more thorough the clearing, the longer the remission.[132] If maintenance dosages are established patients may remain in remission for 6 to 8 months.[104] The average relapse occurs within 2 weeks to 8 months after discontinuation of therapy.[17,104] Episodes of relapse can be successfully managed by the reintroduction of cyclosporin therapy.[9]

The adverse effect most concerning to physicians using cyclosporin for psoriasis is renal toxicity that may be acute or chronic and is the primary factor which limits the use of this drug for psoriasis. Acute nephrotoxicity is caused by renal vasoconstriction of the afferent arterioles, with a subsequent decrease in glomerular filtration rate (GFR).[133] These acute effects, without structural changes, are reversible with reduction of the dose. Rarely, the acute decrease in GFR is associated with histological changes on kidney biopsy that may not be reversible. Thus, if serum creatinine does not rapidly improve with dose reduction, other forms of therapy should be considered. Chronic nephrotoxicity is a progressive, irreversible, and less clearly dose-related impairment in renal function associated with interstitial fibrosis occurring in some patients after 6 to 12 months of cyclosporine therapy.[134-136] Progression from acute to chronic nephrotoxicity may be due to an increase in endothelin production, leading to increased synthesis and activation of transforming growth factor-β1.[116,137] Tubular epithelial cell vacuolation, atrophy and microcalcification may also be associated with the development of irreversible interstitial fibrosis. Abnormalities in the renin-angiotensin system, renal prostaglandins and adrenergic receptors may also play a role in nephrotoxicity.[138] Indications of renal toxicity include increase of serum creatinine of >30% and/or a decrease in GFR of >25% compared with baseline.[139]

Chronic renal toxicity is recognisable with both laboratory evaluation of renal function and kidney biopsy in a large population of patients treated with long-term cyclosporin. Two long-term treatment studies show that the likelihood of a significant serum creatinine increase varies from 24 to 46% in patients treated with low to moderate doses of cyclosporin (up to a maximum of 5 mg/kg/day).[127,140] Nearly all patients experienced interstitial hyalinosis when treated continuously. However, there seemed to be a rapid increase in the percentage of patients with histological changes between 2.5 and 3.5 years of treatment.[141] In all of these studies, renal toxicity was closely related to dose and to duration of treatment. Thus, it seems clear that in the treatment of psoriasis, cyclosporin dose should not exceed 5 mg/kg/day and the duration should not exceed 2 years. Serum creatinine should be monitored frequently and the dose should be adjusted if this value increases to a level greater than 25% of baseline. Recommended monitoring frequency includes: two separate occasions prior to baseline (to accurately determine baseline values), and at days 0, 15, 30 of each treatment course or after any increase in dose.[128] Interestingly, there has never been a single documented case to date of significant renal damage with the use of cyclosporin when the aforementioned guidelines have been followed.[4]

Hypertension is a very common and usually mild adverse effect reportedly seen in 8.5 to 27% of patients treated with cyclosporin for psoriasis.[4,17,127] It is not usually seen with the short-term use of cyclosporin, but develops gradually over several months.[25] Concern arises with a systolic blood pressure greater than 160mm Hg or a diastolic blood pressure above 95mm Hg.[17] Reduc-

tion of dose is often sufficient for the resolution of this difficulty without the need for antihypertensive therapy. However, if antihypertensive therapy is needed, calcium channel antagonists are considered the treatment of choice since much of the renal toxicity of cyclosporin may be related to alterations in cellular calcium fluxes.[17] If these options fail to control the hypertension, cyclosporin should be discontinued.

Cyclosporin has been used as an immunosuppressant in transplant patients along with other immunosuppressants at higher doses than those used for psoriasis.[129] Reports of cyclosporin associated malignancies in transplant patients are well documented and not uncommon in this context. Cutaneous malignancies including SCC and basal cell carcinoma have been reported.[142,143] Melanoma has been reported in patients receiving cyclosporin, but a causal relationship is not established.[144] Other reported malignancies include: renal carcinoma, hepatocellular carcinoma, gastrointestinal tumours, respiratory tumours, urogenital tumours and lymphoproliferative disorders.[142,145] Cyclosporin, at the low doses used for the treatment of psoriasis, has not been directly linked to any increased incidence of skin cancers or internal malignancies if used for no more than 2 years.[4] However, the risk for NMSC does increase for patients who have received cyclosporin and who have a history of extensive PUVA therapy.[146]

5. Combination Therapies

Combined systemic treatment can be useful when systemic monotherapy is not effective. It is important to select agents that differ in their mechanism for potential synergy. Moreover, if two medications have differing toxicities, the combination of agents may allow for lower doses of each therapy, thereby potentially reducing adverse effects. As mentioned above, retinoids can be effectively combined with phototherapy. Methotrexate may be effectively combined with topicals treatments or cyclosporin. However, care should be taken not to increase potential toxicity by the use of combination therapy. For example, it is not advisable to use PUVA in combination with cyclosporin, since it may have limited efficacy and cyclosporin is a potent immunosuppressant, which may potentiate PUVA-induced skin tumours.[146,147] The combination of acitretin and cyclosporin can be effective, but must be limited to no more than 1 year because of the cumulative adverse effects, specifically renal toxicity.[91] Though many psoriasis experts discourage combining acitretin and methotrexate, an increase in hepatotoxicity when combining these medications has not been seen.[148,149] Further data on this combination needs to be established prior to establishing its safety.

6. Rotational Strategies

Rotational therapies can be quite useful when aiming to limit the cumulative toxicities of the different agents by having long periods off each therapy. Weinstein and White[150] recommend that each of the available systemic therapies should be rotated every 1 to 2 years, thereby allowing 4 to 6 years to pass before having to return to the first treatment. In general, while rotating to a new therapy, the first drug is gradually tapered while introducing the next medication. Rotating to a new therapy is warranted with a new flare, when the drug becomes ineffective, gives intolerable adverse effects, or when the cumulative dose nears toxic levels. Methotrexate and PUVA should not be given on the same day during the overlap phase in order to avoid phototoxicity.[151] Rotating from PUVA to cyclosporin is not advised because of the subsequent immunosuppression with cyclosporin after PUVA will increase the risk of skin cancer.[146] A rotation of cyclosporin to PUVA is theoretically acceptable because after discontinuation of low-dose cyclosporin, the immunosuppression is stopped. Retinoids have been viewed as 'bridging' compounds and when rotating from one therapy to another, they are initiated in low doses and can sustain an acceptable remission for 3 to 9 months.[151]

7. Conclusion

It is inevitable that each of the current systemic therapies used for the treatment of plaque-type

psoriasis is not without certain serious risks and unpleasant adverse effects. Patients must be evaluated on an individual basis and a benefit-risk analysis performed. With regard to combination therapies, it is important to pair drugs with different mechanisms of action that target two or more pathways of inhibition within the cells not only to limit adverse effects, but to provide a potential synergistic effect. Rotational strategies are especially useful in helping to reduce the cumulative toxicities of the different agents. Tolerability of these systemic agents, in general, is improved by appropriate patient selection, symptomatic treatment, careful follow-up, and patient reassurance.

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