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# Systemic therapies for psoriasis: methotrexate, retinoids, and cyclosporine☆

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**Abstract** Despite the current use and ongoing development of the biological therapies 'traditional' systemic agents will continue to form a key part of the therapeutic armamentarium for patients with severe psoriasis. Long-term maintenance therapy with retinoids and methotrexate is cost-effective and, for many patients with psoriasis, life changing. Regular monitoring is required for both treatments, particularly methotrexate to prevent significant bone marrow suppression and hepatotoxicity. Ideally, cyclosporine should be used for short courses of 3 to 4 months duration, within which it provides excellent disease control. Close assessment of renal function and blood pressure is essential.


## Methotrexate

Methotrexate has been in use in dermatology for more than 50 years, but it originally evolved from aminopterin, a drug applied successfully in producing temporary remissions in leukemia in young children.[1] Too toxic for sustained use, aminopterin was soon replaced by 4-amino-10-methyl pteroylglutamic acid, otherwise known as 'methotrexate,' which was found to have a better risk profile than aminopterin. For a few years, the use of folate antagonists was confined to oncology, but the serendipitous observation of Gubner[2] on the improvement of psoriasis in patients with cancer who were treated with methotrexate changed this. In fact, dermatologists were among the first to embrace methotrexate as an anti-inflammatory/immune-modulating agent, with Edmunson and Guy[3] reporting its efficacy in the treatment of psoriasis in 1958.

## Chemistry and mechanism of action of methotrexate

The mechanism of action of methotrexate in psoriasis is not fully understood. Consideration of methotrexate transmembrane transport; activation of methotrexate to a polyglutamated form; methotrexate's inhibition of enzymes involved in purine, pyrimidine, and folate synthesis; and subsequent potential to influence adenosine levels does allow insight into its postulated mechanism of action in psoriasis.

### Transmembrane transport

Methotrexate enters the cell predominantly via the reduced folate carrier.[4] Efflux of methotrexate occurs through energy-dependant mechanisms. Recently, multidrug resistance–associated proteins, which transport folic acid, methotrexate, and leucovorin out of cells, have been identified.[5] These multidrug resistance–associated proteins belong to a group of transporters known as the ATP binding

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cassette family, of which ABCC1, ABCC2, ABCB1, ABCC3, and ABCC4 have been shown to influence methotrexate excretion.

## Intracellular transformation

Methotrexate can, to a large extent, be considered a prodrug. Once methotrexate has entered a cell, the action of folylpolyglutamyl synthetase can add up to 7 glutamyl groups to it.[6] Polyglutamation serves 3 main purposes: (1) it facilitates the accumulation of intracellular methotrexate, in vast excess of the monoglutamate pool, which is freely transportable into and out of cells; (2) it allows selective intracellular retention of these relatively large anionic molecules; and (3) it greatly enhances methotexate's affinity for several folate-dependent enzymes.[7]

## Methotrexate enzyme inhibition

The folate metabolic pathway is complex (Fig. 1). Methotrexate is a structural analogue of folic acid and thereby competitively inhibits dihydrofolate reductase. Such inhibition ultimately influences the conversion of homocysteine to methionine and the synthesis of polyamines.[8] In addition, methotrexate directly inhibits thymidylate synthase, which converts deoxyuridylate to deoxythymidylate[9] and glycinamide ribonucleotide transformylase, which is important in the de novo synthesis of purines.[10] Methotrexate also influences the activity of the enzyme methylentetrahydrofolate reductase. Methylentetrahydrofolate reductase is necessary for the generation of 5 methyl-THF, which is the methyl donor for the conversion of homocysteine to methionine.

## Anti-inflammatory mechanisms

It is clear that methotrexate inhibits the proliferation of malignant cells by inhibiting the de novo synthesis of purines and pyrimidines. Administration of high doses of folic acid can reverse the antiproliferative effects of methotrexate, providing evidence that its mechanism of action in oncology is via folate inhibition.[11] During the last 20 years, it has become clear that administration of folic acid in doses of 5 mg/d helps to prevent much of the toxicity of methotrexate without interfering with the anti-inflammatory efficacy of the drug. This therefore raises the question of how methotrexate works in inflammatory conditions such as psoriasis? There have been a number of suggested mechanisms, most of which involve an intracellular elevation of adenosine as a key step.[12] Adenosine may then influence leukotriene production and T-cell and adhesion molecule expression.

Methotrexate polyglutamates inhibit the enzyme aminoadenosineribonucleotide (AICAR) transformylase.[13,14] The accumulation of AICAR and its metabolites has a direct inhibitory effect on adenosine deaminase and AMP

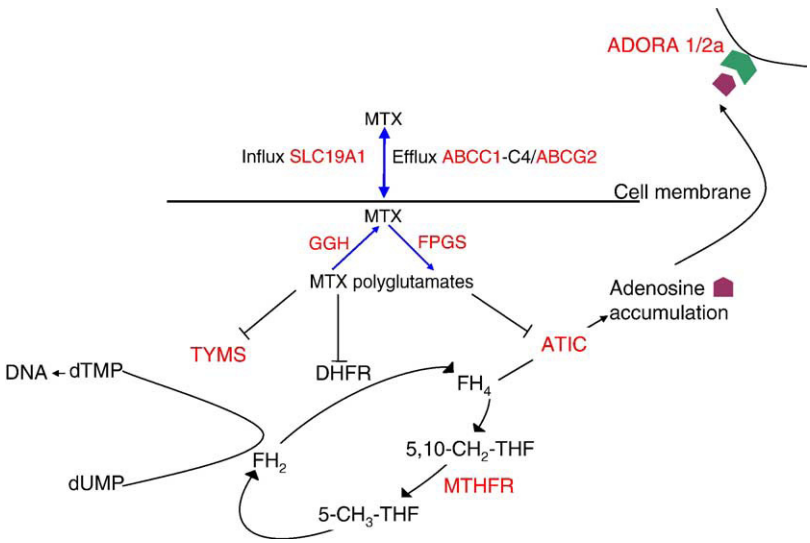


**Fig. 1** Methotrexate (MTX) is transported into the cell via the solute carrier family 19, member 1 (SLC19A1), otherwise know as the reduced folate carrier (RFC). It can be actively transported out of the cell by the ATP-binding cassette transporters including ATP-binding cassette, sub-family C (CFTR/MRP), member 1-4 (ABCC1-4) and ATP-binding cassette, sub-family G, member 2 (ABCG2). Within the cell it undergoes polyglutamation (activation) under the enzymatic control of folypolyglutamate synthase (FPGS). This is a dynamic process where glutamate residues can be removed by gamma-glutamyl hydrolase (GGH). In the polyglutamated form MTX inhibits aminoimidazole-4-carboxamide ribonucleotide transformylase (ATIC) which is likely to account for some of its anti-inflammatory effects via a rise in adenosine acting on a number of adenosine receptors (ADORA) including ADORA A1 and 2a. MTX also inhibits the enzymes dihydrofolate reducates (DHFR), 5,10-methylenetetrahydrofolate reductase (MTHFR) and thymidylate synthase (TYMS), although these effects may be less important in MTX's mechanism of action in psoriasis.

deaminase, the result of this is an elevation in the levels of adenosine.[13] This nucleoside, acting on one or more of its receptors, is a potent endogenous anti-inflammatory mediator. To date, it appears that adenosine acts on 4 types of adenoreceptors (A1, $A2_A$, $A2_B$, and A3), with anti-inflammatory effects mediated through the A2 receptors.[15] CGS-21680, an A2 receptor agonist, is a potent inhibitor of neutrophil leukotriene synthesis in vitro.[16]

T-cells are now known to play a fundamental role in psoriasis pathogenesis. It has been reported that methotrexate diminishes antigen-stimulated T-cell proliferation both in vitro and in T-cells of patients taking methotrexate.[17] Furthermore, low-dose methotrexate causes apoptosis of mitogen-activated T-cells.[17] Resting T-cells have the potential to take up methotrexate where upon it is converted to the polyglutamated form. This has then been reported to sensitize the T-cell to apoptosis. There is evidence that adenosine has proapoptotic properties.[18]

A recent study has disputed T-cell apoptosis as the main anti-inflammatory effect of methotrexate.[19] It has proposed that methotrexate has 2 main actions: first, through folate-dependant mechanisms, it decreases the activation state of antigen-stimulated cells; and second, via folate-independent mechanisms, it may alter the expression of adhesion molecules. This second mechanism required polyglutamation of methotrexate and was postulated to be mediated by adenosine.

Although our understanding of methotrexate has increased over time, there are still many unanswered questions. Evidence suggests that for methotrexate to have an anti-inflammatory and or immune-modulating effect, it requires transport into the cell, cellular retention, polyglutamation, and inhibition of enzymes involved in purine synthesis. Adenosine, via its receptors, appears be involved in the final pathway.

## Therapy with methotrexate

There are a number of different dosing regimens in use for psoriasis. Historically, it was suggested that methotrexate should be given in 3 doses at 12-hourly intervals once weekly.[20] This regimen was based upon cell-cycle kinetic studies.[21] Nowadays, most dermatologists use a once weekly single oral dosage schedule with a maximum dose of 30 mg. Parenteral intramuscular methotrexate is still used, particularly in those patients where it is thought absorption and/or gastrointestinal side effects are a problem. There is little or no evidence to substantiate which regimen, if any, is superior.

Placebo-controlled trials designed to test the efficacy of methotrexate for psoriatic arthritis were carried out in 1964.[22] In addition to improvement of arthritis, a significant improvement in psoriasis was observed. Efficacy was assessed using different doses and dosing regimens that are used nowadays. Although the literature is sparse, there are a number of more recent studies demonstrating methotrexate efficacy for psoriasis. One of the earliest studies, in 50 patients, reported more than 50% improvement in psoriasis in 82% of patients.[23] It has since been claimed that greater than 90% clearance could be achieved in 30% to 50% of patients treated aggressively with methotrexate.[24] There is good evidence to demonstrate that methotrexate is effective as maintenance therapy.[25] More recently, methotrexate has been compared directly with cyclosporine therapy in a randomized controlled trial (RCT) for the treatment of moderate to severe psoriasis. At 16 weeks of treatment, there was no significant advantage of one drug over the other with a psoriasis area severity index (PASI) 75 of 60% and 71% for methotrexate and cyclosporine, respectively.[26] However, 28% of patients randomized for methotrexate dropped out of the study because of elevated liver enzyme levels vs 2% (elevated bilirubin) in the cyclosporine group.[26] There have been differing experiences in success rates of treating pustular variants of psoriasis, some claiming a higher success rate in these subgroups and others lower.[27,28]

Methotrexate is an effective treatment for psoriatic arthritis at doses similar to those used for psoriasis, with lower doses being possible in the maintenance phase of therapy.[29] In addition, methotrexate can significantly improve psoriatic nail dystrophy in a proportion of patients.[30]

Much lower doses of methotrexate are effective in controlling psoriasis in the elderly, probably as a consequence of reduced renal clearance. Patients older than 80 years have been adequately controlled on only 2.5 mg of methotrexate per week.[31] It is prudent to accept that some residual areas of psoriasis will remain to prevent relative over treatment. Complete clearance of psoriasis should not be a goal of treatment. Although the use of methotrexate can have fatal consequences, most of such cases are attributable to absolute or relative overdosage.[32]

## Combination therapy

Methotrexate may be combined with psoralen ultraviolet A therapy (PUVA),[33] ultraviolet B therapy (UVB),[34,35] and etretinate.[36] The aim of such combinations being to reduce dosage and subsequent toxicity, however, concerns over the potential for cancer induction, with methotrexate and phototherapy,[37] and hepatitis, with methotrexate and retinoids,[38] has limited such approaches. Colchicine has been combined with methotrexate for treatment of generalized pustular psoriasis.[39]

Methotrexate has also been combined successfully with cyclosporine in patients with severe, recalcitrant psoriasis, most of which had psoriatic arthropathy.[40] This allowed reduction in dosages of both drugs, and few adverse events were recorded during the study. More recently, a prospective study of 20 patients severely affected with psoriasis on this

combination of therapies found the treatment effective with limited manageable toxicity.[41] The combination has not been studied in the long term.

## Methotrexate side effects

Unfortunately, methotrexate has a number of significant side effects that demand close supervision of all patients treated with this therapy. Common and manageable side effects include nausea, stable leucopenia, and mild elevation of liver transaminases. Addition of folic acid (5 mg daily) can help to alleviate gastrointestinal side effects, and close monitoring of liver function and full blood count allow continued therapy in most. A recent study has suggested that folic acid supplementation may reduce the treatment efficacy of methotrexate in the control of psoriasis.[42] Total numbers in this study were small, and firm conclusions not possible. Currently, it is recommended that patients on methotrexate therapy should have supplemental folic acid at 5 mg/d including the day of methotrexate dosing.[43] Rarely, hematopoietic suppression can be significant, particularly as a result of overdosing of methotrexate. In this situation, folinic acid administered intramuscularly at a dose of 10 mg/m$^2$, repeated every 6 hours (dependent on serum methotrexate levels), is the treatment of choice.[44]

Nausea can lead to discontinuation of methotrexate therapy. Antiemetics may help to alleviate this problem, with ondansetron, given at a dose of 8 mg 1 hour before methotrexate ingestion, proving particularly effective. Anagen alopecia, oral ulceration, and cutaneous erosions are fortunately rare when a weekly dosing schedule is used.[45] Other rare complications include cutaneous ulceration,[45] ataxia,[46] folliculitis, reactivation of tuberculosis,[47] depression, and other psychotic symptoms.[32]

Individuals who consume alcohol while on methotrexate, are diabetic, and/or are obese are more likely to develop significant liver toxicity. Roenigk et al[48] have published recommendations on methotrexate therapy for psoriasis and suggest liver biopsy at a cumulative dose of 1.5 g. Liver biopsy is associated with significant comorbidity and rarely mortality; therefore, novel noninvasive ways to monitor for hepatotoxicity have been explored. Three monthly monitoring of serum levels of the aminoterminal propeptide of type III collagen (PIIINP) may allow 70% of patients to be monitored without liver biopsy.[49-51]

Other rare but important complications include pulmonary fibrosis/alveolitis, infection, osteopathy, and mutagenicity. Methotrexate osteopathy presents as a triad of severe pain localized to the distal tibia, osteoporosis, and compression fractures of the distal tibia. Withdrawal of methotrexate appears to be the only treatment.[52] Ideally, methotrexate should not be given to females of childbearing potential because of its significant teratogenic potential. In addition, males should also be advised to use contraception while on methotrexate therapy and for 3 months after completing treatment. In addition, it is important to discuss the potential for persistent oligospermia with all males before therapy commences.[53]

Methotrexate carries a theoretical risk of carcinogenesis. Indeed, there has been a report of metastasizing squamous cell carcinoma of the skin in a patient on long-term methotrexate therapy.[54] Furthermore, long-term follow-up of a cohort of patients on PUVA and other therapies for psoriasis has suggested a relative risk of 2:1 for squamous cell carcinoma of the skin in those who have had high-dose methotrexate exposure vs low or no exposure.[55] This risk was independent of PUVA, and thus, close surveillance of patients on long-term methotrexate therapy is advisable.

Despite the potential for significant adverse events, minimized by close supervision of patients, methotrexate remains a first-line systemic therapy for psoriasis and its associated nail and joint disease. It is likely that the safety and efficacy of methotrexate therapy will be enhanced by the application of early, promising results from pharmacogenetic research.[56]

## Retinoids

The term ‘retinoids’ applies to a group of substances comprising naturally occurring molecules and synthetic derivatives that are closely related to vitamin A. Retinol (vitamin A) was first used as a treatment in the 1930s when phrynoderma, a disorder of skin hyperkeratosis and follicular keratinisation, was discovered to be due to deficiency of retinol. Moderate to high doses of oral retinol lead to severe hypervitaminosis A syndrome, and it was not until some 40 years later that synthetic retinoids with an acceptable therapeutic index were developed. Systemic retinoids are used for the treatment of a number of dermatological conditions. Isotretinoin (13-*cis*-retinoic acid) is a highly effective therapy for cystic forms of acne,[57] and bexarotene is used for the treatment of cutaneous T-cell lymphoma.[58] It is their role in psoriasis that dominates the use of systemic retinoids. Currently, acitretin, a derivative of etretinate, is the systemic retinoid treatment of choice for severe psoriasis. Tazarotene, a synthetic retinol receptor selective inhibitor, is used in topical formulation for the treatment of psoriasis.[59]

## Chemistry and pharmacology

The use of the first-generation, naturally occuring synthetic retinoids, tretinoin (all-*trans*-retinoic acid) and isotretinoin (13-*cis*-retinoic acid), represented a watershed in the treatment of acne; however, it is the second generation of monoaromatic retinoids that have proven valuable for the treatment of psoriasis. Etretinate is the ethyl ester form of acitretin, which is its principle active metabolite. This difference is significant; under physiological conditions,

etretinate is in an uncharged state and therefore 50 times more lipophilic than acitretin, which carries a negative charge.[60] Subsequent accumulation of etretinate within the subcutaneous adipose tissue means its elimination half-life is 120 days vs 2 days for acitretin. With teratogenicity being a significant problem with this class of drug, etretinate was withdrawn due to these unfavorable pharmacokinetics. Unfortunately, subsequent studies have shown that in the presence of ethanol, acitretin is re-esterified to etretinate[61]; therefore, the same stringent posttreatment contraceptive measures are needed after cessation of acitretin therapy. The package insert recommends that acitretin should not be prescribed to women of childbearing potential who may wish to become pregnant within 3 years of cessation of therapy.

## Mechanism of action

The exact molecular mechanism of action of retinoids in psoriasis remains unclear. It is likely that the biological effects of retinoids are to a large extent promulgated via cytoplasmic retinoid binding proteins and nuclear retinoid receptors regulating gene expression. Cellular retinoic acid binding proteins I and II bind retinol and retinoic acid in the cytoplasm.[62] In addition, they facilitate transport of these molecules to the cell nucleus. Cellular retinoic acid binding protein is found in high concentrations in epidermal tissues of patients who have conditions such as Darier disease and pityriasis rubra pilaris, diseases that show a good clinical response to acitretin. In addition, acitretin has been shown to compete with retinoic acid for binding with cellular retinoic acid binding protein.[62]

There are 2 classes of nuclear retinoid receptors: retinoic acid receptors and retinoid X receptors. These receptors exist as $\alpha$, $\beta$, and $\gamma$ types, including isoforms of each type and function via polymorphic responsive elements located in the promoters of retinoid-responsive genes culminating in pleiotropic effects.[63] Cell-specific expression of nuclear receptors is important in differentiation of basal keratinocytes and the formation of other epidermal cell layers. Acitretin activates all subtypes of retinoic acid receptor, whereas tazarotenic acid selectively binds to retinoic acid receptors $\alpha$ and $\gamma$ with little affinity for retinoid X receptors.[64] Acitretin directly affects epidermal keratinocytes in psoriasis, effectively normalizing their hyperproliferation and loss of differentiation.[65]

Retinoids may also influence angiogenesis. Vascular endothelial growth factor promotes angiogenesis, and elevated levels are found in plaques of psoriasis.[66] Retinoids inhibit the action of vascular endothelial growth factor, although this is via activator protein 1 transcription factors and not nuclear retinoic acid receptors.[67] Finally, it has been shown that retinoids can also modulate T-cell responses, inhibit chemotactic responses, and activation of polymorphonuclear leukocytes, thereby acting in an anti-inflammatory manner.[68,69]

## Therapy with Systemic Retinoids

A number of trials have demonstrated the efficacy of acitretin for the treatment of various types of psoriasis.[70-75] Exfoliative erythrodermic psoriasis and pustular psoriasis are more responsive to acitretin monotherapy than is chronic plaque psoriasis.[76] Combination therapy of a retinoid with topical agents or phototherapy can be highly effective for chronic plaque psoriasis.[77,78]

## Pustular and exfoliative erythrodermic psoriasis

Acitretin remains the first-line systemic therapy for generalized pustular psoriasis. It is most often used as monotherapy in this setting with a starting dose of between 25 and 50 mg/d, higher doses being reserved for severe or resistant cases.[79] Clinical response is often within 2 weeks, at which point tapering of the dose to around 10 to 25 mg/d is often adequate as maintenance therapy. Similar dosing regimens are effective in the treatment of exfoliative erythrodermic psoriasis.[80]

Acitretin is also effective for the treatment of palmoplantar pustulosis, where it not only decreases the level of pustulation but also aids control of coexistent hyperkeratosis. In resistant cases of palmoplantar pustulosis, the addition of PUVA therapy is useful.[79]

## Acitretin therapy for moderate to severe plaque psoriasis

Randomized placebo controlled trials have demonstrated acitretin to be effective as monotherapy for induction of remission of chronic plaque psoriasis.[70,73,75] In one study, patients treated with 50 mg/d of acitretin over 8 weeks of treatment achieved a PASI 75 of 23.1%.[81] In a RCT assessing 3 different doses of acitretin (10, 25, and 50 mg/d) vs placebo in patients with long-standing severe psoriasis over a 6-month period, acitretin was found to be no more effective than placebo.[73]

Acitretin, in combination with other forms of treatment, is more effective than monotherapy for psoriasis.[82] Acitretin can be combined successfully with PUVA, and this regimen has been shown to be superior to PUVA alone.[83] Acitretin at a dose of 50 mg/d for 2 weeks followed by up to 10 weeks of 25 mg/d combined with PUVA significantly reduced the number of PUVA treatments required for clearance and the cumulative dosage of UVA.[84] Combinations of acitretin and broadband UVB have also proved effective with 60% of patients with psoriasis treated with combination therapy improving or clearing vs 24% for UVB therapy alone in one study[85] and 74% and 35%, respectively, in another.[86] In the

latter study, a subgroup of patients treated with acitretin alone had a 42% reduction in severity of psoriasis. Interestingly, retinoids have been shown to act as chemopreventative agents against the development of cutaneous malignancy in kidney transplant recipients.[87,88] To date there is no proven data to show that retinoids alter the photoaging or potential cutaneous malignancy risks associated with phototherapy.

## Side effects of retinoids

Systemic retinoids are highly teratogenic.[89] Fetal abnormalities consequent on retinoid therapy include cardiovascular malformations, facial dysmorphia, meningomyelocele, meningoencephalocele, bony malformations, and high palate.[89]

Elevation of serum cholesterol and triglycerides may occur but can often be managed by low-fat diets, reduced alcohol intake, and exercise. Polyunsaturated fish-oil supplements and lipid-lowering drugs may be used in cases of more significant hypertriglyceridaemia and hypercholesterolaemia. Liver function should also be monitored during retinoid therapy. It has been reported that 1.5% of patients on acitretin therapy may develop a toxic hepatitis, although examination of liver biopsies from such patients revealed no histological evidence of hepatotoxicity.[90] Minor elevations of hepatic transaminases are thought to be of little importance and return to normal on cessation of treatment.

Prolonged therapy with retinoids is associated with skeletal abnormalities such as anterior spinal ligament calcification and osteophyte formation, similar to those seen in diffuse idiopathic skeletal hyperostosis.[91] Although these skeletal changes are usually painless, periodic spinal radiographical assessment should be considered if long-term therapy is planned. Arthralgia and myalgia are common musculoskeletal complaints, occurring in up to 25% of patients treated with retinoids.[38]

The most common clinical side effects are cheilitis and dryness of other mucous membranes including nose, eyes, mouth, throat, and vagina. These mucocutaneous side effects are dose related. Higher doses may induce exfoliative cheilitis, balanitis, urethritis, gingivitis, and corneal ulceration. A paronychia can occur, and in some instances, this is severe enough to necessitate cessation of therapy.[92] Thinning of palmar and plantar skin combined with nail fragility is a common complaint. Patients may also have stickiness and fragility of the skin—women should be warned that waxing to remove unwanted hair can on occasion lead to significant skin erosions. “Sticky skin” is due to retinoid-induced deposits of glycosaminoglycans in the epidermis,[93] and skin fragility a consequence of down-regulation of epidermal desmosomal proteins.[94] Alopecia is a relatively common side effect necessitating withdrawal of retinoids. It is also important to be aware of the association of retinoids with benign intracranial hypertension, a risk that is increased if retinoids are taken alongside tetracyclines. Symptoms include severe headache, nausea, vomiting, and visual disturbance. Papilloedema may be evident on ophthalmologic examination.

Although there is a high incidence of nuisance side effects, acitretin therapy continues to have an important role as a therapy for psoriasis. This is particularly the case in pustular variants of psoriasis and when used as a combination therapy for chronic plaque psoriasis.

## Cyclosporine

Cyclosporine, an undecapeptide derived from the soil fungus *Tolypocladium inflatum* Gams, belongs to the family of immunosuppressant drugs known as calcineurin inhibitors.[95] Cyclosporine acts as a “prodrug,” as it is inactive until binding with a cognate cytoplasmic receptor known as ciclophilin.[96] Within T-cells, the cyclosporine-ciclophilin complex inhibits the activity of a key cytoplasmic enzyme—calcineurin phosphatase—responsible for the dephosphorylation of nuclear factor of activated T-cells. Dephosphorylation permits translocation of nuclear factor of activated T-cells from cytoplasm to nucleus, thereby activating the T-cell leading to production of cytokines such as interleukin-2 and interferon-$\gamma$. It appears that T-cells are particularly sensitive to the inhibitory effects of cyclosporine.[97] Some researchers believe that cyclosporine has, via inhibition of calcineurin, direct effects on keratinocyte proliferation.[98] Careful in vivo assessment of cyclosporine in epidermal keratinocytes following standard oral dosing indicates it is unlikely that intrakeratinocyte concentrations of cyclosporine in vivo reach levels capable of direct inhibition of keratinocyte proliferation.[99]

The original observation[100] that cyclosporine is an effective therapy for psoriasis came about not by a logical, reductionist process but by chance. Cyclosporine was under investigation for the treatment of arthritis; four patients in the study group had psoriatic arthritis, and in these patients, the high doses of cyclosporine in use at that time, that is, 14 mg $kg^{-1}$ $d^{-1}$, cleared the patients of psoriasis within 2 weeks of therapy initiation. Indeed, it was this and subsequent observations in the 1980s[101-103] that provided added evidence that psoriasis is a T-cell–mediated dermatosis.

Since that time, significant RCT evidence has underscored the undoubted efficacy of cyclosporine in the treatment of chronic plaque, and other forms of, psoriasis.[104] There are 18 RCTs that demonstrate efficacy of cyclosporine for psoriasis—13 trials of remittive therapy and 5 of maintenance therapy.[105] Studies of cyclosporine have by necessity been over the short term, 12 weeks on average. Cyclosporine at doses of 2.5 to 5.0 mg $kg^{-1}$ $d^{-1}$ over 12 to 16 weeks produces significant improvement in psoriasis, in some cases complete clearance of the disease, in up to 90% of patients treated.[106-111] Now, because of concerns of organ toxicity (see below), cyclosporine is used mainly in short-

term, intermittent courses. Evidence for this treatment regimen is derived from the psoriasis intermittent short course of efficacy of Sandimmune Neoral (PISCES) studies,[109,110] in which intermittent, 12-week maximum treatment duration courses of cyclosporine, 2.5 to 5.0 mg $kg^{-1}$ $d^{-1}$, were used for up to 4 consecutive cycles of therapy. Intermittent, short-course therapy provided evidence that control of psoriasis could be maintained for up to 2 years[110] but with significant reduction in cumulative, continuous exposure to cyclosporine. Remission of at least 4 months could be achieved after one course of cyclosporine in up to 45% of patients. For some patients, continuous cyclosporine therapy may be required.[112-114] The average dose required for long-term, continuous therapy is 3.4 mg $kg^{-1}$ $d^{-1}$, although in one study,[115] 12.5% of patients remained clear for up to 1 year on only 1.25 mg $kg^{-1}$ $d^{-1}$. Current clinical practice dictates that cyclosporine is best used as short-term remittive therapy, with long-term maintenance therapy the exception.

## Side effects

The main concerns when cyclosporine is used for the treatment of psoriasis are 3-fold: hypertension, renal toxicity, and cancer. Cyclosporine produces increased vascular resistance that may lead to reduced renal plasma flow.[104] It is accepted that risk of renal toxicity is directly related to the dose of cyclosporine, particularly greater than 5 mg $kg^{-1}$ $d^{-1}$, and the length of continuous treatment, that is, more than 4 months. Consensus guidelines[104] mandate a reduction (25%-50%) in dose of cyclosporine if serum creatinine increases by greater than 30% above baseline value, that is, at the start of cyclosporine therapy, even if the increased level of creatinine remains within the normal laboratory range.[116,117] Baseline blood pressure should be assessed (on at least 2 separate occasions before therapy) to screen for hypertension. If blood pressure increases beyond the upper limits of normal, that is, greater than 139 mm Hg systolic and/or greater than 89 mm Hg diastolic, it should be controlled using methods that include reduction in cyclosporine dose by up to 50% and/or addition of an appropriate antihypertensive agent such as dihydropyridin-type calcium channel blockers.[104] The RCTs show that only few patients (<12%) develop new onset hypertension during short-course, intermittent cyclosporine therapy.[109]

Patients with psoriasis treated with cyclosporine have a significant 6-fold risk of nonmelanoma skin cancer as compared with the nonpsoriatic population.[118] This risk is observed exclusively in patients who have had significant prior PUVA therapy. Evidence is derived mainly from a prospective cohort study[118] involving 1252 patients with psoriasis, mean length of cyclosporine treatment is 1.9 years. Most nonmelanoma skin cancers in this cohort were

**Table 1** Potential drug interactions with cyclosporine therapy

| Drug interaction | Details |
|---|---|
| Drugs increasing CsA plasma levels (mainly by inhibition of cytochrome $P_{450}$ system) | Calcium antagonists: diltiazem, nicardipine, verapamil<br>Antimycotics: ketoconazole, itraconazole, fluconazole<br>Antibiotics: macrolides<br>Corticosteroids: high-dose methylprednisolone<br>Antiemetics: metoclopramide<br>Antiarrhythmics: amiodarone<br>Others: oral contraceptives, allopurinol, danazole, cholic acid |
| Drugs lowering CsA plasma levels (mainly by induction of cytochrome $P_{450}$ system) | Antiepileptics: carbamazepine, phenytoin<br>Barbiturates<br>Somatostatin analogues: octreotide<br>Tuberculostatics: rifampicin<br>St. John's wort: *Hypericum perforatum* |
| Drugs increasing risk of nephrotoxicity | Aminoglycosides: gentamycin, tobramycin<br>NSAIDs: diclofenac, naproxen, sulindac<br>Antimycotics: amphotericin-B<br>Antibiotics: ciprofloxacin<br>Alkylating agents: melphalan<br>Others: $H_2$ antagonists, trimethoprim |
| Drugs with increased plasma levels when used concomitantly with CsA | Antigout agents: colchicine<br>NSAID[a] with strong first pass effect: diclofenac<br>Cardia glycosides: digoxin<br>Corticosteroids: prednisolone |

Note: clinicians should consult an up-to-date pharmaceutical reference whenever concomitant medication is used during cyclosporine therapy
CsA indicates cyclosporine; NSAID, nonsteroidal anti-inflammatory drug.
Reproduced with permission from Griffiths et al.[104]
[a] Salicylic acid can be used.

squamous cell carcinoma. Management guidelines suggest that "ideally" cyclosporine should be used before initiation of PUVA therapy—this may not be such of a problem in future because the use of PUVA is rapidly diminishing with the introduction of narrowband UVB. The risk of noncutaneous malignancy does not appear to be increased in patients with psoriasis treated with cyclosporine, although long-term pharmaco-vigilance is required to confirm this.

Patients with psoriasis treated with cyclosporine experience a number of minor side effects,[104] namely, gastrointestinal (nausea, diarrhea), hypertrichosis, joint pain, leg cramps, headache, tremor, paraesthesia, and fatigue. Laboratory abnormalities include hyperbilirubinaemia and hyperlipidemia. Blood lipids should be monitored on a regular basis. Gingival hyperplasia occurs most commonly in patients who have poor oral hygiene; regular dental checkups should be encouraged. Nifedipine may exacerbate gingival hyperplasia.

Cyclosporine is metabolized by hepatic cytochrome $P_{450}$ enzymes. Thus, there are a number of potential drug interactions with cyclosporine,[119] for instance, drugs may increase blood levels of cyclosporine by inhibition of cytochrome $P_{450}$ and conversely some drugs may lower cyclosporine levels by induction of cytochrome $P_{450}$. The important drug interactions with cyclosporine are listed in Table 1.

Overall, cyclosporine is a highly effective treatment for psoriasis. It can be used effectively for chronic plaque psoriasis, palmoplantar pustulosis, and pustular psoriasis.[120] Now, cyclosporine is used mainly as short-term intermittent therapy, thereby limiting cumulative dose-related organ toxicity. In patients who are reliant on cyclosporine but can only tolerate low doses, there is good evidence that combination with methotrexate in low dose is effective,[40] particularly for patients with concomitant psoriatic arthritis. Mycophenolate mofetil also may be used as a "cyclosporine-sparing" agent in patients on longer-term therapy.[121] The T-cell targeted biologic therapies alefacept and efalizumab have enhanced efficacy if used as maintenance therapy for psoriasis following clearance by short-course cyclosporine.[104]

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