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# Systemic Cyclosporin in the Treatment of Psoriasis

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## 1. Introduction

Cyclosporin was isolated in 1970, by Jean François Borel at Sandoz Laboratories (Basel, Switzerland), from the soil fungus *Tolypocladium inflatum* (Borel et al., 1995; Amor et al., 2010). The compound was initially identified as a possible antifungal agent, but it was subsequently shown to have limited antifungal activity. However, in 1976, the drug demonstrated potent immunosuppressive properties, and two years later, it was successfully shown to prevent renal allograft rejection in renal transplant recipients. A year later, a pilot study showed that cyclosporin improved psoriasis in patients treated for rheumatoid and psoriatic arthritis. Ultimately, in the early 1990s, cyclosporin was approved in Europe for the treatment of psoriasis and atopic dermatitis. In 1997, the United States Food and Drug Administration approved a microemulsion formulation of cyclosporin (Neoral®; Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA) for the treatment of severe psoriasis in adults. Worldwide, cyclosporin has been used extensively in various dermatological disorders: e.g. pyoderma gangrenosum, and refractory chronic idiopathic urticaria (Amor et al., 2010; Vena et al., 2006).

Despite such a distinguished clinical history, some dermatologists have been rather hesitant to use cyclosporin because of concerns about possible adverse effects (Amor et al., 2010; Ryan et al., 2010); however a 'framework' of detailed clinical data now widely supports the effective and safe use of cyclosporin within dermatologists' prescribing guidelines, especially when the drug is used as a 'rescue', or intermittent short-term treatment for severe psoriasis, psoriatic arthritis, or atopic dermatitis (Amor et al., 2010).

Another particularly pertinent consideration is that 'conventional' and generic (including generic microemulsion) formulations of cyclosporin are associated with marked intra- and interindividual variability in absorption, thus creating the potential for subtherapeutic dosing at one extreme and toxicity at the other (Colombo & Egan, 2010; Ryan et al., 2010). For this reason, generic formulations have not yet been approved in several countries. Conversely, the microemulsion Neoral® preparation is associated with low intra- and interpatient variability in cyclosporin absorption and with a consistent dose-exposure relationship. This highlights the importance of prescribing the most clinically appropriate

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cyclosporin preparation, and of avoiding any confusion between the various cyclosporin formulations available (Colombo & Egan, 2010). Indeed, a Canadian survey reported that up to 20% of new cyclosporin recipients may be given a cyclosporin formulation different from that actually prescribed (Davies & Gupta 2000).

This chapter will review the following with respect to psoriasis treatment:

- The mechanism of cyclosporin action
- The pharmacokinetic properties of cyclosporin
- The efficacy of cyclosporin in well-designed, randomised controlled trials, with important economic information from certain key clinical trials
- The role of cyclosporin in current combination therapy
- Side effects of the compound.

## 2. Mechanism of action

Cyclosporin, an 11-amino acid, cyclic polypeptide produced from the fungal species *Beauveria nivea*, is a calcineurin inhibitor that acts selectively on T cells (Amor et al., 2010). Cyclosporin binds to the intracellular immunophilin cyclophilin to form a complex, which then binds to and inhibits the enzymatic activity of calcineurin phosphatase, a serine-

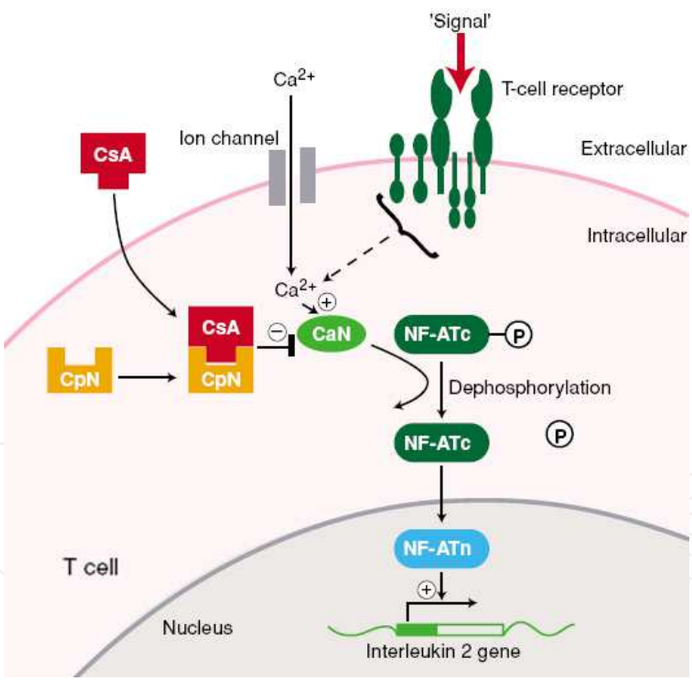


Fig. 1. Mechanism of cyclosporine action. Cyclosporine (CsA) binds to cyclophylin (CpN), forming a complex that binds and blocks the function of the enzyme calcineurin (CaN). As a result, CaN fails to dephosphorylate the cytoplasmic component of the nuclear factor of activated T cells (NF-ATc), and the transport of NF-ATc to the nucleus and the binding of NF-ATc to the nuclear component of the nuclear factor of activated T cells (NF-ATn). The NF-ATc–NF-ATn complex binds to the promoter of the interleukin 2 (IL-2) gene and initiates IL-2 production. Consequently, T cells do not produce IL-2, which is necessary for full T-cell activation.(Modified from Stepkowski, S.M. 2000)

threonine phosphatase that depends on calcium and calmodulin for activity (Amor et al., 2010; Giese et al., 2004; Stepkowski 2000). Consequently, calcineurin cannot dephosphorylate an important transcription factor: the cytoplasmic component of nuclear factor of activated T cells (NF-ATc) [Fig.1]. Transport of NF-ATc to the cell nucleus, and binding of NF-ATc to the promoter region of the IL-2 gene nuclear component of NF-AT (NF-ATn), is therefore blocked and T cells can no longer produce IL-2, a cytokine required for complete activation of the T-cell pathway, granulocyte-macrophage colony-stimulating factor, and interferon-γ production (Amor et al., 2010; Giese et al., 2004). The consequences of cyclosporin action include (Amor et al., 2010):

- Depletion of lymphocytes and macrophages in the epidermis and dermis
- Downregulation of cellular adhesion molecule expression in the dermal capillary endothelium
- Restricted activation of antigen-presenting cells, natural killer cells, and T cells
- Inhibition of keratinocyte hyperproliferation
- Restricted release of histamine from mast cells.

## 3. Pharmacokinetic properties

Cyclosporin is a lipophilic molecule that is poorly absorbed from 'conventional' orally administered formulations, with major variations in intra- and inter-patient bioavailability (Ryan et al., 2010). A microemulsion preparation (Neoral®; Novartis, East Hanover, New Jersey, USA) was therefore developed with greater hydrophilicity, and higher bioavailability (Colombo & Egan, 2010). There is marked variability among conventional formulations, and for the microemulsion vs conventional formulations : oral forms of cyclosporin are generally not bioequivalent,(Colombo & Egan, 2010) except for Neoral® soft gelatin capsules and Neoral® oral solution, which are bioequivalent (Novartis Pharmaceuticals UK Ltd 2011). Conventional and generic (including generic microemulsion) formulations of cyclosporin are characterised by considerable intra- and inter-individual variability in absorption (Colombo & Egan, 2010; Ryan et al., 2010). By contrast, there is low variability in cyclosporin absorption from the microemulsion Neoral® preparation, which provides a consistent dose-exposure relationship (Colombo & Egan, 2010).

Peak plasma cyclosporin concentrations are attained 1–6 hours after administration of a conventional soft gelatin capsule formulation (Sandimmune®; Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, USA), but 1.5–2.0 hours after oral administration of the microemulsion formulation (Neoral®) (Novartis Pharmaceuticals Corporation 2009; Novartis Pharmaceuticals UK Ltd 2011). Mean peak plasma cyclosporin concentration ($C_{max}$) after administration of the microemulsion versus conventional preparation is 40–106% greater, and mean area under the plasma concentration versus time curve (AUC) is 20–50% greater (Novartis Pharmaceuticals Corporation 2009; Novartis Pharmaceuticals UK Ltd 2011). After 4 weeks' administration of Neoral® at a mean dosage of 2.48 mg/kg/day in 18 patients with psoriasis, mean $C_{max}$ was 655 ng/mL and mean AUC was 2324 ng•h/mL.(Novartis Pharmaceuticals Corporation 2009)

Cyclosporin is extensively distributed throughout the body, in plasma (33–47% of an administered dose), lymphocytes (4–9%), granulocytes (5–12%), and erythrocytes (41–58%) (Novartis Pharmaceuticals Corporation 2009). In plasma, cyclosporin is extensively bound

to proteins (~90%), primarily lipoproteins,(Novartis Pharmaceuticals Corporation 2009) and transfer of the drug may occur between various lipoprotein subfractions, and between albumin and lipoproteins (Ryan et al., 2010). Cyclosporin is excreted in breast milk, such that mothers treated with the compound should not breastfeed (Novartis Pharmaceuticals Corporation 2009).

Cyclosporin is metabolised by the cytochrome P450 (CYP) system, primarily by isozymes CYP3A4 and CYP3A5 in the liver and small intestine; the p-glycoprotein pump also has a major influence on cyclosporin bioavailability and clearance (Novartis Pharmaceuticals Corporation 2009; Ryan et al., 2010). Cyclosporin is eliminated primarily via the bile. The terminal half-life of cyclosporin in plasma has varied from 6–24 hours in various populations,(Novartis Pharmaceuticals UK Ltd 2011; Ryan et al., 2010) but in patients with psoriasis, the value is probably closer to the lower end of this range (Berth-Jones 2005).

## 4. Clinical efficacy

Cyclosporin is one of the most effective antipsoriatic agents available because of its rapid onset of effect and potent immunosuppressive activity against disease flares (Amor et al., 2010; Ryan et al., 2010). Thus, in patients with severe psoriasis refractory to other agents, cyclosporin can produce rapid remission and serve as a useful 'bridge' to other treatments (Menter et al., 2009).

The efficacy of cyclosporin is dose-dependent, and times to psoriasis remission are shorter at higher doses (Faerber et al., 2001; Timonen et al., 1990). Results from key dose-finding studies and meta-analyses for cyclosporin in psoriatic patients are shown in Table 1. In patients treated with cyclosporin 1.25–5 mg/kg/day for 10–36 weeks, the PASI70 or PASI75 response rate (i.e. the proportion of patients with a decrease in Psoriasis Area and Severity Index [PASI] score of ≥70% or ≥75% from baseline, or with a decrease to a PASI score of ≤8)

| Reference | Study design | No. of patients | Cyclosporin dosage (mg/kg/day) | Study duration | Clinical response | |
|---|---|---|---|---|---|---|
| | | | | | PASI75[a] | Global disease severity score[b] |
| Christophers et al., 1992 | r, df | 217 | 1.25–5 | 12–36 wks | 18–56 | - |
| Ellis et al., 1991 | r, db | 85 | 3–7.5 | 16 wks | - | 59–77 |
| Faerber et al., 2001 | ma | 597 | 1.25–5 | 10–12 wks | 16–50[c] | - |
| Timonen et al., 1990 | ma | 457 | 1.25–5 | 3 mos | 24–88 | - |

[a] Proportion of patients with a decrease in Psoriasis Area and Severity Index (PASI) score of ≥75% from baseline, or with a PASI score ≤8.
[b] Percentage decrease in score from baseline.
[c] PASI70 response.
db = double-blind; df = dose-finding; ma = meta-analysis; mos = months; r = randomised; wks = weeks.

Table 1. Key dose-finding studies and meta-analyses for cyclosporin in psoriatic patients.

was 16–88% (Christophers et al., 1992; Faerber et al., 2001; Timonen et al., 1990). Moreover, in a 16-week study in 85 patients with severe psoriasis, cyclosporin 3–7.5 mg/kg/day reduced global disease severity score by 59–77% (Ellis et al., 1991); however, although major, additional efficacy benefits can be obtained at cyclosporin doses >5 mg/kg/day, these benefits are offset by increased toxicity (Amor et al., 2010).

Psychological distress is common in psoriatic patients (Colombo et al., 2010c; Finzi et al., 2007). A large, observational, follow-up study of more than 1500 psoriatic patients (the PSYCHAE study) revealed that methotrexate and topical corticosteroids were associated with a significantly increased risk of minor psychological distress, whereas cyclosporin significantly reduced such distress, perhaps because of patients' overall perceptions of efficacy and tolerability (Colombo et al., 2010c). This finding has potentially major clinical significance, since it outlines the possibility for markedly improved quality of life during cyclosporin therapy, but the possibility for detrimental effects on quality of life for certain other psoriasis treatments. Additional, comparative investigations are now warranted to clearly define the relative effects of cyclosporin and other antipsoriatic agents on quality of life (see section 8).

### 4.1 Intermittent short-term therapy

Intermittent short-term therapy for 12–16 weeks is the most widely recommended dosing schedule for psoriasis: that is, short courses of cyclosporin are administered until marked improvement is evident, whereupon treatment is stopped; if relapse manifests, cyclosporin is re-started at the dosage that was earlier effective (Menter et al., 2009).


Fig. 2. Maintained efficacy of intermittent short-term cyclosporin therapy during a large, 1-year, multicentre, randomised trial in patients with plaque psoriasis (Ho et al., 1999). Values shown are the probability of a PASI75 response after 12 weeks' treatment with cyclosporin 2.5–5 mg/kg/day.

In a large, multicentre, randomised trial (the Psoriasis Intermittent Short Courses of Efficacy of Sandimmun Neoral® [PISCES] study), 400 patients with plaque psoriasis were initially treated with cyclosporin 2.5–5 mg/kg/day until clearance of psoriasis, or for a maximum of 12 weeks; patients were then randomised to abruptly or gradually discontinue (dosage reduction of 1 mg/kg/day each week) cyclosporin therapy. If relapse occurred, patients received another course of cyclosporin therapy. After 1 year of follow-up, 117 patients had

received 3 cyclosporin courses, and 26 had received 4. After the first treatment course, abrupt versus gradual cessation of cyclosporin therapy was associated with a slightly, but significantly, shorter time to disease relapse (median 109 vs 113 days; p=0.038). Overall, the Kaplan-Meier probability of achieving a ≥75% decrease in disease area after 12 weeks' treatment was 83% after the first cyclosporin course, 76% after the second, 73% after the third, and 66% after the fourth [Fig. 2] (Ho et al., 1999).

In an extension of the PISCES trial, 76 patients were followed-up for a total of 2 years. The time in remission during the follow-up period was not significantly different between patients stopping cyclosporin therapy abruptly versus gradually (time in remission: 56.2% vs 61.8%); overall, the mean proportion of follow-up for which patients received cyclosporin was 42.8%. After the first treatment course, the median time to relapse was 115.5 days, but this became progressively shorter with an increasing number of cyclosporin courses (Ho et al., 2001).

### 4.1.1 Prevention of relapse

The well-designed PREWENT study assessed the efficacy of microemulsion cyclosporin 5 mg/kg/day, administered each weekend for 24 weeks in a total of 243 adults with chronic plaque psoriasis. The primary study endpoint in this multicenter, randomised, double-blind, placebo-controlled trial was relapse rate at 24 weeks: thus, 66.9% of cyclosporin-treated patients versus 53.2% of placebo recipients (p=0.072) had no worsening of psoriasis (i.e. no increase in PASI score to ≥75% of the value recorded before 8–16 weeks' induction therapy with cyclosporin). Although this difference only approached statistical significance, the time to first relapse was significantly longer in the cyclosporin than placebo group (p=0.0233), and in a *post hoc* analysis of patients with mild-to-moderate psoriasis, significantly more cyclosporin-treated patients than placebo recipients had no worsening of psoriasis (69.9% vs 46.3%; p=0.011) [Fig. 3] (Colombo et al., 2010a).

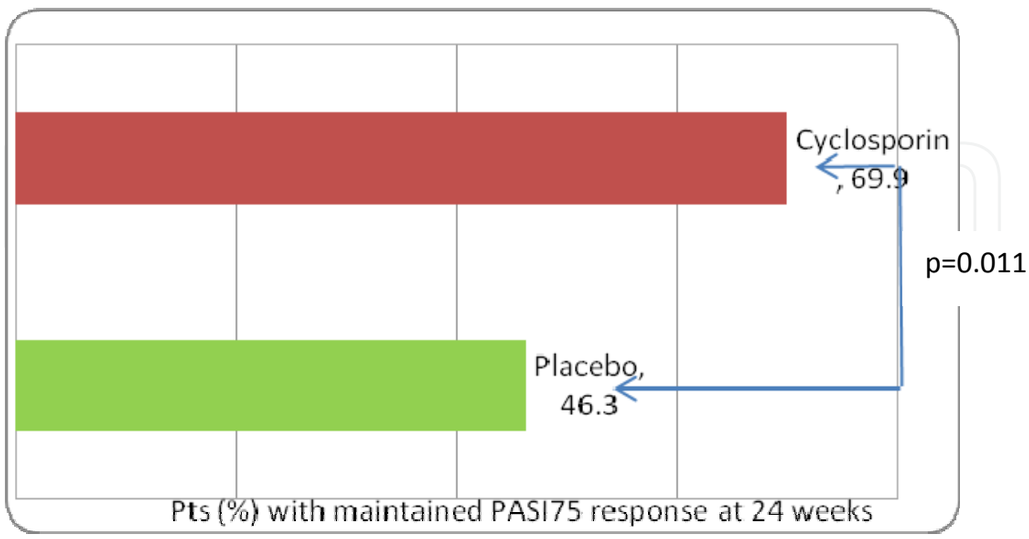


Fig. 3. Weekend cyclosporin therapy (5 mg/kg/day) prevents relapse in patients with mild-to-moderate psoriasis: results from the PREWENT trial (Colombo et al., 2010a).

### 4.2 Rescue therapy

Short-term cyclosporin therapy has a rapid onset of effect, and can therefore be administered as a rescue or bridging treatment for severe disease flares: that is, until a different maintenance therapy is started. As a bridging therapy, cyclosporin can be 'dovetailed' with the new maintenance regimen (e.g. biological therapy, methotrexate) to avoid clinical deterioration while the new schedule is taking effect. Cyclosporin can then be stopped without a risk of flares, and with a limited risk of adverse effects for only the short time that the cyclosporin bridging schedule and the new maintenance regimen are dovetailed (Amor et al., 2010).

Rescue cyclosporin therapy is especially effective in patients with erythrodermic, generalised, or suberythrodermic pustular psoriasis; a reducing-dosage strategy is employed after starting treatment at 5 mg/kg/day (Menter et al., 2009; Pathirana et al., 2009). In a study of 33 patients with erythrodermic psoriasis, the initial intervention was cyclosporin 4.2 mg/kg/day; after remission, the dosage was reduced by 0.5 mg/kg/day every 2 months. At 2–4 months, two-thirds of patients had attained complete remission, and marginally more than one-quarter had attained significant clinical improvement (Rosenbach et al., 2010).

### 4.3 Long-term therapy

European guidelines recommend that the maximum period of continuous cyclosporin therapy in patients with psoriasis should be no more than 2 years (Griffiths et al. 2004; Menter et al. 2009; Pathirana et al. 2009). This is primarily because the incidence of renal dysfunction and nonmelanoma skin cancer may increase markedly with high doses of cyclosporin administered for longer periods (Paul et al. 2003; Ryan et al. 2010). In addition, any cyclosporin-related hypertension or renal dysfunction is generally reversible if the dose is maintained at ≤5 mg/kg/day and treatment duration at ≤2 years (Ryan et al. 2010).

Long-term cyclosporin therapy (for up to 2 years or more) maintains its efficacy in most psoriatic patients; however, the principal goal of maintenance therapy is not routine attainment of clinical remission, but rather attainment of marked clinical improvement with the minimum cyclosporin dosage — generally 3–3.5 mg/kg/day (Griffiths et al., 2000). Rather surprisingly, given the long-term nature of psoriasis, and in contrast to European guidelines, US guidelines stipulate that the duration of cyclosporin therapy should be restricted to ≤1 year in psoriatic patients (Amor et al. 2010; Menter et al. 2010). This restriction appears rather strange when it is considered that, only with longer-term treatment (3–5 years or more) may a substantial proportion of patients experience glomerulosclerosis (Menter et al. 2010).

In a large-scale study involving 285 patients with psoriasis, cyclosporin 1.25–5 mg/kg/day administered continuously for 6–30 months reduced mean PASI scores by approximately 75–94% from baseline, but after cyclosporin cessation, approximately 50% of patients experienced a relapse requiring antipsoriatic therapy (Mroweitz et al., 1995). Similarly, in another large-scale study (n=181), 86% of patients treated with cyclosporin at a dosage of ~5 mg/kg/day for 16 weeks had a PASI70 response, and subsequent maintenance therapy with cyclosporin 3 mg/kg/day was associated with a significantly longer median time to relapse than placebo ($p<0.001$); at the end of the 24-week maintenance phase, 42% of patients

treated with cyclosporin 3 mg/kg/day compared with 84% of placebo recipients had relapsed (Shupack et al., 1997).

A recent, retrospective evaluation of 193 patients with moderate-to-severe psoriasis revealed that cyclosporin 1.5–3.1 mg/kg/day (mean dosage) administered for 12–36 (mean 14) months reduced mean PASI score from 23.3 to 5.6; the PASI75 response rate was 73.9%. In this trial, 83/193 patients (43%) received cyclosporin monotherapy, whereas the remainder received polytherapy. Among monotherapy recipients, the physician's judgement of therapeutic success (total clearance of lesions) was 71% of patients, whereas that of clinical remission (clearance of lesions with some remaining pigmentation) was 19% of patients. Costs to the Italian healthcare system, based on a mean 1.5 cyclosporin courses administered over 14 months, were estimated at €2,984 per patient overall; the direct costs of cyclosporin acquisition were €2,058 per patient, which are approximately 4½–7 times less than annual treatment courses of etanercept and infliximab (Colombo et al., 2010b). To support and extend these cost findings, the design and execution of comparative economic evaluations of cyclosporin versus biological therapies in patients with moderate-to-severe psoriasis would now be particularly pertinent (see section 8).

In smaller studies, continuous versus intermittent cyclosporin therapy was significantly more effective over a 1-year period in 51 patients with chronic plaque psoriasis (PASI75 response rate: 92% vs 62%, p=0.008), although the mean cumulative annual dose of cyclosporin was 1.4-fold greater for continuous therapy (Chaidemenos et al., 2007). Furthermore, 60 patients with clearance or near clearance of psoriasis during cyclosporin induction therapy (3–7.5 mg/kg/day for 4 months) subsequently received cyclosporin maintenance therapy 1.5 or 3 mg/kg/day, or placebo, for up to 4 months (Ellis et al., 1995). Mean time to relapse was significantly longer in the higher-dose versus lower-dose cyclosporin group (12 vs 9 weeks; p=0.04), and in the higher-dose group versus placebo recipients (12 vs 7 weeks; p=0.002). At study completion, markedly fewer patients in the higher-dose versus lower-dose versus placebo group had relapsed: 43% vs 79% vs 95% (Ellis et al., 1995).

### 4.4 Rotational therapy

Rotational therapy with various systemic agents (e.g. acitretin, fumaric acid esters, methotrexate, mycophenolate mofetil) has occasionally been advocated as a means of reducing the duration, and any potential toxicity, of cyclosporin therapy (Amor et al., 2010). While most patients require additional antipsoriatic therapy after cyclosporin cessation (Amor et al., 2010), some patients may have an extended period of remission after cyclosporin therapy (Ho et al., 1999, 2001).

## 5. Indications/dosage

In Europe, cyclosporin is indicated for the treatment of severe psoriasis in patients for whom conventional therapy is ineffective or inappropriate. After starting treatment with oral cyclosporin, psoriatic patients should not be switched to another oral cyclosporin formulation without relevant monitoring of plasma cyclosporin levels, creatinine levels, and blood pressure; indeed, except for Neoral® soft gelatin capsules and Neoral® oral solution, which are bioequivalent, the various oral forms of cyclosporin are not bioequivalent. To

avoid any possible confusion among healthcare professionals, and to avoid any potential for major fluctuations in cyclosporin bioavailability, cyclosporin should be prescribed by brand (Neoral® SPC, 2011).

To induce remission of psoriasis, the recommended starting dosage of oral cyclosporin is 2.5 mg/kg actual bodyweight each day, administered in two divided doses; however, when a rapid initial response is required, a starting dosage of 5 mg/kg/day can be used (Neoral® SPC, 2011). If no improvement is evident after 1 month of 2.5 mg/kg/day, the dosage can be gradually increased in 0.5–1 mg/kg increments, at intervals of 2–4 weeks, up to a maximum of 5 mg/kg/day (Menter et al., 2009; Neoral® SPC, 2011). Cyclosporin should be stopped if the response is inadequate after 6 weeks' administration of 5 mg/kg/day. However, after an initially good response, the cyclosporin dosage can be reduced for maintenance therapy in steps of 0.5–1 mg/kg, at intervals of 2 weeks, until the lowest effective dosage level is attained (Amor et al., 2010; Neoral® SPC, 2011). Intermittent cyclosporin therapy may be appropriate for some psoriatic patients: that is, when an initial satisfactory response has been attained, cyclosporin therapy can be stopped and any subsequent relapses treated with reintroduction of cyclosporin at the previously effective dosage (Neoral® SPC, 2011).

Before starting cyclosporin therapy, baseline renal function and blood pressure should be measured. Plasma creatinine should be measured every month. If an increase in plasma creatinine occurs to ≥30% above baseline, cyclosporin dosage should be reduced by 25–50%, even if levels are within the reference range (see section 7.2.2). If such dosage reduction does not successfully reduce plasma creatinine within 1 month, cyclosporin should be stopped. Similarly, if elevated blood pressure occurs and cannot be controlled by cyclosporin dosage reduction, or by intervention with antihypertensive therapy, cyclosporin cessation is advocated (Neoral® SPC, 2011).

## 6. Combination therapy

### 6.1 Topical treatments

To improve clinical efficacy, cyclosporin has been administered with various topical therapies (e.g. corticosteroids, dithranol, vitamin $D_3$ analogues [e.g. calcipotriol]) (Amor et al., 2010). However, data supporting such strategies stem mainly from small-scale, uncontrolled studies (Gottlieb et al., 1995; Griffiths et al., 1989). For example, in 12 psoriatic patients treated with cyclosporin 5 mg/kg/day for up to 18 weeks, and who applied topical dithranol to plaques on half of their bodies, improved clinical efficacy (e.g. significantly reduced severity index) was noted for combination therapy in 58% of patients (Gottlieb et al., 1995). In 13 patients with severe persistent psoriasis, cyclosporin 1–4 mg/kg/day was administered for 12–25 months, and an 81% decrease was noted in mean PASI score; 85% of the patients had received topical corticosteroid therapy after the first 3 months of cyclosporin (Griffiths et al., 1989). A larger randomised, double-blind, placebo-controlled trial in 69 cyclosporin-treated (2 mg/kg/day) patients with severe chronic plaque psoriasis revealed clinical improvement in a significantly greater proportion of patients who used concomitant calcipotriol 50 μg/g ointment versus vehicle: 50% vs 12% of patients (p=0.0019) had complete clearing of psoriasis or a ≥90% improvement in PASI score (Grossman et al., 1994).

### 6.2 Systemic treatments

Combination schedules of cyclosporin plus other systemic antipsoriatic agents (e.g. fumaric acid esters, methotrexate, mycophenolate mofetil) have been used in patients with severe psoriasis to facilitate cyclosporin dosage reduction and to reduce the risk of potential adverse effects (Amor et al., 2010). For instance, in small-scale, uncontrolled trials:

- Cyclosporin plus methotrexate was administered for a mean of up to about 3½ years in 19 patients with severe recalcitrant psoriasis, and the combination schedule produced good control of psoriasis using lower doses of each agent than would have been used for monotherapy; however, 6 patients developed renal impairment, which normalised (n=3), or which improved but did not normalise (n=3), after cyclosporin dosage reduction (Clark et al., 1999).
- Cyclosporin 2.5 mg/kg/day plus mycophenolate mofetil 3 g/day led to moderate or good clinical improvement over 3–11 months' follow-up in 78% of patients with severe recalcitrant psoriasis (Ameen et al., 2001).

Interestingly, in a retrospective assessment of 193 cyclosporin-treated patients with moderate-to-severe plaque psoriasis, 110 patients (57%) had received concurrent therapy with systemic methotrexate or retinoids, or topical and/or phototherapy. In the physician's judgement, a clinical response (therapeutic success or clinical remission) occurred in 80% of combination therapy recipients (Colombo et al., 2010b). Cyclosporin was also investigated in combination with phototherapy. In a study comparing sequential cyclosporin and narrow-band (NB) UVB phototherapy versus NB UVB phototherapy alone in patients with severe psoriasis, both treatments were effective and well tolerated, but the sequential therapy showed a greater efficacy on lesions of UV-shielded body areas and on itching (Calzavara-Pinton et al., 2005). The increased efficacy of the sequential therapy allowed for the reduction of NB UVB dosage and exposure. Nonetheless, it should be remembered that psoriatic patients previously treated with psoralen and ultraviolet A (PUVA), and to a lesser extent UVB, have increased risks of skin malignancies during cyclosporin therapy. Psoriatic patients receiving cyclosporin should not receive concomitant PUVA or UVB therapy (Neoral® Prescribing Information, 2009).

## 7. Side effects

Side effects, such as hypertension and renal impairment, may be associated with continuous cyclosporin therapy and appear related to treatment duration and dose (Colombo et al., 2010a). Generally, such side effects are reversible after cyclosporin discontinuation, although rarely chronic renal impairment and structural abnormalities in the kidneys may persist and be irreversible (Ryan et al., 2010). To minimise the risk of nephrotoxicity, the most widely recommended cyclosporin regimen in psoriasis is a short-term schedule of 2.5–5.0 mg/kg/day for 12–16 weeks (see section 5); this short course is repeated if subsequent disease flares occur (Amor et al., 2010; Griffiths et al., 2004). Adhering to present guidelines about appropriate dosage and monitoring protocols for cyclosporin use in psoriatic patients will substantially reduce the risk of side effects (Griffiths et al., 2004; Menter et al., 2009; Pathirana et al., 2009).

Although the mechanisms for many cyclosporin-related adverse effects have not been clearly defined, immunophilin inhibition (especially inhibition of immunophilins involved

in the regulation of mitochondrial ion channels) and mitochondrial dysfunction may have significant pathogenetic roles (Ryan et al., 2010). Adverse effects reported in large-scale randomised controlled trials and meta-analyses of short-term or longer-term cyclosporin therapy in psoriatic patients are documented in Table 2. As can be seen, in short-term

| Study features/AEs[a] | Short-term cyclosporin therapy | | Longer-term cyclosporin therapy | | | |
|---|---|---|---|---|---|---|
| | Ellis et al., 1991 | Faerber et al., 2001 | Christophers et al., 1992 | Krupp & Monka, 1990 | Mrowietz et al., 1995 | Shupack et al., 1997 |
| No. of patients | 85 | 579 | 285 | 631 | 88 | 181 |
| Dosage (mg/kg/day) | 3–7.5 | 1.25–5 | 1.25–5 | 1.25–5 | 1.25–5 | 1.5–6 |
| Duration | 16 wks | 10–12 wks | 12–36 wks | 12 wks–16 mos | 6–30 mos | 40 wks |
| AEs requiring discontinuation | 4.7 | 4.1 | 1.6–3.2 | 5.9 | 5.7 | 7.0–11.0 |
| Renal dysfunction | 18[e] | ≤8 | 1–13 | na | 5 | 17–43 |
| Hypertension | na | 5–14 | 11–26 | na | 8 | 9[f] |
| GI side effects | 28–55 | 3–8 | 4–5 | 12 | 22 | 12[f] |
| Headache | 20–53 | 2–4 | ≤5 | 6 | 3 | 30[f] |
| Tremor | 4–25 | na | ≤2 | 1 | 2 | na |
| Paraesthesias | 16–40 | na | ≤1 | 11 | na | 18[f] |
| Hypertrichosis | 24–27 | ≤5 | 1–2 | 7 | 2 | 17[f] |
| Hypercholesterolaemia | na | na | 12–25 | na | na | na |
| Hypertriglyceridaemia | na | na | 20–53 | na | 13 | na |
| CV symptoms[b] | 5–8 | na | na | na | na | na |
| CNS symptoms[c] | 7–25 | 1–6 | na | na | na | na |
| Fatigue | 12–20 | ≤4 | 1–2 | 3 | na | 11[f] |
| Influenza-like symptoms | 5–20 | na | na | na | 9 | na |
| Infection[d] | 20–27 | na | 2 | na | na | na |
| Gum hypertrophy | 8–15 | na | 1–2 | 4 | 2 | na |

[a] Percentage of patients, unless otherwise stated.
[b] Chest pain, premature ventricular contraction, tachycardia.
[c] Anxiety, depression, dizziness, insomnia, nervousness, syncope, visual changes, transient ischaemic attack.
[d] Non-influenza-like viral, bacterial, and fungal infections.
[e] ≥15% decrease in glomerular filtration rate.
[f] During 16-wk induction phase (5 mg/kg/day).
AE = adverse effect; CNS = central nervous system; CV = cardiovascular; GI = gastrointestinal; mos = months; na = not available; wks = weeks.

Table 2. Principal side effects reported in large-scale, well-designed clinical trials and meta-analyses of cyclosporin therapy in patients with psoriasis.

studies of up to 16 weeks' duration, about 4–5% of cyclosporin-treated patients had adverse effects requiring treatment discontinuation (Ellis et al., 1991; Faerber et al., 2001). In a meta-analysis of 3 major German studies in approximately 600 patients with severe plaque psoriasis, and across the dosage range 1.25–5.0 mg/kg/day, the principal side effects were hypertension (5–14% of patients), renal dysfunction (≤8%), and gastrointestinal problems (3–8%); increased plasma creatinine levels required intervention in only 3.4% of the total 756 cyclosporin treatment cycles (Faerber et al., 2001).

In longer-term studies of up to 30 months' duration, but across the same dosage range 1.25–6 mg/kg/day, up to 11% of patients discontinued cyclosporin because of adverse effects; hypertension occurred in 8–26% of patients, gastrointestinal problems in 1–22%, and renal dysfunction in 1–43%. Lipid disorders also manifested: hypercholesterolaemia in 12–25% of patients, and hypertriglyceridaemia in 13–53% of patients (Christophers et al., 1992; Krupp & Monika, 1990; Mrowietz et al., 1995; Shupack et al., 1997).

Interestingly, in a recent, well-designed evaluation of relapse rates in patients with chronic plaque psoriasis who had achieved clinical remission after continuous cyclosporin therapy, 243 patients were randomised to 24 weeks of weekend cyclosporin microemulsion therapy 5 mg/kg/day or placebo (the Psoriasis Relapse Evaluation with Week-End Neoral Treatment [PREWENT] study) (Colombo et al., 2010a). In this investigation in a 'real-life' clinical setting, rather than in a group of carefully selected psoriatic patients, cyclosporin was well tolerated: no significant difference was evident in the incidence of adverse events between cyclosporin and placebo recipients (38.4% vs 21.5%). Only one patient (a cyclosporin recipient) had a serious adverse event (breast mass), but this was considered unrelated to study treatment. Furthermore, at no time during the study were mean plasma creatinine levels, or systolic and diastolic blood pressure values, different between the two groups; the incidence of plasma creatinine levels >30% above baseline was similar in the two groups (5.0% vs 3.8% of patients) (Colombo et al., 2010a)

In a retrospective assessment of 193 patients with moderate-to-severe psoriasis who had received a mean cyclosporin dosage of 1.5–3.1 mg/kg/day for 14 months, 83 patients (43%) received cyclosporin as monotherapy (Colombo et al., 2010b). Altogether, marginally more than one-third of patients experienced at least one adverse event. The most frequent events were hypertension (17.6% of patients), hypercholesterolaemia (14.0%), raised plasma creatinine level to >30% above baseline (6.7%), and gastrointestinal symptoms (6.2%). The clinician's assessment of cyclosporin tolerability was 'very good' or 'good' in 90% of cases (Colombo et al., 2010b).

Overall, the possibilities of cyclosporin-induced hypertension and renal dysfunction are perhaps the major tolerability concern among prescribers, and might explain a certain degree of cyclosporin 'under-utilisation' by dermatologists (Ryan et al., 2010). These two side effects are discussed in more detail below, whereas other potential tolerability issues are addressed relatively briefly.

### 7.1 Hypertension

The incidence of new-onset hypertension during cyclosporin administration to psoriatic patients has varied somewhat in short-term studies (5-14% of patients) and longer-term

trials (8–26%; Table 2). Such hypertension is generally reversible after the cyclosporin dosage is reduced, or after antihypertensive medications are added (Ho et al., 1999; Ryan et al., 2010). Importantly, besides specific drug therapy, psoriasis per se may contribute to an increased risk of hypertension, since psoriatic patients have increased incidences of obesity and metabolic syndrome (Gelfand et al., 2006).

Pooled data from 10 studies involving 563 patients with severe psoriasis revealed an overall incidence of new-onset hypertension of 10.6% during cyclosporin therapy (Feutren et al., 1990). However, the occurrence of hypertension was not dose-related (10.0% of patients at 2.5 mg/kg/day; 11.9% at 5.0 mg/kg/day) (Feutren et al., 1990), and this finding agrees with that of several randomised trials (Ryan et al., 2010). The implication, therefore, is that a subset of psoriatic patients exists with heightened sensitivity to cyclosporin, and enhanced susceptibility to hypertension, even at low cyclosporin doses (Ryan et al., 2010). Thus, cyclosporin-induced hypertension may best be managed with antihypertensive therapy rather than with a reduced cyclosporin dosage (Feutren et al., 1990; Ryan et al., 2010).

#### 7.1.1 Management of hypertension

Psoriatic patients have an increased risk of cardiovascular morbidity and mortality (Gelfand et al., 2006). Regular blood pressure monitoring (e.g. weekly self-monitoring) is therefore important in cyclosporin-treated patients with psoriasis. If hypertension occurs, current guidelines advocate a cyclosporin dosage reduction of 25–50%, or commencement of antihypertensive therapy (Griffiths et al., 2004; Pathirana et al., 2009). Dihydropyridine calcium-channel blockers (e.g. amlodipine, isradipine) are generally the interventions of choice, since they confer some degree of nephroprotection (Ryan et al., 2010).

### 7.2 Renal dysfunction

Though renal dysfuntion is recognized as a cyclosporin-related side effect, the real impact of cyclosporin on kidney function may need to be reassessed. The experience in transplant patients, particularly in kidney transplant recipients where cyclosporin is used at higher doses in life-long regimens shows, that these regimens are well tolerated (Cho & Terasaki, 1988; Opelz, 1994). An Italian study conducted in 573 kidney transplant recipients showed that creatinine plasma levels remain constant and around 1.5 mg/dl over 15 years after the intervention, a clear indication of stable kidney function ( Sandrini, data presented at SIN 2003 Bologna).

When renal dysfunction persists during cyclosporin therapy, it is usually related to higher doses (>5 mg/kg/day) or extended treatment (>2 years), and both of these factors may lead to structural renal damage. Renal dysfunction may also comprise functional impairment (i.e. vascular or tubular dysfunction), which may be evident soon after starting treatment. The consequences of vascular dysfunction are reduced glomerular filtration rate and renal blood flow, and reduced creatinine clearance, whereas the consequences of tubular dysfunction may include hypomagnesaemia, reduced plasma bicarbonate levels, hyperuricaemia, and hyperkalaemia. Acute functional impairment is generally reversible when cyclosporin treatment is discontinued; thus, the risk of renal toxicity is minimised when intermittent

cyclosporin therapy is prescribed in psoriasis, since such therapy is associated with normalisation of renal function between treatment courses (Ryan et al., 2010).

Besides raised plasma creatinine levels, other predictors of cyclosporin-related nephropathy include advanced age, obesity, new-onset or pre-existing hypertension or renal disorders, and other nephrotoxic treatments. Altogether, as relatively low cyclosporin dosages are now used in psoriasis, tubulopathic changes are rare and reversible (Ryan et al., 2010).

### 7.2.1 Management of renal dysfunction

If plasma creatinine levels are ≥30% above baseline on two consecutive occasions, 2 weeks apart, the cyclosporin dosage should be reduced by 25–50% for at least 4 weeks; this applies even if creatinine values are within the normal reference range (Griffiths et al., 2004; Menter et al., 2009; Pathirana et al., 2009). After 4 weeks of reduced-dosage treatment, if plasma creatinine levels remain elevated, cyclosporin should be discontinued (Neoral® SPC, 2011).

As a preventive measure against renal dysfunction, it is recommended that psoriatic patients receiving long-term cyclosporin therapy should have glomerular filtration rate measured at least once each year (Griffiths et al., 2004; Pathirana et al., 2009). Guidelines from the European Association of Dermatology and Venereology and from the British Association of Dermatology stipulate that the maximum period of continuous cyclosporin therapy in psoriatic patients should not exceed 2 years (Griffiths et al., 2004; Menter et al., 2009; Pathirana et al., 2009). As a comparison, it should be reminded that in graft recipients, life-long regimens with higher cyclosporin doses are routinely used in clinical practice and have proved well tolerated after many years of use.

Generally, if the cyclosporin dosage is ≤5 mg/kg/day, and if patients are closely monitored so that plasma creatinine levels remain ≤30% above baseline, any renal side effects will be wholly reversible after cyclosporin treatment is stopped (Ryan et al., 2010).

## 7.3 Central nervous system effects

Headache may occur in up to 53% of cyclosporin-treated patients with psoriasis, paraesthesias in up to 40%, and tremor in up to 25% (Table 2). The latter two effects generally occur during the first few weeks of cyclosporin administration and dissipate after a decrease in cyclosporin dosage; hypomagnesaemia has been postulated as a cause of these effects (Ryan et al., 2010).

Seizures have been reported rarely during cyclosporin therapy, but cyclosporin does have the potential to reduce seizure threshold in epileptic patients; the seizure risk is increased in patients taking concurrent, high-dose corticosteroid therapy. Furthermore, patients taking antiepileptic drugs may have reduced circulating cyclosporin levels because of increased metabolism by the cytochrome P450 system (Ryan et al., 2010).

## 7.4 Gastrointestinal effects

The rates of cyclosporin-induced gastrointestinal side effects (e.g. abdominal pain, diarrhoea, dyspepsia, nausea, and vomiting) vary markedly: however, a meta-analysis

involving 631 psoriatic patients reveals rates of 2.3%, 2.0%, 2.0%, 3.8%, and 1.1%, respectively (Krupp & Monka, 1990).

### 7.5 Gingival hyperplasia

Gingival hyperplasia may occur in up to 30% of patients taking cyclosporin and is often linked with poor oral hygiene (Ryan et al., 2010). Thanks to increased oral health awareness, improved oral hygiene, and better public health service this condition occurs rarely in developed countries. If it occurs, this side effect usually manifests within the first 3–6 months of treatment.

### 7.6 Hyperlipidaemia

Hypertriglyceridaemia (>750 mg/dL) occurs in approximately 15% of cyclosporin-treated patients, and hypercholesterolaemia in <3% (Neoral® Prescribing Information, 2011). Importantly, hyperlipidaemia normalizes when cyclosporin therapy is stopped (Shupack et al., 1997).

Severe psoriasis is associated with increased cardiovascular morbidity and mortality (see section 7.1.1); thus, hyperlipidaemia should be actively managed in cyclosporin-treated patients with psoriasis. If cyclosporin therapy is continued, the initial intervention is a lipid-lowering diet. If this is unsuccessful, the cyclosporin dosage should be reduced, or treatment with a lipid-lowering agent started. Fluvastatin was shown to be well tolerated in association with cyclosporin (Holdaas et al., 1995; Launay-Vacher 2005). In general, however, statins should be used with caution because of the risk, albeit very low, of rhabdomyolysis, as reported in a few cases of transplanted patients treated with cyclosporin and lovastatin or simvastatin (Ryan et al., 2010; Corpier et al., 1988).

### 7.7 Hypertrichosis

In large-scale clinical trials and meta-analyses in cyclosporin-treated patients with psoriasis, the incidence of hypertrichosis has varied widely from 1–27% (Table 2); the cause of this side effect is unclear, but it is unlikely to be an altered endocrine status (Ryan et al., 2010).

### 7.8 Infections

Cyclosporin-induced infections occur rarely, and are rarely severe; controlled studies in psoriasis report no difference in the incidence of infections between cyclosporin and placebo recipients. Moreover, an overview of 20 years' safety data for cyclosporin in dermatology patients revealed no increases in the risks of opportunistic infections or tuberculosis reactivation (Ryan et al., 2010).

### 7.9 Malignancies

#### 7.9.1 Lymphomas

B- and T-cell lymphomas have rarely been reported in cyclosporin-treated patients with psoriasis (Ryan et al., 2010). For instance, 2/842 patients (0.2%) developed these lymphomas

in a large-scale trial (Krupp & Monka, 1990), whereas no increase in the incidence of lymphomas was noted in another large-scale trial (Paul et al., 2003). Significantly, psoriasis itself leads to chronic immunological overactivation, and to greater risks of lymphoma and other malignancies than in the general population (Ryan et al., 2010).

### 7.9.2 Nonmelanoma skin cancers

In 1252 patients with severe psoriasis, low-dosage cyclosporin (2.7–3.1 mg/kg/day) was associated with a 6-fold increase in cutaneous squamous cell carcinomas after up to 5 years' follow-up. The greatest risks of these nonmelanoma skin cancers were in patients treated with cyclosporin for >2 years, in patients previously exposed to PUVA, and in patients exposed to other immunosuppressants or methotrexate (Paul et al., 2003). In another large-scale study, 6/842 psoriatic patients (0.7%) developed premalignant or malignant skin lesions during cyclosporin therapy, but nearly all of these patients had received previous treatment with PUVA, ultraviolet B, or methotrexate (Krupp & Monka, 1990).

The current recommendation is that if phototherapy is considered in psoriatic patients, narrowband ultraviolet B should be the first choice; cyclosporin can then be reserved for future therapy, if necessary (Griffiths et al., 2004; Pathirana et al., 2009). Cyclosporin should not be used together with phototherapy, or immediately before or after PUVA (see section 5); in patients with a high total dose of PUVA, or with a history of squamous cell carcinoma or melanoma, cyclosporin should be avoided (Griffiths et al., 2004; Pathirana et al., 2009).

### 7.9.3 Solid organ tumours

Numerous case reports exist of solid organ tumours developing during cyclosporin treatment in dermatology patients (Ryan et al., 2010). However, no increase in the incidence of solid organ tumours was noted in a study of 1252 psoriatic patients treated with cyclosporin (Paul et al., 2003), and although another large-scale study reported solid organ tumours in 5/842 patients (0.6%), the lead investigator considered any relationship between these tumours and cyclosporin to be unlikely (Krupp & Monka, 1990). Large case-control studies suggest that cyclosporin plus other immunosuppressive therapies may actually have immunoprotective effects against, and reduce the risks of, some tumour types (e.g. breast and rectal cancers) (Ryan et al., 2010).

## 7.10 Other side effects

Fatigue and influenza-like symptoms may occur in up to 20% of cyclosporin-treated patients (Table 2), and joint pain and muscle aches are also frequently reported (10–40% of patients) (Pathirana et al., 2009).

Hyperbilirubinaemia manifests in up to one-third of cyclosporin recipients (Pathirana et al., 2009), but this effect is usually dose-related, and does not require further investigation if other liver function abnormalities are absent (Ryan et al., 2010). Transaminase elevations may also occur in up to one-third of cyclosporin-treated patients. If plasma bilirubin or

transaminase levels are >2 x the upper limit of normal, the cyclosporin dosage should be reduced by 25% (Pathirana et al., 2009).

## 8. Drug interactions

Several drug interactions have been documented for cyclosporin, which is extensively metabolised by the CYP 3A system in the liver and small intestine. Some of the key interactions include the following: (Novartis Pharmaceuticals Corporation 2009; Ryan et al., 2010)

- Erythromycin should be used with caution in cyclosporin-treated patients with infected eczema, since the former compound can increase cyclosporin toxicity.
- Grapefruit juice inhibits cyclosporin metabolism and should be avoided in cyclosporin recipients.
- Heavy alcohol ingestion should be avoided, as it can increase cyclosporin levels.
- Nephrotoxic drugs, including aminoglycosides, ciprofloxacin, clotrimazole, fibrates, and nonsteroidal anti-inflammatory drugs (NSAIDs), should not be administered, if at all possible, to cyclosporin-treated patients. NSAIDs, especially in dehydrated patients, are likely to potentiate the deleterious effect of cyclosporin on renal function, and importantly, intermittent NSAID use is often not disclosed by patients.
- Cyclosporin may restrict the metabolism of many drugs (e.g. diclofenac, digoxin, methotrexate, prednisolone, repaglinide, simvastatin), thus increasing plasma levels and toxicity.
- Cyclosporin should not be used concomitantly with potassium-sparing diuretics because of the risk of hyperkalaemia, and care should also be exercised if cyclosporin is administered concurrently with potassium-sparing drugs such as angiotensin-converting enzyme inhibitors or angiotensin II receptor antagonists.

## 9. Conclusions

Cyclosporin was first approved for the treatment of severe psoriasis in the 1990s, and indeed, it is one of the most effective antipsoriatic agents available because of its fast onset of action and potent immunosuppressive activity. Besides psoriasis, other dermatological disorders — most notably, pyoderma gangrenosum and refractory chronic idiopathic urticaria — have seen substantial off-label cyclosporin use in recent years. Nonetheless, concerns remain among some dermatologists about the safety of cyclosporin, even though a growing evidence base exists of a favourable benefit : risk profile for the compound, especially in the management of psoriasis, psoriatic arthritis, and atopic dermatitis.

Perhaps the most frequent safety concerns, and those potentially explaining under-utilisation of cyclosporin by some dermatologists, are hypertension and renal impairment. However, it should be remembered that psoriasis itself is associated with increased cardiovascular morbidity, and any new hypertension emerging during cyclosporin therapy can be managed effectively by dosage reduction and/or antihypertensive therapy. Moreover, persistent renal dysfunction during cyclosporin therapy is usually associated with dosages >5 mg/kg/day, or treatment periods of >2 years; usually, if the dosage is kept

at ≤5 mg/kg/day, and if renal function is monitored closely so that plasma creatinine levels remain ≤30% above baseline, any renal side effects occurring during cyclosporin therapy will be reversible when treatment is stopped.

Safety concerns may also exist about possible malignancies during cyclosporin administration. Again, however, it should be emphasised that the disease itself leads to long-term immunological overstimulation, such that psoriatic patients have greater risks of lymphoma and other malignancies compared to the general population. Any risk of nonmelanoma skin cancer during cyclosporin administration appears to be minimised if the duration of continuous therapy is kept to ≤2 years, and if PUVA is avoided; and some studies suggest that cyclosporin plus other immunosuppressant therapy may actually reduce the risks of some cancers (e.g. breast, rectal).

Additional well-designed assessments of various cyclosporin schedules are now warranted in the treatment of psoriasis. Such assessments should include:

- Comparative studies — i.e. vs traditional treatments (e.g. methotrexate) and/or newer agents (e.g. etanercept, infliximab).
- Measures of economic and quality-of-life endpoints, such that relative cost-utility and cost-effectiveness, and important considerations such as effects on psychological distress, can be quantified and clarified.
- Careful evaluation of the clinical potential of specific combination therapy schedules (e.g. cyclosporin plus topical calcipotriol; low-dose cyclosporin plus mycophenolate mofetil, with a possible view to the development of a fixed-dose combination 'pill' with enhanced tolerability). This is particularly pertinent given that most studies of combination therapy to date have been small-scale, uncontrolled evaluations.
- Long-term studies of ≥2 years' duration.

In summary, the immunosuppressive properties of cyclosporin in the transplant and non-transplant settings have been widely recognised for approximately 3½ decades. As such, there is much clinical knowledge and experience of cyclosporin use in non-dermatological settings, but in the dermatological arena, clinical experience is 'catching up'. Cyclosporin has now been used in the treatment of psoriasis for almost 15 years, and with the relatively low doses used, dermatologists appear to be moving beyond any potential safety concerns about the compound, and are increasingly embracing the established antipsoriatic efficacy of the drug. As further clinical, economic, and quality-of-life data accrue from well-conducted clinical trials of cyclosporin monotherapy and combination therapy schedules, dermatologists, policy makers, and patients are likely to gain even more confidence in the favourable efficacy and tolerability profiles of cyclosporin in the treatment of psoriasis and other dermatological disorders.

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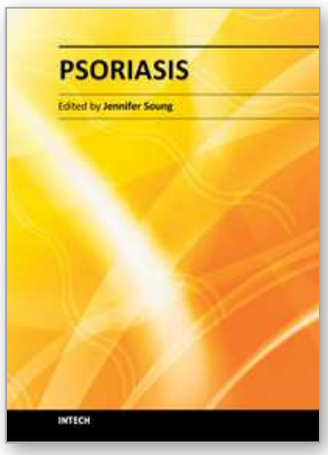


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