Cyclosporin in atopic dermatitis
Disclaimer

- This slide kit includes material on published preclinical and clinical studies in psoriasis that, in some instances, reflect off-label use.

- For each information mentioned in this slide kit, please ensure that you follow the appropriate prescribing information.

- The opinions expressed are those of the speaker and not of Novartis.
Dermagora overview

- Experts from throughout Europe came together in July 2011 to:
  - Outline the rationale for the use of cyclosporin in psoriasis and atopic dermatitis
  - Present an overview of its clinical efficacy, safety and effect on quality of life in psoriasis and atopic dermatitis
  - Outline existing guidelines for monitoring patients receiving cyclosporin therapy
  - Provide practical case examples

- This educational slide kit is the output from that meeting

- Dermagora faculty included:
  - Prof. Hervé Bachelez, Saint-Louis University Hospital, Paris, France
  - Dr Delia Colombo, Marchesi Hospital, Milan, Italy
  - Prof. Serhat İnalöz, University of Gaziantep, Gaziantep, Turkey
  - Prof. Dimitrios Ioannidis, Aristotle University School of Medicine, Thessaloniki, Greece
  - Prof. Thomas Luger, University of Münster, Münster, Germany
  - Prof. Francisco Vanaclocha, Hospital 12 de Octubre, Madrid, Spain
  - Prof. Gino A. Vena, University of Bari, Bari, Italy
Contents

- Psoriasis – an overview
  - Pathophysiology and epidemiology
  - Burden of atopic dermatitis
  - Assessing disease severity
  - Treatment algorithm
- Cyclosporin in the treatment of atopic dermatitis
  - Overview
  - Mechanism of action
  - Cyclosporin is a critical dose drug
  - Treatment overview
  - Efficacy data
- Cyclosporin safety management
  - Important adverse events
  - Monitoring
  - Tolerability profile
  - Cyclosporin and nephrotoxicity
  - Cyclosporin and hypertension/hyperlipidemia
  - Other safety considerations
- Identifying the cyclosporin patient
  - Patient case studies
- Conclusions
  - Summary
  - The ‘ideal’ cyclosporin patient
Atopic dermatitis – an overview
Pathophysiology and epidemiology

Atopic dermatitis (AD) is one of the most common chronic relapsing childhood dermatoses


AD is often the first manifestation of the ‘atopic march’

A variety of defects in the innate immune system collectively affect the development and severity of AD

<table>
<thead>
<tr>
<th>Innate immune dysfunction in AD</th>
<th>Microbes Toxins Allergens</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Epithelial barrier</strong></td>
<td></td>
</tr>
<tr>
<td>Genetic (FLG)</td>
<td>(\downarrow)FLG, (\downarrow)LOR and (\downarrow)INV, lipid defects, TJ defects</td>
</tr>
<tr>
<td>Acquired (Th2 cytokines, itch-scratch cycle)</td>
<td></td>
</tr>
<tr>
<td><strong>Proteases</strong></td>
<td></td>
</tr>
<tr>
<td>Genetic (SPINK5, KLK7)</td>
<td>(\uparrow)Proteases</td>
</tr>
<tr>
<td>Acquired (proteases-allergens and microbes)</td>
<td></td>
</tr>
<tr>
<td><strong>Antimicrobial proteins</strong></td>
<td></td>
</tr>
<tr>
<td>Genetic (?)</td>
<td>(\downarrow)AMPS (HBD2, HBD3, LL37)</td>
</tr>
<tr>
<td>Acquired (Th2 cytokines)</td>
<td></td>
</tr>
<tr>
<td><strong>Innate receptors</strong></td>
<td></td>
</tr>
<tr>
<td>Genetic (?)</td>
<td>Altered expression or function of PRRs (TLR2, TLR9, NOD1-2, CD14, MBL)</td>
</tr>
<tr>
<td>Acquired (?)</td>
<td></td>
</tr>
<tr>
<td><strong>Innate immune cells</strong></td>
<td></td>
</tr>
<tr>
<td>Genetic (?)</td>
<td>(\downarrow)PMN</td>
</tr>
<tr>
<td>Acquired ((\downarrow)IL-8/CXCL8, (\downarrow)MIP3(\alpha)/CCL20, PMN chemotaxis defect)</td>
<td></td>
</tr>
</tbody>
</table>

- Affects 10–30% of children
- Vast majority develop disease before age of 5 years
- Persists into adulthood for 1–3%
- Increase in cases in industrialised nations over past few decades

A variety of defects in the innate immune system collectively affect the development and severity of AD.
**Burden of atopic dermatitis**

Impairment of quality of life is greater than or equal to other common childhood diseases such as asthma and diabetes\(^1\)

- **Sleeplessness in over 60%\(^1\)**
  - Tiredness, mood changes and impaired psychosocial functioning of child and family

- **Embarrassment, teasing and bullying cause social isolation\(^1\)**
  - Depression or school avoidance

- **Lifestyle limited\(^1\)**
  - Clothing, holidays, staying with friends, owning pets, sports

- **Parental exhaustion\(^1\)**
  - Restriction of normal family life
  - Increased work in caring for child
  - Costs involved in management

Patients with AD have inferior health-related quality of life scores compared with general population\(^2\)

---

Assessing disease severity

- HRQoL scores should be used in conjunction with objective measures of severity, as part of the assessment process of a patient with atopic dermatitis.
- Clinical severity may be disproportionate to the clinical symptoms of the condition.
- Definition of ‘severe’ atopic dermatitis includes:
  - Extensive skin involvement at risk for exfoliation
  - Requirements for ongoing or frequent treatment with high-potency topical glucocorticoids or systemic glucocorticoids
  - Hospitalization for severe eczema or skin infections related to the atopic dermatitis
  - Ocular or infectious complications
  - Erythrodermic
  - Significant disruption of quality of life (e.g. sleepless nights, school or work days lost, etc)

Treatment algorithm for atopic dermatitis: ICCAD II*

**Initial assessment of disease history, extent and severity**
Include assessment of psychological distress, impact on family

**Emollients, education**

**Disease remission**
(No signs or symptoms)

**Acute control of pruritus and inflammation**
- Topical corticosteroids or
- Topical calcineurin inhibitors
- Pimecrolimus BID or
- Tacrolimus BID

**Maintenance therapy**
For disease persistence and/or frequent recurrences
- At earliest signs of local recurrence use topical calcineurin inhibitors to prevent disease progression
- Long-term maintenance use of topical calcineurin inhibitors
- Intermittent use of topical corticosteroids

**Severe refractory disease**
- Phototherapy
- Potent topical steroids
- Cyclosporin
- Methotrexate
- Oral steroids
- Azathioprine
- Psychotherapeutic

**Adjunctive therapy**
- Avoidance of trigger factors
- Bacterial infection: oral and/or topical antibiotics
- Viral infections: antiviral therapy
- Psychological interventions
- Antihistamines

Systemics, including cyclosporin, are recommended for the treatment of severe refractory disease

*International Consensus Conference on Atopic Dermatitis II
Cyclosporin in the treatment of atopic dermatitis
Overview

Cyclosporin is a cyclic polypeptide immunosuppressant consisting of 11 amino acids

Immunosuppressive effects first discovered in the 1970’s by scientists at Sandoz (Novartis)\(^1\)

Indicated for the short term treatment (8 weeks) of patients with severe atopic dermatitis in whom conventional therapy is ineffective or inappropriate\(^2\)

Calcineurin inhibitor that acts selectively on T-cells\(^1\)

Highly effective treatment due to its rapid onset\(^1\)

Cyclosporin is a cyclic polypeptide consisting of 11 amino acids. It is used for the short-term treatment of severe atopic dermatitis when conventional therapy is ineffective or inappropriate. It is a calcineurin inhibitor that acts selectively on T-cells. The molecular formula is \(C_{62}H_{111}N_{11}O_{12}\) with a molecular weight of 1202.63.
Mechanism of action
Cyclosporin induces immunosuppression by inhibiting the first phase of T-cell activation

Inhibition of the enzyme calcineurin (CaN) by cyclosporin (CsA) reduces the activation of the transcription factor, nuclear factor of activated T-cells (NF-ATc), causing a reduction in the transcription of a number of cytokine genes, particularly interleukin 2.\(^1,2\)


This tool may contain scientific/medical information on unapproved products or product uses. This information is for educational purposes only. Please consult the applicable prescribing information for details on approved uses of products.
Cyclosporin is a critical dose drug
Switching between formulations may lead to clinically important changes in bioavailability and efficacy

- Cyclosporin is a critical dose drug with a narrow therapeutic index
- With the use of cyclosporin generics, an average of 20% lower bioavailability can be expected, which means that efficacy may be unsatisfactory in isolated cases
- The Medicines and Healthcare Products Regulatory Agency (MHRA) in the UK states that:

Cyclosporin must be prescribed and dispensed by brand name
Patients should be stabilised on a single brand of cyclosporin because switching between formulations without close monitoring may lead to clinically important changes in bioavailability
All products that contain cyclosporin are interchangeable only if careful therapeutic monitoring takes place
Prescribing and dispensing of cyclosporin should be by brand name to avoid inadvertent switching

## Treatment overview

Cyclosporin offers patients rapid and effective relief from the symptoms of atopic dermatitis\(^1\)–\(^5\)

<table>
<thead>
<tr>
<th>Cyclosporin</th>
<th>The short-term treatment of severe atopic dermatitis that cannot be controlled with topical therapy (Europe) Although not FDA approved, cyclosporin is recommended for the treatment of atopic dermatitis refractory to conventional treatment by:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indication</td>
<td>● American Academy of Dermatology (AAD) Guidelines of Care committee ● European Academy of Dermatology and Venereology (EADV) European Task Force on Atopic Dermatitis ● Japanese Dermatological Association committee for Guidelines for the Management of Atopic Dermatitis</td>
</tr>
<tr>
<td>Recommended initial dosage</td>
<td>5 mg/kg daily, gradual tapering as dictated by the clinical response over the next 3 months to a dose of 1.5 mg/kg/day</td>
</tr>
<tr>
<td>Recommended maintenance dosage</td>
<td>If maintenance therapy is needed, the lowest effective dose should be used</td>
</tr>
<tr>
<td>Response rate</td>
<td>Dose-dependent, patients treated with a higher initial dose (4–5 mg/kg/day) have a 40% decrease in severity at 2 weeks Patients treated with a lower initial dose (2.5–3 mg/kg/day) have a 22% decrease in severity</td>
</tr>
</tbody>
</table>

**Efficacy of cyclosporin**

Numerous clinical trials confirm the efficacy of cyclosporin in the treatment of atopic dermatitis

Meta-analysis: Mean relative change in severity of atopic dermatitis compared to baseline after 6–8 weeks of continuous treatment with cyclosporin

- Mean clinical improvement in disease severity was 55% (95% CI 48–62%)
- Most of these patients were not adequately controllable with standard topical treatments

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Mean change (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harper 2000</td>
<td>-0.57 (−0.69,−0.45)</td>
</tr>
<tr>
<td>Berth Jones 1996</td>
<td>-0.57 (−0.68,−0.45)</td>
</tr>
<tr>
<td>Czech (300 mg) 2000</td>
<td>-0.58 (−0.66,−0.50)</td>
</tr>
<tr>
<td>Czech (150 mg) 2000</td>
<td>-0.48 (−0.56,−0.40)</td>
</tr>
<tr>
<td>Swoden 1991</td>
<td>-0.56 (−0.73,−0.39)</td>
</tr>
<tr>
<td>Berth Jones 1997</td>
<td>-0.35 (−0.43,−0.27)</td>
</tr>
<tr>
<td>Zurbriggén (S) 1999</td>
<td>-0.68 (−1.19,−0.17)</td>
</tr>
<tr>
<td>Zurbriggén (N) 1999</td>
<td>-0.69 (−0.99,−0.39)</td>
</tr>
<tr>
<td>Bunikowski 2001</td>
<td>-0.58 (−0.91,−0.24)</td>
</tr>
<tr>
<td>Granlund 1995</td>
<td>-0.62 (−0.88,−0.37)</td>
</tr>
<tr>
<td>van Joost 1994</td>
<td>-0.56 (−0.86,−0.26)</td>
</tr>
<tr>
<td>Caproni 2000</td>
<td>-0.54 (−0.62,−0.46)</td>
</tr>
<tr>
<td>Overall (95% CI)</td>
<td>-0.53 (−0.59,−0.47)</td>
</tr>
</tbody>
</table>

This tool may contain scientific/medical information on unapproved products or product uses. This information is for educational purposes only. Please consult the applicable prescribing information for details on approved uses of products.
Rapid response to treatment
Cyclosporin is associated with a rapid response to treatment in patients with atopic dermatitis

Meta-analysis: Relative change in mean disease severity after 2 weeks of treatment with cyclosporin (mean and 95%-CI) stratified by initial cyclosporin dosage

- Patients treated with an initial dose of 4–5 mg/kg/day have a rapid response
  - 40% decrease in severity at 2 weeks
- Patients treated with a lower initial dose of 2.5–3 mg/kg/day have a 22% decrease in severity at 2 weeks

Improvement in quality of life
Short-course cyclosporin improves quality of life and clinical outcome in patients with AD

Cyclosporin short-course therapy: Quality of life and clinical outcome

- 106 Adults randomized to receive 150 mg (low) or 300 mg (high) of cyclosporin microemulsion daily
- 45% improvement in TBSA score by week 2; 58% by week 8
- 59% improvement in sleep loss by week 8
- 52% improvement in DLQI scores by week 2

Atopic dermatitis is often associated with severe itching
A 47% improvement in itching was seen within 2 weeks in patients treated with the high dose of cyclosporin

TBSA = total body surface area; DLQI = dermatology life quality index

This tool may contain scientific/medical information on unapproved products or product uses. This information is for educational purposes only. Please consult the applicable prescribing information for details on approved uses of products.
Cyclosporin safety management
## Overview of adverse events
The adverse event profile and risk-benefit ratio of cyclosporin is well understood

<table>
<thead>
<tr>
<th>Category</th>
<th>Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very frequent</td>
<td>• None</td>
</tr>
</tbody>
</table>
| Frequent       | • Renal failure (dose-dependent)  
• Hypertension  
• Gingival hyperplasia  
• Reversible hepatogastric complaints  
• Tremor  
• Weariness  
• Headache  
• Burning sensation in hands and feet  
• Reversible elevated blood lipids (esp. in combination with corticosteroids)  
• Hypertrichosis |
| Occasional     | • Seizures  
• Gastrointestinal ulcerations  
• Weight gain  
• Hyperglycemia  
• Hyperuricemia  
• Hyperkalemia  
• Hypomagnesemia  
• Acne  
• Anemia |
| Rare           | • Ischemic heart disease  
• Pancreatitis  
• Motor polyneuropathy  
• Impaired vision  
• Defective hearing  
• Central ataxia  
• Myopathy  
• Erythema  
• Itching  
• Leucopenia  
• Thrombocytopenia |
| Very rare      | • Microangiopathic hemolytic anemia  
• Hemolytic uremic syndrome  
• Colitis (isolated cases)  
• Papillary  
• Oedema (isolated cases)  
• Idiopathic intracranial hypertension (isolated cases) |

- Rate of adverse events generally demonstrates a clear dose-dependency

This list is not exhaustive; please refer to the local prescribing information.

Monitoring before and during therapy with cyclosporin

- Complete physical examination
- Review of medical history
- Complete skin inspection
  - All suspicious lesions should be biopsied and adequately treated before initiation of cyclosporin
- Blood pressure
  - Two measurements
- Baseline laboratories
  - Serum creatinine (two measurements), serum urea nitrogen, CBC, serum magnesium, potassium, uric acid, lipids, liver enzymes, serum bilirubin
- Malignancy screening
- Tuberculin skin test (>5 mm induration considered positive)

Monitoring on therapy

- Serum creatinine and blood pressure
  - Monitor monthly
- Other laboratory monitoring
  - CBC, uric acid, potassium, lipids, liver enzymes, serum bilirubin, and magnesium should be monitored monthly

CBC; Complete blood count.

This tool may contain scientific/medical information on unapproved products or product uses. This information is for educational purposes only. Please consult the applicable prescribing information for details on approved uses of products.

Tolerability profile of cyclosporin

Hypertension, hypercholesterolemia and increased creatinine the most frequently reported adverse events

- The overall frequency of clinical events after treatment of 57% was distributed as follows:

- Only 14% of patients were treated with:
  - Antihypertensives
  - Lipid lowering therapy

This tool may contain scientific/medical information on unapproved products or product uses. This information is for educational purposes only. Please consult the applicable prescribing information for details on approved uses of products.
Cyclosporin and nephrotoxicity
Incidence
At low cyclosporin doses, nephrotoxicity is infrequent and reversible\(^1,2\)

- The best predictive factor of nephrotoxicity is the percentage of serum creatinine increase over baseline value\(^2,3\)
  - 2.5 mg/kg/day cyclosporin for 12 weeks
    - 4% of patients have increase in creatinine of 50% above baseline
    - Reversible upon withdrawal of cyclosporin\(^1\)
  - 5 mg/kg/day cyclosporin for 12 weeks
    - 13% of patients have increase in creatinine of 50% above baseline
    - Reversible upon withdrawal of cyclosporin\(^1\)

- Treatment duration longer than 3 years is a risk factor for interstitial renal fibrosis\(^2-4\)
- Older age, obesity and hypertension are also risk factors for kidney toxicity\(^2,3\)
- Scheme of administration does not appear to influence kidney toxicity\(^2,3\)
- Reversibility of nephrotoxicity after treatment withdrawal has been demonstrated\(^1,2\)

Managing nephrotoxicity

Increases in serum creatinine can be reversed by dose reduction or withdrawal of treatment

Serum creatinine $\uparrow$ to $\geq 30$–$50\%$ above baseline value (even if within normal range)
- Reduce dose by at least 25%
- Repeat measurement within 30 days

Creatinine $\downarrow$ to $<30\%$ above baseline value
- Continue cyclosporin treatment

Serum creatinine $\uparrow$ to $\geq 50\%$ above baseline value (even if within normal range)
- Reduce dose by at least 50%
- Repeat measurement within 30 days

Creatinine remains $\geq 30\%$ above baseline value
- Stop cyclosporin therapy

This tool may contain scientific/medical information on unapproved products or product uses. This information is for educational purposes only. Please consult the applicable prescribing information for details on approved uses of products.
Drug interactions
There are a number of drugs that may potentiate nephrotoxicity

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>Antineoplastics</th>
<th>Anti-inflammatory drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gentamicin</td>
<td>Melphalan</td>
<td>Diclofenac</td>
</tr>
<tr>
<td>Tobramycin</td>
<td></td>
<td>Indomethacin</td>
</tr>
<tr>
<td>Vancomycin</td>
<td></td>
<td>Naproxen</td>
</tr>
<tr>
<td>Trimethoprim-sulfamethoxazole</td>
<td></td>
<td>Sulindac</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Antifungals</th>
<th>Immunosuppressives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphotericin B</td>
<td>Tacrolimus</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td></td>
</tr>
</tbody>
</table>
Cyclosporin and hypertension/hyperlipidemia
Incidence

Hypertension and hyperlipidemia often resolve after discontinuation of cyclosporin\(^1,2\)

- **Arterial hypertension**
  - Arterial hypertension in 2 to 15% of patients on cyclosporin\(^1\)
  - Reversible upon withdrawal of cyclosporin\(^2\)

- **Hyperlipidemia**
  - Elevated triglycerides in 15% patients on cyclosporin\(^2\)
  - Hypercholesterolemia in <3% of patients on cyclosporin\(^2\)
  - Reversible upon withdrawal of cyclosporin\(^2\)

---


This tool may contain scientific/medical information on unapproved products or product uses. This information is for educational purposes only. Please consult the applicable prescribing information for details on approved uses of products.
Managing hypertension

Hypertension can be controlled with antihypertensive agents

- Sustained increased BP reading: Diastolic ≥90 mmHg or systolic ≥140 mmHg
  - Reduce cyclosporin dose by 25–50%
- Increased BP sustained after several dose reductions
  - Discontinue treatment
  - OR
  - Treat with antihypertensive agent

*Calcium channel blockers are a preferred choice although nifedipine should be avoided because of increased risk of gingival hyperplasia.

Isradipine and amlodipine do not alter cyclosporin levels and are good choices. Beta-blockers may also be used.

Angiotensin-converting enzyme inhibitors and potassium-sparing diuretics should be avoided as they may cause hyperkalemia.

Managing hyperlipidemia
Hyperlipidemia can be controlled with diet or the use of statins*

Check lipids at the initiation of therapy and every 6 months for patients on prolonged continuous therapy

Hypercholesterolemia (>300 mg/dL) and/or elevated triglycerides (>750 mg/dL)

Low cholesterol, low-fat diet recommended

If no improvement, reduction in dose or discontinuation of therapy with cyclosporin should be considered, depending on the degree of hyperlipidemia and the patient’s risk profile

*Close monitoring of patients in whom cyclosporin and statins are used together is recommended to detect myopathy at an early stage.

Cyclosporin may reduce the clearance of some HMG–CoA reductase inhibitors.

Fluvastatin is the most studied drug
➢ Starting dose (20 mg daily for 12 weeks), increasing to 40 mg daily for 8 weeks

Pravastatin, atorvastatin and lovastatin have cases of muscle toxicity when combined with cyclosporin

This tool may contain scientific/medical information on unapproved products or product uses. This information is for educational purposes only. Please consult the applicable prescribing information for details on approved uses of products.
Other safety considerations
Managing other adverse events

- **Gingival hyperplasia**
  - Better dental hygiene/antiseptic therapy
  - Dose reduction
  - Azithromycin administered for 3 days

- **Increases in liver function tests**
  - Dose reduction of 25% and reassessment within 30 days
  - If values continue to deviate, cyclosporin should be discontinued

- **Gastrointestinal disorders**
  - Taking of cyclosporin on a full stomach

- **Vasomotor disturbances/paresthesia**
  - If clinically relevant, dose reduction

**Absolute contraindications:**
- Impaired renal function
- Insufficiently controlled arterial hypertension
- Severe infectious disease
- History of malignancy
- Current malignancy
- Simultaneous PUVA therapy

Necessary measures before and during treatment include avoidance of sun exposure

Malignancy and cyclosporin
Incidence of nonskin malignancy was not higher in patients treated with cyclosporin

- Prospective long-term cohort study investigating the incidence of malignancies in severe psoriasis patients treated with cyclosporin
  - Total of 1252 patients followed prospectively for up to 5 years
  - Malignancies were recorded prospectively. Incidence rates for malignancies were compared with the general population using standardized incidence ratios (SIR)

<table>
<thead>
<tr>
<th></th>
<th>SIR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any malignancy</td>
<td>2.1</td>
<td>1.6–2.9</td>
</tr>
<tr>
<td>Any skin malignancy</td>
<td>6.1</td>
<td>3.8–9.1</td>
</tr>
<tr>
<td>Any nonskin malignancy</td>
<td>1.3</td>
<td>0.8–1.9</td>
</tr>
</tbody>
</table>

- The incidence of nonskin malignancy overall was not significantly higher in this study than in the general population
- Duration of exposure to cyclosporin, exposure to psoralen and UVA, exposure to methotrexate, and exposure to immunosuppressants showed a significant effect on the incidence of nonmelanoma skin malignancies

Immunosuppressant effects of cyclosporin and risk of infection

- Cyclosporin may increase the general risk of bacterial, parasitic, viral, and fungal infections, as well as the risk of infection with opportunistic pathogens.\(^1\)
  - This increased risk of infection plays a minor role when treating psoriasis with cyclosporin.\(^1\)

- Vaccinations given concomitantly with cyclosporin may be less effective.\(^1,2\)
  - Studies in patients with transplantation taking cyclosporin have shown inconsistent effectiveness of the influenza vaccine.\(^2\)
  - Live vaccines are contraindicated and should be avoided.\(^1,2\)

- Severe infectious disease is an absolute contraindication for cyclosporin use.\(^1\)
  - Hepatitis profile including anti-HAV, HBsAg, anti-HBs, anti-HBc, anti-HCV and also anti-HIV should be checked in patients treated with cyclosporin.\(^2,3\)

---

Pregnancy and cyclosporin

There is no indication of teratogenesis in the limited experience of administering cyclosporin to pregnant women.

Of the oral medications approved for psoriasis, only cyclosporin should be considered in pregnant women.


- NTPR (National Transplant Pregnancy Registry) data suggest that parental exposure to cyclosporin does not induce defects in children.
- Although cyclosporin crosses the placenta, there is no evidence that it causes harm to the foetus.

This tool may contain scientific/medical information on unapproved products or product uses. This information is for educational purposes only. Please consult the applicable prescribing information for details on approved uses of products.
Pregnancy and cyclosporin

Experience with cyclosporin in pregnant women is limited

- Pregnant women receiving immunosuppressive therapies after transplantation, including cyclosporin and cyclosporin containing regimens, are at risk of premature delivery (<37 weeks)

- A limited number of observations in children exposed to cyclosporin in utero are available, up to an age of approximately 7 years. Renal function and blood pressure in these children were normal

- However there are no adequate and well controlled studies in pregnant women and, therefore, cyclosporin should not be used during pregnancy unless the potential benefit to the mother justifies the potential risk to the foetus
Drug interactions
There are a number of drugs that may affect serum cyclosporin levels

Drugs that increase cyclosporin concentrations
- Antiarrhythmic agents: amiodarone
- Calcium channel blockers: diltiazem, nicardipine, verapamil
- Diuretics: thiazides, furosemide, carbonic anhydrase inhibitors
- Antifungals: ketoconazole, itraconazole, fluconazole, voriconazole
- Antibiotics, macrolides: erythromycin, clarithromycin, telithromycin, azithromycin
- Antibiotics, fluoroquinolones: ciprofloxacin, norfloxacin
- Antibiotics, other: cephalosporins, doxycycline

Drugs that decrease cyclosporin concentrations
- Antibiotics, beta lactams: nafcillin
- Antibiotics, rifamycins: rifabutin, rifampin, rifapentine
- Antifungals: griseofulvin
- Anti-HIV drugs: efavirenz
- Anticonvulsants: carbamazepine, oxcarbazepine, phenobarbital, phenytoin, valproic acid
- Retinoids: bexarotene
- Herbals: St John wort
- Other drugs: octreotide, ticlopidine, bosentan

This list is not exhaustive; please refer to the local prescribing information.


This tool may contain scientific/medical information on unapproved products or product uses. This information is for educational purposes only. Please consult the applicable prescribing information for details on approved uses of products.
Identifying the cyclosporin patient
Case studies in atopic dermatitis
Case 1: Atopic dermatitis
Atopic dermatitis
Case study 1

Patient profile: 22 year old female, 52 kg, student, intermittent allergic rhinitis, contact allergy to lanolin and fragrance mix
Disease status: Atopic dermatitis with onset in early childhood and long remission (at least 10 years), reappearance during the last 4 years

- Relapsing eczematous lesions, especially on the cutaneous folds and the hands
- Worsening of AD in the last 3 months with diffuse lesions
  - Marked involvement of the face, neck and hands
  - Deterioration of the quality of life
    - Severe generalized itch
    - Interference with sleep and daily activities
    - Psychosocial problems

This tool may contain scientific/medical information on unapproved products or product uses. This information is for educational purposes only. Please consult the applicable prescribing information for details on approved uses of products.
Previous therapy

Case study 1

- **Topical corticosteroids (short intermittent courses) sufficient to control lesions until the recent flare of AD**
- **Treatment with topical calcineurin inhibitors (TCIs)**
  - Intense burning at the site of application, especially on the face
  - For this reason the patient refused to continue the use of TCIs
- **Constant use of preventive measures against contact allergens**
Cyclosporin therapy and outcome

Case study 1

- Cyclosporin dose
  - 250 mg/day (5 mg/kg/day)

- Disappearance of itch after a few days

- Notable improvement of skin lesions within a week

- Continuation of treatment with 200 mg/day for another 2 weeks and then gradual reduction of frequency by removing a day per week

- Good tolerability
Case 2: Atopic dermatitis
Atopic dermatitis
Case study 2

Patient profile: 16 year old female, 55 kg, secondary school student
Disease status: Atopic dermatitis for the last 2 years, with erythema, skin dryness, excoriations and sleep loss, SCORAD >40

Previous therapy:

- Treated with topical therapy for 2 years
- Local agents including
  - Tacrolimus, pimecrolimus, steroids, emollients
- Noncompliance and uncontrolled disease
Cyclosporin therapy and outcome
Case study 2

- Treatment with cyclosporin 3 mg/kg/day for 2 weeks
  - Insufficient efficacy
  - SCORAD < 35% reduction
- Increased dose by 0.5 mg/kg/day per month
  - Significant improvement at maximum dose (5 mg/kg/day)
  - SCORAD reduction 70%
  - Maintenance at the efficient dose for 2 months & treatment cessation with dose tapering
  - Now 2 months off treatment at remission
- Total treatment duration: 7 months
- Side effects
  - Hypertrichosis on the fifth month, reversed after treatment cessation.
  - Herpes labialis treated with topical therapy
- This case illustrates that maximum dosing of cyclosporin in atopic dermatitis should be pursued in case of partial initial response

This tool may contain scientific/medical information on unapproved products or product uses. This information is for educational purposes only. Please consult the applicable prescribing information for details on approved uses of products.
Case 3: Atopic dermatitis
Atopic dermatitis
Case study 3

Patient profile: 20 year old male, with personal history of asthma and allergic rhinoconjunctivitis and familial history of both parents with allergic rhinoconjunctivitis
Disease status: Atopic dermatitis for the last 6 years, with a clinical report of almost continuous outbreaks of cutaneous lesions since 1 year old

Previous therapy:
- Treated with emollients and topical corticosteroids
- Frequent periods of oral prednisone with short and partial improvements
Cyclosporin therapy and outcome
Case study 3

- Treatment with oral cyclosporin 5 mg/kg/day over 3 months
- Tapered to 3.7 and 2.5 mg/kg/day during the following 2 months
- Almost total control was achieved
- Relapses occurred later
Conclusions
Summary

- Cyclosporin offers patients rapid relief from the signs and symptoms of atopic dermatitis
- Cyclosporin has a well established efficacy and safety profile
- Cyclosporin improves the quality of life of patients with atopic dermatitis
- Cyclosporin is a critical-dose drug and bioequivalence does not necessarily mean therapeutic equivalence

Cyclosporin is an effective systemic therapy for severe atopic dermatitis
Cyclosporin provides patients with a rapid reduction in the signs and symptoms of atopic dermatitis
The ‘ideal’ cyclosporin patient

<table>
<thead>
<tr>
<th>Male or female adult patient, collaborative and trustworthy</th>
</tr>
</thead>
<tbody>
<tr>
<td>With moderate to severe disease resistant to topical/conventional therapies(^1,2)</td>
</tr>
<tr>
<td>With blood pressure values within the normal limit(^1,2)</td>
</tr>
<tr>
<td>With liver and kidney function tests within the normal range(^1,2)</td>
</tr>
<tr>
<td>Without immune deficiency, active infection and/or history of neoplastic disorders(^1,2)</td>
</tr>
<tr>
<td>Without concomitant use of nephrotoxic and/or immunosuppressive drugs, as well as drugs with potential interactions with cyclosporin metabolism(^1,2)</td>
</tr>
<tr>
<td>Without history of excessive photo(chemo)therapy, and/or recent use of radiotherapy(^1,2)</td>
</tr>
</tbody>
</table>

2. Sandimmun Neoral Core Data Sheet.