H.11 Systemic therapy (second line, non-biologic therapy)

H.11.1 INDUCTION OF REMISSION

H.11.1.1 Methotrexate vs placebo

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
J. H. Saurat, G. Stingl, L. Dubertret, K. Papp, R. G. Langley, J. P. Ortonne, K. Unnebrink, M. Kaul, A. Camez, and Champion Study Investigators. Efficacy and safety results from the randomized controlled comparative study of adalimumab	RCT **CHAMPION trial** Multi-centre, 28 centres in Europe and Canada • Randomised (2:1) by central computer-generated scheme stratified by centre (block size =	Total N: **163** for our comparison (plus 108 receiving adalimumab) **Drop-outs (don't complete the study):** 11 (plus 4 using ADA) MTX: 6 due to AEs Placebo: 5 (1 AE; 4 lack of efficacy)	**Inclusion criteria:** ≥18 years of age; moderate-to-severe psoriasis (BSA ≥10% and PASI ≥10); plaque psoriasis for at least 1 year and stable plaque psoriasis for at least 2 months; candidate for systemic or phototherapy; active psoriasis despite topical treatment **Exclusion criteria:** previous treatment with TNF-antagonist or MTX; Patients with a history of clinically significant haematological, renal or liver disease /abnormal laboratory values; with a history of demyelinating disease, cancer, or other lymphoproliferative disease (other than successfully treated nonmetastatic cutaneous squamous cell or basal cell	N=110 **MTX** **Encapsulated tablets** **7.5 mg –** increased as needed and as tolerated to **25 mg/wk** Administered as a single weekly dose	N=53 **Placebo encapsulated tablets (or injection for adalimumab control – data not given separately for the 2 placebo groups)** Administered as a single weekly dose	16 weeks (plus 70 days after last treatment for adverse events)	**1° outcome:** PASI75 **2° and other outcomes :** AEs; PASI50; PASI90; PASI100; PGA PASI and PGA measured at weeks 1, 2 ,4 , 8, 12 and 16	Abbott laboratories

<table>
<tr>
<td>vs. methotrexate vs. placebo in patients with psoriasis (CHAMPION). Br.J.Dermatol. 158 (3):558-566, 2008.

Ref ID: SAURAT2008</td>
<td>4)
• Washout period: 2 weeks for topical therapies and phototherapy, 4 weeks for nonbiologic systemic therapies, and 12 weeks for biologic therapies
• Double blind (patients, investigators, study site personnel and Abbott unaware of assignments)
• Allocation concealment (centrally assigned)
• Sample size calculation for PASI75 at 16 wks</td>
<td></td>
<td>carcinoma and ⁄or localized carcinoma in situ of the cervix); or who were immunocompromised

Note: Patients with evidence of latent TB were permitted to enrol if they had received prophylactic treatment for TB, or if prophylactic treatment was initiated before administration of study drug

<table>
<tr><th>Mean baseline</th><th>Placebo (N=53)</th><th>MTX (N= 110)</th></tr>
<tr><td>Age (years)</td><td>40·7 ± 11·4</td><td>41·6 ± 12·0</td></tr>
<tr><td>Age ≥ 65 years (%)</td><td>1·9</td><td>4·5</td></tr>
<tr><td>Gender M/F</td><td>66/44</td><td>66·4/43.6</td></tr>
<tr><td>Caucasian (%)</td><td>92·5</td><td>95·5</td></tr>
<tr><td>Weight (kg)</td><td>82·6 ± 19·9</td><td>83·1 ± 17·5</td></tr>
</table>
</td>
<td>----------

BOTH ARMS: concomitant therapies

Concomitant psoriasis therapies were not permitted during the study except shampoos free of corticosteroids; bland emollients; and low-potency topical corticosteroids for the palms, soles, face, infra-mammary areas and groin only, provided they were not used within 24 h of a study</td>
<td></td>
<td></td>
<td>AEs assessed up to 70 days after last treatment</td>
<td></td>
</tr>
</table>

	(for comparisons with adalimumab not placebo); recruitment achieved this • ITT analysis for efficacy analyses (using non-responder imputation or LOCF for continuous variable) • Drop-outs/withdrawals due to AEs: MTX = 6; placebo = 1		Duration of psoriasis (years)	18·8 ± 8·7	18·9 ± 10·2	visit. All received dietary supplement of oral folate (~5 mg weekly) beginning 48 h after ingestion of oral medication			
			BSA affected by psoriasis (%)	28·4 ± 16·1	32·4 ± 20·6				
			Patients with psoriatic arthritis (%)	20·8	17·3				
			Previous systemic and/or phototherapy (%)	90·4	87·2				
			PASI (range)	19·2 ± 6·9 (6·5–38·1)	19·4 ± 7·4 (9·3–46·6)				
			Physician's global assessment (%)						

			Very severe psoriasis	3·8	5·5						
			Moderate to severe psoriasis	58·5	41·8						
			Moderate psoriasis	37·7	52·7						

Effect Size

Outcomes

NOTE: 89 of 95 (94%) patients in the MTX group received a MTX dosage of ≥ 15 mg at week 12. Six patients (6%) received a dosage of < 15 mg at week 12 because of elevations of alanine aminotransferase or aspartate aminotransferase concentrations > 1·5 times the upper limit of normal value, which necessitated decreasing the methotrexate dosage.

NOTE: Treatment compliance (mean ± SD) was high for MTX (99·7 ± 2·5%).

NOTE: The use of low-potency (grade VI or VII) topical corticosteroids was roughly balanced between groups (8% placebo, 11% methotrexate).

Efficacy

Outcome	MTX (% patients) (N= 110)	Placebo (% patients) (N=53)
Week 16		
PASI 100	7.3 (n=8)	1.5 (n=1)
PASI 90	13.6 (n=15)	11.3 (n=6)
PASI 75	35.5 (n=39)	18.9 (n=10)
PASI 50	61.8 (n=68)	30.2 (n=16)
Change in PASI	-10.9± 8.3	-4.6± 9.9
Mean % PASI improvement (based on LOCF)	54.3	21.5
PGA (clear or minimal)	30% (n=33)	11.3 (n=6)
Week 12		
PASI 100	0.9	0.0
PASI 90	9.1	7.5
PASI 75	15.1	24.5
PASI 50	54.5	26.4
Mean % PASI improvement	48.6	21.0

Safety

Outcome	**Placebo (N= 53)**	**MTX (N= 110)**
Total adverse events	42 (79·2%)	90 (81·8%)
Serious adverse events	**1 (1·9%)** ***Hepatitis***	**1 (0·9%)** ***Calculus***
Serious infections	0	0
Adverse events leading to discontinuation	**1 (1·9%)**	**6 (5·5%)**
Adverse events		
Infections, nonserious	23 (43·4%)	46 (41·8%)
Nasopharyngitis	11 (20·8%)	26 (23·6%)
Headache	5 (9·4%)	12 (10·9%)
Pruritus	6 (11·3%)	2 (1·8%)
Rhinitis	4 (7·5%)	4 (3·6%)
Nausea	4 (7·5%)	8 (7·3%)
Rhinorrhea	3 (5·7%)	0
Viral infection	1 (1·9%)	6 (5·5%)

Arthralgia	1 (1·9%)	5 (4·5%)	
Liver function tests			
Glutamyltransferase elevation	**3 (5·7%)**	**0**	
Alanine aminotransferase > 2·5 times the ULN	**1 (1·9%)**	**4 (3·6%)**	
Aspartate aminotransferase > 2·5 times the ULN	**0**	**2 (1·8%)**	
Total bilirubin > 1·5 times the ULN	**0**	**4 (3·6%)**	
Total elevated liver enzyme concentrations	**4 (7.5%)**	**10 (9.1%)**	

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>S. G. Ho, C. K. Yeung, and H. H. Chan. Methotrexate versus traditional Chinese medicine in psoriasis: a randomized, placebo-controlled trial to determine efficacy, safety and quality of life. Clin.Exp.Dermatol. 35 (7):717-722, 2010.

Ref ID: HO2010</td>
<td>RCT

Two centres, Hong Kong

• Randomised (1:1) by drawing random cards
• Washout period: 4 weeks for topical corticosteroids, phototherapy, systemic therapies and Traditional Chinese medicine (TCM); 2 weeks for moderate potency topical</td>
<td>Total N: 40 for our comparison (plus 21 on TCM)

Drop-outs (don't complete the study): 4 (plus 7 using TCM)

MTX: 1

Placebo: 3

Reasons unclear</td>
<td>Inclusion criteria: ≥18 years of age; chronic plaque psoriasis (BSA ≥20%); psoriasis for at least 1 year

Exclusion criteria: renal or liver disease, active infection, immunosuppression or other serious concomitant illness; pregnant or lactating women

<table>
<tr><th>Mean baseline</th><th>MTX (N=20)</th><th>Placebo (N= 20)</th></tr>
<tr><td>Age (range)</td><td>38.45 (21-68)</td><td>43.45 (27-61)</td></tr>
<tr><td>Gender M/F</td><td>90/10</td><td>90/10</td></tr>
<tr><td>PASI (mean ± SD)</td><td>22.82 ± 13.36 (4.1–61.2)</td><td>21.35 ± 9.17 (7.2–42·6)</td></tr>
<tr><td>PDI (mean ± SD)</td><td>52.6 ± 20.6</td><td>48.1± 18.8</td></tr>
</table>
</td>
<td>N=20

MTX

Initial doses 2.5-5.0 mg/wk – if parameters of complete blood count were within normal limits dose increased to 10 mg/wk, followed by further increases of 2.5 mg/wk (up to a max of 30 mg/wk) until a good clinical response was seen</td>
<td>N=20

Placebo encapsulated tablets</td>
<td>Treated for 6 months (assessed at monthly intervals)</td>
<td>1° outcome: PASI, PGA, PDI

2° and other outcomes: AEs</td>
<td>None stated</td>
</tr>
</table>

	corticosteroids, vit D analogues, keratolytics and coal tar • Single blind (assessors only) • Allocation concealment (not stated) • Sample size calculation not reported • ITT analysis not performed • Drop-outs/withdrawals due to AEs: unclear			Folic acid 5 mg/day also given ---------- **BOTH ARMS: concomitant therapies** Concomitant psoriasis therapies were not permitted during the study except fluocinolone 0.0125% cream and aqueous cream				
Effect Size Outcomes								

Efficacy

Note: the difference between placebo and MTX was significant at 2, 4 and 6 months ($p<0.01$; $p<0.001$; $p<0.01$)

Outcome	**MTX (N= 19)**	**Placebo (N=17)**	**p-value**
At end of study (6 months)			
Baseline PASI (mean ± SD)	22.0 ± 11.3	20.4 ± 10.8	
Final PASI (mean ± SD)	5.7 ± 8.5	13.9 ± 10.1	<0.01
Mean % PASI improvement	73.9%	32%	
PASI 75	12 (63%)	3 (18%)	
PASI 50	15 (79%)	4 (24%)	
Improvement in PDI	34.8%	21.4%	NS

Safety

AEs reported by 65% of MTX group and 30% of placebo group

No serious AEs reported and no numerical data for specific AEs in each group

Summary

- The results verify the therapeutic effect of methotrexate for the management of psoriasis

H.11.1.2 Methotrexate vs ciclosporin

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
I. Flytstrom, B. Stenberg, A. Svensson, and I. M. Bergbrant. Methotrexate vs. ciclosporin in psoriasis: effectiveness, quality of life and safety. A randomized controlled trial.	RCT Multi-centre (Sweden) Recruitment Sept-Feb 2002/3 and 2004/5 (to avoid sunny seasons) • Randomised (1:1) by	Total N: **84** **Drop-outs (don't complete the study):** 20 **MTX**: 4 - withdrawn before first dose (2 due to laboratory abnormalities and 2 withdrew consent) **CSA**: 16 – 12	**Inclusion criteria:** ≥18 years of age; moderate-to-severe psoriasis (classified by physician and patient); chronic plaque psoriasis; insufficient response to topical and/or UV treatment; **Exclusion criteria:** Patients with haematological, renal or liver disease; with a history of cancer; immunocompromised; medication contraindicated by MTX or ciclosporin; problems of abuse, planned or ongoing pregnancy, breastfeeding or non-compliance	N=37 MTX **Initial dose** **7.5 mg/wk (3-divide dose at 12-h intervals) –** increased gradually if response inadequate (<PASI50)	N=31 Ciclosporin **Initial dose 3 mg/kg daily (divided into 2 doses) –** increased gradually if response inadequate	12 weeks (examined monthly)	**1° outcome:** PASI (assessors given 2-day training in using PASI) **2° and other outcomes :** DLQI; AEs	Swedish Psoriasis Association; Welander Foundation

<table>
<tr>
<td>*Br.J.Dermatol.* 158 (1):116-121, 2008.

Ref ID: FLYTSTROM2008</td>
<td>central computer-generated random numbers
• Washout period: 2 weeks for phototherapy, 4 weeks for nonbiologic systemic therapies
• Assessor blind
• Allocation concealment (centrally assigned)
• Sample size calculation to detect a difference of one Tx producing PASI75 and the other PASI50 (need 35 in each group);
• ITT analysis of all who began</td>
<td>withdrawn before first dose (7 due to laboratory abnormalities and 5 withdrew consent); 4 discontinued treatment (due to AEs)</td>
<td>
<table>
<tr><th>Mean baseline</th><th>MTX (N=37)</th><th>CSA (N=31)</th></tr>
<tr><td>Age (years), mean (range)</td><td>48 (23-78)</td><td>45 (18-70)</td></tr>
<tr><td>Gender M/F</td><td>75.7/24.3</td><td>87.1/12.9</td></tr>
<tr><td>Weight (kg), mean (range)</td><td>85 (56-132)</td><td>87 (61-130)</td></tr>
<tr><td>PASI mean ± SD (range)</td><td>14.1 ± 7.0 (3.8-35.0)</td><td>15.5 ± 6.3 (4.3-26.2)</td></tr>
<tr><td>DLQI mean ± SD</td><td>7.9 ± 5.8</td><td>9.3 ± 6.0</td></tr>
<tr><td colspan="3">Previous therapies (n)</td></tr>
<tr><td>UVB</td><td>33</td><td>25</td></tr>
<tr><td>PUVA</td><td>3</td><td>5</td></tr>
<tr><td>Acitretin</td><td>2</td><td>1</td></tr>
<tr><td>MTX</td><td>2</td><td>1</td></tr>
<tr><td>CSA</td><td>0</td><td>2</td></tr>
<tr><td>Topical only</td><td>3</td><td>6</td></tr>
</table>
</td>
<td>and no considerable AEs to a max of 15 mg/wk

Folic acid (5 mg) give daily except MTX days

BOTH ARMS: concomitant therapies

Concomitant psoriasis therapies were not permitted during the study except topicals</td>
<td>(<PASI50) and no considerable AEs up to a max of 5 mg/kg daily</td>
<td></td>
<td></td>
<td></td>
</tr>
</table>

	treatment • Drop-outs/withdrawals due to AEs: MTX = 0; CSA = 4 (fatigue and GI symptoms)		**Current therapy (n)**					
			Topical (calcipotriol /steroids (group I-IV)	22	20			
			Emollients only	10	7			
			No topicals	5	4			

Effect Size

Outcomes (**ITT**)

Efficacy

PASI

Outcome	**MTX (N=37)**	**CSA (N= 31)**	**p-value**
Baseline PASI mean ± SD	14.1 ± 7.0	15.5 ± 6.3	
Week 12			
PASI mean ± SD	5.6 ± 3.8	3.6 ± 3.0	
Mean % PASI improvement	58	72	0.0028
Percentage achieving (n):			

PASI 90	11% (4)	29% (9)	NS
PASI 75	24% (9)	58% (18)	0.0094
PASI 50	65% (24)	87% (27)	NS

DLQI

Mean change from baseline in DLQI	**MTX (N=37)**	**CSA (N= 31)**	**p-value**
Week 12			NS
Week 8	42%	71%	0.0078

Safety

No serious AEs reported (but 2 patients on CSA developed mild hypertension – no anti-HT treatment was needed)

Temporary discontinuation of treatment occurred in 4 MTX and 1 CSA patients due to infections (2 MTX and 1 CSA patient required antibiotics)

Outcome	**MTX (N=37) n (%)**	**CSA (N= 31) n (%)**	**p-value**
Total adverse events	29 (78%)	30 (97%)	0.03
Serious adverse events	**0**	**0**	**NS**

Adverse events leading to discontinuation	**0**	**4 (12.9%)**	
Adverse events			
Fatigue	6 (16)	15 (48)	0.008
GI	13 (35)	12 (39)	0.80
Infections	11 (30)	11 (35)	0.80
Headache	5 (14)	9 (29)	0.14
Paraesthesia	0	11 (35)	<0.0001
Arthralgia	4 (11)	5 (16)	0.72
Myalgia	0	5 (16)	0.02
Muscle cramp	0	4 (13)	0.04
Hypertrichosis	0	4 (13)	0.04
Urgency	1 (3)	4 (13)	0.17
Elevation in liver enzymes	**7 (19%)**	**0**	**0.01**
Elevated creatinine	**0**	**6 (19%)**	**0.007**

Summary

- Treatment with methotrexate or ciclosporin for chronic plaque psoriasis brings satisfactory disease control, improved quality of life and tolerable side-effects.
- A statistically significant difference in effectiveness between treatment groups was recorded, showing ciclosporin to be more effective than methotrexate in a short-term perspective.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
V. M. Heydendael, P. I. Spuls, B. C. Opmeer, C. A. De Borgie, J. B. Reitsma, W. F. Goldschmidt, P. M. Bossuyt, J. D. Bos, and M. A. de Rie. Methotrexate versus cyclosporine in moderate-to-severe chronic plaque psoriasis. *New England Journal of Medicine* 349 (7):658-	RCT Multi-centre (The Netherlands) Recruitment Oct 1998-June 2000 • Randomised (1:1) by central computer-generated random numbers (block size of 8) • Washout period: 2 weeks for topicals, 4 weeks for UVB, PUVA	Total N: **88** **Drop-outs (don't complete the study):** 35 (16 in primary analysis) **Primary analysis** **MTX**: 13 - 1 withdrew consent before first dose; 12 discontinued owing to abnormal laboratory values **CSA**: 3 – 2 found to be ineligible; 1 discontinued owing to abnormal laboratory bilirubin values	**Inclusion criteria:** ≥18 years of age; moderate-to-severe chronic plaque psoriasis (≥PASI of 8); chronic plaque psoriasis; insufficient response to topical and/or UVB treatment; not previously treated with either methotrexate or ciclosporin **Exclusion criteria:** liver or renal impairment; insulin-dependent diabetes mellitus; a high risk of liver-function abnormalities; a positive serologic test for hepatitis B virus; uncontrolled hypertension; a history of cancer, including skin cancer or severe cardiovascular, pulmonary, cerebral, neurologic, or hematologic disease; or acute infection requiring antimicrobial therapy or associated with human immunodeficiency virus infection. Patients were also excluded if they were pregnant, breast-feeding, or noncompliant with an effective regimen of contraception. Patients with moderate or severe	N=44 **MTX** **Initial dose** **15 mg/wk (3-divide dose at 12-h intervals)** – if <25% reduction in PASI, dose increased up to **22.5 mg/wk** after 4 wks of treatment ---------- **BOTH ARMS:** Dose	N=44 **Ciclosporin** **Initial dose 3 mg/kg daily (divided into 2 doses) –** if <25% reduction in PASI, dose increased up to **5 mg/kg** daily after 4 wks of treatment ---------- **BOTH ARMS:** During the	16 weeks treatment (examined twice during the first month and then monthly); plus 36-wk off treatment follow-up	**1° outcome:** PASI **2° and other outcomes:** PGA; SF-36; AEs; time to relapse **Relapse**: PASI > 50% of the base-line score or the need for UVB or systemic therapy.	Dutch Health Authorities

<table>
<tr>
<td>665, 2003.

Ref ID: HEYDENDAEL2003

R. J. Rentenaar, V. M. Heydendael, F. N. van Diepen, M. A. de Rie, and I. J. ten Berge. Systemic treatment with either cyclosporin A or methotrexate does not influence the T helper 1/T helper 2 balance in psoriatic patients. Journal of Clinical Immunology 24 (4):361-369,</td>
<td>or systemic therapies
• Assessor blind
• Allocation concealment (centrally assigned)
• Sample size calculation to rule out a difference of 2 points or more in mean PASI at 95% power (need 42 in each group);
• ITT analysis (LOCF)
• Drop-outs/withdrawals due to AEs (abnormal laboratory values): MTX = 12 (liver enzymes); CSA = 1 (bilirubin)</td>
<td>Lost to follow-up post Tx

MTX: 2 at wk 32; 10 at wk 52

CSA: 1 at wk 32; 6 at wk 52</td>
<td>steatohepatitis (as established by ultrasonography of the liver)

<table>
<tr><th>Mean baseline</th><th>MTX (N=43)</th><th>CSA (N= 42)</th></tr>
<tr><td>Age (years), mean ±SE</td><td>41.6 ± 13.0</td><td>38.3 ± 12.4</td></tr>
<tr><td>Gender M/F</td><td>65.1/34.9</td><td>69.0/31.0</td></tr>
<tr><td>PASI mean ± SE</td><td>13.4 ± 3.6</td><td>14.0 ± 6.6</td></tr>
<tr><td>Age at onset, mean ± SE</td><td>41.6 ± 13.0</td><td>38.2 ± 12.4</td></tr>
<tr><td>PsA (n)</td><td>3</td><td>1</td></tr>
<tr><td colspan="3">Previous therapies (n)</td></tr>
<tr><td>UVB</td><td>28</td><td>25</td></tr>
<tr><td>PUVA</td><td>10</td><td>8</td></tr>
<tr><td>Acitretin</td><td>5</td><td>5</td></tr>
</table>
</td>
<td>decreased according to guidelines in case of AEs

Concomitant therapies

Concomitant psoriasis therapies were not permitted during the study except emollients</td>
<td>follow-up period, active therapy for psoriasis

was allowed if necessary. Drugs known to interfere with psoriasis

and/or with the systemic treatments were not allowed.</td>
<td></td>
<td></td>
<td></td>
</tr>
</table>

2004. Ref ID: RENTENAAR2004			Fumaric acid	3	0					
			Topical only	8	14					

Effect Size

Outcomes (**ITT**)

Note: an increase in dose was needed in 4 MTX patients and 6 CSA patients

Efficacy

PASI

Outcome	**MTX** **(N=43; 21 completed)**	**CSA (N= 42; 41 completed)**	**p-value**
Week 16			
Initial PASI (mean ± SE)	13.4 ± 3.6	14.0 ± 6.6	
Final PASI (mean ± SE)	5.0 ± 0.7	3.8 ± 0.5	
Mean difference in PASI (adjusted for baseline by ANCOVA)		1.3 points lower	0.09 (95% CI: -0.2 to 2.8)

Mean % change in PASI	64%	72%	0.14 (95% CI: -2 to 18)
Number achieving:			
PASI 90	17	14	0.55
PASI 75	26	30	0.29
Time-to-remission (PASI75)	-	-	NS: p = 0.07 (log rank test)
Time-to-remission (PASI90)	-	-	NS: p = 0.70 (log rank test)
Duration of remission (PASI75)			p = 0.43 (log rank test)
Duration of remission (PASI90)			p = 0.34 (log rank test)
Median time to relapse (requiring active therapy)	4 weeks	4 weeks	

Safety

Note: 2 in CSA group were given anti-**hypertensive** treatment

No serious or irreversible AEs reported

Outcome	MTX (N=43)	CSA (N= 42)
Total adverse events	29	35

Summary

- No significant differences in efficacy were found between methotrexate and ciclosporin for the treatment of moderate-to-severe psoriasis.
- As the effectiveness and tolerability of methotrexate are similar to those of ciclosporin in patients with moderate-to-severe psoriasis differences between the treatments in terms of side effects, long-term adverse effects, ease of administration (once-daily vs. twice-daily treatment), and costs can be used to guide treatment decisions in individual cases.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
K. Sandhu, I. Kaur, B. Kumar, and A. Saraswat. Efficacy and safety of cyclosporine versus methotrexate in severe psoriasis: a study from north India. *J.Dermatol.* 30 (6):458-463, 2003. Ref ID: SANDHU2003	RCT Single-centre (India) 30 consecutive patients • Randomised (method not stated) • Washout period not stated • Blinding not stated • Allocation concealment (not stated) • Sample size calculation not stated • ITT analysis	Total N: **30** **Drop-outs (don't complete the study):** Not stated	**Inclusion criteria:** severe psoriasis (>40% BSA **Exclusion criteria:** Patients with renal or liver disease; with a history of cancer; uncontrolled hypertension; epilepsy; gout; alcoholism; pregnant or lactating women	N=15 **MTX** **Initial dose** **0.5 mg/kg/wk–** ---------- **BOTH ARMS: concomitant therapies** No concomitant psoriasis therapies (topical or systemic) were not permitted during the	N=15 **Ciclosporin** **Initial dose 3 mg/kg daily (divided into 2 doses) –** increased up to a max of 4 **mg/kg** daily if no change or a rise in PASI after 2 weeks of therapy ---------- **BOTH ARMS:** Consensus	12 weeks (examined fortnightly)	**1° outcome:** PASI75 **2° and other outcomes:** clearance; AEs	None stated

	not stated • Drop-outs/withdrawals due to AEs: not stated			study; neither was concomitant therapy with nephrotoxic compounds nor drugs known to interact with MTX or CSA **Dose tapering** Tapering initiated once PASI75 achieved	guidelines followed in cases of persistent abnormal laboratory values After 4 weeks on optimum dose all patients reassessed and those with <25% reduction on PASI were regarded as non-responders			

Demographics

Mean baseline	**MTX (N=15)**	**CSA (N= 15)**
Age (years), mean ± SE	39.3±3.0	46.2±2.5

Gender M/F (%)	80/20	87.5/12.5
PASI mean ± SE	27.6 ± 2.3	29.6 ± 2.1
Duration (months) mean ± SE	65.4 ± 14.2	62.5 ± 14.9
Duration (years) mean ± SE	33.5±3.0	41±2.5
BSA (%)mean ± SE	70.6%	72%
Nail involvement (%)	8 (53.5%)	7 (46.6%)
Joint involvement (%)	1 (6.6%)	2 (13.3%)
Type of psoriasis		
Plaque (%)	11 (73.3%)	11 (73.3%)
Erythroderma (%)	4 (26.6%)	4 (26.6%)

Effect Size

Outcomes (**ITT**)

Efficacy

To achieve satisfactory results the initial dose of CYA had to be increased in 7/15 (46.6%) – the response then became comparable to the rest of the group

During tapering 13/15 CSA-treated patients experienced a gradual rise in PASI score (which was not seen in the MTX group)

Change in PASI

Outcome	MTX (N=15)	CSA (N= 15)	p-value
Week 12			
Baseline PASI (mean ± SE)	27.6 ± 2.3	29.6 ± 2.1	NS
Final PASI (mean ± SE)	0.4 ± 0.2	4.3 ± 1.7	-
Mean % PASI improvement	98.5%	85.6%	<0.05
Week 10			
Baseline PASI (mean ± SE)	27.6 ± 2.3	29.6 ± 2.1	NS
Week 10 PASI (mean ± SE)	1.1 ± 0.94	2.4 ± 0.8	-
Mean % PASI improvement	95.8%	91.7%	NS

Time to remission/PASI/clear

Outcome	MTX (N=15)	CSA (N= 15)	p-value
Time-to-PASI75 (mean; range)	5.3 (2-12) weeks	6.8 (4-8) weeks	<0.05
Complete clearance	13 (86.6%)	6 (40%)	-
Remaining clear at 12 weeks (after tapering)	13/13	2/6	-

Safety

No abnormal biochemical parameters (except slight rises in serum creatinine below the 30% threshold for dose reduction in CSA group)

Outcome	MTX (N=15)	CSA (N= 15)
Diastolic hypertension	0	4

Author's summary

- Patients on methotrexate were found to have more rapid and complete clearance than those on ciclosporin.
- Both drugs were well tolerated.
- Side effects in both the treatment groups were minor, transient, and manageable.
- At doses with comparable short-term safety profiles, methotrexate resulted in more rapid and cost effective clearance of patients with severe psoriasis. Ciclosporin can provide an effective and safe alternative.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
M. Gumusel, M. Ozdemir, I. Mevlitoglu, and S. Bodur. Evaluation of the efficacy of methotrexate and cyclosporine therapies on psoriatic nails: a one-blind, randomized study. Journal of the European Academy of Dermatology & Venereology 25 (9):1080-1084, 2011. Ref ID: GUMUSEL2011	RCT Single-centre (Turkey) Consecutive in- and out-patients in Dermatology Department (recruited Jan-Nov 2007) • Randomised (roll of a die - inadequate) • Washout period: topicals 4 weeks; systemics 6 months • Blinding unclear	Total N: **37** **Drop-outs (don't complete the study):** 3	**Inclusion criteria:** moderate-to-severe psoriasis; nail involvement; BSA >10% and PASI ≥10 and NAPSI >10 (or less severe disease but distressed by condition) Note: only 2 patients had BSA<10 and PASI<10, and they had severe, resistant nail psoriasis **Exclusion criteria:** Age <18 years, renal or liver disease; history of skin cancer or other systemic malignancy; uncontrolled hypertension; pregnant or lactating women or plans to conceive; haematological problems; hyperlipoproteinamia; severe cardiac or neurological disease; risk of abuse of treatment; fungal infection; current systemic therapy for psoriasis or UV and acitretin in the last 2 years; guttate, erythrodermic, pustular or localised palmoplantar psoriasis	N=18 **MTX** Initial dose **15 mg weekly** (plus 5 mg folic acid on day not taking MTX) for 3 months, reduced to **10 mg/wk** for second 3 months ---------- **BOTH ARMS: concomitant therapies**	N=19 **Ciclosporin** **Initial dose 5 mg/kg daily (divided into 2 doses) –** decreased to **2.5-3.5 mg/kg daily** for second 3 months	6 months	**1° outcome:** NAPSI **2° and other outcomes:** clearance of nails; AEs	None stated

	• Allocation concealment (adequate) • Sample size calculation performed • ITT analysis not performed • **Drop-outs/withdrawals due to AEs: 1 MTX; 2 CSA**		Note: no statistically significant difference in any characteristic	No concomitant psoriasis therapies were not permitted during the study; only once daily emollients				

Demographics

Mean baseline	**MTX (N=17)**	**CSA (N= 17)**
Age (years), mean ± SD	42.5±12.5	34.8±10.2
Gender M/F (%)	58.8/41.2	47.1/52.9
PASI mean ± SD	10.7 ± 6.0	12.9 ± 6.4
Duration (years) mean ± SD	12.6 ± 8.4	13.6 ± 10.8
NAPSI (mean ± SD)	39.1±19.9	42.1±26.4
BMI (kg/m^2)mean ± SD	27.8±4.1	26.7±5.8

Effect Size

Outcomes (**ACA**)

Efficacy

Outcome	**MTX (N=17)**	**CSA (N= 17)**	**p-value**
Baseline NAPSI (mean ± SD)	39.1±19.9	42.1±26.4	0.9
Final NAPSI (6 months; mean ± SD)	18.0 ± 11.5	25.8 ± 19.2	-
Mean NAPSI improvement	21.1	16.3	0.27
Mean % NAPSI improvement	43.3%	37.2%	0.49
Moderate improvement (>50-99%)	7 (41.1%)	7 (41.1%)	-
Complete improvement (100%)	0	1 (5.8%)	-

Time to remission/PASI

- Graph of PASI over time shows the maximum response is achieved at 8 weeks for MTX and 12 weeks for CSA

Safety

All 3 patients withdrawn

Outcome	MTX (N=18)	CSA (N= 19)
Increased transaminase	1	0
Elevated serum creatinine	0	2

Author's summary

- Moderate effectiveness on psoriatic nail was found in the two treatment agents and there were no significant differences in efficacy between the groups.
- Both drugs were well tolerated.

H.11.2 INDUCTION OF REMISSION

H.11.2.1 Actitretin dosing schedules

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
P. Berbis, J. M. Geiger, C. Vaisse, C. Rognin, and Y. Privat. Benefit of progressively increasing doses during the initial treatment with acitretin in psoriasis. *Dermatologica* 178 (2):88-92, 1989. Ref ID: BERBIS1989	RCT • Randomised (method not stated) • Washout period (see exclusion criteria) • Double blind • Allocation concealment (not stated) • Sample size calculation not stated • ITT analysis not performed • Drop-outs/withdrawals due	Total N: **66** **Drop-outs (don't complete the study):** 8 Group I: 1 (cleared at 2 wks) Group II: 4 (2 abnormal LFTs; 1 mucocutaneous AEs; 1 non-treatment related) Group III: 3 (1 abnormal LFTs; 1 mucocutaneous AEs; 1 non-treatment related) **Note:** 7 additional	**Inclusion criteria:** severe psoriasis **Exclusion criteria:** Impaired renal or hepatic function; severe cardiological or neurological disease; female of childbearing potential not willing to use effective contraception; received MTX, etretinate, PUVA, UVB, topical corticosteroids, tar derivatives, or anthralin 4 weeks before entry into the study	N=21 Acitretin **Group I: low initial dose increased at 2-wk intervals (10, 30, 50 mg/day) (n=21)** --- **BOTH ARMS: concomitant therapies** Topical	N=45 Acitretin **Group II: constant dose (30 mg/day) (n=23)** **Group III: high initial dose decreased at 2-wk intervals (50, 30, 10 mg/day) (n=22)** ---	12 weeks (6 wk double blind phase; 6 wk open phase)	**1° outcome:** change in PASI **2° and other outcomes:** clinical and laboratory AEs	None stated

	to AEs: Group I: 0; Group II: 3; Group III: 2	patients dropped out during the open phase (6 due to clearance and 1 pregnancy)		corticosteroid allowed after week 8 on limited areas (32 patients received moderately strong preparations). No other antipsoriatic therapy permitted 19 patients received drugs for concomitant diseases	**BOTH ARMS:** Daily dose dispensed in a blister pack containing 5 identical capsules (10 mg acitretin and placebo). Boxes dispensed for 2-weeks at each visit During open phase dose adjusted to 10, 30 or 50 mg/day according to improvement and AEs (mean dose = 33.9 mg/day)			

Demographics

Mean baseline	**Group I - increasing** **(n=21)**	**Group II - constant** **(n=23)**	**Group III - decreasing** **(n=22)**

Age (years), mean ± SD	38.9±14.5	50.3±12.4	46.7±14.3
Gender M/F (%)	81/19	65.2/34.8	68.2/31.8
Weight (kg) mean ± SD	66.0± 12.4	70.0 ± 12.3	71.1 ± 12.2
PASI (mean ± SEM)	22.0±1.9	22.0±2.1	21.8±1.8
Type of psoriasis (n)			
Psoriasis vulgaris (plaque, nummular)	14	18	12
Guttate psoriasis	2	1	3
Psoriasis vulgaris (partim pustulosa)	3	1	5
Erythrodermic psoriasis	0	1	1
Palmoplantar pustular psoriasis	1	1	1
Acrodermatitis continua (Hallopeau)	1	1	0

Effect Size

Outcomes

Efficacy

- An improvement of >80% was obtained in 42/58 patients by the end of the open trial phase

Outcome	Group I (n=21)	Group II (n=23)	Group III (n=22)	p-value
Initial PASI (mean ± SEM)	22.0±1.9	22.0±2.1	21.8±1.8	
PASI at 2 wk	Dose dependent improvement (presented graphically)			0.07
% change in PASI at end of double blind phase (6 wk)	(n=20) 62.7%	(n=19) 55.9%	(n=19) 67.1%	0.42
% change in PASI; mean ± SEM (12 wk – end of open phase) note that numbers in each group are unclear at 12 wks	81±4	87±4	88±3	

Safety

- The adverse reactions were dose dependent: their frequency and intensity increased progressively with increasing dose in group I and decreased with decreasing dose in group 3

	During double blind phase			During whole treatment (n=65)
Outcome	**Group I (n=21)**	**Group II (n=23)**	**Group III (n=21)**	
Experienced side effects	21	23	21	65
Mucous membrane				
Dry lips/cheilitis	21	23	21	65

Dry mouth	13	18	14	54
Dry nose	11	16	10	45
Epistaxis	1	1	0	2
Rhinorrhea	0	0	0	1
Conjuntivitis/dry eyes	2	6	8	29
Skin				
Dry skin	16	16	16	51
Scaling (palms/soles)	18	18	18	57
Scaling (elsewhere)	13	12	15	48
Pruritis	0	4	1	7
Facial dermatitis	2	0	3	5
Localised erythroderma	0	0	0	1
Phototoxicity	0	1	0	2
Sticky skin	0	1	0	1
Folliculitis	0	0	0	2
Hair and nails				
Hair loss	1	2	6	13
Nail fragility	3	5	2	16

Severe clinical adverse reactions

Treatment period	Group I		Group II		Group III	
	Dose (mg/day)	N'/n	Dose (mg/day)	N'/n	Dose (mg/day)	N'/n
Week 0-2*	10	0/21	30	7/23	50	9/21
Week 3-4	30	3/20	30	7/22	30	5/20
Week 5-6**	50	8/20	30	9/21	10	2/19
*Group I vs group II and group I vs III: p<0.01 ** Group III vs group I: p =0.06; group III vs group II: p<0.05						

Author's summary

- Acitretin is efficacious at doses between 10-50 mg/day and the 3 therapeutic schemes appeared to have similar efficacy
- The undesirable effects on skin and mucous membranes are dose-dependent
- The number of severe adverse reactions was lower in the group with increasing dosage and no patient in this group had to interrupt treatment because of adverse reactions in this group
- The acceptability of acitretin is better when treatment is started at a low dose and progressively increased

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>T. P. Kingston, L. H. Matt, and N. J. Lowe. Etretin therapy for severe psoriasis. Evaluation of initial clinical responses. Arch.Dermatol. 123 (1):55-58, 1987.

Ref ID: KINGSTON1987</td>
<td>RCT

• Randomised (method not stated)
• Washout period 1 month for systemic treatments for psoriasis
• Double blind
• Allocation concealment (not stated)
• Sample size calculation not stated
• ITT analysis not performed
• Drop-outs/withdrawals due to AEs: 0</td>
<td>Total N: 21

Drop-outs (don't complete the study):
6

Placebo: 3 switched to high dose acitretin because of increased disease severity at 4 weeks

3 due to administrative reasons</td>
<td>Inclusion criteria: psoriasis affecting 21-95% of the body

Exclusion criteria: Fertile women

<table>
<tr><th>Mean baseline</th><th>All (n=21)</th></tr>
<tr><td>Age (years), range</td><td>31-74</td></tr>
<tr><td>Gender M/F (%)</td><td>81/19</td></tr>
</table>

Note: unclear if suitably matched at baseline</td>
<td>N=15 (5 in each group)

Acitretin

10, 50 or 75 mg/day (mean doses 0.14, 0,66 or 0.85 mg/kg/day)

BOTH ARMS: concomitant therapies

1% hydrocortison</td>
<td>N=6

Placebo

BOTH ARMS:

During open phase dose adjusted to clinical response</td>
<td>8 months (2 months double blind phase; 6 month open phase)</td>
<td>1° outcome: extent of psoriasis involvement (0-100%) and scaling, erythema, thickness and pustulation on 0-6 scale (0 = absent)

Excellent responders >75% clearing; good responders = 50-75% reduction in % BSA; minimal reposnders = <50% clearing

2° and other outcomes: clinical and laboratory AEs</td>
<td>None stated</td>
</tr>
</table>

				e ointment permitted on local areas (≤5% BSA) but no other anti-psoriatic treatment permitted				

Effect Size

Outcomes

Efficacy (8-wk double blind period)

- Patients who received 50 or 75 mg/day showed significant improvement on every parameter, whereas those receiving 0 or 10 mg/day did not
- The group receiving 75 mg/day did not show greater improvements than 50 mg/day
- Most patients needed daily doses of 0.66 mg/kg or more to initiate remission

Safety

- There were more side effects at higher doses
- 3 patients required dose adjustment because of transient increases in liver enzymes and hypertriglyceridaemia (group not stated)

Outcome	**% of those receiving ≥0.66 mg/kg with the outcome**
Cheilitis and mucosal dryness	89

Palmoplantar peeling	86
Alopecia	58
Sticky skin	32
Paronychia and other nail problems	31
Skin fragility	62

Author's summary

- Acitretin is an effective treatment for severe recalcitrant psoriasis

H.11.3 INDUCTION & MAINTENANCE OF REMISSION

H.11.3.1 Acitretin vs placebo

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
A. Lassus, J. M. Geiger, M. Nyblom, T. Virrankoski, M. Kaartamaa, and L. Ingervo. Treatment of severe psoriasis with etretin (RO 10-1670). *Br.J.Dermatol.* 117 (3):333-341, 1987. Ref ID: LASSUS1987	RCT Volunteers from the Finnish Psoriasis Association Recruitment Dec 1984-Jan1985 • Randomised (method not stated) • Washout period not stated • Double blind (details not stated) • Allocation	Total N: **80** **Drop-outs (don't complete the study):** 7 3 for protocol violation (group not stated) Group I: 1 due to lack of efficacy Group II: 1 due to side effects Group III: 1 due to lack of efficacy	**Inclusion criteria:** long-standing severe psoriasis **Exclusion criteria:** not stated	N=60 **Acitretin** **Group I: 10 mg/day (n=20)** **Group II: 25 mg/day (n=20)** **Group III: 50 mg/day (n=20)** After 2 months (induction) the dose was reduced owing	N=20 **Placebo**	6 months (examined monthly) **Induction** of remission (8-week phase) and **maintenance** treatment (26-week phase) **Note**: final evaluation at 6 months was during the summer when there may have been	**1° outcome:** PASI **2° and other outcomes:** AEs, g-GT, SGOT, SGPT, cholesterol, triglycerides	None stated

	concealment (not stated) • Sample size calculation not stated • ITT analysis not performed • Drop-outs/withdrawals due to AEs: 1 in group II	Group IV: 1 due to lack of efficacy		to AEs or good clinical response ---------- **BOTH ARMS: concomitant therapies** 0.1% diflucortolone valerate ointment permitted on request		partial spontaneous remission		

Demographics

Note: baseline severity not reported

Mean baseline	**Acitretin 10 mg/day (n=20)**	**Acitretin 25 mg/day (n=20)**	**Acitretin 50 mg/day (n=20)**	**Placebo (n=20)**
Age (years), mean ± SD	48.5±11.2	52.7±11.3	45.9±13.2	47.5±11.9
Gender M/F (%)	55/45	50/50	50/50	55/45

Duration (years) mean ± SD	23.7 ± 14.5	20.1 ± 21.3	17.9 ± 10.6	19.2 ± 12.2
Weight (kg) mean ± SD	73.2 ± 10.4	78.5 ± 18.1	75.8 ± 17.9	71.7 ± 11.7
Height (cm) mean ± SD	172 ± 11	171 ± 10	172 ± 11	170 ± 9
Type of psoriasis (n)				
Psoriasis vulgaris	15	18	17	20
Psoriasis pustulosa	1	1	2	0
Erythrodermic psoriasis	4	1	1	0

Effect Size

Outcomes

INDUCTION (2 months – during this time 2 in group I; 3 in group II, 2 in group III and 1 in group IV did not take the dosage stated)

Efficacy

- There was a significantly greater reduction in PASI in the groups receiving 25 mg/day and 50 mg/day compared with placebo ($p<0.05$)
- There was no significant difference between the 25 and 50 mg groups
- The mean percentage decrease in PASI score in the 10 mg group was greater than in the placebo group, but did not differ significantly from any other group

Outcome	Acitretin 10 mg/day (n=20)	Acitretin 25 mg/day (n=20)	Acitretin 50 mg/day (n=20)	Placebo (n=20)
PASI75 (n)	8	12	14	5
Requiring topical steroid	6	7	4	12

Safety

In patients in whom the initial dose was maintained

Outcome	Acitretin 10 mg/day (n=18)	Acitretin 25 mg/day (n=17)	Acitretin 50 mg/day (n=18)	Placebo (n=19)
Experienced side effects	15	16	17	9
Mucous membrane				
Dry lips	15	13	16	5
Dry mouth	1	1	2	1
Dry nose	3	4	4	1
Conjuntivvitis	5	2	2	1
Skin				
Dry skin (palms/soles)	0	1	1	0
Dry skin (elsewhere)	7	6	10	4
Scaling (palms/soles)	0	0	2	0

Scaling (elsewhere)	1	2	3	1
Skin thinning	0	0	0	0
Pruritis	3	5	3	1
Retinoid dermatitis	1	0	4	0
Vesicular lesion	0	0	0	0
Hair and nails				
Hair loss	0	0	6	0
Paronychia	0	0	3	0
Nail fragility	0	0	0	0

Outcome (increase in lab values to above ULN when previously normal)	**Acitretin 10 mg/day (n=18)**	**Acitretin 25 mg/day (n=17)**	**Acitretin 50 mg/day (n=18)**	**Placebo (n=19)**
Gamma GT > 50 U/l	1	0	0	0
SGOT > 40 U/l	2	0	0	0
SGPT > 40 U/l	0	0	0	0
Cholesterol > 6.9 mmol/l	2	5	3	3
Triglycerides >1.7 mmol/l	2	2	2	1

Dose

Daily doses used during whole treatment period

- Group I: 9.0 ± 1.5 mg
- Group II: 21.4 ± 4.0 mg
- Group III: 37.4± 7.7 mg

MAINTENANCE (subsequent 4 month phase)

Efficacy

- After 6 months there was no significant difference in PASI between the 4 groups, and all were markedly improved

Outcome	**Acitretin 10 mg/day (n=20)**	**Acitretin 25 mg/day (n=20)**	**Acitretin 50 mg/day (n=20)**	**Placebo (n=20)**
Requiring topical steroid during whole study	13	12	13	18

Safety

Outcome	**Acitretin 10 mg/day (n=20)**	**Acitretin 25 mg/day (n=20)**	**Acitretin 50 mg/day**	**Placebo (n=20)**

			(n=20)	
Experienced side effects	17	19	20	11
Mucous membrane				
Dry lips	16	17	19	6
Dry mouth	1	2	3	1
Dry nose	3	6	7	1
Conjuntivvitis	5	3	2	1
Skin				
Dry skin (palms/soles)	0	2	7	0
Dry skin (elsewhere)	8	6	15	5
Scaling (palms/soles)	0	0	2	0
Scaling (elsewhere)	1	3	4	1
Skin thinning	0	1	0	0
Pruritis	3	6	5	4
Retinoid dermatitis	1	1	5	0
Vesicular lesion	0	1	0	0
Hair and nails				
Hair loss	3	3	15	2
Paronychia	1	0	4	1
Nail fragility	0	0	1	0

Outcome (increase in lab values to above ULN when previously normal)	Acitretin 10 mg/day (n=18)	Acitretin 25 mg/day (n=17)	Acitretin 50 mg/day (n=18)	Placebo (n=19)
Gamma GT > 50 U/l	0	1	1	1
SGOT > 40 U/l	1	2	1	0
SGPT > 40 U/l	1	3	2	0
Cholesterol > 6.9 mmol/l	2	0	Value missing	1
Triglycerides >1.7 mmol/l	1	1	0	1

Author's summary

- The optimal initial dose seems to be approximately 25 mg/day and the maintenance dose somewhat lower.
- Six months after the start of treatment there were no significant differences between the four groups; the last follow-up examination took place during the summer and some of the patients probably experienced spontaneous improvement.
- Although clinical adverse effects were frequent in all groups, severe side effects, namely hair loss and paronychia, occurred frequently only among patients treated with an initial dose of 50 mg of etretin daily.
- The effect of treatment on liver enzymes, cholesterol and triglycerides was minimal.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
M. T. Goldfarb, C. N. Ellis, A. K. Gupta, T. Tincoff, T. A. Hamilton, and J. J. Voorhees. Acitretin improves psoriasis in a dose-dependent fashion. *J.Am.Acad.Dermatol.* 18 (4 Pt 1):655-662, 1988. Ref ID: GOLDFARB1988	RCT • Randomised (method not stated) • Washout period: 1 month for systemics; 2 weeks for topicals • Blinding (not stated) • Allocation concealment (not stated) • Sample size calculation not stated • ITT analysis not performed • Drop-outs/withdrawals due	Total N: **38** **Drop-outs (don't complete the study):** 5 to end of 8-wk DB phase – had to enter open phase early due to flaring of psoriasis (3 in placebo; 1 on 10 mg 1 on 25 mg); 12 to end of 24-wks acitretin (6 clinical or lab side effects; 2 failure to improve; 2 clearance of psoriasis; 2 noncompliance)	**Inclusion criteria:** adults; 10-70% BSA or disabling disease; **Exclusion criteria:** women of childbearing potential **Note:** baseline characteristics not reported but states that there was no significant difference in mean weight age or sex distribution	N=26 **Acitretin** **10 mg/day (n=5)** **25 mg/day (n=5)** **50 mg/day (n=11)** **75 mg/day (n=5)** ----------	N=12 **Placebo**	8 weeks double-blind phase then open phase of 24 wk for placebo and 16 for acitretin groups (second phase non-comparative) Evaluated monthly **Note**: daily doses of acitretin during the open phase could be 10, 25, 30, 50 or 75 mg determined by the investigator based on response to therapy, side effects and lipid levels; all placebo patients started on 50 mg **Note**: after 24 weeks	**1° outcome:** global severity scale: % skin involvement and overall scaling, erythema, thickness and global extent on 0-6 scale (0 absent/clear to 6 severe) After 8 weeks, overall improvement ranked as worse (>10% worse); unchanged (10% worse to 10% better); fair (11-50% improvement); good (51-75% improvement); or excellent (>75% improvement) **2° and other outcomes:** AEs, blood count,	None stated

	to AEs: 6 (group not specified)			**BOTH ARMS: concomitant therapies** No topicals except bland emollients and limited amounts of 1% hydrocortisone cream		of acitretin therapy patients were required to stop treatment for at least 1 month, but could receive additional 1 month courses if psoriasis recurred (worsening of global score by 2 points)	urinalysis, LFTs, cholesterol, triglycerides	

Effect Size

Outcomes

8-wk DB period

Efficacy

- Overall improvement scores and individual parameters showed a dose-response relationship (p=0.002)
- NS difference between 10 or 25 mg acitretin and placebo on any parameter
- At the initial 2-wk evaluation 19% of all patients experienced an initial expansion in extent of psoriasis

Outcome (change from baseline – positive numbers indicate improvement)	Placebo (n=12)	Acitretin 10 mg/day (n=5)	Acitretin 25 mg/day (n=5)	Acitretin 50 mg/day (n=11)	Acitretin 75 mg/day (n=5)
Scaling	0.6±0.5	-0.8±0.5	1.2±0.4	2.2±0.4	3.2±0.6
Erythema	0.5±0.5	-0.2±0.5	0.6±0.4	1.5±0.5	3.0±0.6
Thickness	0.6±0.3	-0.4±0.2	1.4±0.2	2.1±0.4	4.2±0.4
Global improvement	0.5±0.3	0.0±0.0	1.0±0.3	1.6±0.4	3.0±0.8
% improvement	-0.8±6.1	-0.3±1.2	-3.2±4.3	5.5±2.5	17.4±5.9
>75% improvement in global score (n)	1	0	0	2	2
Clearance	1	0	0	0	0

Safety during 8 wk double-blind phase

Symptom	% showing the symptom					
	Placebo (n=12)	Acitretin 10 mg/day (n=5)	Acitretin 25 mg/day (n=5)	Acitretin 50 mg/day (n=11)	Acitretin 75 mg/day (n=5)	During first 24 wk (average 50 mg/day)
Cheilitis	25 (n=3)	40 (n=2)	100 (n=5)	100 (n=11)	80 (n=4)	95
Peeling palms and soles	17	0	50	64	20	78
Alopecia	8 (n=1)	0	25 (n=1)	18 (n=2)	40 (n=2)	73

Dry nose	0	0	50	36	60	41
Dry eyes	17	0	50	18	60	35
Chills	0	0	25	27	0	27
Pruritis	0	0	50	18	20	22
Muscle pain	0	0	25	18	0	22
Joint pain	8	0	0	9	20	22
Fatigue	8	0	0	0	40	19
Sticky skin	0	0	0	0	0	16
Xerosis	17	0	25	9	0	14
Tender skin	8	0	0	18	0	11
Fragile skin	0	0	0	9	20	8
Granulation tissue	0	0	0	0	20	8
Headaches and edema	8	0	0	9	0	3

Full 24-wk period (includes DB and open phase); n=37- completed by 25

- Average patient achieved 51-75% improvement in psoriasis
- On average 13.3 ± 2.4 wks without acitretin elapsed before psoriasis returned strongly enough to require treatment

Author's summary

- After the double-blind period, patients continued treatment in an open fashion until they had received a total of 24 weeks of acitretin therapy. Most patients received 50 mg of acitretin daily, which adequately cleared their psoriasis.
- After approximately 3 months without acitretin, most patients required retreatment. Subsequent 24-week courses of therapy were generally effective and well tolerated.
- The most common laboratory abnormalities were elevations of triglyceride, cholesterol, and liver transaminase levels.
- The efficacy and side effects of acitretin appear to be similar to those of etretinate; the principal advantage of acitretin is its shorter half- life. Although acitretin is a potent teratogen, its rapid elimination makes it a viable treatment for psoriasis among women of childbearing potential.

H.11.4 INDUCTION OF REMISSION

H.11.4.1 Ciclosporin vs placebo

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
C.N. Ellis, M. S. Fradin, J.M. Messana, M.D. Brown, M.T. Siegel, T.A. Hamilton, T.G. Parish, M. Ellis-Madu, E. Duell, T.N. Annesley, K.D. Cooper, J.J. Voorhees. Cyclosporine for plaque-type psoriasis results of a multidose double-blind trial.	RCT USA Randomised: computer generated random code in blocks of 17 Blinding: Double-blinded: Patients blinded & patients	Total N=85 **Drop-outs (don't complete the study):** 4 withdrawals due to AEs, 3 withdrawals due to protocol violation,	**Inclusion criteria:** Outpatients with chronic plaque psoriasis affecting >25% BSA, or disabling psoriasis (mainly hands) Patients had not responded to at least one of the major agents for psoriasis i.e. UVB, pUVA, etretinate, or methotrexate Washout: Patients stopped receiving systemic therapy/phototherapy 30 days prior to enrolment, 14 days prior for topicals (except emollients) **Exclusion criteria:** Women of childbearing potential **Baseline characteristics** Stated baseline characteristics	**Ciclosporin (CSA)** N=60 Three groups given 8 weeks of fixed dose oral ciclosporin 7.5 mg/kg (n=15) 5 mg/kg (n=20) 3 mg/kg (n=25)	**Placebo** N=25 Placebo followed by 8 week period of crossover (i.e. to CSA 3 mg/kg/day started) titrated according to clinical response further increases at 12 weeks	8 weeks Placebo comparison only valid at 8 weeks due to crossover of placebo group (trial 16 weeks in total however)	**1° outcome:** Clear/almost clear **2° and other outcomes:** Global severity scale PASI BSA AEs	Sandoz Research Institute, Babcock Dermatologic Endowment, NIH Clinical Research Center Grant

<table>
<tr>
<td>*NEJM*. 324(5):277-284,1991.

Ref ID: ELLIS1991</td>
<td>directly evaluated by blinded physicians. Lab results reviewed by unblinded physician who adjusted dosage of CSA

Allocation concealment: not mentioned

Sample size calculation: to provide 95% power to detect ‘dose-response relation’ by 8th week of study

ITT analysis:</td>
<td></td>
<td>similar; slightly higher %male in 3mg CSA group
<table>
<tr><td></td><td colspan="3">Ciclosporin</td><td>Placebo</td></tr>
<tr><td></td><td>3mg</td><td>5mg</td><td>7.5mg</td><td></td></tr>
<tr><td>No. Of pts</td><td>25</td><td>20</td><td>15</td><td>25</td></tr>
<tr><td>Sex – M/F</td><td>23/2</td><td>15/5</td><td>12/3</td><td>16/9</td></tr>
<tr><td>Mean age</td><td>46</td><td>42</td><td>46</td><td>43</td></tr>
<tr><td>Mean weight</td><td>87</td><td>82</td><td>84</td><td>84</td></tr>
<tr><td>Mean %BSA involving</td><td>41</td><td>46</td><td>46</td><td>38</td></tr>
<tr><td>Mean global severity score</td><td>6.2</td><td>6.5</td><td>6.5</td><td>6.1</td></tr>
</table>
</td>
<td>followed by 8 week period of dose adjustment

according to clinical response

further increases at 12 weeks to max 10 mg/kg/day

dose reduction if: rise in creatinine or bilirubin or uncontrollable rise in DBP >90 mmHg, CSA trough blood level >800 ng/ml,</td>
<td>dose reduction if: rise in creatinine or bilirubin or uncontrollable rise in DBP >90 mmHg, CSA trough blood level >800 ng/ml, marked reduction in renal function, serious clinical side effects</td>
<td></td>
<td>Renal function

Blood pressure changes

Uric acid

LFTs</td>
<td></td>
</tr>
</table>

	Yes			marked reduction in renal function, serious clinical side effects				

Effect Size

Clear/nearly clear

	CSA 3 mg/kg/day	CSA 5 mg/kg/day	CSA 7.5 mg/kg/day	Placebo
Clear/nearly clear at 8 weeks	36%	65%	80%	0%
PASI75	7/25	12/20	NA	1/25

PASI

PASI data not extractable: PASI improved significantly in all groups receiving CSA compared to placebo at 8 weeks (P<0.001 for each), no sig difference in score between 5 and 7 mg/kg (P>0.4), but each better than the response in the group receiving the lowest dose (P<0.01 for each comparison).

Withdrawal due to adverse events

4 patients withdrawn in CSA group due to adverse events at **16 weeks**

Severe adverse events

1 high creatinine requiring dose reduction (CSA 7.5 mg/kg)

Renal function

	CSA 3 mg/kg/day	CSA 5 mg/kg/day	CSA 7.5 mg/kg/day	Placebo	*P* value
Median % decrease in GFR at 8 weeks	6%	15%	19%	2%	**CSA 7.5mg vs. Placebo = 0.05**
decrease ≥15% in GFR during first 8 weeks	4/12	5/10	9/12	0/9	

18/34 patients had decrease ≥15% in GFR during first 8 weeks (

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>C.N. Ellis, D.C. Gorsulowsky, T.A. Hamilton, J.K. Billings, M.D. Brown, J.T. Headington, K.D. Cooper, O. Baadsgaard, E.A. Duell, T.M. Annesley, J.G. Turcotte, J.J. Voorhees.

Cyclosporine improves psoriasis in a double-blind study. JAMA.256(22) :3110-3116. 1986

Ref ID: ELLIS1986</td>
<td>RCT

USA

Randomised: random number tables

Blinding:

Double-blinded: Patients blinded & patients directly evaluated by blinded physicians. Lab results reviewed by unblinded physician who adjusted dosage of CSA.</td>
<td>Total N=21

Drop-outs (don't complete the study): Nil</td>
<td>Inclusion criteria:
Outpatients aged ≥18 years with severe chronic large plaque-type psoriasis vulgaris and >20% BSA involvement, failed to improve with UVB, pUVA, or methotrexate.

Patients selected who were 'thought to be reliable'

Washout:No systemic / intralesional / UV / topicals (other than emollients) for 4 weeks prior

Exclusion criteria:

Patients with other types of psoriasis

Women of childbearing potential

Baseline characteristics
<table>
<tr><th></th><th>CSA</th><th>Placebo</th></tr>
</table>
</td>
<td>Ciclosporin (CSA)

N=11

Oral ciclosporin 14 mg/kg per day (single dose)

For 4 weeks then stopped

Dose adjusted according to trough ciclosporin levels if >350 ng/ml</td>
<td>Placebo

N=10

Placebo for 4 weeks, then switched to ciclosporin 14mg/kg/day open-label</td>
<td>4 weeks (double-blinded)</td>
<td>1° outcome:

Clear/almost clear

2° and other outcomes:

Global severity scale

Improvement

AEs

Renal function

Blood pressure changes</td>
<td>Babcock Dermatologic Endowment</td>
</tr>
</table>

	Open-label crossover after 4 weeks. Allocation concealment: not stated Sample size calculation: Not stated ITT: Yes		<table><tr><td>Age</td><td>36 yrs</td><td>36 yrs</td></tr><tr><td>Sex: M/F</td><td>9/2</td><td>7/3</td></tr></table> Other baseline characteristics not detailed				LFTs	

Clear

	CSA (n=11)	Placebo (n=10)
Clear	2	0

Hypertension

	CSA (n=11)	Placebo (n=10)
Hypertension (DBP >90 mmHg or SBP >150 mmHg)	7	7

No withdrawals due to adverse events

No withdrawals due to deranged lab values

Number of patients with creatinine above normal range in ciclosporin group: at baseline 1, at end of therapy 4, 2 weeks after end of therapy 0

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
H. Meffert, M. Brautigam, L. Farber, G. Weidinger. Low-dose (1.25 mg/kg) cyclosporin A: treatment of psoriasis and investigation of the influence on lipid profile. Acta Derm Venereol (Stockh). 77:137-141.1997 Ref ID: MEFFERT1997	RCT Multi-centre Germany Randomised: method not stated Blinding: Double-blind Allocation concealment: not stated Sample size calculation: not stated ITT analysis:	Total N=133 Drop-outs (don't complete the study): 6	**Inclusion criteria:** Patients 18-70 years with psoriasis vulgaris with an indication for systemic therapy, starting PSI score of 8-25 (mean 16) **Exclusion criteria:** Creatinine > 10% above upper limit of normal, cholesterol >350 mg/dl, bilirubin and liver enzymes >150% of upper lab normal value, hyperkalaemia, hyperuricaemia, hypertension (DBP >95 mmHg), leucopaenia, thrombocytopaenia, concomitant therapy with potentially nephrotoxic drugs Drug-induced psoriasis, erythrodermia, Rx with MTX, retinoids, PUVA or CSA in 4 weeks prior, specific topical Rx in previous week	**Ciclosporin** N= 85 Period 1 CSA 1.25 mg/kg/day PO (n=41) or CSA 2.50 mg/kg/day PO (n=44) Period 2 Dose inc. up to 5 mg/kg/day PO if inc. in PASI >50%	**Placebo** N=43 In period 2 patients given CSA 2.5 mg/kg/day inc. to 5 mg/kg/day if PASI reduction <10% in week 13, or <30% in week 16	10 weeks Period 1 10 weeks (DB phase) Period 2 12 week open label study Period 3 4 week no treatment follow-up period Total 26 weeks	**1° outcome:** PASI change **2° and other outcomes:** Adverse events	Not stated

	No		Pregnant/breastfeeding women **Note:** 85 men, 48 women Mean age 38.2±11.6 years No significant difference between groups with respect to age, sex, BMI, severity of psoriasis					

Effect Size

PASI scores

	Placebo (n=39)		**CSA 1.25 mg/kg (n=40)**		**CSA 2.5 mg/kg (n=41)**	
	Mean	SD	Mean	SD	Mean	SD
Baseline	15.6	5.1	16.7	5.7	15.1	5.0
% change						
1 week	-3.2	6.5	-4.3	9.8	-10.2	15.3

3 weeks	-7.3	19.2	-11.7	22.3	-22.9	26.3
6 weeks	-11.0	28	-22.1	29.0	-39.3	28.8
10 weeks	**-5.9**	**36.1**	**-27.2**	**34.6**	**-51.0**	**30.9**
End of period 1	14.9	7.9	11.8	6.8	7.6	6.2
PASI75	2/43		4/41		12/44	

Creatinine

11/133 patients serum creatinine increased by 30% or more from baseline on at least 1 occasion

No discontinuations due to renal side effects

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>T.H. van Joost, J.D. Bos, F. Huele, M.M.H.M. Meinardi. Low-dose cyclosporin A in severe psoriasis. A double-blind study. Br J Dermatol. 118:183-190. 1988

REF ID: VANTOOST1988A

Data also reported in:

F. Huele, M.M.H.M. Meinardi, T. van Joost, J.D. Bos. Low-dose cyclosporine effective in severe psoriasis: A double-blind study.</td>
<td>RCT

Two centre, Netherlands

Randomisation: ‘Randomly treated’, no further information

Blinding:

Double-blind

Allocation concealment:

Not</td>
<td>Total N=20

Drop-outs (don’t complete the study): None during 4 weeks</td>
<td>Inclusion criteria:
Chronic plaque psoriasis of a progressive character over more than 10 years, no effect from conventional therapy. Starting PASI score of 20 or above.

Active antipsoriatic treatment (MTX, retinoids, PUVA) stopped four weeks prior, topically applied agents (two weeks)

Exclusion criteria:

Pregnancy or acutre uncontrolled infections, impaired renal function with a serum creatinine >100 umol/L, bilibrubin or liver enzymes >2 x upper limit of normal, uncontrolled HTN, epilepsy, malabsorption syndrome, past or present malignancies, pharmacokinetic interactions

Baseline characteristics:
<table>
<tr><td></td><td>CSA</td><td>Placebo</td></tr>
<tr><td>Mean age</td><td>54.6 yrs</td><td>45.6 yrs</td></tr>
</table>
</td>
<td>Ciclosporin

N=10

Divided doses

Phase 1 –

Dosing by body weight:

≤59 kg: 300 mg

60-80 kg: 400 mg

>80 kg: 500 mg

CSA dose reduced by 1 ml if: rise in serum creatinine >50% above baseline, rise</td>
<td>Placebo

N=10

Partial crossover:

Placebo patients switched to CSA in open-label outpatient trial</td>
<td>4 weeks (for this comparison)

(24 weeks

in total 12 weeks treatment + post-treatment observation for 12 weeks)</td>
<td>1° outcome:
PASI

2° and other outcomes:

Relapse: increase in PASI ≥50% baseline score

AEs</td>
<td></td>
</tr>
</table>

Transplantation Proceedings. 20(3):32-41. 1988 Ref ID: HEULE1988	mentioned Sample size calculation: Not performed ITT:		<table><tr><td>Sex – M/F</td><td>8/2</td><td>5/5</td></tr><tr><td>Mean weight</td><td>70.2 kg</td><td>72.6 kg</td></tr><tr><td>Mean duration of disease, yr</td><td>27.2</td><td>22.7</td></tr></table>	in potassium, raise in LFTs, hypertension unresponsive to treatment, or CSA trough levels >900 ng/ml Dose reduced by 1 ml (100 mg) if increase in creatinine, potassium, LFTs, hypertension unresponsive to therapy, or whole blood CSA trough levels >900 ng/ml Phase 2 – patients who responded with >50% improvement after 4				

				weeks continued for another 2 months (5-12 weeks) – double-blinded, doses tapered. If relapse during tapering test med stopped Phase 3 Post-treatment observation period for 12 weeks				

Effect Size

PASI

	CSA (n=10)	Placebo (n=10)
Mean PASI score at baseline	36.5	30.0
Mean PASI score at 4 weeks	9.6	29.1

Mean PASI score at 12 weeks (responders, n=9)	6.9	n/a
Mean % reduction in PASI core at week 4	72%	3% (P<0.001)
Mean % reduction in PASI score at week 12 (responders, n=9)	82%	n/a
PASI50 at week 4	9	0

No withdrawals due to adverse events

No dose reductions due to clinical or biochemical side-effects

Hypertension

Mild hypertension in 5 patients/18 receiving CSA

Creatinine

Non-significant increase in creatinine in placebo versus CSA (P=0.08)

Slight increase in creatinine in 7 patients (< 40% above respective individual baselines), returned to normal in all patients on stopping CSA

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
L. Guenther, D.M. Wexler. Inducing remission of severe psoriasis with low-dose cyclosporin A. *Canad. J. Dermatol.* 163-167. 1991 REF ID: GUENTHER1991	RCT Multicentre, Canada Randomisation: Method not stated Blinding: Double-blinded Allocation concealment: No Sample size calculation: Not stated	N=23 9 drop-outs (1 in CSA group due to concomitant therapy and 8 in placebo group due to treatment failure)	**Inclusion criteria** Patients with extensive and disabling large plaque psoriasis involving ≥25% BSA and a PASI ≥12. Washout period: no systemic, intralesional, or UV therapy for at least 3 weeks, no topical therapy at least 1 week prior **Exclusion criteria** Patients with hepatic or renal impairment, or patients with DBP >95 mmHg Comparable baseline demographics: CSA group slightly older	**Ciclosporin** N=12 2.5 mg/kg/day in divided doses Increased at week 2 to 5 mg/kg/day Dose adjusted if trough levels outside range: 50-275 ng/ml	**Placebo** N=11	10 weeks	**1º outcome** PASI 50 **2º outcomes** Pruritus AEs	

	ITT: Modified ITT		than placebo group (42.5 years vs. 37 years).					

Effect Size

PASI 50 (Mod ITT)

	CSA (n=12)	**Placebo (n=11)**
Number of patients achieving PASI 50 at week 4	**9**	**0**
Number of patients achieving PASI 50 at week 6	**11**	**0**
Number of patients achieving PASI 50 at week 10	**11**	**1**

Stated no alteration in kidney function or hepatic function

Increased BP in 2 patients (CSA) and 1 patients (placebo)

H.11.5 INDUCTION OF REMISSION

H.11.5.1 Ciclosporin dose-finding studies

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Christophers E et al. Cyclosporine in psoriasis: a multicenter dose-finding study in severe plaque psoriasis. J Am Acad Dermatol 1992; 26: 86-90. Ref ID CHRISTOPHERS1992	**RCT** **Randomisation:** not stated **Allocation concealment:** not stated **Blinding:** no **Sample size calculation:** not stated	285 randomised; this paper reports on 217 patient who had completed study (but some patients re-entered the study more than once at different dosage so n's in table 1 for example add up to more than 285, while	**Inclusion:** 18-70 years; severe generalised chronic plaque psoriasis; Psoriasis Area Severity Index (PASI) at least 15. **Exclusion:** treatment with methotrexate, retinoids, glucocorticoids or PUVA in last 2 weeks; treated with compounds	Ciclosporin 1.25mg/kg/day (n=109 excluding drop-outs and those still in trial). After 2 weeks, patients with a reduction of >10% of baseline PASI, and after 6 weeks reduction of >30%, continued with unchanged dose until week 12. Patients not	Ciclosporin 2.5mg/kg/day (n=108 excluding drop-outs and those still in trial). After 2 weeks, patients with a reduction of >10% of baseline PASI, and after 6 weeks reduction of >30%, continued with unchanged dose until week 12. Patients not	12-36 weeks	"Success" = PASI declined by >75% of baseline (i.e. to <25% of baseline) or to below 8. Severity of lesions: erythema, infiltration and desquamation rated (0=complete absence, 4=most severe involvement). Involvement	Sandoz AG

	ITT analysis: no; patients moved between dosage groups and not all patients analysed (only completers, some still in trial) **Drop outs:** 18/109 on 1.25mg/kg/day dropped out (2 adverse events, 1 concomitant disease, 5 noncompliance, 9 lack of efficacy, 1 other). Unclear how many dropped out of 2.5mg/kg/day initial randomisation group as data presented for drop-outs while on 2.5mg/kg/day (i.e. from the initial 2.5 mg/kg/day group or those in initial 1.25mg/kg/day group who had had dosage increased; 32 dropped out: 6 adverse events, 1 concomitant disease, 8 noncompliance, 14 lack of efficacy, 3 other) and	outcomes are not given for all patients as some still in the trial)	known to interact with ciclosporin metabolism; pregnant or nursing women; impaired renal or liver function; infectious or neurological disorders; history of malignancy; alcohol abuse. **Baseline characteristics:** Ciclosporin 1.25mg/kg/day : 29 female, 80 male; Ciclosporin 2.5mg/kg/day: 28 female, 80 male. Mean age of both groups 42 years. No other details given.	achieving a reduction of >10% of baseline PASI at 2 weeks or reduction of >30% after 6 weeks re-entered study at double dose. Patients whose PASI declined by >75% of baseline (i.e. to <25% of baseline) or to below 8 = success; if not, re-entered study at double dose. Dose halved if 1) increase in serum creatinine >30%; 2) increase of serum potassium above upper limit of normal; 3) increase in serum total bilirubin or	achieving a reduction of >10% of baseline PASI at 2 weeks or reduction of >30% after 6 weeks re-entered study at double dose. Patients on 5mg/kg/day who failed to show these reductions were withdrawn from study. Dose halved if 1) increase in serum creatinine >30%; 2) increase of serum potassium above upper limit of normal; 3) increase in serum total bilirubin or liver enzymes of >100% above baseline		of nails (4-point scale), severity of arthropathy (intensity of inflammation, pain, swelling and impairment of daily activities each on a 4-point scale), pruritis (4-point scale). Laboratory values.	

	while on 5mg/kg/day (i.e. from initial 1.25mg/kg/day group who had had 2 dose increases or from initial 2.5mg/kg/day group who had had 1 dose increase; 11 dropped out: 1 adverse events, 1 concomitant disease, 1 noncompliance, 7 lack of efficacy, 1 other).			liver enzymes of >100% above baseline or above three-fold upper limit of normal, or 4) ciclosporin trough level >250ng.mL on 2 consecutive measurements .	or above three-fold upper limit of normal, or 4) ciclosporin trough level >250ng.mL on 2 consecutive measurements .			

Effect size

	Initial dose 1.25mg/kg/day (n=109)				**Initial dose 2.5mg/kg/day (n=108)**		
	Stayed on 1.25mg/kg/day	Increased to 2.5mg/kg/day	Increased again to 5mg/kg/day	Total number of responders in the 1.25mg/kg/day randomisation group	Stayed on 2.5mg/kg/day	Increased to 5mg/kg/day	Total number of responders in the 2.5mg/kg/day randomisation group
Number of responders	19 (18%)	27 (25%)	22 (20%)	68 (62%)	60 (56%)	18 (17%)	78 (72%)

In all other analyses, the patient groups were combined into a) 1.25mg/kg/day; 2) 2.5mg/kg/day and 3) 5mg/kg/day, i.e. the doses that the patients ended up on, not the groups of randomisation. Outcomes were given as percentages but the denominators were sometimes unclear due to patients

moving between dosage groups.

	Patients on 1.25mg/kg/day (n=109)*	Patients on 2.5mg/kg/day (n=183)*	Patients on 5mg/kg/day (n=60)*
Decrease in pruritis score at end of treatment	27.8%	61%	42.8%
Percentage of patients with creatinine level >130micromol/L (none discontinued treatment)	1%	5%	13%
Number of patients in whom dose of ciclosporin reduced because of increased serum creatinine	1	2	2
Blood urea nitrogen >8.3mmol/L	4%	13%	18%
Uric acid >400micromol/L	19%	28%	43%
Cholesterol>6.7mmol/L	12%	21%	25%
Triglyceride >2.0mmol/L	20%	40%	53%
Serum glutamic-oxaloacetic transaminase (SGOT=Aspartate transaminase [AST]) >20U/L	11%	15%	33%
Bilrubin level >17 micromol/L	8%	20%	31%
Alkaline phosphatise >180U/L	11%	13%	20%
Blood pressure >160mmHg systolic and/or >95mmHg diastolic on two consecutive visits	11%	21%	26%
Adverse events (%)	10%	20%	32%
Gastrointestinal (n)	4†	8	3
Common cold	1	7†	2

Viral infections	2	3	1
Headache	0	1	3†
Tremor	2	1	1
Fatigue	0	2	1
Gingival hyperplasia	1	1	1
Oedema of lower limbs	0	3	0
Hypertrichosis	1	1	1
Parasesthesia	0	2	0
Also single reports of the following adverse effects but not stated which group the patient was in: photoallergic eczema, haematuria†, swelling of lymph nodes†, alopecia, diabetes mellitus†, arthralgia†, squamous cell carcinoma†, lumbago† and extrasystoles†.			
† = the drug was withdrawn because of the side effect.			

* NB numbers of patients add up to more than the number originally randomised because patients moved between groups and some were therefore counted more than once

Author's conclusion

- We recommend 2.5mg/kg/day as the initial dosage for treatment of severe psoriasis; in case of insufficient response this can be increased to 5mg/kg/day.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
C. Laburte, R. Grossman, J. Abi-Rached, K.H. Abeywickrama, L. Dubertret. Efficacy and safety of oral cyclosporine A (CyA; Sandimmun) for long-term treatment of chronic severe plaque psoriasis. *Br J Dermatol*.130:366-375. 1994 REF ID: LABURTE1994	RCT Three-part multinational multicentre study Part 1: induction – open, randomised 2.5 vs. 5 for 3 months 2.5 mg non-responders switched to 5 mg. Part 2: Pts achieving remission entered open 12 month maintenance	N=251 Drop-outs: 88 patients discontinued Rx at end of Part II 163 patients treated for 16-22 months	**Inclusion criteria** Patients with severe chronic plaque psoriasis (PASI ≥18) resistant to topical therapy and requiring systemic treatment. 2 week washout period for systemic Rx and 1 week washout period for topical Rx **Exclusions** Patients with 'abnormal screening lab values', patients with serum creatinine > 100 µol/L, patients with pre-existing hypertension or hx of malignancy, concomitant Rx with nephrotoxic medications **Baseline characteristics:** Differences in mean body weight 2.5 mg (n=119) 5 mg (n=132)	N=119 CSA 2.5 mg/kg/day Induction and maintenance Maintenance Responders: 62 pts exposed to mean dosage of 2.7 mg/kg/day for mean 12.2 months Non-	N=132 CSA 5 mg/kg/day Maintenance 132 pts exposed to mean dose of 4.0 mg/kg/day for mean duration of 11.3 months	12 weeks (part 1 – open, randomised phase) 21 months in total	PASI - ≥75% reduction of baseline PASI, or PASI ≤8 at week 12 Overall assessment of efficacy 5-point scale Simple severity scoring system (0-4) used Relapse defined as increase in PASI ≥50% of baseline	Sandoz Pharma

<table>
<tr>
<td></td>
<td>study at 2.5 mg or 5 mg (tapering over 3 months to 2.5 mg) inc. to 5 mg if relapse. Dose tapered in last 3 months in all pts.

Part III

3 month post-treatment observation period (inc.pts who discontinued)

Randomisation:

Method not stated

Blinding:

Open

Allocation concealment:</td>
<td></td>
<td>
<table>
<tr><td>Age</td><td>42.0±12.6</td><td>40.7±12.3</td></tr>
<tr><td>Weight</td><td>77.4±15.5</td><td>72.9±13.4</td></tr>
<tr><td>%Male</td><td>72%</td><td>68%</td></tr>
<tr><td>Disease duration, years</td><td>18.4±11.0</td><td>17.7±11.1</td></tr>
<tr><td>Baseline PASI</td><td>24.9±7.0</td><td>25.1±8.0</td></tr>
<tr><td colspan="3">Previous treatment %</td></tr>
<tr><td>MTX</td><td>32%</td><td>28%</td></tr>
<tr><td>Retinoids</td><td>58%</td><td>54%</td></tr>
<tr><td>PUVA</td><td>73%</td><td>67%</td></tr>
</table>
</td>
<td>responders:

57 pts exposed to mean dose of 3.7 mg/kg/day for mean duration 11.2 months</td>
<td></td>
<td></td>
<td>Safety</td>
<td></td>
</tr>
</table>

	no Sample size calculation: not stated ITT: No							

Effect Size

Induction of remission

	2.5 mg group (n=119)	**5 mg group (n=132)**	**P-value**
Mean reduction in PASI score, %	69%	89%	0.0001
Success (PASI 75 or a PASI score ≤8)	57 patients	117 patients	0.001
Median time to first success	3 months	6 weeks	

Maintenance of remission – Mean PASI score

	2.5 mg group	**5 mg group**	**2.5 mg non-responders**
Beginning of maintenance	4.2 (n=52)	3.6 (n=116)	3.9 (n=41)
End of maintenance	5.9 (n=40)	6.3 (n=79)	8.3 (n=25)

Safety

	2.5 mg group	**5 mg group**
Serious adverse events related to CSA Rx	2	17
Development of hypertension (DBP ≥95 mmHg on two consecutive visits)	17 patients	20 patients
High uric acid level (≥625 µmol/l in males, ≥506 µol/l in females)	5	8

Hypertension

Hypertension developed in 41 patients during treatment with CSA: 17 patients in 2.5 mg group, 20 in 5 mg group, 4 receiving a mean dose of 3.6 mg

50 patients received antihypertensive therapy

10 CSA discontinuations due to hypertension

Creatinine

Maximum % increase in creatinine above baseline by month 12: 10% (2.5 mg group), 14% (5 mg group)

Increase in serum creatinine >30% above baseline seen at least once in:

22% of patients (2.5 mg group): decreasing to 2 patients (3%) having persistently raised creatinine 3 months after discontinuation of CSA

55% of patients (5 mg group): decreasing to 9 patients (9%) having persistently raised creatinine 3 months after discontinuation of CSA

Discontinuation due to raised serum creatinine in 24 patients (10%)

Withdrawal due to AEs: 16 patients

H.11.6 MAINTENANCE OF REMISSION

H.11.6.1 Ciclosporin regimens: continuous vs intermittent

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>A. Ozawa, J. Sugai, M. Ohkido, M. Ohtsuki, H. Nakagawa, H. Kitahara, K. Tamaki, K. Urabe, J. Nakayama, T. Horikoshi, Y. Morimoto, and K. Jimbow. Cyclosporin in psoriasis: continuous monotherapy versus intermittent long-term therapy. Eur.J.Dermat</td>
<td>RCT

Multicentre (4 medical school hospitals in Japan)

• Randomised (envelope method)
• Washout period: 2 months for MTX, retinoid or PUVA
• Blinding (not stated)
• Allocation</td>
<td>Total N: 94

Drop-outs (don't complete the study): 29

Note: data from all 94 analysed for adverse reactions

Continuous (n=16): 1 AEs; 2 aggravation of complications; 3 lost to follow-up; 1 change of location; 1 relapse; 8 remission</td>
<td>Inclusion criteria: psoriasis vulgaris with PASI >20; psoriatic arthritis; generalised pustular psoriasis; erythrodermic psoriasis

Exclusion criteria: treated with MTX, retinoid or PUVA within the past 2 months; use of drug with renal toxicity; hypertension (BP>95/160); acute or chronic bacterial or viral infections; malignant tumours; severe hepatic function abnormality; pregnant women

<table>
<tr><th>Mean baseline</th><th>Continous CSA (N=17)</th><th>Intermittant CSA (N= 20)</th></tr>
<tr><td>PASI mean ±</td><td>29.9 ± 2.19</td><td>35.08 ± 3.54</td></tr>
</table>
</td>
<td>N=50

Continuous CSA

Initial dose 3-5 mg/kg/day

After remission: reduced by 0.5-1.0 mg/kg/day every week

Maintenance</td>
<td>N=44

Intermittent CSA

Initial dose 3-5 mg/kg/day

After remission: dose reduced by 0.5 -1.0 mg/kg/day every other week followed by</td>
<td>48 months

Remission = a decrease in PASI by 80% from baseline

Relapse = an increase in PASI by 50% from baseline</td>
<td>1° outcome: Change in PASI; time-to-remission; time-to relapse

2° and other outcomes: AEs, laboratory tests: blood pressure, peripheral blood counts, serological tests (GOT, GPT, gamma-</td>
<td>None stated</td>
</tr>
</table>

<table>
<tr>
<td>*ol.* 9 (3):218-223, 1999.

Ref ID: OZAWA1999</td>
<td>concealment (not stated)
• Sample size calculation not stated
• ITT analysis not performed
• Drop-outs/withdrawals due to AEs: 1 in continuous; 2 in intermittent</td>
<td>Intermittent (n=13): 2 AEs; 2 change of location; 4 relapse; 5 remission</td>
<td>
<table>
<tr><td>SD</td><td></td><td></td></tr>
<tr><td colspan="3">Type of psoriasis in the full sample (n=94)</td></tr>
<tr><td>Psoriasis vulgaris (n)</td><td colspan="2">85</td></tr>
<tr><td>Psoriatic arthritis (n)</td><td colspan="2">4</td></tr>
<tr><td>Generalised pustular psoriasis (n)</td><td colspan="2">2</td></tr>
<tr><td>Erythrodermic psoriasis (n)</td><td colspan="2">3</td></tr>
</table>
</td>
<td>treatment continued at a dose ranging from 0.5 to 3 mg/kg/day at as low a dose as possible

If a relapse was noted, the dose was increased to 3 to 5 mg/kg/day until remission was achieved, and the same procedure was repeated.</td>
<td>withdrawal.

During withdrawal period, topical steroids (10 g/day or less) of strong or medium class were applied to the lesion.

If any relapse was noted, the dose was increased to 3-5 mg/kg/day until remission was achieved.

Oral ciclosporine was withdrawn</td>
<td></td>
<td>GTP, creatinine, BUN, uric acid, Na, K, Cl, Mg, glucose, total cholesterol and triglyceride), qualitative urinalysis, and serum ciclosporine trough level</td>
<td></td>
</tr>
</table>

					on remission and the treatment depended on topical steroids only.			

Effect Size

Outcomes

Dose

The mean daily dose was 3.20 ± 0.21 mg/kg/day in the continuous monotherapy group and 3.06 ± 0.21 mg/kg/day in the intermittent therapy group. There was no significant difference between the groups.

Efficacy

- Remission was not observed in one patient in the continuous group and four patients in the intermittent therapy group

Outcomes	**Continuous CSA (N=17)**	**Intermittent CSA (N= 20)**	**p-value**
Baseline PASI; mean ± SD	29.9 ± 2.19	35.08 ± 3.54	
48 month PASI; mean ± SD	9.93 ± 1.79	9.96 ± 2.12	

48 month mean PASI improvement rate ± SD	61.96 ± 4.80%	71.16 ± 5.27%	NS
Time to remission			
Mean time to first remission (months)	4.7 (n=16)	3.0 (n=16)	
Mean time to second remission after relapse (months)	4.4 (n=4)	6 (n=13)	
Mean time to third remission after relapse (months)	-	7 (n=6)	
Mean time to fourth remission after relapse (months)	-	12 (n=2)	
Mean time to fifth remission after relapse (months)	4.4 (n=2)		
Time to relapse			
Mean time to first relapse (months)	20±4.2 (n=11)	10 (n=15)	
Mean time to relapse after second remission (months)	13.4±4.3 (n=6)	8 (n=8)	
Mean time to relapse after second remission (months)	11.95 (n=1)	3.0 (n=6)	

Safety

No difference in incidence between the 2 groups

Symptom	Full sample (n=94)
BUN	17
Creatinine	9
Hypertension	21
Infection	29

Author's summary

- The PASI score evaluated at each visit was maintained between 5 and 10 by both treatment methods and the improvement rate was more than 70%, while there was no difference in the daily dose between the two treatment methods
- The period required to achieve remission tended to be prolonged by intermittent therapy, while no change was observed with continuous monotherapy
- The period up to relapse tended to become shorter with both treatment methods but this tendency was more marked with intermittent therapy
- E-PAP(evaluation for prognosis with averaged PASI) was lower in the continuous monotherapy group and the patients were more satisfied
- The incidence of adverse reactions was similar to that reported in previous studies, with no difference between the two treatment methods in this regard
- A significant increase in BUN levels was observed in elderly patients
- There were only three cases in which the drug was discontinued due to exacerbation and adverse reactions.
- Based on the above findings, continuous monotherapy seems to be of greater clinical usefulness than intermittent therapy.

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>Ohtsuki M et al. Long-term continuous versus intermittent cyclosporine: therapy for psoriasis. J Dermatol 2003; 30: 290-298.

Ref ID OHTSUKI2003</td>
<td>RCT

Randomisation: “by the envelope method”

Allocation concealment: see above

Blinding:
no

Sample size calculation: not stated

ITT analysis: not stated.</td>
<td>122 recruited (111 psoriasis vulgaris, 5 psoriatic arthropathy, 3 generalised pustular psoriasis, 3 psoriatic erythroderma)</td>
<td>Inclusion: PASI score >20 and meeting eligibility criteria specified in the Japanese Guidelines for Ciclosporin Therapy in Psoriasis

Exclusion: Treatment with methotrexate, retinoids or PUVA in previous 2 months; absolute need for concomitant therapy with any nephrotoxic drug; hypertension (BP ≥160/95mmHg); acute or chronic active bacterial or viral infection; malignancy; severe hepatic dysfunction; pregnancy

<table>
<tr><th>Baseline</th><th>Intermittent (N=61)</th><th>Continuous (N=61)</th></tr>
<tr><td>PASI mean (range)</td><td>35.54 (13.6)</td><td>29.17 (10.6)</td></tr>
</table>

Groups reported to be similar also</td>
<td>n=61

Intermittent ciclosporin 3-5mg/kg/day; once remission (decrease of PASI score by at least 80% from baseline) achieved, dose reduced by 0.5-1mg/kg/day every 2 weeks until tapered off. While ciclosporin being withdrawn, topical application of “strong” or less</td>
<td>n=61
Continuous ciclosporin 3-5mg/kg/day; once remission (decrease of PASI score by at least 80% from baseline) achieved, dose reduced by 0.5-1mg/kg/day every 2 weeks until lowest dose that could maintain remission reached (range 0.5-3mg/kg/day). If relapse (return to</td>
<td>Planned for 5 years; only 25% of patients followed for >48 months; this paper reports these patients followed >48 months (mean follow up for these patients 55.9 SD 4.6 months</td>
<td>PASI score, itching, pustules, articular symptoms, local/systemic adverse events; routine laboratory tests; trough ciclosporin level; blood pressure; mean ciclosporin dose; Evaluation for Prognosis with Averaged PASI [E-PAP] score calculated by dividing the PASI score versus</td>
<td>not stated</td>
</tr>
</table>

	Paper states that "most of the patients in the intermittent group suffered from recurrence of psoriasis soon after withdrawal of ciclosporin; ciclosporin was resumed in the patients who violated the study protocol at their strong request before the PASI score returned to ≥50% of baseline, especially after the second relapse" i.e. many patients restarted ciclosporin earlier than in the protocol (so regimen		with respect to sex ratio, age, diagnosis and concomitant illness.	potent corticosteroids allowed. If relapse (return to 50% or more of baseline PASI), ciclosporin restarted and dose escalated to 3-5mg/kg/day until remission obtained again. Ciclosporin dose reduced if serum creatinine increased by 30% or more from baseline. Mean daily dose 2.78 (0.26) mg/kg/day	50% or more of baseline PASI), dose gradually escalated to 3-5mg/kg/day until remission obtained again. Ciclosporin dose reduced if serum creatinine increased by 30% or more from baseline. Mean daily dose 3.24 (0.27) mg/kg/day	)	time curve integrated over follow up period divided by time period (i.e. average severity of psoriasis during treatment).	

	more like the continuous treatment than planned) **Drop outs:** 53 failed to revisit or changed hospital; 14 had sustained remission; 11 had adverse events or exacerbation of complications (of whom **4 withdrawn due to adverse reactions** – 1 back pain, 1 hyperuricaemia, 1 gum hyperplasia, 1 increase in blood urea nitrogen and serum creatinine); 6 changed therapy because of							

	relapse; 3 changed therapy because of **lack of efficacy**; 3 withdrew consent; 1 withdrawn for other reasons, i.e. **75% drop out.**							

Effect size

	Intermittent ciclosporin (n=16)		Continuous ciclosporin (n=15)		p value
Mean PASI score at 54 months	9.59 (2.22)		6.03 (0.95)		NS
Adverse events:	Total over 5 years N=18	Total at 1 year N=61	Total over 5 years	Total at 1 year N=19	NS

increase in blood urea nitrogen (BUN) hypertension increase in serum creatinine hyperuricaemia hyperlipidaemia bilirubinaemia ALP increased hyperglycaemia **gastric cancer** **hepatocellular carcinoma**	23 **19** **15** **16** **11** 9 **7** 5 1 1	5 10 3 6 1 4 3 0	26 **17** **15** **13** **8** 0 **1** 2 0 0	4 6 2 3 3 0 0 1		

Author's conclusion

The intermittent and continuous regimens were found to be equally effective for the long-term management of psoriasis, with a slightly better response obtained with continuous therapy, but malignancy developed in 2 patients on continuous therapy. Our conclusions may have been influenced by the inclusion of patients with good tolerance and better follow up (i.e. acknowledging potential bias due to large loss to follow up).

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>Chaidemenos GC et al. Intermittent vs. continuous 1-year cyclosporine use in chronic plaque psoriasis. JEADV 2007; 21: 1203-8.

Ref ID: CHAIDEMONAS2007</td>
<td>RCT

Single centre (Greece)

Randomisation: Quasi-randomised (alternate allocation)

Allocation concealment: inadequate

Blinding:
no

Sample size calculation:</td>
<td>51 enrolled in induction phase; 3 patients non-compliant in induction phase so excluded from entry into maintenance phase; 3 did not achieve 50% reduction in PASI from baseline during induction phase so not eligible for randomised maintenance phase.</td>
<td>Inclusion: over 18 years; moderate to severe chronic plaque psoriasis (CPP) i.e. PASI 8 or more; insufficient response to topical (corticosteroids, calcipotriol and dithranol) and/or UVB therapy; effective contraception for women of child-bearing potential; stop other treatment for 3 weeks (apart from emollients); 1st phase of study – all patients received ciclosporin 2.5-2.7mg/kg daily, increased to a maximum of 5mg/kg/day if <30% response in 1st 3 weeks; had to achieve >50% reduction in PASI from baseline to enter maintenance phase

Exclusion: history of malignancy, abnormal renal and liver function

<table>
<tr><th>Baseline at start of induction phase for the participants going on to maintenance phase</th><th>A
(N=21)</th><th>B
(N=24)</th></tr>
</table>
</td>
<td>N=21

Intermittent ciclosporin for maintenance (Group A); i.e. abruptly stopped ciclosporin after induction, then received additional 12-week course “when investigator and patient considered that their disease had deteriorated adequately</td>
<td>N=24

Continuous ciclosporin for maintenance (Group B); i.e. dose tapered by 0.5mg/kg/day bi-monthly down to maintenance level, i.e. the dose considered marginally effective for that individual i.e. not a standard regimen for all patients</td>
<td>9 months maintenance phase (after achieving >50% reduction in PASI from baseline in induction phase of 3 months)</td>
<td>PASI; endpoints were improvement by 50%, 75% and 90% from baseline and Dermatology Life Quality Index DLQI: at end of induction phase, 1 year, and prior to and after each repeat course of treatment</td>
<td>Not stated</td>
</tr>
</table>

	none reported **ITT analysis:** yes **Drop outs:** 3 patients non-compliant in induction phase so excluded from entry into maintenance phase; 3 did not achieve 50% reduction in PASI from baseline during induction phase so not eligible for randomised maintenance phase. **No drop-outs reported in**		<table><tr><td>Age (years), mean (range)</td><td>40 (18-73)</td><td>51 (18-75)</td></tr><tr><td>Gender M/F</td><td>15 (62.5%)/ 9 (37.5%)</td><td>15 (50%)/ 12 (50%)</td></tr><tr><td>Duration of psoriasis (years) mean (range)</td><td>15 (15-40)</td><td>12 (1-41)</td></tr><tr><td>PASI median (range)</td><td>10.2 (8-35)</td><td>10.12 (8-47)</td></tr><tr><td>DLQI median (range)</td><td>9.5 (3-23)</td><td>9 (3-22)</td></tr></table>	in order for ciclosporin to be re-instituted" i.e. not objective criteria for re-treatment	Both arms received 2.5-2.7 mg/kg/day CSA for induction initially (up to a max of 5 mg/kg/day if PASI reduction <30%)		Relpase: further treatment required	

	maintenance phase							

Effect size

- **Improvement under ciclosporin therapy was significant at the end of the induction phase; PASI decreased by 77.8%, achieving a median value of 2.7 (range 0-25.5), p=0.003 from baseline; DLQI dropped by 89%, median 1 (range 0-14), p=0.002**

Treatment period	**Outcome**	**Overall**	**Group A (Intermittent ciclosporin)**	**Group B (Continuous ciclosporin)**	**p value**
12 weeks (i.e. end of induction phase when all patients treated with ciclosporin)	PASI 50	45/48 (94%)			
	PASI 75	31/48 (65%)			
	PASI 90	14/48 (29%)			
12 months (i.e. end of 9-month randomised maintenance phase)	PASI 50	43/45 (96%)	20/21 (95%)	23/24 (96%)	0.348
	PASI 75	35/45 (78%)	13/21 (62%)	22/24 (92%)	0.008
	PASI 90	18/45 (40%)	4/21 (19%)	14/24 (58%)	0.006
	DLQI median (range)	1 (0-9)			
	Median (range) maintenance dose (mg/kg/day)		3 (2.5-3.8)	1.8 (0.7-3)	

	Number of courses of intermittent ciclosporin given		1 course: 7/21 (33%) 2 courses: 9/21 (43%) 3 courses: 5/21 (24%)	NA	
	Mean (SD) PASI at relapse		59 (13%) of initial value	NA	
	Median PASI at relapse		62% (35-79%) of initial value (i.e. variability of disease severity perceived as “relapse”)	NA	
	Increase in serum creatinine to 30% above baseline value		2/21	2/24	
	Increase in blood pressure necessitating treatment adjustment (not stated what criteria of increase were)		0	1/24	
	Gingival hyperplasia		1/21	0	
	Gastrointestinal disturbance		0	1/24	

Author’s conclusion

- Despite the high efficacy and safety of continuous ciclosporin in the trial, these patients received 139% of the mean cumulative dose used for the intermittent schedule. Effectiveness and safety are known to be time- and dose-dependent, so although it appears that continuous dosing offers greater PASI improvement without compromise in tolerability, this option should be reserved for patients who do not respond to, or are uncooperative with, intermittent ciclosporin use.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
INTERMITTENT TREATMENT STUDY V.C. Ho, C.E.M. Griffiths, G. Albrecht, F. Vanaclocha, G. Leon-Dorantes, N. Atakan, S. Reitamo, A. Johannesson, N.J. Mork, P. Clarke, P. Pfister, C. Paul. Intermittent short courses of cyclosporine (Neoral) for psoriasis unresponsive to topical therapy: a 1-year multicentre, randomized study. *Br J Dermatol*. 141:283-291.1999 PISCES study REF ID: HO1999	RCT Multicentre Europe/N. America Randomised: After 12 weeks of treatment, method not stated Blinding: Open Allocation concealment: No	N=400, 365 eligible for randomisation at end of 1st treatment period Drop-outs: 39 (before randomisation)	**Inclusion criteria:** Patients 17-81 years with plaque psoriasis unresponsive to topical therapies Washout period: stopped systemic therapy 14 days prior to enrolment; 30 days for PUVA Topical therapy continued throughout **Exclusion criteria:** Abnormal renal function (serum creatinine above 10% of upper limit of ref range), abnormal liver function, hyperkalaemia or hyperuricaemia, received >12 weeks of systemic therapy with corticosteroids, immunomodulating or cytotoxic drugs or retinoids, history of malignancy, acute uncontrolled bacterial, viral or	Ciclosporin (Neoral): Abrupt cessation N=192 Ciclosporin 2.5 mg/kg/day titrated to max 5 mg/kg/day Treatment continued until clearance or for a maximum of 12 weeks Stop ciclosporin or abruptly	Ciclosporin (Neoral) Tapering dose N=173 Ciclosporin 2.5 mg/kg/day titrated to max 5 mg/kg/day. Treatment continued until clearance or for a maximum of 12 weeks Tapering	1 year	**1° outcome:** Time to relapse after first treatment period (Relpase: when investigator or patient deemed CSA should re-start or recurrence of psoriasis affecting ≥75% surface area) **2° and other outcomes:** %BSA Global	Novartis Pharma A.G.

<table>
<tr>
<td></td>
<td>Sample size calculation:

Not mentioned

ITT:

yes</td>
<td></td>
<td>fungal infection, uncontrolled hypertension, clinically significant impairment of haematopoietic, cardiovascular and/or cerebral function and concomitant therapy with nephrotoxic medications.

Baseline characteristics similar:
<table>
<tr><th></th><th>CSA Abrupt</th><th>CSA Tapered</th></tr>
<tr><td>Mean age</td><td>41 years</td><td>40 years</td></tr>
<tr><td>Mean weight</td><td>77 kg</td><td>77 kg</td></tr>
<tr><td>Psoriatic area %</td><td>24</td><td>25</td></tr>
<tr><td>Modified PASI</td><td>13</td><td>14</td></tr>
</table>
</td>
<td>On relapse patients given another course of ciclosporin

At end of treatment period, patients stop ciclosporin according to treatment plan specified at randomisation. Up to 4 treatment courses during the year</td>
<td>dose (1 mg/kg daily each week) until stopping within 4 weeks

On relapse patients given another course of ciclosporin

At end of treatment period, patients stop ciclosporin according to treatment plan specified at randomisation. Up to 4 treatment courses during the year</td>
<td></td>
<td>response

Modified PASI (0-54)

Time to relapse
Time to clinical response
Safety</td>
<td></td>
</tr>
</table>

Median time to relapse

	Abrupt stopping	**Tapered stopping**	**P-value**
After ciclosporin cessation (first treatment)	109 days	113 days	**0.04**
After second treatment	60 days	95 days	-
After third treatment	52	63	-

Median time to achieve satisfactory clinical response in 1st treatment period 68 days using a mean ±SD daily dose of 3.3 ± 1.1 mg/kg, 70 days after second period, 74 days after third period, 63 days after fourth period

Serious adverse events

15 events in 11 patients

Withdrawals due to adverse events

33 patients

3 patients withdrawn due to hypertension, 2 due to serum creatinine increase

Creatinine

% of patients with serum creatinine increase >30% from baseline =10% during first treatment period, 18% during second treatment period, 20% during third treatment period, 27% during fourth treatment period

32 patients 3 or more rises in serum creatinine of more than 30% above baseline in 1 year period

Number of patients with elevation of serum creatinine >30% above baseline during treatment = 120, off treatment = 37

New onset hypertension

45 patients (12%), one patient experience severe hypertension, initiation on antihypertensive medication in 21 patients (5%)

Dose reduction due to hypertension in 26 patients (7%)

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
V.C.Y. Ho, C.E.M. Griffiths, J. Berth-Jones, K.A. Papp, F. Vanaclocha, E. Dauden, A. Beard, L. Purvanarjan, C. Paul. Intermittent short courses of cyclosporine microemulsion for the long-term management of psoriasis: A 2-year cohort study. *J Am Acad Dermatol*. 44:643-51. 2001 REF ID: HO2001	RCT Multicentre, Europe and N. America Randomised: Method not stated Blinding: Open Allocation concealment: No Sample size calculation:	N=76	**Inclusion criteria** Patients with plaque psoriasis unresponsive to topical therapies and requiring systemic therapy Washout period: no systemic therapy within 2 weeks prior to entry/PUVA 4 weeks prior Exclusion History of >12 weeks systemic therapy with corticosteroids and immunomodulating or cytotoxic drugs or retinoids. Concomitant therapy with nephrotoxic drugs/pharmacokinetic interactors, history of malignancy, acute uncontrolled bacterial, viral or fungal infection, abnormal renal function/LFTs, hyperkalaemia, hyperuricaemia, clinically significant imapairment of haematopoietic, cardiovascular, and/or cerebral function, psychotic disorders or	Ciclosporin: Abrupt cessation N=46 Ciclosporin 2.5 mg/kg/day titrated to max 5 mg/kg/day (divided doses) Dosage reductions according to guidelines (rise in creatinine or hypertension) Treatment	Ciclosporin: Tapering dose N=30 Ciclosporin 2.5 mg/kg/day titrated to max 5 mg/kg/day. Dosage reductions according to guidelines (rise in creatinine or hypertension) Treatment continued until clearance or for a	2 years	Median time to relapse (Relpase: when investigator or patient deemed CSA should re-start or recurrence of psoriasis affecting ≥75% surface area) %BSA Global assessment Modified PASI (0-54: excludes	

<table>
<tr>
<td></td>
<td>Not stated

ITT:</td>
<td></td>
<td>mental instability

Similar baseline patient characteristics:
<table>
<tr><th></th><th>Abrupt</th><th>Tapered</th></tr>
<tr><td>Mean age</td><td>41.9</td><td>38.2</td></tr>
<tr><td>M/F ratio</td><td>24:22</td><td>17:13</td></tr>
<tr><td>Weight kg</td><td>77.9</td><td>78.7</td></tr>
<tr><td>Psoriasis duration</td><td>14.71 years</td><td>14.70 years</td></tr>
<tr><td>Psoriatic area %</td><td>16.05</td><td>17.87</td></tr>
</table></td>
<td>continued until clearance or for a maximum of 12 weeks

Stop ciclosporin or abruptly

On relapse patients given another course of ciclosporin

At end of treatment period, patients stop ciclosporin according to treatment plan specified at randomisation. Up to 8 treatment courses during the 2 years</td>
<td>maximum of 12 weeks

Tapering dose (1 mg/kg daily each week) until stopping within 4 weeks

On relapse patients given another course of ciclosporin

At end of treatment period, patients stop ciclosporin according to treatment plan specified at randomisation. Up to 8 treatment courses during the 2 years</td>
<td></td>
<td>head)

DLQI</td>
<td></td>
</tr>
</table>

Effect Size

Median time to relapse (days)

Relapse number	Abrupt	Tapered
1	115	119.5
2	87	104
3	64	112
4	59	110
5	58	62
6	45	63
7	34	56

DLQI

Overall reduction – data not reported for each group

Hypertension

18 patients had elevated blood pressure on 2 or more occasions. no patients experienced severe hypertension. Reduction in ciclosporin dose due to raised BP in 8 patients. 7 patients required initiation of antihypertensive therapy. No discontinuations due to hypertension.

%patients with increase in creatinine >30% & >50% baseline

18 patients had 3 or more rises in serum creatinine >30% above baseline. No discontinuations due to elevated serum creatinine. **8 serious adverse events reported (1 meningitis, 2 cataract, 2 requiring surgical intervention not related to study medication), 1 fever, 1 severe arthralgia.** **5 patients discontinued study due to adverse events**

H.11.7 MAINTENANCE OF REMISSION

H.11.7.1 Ciclosporin vs placebo

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
C.N. Ellis, M.S. Fradin, T.A. Hamilton, J.J Voorhees. Duration of remission during maintenance cyclosporine therapy for psoriasis. *Arch*	RCT USA Randomised: To three groups, method not stated	N=61 Drop-outs: 3	Inclusion criteria Follow-on maintenance study from ELLIS1991. Patients who had cleared/nearly cleared with induction CSA (3/5/7.5 mg/kg/day) continued on in low-dose CSA for maintenance. Comparable for baseline demographic characteristics: **CSA 1.5 mg** | **CSA 3 mg** | **Placebo**	**Ciclosporin (CSA)** **N=41** Group 1: 1.5 mg/kg/day (N=20) Group 2:	**Placebo** **N=20**	4 months However, patients removed from study earlier if relapse	**1° outcome:** Clear/nearly clear **2° and other outcomes:** PASI	Sandoz Research Institute, Babcock Dermatologic Endowment, Alumni of Univ. Of Michigan Dermatology Department, NIH grant

<table>
<tr>
<td>*Derrmatol*.131:791-795. 1995

REF ID: ELLIS1995</td>
<td>Blinding:

double-blinded, patients and investigators

Allocation concealment:

Not stated

Sample size calculation:

Not stated

ITT: modified</td>
<td></td>
<td>
<table>
<tr><td>Mean age</td><td>43 (19-74)</td><td>42 (22-65)</td><td>48 (21-64)</td></tr>
<tr><td>Sex – m/F</td><td>12/8</td><td>17/4</td><td>17/3</td></tr>
<tr><td>Mean PASI at end of Induction</td><td>2±0</td><td>2±0</td><td>2±0</td></tr>
<tr><td>Average daily dose during induction</td><td>4.3 mg/kg</td><td>4.4 mg/kg</td><td>3.9 mg/kg</td></tr>
</table>
</td>
<td>3 mg/kg/day (n=21)

No dose adjustment</td>
<td></td>
<td></td>
<td>Cumulative relapse rate

Creatinine

AEs</td>
<td></td>
</tr>
</table>

Relapse

	CSA 1.5 mg/kg (N=20)	**CSA 3 mg/kg (N=21)**	**Placebo (N=20)**
Relapse	14 patients	8 patients	18 patients
Mean time to relapse ±SE	9±1 weeks	12±1 weeks	7±1 weeks

Mean time to relapse ±SD	9±4.47 weeks	12±4.58 weeks	7±4.47 weeks

Stated no significant difference between CSA 1.5 mg group and placebo (P=.3), significant difference between CSA 1.5 mg and CSA 3 mg (P=0.04) and CSA 3 mg and placebo group (P=0.002)

PASI

Not reported

No severe adverse events

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Shupack J et al. Cyclosporine as maintenance therapy in patients with severe psoriasis. J Am Acad Dermatol 1997; 36: 423-32. Ref ID SHUPACK 1997	**RCT** **Randomisation:** Method not stated **Allocation concealment:** Not stated **Blinding:** yes double blind **Sample size calculation:** yes, minimum 36 patients needed to provide 80% power to detect therapeutically meaningful and statistically significant	181 enrolled in 16-week induction phase (ciclosporin 5mg/kg/day; increased to 6mg/kg/day if 25% clearing or more or exacerbation after 6 weeks at 5mg/kg/day; decreased in steps of 1mg/kg/day to minimum 3mg/kg/day if adverse event, abnormal laboratory value [high drug levels i.e. trough >600ng/mL or renal dysfunction	**Inclusion:** History of either extensive psoriasis (88% of patients) involving >25% of body surface area or disabling psoriasis (12% of patients) that impaired their ability to carry out daily activities; plus responded poorly or not appropriate for treatment with conventional therapy; achieving 70% reduction in involved body surface area for 2 weeks **Exclusion:** History of pustular or erythrodermic psoriasis; significant hepatic, renal or bone marrow disease; history of malignancy; concurrent use of other immunosuppressants; significant infection; clinically significant laboratory abnormalities including elevated serum creatinine or uncontrolled hypertension; systemic therapy for psoriasis within last 30 days; topical medications for psoriasis within 2 weeks; any previous therapy with ciclosporin.	Ciclosporin 3mg/kg/day (n=86) or 1.5mg/kg/day (n=7, randomisation to this arm discontinued when other data published suggesting this dose ineffective and higher dose used instead for people randomised to this group)	Placebo (n=49)	16 week induction phase + 24 week maintenance phase	% body surface area involved with psoriasis (relapse = the point at which BSA returned to 50% or more of baseline). Overall change compared with baseline (1=cleared through to 8=markedly worsened). Global evaluation (1=totally	Sandoz Research Institute

<table>
<tr>
<td></td>
<td>difference in relapse rates between groups (based on relapse rate of 60% with ciclosporin 3mg/kg/day and 95% for placebo

ITT analysis:

not stated

Drop outs:
13/181 discontinued in induction phase due to adverse event (includes 8 serious AE including 3 considered drug-related: hypertension, gout/fluid retention, diarrhoea), i.e. leaving 168 patients.

Other patients</td>
<td>i.e. serum creatinine 50% or more over baseline or absolute value >1.8mg/dL or liver dysfunction i.e. ASAT/ALAT increased by more than twice the upper normal limit or total bilirubin >2mg/dL] or increased blood pressure defined as “uncontrollable hypertension”); 142 entered maintenance phase</td>
<td>Baseline characteristics at beginning of induction phase:
<table>
<tr><th>Baseline</th><th>All (n=181)</th></tr>
<tr><td>Mean age</td><td>44.9 years (range 21-78)</td></tr>
<tr><td>Gender (M/F%)</td><td>85/15</td></tr>
<tr><td>Mean weight (kg)</td><td>85.9 (range 46.8-138.8)</td></tr>
<tr><td>Mean duration psoriasis (years)</td><td>17.5 (range 1.1-51.0)</td></tr>
<tr><td>Mean % BSA affected</td><td>42.3% (SD22.6%)</td></tr>
<tr><td>Mean PASI score</td><td>23.2 (SD 12.7)</td></tr>
<tr><td>Mean indicator lesion severity score</td><td>5.9 (SD 1.0)</td></tr>
<tr><td>Mean global evaluation score</td><td>6.1 (SD 1.0)</td></tr>
<tr><td colspan="2">Previous treatment with:</td></tr>
<tr><td>Photochemother</td><td>48%</td></tr>
</table></td>
<td></td>
<td></td>
<td></td>
<td>clear to 7=severe).

PASI (range 0-72; 18 or higher represents moderately severe to severe).

Severity of 3 selected indicator lesions for scaling erythema, pustules, thickness and overall severity (1=totally clear to 7=severe).</td>
<td></td>
</tr>
</table>

	were to be discontinued if they did not achieve 70% clearance by end of induction phase (number this applied to not stated) or presumably if they withdrew consent (not stated) – a further 26 patients withdrew for some reason (not stated) as only **142 entered maintenance phase**. **9**/86 on ciclosporin 3mg/kg/day dropped out of maintenance phase due to **adverse effects** (7 clearly related to study drug i.e. decreased renal function 5 [increased serum creatinine 3,		apy Etretinate 30% Methotrexate 49% None of these 30% Previous treatment with: Tar 89% Anthralin 46% Corticosteroids 96% UVB 73%					

	decreased urine creatinine clearance 1 and decreased GFR 1]; laboratory abnormality 1; worsening gynaecomastia/ hypertension 1; and a further 2 uncertain relation to study drug i.e. 1 squamous cell carcinoma of skin and 1 flare of pustular psoriasis). Also 1 dropped out for **illness unrelated to study drug**. Drop-outs in placebo or 1.5mg/kg/day ciclosporin groups not stated.							

Effect size

Outcome	**Induction phase**	**Maintenance phase**	

	Ciclosporin 5mg/kg/day		**Placebo**			**Ciclosporin 3mg/kg/day**			
	No. of patients	Mean % improvement from baseline	No. of patients	Start % of baseline	End % of baseline	No. of patients	Start % of baseline	End % of baseline	p value for difference between groups
Body surface area	181	81	49	89	39	85	89	64	p<0.001
Global evaluation	181	73 (mean rating 2.4, representing "almost clear to mild")	49	81	18	85	82	50	p<0.001
PASI score	181	86	47	91	29	76	91	59	p<0.001
Indicator lesions	181	83 (mean lesion severity rating 1.9 reflecting "absent to trace")	49	85	39	85	88	67	p<0.001

Median time in **induction** phase to achieve 70% reduction in BSA was 8 weeks and to achieve 90% reduction was 12 weeks. 84% of patients were clear of psoriasis or markedly improved by end of induction phase; 95% achieved moderate or marked improvement. Adverse events in induction phase reported by 88% of patients: headache (30%), paraesthesia (18%) and hirsutism (17%) the most frequent. New onset hypertension (i.e. systolic BP >150mmHg and/or diastolic >90mmHg) in 8.8% of sample.

In **maintenance** phase, percentage of patients who had a **relapse** (defined as BSA returned to 50% or more of baseline) in ciclosporin 3mg/kg/day group was 42% (n=83) vs. 84% on placebo (n=48), p<0.001. Median **time to relapse** for placebo group or ciclosporin 1.5mg/kg/day group was 6 weeks vs. >24 weeks (i.e. not seen in duration of study) for ciclosporin 3mg/kg/day group. The most frequently noted adverse events during maintenance phase were headache and hirsuitism; most rated as mild to moderate in severity (numbers of patients affected not stated). 3 patients on ciclosporin 3mg/kg/day had

a **fall in GFR** to 33% or more below baseline. New or worsening **serum creatinine** abnormalities (defined as new elevations or increases of 15% or more above abnormal baseline) in 17% of those on ciclosporin 3mg/kg/day and 10% of placebo group (denominators unclear as not all patients had all investigations).

Author's conclusion

- Ciclosporin 3mg/kg/day adequately and safely maintained 58% of patients with psoriasis for a 6-month period after clearing their psoriasis with doses of around 5mg/kg/day.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Maintenance study (weekend maintenance schedule) Colombo et al., Psoriasis relapse evaluation with week-end cyclosporine A treatment: results of a randomized, double-blind, multicenter study. Int J Immunol & Phamacol. Vol. 23, no.4,1143-1152 (2010) PREWENT Trial REF ID: COLOMBO2010	RCT Multicenter Italy Randomised: 2:1, method not stated Blinding: Double-blind Allocation concealment: Not mentioned Sample size calculation: Yes, power 88%	N=243 (randomised) 4 patients (2 in each group) did not take drug/placebo – excluded from ITT	**Inclusion** Patients 18-65 years with chronic plaque psoriasis on continuous treatment with any dose regimen for 8-16 weeks (**induction treatment**) and who had achieved remission (i.e. PASI reduction ≥75% from pre-treatment) CSA washout period **Exclusion** Body weight >110 kg, uncontrolled hypertension, malignancies, infections and severe haematological, immunological, cardiovascular metabolic or neurological disorders. Patient baseline characteristics	**Ciclosporin** N=160 CSA microemulsion 5mg/kg/day PO Two divided daily doses 2 consecutive days per week (weekends)	**Placebo** N =79	24 weeks	**1° outcome** Relapse rate at 24 weeks – worsening of psoriasis PASI ≥75% of baseline **2° outcome** Time to relapse Change in baseline PASI score BSA Itch intensity Safety AEs, lab values	Funding from Novartis Farma SpA

<table>
<tr>
<td></td>
<td>to detect 20% risk reduction with α5% (N=264)

ITT:

Primary analysis per-protocol, supplementary ITT for primary and secondary outcomes. ITT safety analysis.

30% drop-out rate</td>
<td></td>
<td>similar:
<table>
<tr><th></th><th>CSA</th><th>Placebo</th></tr>
<tr><td>Mean Age</td><td>41.8 (11.0)</td><td>41.8 (12.7)</td></tr>
<tr><td>%Male</td><td>65.6</td><td>59.5</td></tr>
<tr><td>Caucasian (%)</td><td>158 (98.8)</td><td>78 (98.7)</td></tr>
<tr><td>Asian</td><td>1 (0.6)</td><td>0</td></tr>
<tr><td>Other</td><td>1 (0.6)</td><td>1 (1.3)</td></tr>
<tr><td>Mean disease duration, years</td><td>14.9 (10.3)</td><td>13.9 (11.0)</td></tr>
<tr><td>Mean PASI ratio (% of baseline score at end of induction)</td><td>8.5</td><td>8.1</td></tr>
</table></td>
<td></td>
<td></td>
<td></td>
<td>Clinical

success rate (proportion of patients with no clinical worsening – no relapse or PASI <75% of pre-treatment PASI)

Time to first relapse

Creatinine

BP</td>
<td></td>
</tr>
<tr>
<td colspan="9">Effect Size

PASI 75 (PP)
<table>
<tr><th></th><th>CSA 5 mg/kg (n=127)</th><th>Placebo (n=62)</th></tr>
</table></td>
</tr>
</table>

PASI 75	85	33

Final Mean PASI (PP)

	CSA 5 mg/kg (n=127)	Placebo (n=62)
Final Mean PASI ±SD	7.3±8.5	8.8±8.8

Time to relapse – not extractable (K-M curve)

Relapse rates: 33.1% CSA and 46.8% placebo

Serious adverse events

CSA 1 (0.6%) – breast mass (considered unrelated), Placebo 0

Rise in creatinine >30% above baseline (ITT)

	CSA 5 mg/kg (n=160)	Placebo (n=79)
Rise in creatinine >30% above baseline	8	3

Stated no significant difference in mean blood creatinine levels between treatment groups at any time during the study

Withdrawal due to AEs (ITT)

	CSA 5 mg/kg (n=160)	Placebo (n=79)

Withdrawal due to AEs	8	2

Hypertension

No significant differences in systolic and diastolic BP reported in either group

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
D. Thaçi, M. Brautigam, R. Kaufmann, G. Wiedinger, C. Paul, E. Cristophers. Body-weight-independent micro-emulsion and three time weekly maintenan	RCT Multicentre Germany Randomised: computer generated list Blinding: Period 1 Open	N=122 3 patients excluded due to lack of creatinine data 15 drop-outs	Inclusion criteria Patients with chronic plaque type psoriasis requiring systemic treatment. One or more conventional systemic therapies failed or inappropriate. Psoriasis stable for at least 3 weeks prior to entry. Minimum PASI of 12. Washout: no methotrexate, sulphasalazine, retinoids, UVB or PUVA 3 weeks prior. No topical therapy at time of entry.	Ciclosporin N=42 Maintenance phase following achievement of PASI75 Twice daily in divided doses	Placebo N=51 Maintenance phase following achievement of PASI75 Patients achieving remission randomised to	Period 2: 12 weeks Treatment stopped if relapse (inc. in PASI >50% of baseline)	1º outcomes Increase in serum creatinine Relapse rate 2º outcomes	

<table>
<tr>
<td>ce regimen in severe psoriasis. Dermatology.205:383-388.2002

REF ID THACI2002</td>
<td>Period 2 DB

Allocation concealment: not stated

Sample size calculation:

ITT:

Modified ITT</td>
<td>N=93 responders in Period I randomised to Period II</td>
<td>Exclusion:

Pregnant/breast feeding women, patients thought to be ‘non-compliant’. Patients with malignancy, uncontrolled bacterial, viral or fungal infections, hypertension or generalised erythrodermic, pustular, or drug-induced psoriasis. Patients with abnormal creatinine or LFTs, intolerant of CSA, previous failed CSA. Those receiving investigational drug within 4 weeks of entry, or taking nephrotoxic drugs or drugs with pharmacokinetic interactions with CSA.

Baseline characteristics at start of maintenance phase similar apart from slightly higher body weight in CSA group
<table>
<tr><td></td><td>CSA</td><td>Placebo</td></tr>
<tr><td>Mean age</td><td>43.1 yrs</td><td>44.6 yrs</td></tr>
<tr><td>Weight</td><td>85.5</td><td>78.1</td></tr>
<tr><td>Sex – M/F</td><td>30/12</td><td>35/16</td></tr>
</table>
</td>
<td>Period 1: open, randomised to body-weight-dependent dosing or body-weight-independent dosing. BWI 200 mg/day starting dose (to max 300 mg/day), BWD 2.5 mg/kg/day starting dose (to max 5 mg/kg/day). Doses increased if PASI had not dec. >40% by wk 4, or >60% by wk 6, or ≥75% by wk

Period 2

Lowest effective dose CSA continued</td>
<td>double-blind trial: CSA maintenance dose or placebo</td>
<td></td>
<td>PASI score

BP

Global assessment</td>
<td></td>
</tr>
</table>

			PASI: 2.7±1.9 / 3.0±2.2 Creatinine: 88.4±19.4 / 86.6±18.6 Previous systemic psoriasis Rx: 88.1% / 86.3%					

Effect Size

15 dose modifications for increased BP or serum creatinine in Period I

3 dose adjustments for increased creatinine (>30% baseline at two consecutive visits)

13 increases in blood pressure reported as adverse events

Withdrawal due to serious increases in BP in 3 patients

Increased serum creatinine in 4 patients

Period II Relapse rate: 17/42 vs 29/51 with placebo (p=0.15) Time to relapse 98 days (intermittent CSA) 69 days (placebo) – log-rank test p = 0.09 PASI increased from 2.7 to 9.9 with CSA, from 3.0 to 11.9 with placebo (n/s) Mild disease or better: 14/31 CSA vs 5/22 placebo No creatinine increases >30% on two consecutive visits during period II

H.11.8 INDUCTION OF REMISSION

H.11.8.1 Ciclosporin vs placebo for palmoplantar pustulosis

Reference	Study type	Number of pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

<table>
<tr>
<td>Reitamo S et al. Cyclosporine in the treatment of palmoplantar pustulosis. Arch Dermatol 1993; 129: 1273-1279.

Ref ID: REITAMO1993</td>
<td>RCT

Randomisation: given numbers 1-40 in consecutive order (each number preassigned to ciclosporin or placebo)

Allocation concealment: no

Blinding:

yes for phase 1 of study

Washout period: Retinoids and PUVA had to be withdrawn 4 and 2 weeks prior to study, respectively; no</td>
<td>40</td>
<td>Inclusion: 18-70 years; clinically defined palmoplantar pustulosis of the palms and/or soles with at least 20 whitish-yellow pustules of diameter at least 2mm.

Exclusion: Abnormal hepatic or renal function; malignancy; active or chronic infection; pregnancy or lactation; drugs known to interact with ciclosporin. Retinoids and PUVA had to be withdrawn 4 and 2 weeks prior to study, respectively; no topical treatments other than emollients allowed in last 2 weeks.

<table>
<tr><th></th><th>Ciclosporin (n=20)</th><th>Placebo (n=20)</th></tr>
<tr><td>Gender (M/F%)</td><td>30/70</td><td>30/70</td></tr>
<tr><td>Mean age (yr) range</td><td>40.80 (11.49) 24-69</td><td>41.65 (10.41) 29-62</td></tr>
<tr><td>Mean weight (kg) range</td><td>66.90 (9.26) 52-91</td><td>70.65 (14.76) 50-104</td></tr>
<tr><td>Smoking</td><td>20</td><td>20</td></tr>
<tr><td>Mean age at</td><td>34.3 (21-</td><td>34.3</td></tr>
</table>
</td>
<td>n=20

Ciclosporin

2.5mg/kg/day

Both arms: intervention administered twice daily as capsules of 25 and 100 mg</td>
<td>n=20

Placebo (vehicle without CSA)</td>
<td>1 month double blind phase; 3 month open, dose-finding phase; 2 months off treatment

Also, 38/40 seen 4-12 months after termination of treatment</td>
<td>Total number of fresh pustules compared with baseline; success = “responder” = 50% or more reduction in number of pustules; others = failure = “nonresponder”; relapse defined as nonresponse after earlier response.

Number of fresh pustules averaged across right and left palm and right and left soles; indexes of severity of affected areas (palms or soles separately, or composite index for palms and soles together) based on erythema, infiltration and scaling (all scored 0= absent through 3 =severe, for total of 18 maximum, then divided by 18 to get percentage (max</td>
<td>Sandoz Pharma, Finska Läkaressällskapet, Paulo Foundation.</td>
</tr>
</table>

	topical treatments other than emollients allowed in last 2 weeks **Sample size calculation:** yes – sample size of 20 for 80% power to detect a difference of 50% of patients improving with treatment compared with 30% improving on placebo. **ITT analysis:** not stated **Drop outs:** 1 from each group – 1 moved away and 1 not willing to come in for evaluation		onset of PPP (yr) range: 67) (21-61) Mean number of fresh pustules (range): 76.5 (21-338) 72.5 (21-282) Location: Palmar 19 18; Plantar 20 20 Mean duration PPP (yr): 7 8 Previous systemic therapy: Methotrexate 0 0; PUVA 10 7; Retinoids 8* 2* * p<0.001				score 100 = all areas severely affected by each symptom). Overall efficacy of treatment scored by patient and investigator individually (1=very good through 5=very poor). Adverse events (occurrence, severity, frequency), vital signs, laboratory and physical examinations. Overall tolerance to treatment.	

Phase 1 of study: double-blind placebo-controlled trial (n=40).

Effect size at week 4:

	Ciclosporin (n=19)	Placebo (n=19)	p value between groups
Responders Nonresponders	17 (89%) 2 (11%)	4 (21%) 15 (79%)	p<0.001
Overall efficacy score	1.9 (1=very good, 2=good)	4.5 (4=poor, 5=very poor)	p<0.001
Number of patients with adverse events	7 (4 headache [of whom 1 stopped treatment], 2 weakness, stiffness or tenderness of feet, 1 cold feet, 1 common cold, 1 diarrhoea, 1 nausea, 1 dry mouth)	6 (2 tiredness, 1 arthralgia, 1 paronychia, 1 maxillar sinusitis, 1 urticaria [who stopped treatment])	not stated

Mean serum creatinine levels increased in ciclosporin but not placebo group but all remained **within normal range**; no patient had to terminate study due to high serum creatinine. No patient stopped therapy due to hypertension and no patients received antihypertensive therapy.

Phase 2 of study – open dose-finding study: nonresponders in placebo group given 1.25mg/kg/day ciclosporin at week 4 and if still did not respond, dose increased at monthly intervals in steps of 1.25mg/kg/day up to maximum of 3.75mg/kg/day until week 16; responders in ciclosporin group continued previous treatment; nonresponders in ciclosporin group had dose increased to 3.75mg/kg/day.

Effect size at week 12:

	Ciclosporin (n=19)	Placebo - (n=13)	p value between groups
Responders	10	10 (1 required >1.25 mg/kg/day)	not stated

Relapse	0	2	
Number of patients with adverse events	12 (3 headache, 3 weakness , stiffness or tenderness of feet, 3 common cold, 1 nausea, 1 paronychia, 1 maxillar sinusitis, 1 hypertension, 1 hypertrichosis, 1 vaginitis, 1 mucous secretion of eyes, 1 increased sweating, 1 dizziness, 1 abdominal pain, 1 paraesthesia)	4 (1 common cold)	not stated

Phase 3 of study: 8-week post-treatment observation period.

Of those succeeding at the start of phase 3

	Ciclosporin (n=10)	Placebo (n=12)	p value between groups
Relapsed Did not relapse	6 4	8 4	not stated
Number of patients with adverse events	7 (2 headache, 2 weakness , stiffness or tenderness of feet, 1 skin infection, 1 eczema)	4 (1 headache, 1 weakness , stiffness or tenderness of feet, 1 urticaria)	not stated

Once CSA was withdrawn, among the 14 who relapsed the time-to relapse was 2 weeks for 13/14 (weeks 17 and 18)

Of the 6 in the CSA group who relapsed, 3 relapsed at week 17 and three at week 18

Additionally, 38 patients seen between 4 months and 1 year after end of official 3-phase study.

27/38 patients in remission and had only minor signs of palmoplantar pustulosis that required no specific treatment.

Author's conclusion

- Ciclosporin at a dose of 1.25-2.5mg/kg/day in an effective treatment for most patients with palmoplantar pustulosis, a disease that is usually resistant to treatment.
- The clinical appearance of palmoplantar pustulosis is of a cyclic nature in many individuals, who can show a wide variation in the number of pustules from day to day; this variation may have accounted for the placebo response rate.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Erkko P et al. Double-blind placebo-controlled study of long-term low-dose cyclosporin in the treatment of palmoplantar pustulosis.	**RCT** Multicentre (Sweden) **Randomisation:**	58	**Inclusion:** 18-70 years; clinically defined palmoplantar pustulosis of the palms and/or soles with at least 20 whitish-yellow pustules (not showing any brownish colour) of diameter at least 1mm. **Exclusion:** Abnormal hepatic or renal	n=27 **Ciclosporin** Sandimmun® 1mg/kg/day for 1 month ----------	n=31 **Placebo** for 1 month	12 months Tx (monthly visits): Part 1: randomised, double blind 4 wks	Total number of fresh pustules compared with baseline; success = "responder" = 50% or more reduction in	Novartis Pharma Ltd

<table>
<tr>
<td>Br J Dermatol 1998; 139: 997-1004.

Ref ID ERKKO1998</td>
<td>given numbers in consecutive order (each number preassigned to ciclosporin or placebo)

Allocation concealment: not stated

Blinding:
yes phase 1

Washout period: Retinoids, PUVA and antimicrobial treatment had to be withdrawn 4 weeks prior to study; no topical treatments other than emollients allowed in last 2 weeks.</td>
<td></td>
<td>function; malignancy; active or chronic infection; pregnancy or lactation; drugs known to interact with ciclosporin; hypertension (diastolic BP >95mmHg treated or untreated). Retinoids, PUVA and antimicrobial treatment had to be withdrawn 4 weeks prior to study; no topical treatments other than emollients allowed in last 2 weeks.
<table>
<tr><th></th><th>Ciclosporin (n=27)</th><th>Placebo (n=31)</th></tr>
<tr><td>Gender (M/F%)</td><td>14.8/85.2</td><td>38.7/61.3</td></tr>
<tr><td>Mean age (yr) range</td><td>45.2 (12.1) 25-70</td><td>43.0 (13.3) 21-65</td></tr>
<tr><td>Mean weight (kg) range</td><td>74.5 (14.2) 56-130</td><td>72.2 (12.3) 46-97</td></tr>
<tr><td>Mean age at onset of PPP (yr) range</td><td>37.0 (10.1) 25-61</td><td>37.6 (12.8) 20-65</td></tr>
<tr><td>Mean number</td><td>56.2 (40.4) 21-</td><td>70.0 (38.3)</td></tr>
</table>
</td>
<td>Both arms: intervention administered twice daily as capsules of 25 and 100 mg</td>
<td></td>
<td>Part 2: open continuation of part 1 (11 months)

Part 3: followed for 1 year after completion of study</td>
<td>number of pustules; others = failure = “nonresponder”; relapse defined as nonresponse after earlier response.

Erythema, infiltration and scaling (all scored 0= absent through 3 =severe) and area of skin affected. Overall efficacy of treatment scored by patient and investigator individually (1=very good through 5=very poor).

Adverse events (occurrence, severity, frequency), vital signs, laboratory and</td>
<td></td>
</tr>
</table>

	Sample size calculation: not stated **ITT analysis:** not stated **Drop outs:** none in phase 1; 6/58 phase 2 (3 AEs, 1 lost to FU, 1 lack of efficacy and 1 protocol violation)		of fresh pustules (range) Location: Palmar Plantar Mean duration PPP (yr) Previous systemic therapy: Methotrexate PUVA Retinoids	178 23 24 7.2 (7.5) 1 11 5	21-186 23 31 5.4 (6.0) 0 10 9				physical examinations. Overall tolerance to treatment.	

Phase 1 of study: double-blind placebo-controlled trial (n=58, all completed).

Effect size at week 4:

	Ciclosporin (n=27)	Placebo (n=31)	p value between groups
Responders	13 (48%)	6 (19%)	p<0.02

Number of patients with adverse events	6 (2 headache, 1 gastrointestinal symptoms [nausea, vomiting, abdominal pain, diarrhoea], 1 musculoskeletal pain, 1 hypertension, 1 paraesthesia)	8 (1 upper respiratory tract infection, 2 gastrointestinal symptoms [nausea, vomiting, abdominal pain, diarrhoea], 3 fatigue, 1 paraesthesia, 1 other)	NS
Hypertension	1	0	

No serious adverse events or malignancies.

Phase 2 – open continuation of Phase 1: code broken if no response to treatment at initial dose level. Patients initially randomised to placebo received ciclosporin 1mg/kg/day; all nonresponders had dose increased in steps of 1mg/kg/day (adjusted every 2 months) until response or to a maximum of 4mg/kg/day. In cases of treatment response, dose reduced by 12mg/kg/day to minimum of 1mg/kg/day. Treatment continued for 12 months. Treatment stopped if no response to maximum dose after 2 months. (52 completed phase 2; 6 discontinued: 1 each for lost to follow up, hypertension, severe pruritis, diarrhoea, lack of efficacy and protocol violation).

Effect size at 12 months:

	Ciclosporin group (n=27)	**Placebo group (n=31)**	**p value between groups**
Mean duration of blinded treatment	5.1 months	2.1 months	p<0.01
Patients in **remission** throughout 12 months of treatment (i.e. not unblinded)	7	2	p<0.05
Number of patients with	166 (53 upper respiratory tract infection ,	11 (7 upper respiratory tract infection, 2	NS

adverse events	15 headache, 10 gastrointestinal symptoms [nausea, vomiting, abdominal pain, diarrhoea], 10 skin infections, 9 musculoskeletal pain 6 fatigue, 7 hypertension, 4 paraesthesia, 6 hypertrichosis, 6 swelling of fingers or feet, 5 herpes simplex, 2 herpes zoster, 4 dizziness, 3 conjunctivitis, 2 vaginitis, 24 other)	headache, 1 gastrointestinal symptoms [nausea, vomiting, abdominal pain, diarrhoea], 1 fatigue)	
Serum creatinine increased by >30% over baseline	2	0	
Diastolic BP increased to >95mmHg	7 (5 needed anti-hypertensives; 1 stopped ciclosporin)		

No serious adverse events or malignancies.

Phase 3: patients follow up for 12 months after completing treatment.

A reduction in activity of disease was seen at 6 and 12 months; 2 patients totally free of lesions 12 months after stopping treatment and 11 had only minor symptoms (erythema and/or scaling without pustulation).

Author's conclusion

- Ciclosporin was well tolerated and side effects were mainly mild and reversible. We recommend treating with 1-2mg/kg/day for 1-2 months; if this does not show a satisfactory response, dose may be increased stepwise up to 4mg/kg/day.