

Review Article

# Cyclosporine in dermatology: Evidence-based review with a special focus on recent updates

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## ABSTRACT

Cyclosporine (CSA) has been used by dermatologists for decades, and this remains one of the most preferred options for treating a wide gamut of dermatological conditions. Although it is US- Food and Drug Administration (FDA) approved for limited number of disorders, it is prescribed as an off-label drug for numerous conditions. Psoriasis, urticaria, Stevens-Johnson syndrome, alopecia areata, and atopic dermatitis are some of the indications for which CSA has been studied extensively. Besides, there are many other conditions such as polymorphous light eruption, chronic actinic dermatitis, vitiligo, Hailey-Hailey disease, granuloma annulare, systemic sclerosis, and cutaneous lupus erythematosus where there are isolated reports of successful use of CSA. Off late, voclosporin has been FDA-approved for lupus nephritis, and its pharmacokinetic properties have placed the drug higher to CSA. This review is an attempt to comprehensively outline the indications (both approved and off-label), dose, monitoring protocol, and guidelines for using CSA in dermatology.

**Keywords:** Atopic dermatitis, Cyclosporine, Psoriasis, Urticaria

## INTRODUCTION

Cyclosporine or cyclosporine A (CSA) is a lipophilic cyclic polypeptide containing 11 amino acids, found in *Tolypocladium inflatum* and *Cylindrocarpum lucidum*.<sup>[1]</sup>

Initially, CSA was introduced for the prevention of hyperacute and acute graft rejection as well as for graft versus host disease, owing to its immunosuppressant and anti-inflammatory properties, which were beneficial. Later on, CSA showed its efficacy as an anti-inflammatory agent in various dermatoses, and in 1997, the US Food and Drug Administration (FDA) approved its use in dermatology for the treatment of psoriasis.<sup>[2]</sup>

With over three decades of clinical use, CSA has been found to be effective in treating various skin conditions, including psoriasis, atopic dermatitis (AD), and other inflammatory and immunological disorders.<sup>[3]</sup> In the era of biologics, which are used in a variety of dermatological conditions, the conventional systemic immunomodulators like CSA are being considered lesser than usual. Nonetheless, CSA has some advantages over newer agents in producing broad-spectrum, immunomodulatory effects on the immunopathogenesis of several dermatological conditions. This makes it efficacious and useful even in this era of biologics. Hence, in this review, we emphasize the merits and demerits of CSA which

needs to be re-considered and re-assessed in the new age of biologics.<sup>[4]</sup>

## METHODOLOGY

A comprehensive English literature search across multiple databases (PubMed, EMBASE, MEDLINE, and Cochrane) for articles on the use of CSA in dermatological conditions was done using the keywords (both MeSH and non-MeSH, alone and in combination) “cyclosporine,” “psoriasis,” “atopic dermatitis,” “vitiligo,” “childhood dermatoses,” “alopecia areata,” and “vitiligo”. The levels of evidence and grade of recommendations have been delineated as per the criteria laid down by the Strength of Recommendation Taxonomy and Oxford Centre for Evidence-Based Medicine.

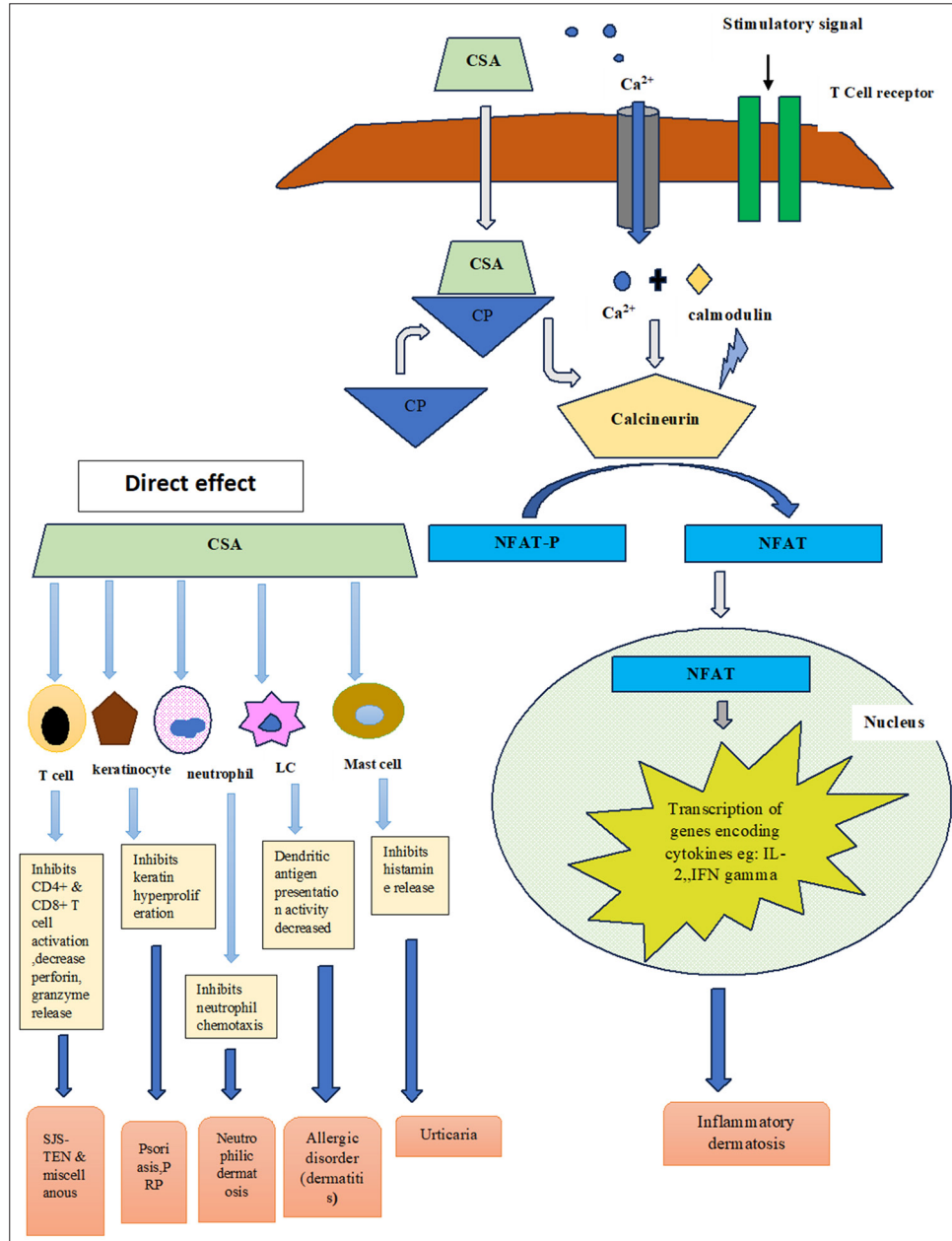
## MECHANISM OF ACTION

The mechanism of action of CSA is not yet fully elucidated. It works as a calcineurin inhibitor, thus inhibiting the synthesis of interleukins (specifically interleukin-2 [IL-2]), responsible for self-activation and differentiation of T lymphocytes. The drug inhibits the lymphocytes in the G0 and G1 phases of the cell cycle [Figure 1]. It primarily targets the T helper cells, apart from suppressing the T suppressor cells. The T lymphocyte-B lymphocyte interaction crucial for the activation of B

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**Figure 1:** Schematic diagram showing the mechanism of action of cyclosporin in various dermatoses. CSA: Cyclosporin, CP: Cyclophilin, NFAT: Nuclear factor for activated T cells, IL: interleukin, IFN: Interferon, LC: Langerhans cell, PRP: Pityriasis rubra pilaris, SJS-TEN: Stevens johnson syndrome-toxic epidermal necrolysis.

lymphocytes is also subject to inhibition. Additional research has shown that it inhibits CD4+ CD25+ Tregs, eventually causing blockade of the host immune tolerance.<sup>[4]</sup>

### PHARMACOKINETIC PROPERTIES

**Metabolism:** Metabolized through CYP3A4, into one N-methylated derivative (AM4N) and certain hydroxylated metabolites, namely A hydroxylated derivative (AM1) and Another hydroxylated derivative (AM9).

**Enzyme interaction:** Inhibits CYP3A4 and P-glycoprotein.

**Half-life:** 8.4–27 hours.

**T-max:** 1.5–2 hours.

**Excretion:** The drug is primarily excreted through bile into the feces.

**Dosage:** Adults: 2.5–5 mg/kg/day, children: 3–5 mg/kg/day.

**Factors altering the absorption:** Duration, post-transplant diet, gastrointestinal condition, biliary flow, hepatic function, length of small intestine, and vehicle used in the formulation.<sup>[4]</sup>

## USES OF CSA

CSA is mostly used as a “rescue drug” or “induction therapy,” mostly for a period of 6 months. However, particularly in the pediatric population, it is still used as a maintenance therapy for a period of up to 1 year. Initially, CSA was approved only for moderate-to-severe psoriasis, and later on, it has been tried in a wide gamut of other inflammatory skin disorders, as an off-label drug.<sup>[1]</sup> Table 1 highlights the FDA approved and off label indications of cyclosporine in dermatology.

### Psoriasis

Psoriasis is a chronic, inflammatory disorder, mediated by T helper 1 (Th1)/Th17 T cells, and dendritic cells, leading to elevated levels of IL-17, IL-23, and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ). The cytokines eventually cause increased proliferation of keratinocytes, and cutaneous vasculature, and influx of inflammatory cells into the psoriatic lesions.<sup>[5]</sup> Attributed to rapid onset of action and effectiveness, CSA remains one of the most preferred alternatives in treating psoriasis.

Indications of CSA in psoriasis:

- Severe flare-ups
- Recalcitrant psoriasis
- Disabling psoriasis
- Major life incidents, where rapid clearance is needed.

### Chronic plaque psoriasis

In practice, CSA is typically used to induce remission at a daily dose of 2.5–5 mg/kg for 3–6 months.<sup>[6]</sup> The magnitude of response and rapidity of clearance of lesions are dose-dependent. However, the chances of adverse events also increase, with an increment in dosage. Therefore, dosing should be individualized and adjusted based on efficacy and tolerability. Some studies suggest that pulse administration of CSA for a few days weekly can be effective for both inducing and maintaining response in psoriasis patients.<sup>[7]</sup>

The relevant studies have been highlighted in Table 2.<sup>[8-17]</sup>

### Erythrodermic psoriasis

CSA is considered a first-line therapy for acute and unstable cases according to the published consensus of the US National Psoriasis Foundation in 2010.<sup>[18]</sup> Table 3 highlights the summary of studies demonstrating the efficacy of CSA in erythrodermic psoriasis.<sup>[19-22]</sup>

### Pustular psoriasis

Due to the rapid onset of action, CSA is considered a valuable treatment option for pustular psoriasis as well as first-line therapy for generalized pustular psoriasis of pregnancy.<sup>[23]</sup> Table 4 shows the use of CSA in pustular psoriasis.<sup>[24-27]</sup>

### Nail psoriasis

CSA can be used in nail psoriasis which eventually may prevent the development of nail dystrophy and psoriatic

**Table 1:** Indications of cyclosporine in dermatology.

FDA approved	Off-label use
Psoriasis <ul style="list-style-type: none"> <li>• Severe</li> <li>• Recalcitrant</li> <li>• disabling</li> </ul>	Eczemas <ul style="list-style-type: none"> <li>• Atopic dermatitis</li> <li>• Chronic hand dermatitis</li> <li>• Dyshidrotic eczema</li> <li>• Perthenium dermatitis</li> </ul> Papulosquamous disorders <ul style="list-style-type: none"> <li>• Lichen planus</li> <li>• Pityriasis rubra pilaris</li> </ul> Neutrophilic dermatoses <ul style="list-style-type: none"> <li>• Bechet's disease</li> <li>• Pyoderma gangrenosum</li> <li>• Sweet syndrome</li> </ul> Alopecia <ul style="list-style-type: none"> <li>• Lichen planopilaris</li> <li>• Alopecia areata</li> </ul> Granulomatous dermatoses <ul style="list-style-type: none"> <li>• Granuloma annulare</li> <li>• Sarcoidosis</li> </ul> Adverse drug reaction <ul style="list-style-type: none"> <li>• SJS-TEN</li> <li>• AGEP</li> <li>• DRESS</li> <li>• Photosensitivity dermatoses</li> <li>• Chronic actinic dermatitis</li> <li>• Polymorphous light eruption</li> </ul> Urticaria <ul style="list-style-type: none"> <li>• Chronic idiopathic urticaria</li> <li>• Cold urticaria</li> <li>• Solar urticaria</li> </ul> Autoimmune connective tissue disorder <ul style="list-style-type: none"> <li>• SLE</li> <li>• Dermatomyositis</li> <li>• Systemic sclerosis</li> </ul> Others <ul style="list-style-type: none"> <li>• Vitiligo</li> <li>• Eosinophilic cellulitis</li> <li>• Morphea</li> <li>• Prurigo nodularis</li> <li>• Reiter's disease</li> <li>• Eosinophilic pustular folliculitis of Ofuji</li> <li>• Kimura's disease</li> </ul>

FDA: Food and Drug Administration, SLE: Systemic lupus erythematosus, SJS-TEN: Stevens-Johnson-Toxic epidermal necrolysis, AGEP: Acute generalized exanthematous pustulosis, DRESS: Drug reaction eosinophilia with systemic symptoms

arthropathy<sup>[28]</sup> Table 5 highlights the efficacy of CSA in treatment of nail psoriasis.<sup>[29-32]</sup>

### Psoriatic arthropathy

Multiple studies have documented the efficacy of CSA either alone or in combination with other Disease-modifying anti-rheumatic drugs (DMARDs).<sup>[33]</sup> A few of these studies are summarized in in Table 6.<sup>[33-40]</sup>

**Table 2:** Studies on efficacy of CSA in treatment of chronic plaque psoriasis.

Author	Year	Type of study	No. of patients	Age	Dose and duration	Result	Conclusion
Marsili <i>et al.</i> <sup>[8]</sup> (Italy)	2022	Observational, cross-sectional, multicenter study	196 patients	Mean age=46.6 years Range= 18–89 years	5 mg/kg/day for ≥12 weeks	For response categories, 39.8%, 22.4%, 16.8%, and 20.9% of patients were responders, suboptimal-responders, partial-responders, and non-responders to CSA treatment. Overall, 28.6% of patients permanently discontinued treatment with CSA.	Patients were only partially satisfied with CSA treatment, reporting measurable impact on quality of life. Only 40% patients showed a satisfactory response to CSA.
Singh <i>et al.</i> <sup>[9]</sup> (India)	2021	Randomized control trial	133 patients	Group 1: (Mean age-38.04±14.97) Group 2: (Mean age-38.77±15.03)	Group 1: MTX intramuscular injection 0.3 mg/kg/week. Group 2: combination of MTX intramuscular injection 0.15 mg/kg/week plus CSA 2.5 mg/kg/day orally rounded off to the nearest 25 mg in two divided doses.	The achievement of PASI-75 ( $P=0.005$ ), PASI-90 ( $P<0.001$ ) and PASI-100 ( $P=0.001$ ) was more in the combination group (Chi-square test)	The combination of reduced doses of MTX and CSA is more efficacious with earlier onset of action and similar adverse effects as with MTX monotherapy.
Oh <i>et al.</i> <sup>[10]</sup> (South Korea)	2018	Prospective observational study	PsO=82 patients PsA=18 patients	PsO=34.15±16.11 years PsA=41.74±15.36 years	3–5 mg/kg/day tapered by 1–1.5 mg/kg according to treatment response	The results suggest that CSA has considerable therapeutic effects on arthritic symptoms in PsA. This is the first study to compare clinical characteristics between PsO and PsA patients and to evaluate treatment responses to CS	Considering its potential benefits for retarding joint destruction, appropriate use of CS in patients with PsA may be a valuable therapeutic option.
Di Lernia <i>et al.</i> <sup>[11]</sup> (Italy)	2016	Multicentric retrospective study	38 patients	Up to 17 years Mean age= 12.3 years	Median dose= 3.2 mg/kg/day Range=2–5 mg/kg/day for 1 to 36 months	Fifteen patients (39.4%) achieved a complete clearance or a good improvement of their psoriasis defined by an improvement from baseline of ≥75% in the PASI at week 16. Eight patients (21.05%) discontinued the treatment due to laboratory anomalies or adverse events. Serious events were not recorded.	CSA was effective and well-tolerated treatment in a significant quote of children. CSA, when carefully monitored, may represent a therapeutic alternative to the currently used systemic immunosuppressive agents for severe childhood psoriasis.

(Contd...)

**Table 2:** (Continued).

Author	Year	Type of study	No. of patients	Age	Dose and duration	Result	Conclusion
Bulbul Baskan E <i>et al.</i> <sup>[12]</sup> (Turkey)	2016	Retrospective study	22 patients	Less than 18 years	Mean therapeutic dose=3.47±0.62 mg/kg/day for a mean duration of 5.68±3.29 months	Seventeen patients were found to be excellent responders. The median time to total clearance of the lesions was 4 weeks.	We conclude that cyclosporine A therapy is equally effective and safe in pediatric psoriasis patients as in adults.
Fernandes <i>et al.</i> <sup>[13]</sup>	2013	Randomized controlled trial	21 patients	Range=27–60 years Mean age=44.3±6.9 years	4 mg/kg/day for 12 weeks (induction phase), 19 patients were randomly allocated to receive either 5 mg/kg/day for 2 consecutive days on weekend or continued 2–3 mg/kg/day for 20 weeks	There were no significant differences between the 2 groups before starting the maintenance phase with regard to the mean PASI score ( $P=81\%$ ). Moreover, at the end of the study PASI 75 was achieved by 80% and 75% of the patients on weekend and continuous therapy, respectively.	Both treatment regimens showed comparable results. The mean daily dose was higher in the continuous therapy group (2.6 versus 1.4 mg/kg/d) and the twice weekly dosing schedule was more convenient for patients.
Shintani <i>et al.</i> <sup>[14]</sup> (Japan)	2011	Randomized controlled trial	40 patients		Group A=100 mg once daily Group B=50 mg twice daily	The improvement rate was 69.4±4.8% in group A and 73.4±4.3% in group B. PASI-50 was achieved by 82% in group A and 84% in group B. At 6 weeks, the number of patients with PASI-50 was significantly higher in group A than in group B. PASI-75 and -90 were also achieved in both groups with no significant difference between groups.	Administration of a fixed-dose cyclosporine microemulsion (100 mg/day) is practical for second-line psoriasis treatment.
Yoon <i>et al.</i> <sup>[15]</sup> (South Korea)	2007	Randomized controlled trial	61 patients	More than 18 years	2.5 mg/kg/day starting dose and an increasing regimen ("standard regimen") or a 5.0 mg/kg/day starting dose and a decreasing regimen ("step-down regimen") group for 12 weeks	According to a 50% PASI reduction (PASI 50), the response rate at 12 weeks was similar for two groups. The percentage of patients achieving a 75% PASI reduction (PASI 75) at 12 weeks was higher in the step-down regimen group. The mean time to PASI 50 or PASI 75 was shorter in the step-down regimen group.	This study suggests that the "step-down" cyclosporine regimen offers an effective and safe therapeutic option for the management of severe psoriasis.

(Contd...)

Table 2: (Continued).

Author	Year	Type of study	No. of patients	Age	Dose and duration	Result	Conclusion
Kokelj <i>et al.</i> <sup>[16]</sup> (Italy)	1998	Open clinical trial	20 patients		Initial dose 4.5 mg/kg/day, dose reduced by 0.5 mg/kg/day every 2 weeks after clinical assessment. Calcipotriol ointment was also applied over unilateral lesion only	Eighteen patients completed the study. 17 of the 18 presented more evident improvement on the side treated with combined therapy, while only one patient showed a better result on the side treated with cyclosporine alone	These results underline the effectiveness of the combination of calcipotriol and cyclosporine in order to decrease the total dosage of cyclosporine.
Meffert <i>et al.</i> <sup>[17]</sup> (Germany)	1997	Clinical trial	133 patients		1.25 or 2.5 mg/kg/day or placebo for 10 weeks (Period I), up to 5 mg/kg/day for 12 weeks (Period II)	After 10 weeks the percentage improvement from baseline in the PASI was 5.9% on placebo, 27.2% on 1.25 mg/kg/day and 51.0% on 2.5 mg/kg/day CSA. The final average dose at the end of study period II was 2.99 mg/kg/day. At this time the PASI was reduced by at least 75% in 63.0% of the patients. From this group of good responder no patient relapsed (PASI>50% of baseline) during the 4 weeks after termination of active treatment	1.25 mg/kg/day is superior to placebo in the treatment of psoriasis vulgaris and that a dose reduction to 1.25 mg/kg/day should be considered in patients responding well to a conventional dose between 2.5 and 5 mg/kg/day.

PASI: Psoriasis area and severity index, PsO: Psoriasis, PsA: Psoriatic arthritis, CSA: Cyclosporine, MTX: Methotrexate

### Comparison with other biologics

Numerous agents (TNF- $\alpha$  inhibitors, Anti-IL-12/23, IL-17) have been implicated as targeted therapy for psoriasis. Notably, biological agents are not the first-line drugs and they should be used when the conventional drugs cannot be used or failed. According to the available data, CSA is preferred as first-line therapy because of its rapid onset of action, better efficacy and tolerability, low cost of therapy, and reversible adverse effects in comparison to biological agents. Re-activation of tuberculosis along with other infections and long pre-workup before initiation of the therapy is also a primary concern during therapy making biological agents inferior to CSA therapy.<sup>[41]</sup>

### Allergic disorders

#### Urticaria

Chronic urticaria is clinically marked by frequently recurring wheals and/or angioedema that are persistent or occur episodically for at least 6 weeks.<sup>[42]</sup> CSA has been recommended in those cases of chronic spontaneous urticaria as well as in chronic inducible urticaria, which have been unresponsive even after the four-fold escalation of the dose of second-generation antihistaminic agents<sup>[43]</sup>. Inhibition of basophil activity and mast cell degranulation has also been observed by CSA.<sup>[44]</sup> Table 7 highlights the studies on efficacy of CSA in treatment of urticaria.<sup>[45-57]</sup>

**Table 3:** Studies on efficacy of CSA in treatment of erythrodermic psoriasis.

Author	Year	Study type	No. of patients	Dose	Result	Conclusion
Bruzzese <i>et al.</i> <sup>[19]</sup> (Italy)	2009	Case report	Single patient	3 mg/kg/day	Complete cure of infliximab induced erythrodermic psoriasis within 3 months.	CSA is effective in therapy for psoriasis induced by anti-TNF $\alpha$ drugs.
Franchi <i>et al.</i> <sup>[20]</sup> (Italy)	2004	Open-label study	24 patients	CSA 200 mg/kg (divided into two daily doses for 3 weeks; dose was titrated down to 100 mg/kg for 2 weeks. The 311 nm radiations were produced by PHILIPS TL01/100 W lamps	The PASI score showed a decrease of about 90% (PASI time 0:23.9–67.2 - mean 56.4; PASI after 9 weeks: 2.1–10.3 - mean 5.45). All patients were responders.	Study confirm the effective symptoms control in patients with erythrodermic psoriasis poorly responsive to treatment of a new therapeutic approach which combines a reduced dose of CSA with UVB phototherapy
Kokelj <i>et al.</i> <sup>[21]</sup> (Italy)	1998	Case report	3 patients	Combined therapy with CSA and etretinate	Clinical response was prompt to the combined therapy. The two drugs were tapering off gradually over 6 months; the patients maintained the remission for prolonged period.	Combined CSA-etretinate therapy may be considered as an effective and well tolerated treatment of erythrodermic psoriasis in patients not responding to monotherapy regimen.
Giannotti <i>et al.</i> <sup>[22]</sup> (Italy)	1993	Uncontrolled Open multicenter study	33 patients	5 mg/kg/day (initial mean dose 4.2 mg/kg/day) Slowly tapered after remission by 0.5 mg/kg every 2 week	After 6.3 $\pm$ 3.4 months, CSA doses of 3–5 mg/kg/day had led to complete remission in 67% of patients in a median time of 2–4 months; in a further 27% of cases, considerable improvement in skin involvement was observed, with a reduction of more than 70% in comparison with baseline	Low dose CSA can be considered as the therapy of choice in patients with erythrodermic psoriasis.

PASI: Psoriasis area and severity index, CSA: Cyclosporine, UVB: Ultraviolet B, TNF- $\alpha$ : Tumor necrosis factor- $\alpha$

### Comparison with other biologics

CSA alone has been proven to be effective in controlling the disease activity in adults with chronic urticaria refractory to omalizumab. However, the impact of CSA was limited by reversible adverse effects which were more common with pre-existing medical conditions.<sup>[57]</sup> Response to omalizumab is slower in comparison to cyclosporine if autologous serum skin test and basophil histamine release assay are positive.

### AD

CSA has been used as an off-label drug for AD, though it is not FDA-approved for the same.<sup>[58]</sup> It is approved for severe

AD in Europe, Japan, and Brazil as a short-term therapy in children above 2 years of age and adult patients. The molecule is useful for both, short-term, and long-term usage. However, no clear dosimetry and schedule are provided in the guidelines, although the dosage for psoriasis is usually followed.<sup>[59]</sup> Owing to the cumulative side effects, long-term therapy is restricted up to 1 year.<sup>[60]</sup> Patients receiving CSA demonstrate excellent improvement of lesions, reduction of itch, improvement of disease severity scores, and quality of life indices. CSA reduces the number of helper/inducer T-cell lymphocytes in affected and perilesional skin. Moreover, CSA rectifies the altered innervations and expression of

**Table 4:** Studies on efficacy of CSA in treatment of pustular psoriasis.

Author	Year	Study type	No. of patients	Dose	Result	Conclusion
Georgakopoulos <i>et al.</i> <sup>[24]</sup> (Canada)	2017	Case report	Single patient	200 mg/kg/day in two divided doses for 2 weeks	Dramatic improvement in disease symptoms including clearance of pustules	This case report supports the use of CSA as a first line agent in rapid symptomatic relief for flares
Hazarika <sup>[25]</sup> (India)	2009	Case report	2 patients	3 mg/kg/day, dose was gradually tapered and stopped after 3 weeks of delivery	The skin lesions started regressing dramatically from second days onwards and complete resolution after 2 weeks	CSA can be an option in the management of pustular psoriasis of pregnancy or psoriasis with pustulation in pregnancy.
Kiliç <i>et al.</i> <sup>[26]</sup> (Turkey)	2001	Case report	3 patients	1–2 mg/kg/day for 2–12 months	Clearance of psoriatic lesions occurred after 2–4 weeks of treatment	CSA is effective and tolerable therapy for generalized pustular psoriasis
Fradin <i>et al.</i> <sup>[27]</sup> (USA)	1990	Case report	Single patient	Initial dose of CSA 7.5 mg/kg/day; then slowly tapered off	PASI score reduced from 33.6 to 14.9 by 4 week. PASI score was 0 by 16 week.	A slow decrease in the CSA dosage (0.5–1 mg/kg/day monthly) may be more effective in maintaining remission of the disease

PASI: Psoriasis area and severity index, CSA: Cyclosporine

neuropeptides, eventually reducing the pruritus in AD. CSA also inhibits mast cell proliferation, thereby suggesting a novel mechanism of CSA in the management of AD. Meta-analysis has shown the possibility of rebound phenomenon during withdrawal is minimal, thus CSA tends to maintain the clinical resolution and prevent relapses.<sup>[61]</sup> Multiple studies have shown that patients with severe AD improve clinically with CSA; however, the rate of relapse and frequency of adverse events vary from patient to patient.

#### Comparison with other biologics and small molecules

Dupilumab (anti IL-4/13) and human immunoglobulin G4 both have received approval for moderate to severe atopic dermatitis, but there are certain limitations of the corresponding data. Discontinuation of therapy among patients attributed to adverse effects, development of flare-ups and lack of a clearcut end point of therapy, are some of the issues which should be kept in mind, while assessing the data. However, CSA alone has been shown to be effective in controlling the disease activity by decreasing the Eczema Area and Severity Index score. Moreover, the studies have shown that CSA has a lesser tendency to produce adverse effects.<sup>[62,63]</sup> Table 8 highlights the studies on efficacy of CSA in treatment of atopic dermatitis.<sup>[64-88]</sup>

Janus kinase inhibitors (abrocitinib, upadacitinib, and tofacitinib) have been also used in the treatment of moderate-to-severe AD who do not respond to conventional therapies. Very limited data on clinical trials including safety, tolerability, and side effects are available whereas ease of availability, cost of therapy, and better tolerability make CSA superior to other biologic therapies.<sup>[89]</sup>

#### Dyshidrotic eczema

In case of severe dyshidrotic eczema, non-responding to first-line treatment, CSA can be an effective therapy. Peterson *et al.* have shown encouraging improvement of severe chronic vesicular hand eczema by treating with high dose CSA (5 mg/kg/day) initially, followed by maintenance in 2.5 mg/kg/day dose. However, recurrence of lesions has been observed once the drug is discontinued.<sup>[90]</sup>

#### Chronic hand dermatitis

Chronic hand dermatitis not responding to conventional therapies may show a good response to CSA. Reitamo and Granlund studied the efficacy of CSA in hand eczema in 7 patients, which showed no improvement at a low dose (1.25 mg/kg), and was effective in 5 out of 7 patients in 2.5–3 mg/kg dose and maintained up to 16 weeks.<sup>[91]</sup> Kim HL *et al.* in their retrospective review of 16 cases revealed significant improvement in statistical physician's global assessment, with relapse on drug withdrawal in some cases. However, there were no severe side effects reported.<sup>[92]</sup>

#### Parthenium dermatitis

CSA is an effective and safe therapeutic agent which can be used in cases of air-borne contact dermatitis, with an atopic background. Verma *et al.* observed 20 patients of parthenium dermatitis with 2.5 mg/kg CSA for 3 months (or up to complete clinical remission) and demonstrated significant improvement within 2–4 weeks of initiation of therapy and complete remission was achieved within 1.5–3 months of therapy in all patients.<sup>[93]</sup> Lakshmi *et al.* showed improvement in clinical severity score and decrease in serum



**Table 5:** Studies on efficacy of CSA in treatment of nail psoriasis.

Author	Year	Study type	No. of patients	Dose	Result	Conclusion
Mittal <i>et al.</i> <sup>[29]</sup> (India)	2018		90 fingernails in 17 patients were assigned into 3 groups with 30 nails each	Intra-matrical injections of triamcinolone acetonide (10 mg/mL), methotrexate (25 mg/mL) and CSA (50 mg/mL)	In both triamcinolone acetonide and methotrexate groups, 15 (50%) nails out of 30 showed >75% improvement. In the CSA group, only ten (33%) nails showed >75% improvement.	Intra-matrical methotrexate injection yielded the most improvement with minimum side effects, results being comparable to intra-matrical triamcinolone acetonide injection. CSA was the least effective drug, with the most side effects.
Gümüşel <i>et al.</i> <sup>[30]</sup> (Turkey)	2011	Randomized controlled trial	37 patients	Treatment with methotrexate (initial dose, 15 mg/week) or CSA (initial dose, 5 mg/kg/day) for 24 weeks.	The mean percentages of reduction of the NAPSI score after methotrexate and CSA treatments were 43.3% and 37.2%, respectively.	A significant improvement was detected in methotrexate group for the nail matrix findings, and in CSA group for the nail bed findings.
Feliciani <i>et al.</i> <sup>[31]</sup> (Italy)	2004	Clinical trial	54 patients Group A-21 patients Group B-33 patients	Group A-CSA (3.5 mg/kg/day) for 3 months Group B-CSA with topical calcipotriol cream	Improvement of the clinical symptoms of nails lesions was seen in 79% patient in group B in comparison to 47% patient in group A	In case of severe nail psoriasis, the use of the combination of topical calcipotriol twice a day with systemic CSA
Cannavò <i>et al.</i> <sup>[32]</sup> (Italy)	2003	Prospective randomized placebo-controlled study	16 patients Group A-8 patients Group B-8 patients	Group A-70% maize-oil-dissolved oral CSA solution Group B-Maize oil alone	Group A-3 patients showed complete resolution of nail lesions and 5 patients showed substantial improvement compare to Group B	Topical therapy with oral CSA solution is safe, effective and cosmetically highly acceptable

CSA: Cyclosporine

immunoglobulin E (IgE) level following CSA therapy in two parthenium dermatitis patients with atopic diathesis<sup>[94]</sup>

#### Miscellaneous disorders

Other than the common uses, CSA is used in a myriad of clinical conditions.

#### Stevens-Johnson syndrome and toxic epidermal necrolysis

CSA is used in Stevens–Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) for the prevention of disease progression and formation of new lesions. CSA inhibits the activation of CD4+ and CD8+ T lymphocytes and inhibits the secretion of granulysin, perforin, and granzyme, thus arresting apoptosis and subsequent disease progression.<sup>[95]</sup> Studies have suggested CSA to be a superior drug to other therapeutic options in the management of SJS-TEN. However, the duration of treatment is not standardized, and the drug is used for a month or till the resolution of skin lesions and

re-epithelialization. Table 9 highlights the studies on efficacy of CSA in treatment of SJS-TEN.<sup>[96-102]</sup>

#### Pyoderma gangrenosum

CSA as a monotherapy or in combination with corticosteroid shows rapid healing of ulcers in the case of pyoderma gangrenosum. The drug has both immunomodulatory and anti-inflammatory action on the disease process. Reduction of inflammation is evident within 24 hours of administration of the drug with maximum benefit seen after 2 weeks. However, long-term treatment with proper monitoring is required, else, the condition tends to recur. Table 10 highlights the studies on efficacy of CSA in treatment of pyoderma gangrenosum.<sup>[103-108]</sup>

#### Lichen planus

CSA gives good results in severe and refractory cases of lichen planus. Pruritus is shown to lessen within 2 weeks of therapy, and resolution of the lesions is observed within

**Table 6:** Studies on efficacy of CSA in treatment of psoriatic arthropathy.

Author	Year	Study type	No. of patients	Dose	Duration	Remarks
Colombo <i>et al.</i> <sup>[34]</sup> (Italy)	2017	Observational, multicenter study	238 patients	NA	12 months	However, taking advantage of the data available from the SYNERGY study, we can conclude from this analysis that CSA in monotherapy confirms its efficacy in cutaneous psoriasis and suggests to be effective also on PsA, at least in this limited subgroup of patients, reducing BASDAI and articular signs and symptoms.
Karanikolas <i>et al.</i> <sup>[35]</sup> (Greece)	2011	Prospective, nonrandomized, unblinded clinical trial	170 patients	57 patients (CSA- 2.5 to 3.75 mg/kg/day) 58 patients' adalimumab (40 mg every other week) 55 patients (combination)	12 months	Combination therapy significantly improved Psoriasis Area and Severity Index-50 response rates beyond adalimumab, but not beyond the effect of CSA monotherapy.
Fraser <i>et al.</i> <sup>[36]</sup> (UK)	2005	Randomized, multicenter, double-blinded placebo-controlled trial	Out of 72 patients recruited, 38 were randomized to receive CSA in addition to methotrexate (15 mg/week), and the remaining 34 were given placebo along with methotrexate in the same dose	CSA was started at a dose of 2.5 mg/kg/day, with increments at weeks 4, 8, and 12, increasing by 0.5 mg/kg till a maximum dose of 4 mg/kg/day was obtained (if tolerated by the patient)	12 months	Significant improvements in the following parameters were observed in the group receiving CSA along with methotrexate, when compared with the group receiving methotrexate alone, respectively: Improvement in swollen joints (11.7% vs. 6.5%) C-reactive protein (17.4% vs. 12.7%) Synovitis (33% vs. 6%)
Salvarani <i>et al.</i> <sup>[37]</sup> (Italy)	2001	Case series	12 patients	3 mg/kg/day	6 months	Seven patients had greater than 50% reduction in joint swelling and pain Four patients, the disease had stabilized One patient had to withdraw from the study due to nephrotoxicity

(Contd...)

**Table 6:** (Continued).

Author	Year	Study type	No. of patients	Dose	Duration	Remarks
Spadaro <i>et al.</i> <sup>[38]</sup> (Italy)	1995	Prospective controlled study	35 patients	Compare the effectiveness and toxicity of CSA (3 mg/kg/day) versus low dose methotrexate (7.5–15 mg/kg/week)	12 months	At the end of 6 and 12 months of treatment, symptoms of PsA were reduced in both treatment groups However, the toxicity profile was more in the CSA group with more patient withdrawing from the CSA group (41.2%), when compared with the methotrexate group (27.8%)
Steinsson <i>et al.</i> <sup>[39]</sup> (Iceland)	1993	Open-label prospective study	7 patients	3.5 mg/kg/day	6 months	All patients had improvement in joint pain and swelling No relapse was documented
Gupta <i>et al.</i> <sup>[40]</sup> (USA)	1989	Prospective study	6 patients	6 mg/kg/day	8 weeks	Significant improvement in joint strength, mean grip strength, and activity level However, within 2 weeks of discontinuing of the drug, symptoms recurred

CSA: Cyclosporine, PsA: Psoriatic arthritis, BASDAI: Bath ankylosing spondylitis activity index

6 weeks. Studies have shown the efficacy of the drug in generalized lichen planus, hypertrophic lichen planus, and actinic lichen planus, but the highest level of evidence and maximum studies are on oral lichen planus and lichen planopilaris. Tables 11-13 highlights the studies on efficacy of CSA in treatment of lichen planus.<sup>[109-119]</sup>

#### ***Alopecia areata***

Oral cyclosporine has been shown to decrease the perifollicular lymphocytic infiltration, thereby arresting the progression of the disease and eventually leading to regrowth of hairs. CSA can be useful in long-term treatment due to its steroid-sparing effects. Table 14 highlights the studies on efficacy of CSA in treatment of alopecia areata.<sup>[120-126]</sup>

#### ***Vitiligo***

CSA can be an effective therapeutic modality of treatment in both unstable and stable vitiligo patients. It has demonstrated its ability to stabilize rapidly progressive vitiligo as well as repigmentation in vitiligo patches. Table 15 highlights the studies on efficacy of CSA in treatment of vitiligo.<sup>[127,128]</sup>

#### ***Prurigo nodularis***

CSA is considered a second line of management in prurigo nodularis. Significant reduction of pruritus and clearance

of lesion is achieved when administered in a dosage of 3 mg/kg/day to 4.5 mg/kg/day for 24–36 weeks.<sup>[129]</sup> The drug acts by a similar mechanism as in AD. Frequently, high dosages of 3 mg/kg/day to 4.5 mg/kg/day for 24–36 weeks are required. When CSA dosage is reduced, the prurigo lesions tend to reappear.

#### ***Sweet syndrome***

Sweet syndrome like other neutrophilic dermatosis can be treated with CSA. It can be used as initial monotherapy, a second-line therapy in steroid-resistant cases, or as a steroid-sparing agent. The dose ranges from 2–4 mg/kg/day to 4 mg/kg/day, with the highest dose being 10 mg/kg/day for the resolution of clinical symptoms in acute presentation with proper monitoring. CSA acts by inhibiting neutrophil chemotaxis, impairing the neutrophil migration and thus reducing inflammation. Van der driesch *et al.* reported a case of a middle-aged lady, treated with a high dose of CSA (10 mg/kg/day), leading to the resolution of skin lesions and systemic symptoms within 9 days. Subsequently, the dose of CSA was reduced within 21 days, without any clinical recurrence.<sup>[130]</sup>

#### ***Behcet's disease***

CSA decreases the mucocutaneous as well as ocular and arthritis symptoms in patients of Behcet's disease. However,

**Table 7:** Studies on efficacy of cyclosporine in treatment of urticaria.

Author	Year	Type of study	No. of patients	Age	Dose and duration	Result	Conclusion
Sehgal <i>et al.</i> <sup>[45]</sup> (India)	2024	Randomized clinical trial	43 patients 26 female and 17 male patients	Mean age=29.05±10.19 years	4–5 mg/kg/day for 4 weeks	Higher doses of CSA (4–5 mg/kg/day) demonstrated better efficacy in controlling symptoms. Majority of the patients did not experience any symptoms at the higher doses (4–5 mg/kg/day) while approximately one-quarter of patients (23.26%) experienced symptom reappearance at lower doses (1–3 mg/kg/day) albeit with reduced severity and frequency.	In this study, CSA has shown significant effectiveness in controlling disease activity in CSU within a short period (3–5 days). We believe that initiating treatment with higher doses of CSA can be safely employed as a short-term therapy for patients with refractory CSU.
Chang <i>et al.</i> <sup>[46]</sup>	2021	Retrospective study	24 patients	9 to 18 years	3 mg/kg/day for 10 weeks to 17 months	Complete control of urticaria symptoms was reported in all 24 patients with a range of 2 days to 3 months. It was reported that more than half of the patients experienced complete control within 2 weeks. Time to relapse after discontinuation of the treatment was reported in 9 out of 24 patients with a range of 1 week to 37 months.	CSA was efficient and well tolerated in management of pediatric CSU.
Kulthanan <i>et al.</i> <sup>[47]</sup> (Thailand)	2018	Meta-analysis Systemic review	909 patients	More than 18 years	Very low (<2 mg/kg/day), low (from 2 to <4 mg/kg/day), and moderate (4–5 mg/kg/day) doses of CSA for up to 12 weeks	After 4 weeks, the mean relative change in urticaria activity score of CSA-treated patients was –17.89, whereas that of controls was –2.3. The overall response rate to CSA treatment with low to moderate doses at 4, 8, and 12 weeks was 54%, 66%, and 73%, respectively. No studies of very low-dose CSA	CSA is effective at low to moderate doses. Adverse events appear to be dose dependent and occur in more than half the patients treated with moderate doses of CSA. We suggest that the appropriate dosage of CSA for CSU may range from

(Contd...)

Table 7: (Continued).

Author	Year	Type of study	No. of patients	Age	Dose and duration	Result	Conclusion
						evaluated response rates at 4, 8, and 12 weeks. Among patients treated with very low, low, and moderate doses of CSA, 6%, 23%, and 57% experienced 1 or more adverse event, respectively.	1 to 5 mg/kg/d, and 3 mg/kg/d is a reasonable starting dose for most patients
Neverman <i>et al.</i> <sup>[48]</sup> (USA)	2014	Retrospective study	46 patients 26 female and 20 male patients	9–18 years Median, 12.5 years	3 mg/kg/day in two doses for 2 months to 17 months	All the patients who were antihistamine resistant were treated with CSA; all experienced complete resolution of urticaria at times that ranged from 2 days to 3 months (median, 7 days). Relapses responsive to repeated CSA occurred in 5 of the patients after 1 week to 15 months (median, 6 months). Adverse effects were not seen in these patients.	Data were consistent with efficacy and safety of CSA for CU in children when even high doses of antihistamines are ineffective.
Guaragna <i>et al.</i> <sup>[49]</sup> (Italy)	2013	Open sequential study	21 patients	Adults	4 mg/kg/day	The results obtained show a reduction in the levels of total IgE and a significant improvement in symptoms; there were no adverse effects.	CSA is an excellent treatment for CU because it reduces the activity of T lymphocytes and reduction of the histamine release from the mast cells and basophils.
Di Leo <i>et al.</i> <sup>[50]</sup> (Italy)	2011	Retrospective study	110 patients 63 female and 47 male patients	22 to 73 years Median=45.6 years	3 groups Group A=1–1.5 mg/kg/day Group B=1.6–2 mg/kg/day Group C=2.1–3 mg/kg/day for 6 months	The mean total symptom severity score decreased by 63% in Group A, 76% in Group B, and 85% in Group C after 6 months. Total disappearance of the symptoms was recorded in 43 patients (39.1%): 7 (28%) of Group A; 12 (37.5%) of Group B and 24 (45%) of Group C. After a mean of 2 months	study indicates that low-dose, long-term CSA therapy is efficacious and safe in severe unresponsive CIU.

(Contd...)

Table 7: (Continued).

Author	Year	Type of study	No. of patients	Age	Dose and duration	Result	Conclusion
						from CSA suspension, 14 patients (11%) had recurrence of symptoms. Minor side effects were noted in 8 patients (7%).	
Godse <sup>[51]</sup> (India)	2008	Open trial	5 patients	20–50 years Mean age=37.8 years	3 mg/kg/day for 6 weeks to 5 years	Average urticaria activity score was 5.4. Within 2 weeks of starting CSA, the score came down to 1.6. The male patient discontinued CSA due to high cost of therapy. Score came down to less than one in all four female patients who continued treatment. Side effects were few	This uncontrolled study has shown that low-dose CSA is effective in treating CIU patients, and can be given safely for 3 months. One study showed that prolonged treatment with CSA is beneficial for maintaining remission in severe cases of CU.
Serhat Inaloz <i>et al.</i> <sup>[52]</sup> (Turkey)	2008	Prospective controlled study	27 patients	Range=17–59 years Mean age=36.18±11.76 years	2.5 mg/kg/day for 4 weeks	In a total of 19 patients (70.37%), the score reduced by 25% after CSA treatment. Thus, these patients were considered to be in total remission. The reduction of the UAS score after CSA treatment was statistically significant in all patients ( $P<0.005$ )	Data of this study demonstrate that CSA therapy is efficient and safe for CIU patients. However, it is necessary to observe long-term CSA treatment in future studies because it may help patients maintain long periods of remissions.
Vena <i>et al.</i> <sup>[53]</sup> (Italy)	2006	Randomized controlled trial	99 patients 16 weeks CSA=31, 8 weeks CSA=33, placebo=35	16 weeks CSA=44.0±9.8 years, 8 weeks CSA=37.1±11.3 years, placebo=41.7±11.5 years	5 mg/kg/day (day 0 to day 13), 4 mg/kg/day (day 14 to day 27), 3 mg/kg/day (from day 28)	Fewer therapeutic failures occurred with 16-week CSA ( $n=3$ ) than with placebo ( $n=11$ ) and 8-week CSA ( $n=8$ ). After 8 and 16 weeks, symptom scores significantly improved in both CSA groups over with placebo. Two patients discontinued because of hypertension.	CSA in addition to background therapy with cetirizine may be useful in the treatment of CIU.

(Contd...)

Table 7: (Continued).

Author	Year	Type of study	No. of patients	Age	Dose and duration	Result	Conclusion
Kessel <i>et al.</i> <sup>[54]</sup> (Israel)	2006	Clinical trial	6 patients	Mean age=40.8±11.9 years	2–3 mg/kg/day for a period of 11.6±4 years	Five patients are favorably maintained on CSA treatment and do not require additional therapy. One patient required the addition of 5–10 mg/d prednisone (while continuing CSA 3 mg/kg/d) reducing the severity of urticaria. Two patients complained of mild hirsutism and peripheral neuropathy and one of a very mild diarrhea.	Prolonged treatment with CSA is beneficial for maintaining remission in severe cases of CU. It spares the need for corticosteroids and is accompanied with mild side effects.
Baskan <i>et al.</i> <sup>[55]</sup> (Turkey)	2004	Randomized clinical trial	20 patients		4 mg/kg/day for 4 weeks or 12 weeks	The clinical improvement was dramatic in the first month of treatment in both groups. There was no significant difference in the frequency of responses, side effects and the reduction of UAS in either group.	The preliminary results of our study suggest that CSA is clinically effective for CU. The prolonged use of this therapy for more than 1 month provides little benefit in the clinical improvement.
Grattan <i>et al.</i> <sup>[56]</sup> (UK)	2000	Randomized clinical trial	29 patients (19 active, 10 controls)	19–72 years Median age=33 years	4 mg/kg/day for 4 weeks	Mean reduction in UAS between weeks 0 and 4 was 12.7 (95% confidence interval, CI 6.6–18.8) for active and 2.3 (95% CI -3.3–7.9) for placebo ( $P=0.005$ ). Seventeen non-responders (seven randomized to active and 10 to placebo) chose open-label CSA and 11 responded after 4 weeks. Six of the eight randomized active drug responders relapsed within 6 weeks. Of the 19 responders to randomized and open-label CSA, five (26%) had not relapsed by the study end-point.	This study shows that CSA is effective for CU and provides further evidence for a role of histamine-releasing autoantibodies in the pathogenesis of this chronic “idiopathic” disease.

IgE: Immunoglobulin E, CI: Confidence interval, CSU: Chronic spontaneous urticarial, CSA: Cyclosporine, CIU: Chronic idiopathic urticarial, CU: Chronic urticaria

neurological manifestations have a poor response to CSA. Masuda *et al.* demonstrated that CSA is superior to colchicine, for treating ocular and mucocutaneous manifestations. However, due to the high dose (10 mg/kg/day), adverse effects were more pronounced in the CSA group than in the colchicine group.<sup>[131]</sup> Avci *et al.* demonstrated significant improvement in oral and genital aphthae as well as ocular and arthritic components associated with Behcet's disease.<sup>[132]</sup>

#### **Granuloma annulare**

Multiple case reports have shown the efficacy of CSA in generalized granuloma annulare suggesting its role in management. Spadino *et al.* reported good improvement of lesions, in 4 patients with disseminated granuloma annulare, treated with oral CSA at a dose of 4 mg/kg/day for 4 weeks, followed by tapering of dose by 0.5 mg/kg/day biweekly.<sup>[133]</sup>

#### **Pityriasis rubra pilaris (PRP)**

CSA has been found beneficial in PRP, especially in erythrodermic cases. It can be used along with acitretin in type I PRP. Usuki *et al.* demonstrated that CSA (5 mg/kg/day) gives satisfactory results in clinical resolution of erythema and scaling in erythrodermic PRP.<sup>[134]</sup>

#### **Polymorphous light eruption (PMLE)**

CSA has a prophylactic role in PMLE. Lasa *et al.* suggested that CSA at a dose of 3–4 mg/kg/day can be administered 1 week before travel to a sunny climate with discontinuation of the drug upon return and thus avoiding flare-up of PMLE.<sup>[135]</sup>

#### **Chronic actinic dermatitis**

Chronic actinic dermatitis cases with poor response or rapid relapse following systemic corticosteroid therapy can be treated with CSA (4–4.5 mg/kg/day). Paquet and Pierard have observed good responses to CSA within 4–12 weeks of therapy.<sup>[136]</sup>

#### **Hailey–Hailey disease (HHD)**

Several case reports have reported the efficacy of CSA in refractory cases, in 3–5 mg/kg/dose. However, there is gradual deterioration during dose tapering. Usmani and Wilson reported a dramatic response with combination therapy of low-dose CSA with acitretin in a recalcitrant case of HHD.<sup>[137]</sup> Varada *et al.* reported an improvement in lesions and quality of life in a 52-year-old female after adding CSA in a patient who was in on continuous treatment with acitretin.<sup>[138]</sup>

#### **Hidradenitis suppurativa**

CSA can be used in chronic, debilitating cases of hidradenitis suppurativa, in combination with antibiotics. Anderson *et al.* in their case series have reported mild-to-moderate improvement in 50% cases out of 18 patients, who were previously treated with other treatment modalities.<sup>[139]</sup>

#### **Cutaneous lupus erythematosus**

CSA is used in the setting of SLE as a concomitant systemic therapy or as a third-line therapy for cutaneous lesions when antimalarials, dapsone, oral prednisolone, or retinoid have already failed. Ogawa *et al.* in their clinical trial have demonstrated 75% improvement with CSA when other immunosuppressives have failed to achieve resolution. They also showed improvement in lupus nephritis along with maintenance of clinical resolution in the SLE patients.<sup>[140]</sup> CSA can be combined with steroids or other immunosuppressants, which allows dose downgrading of other immunosuppressants and sparing of steroid side effects.

#### **Dermatomyositis**

CSA may be used in treatment-refractory cases where methotrexate, azathioprine, and others have failed to provide clinical resolution. Vencovsky *et al.* have compared CSA with methotrexate and it has shown that methotrexate is more beneficial for myopathy and CSA is more beneficial for interstitial lung disease.<sup>[141]</sup> The drug has been found to be effective in esophageal disease, pulmonary involvement, and amyopathic dermatomyositis.<sup>[142,143]</sup>

#### **Systemic sclerosis**

CSA has shown antifibrotic effect as well as improvement of digital infarcts in some case reports. However, extra caution needs to be followed while administering CSA in systemic sclerosis otherwise the patient may develop malignant hypertension and scleroderma renal crisis.<sup>[144]</sup>

#### **Eosinophilic pustular folliculitis of Ofuji**

CSA gives satisfactory results in eosinophilic pustular folliculitis of Ofuji.<sup>[145]</sup> Fukamachi *et al.* in a case series of six patients reported 100% efficacy of CSA at 100–150 mg/day/dose for 2–12 weeks without any drug-related adverse events.<sup>[146]</sup>

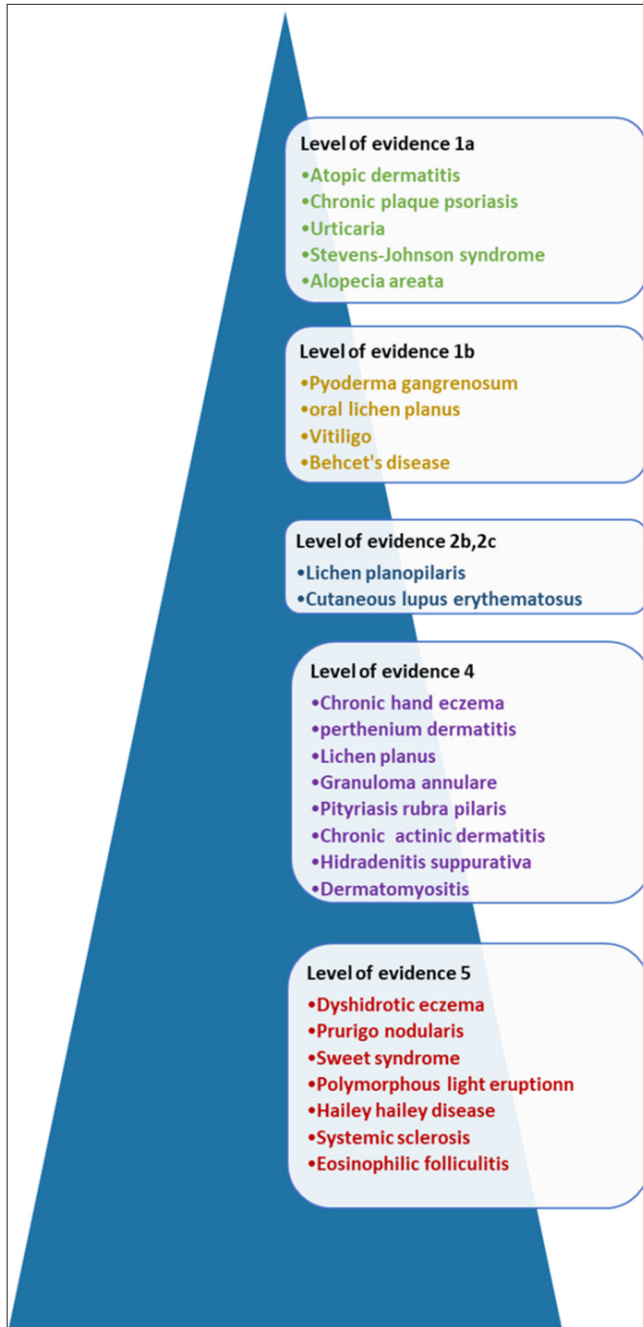
### **EVIDENCE-BASED REVIEW**

The salient features of evidence in support of using cyclosporine is summarised in Table 16 and Figure 2. Level of evidence as per the criteria set by Oxford CEBM (centre of evidence based medicine) is depicted in box 1 [Table 16 and Figure 2].

### **CSA CONGENERS**

CSA as a systemic drug in dermatological indications has been used for long with satisfying results. Other than CSA, the drugs that act by a similar mechanism of immunomodulation are oral tacrolimus and recently, oral voclosporin. Drugs in this group have been used in organ transplant recipients with success and with favorable side effect profile. Although not approved for dermatological conditions, the drugs have been used in a number of dermatologic conditions as off-label drugs.





**Figure 2:** Figure depicting the level of evidence of cyclosporin in dermatological indications.

### Systemic tacrolimus

Oral tacrolimus was approved by FDA in 1994, for preventing liver transplant rejection.<sup>[147]</sup> It inhibits calcineurin phosphatase in T lymphocytes and thus prevents transcription of IL-2, similar to CSA, but it is 100 times more potent than CSA. Common side effects are comparable to CSA; however, nephrotoxicity and cardiovascular risk profile have been found better in oral

tacrolimus.<sup>[148]</sup> Oral tacrolimus at a dose of 0.05–0.6 mg/kg/day has been found efficacious in psoriasis, eczema, and urticaria.

### Voclosporin

Voclosporin is the most recent calcineurin inhibitor and was FDA-approved for lupus nephritis in 2021. Pharmacokinetic properties have shown voclosporin (0.4–1.5 mg/kg/day) to be more potent than CSA. The side effect profile is more or less similar to CSA and its use in dermatology till now has been limited to psoriasis.<sup>[149]</sup> Table 17 highlights the comparison of cyclosporine with its congeners.<sup>[150–152]</sup>

### PLACE OF CSA IN GUIDELINES

There are multiple views on the role of CSA in indications which differ from country to country. Expert consensus statements have placed CSA as an effective drug in the management of different indications, in accordance with the level of evidence and strength of recommendation.

#### AD

##### *American Association of Dermatology (AAD) guideline (2023)*

According to AAD guidelines, CSA may be used in moderate-to-severe cases of refractory AD, for a limited duration, and with proper monitoring. The initial dose is recommended as 3.5 mg/kg. The guideline has placed the drug as a conditional recommendation in favor of intervention with low certainty of evidence.<sup>[153]</sup>

##### *European Guideline (EuroGuiDerm) (2022)*

EuroGuiDerm strongly recommended the use of CSA to achieve the control of disease in atopic eczema patients who are candidates for systemic therapy.

The guideline also mentions the dose for ≥16 years of age patients as 2.5–5 mg/kg in two divided doses. CSA may be started at higher doses, with meticulous monitoring of blood pressure and serum creatinine.<sup>[154]</sup>

##### *American Academy of Allergy, Asthma and Immunology/ American College of Allergy, Asthma and Immunology Joint Task Force guideline (2024)*

This guideline contributed by patients, caregivers, clinical experts such as allergists and dermatologists, and front-line clinicians has suggested CSA in moderate-to-severe AD as conditional in strength and low certainty of evidence. The initial dose (low or high) depends on the severity of the disease at presentation and the patient's expectation of rapidity of response. However, it must be remembered that the patients should be kept on the lowest possible (yet effective) dose so the adverse effects are minimized without hampering clinical benefit.<sup>[155]</sup>

**Table 8:** Studies on efficacy of CSA in treatment of atopic dermatitis.

Author	Year	Type of study	No. of patients	Age group	Dose and duration	Results	Conclusion
Van der Rijst <i>et al.</i> <sup>[62]</sup> (Netherlands)	2025	Multicentric cohort study	362 pts; 216 pts CSA administered, 94 pts: MTX 192 pts: dupilumab	2-17 years (14.9±3.8 years)	Starting dose 4 mg/kg/day, drug survival rate detected for 1, 2 and 3 year	Drug survival rate for 1 year, 2 year and 3 year is 43.9%, 21.5%, and 10.4% respectively. Discontinuation contributed by ineffectiveness and adverse effects	Drug survival rate is less in relation to MTX and dupilumab, which may reflect effectiveness and safety of CSA
Alexander <i>et al.</i> <sup>[63]</sup> (UK)	2024	Prospective observational cohort study	488 pts, CSA in 57 pts, MTX in 149 pts, Dupilumab in 282 pts	3–82 years (27.4±15.6 years)	1.4–5 mg/kg 28 days to 1 year (mean 8 months)	EASI-50,75 and 90 achieved rapid reduction in CSA than methotrexate. In severe disease, EASI, POEM, PP-NRS reduction is more in CSA than dupilumab and methotrexate	CSA most effective in very severe AD with significant improvement in itch and quality of life
Flohr <i>et al.</i> <sup>[64]</sup> (UK and Ireland)	2023	Multicentric parallel group assessor blinded RCT	103 pts, 52 pts were given CSA and 51 pts were given MTX	2–16 years (10.34±4.21)	4 mg/kg for 36 weeks, follow up for more 24 weeks	CSA showed better response in 12 weeks with O-SCORAD mean difference –5.69, in 60 weeks, MTX was better with ≥75% SCORAD, EASI, 50, 75 decrease. Post treatment flare more reported in CSA	CSA was superior in achieving rapid clearance, and MTX showed sustained disease control following discontinuation
Proenca <i>et al.</i> <sup>[65]</sup> (Brazil)	2023	Retrospective observational study	16 pts	5–19 years (11.94±4.37)	3 mg/kg for 6 months	>30% reduction of SCORAD in 75% pts. No serious side effect (4 hypertrichosis, 3 infection)	CSA well tolerated and well effective in children and adult age group in moderate to severe atopic dermatitis
Vyas <i>et al.</i> <sup>[66]</sup> (India)	2023	Randomized open label parallel group study	50 pts, allotted in 1:1 ratio in CSA and apremilast group	12–65 years of age (35±16.43)	5 mg/kg for 24 weeks and 12 weeks follow up	Mean percentage change in apremilast was 67.79% and in CSA was 83.06%. Adverse effect encountered 28.57% in apremilast group and 1.74% in CSA group	CSA has better efficacy and favorable safety and drug tolerance profile than apremilast
Patro <i>et al.</i> <sup>[67]</sup> (India)	2020	Retrospective observational study	14 pts	0.5–10 years	3-4 mg/kg for 4 to 12 weeks	TIS score decreased from 5–9 to 0–1; no serious side effect other than GI intolerance	CSA Can be used safely in recalcitrant atopic dermatitis within therapeutic dose

(Contd...)

**Table 8:** (Continued).

Author	Year	Type of study	No. of patients	Age group	Dose and duration	Results	Conclusion
Sarıcaoğlu <i>et al.</i> <sup>[68]</sup> (Turkey)	2018	Retrospective observational study	43 pts	6–17 years	2.5–5 mg/kg with median dose of 3 mg/kg for 3–14 months (4.9±4.24)	39.5% achieved good response, 23.5% achieved moderate response and 32.5% did not response. Side effects were milder	Low dose CSA is effective and safe for children in severe and recalcitrant atopic dermatitis, while higher dose is required for acute and very severe disease
Goujon <i>et al.</i> <sup>[69]</sup> (France)	2018	Randomized control trial	97 pts: Group A (MTX in 50 pts) Group B (CSA in 47 pts)	32.48±9.40	2.5 mg/kg for 8 week, if 50% reduction of SCORAD did not occur, then 5 mg/kg for next 16 weeks	At week 8, SCORAD 50 reduction was 8% in MTX and 42% in CSA. Treatment related adverse events were more common in CSA group	CSA was superior than MTX in week 8 in case of SCORAD reduction.
Hernández-Martín <i>et al.</i> <sup>[70]</sup> (Spain)	2017	Retrospective study	63 pts	8.4±3.6 years	4.27±0.61 mg/kg for 4.6 months (mean); range 3-12 months	Good to excellent response (64%). Response better without eosinophilia. Prolonged remission in 20% cases	Efficacious and rapidly acting in children; can provide sustained remission in some pts; drug is well tolerated but strict monitoring required
Kim <i>et al.</i> <sup>[71]</sup> (Korea)	2016	Prospective RCT	60 pts divided into group A (oral CSA+topical therapy) and group B (oral CSA) in 1:1 ratio	Mean 22.63 (group A) and 23.43 (group B)	4.5 mg/kg initial dose, tapered by 1–1.5 mg/kg; Average 3–6 mg/kg; Duration: Till successful treatment (group A [12.1±5.7 weeks]; group B [16.1±6.1 weeks])	85.15% pts achieved successful treatment with oral CSA and topical corticosteroid/ calcineurin inhibitor group while in CSA monotherapy it was 58.6%.	Though CSA is effective as monotherapy, but concomitant topical therapy improves the efficacy
Van der Schaft <i>et al.</i> <sup>[72]</sup> (Netherlands)	2015	Multicentric Retrospective cohort study	356 pts	37.6±14.2 years	2 groups ; one group (195 pts) had initial 3.5–5 mg/kg dose with gradual tapering in 3–6 weeks, another group (160 pts) had ≤3.5 mg/kg dose with increased dose in insufficient response; duration 3–2190 days with median of 356 days	Intermediate to high dose is related to increased drug survival, related to ineffectiveness, Reasons for discontinuation was disease controlled (26.4%), Side effects (22.2%), ineffectiveness (16.3%) and both side effect and ineffectiveness (6.2%) of the drug	Older age is associated with decreased drug survival due to side effects and disease control. Discontinuation due to ineffectiveness is less in high dose group

(Contd...)

**Table 8:** (Continued).

Author	Year	Type of study	No. of patients	Age group	Dose and duration	Results	Conclusion
Jin <i>et al.</i> <sup>[73]</sup> (South Korea)	2015	Placebo controlled double blinded RCT	43 pts divided into group A (glucosamine and CSA) and group B (CSA and placebo)	20.03±9.36 years	2 mg/kg for 8 weeks	Group A significantly reduced SCORAD, chemokine ligand 17 than group B but not IL 31, No increase in adverse events	Low dose CSA and glucosamine combination is beneficial in long term treatment of moderate to severe atopic dermatitis.
Sibbald <i>et al.</i> <sup>[74]</sup> (Canada)	2015	Retrospective study	15 pts	11.2±3.4 years	2.8±0.6 mg/kg; duration 7–15 months, (10.9±2.7)	80% responded but 42% encountered relapse, Treatment for longer duration prevented relapse, Adverse event led to discontinuation in 3 pts	Low dose and longer duration of treatment decrease the relapse in atopic dermatitis
Garrido Colmenero <i>et al.</i> <sup>[75]</sup> (Spain)	2015	Case series	5 pts	1–14 years	5 mg/kg in weekend (2 days), for 20 weeks	Significant decrease in SCORAD ( $\leq 30$ ) with reduction in cumulative dose and serum concentration of CSA	Weekend CSA therapy lead to clinical improvement and less serum concentration of CSA, thus allowing prolonged treatment and preventing relapse
El-khalawany <i>et al.</i> <sup>[76]</sup> (Egypt)	2013	Multicentric RCT	40 pts; group A (MTX, 20 pts) group B (CSA, 20 pts)	10.73±2.21 years	2.5 mg/kg for 12 weeks	SCORAD reduction in CSA group was more (31.35±8.89) than MTX group (26.25±7.03), Side effects were temporary and milder.	CSA is safe, effective and well tolerated in low dose in severe AD.
Kwon <i>et al.</i> <sup>[77]</sup> (South Korea)	2013	Crossover pilot study	10 pts	22.28±8.6	3 mg/kg for 26 weeks	Glucosamine combination decreased mean percentage of SCORAD and IL-4,5 level more than CSA monotherapy	CSA and glucosamine combination is an effective treatment in AD.
Beaumont <i>et al.</i> <sup>[78]</sup> (UK)	2012	Retrospective observational cohort study	35 pts	6–13 years; mean age 8 years	5 mg/kg/day for 10–32 weeks (mean 20 weeks)	CSA resulted in 91% reduction of SCORAD in infection triggered AD. SCORAD index reduction was only 44% when there is persistence or recurrence of infection	CSA provides better results in infection driven AD than in non-infectious triggers and in case of recurrent infection.

(Contd...)

**Table 8:** (Continued).

Author	Year	Type of study	No. of patients	Age group	Dose and duration	Results	Conclusion
Haeck <i>et al.</i> <sup>[79]</sup> (Netherlands)	2011	Observer blinded RCT	55 pts; group A (CSA) and group B (Mycophenolate enteric capsule)	36.56±12.87 years	3 mg/kg for 30 weeks	SCORAD and TARC level was higher in group B (mycophenolate) than CSA, after medication withdrawal disease activity was more in CSA	Encapsulated mycophenolate is as effective as CSA, but clinical improvement is rapid in case of CSA
Schmitt <i>et al.</i> <sup>[80]</sup> (Germany)	2010	Double blinded placebo controlled RCT	38 pts, one group treated with prednisolone followed by placebo, another group by CSA.	18–55 years	2.7–4 mg/kg for 6 weeks with 12 weeks follow up	Stable remission achieved in 6/17 pts in CSA group and 1/21 pts in prednisolone group	CSA is significantly more effective in achieving stable remission in severe atopic eczema than prednisolone
Bemianian <i>et al.</i> <sup>[81]</sup> (Iran)	2005	RCT	14 pts, divided into group A: 8 pts in CSA group and 6 pts in IVIg group	11.91±4.29 years	4 mg/kg for 13 weeks	Reduction of SCORAD occurred in both group, but continued deceleration noted in CSA group. All side effects of drug were transient	CSA is safe, relatively cheaper, easily available and effective drug than IvIg
Pacor <i>et al.</i> <sup>[82]</sup> (Italy)	2004	RCT	30 pts, divided into topical tacrolimus and CSA group in 1:1 ratio	13–45 years (26.85±10.29)	3 mg/kg for 6 weeks	Tacrolimus ointment group reported significantly lower SCORAD than the CSA group, Area under curve (AUC) day (0-42) was lower in tacrolimus than CSA	Both topical tacrolimus and oral CS group showed efficacy, but tacrolimus had faster mode of action
Granlund <i>et al.</i> <sup>[83]</sup> (Finland)	2001	Multicentric open label trial	72 pts divided into 1:1 ratio into group A (UVAB phototherapy) and group B (CSA)	18–70 years	Maximum 4 mg/kg to minimum 1 mg/kg for 8 weeks	No difference in quality of life but CSA has significantly more days in remission in 1 year study period	CSA seems to be more effective than UVAB in maintaining remission and reasonably safe
Bunikowsky <i>et al.</i> <sup>[84]</sup> (Germany)	2001	Open prospective study	10 pts	22–106 months	2.5 mg/kg starting dose, increased stepwise in non-responders to maximum of 5 mg/kg dose	9/10 pts had SCORAD reduction, 4 pts at 2.5 mg/kg dose, 3 pts at 3.5 mg/kg dose and 2 pts at 5 mg/kg dose, with significant reduction in IFN gamma, IL-2, 4, 13	Low dose microemulsion improves clinical measures and reduces T cell cytoproduction

(Contd...)

**Table 8:** (Continued).

Author	Year	Type of study	No. of patients	Age group	Dose and duration	Results	Conclusion
Pacor <i>et al.</i> <sup>[85]</sup> (Italy)	2001	Open uncontrolled study	15 pts	35.5 years (median)	5 mg/kg for 8 weeks	90% reduction in mean extent score in Likert scale	CSA is effective and safe for treating AD
Caproni <i>et al.</i> <sup>[86]</sup> (Italy)	2000	Open uncontrolled study	10 pts	17–56 years	5 mg/kg for 6 weeks	CD30 level decreased after treatment (135.7–96.2). ECP level also decreased (57.78–18.69). No significant difference in serum IgE level.	CSA therapy results in clinical improvement along with significant reduction in CD30 and ECP level
Harper <i>et al.</i> <sup>[87]</sup> (UK)	2000	Retrospective observational study	40 pts	2--16 years (10.05±3.2)	5 mg/kg one group for 12 weeks and another group with 52 weeks	No significant difference in between groups in SASSAD area disease activity monitoring, but improvement were consistent in continuous arm. No clinically significant changes in mean serum creatinine and blood pressure	More consistent control is achieved with continuous treatment. However, short course therapy was adequate for some pts, so the treatment should be tailored according to patient.
Czech <i>et al.</i> <sup>[88]</sup> (Germany)	2000	Double blinded RCT	106 pts	≥18 years (34±8.93)	Divided into group A (150 mg) and group B (300 mg) for 8 weeks	Symptom score decreased from 59 to 39.3 in group A and 60.7 to 33.2 in group B. Serum creatinine rise 0.6% in group A and 5.8% in group B	Although 300 mg more effective, 150 mg is preferred due to better renal tolerability.

ECP: Eosinophil cationic protein, IgE: immunoglobulin E, RCT: Randomized controlled trial, pts: Patients, IL: Interleukin, GI: Gastrointestinal, CSA: Cyclosporine, MTX: Methotrexate, EASI: Eczema area and severity index, SCORAD: Scoring atopic dermatitis, PP-NRS: Peak pruritus numerical rating scale, POEM: Patient oriented eczema score, SASSAD: Six area six sign atopic dermatitis score, RCT: Randomized control trial, TIS score: Three item severity score, AD: Atopic dermatitis, UVAB: Ultraviolet light A and B, SASSAD: Six area, six sign atopic dermatitis severity score, TARC: Thymus and activation regulated chemokine, CD: Cluster differentiation, CS: Corticosteroid

### Japanese guidelines for AD (ADGL 2021)

According to Japanese guidelines, the initial dose recommended is 3 mg/kg/day which should be increased or decreased according to disease severity, and the therapy must be completed within 8–12 weeks. The guideline also recommends switching to conventional topical agents as soon as symptoms improve.<sup>[156]</sup>

### Psoriasis

#### Joint AAD/National Psoriasis Forum Guideline (2021)

Guideline has recommended strongly for CSA in severe, recalcitrant psoriasis (strength of recommendation (A). Consensus has also recommended the drug for generalized

pustular, erythrodermic, or palmoplantar psoriasis (Strength of recommendation B). Drugs can also be used during acute flare of the pre-existing disease as a short-term interventional therapy (Strength of recommendation C).<sup>[157]</sup>

#### S3 guideline for treatment of psoriasis (2021)

Consensus recommends CSA for induction therapy of moderate-to-severe cases of psoriasis. Combination therapy with CSA and topical preparations are also suggested for treating moderate-to-severe disease.<sup>[158]</sup>

#### EuroGuiderm guideline for treatment of psoriasis (2021)

Guideline has recommended CSA as one of the conventional first-line drugs that can be used in moderate-to-severe psoriasis.

**Table 9:** Studies on efficacy of CSA in treatment of SJS-TEN.

Author	Year	Type of study	Number of patients	Dose and duration	Result	Conclusion
Poizeau <i>et al.</i> <sup>[96]</sup> (France)	2018	Retrospective cohort study	95 (received CSA) 79 patients (only supportive care)	3 mg/kg/day for 10 days	Outcomes did not significantly favour cyclosporine either by exposed/unexposed method or propensity score method. Acute kidney injury were more in patients receiving CSA ( $P=0.05$ ).	The study did not find CSA to be significantly superior than supportive care
Mohanty <i>et al.</i> <sup>[97]</sup> (India)	2017	Record based, observational study	28 Patients (19 patients in CSA group and 9 patients in supportive care)	5 mg/kg/day for 10 days	Stabilization, reepithelialization and recovery time were significantly lower in the CSA group ( $P<0.001$ , $P=0.007$ , $P=0.01$ , respectively). The standardized mortality ratio (0.32) 3.3 times lower than the only supportive treatment in CSA group	CSA (5 mg/kg/day) for 10 days may reduce the risk of dying, may fasten the healing of lesions and may lead to early discharge from hospital.
Lee <i>et al.</i> <sup>[98]</sup> (Singapore)	2017	Retrospective cohort study	44 patients (24 patients on CSA and 20 patients on supportive care)	3 mg/kg for 10 days then 2 mg/kg for 10 days then 1 mg/kg for 10 days	3 deaths were observed within 7.2 SCORTEN predicted deaths in the CSA treated group, whereas 6 deaths were observed among 5.9 predicted deaths in supportive care group. The standardized mortality ratio of SJS/TEN treated with CSA was 0.42 (95% confidence interval 0.09–1.22).	CSA may improve the survival rate in SJS-TEN patients
Kirchhof <i>et al.</i> <sup>[99]</sup> (Canada)	2014	Retrospective cohort study	64	3–7 mg/kg/day (mean) for 3–5 days oral or 7 days IV	Standardized mortality ratio was better in CSA (0.43) than IVIg (1.43) group	CSA may provide better mortality benefit than IVIg.
Singh <i>et al.</i> <sup>[100]</sup> (India)	2013	Prospective open study with retrospective comparison	11 patients treated with CSA compared with 6 patients in corticosteroid	3 mg/kg/day for 7 days followed by dose tapering by 7 days	Mean duration of re-epithelialization, hospital stay was lower in CSA group than corticosteroid group	CSA has encouraging role in SJS-TEN management by reducing the time period for re-epithelialization and decreasing the hospital stay

(Contd...)

**Table 9:** (Continued).

Author	Year	Type of study	Number of patients	Dose and duration	Result	Conclusion
Reese et al. <sup>[101]</sup> (USA)	2011	Case series	4	Initially 5 mg/kg/day in 2 divided dose, one patient was treated for 5 days, other were tapered over 1 month	All patients showed rapid response	CSA is beneficial for rapid response in SJS-TEN management
Valeyrie-Allanore et al. <sup>[102]</sup> (France)	2010	Open prospective trial	29 patients (12=SJS/TEN overlap, 10=SJS, TEN=7)	3 mg/kg/day for 10 days	No death occurred while prognostic score predicted 2.75 deaths, Mean epidermal detachment remained stable in 62% cases.	Both death rate and progression of epidermal detachment improved with CSA, suggesting its beneficial role in SJS-TEN.

IVig: Intravenous immunoglobulin, SJS: Stevens–Johnson syndrome, TEN: Toxic epidermal necrolysis, CSA: Cyclosporine, SCORTEN: Score of Toxic Epidermal Necrolysis

During therapy with low-dose CSA, 2.5–3 mg/kg daily, follow-up intervals may be increased to 2 months or more.<sup>[159]</sup>

#### **Dutch evidence and consensus-based guideline on psoriasis (2017)**

CSA is recommended as induction therapy in moderate-to-severe cases of plaque-type psoriasis. The drug may be prescribed in individual cases for 2 years, with close monitoring of hypertension and serum creatinine levels.<sup>[160]</sup>

#### **Japanese guidelines for treatment of pustular psoriasis (2018)**

Japanese guideline recommends CSA at a dose of 2.5–5 mg/kg (level of recommendation C1[B]) and also advised to avoid long-term aimless treatment to avoid unnecessary adverse events, by limiting its use to up to 1 year.<sup>[161]</sup>

#### **Urticaria**

##### **Skin Allergy Research Society guideline (2022)**

The consensus suggests using CSA in refractory chronic urticaria even after updating second-generation antihistaminics, where omalizumab is contraindicated or not affordable. They also mentioned positive histamine release assay and low serum IgE level as a good predictor of CSA efficacy.<sup>[162]</sup>

##### **The international European Academy of Allergy and Clinical Immunology/Global Allergy and Asthma European Network/EuroGuiDerm/Asia Pacific Association of Allergy, Asthma, and Clinical Immunology guideline (2021)**

This guideline suggests using CSA in patients unresponsive to high doses of second-generation antihistaminics and

omalizumab (3.5–5 mg/kg/day, strong consensus; ≥90% agreement).<sup>[163]</sup>

#### **ADVERSE EFFECTS**

Along with its needed effects, CSA may cause some adverse effects, most of which are reversible when the drug is discontinued.

- **Mucocutaneous:** Common mucocutaneous adverse effects include generalized hypertrichosis (reversible), gum hypertrophy, acne and acneiform eruption, pyogenic granuloma, warts, and pseudofolliculitis barbae.<sup>[164]</sup> Some rare complications are keratosis pilaris, sebaceous hyperplasia, epidermal inclusion cysts, gynecomastia, and disseminated molluscum contagiosum.
- **Hypertension:** It may happen in 20% of patients.<sup>[165]</sup> The risk factors for the development of hypertension include age >45 years and those with pre-diagnosed hypertension.
- **Nephrotoxicity:** It is dose as well as duration-dependent, which can be modulated and controlled by titration of dose.
- **Hyperlipidemia:** An increase in triglyceride and cholesterol levels has been noted, which develops within 2 weeks of initiation of therapy.<sup>[166]</sup>
- **Neurotoxicity:** Paresthesias, tremor, asthenia, muscle cramps, headaches, and fatigue are some of the events reported.
- **Malignancy risk:** Cutaneous and lymphoproliferative malignancies such as malignant lymphomas, non-melanoma skin cancers, Kaposi sarcoma, and melanoma have been reported.



**Table 10:** Studies on efficacy of cyclosporine in treatment of pyoderma gangrenosum.

Author	Year	Study type	No. of patients	Dosage	Result	Conclusion
Shah <i>et al.</i> <sup>[103]</sup> (USA)	2023	Case series	7 patients	2 CSA 100 mg capsules are mixed with 98 mL of 100% vitamin E oil to form topical formulation and applied daily, till healing	6 out of 7 patients had decreased pain, size and depth of ulcer within 4 weeks of treatment, with earliest in 10 days, however new satellite lesion tends to develop	Topical CSA can be a cost effective, efficacious in pyoderma gangrenosum as a monotherapy and adjuvant
Mason <i>et al.</i> <sup>[104]</sup> (UK)	2017	multicentre, parallel-group, observer-blind RCT	112 patients (CSA in 59 patients and corticosteroid in 53 patients)	4 mg/kg/day	CSA was found to be cost effective than corticosteroid (net cost: $-\leq 1160$ ; 95% CI $-2991$ to $672$ ); Quality of life improved more with CSA than corticosteroid (net QALYs: 0.055; 95% CI 0.018–0.093)	CSA is cost effective and provides better outcome in relation to quality of life, especially in larger lesions
Ormerod <i>et al.</i> <sup>[105]</sup> (UK)	2015	Multicentre, parallel group, observer blind, RCT	112 patients (CSA in 59 patients and corticosteroid in 53 patients)	4 mg/kg/day	Mean speed of healing is faster in CSA ( $-0.21$ cm/day) than corticosteroid ( $-0.14$ cm/day) in initial 6 weeks duration. By 6 months, 28/59 patients in CSA group and 25/53 patients in corticosteroid group achieved complete healing	No significant difference in response in between CSA and corticosteroid other than rapid healing in initial stages in CSA.
Vidal <i>et al.</i> <sup>[106]</sup> (Spain)	2004	Case series	21 patients	5 mg/kg	96% patients had complete remission, however patient had recurrences during treatment discontinuation	CSA showed better efficacy with rapid response and acceptable toxicity
Friedman <i>et al.</i> <sup>[107]</sup> (USA)	2001	Retrospective chart analysis followed by prospective trial	11 patients (5 ulcerative colitis, 6 Crohn's disease)	IV CSA 4 mg/kg for 7–22 days followed by oral CSA 4–7 mg/kg/day	Mean time of response was 4.5 days and mean time of closure was 1.4 months. 9 patients were able to discontinue steroid with 7 patients achieved bowel activity remission. No significant toxicity noted	IV CSA is the treatment of choice for steroid refractory bowel associated pyoderma gangrenosum
Elgart <i>et al.</i> <sup>[108]</sup> (USA)	1991	Case series	7 patients	5–7 mg/kg/day	6 out of 7 patients responded with 3 cases among them achieved complete remission without any relapse. Side effects minimal, (one patient had reactivation of tuberculosis)	CSA is an useful treatment modality in refractory pyoderma gangrenosum

CSA: Cyclosporine, CI: Confidence interval, RCT: Randomized controlled trial, QALY: Quality-adjusted life year, IV: Intravenous

- Infection: Minor skin infections have been noted in patients, but the risk is not higher with CSA.<sup>[167,168]</sup>
- Vaccination: Live-attenuated vaccines should not be administered in patients receiving CSA. It is recommended that live vaccination should be avoided till 12 weeks of discontinuation of the drug, and there should be a minimum duration of 1 month between vaccination and commencement of immunosuppressive drugs.
- Metabolic: Other metabolic abnormalities include hypomagnesemia, hyperkalemia, and hyperuricemia.

**Table 11:** Studies on efficacy of CSA in treatment of oral LP.

Author	Year	Study type	No. of pts	Dosage	Result	Conclusion
Georgaki et al. <sup>[109]</sup> (Greece)	2022	RCT	32 divided into two groups (Dexamethasone and CSA) (topical)	100 mg/mL thrice daily for 4 weeks, topically In swish and spit method	At end of 4 weeks treatment period, both showed significant improvement and decrease in pain and dysphagia. Improvement scoring better with dexamethasone.	CSA is beneficial in reducing symptom and signs in symptomatic OLP, however efficacy less pronounced than topical dexamethasone
Monshi et al. <sup>[110]</sup> (Austria)	2021	Open label observational study	21 pts	CSA mouthrinse (200 mg/ twice daily) for 4 weeks	Visual analogue scale, physician's global assessment and dermatology life quality index decreased significantly after 4 weeks, but relapse occur after treatment discontinuation	Pain, extent of disease, quality of life improved with CSA mouthrinse in early phase.
Thongprasom et al. <sup>[111]</sup> (Thailand)	2007	RCT	13 pts; 6 receiving CSA and 7 receiving triamcinolone acetonide	100 mg/mL thrice daily	Partial response in 2 cases, no significant difference in response with topical steroid	Topical CSA did not provide significant benefit than topical steroid
Yoke et al. <sup>[112]</sup> (Singapore)	2006	RCT	139 pts; CSA: 68 pts and TCS: 71 pts	100 mg/mL thrice daily for 8 weeks	Pain, burning, reticulation, ulceration are found less responsive to topical CSA than TCS	Topical CSA no more effective than TCS in OLP management
Eisen et al. <sup>[113]</sup> (USA)	1990	Double blinded clinical trial	16 pts in 1:1 ratio in topical CSA and vehicle group	5 mL thrice daily (100 mg/mL) for 8 weeks	CSA group had marked improvement in erythema, erosion, reticulation, pain. Did not encounter any significant side effects	Topical CSA is useful in management of OLP

LP: Lichen planus, CSA: Cyclosporine, OLP: Oral lichen planus, TCS: Topical corticosteroid, RCT: Randomized controlled trial, pts: Patients

- Musculoskeletal: It can be presented with myalgia, lethargy, arthralgia, and even severe myopathy due to mitochondrial dysfunction due to CSA.<sup>[169]</sup>
- Gastrointestinal: Colicky abdominal pain is one of the most common adverse effects, apart from nausea, vomiting, and diarrhea.

## MONITORING

### Baseline

#### Examination

- History taking followed by physical examination
- Two readings of blood pressure at least 24 hours apart.

#### Laboratory

- Complete hemogram with differential white blood cell and platelet count
- Renal function test: Blood urea nitrogen, serum

creatinine (two values at least 24 hours apart; if discrepancy of more than 10%, repeat again)

- Liver function test: Especially liver enzymes
- Fasting lipid profile
- Urinalysis
- Other: Serum potassium, serum magnesium, serum uric acid levels

### Follow-up

#### Examination

- Re-evaluation should be done, two weekly for 1–2 months, followed by evaluation every 4–6 weeks
- Blood pressure should be checked at every visit.

#### Laboratory

- Should be done every 2 weeks for the first 1–2 months, then monthly while on CSA
- Complete hemogram

**Table 12:** Studies on efficacy of CSA in treatment of LPP.

Author	Year	Study type	No. of patients	Dosage	Result	Conclusion
Fatemi Naeini <i>et al.</i> <sup>[114]</sup> (Iran)	2020	RCT	33; 17: CSA 16: MTX	3–5 mg/kg/day for 6 months	Both have beneficial effects and relatively similar efficacy in decreasing mean LPPAI	Both options are preferable, however authors advised methotrexate as an earlier option
Bulbul Baskan and Yazici <sup>[115]</sup> (Turkey)	2018	Retrospective study	16 patients; 6 on CSA and 10 on MTX	3–5 mg/kg/day	Both have shown similar efficacy, however side effect was less in MTX group	Both CSA and MTX are useful option for LPP, however MTX is better tolerated
Mirmirani <i>et al.</i> <sup>[116]</sup> (USA)	2003	Case series	3 patients	3.5 mg/kg short course	Remission achieved in symptoms in highly symptomatic cases in 3 months and they remain asymptomatic for next 12 months	CSA helps in alleviating symptoms in LPP

LPP: Lichen planopilaris, CSA: Cyclosporine, MTX: Methotrexate, LPPAI: Lichen planopilaris activity index

**Table 13:** Studies on efficacy of CSA in treatment of lichen planus.

Author	Year	Study type	No. of patients	Dosage	Result	Conclusion
Schwager <i>et al.</i> <sup>[117]</sup> (USA)	2019	Retrospective study	18 out 444 patients were administered CSA	100–400 mg mean 300 mg)	10 patients (56%) had moderate response, 6 patients had significant (33%) response, 1 worsened and one 1 patients had no change	CSA is effective in lichen planus but response may be variable
Grattan <i>et al.</i> <sup>[118]</sup> (UK)	1989	Open uncontrolled study	4 patients with lichen planus hypertrophicus	5% W/W CSA IV solution under polyethelene occlusion for a month	Scaling decreased, plaques get thinner, and irritation decreased in two cases. Dermal T helper: suppressor cell ratio decreased	Topical CSA is effective in lichen planus hypertrophicus
Ho <i>et al.</i> <sup>[119]</sup> (USA)	1990	Case series	2 patients	6 mg/kg for 6 months	Rapid response in 4 weeks and complete resolution in 8 weeks, no side effect encountered	CSA has encouraging efficacy and safe in management of generalised lichen planus.

CSA: Cyclosporine, IV: Intravenous

- Renal and liver function test
- Fasting lipid profile
- Blood potassium, magnesium, uric acid.

#### **Some tests indicated infrequently in some high-risk patients**

- Blood CSA levels
- Creatinine clearance (if therapy has gone for more than 6 months, then this needs to be considered)
- Rarely renal biopsy.

#### **Renal function monitoring**

Renal dysfunction requires monitoring of serum creatinine

levels while administering CSA. This has been elaborated in the flowchart 1.

#### **Blood pressure monitoring**

In the case of CSA-induced hypertension, either the dosage should be reduced or antihypertensives such as nifedipine or isradipine may be prescribed [Flowchart 2].

#### **CONTRAINDICATIONS**

Absolute: Severe renal dysfunction, uncontrolled hypertension, hypersensitivity to CSA or any ingredient in the formulation; cutaneous T cell lymphoma; and malignancies (clinically cured or persistent)

**Table 14:** Studies on efficacy of CSA in treatment of AA.

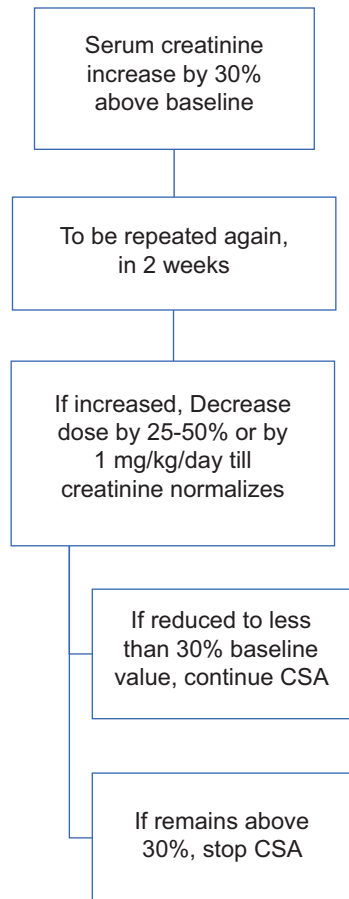
Author	Year	Study type	No. of patients	Dosage	Result	Conclusion
Lai <i>et al.</i> <sup>[120]</sup> (Australia)	2019	Double-blind, randomized, placebocontrolled trial	32 patients, 1:1 ratio in CSA and placebo	4 mg/kg/day for 3 months	The CSA group had a greater proportion of participants achieving at least a 50% reduction in Severity of alopecia tool score (31.3% vs. 6.3% [ $P=0.07$ ]) and greater proportion of participants achieving a 1-grade improvement in eyelash (18.8% vs. 0% [ $P=0.07$ ]) and eyebrow (31.3% vs. 0% [ $P=0.02$ ]) scale score	CSA is effective in AA, with improvement in severity of alopecia tool along with improvement in eyelashes and eyebrow.
Jang <i>et al.</i> <sup>[121]</sup> (Korea)	2016	Retrospective comparative study	88 (CSA 51 patients and Betamethasone 37 cases)	50–400 mg/day with median 200 mg over 13.2 months (mean)	54.9% responded in CSA group and 37.8% responded in betamethasone group	Oral CSA is superior than betamethasone pulse treatment of AA in respect to efficacy and safety profile
Açıkgöz <i>et al.</i> <sup>[122]</sup> (Turkey)	2013	Open uncontrolled clinical trial	25	2.5–6 mg/kg/day for 2-12 months	Significant hair growth was seen in 10 (45.4%) patients; among them five patients were with multifocal AA, three patients with alopecia universalis and two patients with alopecia totalis. Patients having more than 4 years duration had poor response to treatment (4/25)	Oral CSA treatment may be a beneficial treatment option for severe AA. In addition to this, disease duration is an important prognostic factor which decreases efficacy of oral CSA treatment
Kim <i>et al.</i> <sup>[123]</sup> (South korea)	2008	Open uncontrolled clinical trial	46	200 mg twice daily CSA which was reduced by 50 mg weekly, total duration 7–14 weeks	38 (88.4%) had significant hair regrowth and five (11.6%) were considered to be treatment failures. Nine (23.7%) relapsed during the observation period of 12 months	CSA in combination with methylprednisolone can give significant improvement in severe AA
Shaheedi-Dadras <i>et al.</i> <sup>[124]</sup> (Iran)	2008	Open uncontrolled clinical trial	18 patients (12 alopecia universalis and 6 alopecia totalis)	Oral CSA 2.5 mg/kg/day for 5 to 8 months along with IV methylprednisolone 500 mg pulse	Adequate response was noted ( $\geq 70\%$ ) cases in 6 cases (3 alopecia totalis and 3 universalis). No relapse seen in 8 months follow up	Patients with severe and resistant AA, if properly selected, may benefit from intravenous methylprednisolone pulse-therapy plus oral CSA
Ferrando and Grimalt <sup>[125]</sup> (Spain)	1999	Open label clinical trial	15	5 mg/kg/day for 6–12 months	Vellus hair regrowth was seen in 12 out of 14 patients	CSA is effective in AA with significant regrowth of hair
Shapiro <i>et al.</i> <sup>[126]</sup> (Canada)	1997	Open label clinical trial	8	5 mg/kg/day	>75% hair growth achieved in 2 out of 8 patients, however relapse occurred after end of therapy	CSA effectively grows hair, however relapse is common

AA: Alopecia areata, CSA: Cyclosporine, IV: Intravenous

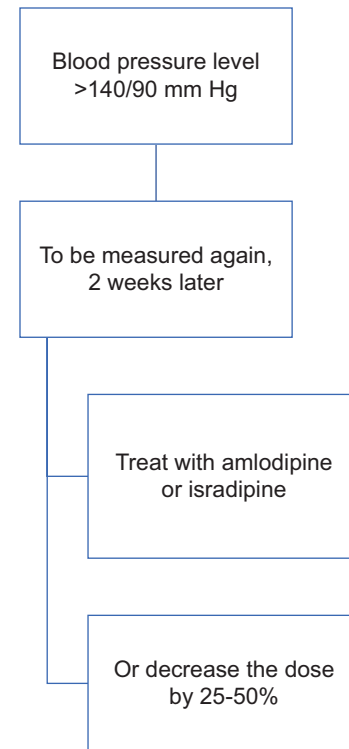
**Table 15:** Studies on efficacy of CSA in treatment of vitiligo.

Author	Year	Study type	No. of patients	Dosage	Result	Conclusion
Mehta <i>et al.</i> <sup>[127]</sup> (India)	2021	Randomized clinical trial	50	Group 1: 2.5 mg of dexamethasone per day for 2 consecutive days each week for a period of 4 months. Group 2: ciclosporine at a dosage of 3 mg/kg/day for the same duration of 4 months.	After 6 months, 21 patients in Group 1 and 22 patients in Group 2 achieved stability, resulting in a similar efficacy of 84% and 88% respectively.	Both CSA and oral steroid is effective in halting the progression of the disease.
Taneja <i>et al.</i> <sup>[128]</sup> (India)	2019	Open uncontrolled clinical trial	18	3 mg/kg/day	Out of 18 patients, 11 patients had achieved stability and among them 9 patients had repigmentation of lesions.	CSA has demonstrated its effectiveness in both stabilization and repigmentation of vitiligo.

CSA: Cyclosporine



**Flowchart 1:** Monitoring of serum creatinine level during cyclosporine (CSA) treatment.



**Flowchart 2:** Monitoring of blood pressure during treatment with cyclosporine (CSA).

## USE OF CSA IN SPECIAL POPULATIONS

### Pregnancy

As it is a pregnancy category C drug [newer rating: probably compatible], adequate contraceptive practice should be counseled while prescribing the drug to reproductive age group females. The risk-benefit ratio must be considered before prescribing, e.g., pustular psoriasis in pregnancy. Eclampsia, intrauterine growth restriction, and low birth

Relative: Age <18 years or >64 years; planned live-attenuated vaccine; active infection; evidence of immune deficiency; concomitantly receiving phototherapy; pregnancy and lactation; and unreliable patients.

**BOX 1:** Levels of evidence as per the criteria set by Oxford CEBM.

1a=Systematic reviews (with homogeneity) of RCTs.

1b=Individual RCT (with narrow confidence interval).

1c=All or none. Met when all patients died before the Rx became available, but some now survive on it; or when some patients died before the Rx became available, but none now die on it.

2a=SR (with homogeneity) of cohort studies.

2b=Individual cohort study (including low quality RCT; e.g., &lt;80% follow-up).

2c="Outcomes" research; Ecological studies.

3a=SR (with homogeneity) of case-control studies.

3b=Individual case-control study.

4=Case-series (and poor quality cohort and case-control studies)

5=Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"

RCT: Randomized controlled trial, CEBM: Centre for evidence-based medicine, SR: Systematic review, Rx: Treatment

**Table 16:** Levels of evidence as per the criteria set by Oxford CEBM.

Indication of CSA	Level of evidence
Atopic dermatitis	1a
Chronic plaque psoriasis	1a
Urticaria	1a
Chronic hand eczema	4
Dyshidrotic eczema	5
Perthenium dermatitis	4
Stevens Johnson syndrome and toxic epidermal necrolysis	1a
Pyoderma gangrenosum	1b
Oral lichen planus	1b
Lichen planopilaris	2b
Lichen planus	4
Alopecia areata	1a
Vitiligo	1b
Prurigo nodularis	5
Sweet syndrome	5
Behcet's disease	1b
Granuloma annulare	4
Pityriasis rubra pilaris	4
Polymorphous light eruption	5
Chronic actinic dermatitis	4
Hailey Hailey disease	5
Hidradenitis suppurativa	4
Cutaneous lupus erythematosus	2c
Dermatomyositis	4
Systemic sclerosis	5
Eosinophilic pustular folliculitis of ofuji	5

CEBM: Centre for evidence-based medicine, CSA: Cyclosporine

weight, preterm births are reported in pregnant females with CSA, thus any pregnancy with CSA should be considered as high risk.<sup>[170]</sup> However, there is no registered teratogenicity even though the drug is known to cross the placental barrier.

**Lactation**

CSA is excreted in breast milk, so lactating mothers are generally advised against breastfeeding.<sup>[171,172]</sup>

**Pediatric age group**

CSA is not approved by FDA below 18 years of age and in the UK, it is licensed for use only in children of <16 years of age. However, the drug has been in use as young as 1 year of age for indications such as nephrotic syndrome, juvenile dermatomyositis, organ transplantation, and autoimmune hemolytic anemias. A dose of 2–4 mg/kg/dose is recommended, with a duration of 6–16 weeks.<sup>[173]</sup>

Rajagopalan *et al.* suggest using the drug in AD, urticaria, psoriasis, lichen planus, vitiligo, alopecia areata, and SJS-TEN. They recommended a dose of 2.5–5 mg/kg/day for up to 14–16 weeks to be safe.<sup>[3]</sup> Children are less susceptible to CSA-induced nephropathy as the renal medullae are relatively larger, and the count of active nephron units is higher up to 18 years of age.

Regarding vaccination, as CSA is known to alter the humoral immune response and reduce antibody synthesis, it is better to avoid live vaccination. It also decreases the efficacy of killed vaccines. Rajagopalan *et al.* have depicted that considering the benefit-on-risk ratio, the drug may be used in vaccinated patients, and also CSA can be used between two doses of vaccination.<sup>[3]</sup>

**Elderly age group**

Tolerability of CSA is relatively less in elderly age group. Age-related comorbid conditions and loss of renal function often

**Table 17:** Comparison between CSA with its congeners.

Property	CSA	Tacrolimus	Voclosporin
Potency	Supresses T cell activation	100 times more potent than CSA	4 times more potent than CSA
Indication	Approved for psoriasis, other indications [Table 1]	Off label use in psoriasis, eczema, urticaria, pyoderma gangrenosum, Behcet's disease, and graft versus host disease	FDA approved for lupus nephritis, Off label use in Psoriasis
Dosage	3–5 mg/kg/day	0.05–0.6 mg/kg/day	0.4–1.5 mg/kg/day
Absorption and bioavailability	Variable	Better, so it is preferable in inflammatory bowel disease associated pyoderma gangrenosum. <sup>[150]</sup>	Better bioavailability than CSA
Common side effects	Common but milder side effects (headache, GI upset, nasopharyngitis, infections) occur	Comparable	Comparable
Hypertrichosis, gingival hyperplasia	Common	Less common	Less common
Cardiovascular profile	More chance of hypertension	Less	Less
Nephrotoxicity	Known to cause reversible and irreversible kidney injury	Less early nephrotoxicity but comparable chronic toxicity <sup>[151]</sup>	Better safety profile <sup>[152]</sup>

CSA: Cyclosporine, FDA: Food and Drug Administration, GI: Gastrointestinal

predispose to CSA-induced nephrotoxicity and hypertension, which warrant close laboratory monitoring.

#### Liver disease

Patients with known liver disease need close monitoring of liver enzyme levels while prescribing CSA. CSA is to be avoided if liver enzyme levels are more than three times of upper normal limit and in severe liver disease (Child pugh C).<sup>[174]</sup> Hepatic insufficiency also prolongs the half-life of the drug due to a decreased rate of hepatic metabolism, thus dose adjustment may be required. Regarding hepatitis B surface antigen reactive patients, there is a moderate risk of reactivation and prophylactic anti-hepatitis B virus treatment should be considered.<sup>[175]</sup> Proper monitoring and caution should also be followed in case of hepatitis C reactive patients.

#### Human immunodeficiency virus (HIV)

CSA is known to decrease the CD4 T cell count, and thus, it is avoided in late-stage HIV patients. Furthermore, due to coexistent other hepatotropic infections, and polypharmacy in HIV patients, the possibility of CSA-induced hepatotoxicity also increases. Also, protease inhibitors due to their inhibitory function on CYP3A4 enzyme, increase the serum concentration of CSA and increase the chance of drug toxicity. However, in the early stage of HIV (CD4 counts more than 500/mm<sup>3</sup>), low dose CSA (2 mg/kg/day) has increased viral load without any increase in occurrence of opportunistic infection or decrease in CD4 T cell count.<sup>[176]</sup>

#### Tuberculosis

As CSA suppresses the T cell-mediated immunity, there is a theoretical possibility of reactivation of latent tuberculosis. However, CSA in dermatological dosage has been found to be safe and the possibility of reactivation is scarce.<sup>[177]</sup>

#### DRUG INTERACTIONS

Clinicians should be conscious of the drug-drug interactions as well as the concomitant therapy with CSA to minimize the potential long-term side effects. A thorough drug history must be taken before the initiation of CSA therapy.

Drugs that can increase CSA levels include calcium channel blockers (verapamil, diltiazem, amlodipine, nifedipine), digoxin, Statins (atorvastatin, lovastatin), antifungals (ketoconazole, fluconazole, itraconazole), antibiotics (erythromycin, clarithromycin, azithromycin), antivirals (indinavir, ritonavir), prednisolone, non-steroidal anti-inflammatory drugs, colchicine.

Conversely, drugs that can decrease CSA levels include anti-tubercular drugs (rifampicin, isoniazid), anti-epileptics (barbiturates, phenytoin, carbamazepine), antibiotics (cotrimoxazole, sulfadimidine, imipenem, cephalosporins, ciprofloxacin), terbinafine, ticlopidine, octreotide, and nefazodone.

There is also an increased risk of carcinogenicity with high cumulative doses of ultraviolet radiation as well as radiation therapy, so caution should be followed in the case of narrow-band ultraviolet B and other phototherapy.<sup>[178]</sup>

## CONCLUSION

In spite of the advent of newer molecules including small molecules and biologics, cyclosporine continues to hold a strong position in the management of immunodermatological conditions. The evidence is robust (Level of evidence 1a) for atopic dermatitis, chronic plaque psoriasis, urticaria, Stevens Johnson syndrome and alopecia areata. Though not approved, but the molecule has been used for numerous off label indications. It must be remembered that cyclosporine is a magic molecule for many conditions, and proper monitoring and screening for serious adverse events should be performed in all cases.

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## REFERENCES

- Bubna AK. Cyclosporine in dermatology: Revisited. *Indian J Drugs Dermatol* 2023;9:62-74.
- Lim KK, Su WP, Schroeter AL, Sabers CJ, Abraham RT, Pittelkow MR. Cyclosporine in the treatment of dermatologic disease: An update. *Mayo Clin Proc* 1996;71:1182-91.
- Rajagopalan M, Saraswat A, Chandrashekar BS, Dhar S, Dogra S, Tahiliani S, et al. Role of cyclosporine (CsA) in immuno-dermatological conditions. *Indian Dermatol Online J* 2022;13:585-99.
- Tapia C, Nessel TA, Zito PM. Cyclosporine. In: StatPearls. Treasure Island, FL: StatPearls Publishing; 2025. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK482450> [Last accessed on 2025 Jan 29].
- Hawkes JE, Chan TC, Krueger JG. Psoriasis pathogenesis and the development of novel targeted immune therapies. *J Allergy Clin Immunol* 2017;140:645-53.
- Berekmeri A, Mahmood F, Wittmann M, Helliwell P. Tofacitinib for the treatment of psoriasis and psoriatic arthritis. *Expert Rev Clin Immunol* 2018;14:719-30.
- Colombo MD, Cassano N, Bellia G, Vena GA. Cyclosporine regimens in plaque psoriasis: An overview with special emphasis on dose, duration, and old and new treatment approaches. *ScientificWorldJournal* 2013;2013:805705.
- Marsili F, Travaglini M, Stinco G, Manzoni R, Tiberio R, Prignano F, et al. Effectiveness of cyclosporine A in patients with moderate to severe plaque psoriasis in a real-life clinical setting in Italy: The TRANSITION study. *J Dermatolog Treat* 2022;33:401-7.
- Singh SK, Singnarpri SR. Safety and efficacy of methotrexate (0.3 mg/kg/week) versus a combination of methotrexate (0.15 mg/kg/week) with cyclosporine (2.5 mg/kg/day) in chronic plaque psoriasis: A randomised non-blinded controlled trial. *Indian J Dermatol Venereol Leprol* 2021;87:214-22.
- Oh EH, Koh WS, Shin JM, Kim JE, Ko JY, Ro YS. Clinical experience of cyclosporin treatment in patients with psoriasis and psoriatic arthritis. *J Dermatol* 2018;45:329-30.
- Di Lernia V, Stingeni L, Boccaletti V, Calzavara Pinton PG, Guarneri C, Belloni Fortina A, et al. Effectiveness and safety of cyclosporine in pediatric plaque psoriasis: A multicentric retrospective analysis. *J Dermatolog Treat* 2016;27:395-8.
- Bulbul Baskan E, Yazici S, Tunali S, Saricaoglu H. Clinical experience with systemic cyclosporine A treatment in severe childhood psoriasis. *J Dermatolog Treat* 2016;27:328-31.
- Fernandes IC, Torres T, Selores M. Maintenance treatment of psoriasis with cyclosporine A: Comparison between continuous and weekend therapy. *J Am Acad Dermatol* 2013;68:341-2.
- Shintani Y, Kaneko N, Furuhashi T, Saito C, Morita A. Safety and efficacy of a fixed-dose cyclosporin microemulsion (100 mg) for the treatment of psoriasis. *J Dermatol* 2011;38:966-72.
- Yoon HS, Youn JI. A comparison of two cyclosporine dosage regimens for the treatment of severe psoriasis. *J Dermatolog Treat* 2007;18:286-90.
- Kokelj F, Torsello P, Plozzer C. Calcipotriol improves the efficacy of cyclosporine in the treatment of psoriasis vulgaris. *J Eur Acad Dermatol Venereol* 1998;10:143-6.
- Meffert H, Bräutigam M, Färber L, Weidinger G. Low-dose (1.25 mg/kg) cyclosporin A: Treatment of psoriasis and investigation of the influence on lipid profile. *Acta Derm Venereol* 1997;77:137-41.
- Singh RK, Lee KM, Ucmak D, Brodsky M, Atanelov Z, Farahnik B, et al. Erythrodermic psoriasis: Pathophysiology and current treatment perspectives. *Psoriasis (Auckl)* 2016;6:93-104.
- Bruzzese V, Pepe J. Efficacy of cyclosporine in the treatment of a case of infliximab-induced erythrodermic psoriasis. *Int J Immunopathol Pharmacol* 2009;22:235-8.
- Franchi C, Cainelli G, Frigerio E, Garutti C, Altomare GF. Association of cyclosporine and 311 nM UVB in the treatment of moderate to severe forms of psoriasis: A new strategic approach. *Int J Immunopathol Pharmacol* 2004;17:401-6.
- Kokelj F, Plozzer C, Torsello P, Trevisan G. Efficacy of cyclosporine plus etretinate in the treatment of erythrodermic psoriasis (three case reports). *J Eur Acad Dermatol Venereol* 1998;11:177-9.
- Giannotti B, Carli P, Veller-Fornasa C. Management of erythrodermic psoriasis with low-dose cyclosporine. *Dermatology* 1993;187:30-7.
- Shah M, Al Aboud DM, Crane JS, Kumar S. Pustular psoriasis. In: StatPearls. Treasure Island, FL: StatPearls Publishing; 2025.
- Georgakopoulos JR, Ighani A, Yeung J. Short- and long-term management of an acute pustular psoriasis flare: A case report. *J Cutan Med Surg* 2017;21:452-6.
- Hazarika D. Generalized pustular psoriasis of pregnancy successfully treated with cyclosporine. *Indian J Dermatol Venereol Leprol* 2009;75:638.
- Kiliç SS, Hacimustafaoglu M, Celebi S, Karadeniz A, Ildirim I. Low dose cyclosporine A treatment in generalized pustular psoriasis. *Pediatr Dermatol* 2001;18:246-8.
- Fradin MS, Ellis CN, Voorhees JJ. Rapid response of von Zumbusch psoriasis to cyclosporine. *J Am Acad Dermatol* 1990;23:925-6.
- Antony AS, Allard A, Rambojun A, Lovell CR, Shaddick G, Robinson G, et al. Psoriatic nail dystrophy is associated with erosive disease in the distal interphalangeal joints in psoriatic arthritis: A retrospective cohort study. *J Rheumatol* 2019;46:1097-102.
- Mittal J, Mahajan BB. Intramatricial injections for nail psoriasis: An open-label comparative study of triamcinolone, methotrexate, and cyclosporine. *Indian J Dermatol Venereol Leprol* 2018;84:419-23.
- Gümüsel M, Özdemir M, Mevlitoğlu I, Bodur S. Evaluation of the efficacy of methotrexate and cyclosporine therapies on psoriatic nails: A one-blind, randomized study. *J Eur Acad Dermatol Venereol* 2011;25:1080-4.
- Feliciani C, Zampetti A, Forleo P, Cerritelli L, Amerio P, Proietto G, et al. Nail psoriasis: Combined therapy with systemic cyclosporine and topical calcipotriol. *J Cutan Med Surg* 2004;8:122-5.
- Cannavò SP, Guarneri F, Vaccaro M, Borgia F, Guarneri B. Treatment of psoriatic nails with topical cyclosporin: A prospective, randomized placebo-controlled study. *Dermatology* 2003;206:153-6.
- Soriano A, Pipitone N, Salvarani C. Cyclosporine in psoriatic arthropathy. *Clin Exp Rheumatol* 2015;33:S101-3.
- Colombo D, Chimenti S, Grossi PA, Marchesoni A, Foti R, Calzavara-Pinton P, et al. Efficacy of cyclosporine A as monotherapy in patients with psoriatic arthritis: A subgroup analysis of the SYNERGY Study. *G Ital Dermatol Venereol* 2017;152:297-301.
- Karanikolas GN, Koukli EM, Katsalira A, Arida A, Petrou D, Komninou E, et al. Adalimumab or cyclosporine as monotherapy and in combination in severe psoriatic arthritis: Results from a prospective 12-month nonrandomized unblinded clinical trial. *J Rheumatol* 2011;38:2466-74.
- Fraser AD, van Kuijk AW, Westhovens R, Karim Z, Wakefield R, Gerards AH, et al. A randomised, double blind, placebo controlled, multicentre trial of



- combination therapy with methotrexate plus ciclosporin in patients with active psoriatic arthritis. *Ann Rheum Dis* 2005;64:859-64.
37. Salvarani C, Macchioni P, Olivieri I, Marchesoni A, Cutolo M, Ferraccioli G, *et al.* A comparison of cyclosporine, sulfasalazine, and symptomatic therapy in the treatment of psoriatic arthritis. *J Rheumatol* 2001;28:2274-82.
  38. Spadaro A, Ricciari V, Sili-Scavalli A, Sensi F, Taccari E, Zoppini A. Comparison of cyclosporin A and methotrexate in the treatment of psoriatic arthritis: A one-year prospective study. *Clin Exp Rheumatol* 1995;13:589-93.
  39. Steinsson K, Valdimarsson H. The case for cyclosporine a in psoriatic arthritis. *Inflammopharmacology* 1993;2:131-9.
  40. Gupta AK, Matteson EL, Ellis CN, Ho VC, Tellner DC, Voorhees JJ, *et al.* Cyclosporine in the treatment of psoriatic arthritis. *Arch Dermatol* 1989;125:507-10.
  41. Greenzaid J, Feldman S. Clinical pharmacokinetic and pharmacodynamic considerations in the treatment of moderate-to-severe psoriasis. *Clin Pharmacokinet* 2024;63:137-53.
  42. Lang DM. Chronic urticaria. *N Engl J Med* 2022;387:824-31.
  43. Zuberbier T, Latiff AH, Abuzakouk M, Aquilina S, Asero R, Baker D, *et al.* The international EAACI/GA<sup>2</sup>LEN/EuroGuiDerm/APAAACI guideline for the definition, classification, diagnosis, and management of urticaria. *Allergy* 2022;77:734-66.
  44. Godse K, De A, Zawar V, Shah B, Girdhar M, Rajagopalan M, *et al.* Consensus statement for the diagnosis and treatment of urticaria: A 2017 update. *Indian J Dermatol* 2018;63:2-15.
  45. Sehgal S, Agarwal S, Balai M, Meghwal L, Mittal A. Real-world clinical experience with oral cyclosporine in antihistamine refractory cases of chronic spontaneous urticaria. *Indian Dermatol Online J* 2024;15:887-90.
  46. Chang J, Cattelan L, Ben-Shoshan M, Le M, Netchiporouk E. Management of pediatric chronic spontaneous urticaria: A review of current evidence and guidelines. *J Asthma Allergy* 2021;14:187-99.
  47. Kulthanan K, Chaweekulrat P, Komoltri C, Hunnangkul S, Tuchinda P, Chularojanamontri L, *et al.* Cyclosporine for chronic spontaneous urticaria: A meta-analysis and systematic review. *J Allergy Clin Immunol Pract* 2018;6:586-99.
  48. Neverman L, Weinberger M. Treatment of chronic urticaria in children with antihistamines and cyclosporine. *J Allergy Clin Immunol Pract* 2014;2:434-8.
  49. Guaragna MA, Albanesi M, Stefani S, Franconi G, Di Stanislao C, Paparo Barbaro S. Chronic urticaria with high IgE levels: First results on oral cyclosporine A treatment. *Clin Ter* 2013;164:115-8.
  50. Di Leo E, Nettis E, Aloia AM, Moschetta M, Carbonara M, Dammacco F, *et al.* Cyclosporine-A efficacy in chronic idiopathic urticaria. *Int J Immunopathol Pharmacol* 2011;24:195-200.
  51. Godse KV. Cyclosporine in chronic idiopathic urticaria with positive autologous serum skin test. *Indian J Dermatol* 2008;53:101-2.
  52. Serhat Inaloz H, Ozturk S, Akcali C, Kirtak N, Tarakcioglu M. Low-dose and short-term cyclosporine treatment in patients with chronic idiopathic urticaria: A clinical and immunological evaluation. *J Dermatol* 2008;35:276-82.
  53. Vena GA, Cassano N, Colombo D, Peruzzi E, Pigatto P, Neo-I-30 Study Group. Cyclosporine in chronic idiopathic urticaria: A double-blind, randomized, placebo-controlled trial. *J Am Acad Dermatol* 2006;55:705-9.
  54. Kessel A, Toubi E. Extended cyclosporine-A-treatment for severe chronic urticaria. *Harefuah* 2006;145:411-4, 471.
  55. Baskan EB, Tunali S, Turker T, Saricaoglu H. Comparison of short- and long-term cyclosporine A therapy in chronic idiopathic urticaria. *J Dermatolog Treat* 2004;15:164-8.
  56. Grattan CE, O'Donnell BF, Francis DM, Niimi N, Barlow RJ, Seed PT, *et al.* Randomized double-blind study of cyclosporin in chronic "idiopathic" urticaria. *Br J Dermatol* 2000;143:365-72.
  57. Kocatürk E, Başkan EB, Küçük ÖS, Özdemir M, Örnek S, Can PK, *et al.* Omalizumab versus cyclosporin-A for the treatment of chronic spontaneous urticaria: Can we define better-responding endotypes? *An Bras Dermatol* 2022;97:592-600.
  58. Bylund S, Kobyletzki LB, Svalstedt M, Svensson Å. Prevalence and incidence of atopic dermatitis: A systematic review. *Acta Derm Venereol* 2020;100:adv00160.
  59. Dehesa L, Abuchar A, Nuno-Gonzalez A, Vitiello M, Kerdel FA. The use of cyclosporine in dermatology. *J Drugs Dermatol* 2012;11:979-87.
  60. Kutlubay Z, Erdogan BÇ, Engin B, Serdaroglu S. Cyclosporine in dermatology. *Skinmed* 2016;14:105-9.
  61. Schmitt J, Schmitt N, Meurer M. Cyclosporin in the treatment of patients with atopic eczema - a systematic review and meta-analysis. *J Eur Acad Dermatol Venereol* 2007;21:606-19.
  62. Van der Rijst LP, Kamphuis E, Schuttelaar ML, Hurmuz R, Seyger MM, Caron AG, *et al.* Drug survival of dupilumab, methotrexate, and cyclosporine a in children with atopic dermatitis. *JAMA Dermatol* 2025;161:12-21.
  63. Alexander H, Malek R, Prieto-Merino D, Gribaleva E, Baden M, Beattie P, *et al.* A prospective observational cohort study comparing the treatment effectiveness and safety of cyclosporin, dupilumab and methotrexate in adult and paediatric patients with atopic dermatitis: Results from the UK-Irish A-STAR register. *Br J Dermatol* 2024;191:988-99.
  64. Flohr C, Rosala-Hallas A, Jones AP, Beattie P, Baron S, Browne F, *et al.* Efficacy and safety of cyclosporin versus methotrexate in the treatment of severe atopic dermatitis in children and young people (TREAT): A multicentre parallel group assessor-blinded clinical trial. *Br J Dermatol* 2023;189:674-84.
  65. Proença CC, Mayor SA, Ragazzo TS, Munhoz SD, Pires CG. Use of cyclosporine in children and adolescents with moderate to severe atopic dermatitis: Clinical experience in a tertiary Hospital. *An Bras Dermatol* 2023;98:526-8.
  66. Vyas HR, Shah SR, Shah BJ, Parmar KS, Jangid N, Choudhary A, *et al.* A single-centre prospective study comparing efficacy and safety of apremilast with cyclosporine in moderate to severe atopic dermatitis. *Australas J Dermatol* 2023;64:e333-9.
  67. Patro N, Panda M, Dash M. Cyclosporine A in recalcitrant pediatric dermatoses-a retrospective analysis of thirty children. *Indian J Paediatr Dermatol* 2020;21:98-104.
  68. Sarıcaoğlu H, Yazıcı S, Zorlu Ö, Bülbül Başkan E, Aydoğan K. Cyclosporine-A for severe childhood atopic dermatitis: Clinical experience on efficacy and safety profile. *Turk J Med Sci* 2018;48:933-8.
  69. Goujon C, Viguier M, Staumont-Sallé D, Bernier C, Guillet G, Lahfa M, *et al.* Methotrexate versus cyclosporine in adults with moderate-to-severe atopic dermatitis: A phase III randomized noninferiority trial. *J Allergy Clin Immunol Pract* 2018;6:562-9.e3.
  70. Hernández-Martín A, Noguera-Morel L, Bernardino-Cuesta B, Torrelo A, Pérez-Martin MA, Aparicio-López C, *et al.* Cyclosporine A for severe atopic dermatitis in children. Efficacy and safety in a retrospective study of 63 patients. *J Eur Acad Dermatol Venereol* 2017;31:837-42.
  71. Kim JE, Shin JM, Ko JY, Ro YS. Importance of concomitant topical therapy in moderate-to-severe atopic dermatitis treated with cyclosporine. *Dermatol Ther* 2016;29:120-5.
  72. Van der Schaft J, Politiek K, van den Reek JM, Christoffers WA, Kievit W, de Jong EM, *et al.* Drug survival for ciclosporin A in a long-term daily practice cohort of adult patients with atopic dermatitis. *Br J Dermatol* 2015;172:1621-7.
  73. Jin SY, Lim WS, Sung NH, Cheong KA, Lee AY. Combination of glucosamine and low-dose cyclosporine for atopic dermatitis treatment: A randomized, placebo-controlled, double-blind, parallel clinical trial. *Dermatol Ther* 2015;28:44-51.
  74. Sibbald C, Pope E, Ho N, Weinstein M. Retrospective review of relapse after systemic cyclosporine in children with atopic dermatitis. *Pediatr Dermatol* 2015;32:36-40.
  75. Garrido Colmenero C, Blasco Morente G, Tercedor Sánchez J. Oral cyclosporine weekend therapy: A new maintenance therapeutic option in patients with severe atopic dermatitis. *Pediatr Dermatol* 2015;32:551-2.
  76. El-Khalawany MA, Hassan H, Shaaban D, Ghonaim N, Eassa B. Methotrexate versus cyclosporine in the treatment of severe atopic dermatitis in children: A multicenter experience from Egypt. *Eur J Pediatr* 2013;172:351-6.
  77. Kwon HB, Ahn BJ, Choi Y, Jin SY, Cheong KA, Lee J, *et al.* Combination of glucosamine improved therapeutic effect of low-dose cyclosporine A in patients with atopic dermatitis: A pilot study. *J Dermatol*. 2013;40:207-10.
  78. Beaumont DR, Arkwright PD. Factors determining the effectiveness of oral ciclosporin in the treatment of severe childhood atopic dermatitis. *J Dermatolog Treat* 2012;23:318-22.
  79. Haeck IM, Knol MJ, Ten Berge O, van Velsen SG, de Bruin-Weller MS, Buijnzeel-Koomen CA. Enteric-coated mycophenolate sodium versus cyclosporin A as long-term treatment in adult patients with severe atopic dermatitis: A randomized controlled trial. *J Am Acad Dermatol*

- 2011;64:1074-84.
80. Schmitt J, Schäkel K, Fölster-Holst R, Bauer A, Oertel R, Augustin M, *et al.* Prednisolone vs. ciclosporin for severe adult eczema. An investigator-initiated double-blind placebo-controlled multicentre trial. *Br J Dermatol* 2010;162:661-8.
  81. Bemanian MH, Movahedi M, Farhoudi A, Gharagozlou M, Seraj MH, Pourpak Z, *et al.* High doses intravenous immunoglobulin versus oral cyclosporine in the treatment of severe atopic dermatitis. *Iran J Allergy Asthma Immunol* 2005;4:139-43.
  82. Pacor ML, Di Lorenzo G, Martinelli N, Mansueto P, Rini GB, Corrocher R. *et al.* Comparing tacrolimus ointment and oral cyclosporine in adult patients affected by atopic dermatitis: A randomized study. *Clin Exp Allergy* 2004;34:639-45.
  83. Granlund H, Erkkö P, Remitz A, Langeland T, Helsing P, Nuutinen M, *et al.* Comparison of cyclosporine and UVAB phototherapy for intermittent one-year treatment of atopic dermatitis. *Acta Derm Venereol* 2001;81:22-7.
  84. Bunikowski R, Staab D, Kussebi F, Bräutigam M, Weidinger G, Renz H, *et al.* Low-dose cyclosporine A microemulsion in children with severe atopic dermatitis: Clinical and immunological effects. *Pediatr Allergy Immunol* 2001;12:216-23.
  85. Pacor ML, Biasi D, Di Lorenzo G, Carletto A, Corrocher R. Cyclosporin in atopic dermatitis. *Recenti Prog Med* 2001;92:390-1.
  86. Caproni M, Salvatore E, Cardinali C, Brazzini B, Fabbri P. Soluble CD30 and cyclosporine in severe atopic dermatitis. *Int Arch Allergy Immunol* 2000;121:324-8.
  87. Harper JL, Ahmed I, Barclay G, Lacour M, Hoeger P, Cork MJ, *et al.* Cyclosporine for severe childhood atopic dermatitis: Short course versus continuous therapy. *Br J Dermatol* 2000;142:52-8.
  88. Czech W, Bräutigam M, Weidinger G, Schöpf E. A body-weight-independent dosing regimen of cyclosporine microemulsion is effective in severe atopic dermatitis and improves the quality of life. *J Am Acad Dermatol* 2000;42:653-9.
  89. Munera-Campos M, Carrascosa JM. Janus kinase inhibitors in atopic dermatitis: New perspectives. *Actas Dermosifiliogr* 2023;114:680-707.
  90. Peterson CS, Menne T. Cyclosporine A responsive chronic severe vesicular hand eczema. *Acta Derm Venereol* 1992;72:436-7.
  91. Reitamo S, Granlund H. Cyclosporin A in the treatment of chronic dermatitis of the hands. *Br J Dermatol* 1994;130:75-8.
  92. Kim HL, Jung HJ, Park MY, Youn JI, Ahn JY. Clinical efficacy of oral cyclosporine on intractable hand eczema: A retrospective review of 16 cases. *Ann Dermatol* 2018;30:475-8.
  93. Verma KK, Bhari N, Kutar BM. Rapid response to ciclosporin in patients with Parthenium dermatitis: A preliminary study. *Contact Dermatitis* 2021;84:134-36.
  94. Lakshmi C, Srinivas CR, Jayaraman A. Ciclosporin in parthenium dermatitis-a report of 2 cases. *Contact Dermatitis* 2008;59:245-8.
  95. Gilbert M, Scherrer LA. Efficacy and safety of cyclosporine in Stevens-Johnson syndrome and toxic epidermal necrolysis. *Dermatol Ther* 2019;32:e12758.
  96. Poizeau F, Gaudin O, Le Cleach L, Duong TA, Hua C, Hotz C, *et al.* Cyclosporine for epidermal necrolysis: Absence of beneficial effect in a retrospective cohort of 174 patients-exposed/unexposed and propensity score-matched analyses. *J Invest Dermatol* 2018;138:1293-300.
  97. Mohanty S, Das A, Ghosh A, Sil A, Gharami RC, Bandyopadhyay D, *et al.* Effectiveness, safety and tolerability of cyclosporine versus supportive treatment in Stevens-Johnson Syndrome/toxic epidermal necrolysis: A record-based study. *Indian J Dermatol Venereol Leprol* 2017;83:312-6.
  98. Lee HY, Fook-Chong S, Koh HY, Thirumoorthy T, Pang SM. Cyclosporine treatment for Stevens-Johnson syndrome/toxic epidermal necrolysis: Retrospective analysis of a cohort treated in a specialized referral center. *J Am Acad Dermatol* 2017;76:106-13.
  99. Kirchhof MG, Miliszewski MA, Sikora S, Papp A, Dutz JP. Retrospective review of Stevens-Johnson syndrome/toxic epidermal necrolysis treatment comparing intravenous immunoglobulin with cyclosporine. *J Am Acad Dermatol* 2014;71:941-7.
  100. Singh GK, Chatterjee M, Verma R. Cyclosporine in Stevens Johnson syndrome and toxic epidermal necrolysis and retrospective comparison with systemic corticosteroid. *Indian J Dermatol Venereol Leprol* 2013;79:686-92.
  101. Reese D, Henning JS, Rockers K, Ladd D, Gilson R. Cyclosporine for SJS/TEN: A case series and review of the literature. *Cutis* 2011;87:24-9.
  102. Valeyrie-Allanore L, Wolkenstein P, Brochard L, Ortonne N, Maitre B, Revuz J, *et al.* Open trial of ciclosporin treatment for Stevens-Johnson syndrome and toxic epidermal necrolysis. *Br J Dermatol* 2010;163:847-53.
  103. Shah R, Ouellette S, Khan S, Truong T, Pappert A, Wassef C. Novel topical cyclosporine as adjuvant therapy for pyoderma gangrenosum: A case series. *JAAD Case Rep* 2023;40:67-73.
  104. Mason JM, Thomas KS, Ormerod AD, Craig FE, Mitchell E, Norrie J, *et al.* Ciclosporin compared with prednisolone therapy for patients with pyoderma gangrenosum: Cost-effectiveness analysis of the STOP GAP trial. *Br J Dermatol* 2017;177:1527-36.
  105. Ormerod AD, Thomas KS, Craig FE, Mitchell E, Greenlaw N, Norrie J, *et al.* Comparison of the two most commonly used treatments for pyoderma gangrenosum: Results of the STOP GAP randomised controlled trial. *BMJ* 2015;350:2958.
  106. Vidal F, Puig L, Gilaberte M, Alomar A. Review of 26 cases of classical pyoderma gangrenosum: Clinical and therapeutic features. *J Dermatolog Treat* 2004;15:146-52.
  107. Friedman S, Marion JF, Scherl E, Rubin PH, Present DH. Intravenous cyclosporine in refractory pyoderma gangrenosum complicating inflammatory bowel disease. *Inflamm Bowel Dis* 2001;7:1-7.
  108. Elgart G, Stover P, Larson K, Sutter C, Scheibner S, Davis B, *et al.* Treatment of pyoderma gangrenosum with cyclosporine: Results in seven patients. *J Am Acad Dermatol* 1991;24:83-6.
  109. Georgaki M, Piperi E, Theofilou VI, Pettas E, Stoufi E, Nikitakis NG. A randomized clinical trial of topical dexamethasone vs. cyclosporine treatment for oral lichen planus. *Med Oral Patol Oral Cir Bucal* 2022;27:e113-24.
  110. Monshi B, Ellersdorfer C, Edelmayer M, Dvorak G, Ganger C, Ulm C, *et al.* Topical cyclosporine in oral lichen planus-a series of 21 open-label, biphasic, single-patient observations. *J Clin Med* 2021;10: 5454.
  111. Thongprasom K, Chaimusig M, Korkij W, Sererat T, Luangjarmekorn L, Rojwattanasirivej S. A randomized-controlled trial to compare topical cyclosporin with triamcinolone acetonide for the treatment of oral lichen planus. *J Oral Pathol Med* 2007;36:142-6.
  112. Yoke PC, Tin GB, Kim MJ, Rajaseharan A, Ahmed S, Thongprasom K, *et al.* A randomized controlled trial to compare steroid with cyclosporine for the topical treatment of oral lichen planus. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2006;102:47-55.
  113. Eisen D, Ellis CN, Duell EA, Griffiths CE, Voorhees JJ. Effect of topical cyclosporine rinse on oral lichen planus. A double-blind analysis. *N Engl J Med* 1990;323:290-4.
  114. Fatemi Naeini F, Mohaghegh F, Jelvan M, Asilian A, Saber M. Cyclosporine or methotrexate, which one is more promising in the treatment of lichen planopilaris?: A comparative clinical trial. *Int Immunopharmacol* 2020;86:106765.
  115. Bulbul Baskan E, Yazici S. Treatment of lichen planopilaris: Methotrexate or cyclosporine a therapy? *Cutan Ocul Toxicol* 2018;37:196-9.
  116. Mirmirani P, Willey A, Price VH. Short course of oral cyclosporine in lichen planopilaris. *J Am Acad Dermatol* 2003;49:667-71.
  117. Schwager Z, Stern M, Cohen J, Femia A. Clinical epidemiology and treatment of lichen planus: A retrospective review of 2 tertiary care centers. *J Am Acad Dermatol* 2019;81:1397-9.
  118. Grattan C, Boon A, Gregory J. A preliminary open study of topical cyclosporine for hypertrophic lichen planus. *J Dermatol Treat* 2009;1:39-41.
  119. Ho VC, Gupta AK, Ellis CN, Nickoloff BJ, Voorhees JJ. Treatment of severe lichen planus with cyclosporine. *J Am Acad Dermatol* 1990;22:64-8.
  120. Lai VW, Chen G, Gin D, Sinclair R. Cyclosporine for moderate-to-severe alopecia areata: A double-blind, randomized, placebo-controlled clinical trial of efficacy and safety. *J Am Acad Dermatol* 2019;81:694-701.
  121. Jang YH, Kim SL, Lee KC, Kim MJ, Park KH, Lee WJ, *et al.* A comparative study of oral cyclosporine and betamethasone minipulse therapy in the treatment of alopecia areata. *Ann Dermatol* 2016;28:569-74.
  122. Açıkgöz G, Çalışkan E, Tunca M, Yeniay Y, Akar A. The effect of oral cyclosporine in the treatment of severe alopecia areata. *Cutan Ocul Toxicol* 2014;33:247-52.
  123. Kim BJ, Min SU, Park KY, Choi JW, Park SW, Youn SW, *et al.* Combination therapy of cyclosporine and methylprednisolone on severe alopecia areata. *J Dermatolog Treat* 2008;19:216-20.
  124. Shaheedi-Dadras M, Karami A, Mollaei F, Moravvej H, Malekzad F. The effect of methylprednisolone pulse-therapy plus oral cyclosporine in the treatment of alopecia totalis and universalis. *Arch Iran Med* 2008;11:90-3.

125. Ferrando J, Grimalt R. Partial response of severe alopecia areata to cyclosporine A. *Dermatology* 1999;199:67-9.
126. Shapiro J, Lui H, Tron V, Ho V. Systemic cyclosporine and low-dose prednisone in the treatment of chronic severe alopecia areata: A clinical and immunopathologic evaluation. *J Am Acad Dermatol* 1997;36:114-7.
127. Mehta H, Kumar S, Parsad D, Bishnoi A, Vinay K, Kumaran MS. Oral cyclosporine is effective in stabilizing active vitiligo: Results of a randomized controlled trial. *Dermatol Ther* 2021;34:e15033.
128. Taneja A, Kumari A, Vyas K, Khare AK, Gupta LK, Mittal AK. Cyclosporine in treatment of progressive vitiligo: An open-label, single-arm interventional study. *Indian J Dermatol Venereol Leprol* 2019;85:528-31.
129. Berth-Jones J, Smith SG, Graham-Brown RA. Nodular prurigo responds to cyclosporin. *Br J Dermatol* 1995;132:795-9.
130. Von Den Driesch P. Sweet's syndrome-Therapy with cyclosporine. *Clin Experimental Dermatol* 1994;19:274-7.
131. Masuda K, Nakayama A, Urayama A, Nakae K, Kogure M, Inaba G. Double masked trial of cyclosporine versus colchicine and long term open study of cyclosporine in Behçet's disease. *Lancet* 1989;1:1093-5.
132. Avci O, Gürlür N, Güneş AT. Efficacy of cyclosporine on mucocutaneous manifestations of Behçet's disease. *J Am Acad Dermatol* 1997;36:796-7.
133. Spadino S, Altomare A, Cainelli C, Franchi C, Frigerio E, Garutti C, *et al.* Disseminated granuloma annulare: Efficacy of cyclosporine therapy. *Int J Immunopathol Pharmacol* 2006;19:433-8.
134. Usuki K, Sekiyama M, Shimada T, Shimada S, Kanzaki T. Three cases of pityriasis rubra pilaris successfully treated with cyclosporin A. *Dermatology* 2000;200:324-7.
135. Lasa O, Trebol I, Gardeazabal J, Diaz-Perez JL. Prophylactic short term use of cyclosporine in refractory polymorphous light eruption. *J Eur Acad Dermatol Venereol* 2004;18:747-8.
136. Paquet P, Piérard GE. Severe chronic actinic dermatitis treated with cyclosporine: 2 cases. *Ann Dermatol Venereol* 2001;128:42-5.
137. Usmani N, Wilson C. A novel treatment for recalcitrant benign familial pemphigus. *J Eur Acad Dermatol Venereol* 2007;21:264-6.
138. Varada S, Ramirez-Fort MK, Argobi Y, Simkin AD. Remission of refractory benign familial chronic pemphigus (Hailey-Hailey disease) with the addition of systemic cyclosporine. *J Cutan Med Surg* 2015;19:163-6.
139. Anderson MD, Zauli S, Bettoli V, Boer J, Jemec GB. Cyclosporine treatment of severe Hidradenitis suppurativa-A case series. *J Dermatolog Treat* 2016;27:247-50.
140. Ogawa H, Kameda H, Amano K, Takeuchi T. Efficacy and safety of cyclosporine A in patients with refractory systemic lupus erythematosus in a daily clinical practice. *Lupus* 2010;19:162-9.
141. Vencovský J, Jarosová K, Macháček S, Studýnková J, Kafková J, Bartůnková J, *et al.* Cyclosporine A versus methotrexate in the treatment of polymyositis and dermatomyositis. *Scand J Rheumatol* 2000;29:95-102.
142. Miyake S, Ohtani Y, Sawada M, Inase N, Miyazaki Y, Takano S, *et al.* Usefulness of cyclosporine A on rapidly progressive interstitial pneumonia in dermatomyositis. *Sarcoidosis Vasc Diffuse Lung Dis* 2002;19:128-33.
143. Shimojima Y, Ishii W, Kato T, Hoshi K, Matsuda M, Hashimoto T, *et al.* Intractable skin necrosis and interstitial pneumonia in amyopathic dermatomyositis, successfully treated with cyclosporine A. *Intern Med* 2003;42:1253-8.
144. Kowal-Bielecka O, Landewe R, Avouac J, Chwiesko S, Miniati I, Czirkaj L, *et al.* EULAR recommendations for the treatment of systemic sclerosis: A report from the EULAR Scleroderma Trials and Research group (EUSTAR). *Ann Rheum Dis* 2009;68:620-8.
145. Ellis E, Scheinfeld N. Eosinophilic pustular folliculitis: A comprehensive review of treatment options. *Am J Clin Dermatol* 2004;5:189-97.
146. Fukamachi S, Kabashima K, Sugita K, Kobayashi M, Tokura Y. Therapeutic effectiveness of various treatments for eosinophilic pustular folliculitis. *Acta Derm Venereol* 2009;89:155-9.
147. Barbarino JM, Staatz CE, Venkataraman R, Klein TE, Altman RB. PharmGKB summary: Cyclosporine and tacrolimus pathways. *Pharmacogenet Genomics* 2013;23:563-85.
148. Dai A, Kim SJ. Systemic calcineurin inhibitors tacrolimus and voclosporin: A review of off-label dermatologic uses. *J Am Acad Dermatol* 2024;90:358-67.
149. Artz MA, Boots JM, Ligtenberg G, Roodnat JJ, Christiaans MH, Vos PE, *et al.* Conversion from cyclosporine to tacrolimus improves quality-of-life indices, renal graft function and cardiovascular risk profile. *Am J Transplant* 2004;4:937-45.
150. Chow DK, Leong RW. The use of tacrolimus in the treatment of inflammatory bowel disease. *Expert Opin Drug Saf* 2007;6:479-85.
151. Nankivell BJ, P'Ng CH, O'Connell PJ, Chapman JR. Calcineurin inhibitor nephrotoxicity through the lens of longitudinal histology: Comparison of cyclosporine and tacrolimus eras. *Transplantation* 2016;100:1723-31.
152. Rovin BH, Solomons N, Pendergraft WF 3<sup>rd</sup>, Dooley MA, Tumlin J, Romero-Diaz J, *et al.* A randomized, controlled double-blind study comparing the efficacy and safety of dose-ranging voclosporin with placebo in achieving remission in patients with active lupus nephritis. *Kidney Int* 2019;95:219-31.
153. Sidbury R, Alikhan A, Bercovitch L, Cohen DE, Darr JM, Drucker AM, *et al.* Guidelines of care for the management of atopic dermatitis in adults with topical therapies. *J Am Acad Dermatol*. 2023;89:1-20.
154. Wollenberg A, Kinberger M, Arents B, Aszodi N, Avila Valle G, Barbarot S, *et al.* European guideline (EuroGuiDerm) on atopic eczema: Part I - systemic therapy. *J Eur Acad Dermatol Venereol* 2022;36:1409-31.
155. AAAAI/ACAAI/JTF Atopic Dermatitis Guideline Panel, Chu DK, Schneider L, Asiniwasis RN, Boguniewicz M, De Benedetto A, *et al.* Atopic dermatitis (eczema) guidelines: 2023 American Academy of Allergy, Asthma and Immunology/American College of Allergy, Asthma and Immunology Joint Task Force on Practice Parameters GRADE- and Institute of Medicine-based recommendations. *Ann Allergy Asthma Immunol* 2024;132:274-312.
156. Katoh N, Ohya Y, Ikeda M, Ebihara T, Katayama I, Saeki H, *et al.* Committee for clinical practice guidelines for the management of atopic dermatitis 2018, The Japanese society of allergology, The Japanese dermatology association. Japanese guidelines for atopic dermatitis 2020. *Allergol Int* 2020;69:356-69.
157. Elms CA, Korman NJ, Prater EF, Wong EB, Rupani RN, Kivelevitch D, *et al.* Joint AAD-NPF Guidelines of care for the management and treatment of psoriasis with topical therapy and alternative medicine modalities for psoriasis severity measures. *J Am Acad Dermatol* 2021;84:432-70.
158. Nast A, Amelunxen L, Augustin M, Boehncke WH, Dressler C, Gaskins M, *et al.* S3 Guideline for the treatment of psoriasis vulgaris, update - Short version part 1 - Systemic treatment. *J Dtsch Dermatol Ges* 2018;16:645-69.
159. Nast A, Smith C, Spuls PI, Avila Valle G, Bata-Csörgő Z, Boonen H, *et al.* EuroGuiDerm Guideline on the systemic treatment of Psoriasis vulgaris - Part 2: Specific clinical and comorbid situations. *J Eur Acad Dermatol Venereol* 2021;35:281-317.
160. van der Kraaij GE, Balak DM, Busard CI, van Cranenburgh OD, Chung Y, Driessen RJ, *et al.* Highlights of the updated Dutch evidence- and consensus-based guideline on psoriasis 2017. *Br J Dermatol* 2019;180:31-42.
161. Fujita H, Terui T, Hayama K, Akiyama M, Ikeda S, Mabuchi T, *et al.* Japanese Dermatological Association Guidelines Development Committee for the Guidelines for the Management and Treatment of Generalized Pustular Psoriasis. Japanese guidelines for the management and treatment of generalized pustular psoriasis: The new pathogenesis and treatment of GPP. *J Dermatol* 2018;45:1235-70.
162. Godse K, Patil A, De A, Sharma N, Rajagopalan M, Shah B, *et al.* Diagnosis and management of urticaria in Indian settings: Skin allergy research society's guideline-2022. *Indian J Dermatol* 2022;67:732-43.
163. Zuberbier T, Abdul Latiff AH, Abuzakouk M, Aquilina S, Asero R, Baker D, *et al.* The international EAACI/GA<sup>2</sup>LEN/EuroGuiDerm/APAAACI guideline for the definition, classification, diagnosis, and management of urticaria. *Allergy* 2022;77:734-66.
164. el-Shahawy MA, Gadallah MF, Massry SG. Acne: A potential side effect of cyclosporine A therapy. *Nephron* 1996;72:679-82.
165. Luke RG. Mechanism of cyclosporine-induced hypertension. *Am J Hypertens* 1991;4:468-71.
166. Stiller MJ, Pak GH, Kenny C, Jondreau L, Davis I, Wachsman S, *et al.* Elevation of fasting serum lipids in patients treated with low-dose cyclosporine for severe plaque-type psoriasis. An assessment of clinical significance when viewed as a risk factor for cardiovascular disease. *J Am Acad Dermatol* 1992;27:434-8.
167. Krupp P, Monka C. Side-effect profile of cyclosporine A in patients treated for psoriasis. *Br J Dermatol* 1990;122:47-56.
168. Imafuku S, Tashiro A, Furue M. Cyclosporin treatment of psoriasis in a patient with chronic hepatitis C. *Br J Dermatol* 2007;156:1367-9.
169. Breil M, Chariot P. Muscle disorders associated with cyclosporine treatment. *Muscle Nerve* 1999;22:1631-6.
170. Ramsey-Goldman R, Schilling E. Immunosuppressive drug use during pregnancy. *Rheum Dis Clin North Am* 1997;23:149-67.
171. Yiu ZZ, Warren RB, Mrowietz U, Griffiths CE. Safety of conventional

- systemic therapies for psoriasis on reproductive potential and outcomes. *J Dermatolog Treat* 2015;26:329-34.
172. Munoz-Flores-Thiagarajan KD, Easterling T, Davis C, Bond EF. Breast-feeding by a cyclosporine-treated mother. *Obstet Gynecol* 2001;97:816-8.
173. Perrett CM, Ilchyshyn A, Berth-Jones J. Cyclosporin in childhood psoriasis. *J Dermatolog Treat* 2003;14:113-8.
174. Nast A, Smith C, Spuls PI, Avila Valle G, Bata-Csörgö Z, Boonen H, *et al.* EuroGuiDerm Guideline on the systemic treatment of Psoriasis vulgaris - Part 1: Treatment and monitoring recommendations. *J Eur Acad Dermatol Venereol* 2020;34:2461-98.
175. Chang Y, Jeong SW, Jang JY. Hepatitis B virus reactivation associated with therapeutic interventions. *Front Med (Lausanne)* 2021;8:770124.
176. Calabrese LH, Lederman MM, Spritzler J, Coombs RW, Fox L, Schock B, *et al.* Placebo-controlled trial of cyclosporine-A in HIV-1 disease: Implications for solid organ transplantation. *J Acquir Immune Defic Syndr* 2002;29:356-62.
177. Behnam SM, Behnam SE, Koo JY. Review of cyclosporine immunosuppressive safety data in dermatology patients after two decades of use. *J Drugs Dermatol* 2005;4:189-94.
178. Campana C, Regazzi MB, Buggia I, Molinaro M. Clinically significant drug interactions with cyclosporin. An update. *Clin Pharmacokinet* 1996; 30:141-79.

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