

Cyclosporine for Chronic Spontaneous Urticaria: A Meta-Analysis and Systematic Review



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What is already known about this topic? Cyclosporine A (CsA) is one of the recommended treatments in most clinical practice guidelines for chronic spontaneous urticaria (CSU). However, a well-designed study of CsA efficacy and safety in CSU is lacking.

What does this article add to our knowledge? CsA is effective in the treatment of CSU. The safety profile of CsA treatment shows dose dependency.

How does this study impact current management guidelines? For antihistamine-refractory patients with CSU, CsA at a dose of 1 to 5 mg/kg/d can provide effective control of the symptoms, with adverse events occurring dose dependently.

BACKGROUND: Despite widely recommended usage of cyclosporine A (CsA) in chronic spontaneous urticaria (CSU), there is no meta-analysis concerning its efficacy and safety. **OBJECTIVE:** To meta-analyze and review the efficacy and safety of CsA in CSU.

METHODS: Efficacy was assessed by the relative change in urticaria activity score at 4 weeks and response rates at 4, 8, and 12 weeks. Safety was assessed by analyzing the number of patients with 1 or more adverse event.

RESULTS: Eighteen studies (909 participants) including 2 randomized controlled trials were included, with 125, 363, and 266 patients with CSU receiving very low (<2 mg/kg/d), low (from 2 to <4 mg/kg/d), and moderate (4–5 mg/kg/d) doses of CsA, respectively. 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 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.

CONCLUSIONS: Given the limited number and quality of studies, our results should be interpreted with caution. 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 1 to 5 mg/kg/d, and 3 mg/kg/d is a reasonable starting dose for most patients. © 2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2018;6:586-99)

Key words: Cyclosporine; Chronic spontaneous urticaria; Meta-analysis; Efficacy; Safety

Chronic spontaneous urticaria (CSU), previously also called chronic idiopathic urticaria, is defined as the occurrence of spontaneous wheals, angioedema, or both for more than 6 weeks.¹ Modern second-generation H₁ antihistamines are recommended by the EAACI/GA²LEN/EDF/WAO guideline as the first-line treatment of CSU on the basis of high-quality evidence and their very good risk/benefit profile. If symptoms persist after 2 weeks of treatment, up to 4-fold dosed second H₁ antihistamines are recommended.¹ For antihistamine-refractory patients, omalizumab is the recommended treatment option. According to the 2017 update and revision of the EAACI/GA²LEN/EDF/WAO guideline, cyclosporine (CsA) should be used in patients with severe disease refractory to antihistamine and omalizumab treatment. The guideline, however, does not provide recommendations on the dosing of CsA or the duration of treatment.¹

CsA is effective in the treatment of CSU on the basis of longstanding and broad experience and several reported studies. These studies include randomized controlled trials (RCTs), noncontrolled prospective studies, retrospective studies, case series, and case reports. CsA inhibits activated T_H cells by

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Abbreviations used

CsA- Cyclosporine A

CSU- Chronic spontaneous urticaria

RCT- Randomized controlled trial

UAS- Urticaria activity score

blocking the production of inflammatory cytokines. CsA binds to cyclophilins and inhibits the activity of calcineurin to dephosphorylate the nuclear factor of activated T cells. As a result, the nuclear factor of activated T cells is not able to translocate to the nucleus, which reduces the production of inflammatory cytokines such as IL-2, IL-3, IL-4, and TNF- α .² IL-4 is involved in the generation of IgE, which can induce and enhance mast cell activation.³ *In vitro* studies showed that preincubating leukocytes with CsA may inhibit histamine secretion after stimulating with sera from patients with urticaria who have functional IgE antibodies directed against the alpha subunit of the IgE receptor. This effect was dose-dependent and was not found for other drugs including methotrexate, diphenhydramine, or hydroxyzine.⁴ CsA also has effects on mast cells. For example, Harrison et al³ showed that CsA inhibits the IgE-mediated release of histamine from mast cells in a concentration-dependent manner. Grattan et al⁵ reported a reduction in serum histamine-releasing activity and the autologous serum skin test response after CsA treatment.⁵ Also, CsA reportedly reduces serum levels of IL-2R, IL-5, and TNF- α .⁶ Taken together, these findings support the notion that the mechanisms of action of CsA in CSU may involve effects on activated T cells, basophils, mast cells, and perhaps other cells.

Despite the fact that CsA is a recommended and widely used treatment option for CSU, it is still an off-label treatment and there is no meta-analysis regarding its efficacy and safety. To close this gap of knowledge, we reviewed the literature and performed a meta-analysis focusing on the evaluation of the effects of CsA on disease activity and response rates as well as rates of adverse events of CsA treatment in patients with CSU.

METHODS

This meta-analysis and systematic review was done following Preferred Reporting Items for Systematic Reviews and Meta-analysis recommendations.⁷

Search strategy and eligibility criteria

A literature search of electronic database (PubMed, MEDLINE, Embase, and Web of Science) from September 1980 until November 2016 was conducted using the search terms “(cyclosporine OR cyclosporin OR ciclosporin) and urticaria.” The eligibility criteria for reports to be included in our systematic review were as follows: (1) RCTs and non-RCTs; (2) patients with CSU treated with CsA; (3) any of the following outcomes were reported: the relative change in CSU activity, response rates, and/or rates of CsA-treated patients with adverse events or number of adverse events. Review articles, case reports, case series, *in vitro* studies, comments, and replies were excluded. Articles that were not published in English as well as non–full-text publications were also excluded. Titles and abstracts of the remaining articles were screened by 2 independent reviewers (K.K. and P.C.) for their eligibility on the basis of inclusion criteria. Full texts were then obtained and reviewed for eligibility by the 2 reviewers (K.K. and P.C.). This search yielded 18 relevant reports, all

of which were systematically reviewed and assessed for eligibility to be included in the meta-analysis (Figure 1).

Inclusion criteria for meta-analysis

The 18 reports identified were then assessed for their suitability to be meta-analyzed. To be included in our meta-analysis, study reports had to include data on 1 or more of the following outcome parameters.

Relative change in urticaria activity score at 4 weeks.

Effects of CsA on CSU activity were assessed by analysis of the relative change in mean urticaria activity score (UAS) between baseline and 4 weeks of CsA treatment. We included only those studies that reported UAS data (mean or difference in mean) and 95% CIs with SD or SEs.

Response rates at 4, 8, and 12 weeks of treatment.

We categorized CsA dosages into 3 groups: (1) very low (<2 mg/kg/d), (2) low (from 2 to <4 mg/kg/d), and (3) moderate (4–5 mg/kg/d). We meta-analyzed the rates of patients who showed a beneficial response to CsA treatment at 4, 8, and 12 weeks of treatment. However, no studies of very low-dose CsA (<2 mg/kg/d) evaluated response rates at 4, 8, and 12 weeks.^{8–10} We also compared 12-week response rates of patients treated with various dosages of CsA.

Safety as assessed by rates of patients with 1 or more adverse event and number of major and other adverse events.

We performed meta-analysis of the rates of patients with adverse events and of the number of major and other adverse events, for treatment groups that received very low, low, or moderate doses of CsA. Hypertension and abnormal renal function detected by increased serum creatinine were categorized as major adverse events.

Data extraction and bias assessments

Data were independently extracted by 2 reviewers and the use of a standardized data extraction form. Relevant information extracted included first author, year of publication, country of study, study design, sex of patients, number of CsA-treated patients and controls, dose and treatment duration of CsA, assessment of outcome, response rates and change in CSU activity after treatment with CsA, as well as rates of relapse and adverse events. Discrepancies identified during data extraction were resolved by consensus meetings of the authors. Quality and risk of bias of included studies were assessed with the Cochrane Collaboration's tool for assessing the risk of bias for RCTs¹¹ and with the Methodological Index for Non-Randomized Studies for non-RCTs.¹²

Statistical analysis

Pooled results were estimated using a random-effects model due to the heterogeneity of included studies. To examine this heterogeneity, we used Cochrane's *Q* statistic and the *I*² statistic to quantify total variation across studies. An *I*² value of 25%, 50%, and 75% was considered to indicate low, moderate, and high heterogeneity, respectively.¹³ Funnel plot and Egger's regression test were done to detect the existence of publication bias. All statistical tests were 2-sided using an alpha level of 0.05. For all results, a 2-sided *P* value of .05 or less was considered to indicate statistical significance. All meta-analyses were performed using Comprehensive Meta-Analysis software version 3 (Biostat, Englewood, NJ).

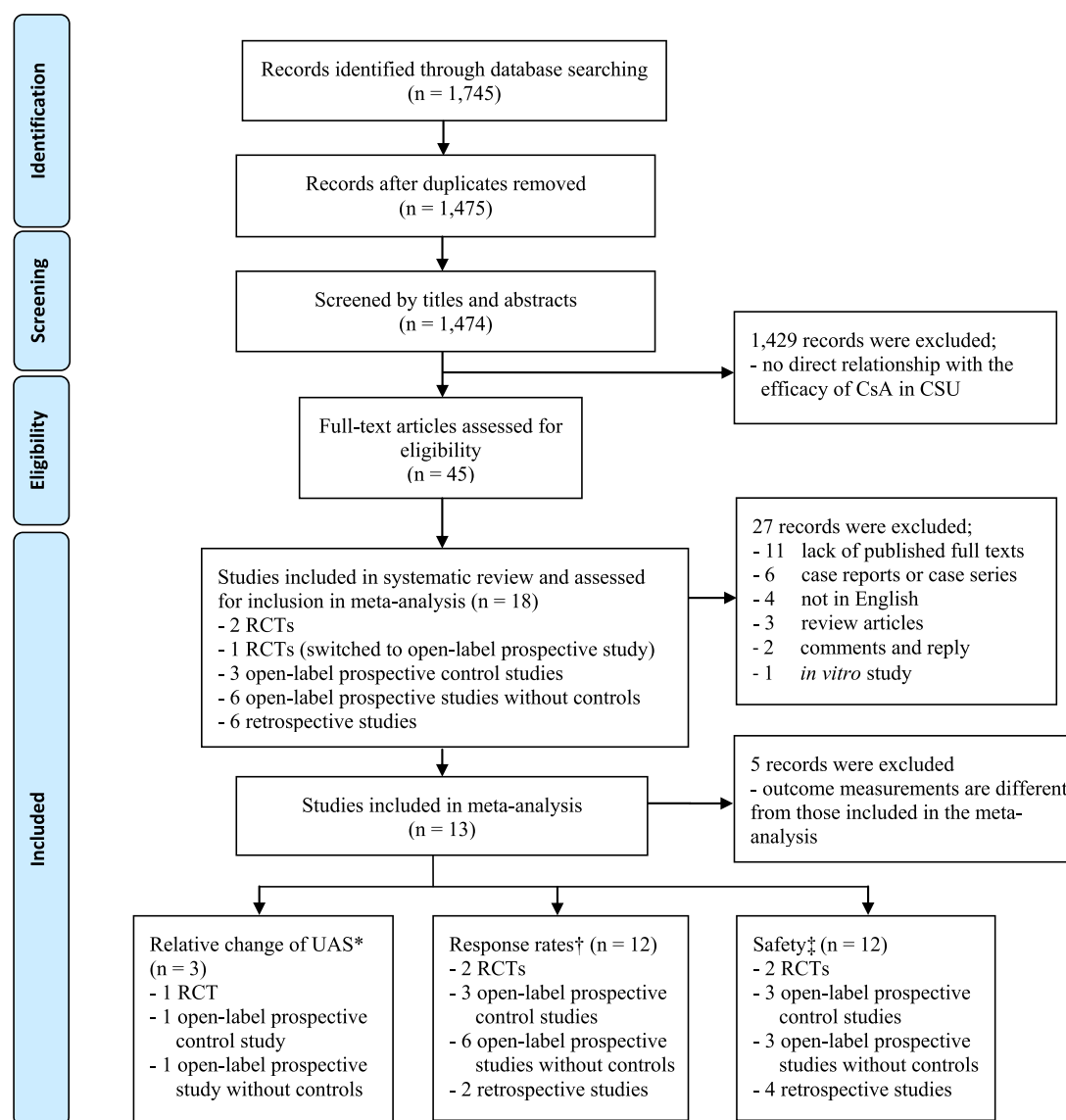


FIGURE 1. Flow diagram of literature review in this study. *In the different studies, various disease activity scores were used to assess the effects of CsA on CSU. Of 5 studies that used the UAS, 3 were included in the meta-analysis.^{5,6,20} Two studies were excluded because one study lacked information on the mean change in UAS¹⁹ and the other one showed UAS results only for omalizumab and not for CsA.²⁵ †Thirteen studies met the inclusion criteria, but we included only 12 in our meta-analysis. The study by Ilter et al²² was excluded from this analysis because of the rapid and aggressive tapering protocol used and the very high dropout rate. We had originally planned to compare response rates of treatment groups with very low, low, and moderate doses at 4, 8, and 12 weeks. However, the number of reports was limited and no studies of very low-dose CsA evaluated response rates at 4, 8, and 12 weeks. Therefore, the pooled response rates for all CsA doses at 4, 8, and 12 weeks of CsA treatment were analyzed (n = 12 studies).^{5,6,10,14,16-21,23,24} In addition, response rates to low-, and moderate-dose CsA were evaluated after 12 weeks of CsA treatment (n = 8 studies).^{10,16-20,23,24} ‡For analysis of CsA safety, 12 studies were included.^{5,6,8-10,14,15,17,20,21,23,25} Safety was assessed separately for different doses of CsA. Dosages of CsA varied among studies from 1 to 5 mg/kg/d. Moderate initial doses of CsA (4-5 mg/kg/d),^{5,14-16,20-22} low initial doses (from 2 to <4 mg/kg/d),^{6,10,17-19,23-25} and very low-dose CsA (<2 mg/kg/d)⁸ were studied in 7, 8, and 1 article, respectively. Another study investigated both low and very low doses of CsA.⁹ CsA was adjusted or tapered off in some studies to the minimal effective dose.^{8-10,14,15,17,18,22-25} The duration of CsA treatment was between 4 and 68 weeks.

RESULTS

Literature search results

CsA treatment in CSU was assessed by 18 studies, and only 2 of them were RCTs. A total of 18 studies met the eligibility criteria and were included in our systematic review

(Figure 1).^{5,6,8-10,14-26} These were 2 RCTs,^{5,14} 3 open-label prospective control studies,^{6,21,23} 6 open-label prospective studies without controls,^{16-20,22} and 6 retrospective studies.^{8-10,24-26} One study was an RCT at first, but was then switched to an open-label prospective study because of control failures.¹⁵

TABLE I. Quality and risk of bias assessment of included articles**A. RCTs**

Study	Random sequence generation (selection bias)	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting
Vena et al ¹⁴ (2006)	+	±	+	+	+	+
Grattan et al ⁵ (2000)	+	+	+	+	+	+

B. Non-RCTs

Study	Criteria								Additional criteria in the case on comparative study						Total
	A stated aim of the study	Inclusion of consecutive patients	Prospective collection of data	End point appropriate to the study aim	Unbiased evaluation of end points	Follow-up period appropriate	Loss to follow- up not exceeding 5%	Prospective calculation of the study size	A control group having the criterion standard intervention	Contemporary groups	Baseline equivalence of groups	Prospective calculation of the sample size	Statistical analyses adapted to the study design		
Asero ¹⁶ (2015)	1	1	2	2	0	2	2	0						10	
Savic et al ²⁵ (2015)	2	1	0	1	0	2	0	0						6	
Neverman and Weinberger ²⁴ (2014)	2	2	0	2	0	2	2	0						10	
Iqbal et al ²⁶ (2012)	1	1	0	0	0	1	0	0						3	
Boubouka et al ¹⁷ (2011)	2	2	2	2	0	2	0	0						10	
Di Leo et al ⁹ (2011)	2	2	0	2	0	2	2	0						10	
Hollander et al ⁸ (2011)	2	2	0	2	0	2	0	0						8	
Kessel and Toubi ¹⁰ (2010)	2	2	0	2	0	2	0	0						8	
Ohtsuka ¹⁸ (2010)	2	2	2	2	0	2	2	0						12	
Godse ¹⁹ (2008)	2	1	2	2	0	2	0	0						9	
Serhat Inaloz et al ⁶ (2008)	2	2	2	2	0	2	2	0	0	2	0	0	2	16	
Baskan et al ²⁰ (2004)	2	2	2	2	0	2	2	0						12	
Di Gioacchino et al ¹⁵ (2003)	2	2	2	2	0	2	2	0						12	
Loria et al ²¹ (2001)	2	2	2	2	0	2	2	0	2	2	2	0	2	20	
Ilter et al ²² (1999)	0	1	2	2	0	2	0	0						7	
Toubi et al ²³ (1997)	2	2	2	2	0	2	0	0	0	2	2	0	2	16	

Note. +, low risk of bias; ±, unclear; –, high risk of bias; 0, not reported; 1, reported but inadequate; 2, reported and adequate. The global ideal score was 16 for noncomparative studies and 24 for comparative studies.

TABLE II. Study characteristics of included articles

Study (year)	Treatment	Concomitant medication	N	CsA dosage (mg/kg/d)	Treatment duration (wk)	Severity assessment	Definition of response	Percent of response (duration)*	Percent of complete response (duration)†	Relapse (%)	Drop out (%)	Main outcome
RCTs												
Vena et al ¹⁴ (2006)	● CsA	Cetirizine 10 mg/d (all groups)	31	5 (wk 1-2) 4 (wk 3-4) 3 (wk 5-16)	16	Breneman severity score‡	Not defined (clinical score improve > 50%)	77.4 (16 wk)	NA	19.4	22.6	- CsA significantly reduced CSU severity after 8 wk compared with placebo.
	● CsA		33	5 (wk 1-2) 4 (wk 3-4) 3 (wk 5-8) placebo (wk 9-16)	8			87 (8 wk)	NA	42.4	36.4	- DLQI significantly decreased in CsA-treated group compared with placebo.
	● Placebo		35	NA	NA			51.4 (16 wk)	NA	31.4	48.6	
Grattan et al ⁵ (2000)	● CsA	Cetirizine 20 mg/d (all groups)	20	4	4	UAS	Reduction in UAS to < 25% of baseline	40 (4 wk)	26 (24 wk) (overall)	75 (overall)	5	- At 4 wk, CsA improved clinical severity of CSU compared with antihistamine.
	- Open CsA trial: from nonresponders		7/20	4	8			57 (8 wk)			14	
	● Placebo		10	NA	4			0 (4 wk)			0	- Some patients with CSU responded to CsA at 8 wk.
	- Open CsA trial: from placebo group		10/10	4	4			70 (4 wk)			0	
Open-label prospective studies												
Asero ¹⁶ (2015)	● CsA	NA	29	4 (most common dose)	12	5-point response score§	Remission: complete absence of symptoms Good: 50%-80% improvement Partial: some benefit	86 (12 wk)	59 (12 wk)	24	NA	- CSU responded to CsA treatment.
Boubouka et al ¹⁷ (2011)	● CsA	NA	30	2.16 (wk 1-4) 1.92 (wk 5-8) 1.33 (wk 9-12) 0.83 (wk 13-16) 0.55 (wk 17-20)	20	4-point severity score	Not defined (clinical score reductions > 30%)	31 (4 wk) 46 (8 wk) 71 (12 wk) 87 (16 wk) 88 (20 wk)	76.7 (20 wk)	13	23.3	- Low-dose CsA was effective in short-term treatment of CSU with minimal side effects.
Ohtsuka ¹⁸ (2010)	● CsA	NA	15	3 (wk 1-12) tapered (wk 13-16)	16	NA	All symptoms resolved	20 (4 wk) 26.6 (8 wk) 60 (12 wk) 73.3 (16 wk) 86.7 (20 wk) 100 (24 wk)	NA	NA	0	- Patients with CSU with elevated high-sensitivity C-reactive protein showed good response to CsA.
Godse ¹⁹ (2008)	● CsA	Cetirizine 10 mg/d	5	3	12	UAS	Not defined (clinical score reductions > 50%)	80 (12 wk)	60 (12 wk)	NA	20	- Short-term low-dose CsA was effective in CSU treatment.
Serhat Inaloz et al ⁶ (2008)	● CsA	NA	27	2.5	4	UAS	Reduction in UAS to <25% of baseline	100 (4 wk)	70.4 (4 wk)	NA	0	- CsA decreased CSU severity and decreased serum cytokine level such as IL-6, IL-8, and TNF-α compared with healthy controls.
	● Healthy control		24	NA								
Baskan et al ²⁰ (2004)	● CsA	NA	10	4	4	UAS	Reduction in UAS to <25% of baseline	50 (4 wk)	NA	20	0	- CsA was effective for CSU.
	● CsA		10	4	12			80 (12 wk)		37.5		- Prolonged use of CsA for more than 1 mo provided further benefits.
Di Gioacchino et al ¹⁵ (2003)	● CsA	NA	40	5 (wk 1-8) 4 (wk 9-16)	16	Relapse severity score¶	Not defined (complete absence of symptoms)	82.5 (1 wk) 100 (3 wk) 100 (16 wk)	100 (3 wk)	60	0	- CsA decreased clinical symptoms of CSU and decreased requirement of oral steroids.
Loria et al ²¹ (2001)	● CsA	NA	10	5	8	Total symptom severity (TSS) score#	Not defined (clinical score = 0 in all patients)	100 (2 wk) 100 (8 wk)	100 (8 wk)	20	0	- TSS score significantly decreased after treatment with CsA.
	● Prednisolone 20 mg/kg/d	10	NA	8	100 (8 wk)							

Ilter et al ²² (1999)	● CsA	NA	15	5 (wk 1) 3.5 (wk 2) 2.5 (wk 3-7)	7	NA	Not defined	13.3 (8 wk)	13.3 (8 wk)	100	86.7	- CsA 5 mg/kg/d could decrease CSU severity but might be ineffective with lower dose.
Toubi et al ²³ (1997)	● CsA	NA	25	3 (wk 1-6) 2 (wk 7-9) 1 (wk 10-12)	12	Breneman [‡] severity score	0: full remission 1: moderate response 2: mild response 3: no response	76 (1 wk) 76 (4 wk) 76 (12 wk) 0	52 (12 wk) 0	15.4	24	- Low-dose CsA was effective in treatment of CSU, and can be given safely for 3 mo.
	● Untreated group		10	NA								
Retrospective studies												
Savic et al ²⁵ (2015)	● CsA	NA	72	3 (most common dose)	19.2 (median)	Clinician comments	Not defined	72 (overall)	17 (overall)	NA	50	- Omalizumab showed greater improvement based on clinical comments and DLQI scores.
	● Omalizumab	NA	46	150-300 mg	4 (most common duration)	Clinician comments - UAS		75 (overall) 77 (overall)	42 (overall) 68 (overall)	NA	NA	- DLQI decreased ≥ 75% in 41% of the CsA group.
Neverman and Weinberger ²⁴ (2014)	● CsA (antihistamine resistant group)	N/A	16	3 (reduced after urticaria was suppressed at least 1 month)	8-68	NA	Not defined (complete resolution of disease)	100 (12 wk)	100 (12 wk)	31.3	0	- CsA was safe and effective for antihistamine-resistant CSU in children.
	● Untreated group (antihistamine responsive)	NA	30	NA								
Iqbal et al ²⁶ (2012)	● CsA	NA	58	No details but stated that only usual starting dose 4 mg/kg/d	No details but stated that only usual duration of 12-16 wk	Clinician assessment	NA	70.7	48.3	NA	NA	- Patients with CSU with a positive basophil activation test result were more likely to respond to CsA treatment.
Hollander et al ⁶ (2011)	● CsA	NA	68	1 (increased 25-50 mg every 2-4 wk after remission, keep stable for 6 mo then weaned off)	20.8 (median)	NA	Complete remission ≤1 d of having urticarial lesion per month	94.1 (overall)	78 (overall)	13.2	29.4	- CsA was an effective treatment for CSU.
Di Leo et al ⁹ (2011)	● CsA 1-1.5 mg/kg/d	Prednisolone 0.1-0.3 mg/kg/d	25	1-1.5	24	TSS score [#]	TSS score decrease to <25% of baseline	63 (24 wk)	28 (24 wk)	11	0	- CsA at 1-3 mg/kg/d could
	● CsA 1.6-2 mg/kg/d		32	1.6-2				76 (24 wk)	37.5 (24 wk)			reduce CSU severity and safe
	● CsA 2.1-3 mg/kg/d		53	2.1-3				85 (24 wk)	45 (24 wk)			for severe unresponsive CSU.
Kessel and Toubi ¹⁰ (2010)	● CsA	NA	120	3 (tapered dose after clinical response)	12	Breneman [‡] severity score	Not defined (clinical score improve > 50%)	68.3 (12 wk)	30 (12 wk)	NA	16.7	- Low-dose CsA improved CSU severity in most cases. - 20% of patients need long-term treatment.
	- CsA-dependent group		20/120 12/120	1-2 1-1.5	32-56 5-10 y			100 NA	0 NA			

DLQI, Dermatology Life Quality Index; NA, data were not available in the study.

*Response, improvement in clinical score at 30%-90%.

†Complete response, improvement in clinical score at >90%.

‡Breneman severity score: number of lesions (0-3), number of separate episodes (0-3), average size of lesions (0-3), average duration of lesions (0-3), and pruritus intensity (0-3).

§Five-point response score: 0 = no response, 1 = partial response, 2 = good response, 3 = excellent, and 4 = remission.

||Four-point severity score: pruritus severity (0-3), number of wheals (0-3), diameter of the largest wheal (0-3), and average pruritus duration (0-3).

¶Relapse severity score: 0 = constant remission of symptoms, 1 = occurrence of relapses resolved spontaneously within 24 h, 2 = occurrence of relapses resolved by H₁ antihistamine, and 3 = occurrence of relapses resolved by steroids.

#TSS score: itching severity (0-3), flare (0-3), and number of wheals (0-3).

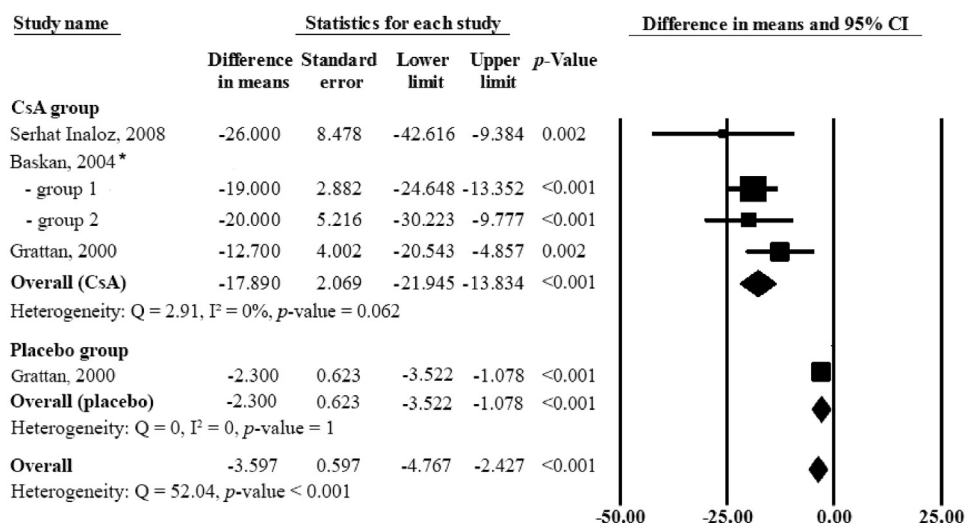


FIGURE 2. Mean relative change in 7-day UAS after treatment with cyclosporine A for 4 weeks. *Patients with CSU in Baskan et al²⁰ were randomized to 4-week (group1) or 12-week (group2) CsA treatment group.

The quality and risk of bias of included studies are presented in Table I.

The 18 studies analyzed included a total of 909 patients with CSU (females 487 [68.5%]) in 8 countries of which 855 were antihistamine-resistant (Table II). Of 909 patients with CSU, 125, 363, and 266 patients received very low (<2 mg/kg/d), low (from 2 to <4 mg/kg/d), and moderate (4–5 mg/kg/d) doses of CsA, respectively. Sixteen studies were conducted in adult patients, 1 in children.²⁴ Three, 12, and 12 of these 1844 studies, respectively, were meta-analyzed for treatment effects,^{5,6,20} response rates,^{5,6,10,14,16–21,23,24} and safety of CsA treatment.^{5,6,8–10,14,15,17,20,21,23,25}

Meta-analysis results

Relative changes in UAS at 4 weeks. After 4 weeks of CsA treatment, the pooled statistical estimate of mean relative UAS7 changes from baseline was -17.89 (95% CI, -21.95 to -13.83) (3 studies; $Q = 2.91$; $I^2 = 0\%$; $P = .06$; Figure 2). The mean relative UAS7 change in the placebo-treated control group was -2.3 (1 study; 95% CI, -3.72 to -0.88). The mean relative UAS change from baseline after treatment with CsA was significantly different from that of treatment with placebo ($Q = 52.04$; $P < .001$).

Response rates at 4, 8 and 12 weeks of treatment. The pooled statistical estimate of response rates after 4, 8, and 12 weeks of CsA treatment was 54.2% (95% CI, 32.9%–74.1%), 65.9% (95% CI, 30.0%–89.7%), and 73.1% (95% CI, 65.4%–79.5%), respectively (Figure 3, A). However, high heterogeneity was observed at 4 weeks ($Q = 24.87$; $I^2 = 75.81$; $P < .001$) and 8 weeks ($Q = 19.69$; $I^2 = 84.97$; $P < .001$). The pooled response rates after treatment with CsA at 4, 8, and 12 weeks were not significantly different ($Q = 2.99$; $P = .22$).

At 12 weeks of treatment, the pooled response rate for low-dose CsA was 69.9% (95% CI, 63.1%–75.9%) ($Q = 4.94$; $I^2 = 0$; $P = .42$) versus 84.3% for moderate-dose CsA (95% CI, 69.3%–92.8%) ($Q = 0.02$; $I^2 = 0$; $P = .65$; Figure 3, B). The

pooled response rates after treatment with low or moderate doses of CsA were not statistically different ($Q = 3.19$; $P = .07$).

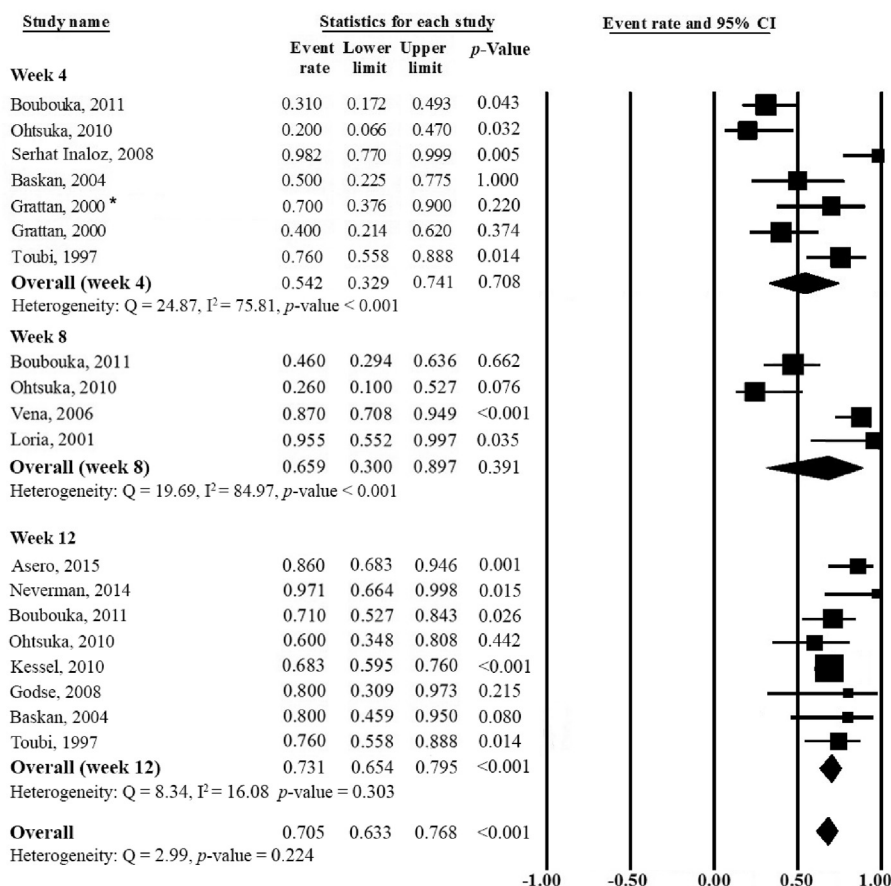
Figure 4 shows funnel plots evaluating the publication bias of studies of the response rates at 4, 8, and 12 weeks. At 4 and 8 weeks, visual inspection of funnel plots could not exclude a publication bias. However, Egger's regression test did not demonstrate publication bias ($P > .05$). At 12 weeks, no publication bias was detected.

Safety. When we meta-analyzed and compared the safety of CsA treatment in patients treated with very low, low, and moderated doses of CsA, 6.2% (95% CI, 1.0%–29.8%; $Q = 14.99$; $I^2 = 73.32$; $P = .005$), 23.4% (95% CI, 14.4%–35.6%; $Q = 20.56$; $I^2 = 75.68$; $P = .001$), and 57.9% (95% CI, 32.3%–79.8%; $Q = 39.61$; $I^2 = 84.85$; $P < .001$) of patients with CSU experienced at least 1 adverse event, respectively (Figure 5, A). The number of patients with at least 1 adverse event was statistically different among CsA dosages ($Q = 9.61$; $P = .008$).

Major adverse events including hypertension and abnormal serum creatinine were detected in 6.2% (95% CI, 1.7%–42.4%; $Q = 8.12$; $I^2 = 50.79$; $P = .09$) of the patients after treatment with very low-dose CsA, 12.8% (95% CI, 8.6%–18.7%; $Q = 1.62$; $I^2 = 0$; $P = .66$) after treatment with low-dose CsA, and 10.3% (95% CI, 6.4%–16.2%; $Q = 2.43$; $I^2 = 0$; $P = .79$) after treatment with moderately dosed CsA (Figure 5, B). The number of major adverse events was not statistically different among CsA dosages ($Q = 1.16$; $P = .56$).

Other adverse events such as gastrointestinal symptoms, headache, hirsutism, infection, and paresthesia were observed in 5.7% (95% CI, 2.1%–14.9%; $Q = 2.48$; $I^2 = 19.49$; $P = .29$), 13.9% (95% CI, 10.1%–18.8%; $Q = 8.34$; $I^2 = 16.08$; $P = .30$), and 46.2% (95% CI, 23.0%–71.2%; $Q = 35.32$; $I^2 = 83.01$; $P < .001$) of patients treated with very low, low, and moderate doses of CsA, respectively. The number of other adverse events was significantly different among CsA dosages ($Q = 12.84$; $P = .002$) (Figure 5, C).

A



B

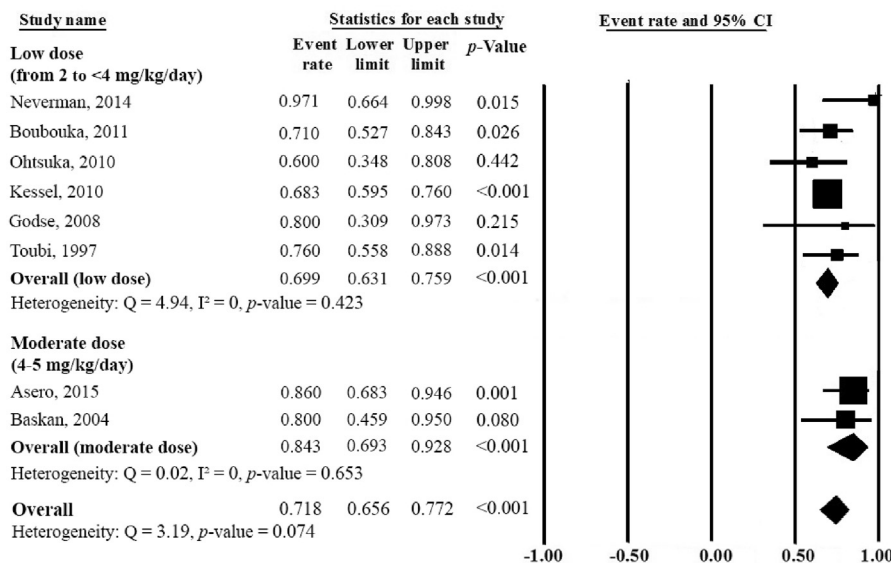


FIGURE 3. Response rates of patients with CSU treated with CsA. **A**, Pooled response rates of CsA-treated patients at 4, 8, and 12 weeks. **B**, Response rates of patients with CSU treated with low and moderate dose after 12 weeks. *Ten patients with CSU who did not respond to placebo in Grattan et al⁵ were then treated with CsA (open CsA trial from placebo group).

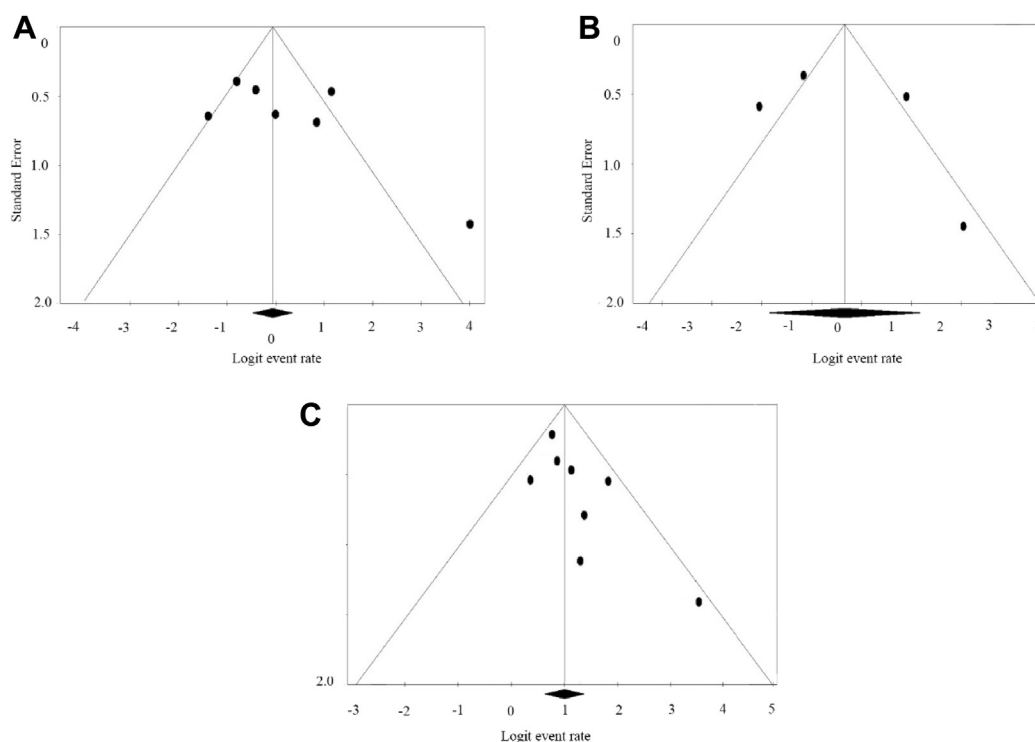


FIGURE 4. Funnel plots of studies evaluating the response rates of patients after treatment with cyclosporine A at (A) week 4, (B) week 8, and (C) week 12.

Results of the systematic review: Insights on the efficacy, safety, quality-of-life improvement, and relapse rates of CsA treatment

Efficacy. CsA was reported to be beneficial in all included studies and to be more efficacious than placebo in the 2 studies that tested this.^{5,14} The response rates at weeks 2, 3, and 4 were 100% in the studies of Serhat Inaloz et al,⁶ Di Gioacchino et al,¹⁵ and Loria et al.²¹ Both CsA and prednisolone showed higher relapse rates compared with that of CsA (40% vs 20%).²¹ The retrospective study by Savic et al²⁵ revealed that patients with CSU treated with omalizumab had higher rates of complete resolution of disease (42%; using UAS7) compared with those treated with CsA (17%; using clinician-documented comments).

Ohtsuka¹⁸ showed that patients with CSU with elevated high-sensitivity C-reactive protein required shorter duration of treatment than did patients without elevation (8.7 ± 1.3 months vs 15.3 ± 2.8 months). Frezzolini et al²⁷ demonstrated that serum-induced basophil CD63 expression (basophil activation test) in patients with chronic urticaria with a positive autologous serum skin test result was significantly decreased during CsA treatment. Iqbal et al²⁶ revealed that patients with CSU with a positive basophil activation test result had higher response rates than did those with a negative basophil activation test.

Hollander et al⁸ used an initial dose of 1 mg/kg/d and increased by 25 to 50 mg every 2 to 4 weeks (average dose, 1.8 ± 1.1 mg/kg/d) until complete remission or until CsA through levels were 100 to 200 ng/mL. The dose was maintained for the next 6 months after complete remission and then tapered off. Of 64 patients (94.1%) who responded to CsA, 53 patients (78%)

had complete remission. Seven patients (13.2%) had recurrence of disease. However, the average treatment duration to achieve remission was 20.8 weeks, which was longer than in other studies.

Di Leo et al⁹ evaluated the efficacy of CsA with different dosing regimens in 110 patients with CSU. Patients were categorized into 3 groups by dosage of CsA as follows: (A) 1 to 1.5 mg/kg/d, (B) 1.6–2 mg/kg/d, and (C) 2.1–3 mg/kg/d. After 24 weeks of treatment, the percentages of responders in groups A, B, and C were 63, 76, and 85, respectively, in a dose-dependent relationship. Complete resolution rates for groups A, B, and C were 28%, 37.5%, and 45%, respectively. However, 13.2% of group C had rising serum creatinine (Table III).

Kessel and Toubi¹⁰ studied long-term CsA in 120 patients with CSU. After treatment with CsA at 3 mg/kg/d for 3 months, 20 CsA-dependent patients had to continue CsA at doses of 1 to 2 mg/kg/d for 8 to 14 months. Twelve of 20 patients needed to continue with low-dose CsA (1–1.5 mg/kg/d) for 5 to 10 years.

Safety. Adverse events in patients with CSU on CsA increased with higher doses and longer duration of treatment (Table III). In all studies, durations of treatment with very low-dose CsA were more than 20 weeks, but with low- and moderate-dosed CsA they were less than 24 weeks and less than 16 weeks, respectively. Elevated serum creatinine due to CsA was found in 4.8% of patients with CSU. Gastrointestinal symptoms such as abdominal pain, nausea, and vomiting were the most common adverse events from CsA. Other frequently observed adverse events were hypertension, paresthesia, headache, hirsutism, and mild infection. However, most of the adverse events from CsA were mild and resolved after reducing the dose.^{6,9,14,15,17,21–23}

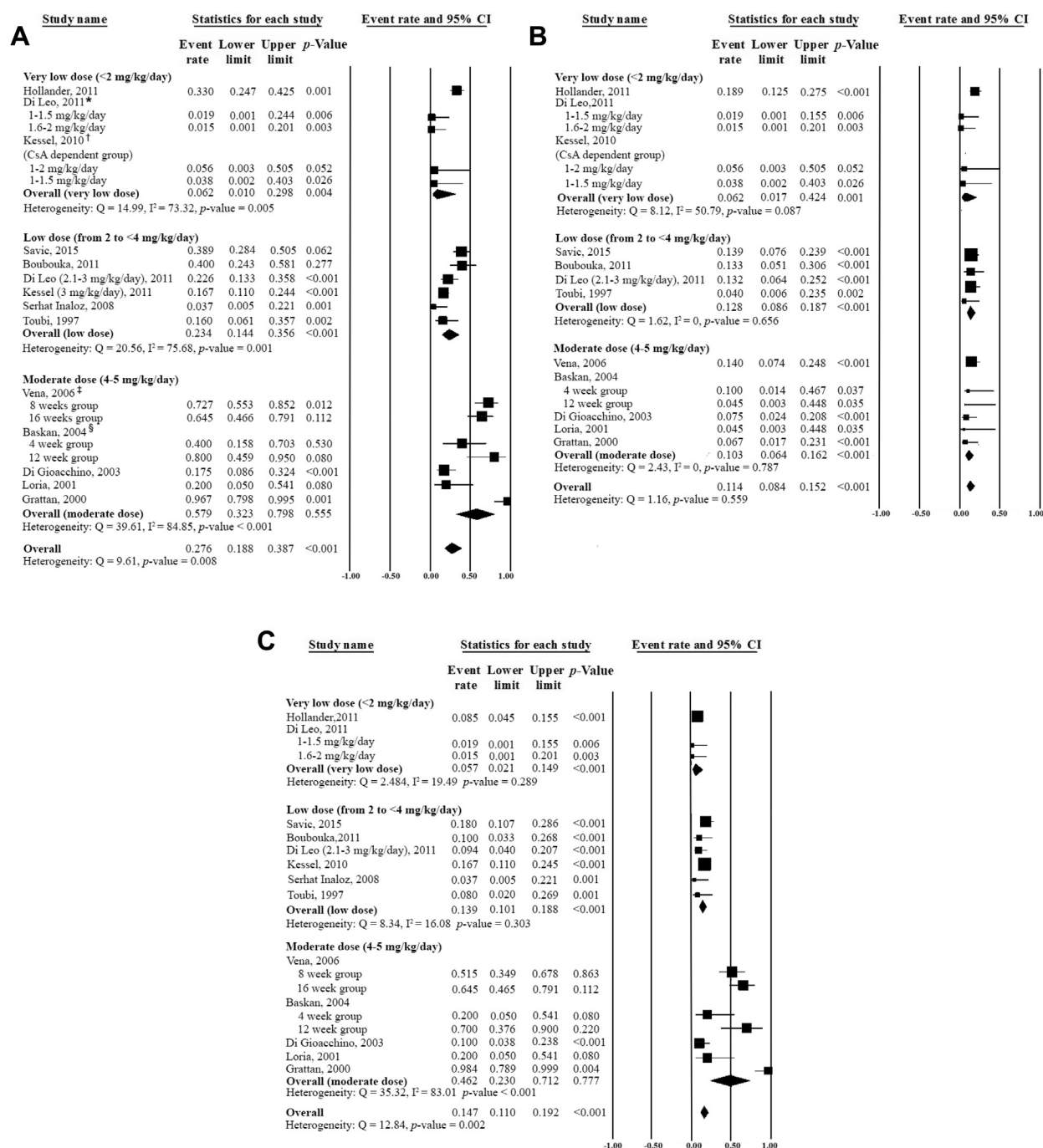


FIGURE 5. Meta-analysis results of CsA safety assessed by (A) rates of patients with 1 or more adverse event, (B) number of major adverse events, and (C) number of other adverse events. *Patients with CSU in Di Leo et al⁹ were categorized and treated with 3 different dosages of CsA (1-1.5 mg/kg/d, 1.6-2 mg/kg/d, and 2-3 mg/kg/d). †Twenty patients with CSU in Kessel and Toubi¹⁰ were treated with 1 to 2 mg/kg/d CsA for 32 to 56 weeks. Of 20 patients, 12 patients could not discontinue CsA and need to continue with 1 to 1.5 mg/kg/d CsA for 5 to 10 years. ‡Patients with CSU in Vena et al¹⁴ were randomized to CsA for 8 or 16 weeks (8-week group and 16-week group). §Patients with CSU in Baskan et al²⁰ were randomized to CsA for 4 or 12 weeks (4-week group and 12-week group).

Kessel and Toubi¹⁰ reported no abnormal glomerular filtration rate, malignancy cases, or increased incidence of infections in their patients with long-term low-dose CsA treatment for up to 5 to 10 years.

Adverse events that led to the discontinuation of CsA included hypertension, severe gastrointestinal adverse events, precordialgia, persistent peripheral neuropathy, and severe headaches.^{8,10,14,17,23,25} Hollander et al⁸ and Savic et al²⁵ reported

TABLE III. Adverse events in patients with CSU treated with CsA

Study	Initial dose (mg/kg/d)	Treatment duration	Patients with adverse events, n (%) [*]	Major adverse events, number of events			Other adverse events, number of events							Withdrawal of patients due to adverse events, n (%)	
				Elevated creatinine	Hypertension	Total	GI symptoms	Paresthesia	Headache	Hirsutism	Infection	Total	Miscellaneous [†]		
Very low dose (<2 mg/kg/d)															
Hollander et al ^{8‡}	1	20.8 wk	35/106 (37)	8	12	20	2	4	3	NA	NA	9	16	Not specified 4 (5.9)	
Di Leo et al ⁹	1-1.5	24 wk	0/25 (0)	0	0	0	0	0	0	0	0	0	0	0	
	1.6-2		0/32 (0)	0	0	0	0	0	0	0	0	0	0		
Kessel and Toubi ^{10§}	1-2	32-56 wk	0/8 (0)	0	0	0	NA	NA	NA	NA	NA	NA	NA		
	1-1.5	5-10 y	0/12 (0)	0	0	0	NA	NA	NA	NA	NA	NA	NA		
Low dose (from 2 to <4 mg/kg/d)															
Serhat Inaloz et al ⁶	2.5	4 wk	1/27 (3.7)	NA	NA	NA	1	NA	NA	NA	NA	1	NA	0	
Boubouka et al ¹⁷	2.16	20 wk	12/30 (40)	0	4	4	NA	NA	3	NA	NA	3	5	Hypertension 4 (13.3)	
Di Leo et al ⁹	2.1-3	24 wk	12/53 (22.6)	7	0	7	5	0	0	0	0	5	0	0	
Kessel and Toubi ^{10§}	3	12 wk	20/120 (16.7)	NA	NA	NA	9	N/A	11	NA	NA	20	NA	GI side effects 9 (7.5), severe headache or peripheral neuropathy 11 (9.2)	
Toubi et al ²³	3	12 wk	4/25 (16)	1	NA	1	2	NA	NA	NA	NA	2	1	GI side effects 2 (8.0)	
Savic et al ²⁵	3	19.2 wk	28/72 (38.9)	2	8	10	4	3	4	1	1	13	26	Not specified 13 (18.1)	
Moderate dose (4-5 mg/kg/d)															
Grattan et al ⁵	4	4 wk	29/30 (96.7)	0	2	2	11	15	12	6	2	46	30	0	
Baskan et al ²⁰	4	4 wk	4/10 (40)	NA	1	1	1	NA	0	1	NA	2	1	0	
		12 wk	8/10 (80)	NA	0	0	2	NA	2	3	NA	7	2		
Ilter et al ²²	5	7 wk	M	M	NA	NA	M	NA	M	NA	NA	NA	NA		
Loria et al ²¹	5	8 wk	2/10 (20)	0	0	0	NA	NA	2	NA	NA	2	NA	0	
Vena et al ¹⁴	5	8 wk	24/33 (72.7)	Total 6	1		7	5	3	2	0	17	27	Hypertension 1 (3.0) Precordialgia 1 (3.0)	

	16 wk	20/31 (64.5)	2	Total 9	7	4	3	1	5	20	26	Hypertension 1 (3.2) Seborrheic dermatitis exacerbation 1 (3.2)
Di Gioacchino et al ¹⁵	5	7/40 (17.5)	3	NA	M	NA	M	NA	NA	4	NA	0

GI, Gastrointestinal; NA, data not available.

*Some patients may have had more than 1 adverse event.

†Some studies reported miscellaneous side effects such as edema, arthralgia, and pruritus.

‡Reported adverse effects of 106 patients (106 patients with CSU were enrolled in Hollander et al⁸ but 86 patients completed the study).

§A total of 120 patients with CSU in the Kessel and Toubi¹⁰ study were treated with CsA at dose 3 mg/kg/d for 3 mo; 20 CsA-dependent patients had to continue CsA treatment at dose 1 to 2 mg/kg/d for 8 to 14 mo. Of 20 patients, 12 patients could not discontinue CsA and need to continue with low-dose CsA (1-1.5 mg/kg/d) for 5 to 10 y.¹⁰

||Side effects were mentioned in the study but not the number of patients.

discontinuation due to adverse events in 4 of 68 (5.9%) and 13 of 72 (18.1%) patients, respectively.

Quality of life

Two studies reported improvement in patient's quality of life after the patients received CsA.^{14,25} At 8 and 16 weeks, Dermatology Life Quality Index values were significantly decreased in CsA-treated patients compared with placebo ($P \leq .05$).¹⁴ Savic et al²⁵ reported an improvement of at least 75% in Dermatology Life Quality Index scores of omalizumab-treated patients and 41% of CsA-treated patients.

Relapse rates. Twelve CSU studies reported relapse rates after CsA treatment discontinuation, which ranged from 11% to 100%.^{5,8,9,14-17,20-24} Ilter et al²² initially started CsA at 5 mg/kg/d for 1 week, decreased to 3.5 mg/kg/d for another week, and then continued with 2.5 mg/kg/d for 5 weeks in 15 patients.²² At the initial dosage, all patients showed disease resolution. But when CsA was tapered, 86.7% of patients dropped out from the study because of uncontrolled disease. Only 2 patients continued CsA until the end of treatment. However, their diseases relapsed within a few days after stopping the treatment.²²

Two studies reported conflicting results in relapse rates with different treatment durations.^{14,20} Vena et al¹⁴ demonstrated that relapse rates after 16 weeks of CsA treatment (19.4%) were lower than after 8 weeks of treatment (42.4%). Conversely, Baskan et al²⁰ showed that patients with CSU treated with CsA for 12 weeks had a higher relapse rate (37.5%) than those treated for 4 weeks (20%).

DISCUSSION

To our knowledge, this is the first meta-analysis of CsA efficacy and safety in CSU treatment. Its results suggest that CsA is effective in the treatment of CSU, and that its safety is dose dependent. But it should be kept in mind that the number of studies in this meta-analysis is small, and many of them are of limited quality. For example, only 3 studies were found to be suitable for meta-analyzing CsA treatment effects on UAS7 in CSU, and only 1 of these 3 studies was an RCT.

Our results provide only limited guidance on how to select the best dosing scheme for the treatment of CSU. Clearly, the efficacy of CsA is dose dependent, and moderate doses of CsA appear to be more effective than lower doses. Little can be said about the benefit of increasing or tapering the dose of CsA in the treatment of CSU. Galindo Bonilla et al²⁸ suggested that the most effective CsA regimen in the treatment of CSU is 3 mg/kg/d for 6 weeks, followed by 2 mg/kg/d for 3 weeks and 1 mg/kg/d for 1 week and subsequent discontinuation. On the other hand, the results of our meta-analysis show that low-dose CsA (from 2 to <4 mg/kg/d) for 12 weeks significantly improves clinical severity in 70% of patients with CSU (Figure 3, B).

CsA is used in the treatment of various other dermatologic diseases including psoriasis and atopic dermatitis. In psoriasis, a common starting dose of CsA is 2.5 mg/kg/d, and doses are frequently increased up to 5 mg/kg/d if the response is inadequate.^{29,30} For atopic dermatitis, CsA is often started at 5 mg/kg/d for 2 weeks and subsequent tapered to 1.5 mg/kg/d with a total 3 months of treatment.³¹⁻³³ Similar to CSU, responses to CsA in both psoriasis and atopic dermatitis are dose dependent, with more rapid responses at higher doses.^{32,34,35} Overall response rates to CsA treatment at 4, 8, and 12 weeks were 54%, 66%,

and 73%, respectively. This suggests that patients who do not respond well within 4 weeks may benefit from continued treatment for up to 12 weeks. But again, more and better studies are needed to assess the benefit and long-term safety of CsA treatment for longer than 3 months.

Adverse events must be expected in CsA-treated patients, and our study demonstrates that rates of adverse events increase with the doses of CsA used, regardless of the duration of treatment. Two important adverse events from CsA are nephrotoxicity, detected by increased serum creatinine, and hypertension. Most previous psoriasis studies found the nephrotoxic effects of CsA to be dose-related, with a high risk of persistent renal dysfunction after more than 2 years of CsA treatment or doses of greater than 5 mg/kg/d³⁶⁻³⁸ and low rates of 1 in 5 patients showing elevated serum creatinine when treated with low doses of CsA (<3 mg/kg/d) for 1 year.³⁹ In contrast, 3 studies did not find a relationship between the dose of CsA and rates of renal side effects or hypertension in patients with psoriasis.³⁹⁻⁴¹ In the studies we analyzed, hypertension was reported in 5.8% of patients with CSU. Interestingly, no abnormal serum creatinine or high blood pressure was observed even in patients with CSU with prolonged treatment of up to 10 years with CsA, albeit at very low doses (1-1.5 mg/kg/d).¹⁰

With CsA treatment, the increased risk of malignancies is another matter of concern. In patients with psoriasis treated with low-dose CsA (2.7-3.1 mg/kg/d) for 2 years, the risk of cutaneous squamous cell carcinoma was reported to be increased to 6-fold after a 5-year follow-up period.⁴² The risk increased further with longer treatment duration or with history of psoralen-ultraviolet A therapy.⁴² Three patients with psoriasis developed a lymphoproliferative disorder during 2 to 3 years of CsA therapy, but the disorder resolved rapidly after withdrawal of CsA.⁴³ However, it should be noted that psoriasis *per se* is linked to a higher incidence of lymphoma and malignancies.^{44,45} The studies we analyzed did not report any evidence that CsA treatment causes malignancies in patients with CSU. Kessel and Toubi¹⁰ reported no incidence of malignancy even after long-term CsA treatment in CSU. Nevertheless, the risk of malignancies in the treatment of CSU with CsA should be kept in mind.

Given the limited number and quality of studies, our meta-analysis results should be interpreted with caution. Our findings suggest that CsA is effective at low (from 2 to <4 mg/kg/d) to moderate doses (4-5 mg/kg/d). 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 1 to 5 mg/kg/d, and that 3 mg/kg/d is a reasonable starting dose for most patients.

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