Cyclosporine (CSA)

Evidence Summary for Use in Chronic Idiopathic Urticaria (CIU)/Chronic Spontaneous Urticaria (CSU)

[Addendum to Omalizumab Evidence Summary in CIU/CSU]

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INTRODUCTION

Cyclosporine (CSA) has long been recognized as an effective treatment for patients with treatment refractory chronic idiopathic or spontaneous urticarial (CIU/CSU). It has also been used in these patients as a means to reduce daily doses of corticosteroids or to limit their chronic use. This addendum is intended to summarize the available evidence for cyclosporine in the management of CIU/CSU.

Although the mechanism for reducing symptoms of CIU with CSA is unknown, it has been postulated that its effect involves modulation of a number of layers of the immune system.[1]

EFFICACY:[2-11]

There are numerous published case series of CSA involving patients who have CIU that is severe and either nonresponsive or inadequately responsive to traditional therapies for CIU, including H1-AH in addition to either H2-receptor blocking agents or leukotriene receptors blockers or both. In many cases, these patients require treatment with corticosteroids in order to manage their severe symptoms. In each of the case series, response to CSA is in the range of 60-70% and prolonged remission from severe symptoms is maintained in ≥ 25% of patients after CSA has been discontinued. Other patients experience relapse either after discontinuation or during treatment with CSA but have more mild symptoms that resolve spontaneously or when treated with H1-AH. There are a few controlled clinical trials of CSA in similar refractory patients that have shown remission or significant improvement from severe symptoms in approximately 60% of patients. Long-term remission was also reported in ≥ 25% of patients after CSA was discontinued. Several of the publications involved use of low dose CSA (e.g., 1-3 mg/kg/d, approx. 100-300 mg), which appeared to provide a response similar to that observed with higher doses, but with a lower incidence of adverse events.

Table 1 Clinical Trials of Cyclosporine in CIU/CSU

Clinical Trial	Population/Intervention	Outcome(s)	Results	Comments/ADEs
Toubi[2] Open trial N=35 12 weeks CSA + 12 weeks observe (Trial of low dose CSA 2-3 mg/kg/d)	Pts with severe CIU, score of 3 with poor response to anti-histamines (H1 and H2) and steroids (prednisolone 10-25 mg daily), mean duration 21 months. CSA 3 mg/kg X 6 wks, 2 mg/kg X 3 wks, 1 mg/kg X 3 wks. (n=25) Tx was D/C if no response in 4 wks. N=10 (No Tx, served as control)	Effect on composite score of signs and symptoms of CIU (# of lesions, # of separate episodes, avg. size and duration of lesions and severity of pruritis. Composite score determines severity of symptoms. 0=no symptoms, 1-mild, 2=moderate, 3=severe Effect of CSA on ASST	6/25 dropped out. 2 due to GI ADEs. 4 no response after 4 wks (these patients had the longest duration of CIU 52-60 months) 19/25 pts were followed for 6 months. Response to treatment was rapid (within 1 wk). All treated patients had their symptom score reduced to 0-1 (none to mild symptoms) from 3 (severe). All other medications were D/C including steroids. At wk 4, symptoms fluctuated making it necessary to restart H1AH in some pts (with score of 2). At wk 12, 13/19 pts were in full remission (68%) while 6/19 had	11/13 pts with no symptoms after treatment with CSA for 12 wks remained in full remission for the 12 wk follow up period. In those pts who symptoms worsened after CSA was D/C, required only H1-AH for symptom control AST did not correlate with disease activity or severity. Mild ADEs were reported in 2/19 pts. One had a rise in SCr

			a score of 1 (mild), requiring only H1-AH. The 10 unTx control pts maintained severe symptoms (score=3)	(1.5 mg%) while another pt reported agitation and sleeplessness.
Inaloz[3] Open trial N=27 pts with severe CIU N=24 healthy controls 4 weeks (Trial of low dose CSA 2.5 mg/kg/d)	Pts with CIU with no response to H1-AH and 8 pts had received steroids. Mean duration of CIU was 50 months. CSA 2.5 mg/kg/d divided BID for 4 weeks	Weekly UAS at baseline and after Tx (# and size of lesions + severity of pruritis were graded on a 3 point scale) and summed. Effect of CSA Tx on serum levels of IL-2R, TNF and IL-5 Tx was considered effective if UAS score was 25% of the score at baseline.	Mean UAS baseline: 32.07 (range 16-42) Mean UAS after Tx: 6.22 (range 0-15) 19/27 (70.37%) pts had UAS 25% of baseline indicating full remission Reduction from baseline in UAS was significant in all pts Tx with CSA ($p<0.005$)	IL-2R, TNF, IL-5 all reduced from baseline with CSA Tx. No change in unTx groups One pt experienced nausea and abdominal pain, stayed on Tx with CSA after addition of PPI The authors conclude that CSA is effective and safe for patients with CIU; with only 1 pts experiencing a minor ADE.
Boubouka[4] Open trial, case series N=30 5 months Tx with CSA, followed for 1 year after end of Tx (Trial of low dose CSA 1.5-2.5 mg/kg/d)	Pts with resistance to H1-AH and response only to steroids CSA 1.5-2.5 mg/kg/d adjusted according to clinical response and ADEs.	Composite of pruritis severity, # wheals, diameter of largest wheal, avg. duration of pruritis. All measures were graded 0-3, 3 representing greatest severity.	23/30 (73.3%) pts completed 5 months Tx. 3/30 (11.5%) had no response to Tx. 4/30 (13.3%) dropped out due to ADE (high blood pressure, 3 were males) Symptom response was greater over time. Response at visit 1 for most symptoms was in the range of 30-35%. At visit 5, response rate for most symptoms neared 90% Doses were reduced monthly according to ADEs and improvement in symptoms. Mean dose month 1: 2.16 mg/kg Month 2: 1.92 mg/kg, Month 3: 1.33 mg/kg, Month 4: 0.83 mg/kg, Month 5: 0.55 mg/kg/d At one-year follow up after Tx ended: 20 (87%) remained free of symptoms; 3 (13%) had relapsed.	4/30 (13.3%) D/C due to HTN Renal function was not affected in any pt. ADEs were noted in 8 other pts (arthralgia n=2, loss of appetite n=3, headache n=3). All of these ADE resolved with dose reduction of CSA.
Grattan[5] R, DB, PC N=30 (20 CSA, 10 P) 4weeks Tx, followed for up to 20 weeks or until relapse	Pt with severe unremitting disease, poor response to H1-AH and a + ASST CSA 4 mg/kg/d or P x 4 wks All took cetirizine 20 mg daily for duration of	UAS-7 (maximum score=42) and VAS indicating the overall severity of urticaria over prior to weeks (0=none, 10=worst ever) Response was defined	29/30 completed the 4 wk trial. 8/19 (42%) responded at 4 wk; none of the P recipients. 3 other pts met response criteria at 2 but not at 4 wks. UAS and VAS were significantly reduced from baseline for Tx. Group. Mean time to response was 5	As per protocol, a 25% dose reduction of CSA was made for HTN in 2 pts, severe paresthesias in one and hypoglycemic episode in one insulin dependent diabetic.

	study After 4 wk Tx., pts were followed for up to 20 wks or until relapse. Pts were offered open-label CSA if no response	as a reduction in UAS to 25% of baseline and relapse as a return of the UAS to >75% of baseline.	days (wheal and pruritis). In 6 pts, urticarial activity stopped within 48 hrs. NNT with CSA at 4 wks=2.4 NNT with CSA at 2 wks=1.7 17 non-responders (CSA n=7, P=10) took OL CSA X 4 wks Overall response (R and OL) 19/29 (65%) 5/19 (26%) responders were still in remission at 6 months.	ADEs were common in CSA but were not severe enough to require withdrawal (tingling of lips, feet or fingers n=11; headache n=12, severe in 3; feeling lightheaded n=2; arthralgia n=4; tiredness n=9; general malaise n=2, flu-like n=3; URI n=2; backache n=2; leg cramps n=2; swollen or bleeding gums n=3; hypertrichosis n=6, etc. 5/10 pts on P noted ADEs as well (GI upset n=3, dry mouth n=1, lethargy n=1) Renal and liver fxn remained normal in all
Loria[6] Open trial, 2 active Tx groups N=20 (CSA=10; Steroid=10) 8 weeks	Pts with CIU unresponsive to H1-AH were broken into 2 groups: CSA 5 mg/kg/d X 8 wks or prednisone 20 mg/d x 8 wks.	Composite symptom score (itch, flare, wheal) rated by severity on scale of 0-3, higher numbers indicate greater severity.	All patients had baseline composite symptom scores of 9, indicating severe urticarial symptoms 9/10 (90%) pts on CSA reported a complete response at day 5 and 10/10 pts recorded UAS of 0 by day 15. After Tx was D/C, 2 patients reported mild urticarial symptoms at 3 months. Complete response was seen in all steroid Tx patients but 4 relapsed with symptoms of urticaria when Tx was interrupted.	CSA group reported mild ADEs with tremors, headache and nausea in 2 pts. These ADE resolved when dose was reduced to 3 mg/kg/d. No pt had an increase in blood pressure or renal fxn abnormality. Prednisone group increase blood pressure in 1 pt and weight gain in 2. A reduction in CD4+ lymphocytes was reported in the prednisone group but not with CSA.
Di Gioacchino[7] R, DB N=40 (CSA=20; Cetirizine=20) 16-18 weeks 9 month follow-up	Pts with severe CIU unresponsive to H1-AH +/- H2RB and positive ASST. Short courses of steroids provided only partial remission, relapsing as soon as steroids were D/C. Pts required chronic Tx with prednisone (8-16 mg/d). CSA 5 mg/kg/d X 8 wks, then 4 mg/kg/d X 8 wks	Clinical severity of disease (0=constant remission of symptoms (wheals and pruritis); 1=occurrence of relapse resolving spontaneously in 24 hrs; 2=occurrence of relapse resolved by H1-AH (after no spontaneous response in 24 hrs; occurrence of relapse resolved	Before CSA, all 40 pts had a severity score of 3 requiring long-term steroids. After 2 weeks, 16/20 (80%) of pts on cetirizine had such severe symptoms, protocol changed and all 40 patients received CSA. Unclear if pts assigned to cetirizine continued to receive both CSA and cetirizine or not. Pruritis resolved within 1-3 days, followed by resolution of wheals and flares within 1st wk	CSA was tolerated well with no dropouts due to ADEs. However, after the 1st month of CSA, 3 pts had mild increases in SCr. CSA was reduced by 0.5 mg/kg/d and SCr returned to baseline. Four pts reported ADEs: headache, abdominal pain and diarrhea but were considered mild and disappeared after

		with steroids (after no response to H1-AH in 48 hrs)	in 33 (82.5%) of pts. 7/40 (17.8%) of pts had resolution of pruritis in 8-10 days and complete remission by the 3rd wk. At the end of Tx (16 or 18 wks) and after follow up, severity scores were significantly lower vs. baseline. During CSA, relapses were reported but resolved either spontaneously or with H1-AH. 16/40 pts (40%) were in full remission after 9-month follow-up. Only 2 pts did not respond to CSA and required chronic steroids. All pts responding to CSA were able to stop their prior medications. Relapses were Tx with H1-AH or resolved spontaneously.	the 1st 2 wks of Tx without reducing CSA dose. Research questions include lowest effective dose and optimal duration of CSA, usefulness of combined or sequential therapy with H1-AH to reduce the dose of CSA to lowest effective dose without losing efficacy.
Bulbul Baskan[8] R, open trial N=20 (CSA 4 wks n=10 vs. CSA 12 wks n=10) 4 vs. 12 wks	Pts with severe CIU with poor response to H1-AH and positive ASST. CSA 4 mg/kg/d for 4 wks or 12 wks	UAS-7 (same as that used in the study by Grattan, et al.) Response was defined as a reduction in UAS to 25% of baseline and relapse as a return of the UAS to >75% of baseline.	8/10 (80%) of pts in the 12 wks vs. 5/10 (50%) in the 4 wks were responsive to therapy. (p=0.35 for differences between groups) Both groups had statistically significant reduction in symptoms (UAS, pruritis) from baseline. Although relapses did occur, all pts had a lower UAS and were able to be Tx effectively with H1-AH or nothing. 3 pts in the 12 wk relapsed, 1 pt in the 4 wks group relapsed. Other responders were still in remission 3 months after therapy stopped. Rebound relapse was not observed. Although two pts saw improvement in their response in the 2 and 3rd month, the most dramatic response was seen within the first month of Tx Overall response when all pts combined 65%	ADEs were not severe enough to require withdrawal from study. ADEs included headache, hirsutism, nausea, dyspepsia, arthralgia, and gingival hyperplasia in the 12 wk and hirsutism, HTN and mild elevation in liver enzymes in the 4 wk group. This was a trial to determine an optimal duration of CSA therapy. There were no differences between groups in response rates or relapses but the numbers are very small.
Vena[9] R, DB, PC N=99 16 weeks Tx, 8 weeks follow-up	Pts with severe CIU poorly controlled with cetirizine. TSS=8 or > 3 groups: CSA X 16 wks or CSA X 8 wks then P X 8 wks or P X 16 wks.	Primary Endpoint: Change in TSS severity score after 8 wks. Other endpoints: # pts requiring rescue Tx, subjects global assessment (SGA)	CSA 16 wks N=31 CSA 8 wks + P 8 wks N=33 P 16 wks N=35 Mean TSS=11 at baseline 38/99 pts did not complete study CSA 16 (n=8), CSA 8 (n=13), P (n=17)	ADEs were common (CSA 16=65%; CSA 8=72.7%; P=45.7%) but led to W/D of Tx in only 6% of pts. W/D due to ADE: CSA 16: 2 (HTN and

	CSA 5 mg/kg/d X 2 wks, 4 mg/kg/d X 2 wks then 3 mg/kg/d X through 8 or 16 wks. All pts received cetirizine 10 mg/d	and Dermatology Quality of Life Index (DLQI)	Lack of efficacy: CSA 16 (n=2, CSA 8 (n=7; 5 during P), P (n=11) W/D due to ADE-see adjacent column TSS severity score was significantly lower in both CSA groups vs. P at 8 and 16 wks but not at 24 wks. Secondary endpoints including SGA and DLQI were statistically better in both CSA groups at 8 wks but not thereafter due to the higher rate of dropouts of non-responders in the P group. There were fewer dropouts due to non-response in the CSA 16 group vs. CSA 8 and P. Also, less pts required rescue Tx in the CSA 16 group vs. CSA 8 and P. One pt in the CSA 16 and 8 groups relapsed after the 16 wk Tx phase.	precordalgia) CSA 8: 2 (HTN and worsened eczema) P=0 There were 2 ADEs that were considered serious (precordalgia and acute gastroenteritis) which were not considered related to Tx. Although the duration of Tx with CSA did not appear to affect degree of response, there was a 15% higher drop out rate due to lack of effect in the CSA 8 group suggesting that prolonged Tx may reduce the risk of relapse.
Kessel[10] Open trial, case series N=120 Up to 10 years	Pts with especially severe CIU and no response to usual Tx (high dose H1-AH +/- H2RA or LTRA) and reduced QOL for at least 6 months. CSA 3 mg/kg/d if tolerated X 2 months. Then their dose was reduced to 2 mg/kg/d and then 1 mg/kg/d during the subsequent month. Whether pts were still on CSA or not, pts were evaluated every 3 months for 3-10 years.	Severity of urticarial symptoms including consideration of # of lesions, # of separate episodes, size of lesions, duration of lesions and pruritis. 0=no symptoms, 1=mild urticaria,(1-4 points) 2=moderate urticaria (5-9 points) and 3=severe urticaria (10 points). UAS was done at baseline during Tx. Pts were followed to assess whether remission was long lasting or if they needed rescue Tx with H1-AH if urticaria persisted (in milder form). When urticaria was severe, and CSA could not be D/C, a low dose (1-1.5 mg/kg/d) was continued and pts followed. In those patients on	100/120 pts (83%) tolerated CSA for at least 3 months. Of these, 30% achieved full remission (score of 0). In 32%, response to CSA was considered as moderately beneficial (score of 1-2. In these pts maintenance with H1-AH provided satisfactory control of symptoms and QOL. Overall, 62% of these pts had some appreciable improvement in their CIU symptoms and Tx was D/C after 3 months. In 20 pts in whom remission was achieved or nearly achieved, when CSA was D/C or dose was reduced, severe urticaria or angioedema recurred. In these pts, CSA 1-2 mg/kg/d was maintained. In 8/20 pts, Tx with CSA was continued for 8-14 months. These pts were able to maintain a reasonable QOL with H1-AH. In 12/20 pts that were unable to D/C CSA, they were maintained	20/120 (16.5%) of pts W/D due to severe ADEs. 9 pts D/C after 2 days due to severe GI ADEs (GI pain and/or diarrhea). In the remaining 11, CSA was D/C after 10-15 days due to persistence of peripheral neuropathy or severe headaches. In the 20 pts that continued on long-term CSA, GFR was assessed over 5-10 years, GFR remained normal. No signal was identified for possible malignancy risk (small sample size) or increased risk of infection.

		CSA for 3 months or > were followed for 3-10 years to check for malignancies, especially in those Tx for 5-10 yrs.	on a dose of 1-1.5 mg/kg/d for variable amounts of time between 5-10 years. 18/100 pts did not respond to CSA within 1 month, Tx D/C	
Guaragna[11] Open trial, case series N=21 4 weeks CSA Tx 4 weeks follow up	Pts with Tx resistant CIU CSA 4 mg/kg/d divided twice daily	Effect of CSA on serum IgE and # of weekly relapses and relapse duration.	Although the article lacked in detailed results, CSA appeared to reduce serum IgE, severity of pruritis, # of relapses and relapse duration.	Trial results lacked in detail, unclear tables which lacked actual before and after treatment results.

ADEs=adverse events, ASST=autologous serum skin test, CSA=cyclosporine A, DB=double-blind, GI=gastrointestinal, H1-AH=H1 anti-histamines, H2RB=Histamine 2 receptor blocker, IL-2F=interleukin-2 receptor, LTRA=leukotriene receptor antagonist, OL=open-label, P=placebo, PC=placebo-controlled, PPI=proton pump inhibitor, QOL=quality of life, R=randomized, SCr=serum creatinine, TNF= tumor necrosis factor, Tx=treatment, TSS=total symptom score, UAS-7=urticaria activity score (week), W/D=withdrawal

ADVERSE EVENTS

Although adverse events were relatively common with CSA, in most cases, they were considered to be of mild to moderate severity and did not lead to discontinuation of CSA. The more common adverse events included gastrointestinal (GI=nausea, diarrhea, abdominal pain, etc.), paresthesia, tremor, headache, arthralgia, agitation, etc. Hypertension and reduced renal function were reported in a few patients, which typically resolved with a reduction in dose of CSA. Withdrawal from trials included in Table 1 occurred in less than 20% of patients and occurred less often in those patients receiving lower doses of CSA (e.g., 1-3 mg/kg/d, approx. 100-300 mg). In a long-term trial of CSA in a small number of patients, a signal for increased risk of malignancy was not observed.

CONCLUSIONS:

Evidence exists from case series and a limited number of randomized controlled clinical trials that CSA is effective in significantly reducing or resolving symptoms of CIU/CSU and in patients with refractory disease; without a significant safety risk. Low daily doses of CSA (e.g., 1-3 mg/kg/d, approx. 100-300 mg) appear to be similarly effective to higher doses but with a lower risk for adverse events. Additionally, more than 25% of patients who discontinue therapy with CSA remain in remission and if a relapse occurs, symptoms are usually mild and resolve spontaneously or with H1-AH. Omalizumab and CSA have not been compared directly in clinical trials, however appear to have similar response rates when treating refractory patients (e.g., 60-70%). Monitoring of blood pressure and renal function is recommended in patients receiving long-term CSA while monitoring for anaphylaxis is recommended for an appropriate amount of time following each subcutaneous injection of omalizumab. If blood pressure or serum creatinine increases in patients receiving CSA, the dose of CSA should be reduced and monitoring continued. An advantage of CSA is that one-fourth of patients were reported to remain in remission after cessation of treatment, while all patients in clinical trials of omalizumab relapsed soon after omalizumab was discontinued. An additional advantage of CSA is that it is taken as an oral dose daily while omalizumab is administered every four weeks in a healthcare setting because of the risk for anaphylaxis. Cyclosporine appears to be a viable option for patients with refractory CIU/CSU who do not have hypertension or impaired renal function.

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