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## Randomized double-blind study of cyclosporin in chronic 'idiopathic' urticaria

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### Summary

**Background** Histamine-releasing activity (HRA) is detectable in up to 50% of patients with chronic ordinary urticaria.

**Objectives** To determine the effect of cyclosporin on clinical features and HRA in patients with chronic urticaria.

**Methods** Thirty patients with severe unremitting disease, responding poorly to antihistamines and showing a positive autologous serum skin test (ASST) as a marker of HRA, were randomized to 4 mg kg<sup>-1</sup> daily of cyclosporin (Sandimmun<sup>®</sup>, *n* = 20) or placebo (*n* = 10) for 4 weeks. Non-responders were offered open-label cyclosporin for 4 weeks. All were followed for up to 20 weeks or until clinical relapse; all took cetirizine 20 mg daily throughout the study. The primary measure of efficacy was a daily urticaria activity score (UAS) of weal numbers and itch (maximum score 42 per week). A positive response was defined as a reduction to < 25% of baseline weekly UAS and relapse as a return to > 75%. The effect of cyclosporin on serum HRA was assessed by *in vitro* basophil histamine release assays and ASSTs before and after treatment.

**Results** Twenty-nine patients (19 active, 10 controls) completed the randomized trial medication. Eight of 19 on active treatment but none on placebo had responded at 4 weeks (*P* < 0.05). Three others on active drug met the criterion for response at 2 weeks but not at 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 cyclosporin 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 cyclosporin, five (26%) had not relapsed by the study endpoint. Mean *in vitro* serum HRA fell from 36% (95% CI 22–49%) to 5% (95% CI 1–8%) after cyclosporin treatment (*n* = 11, *P* < 0.0001). The ASST response to post-treatment serum was also reduced (*P* < 0.05).

**Conclusions** This study shows that cyclosporin is effective for chronic urticaria and provides further evidence for a role of histamine-releasing autoantibodies in the pathogenesis of this chronic 'idiopathic' disease.

**Key words:** autoantibodies, chronic idiopathic urticaria, cyclosporin, randomized controlled trial

Chronic ordinary urticaria is called 'idiopathic' if no physical, allergic, infectious, drug-related or vasculitic cause can be identified. The presence of histamine-releasing autoantibodies to the high-affinity IgE receptor (FcεRI) or, less often, to IgE, in the sera of 30–50% patients with chronic 'idiopathic' urticaria<sup>1–6</sup> identifies a subgroup with a probable autoimmune aetiology.

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Routine laboratory assays for these autoantibodies are not yet available but the autologous serum skin test (ASST) is a reasonably sensitive (about 70%) and specific (about 80%) marker.<sup>7</sup>

Antihistamines remain the cornerstone of chronic urticaria management, although some patients derive little or no benefit from them. Cyclosporin inhibits cell-mediated immunity by downregulating Th1 lymphocyte responses and T cell-dependent antibody formation

**Table 1.** Baseline clinical characteristics of patients randomized to cyclosporin or placebo. Results expressed as median (range)

	Active	Placebo
Number	20	10
Women	16 (80%)	8 (80%)
Age (years)	32.5 (19–72)	33.5 (23–60)
Duration (months)	12 (3–60)	8.5 (3–192)
Previous steroid use	14 (70%)	4 (40%)
Baseline urticarial activity score (max. 42)	20 (9–36)	28 (17–41)
Baseline visual analogue score (max. 10)	5.6 (2–10)	7.4 (5.4–8.7)

by B lymphocytes. It also has inhibitory effects on anti-IgE-induced histamine release from human basophils<sup>8</sup> and skin mast cells *in vitro*.<sup>9</sup> Open studies of cyclosporin (Sandimmun<sup>®</sup>, Novartis Pharmaceuticals, Camberley, U.K.) have shown encouraging results in severe chronic 'idiopathic' urticaria.<sup>10–13</sup>

## Subjects and methods

### Patients

Thirty patients who had had severe daily or almost daily chronic 'idiopathic' urticaria for over 6 weeks (median duration 12 months, range 3–192; median age 33 years, range 19–72; 24 women) were recruited from urticaria clinics at the St John's Institute of Dermatology ( $n = 20$ ) and general dermatology clinics at the Norfolk and Norwich Hospital ( $n = 10$ ) between 1992 and 1996. All had a positive ASST as an entry requirement (see Skin tests) and a poor response to antihistamine therapy. Eighteen had required prednisolone for their urticaria at some time before the study, reflecting the severity of their disease. The baseline characteristics of the patients are summarized in Table 1.

Exclusion criteria were: chronic urticaria due to predominantly physical causes, urticarial vasculitis and C1 esterase inhibitor deficiency; known transmissible viral infections; known malignant disease including skin cancer; use of systemic steroids within 2 weeks of entry; use of antihypertensives, potentially nephrotoxic drugs and other drugs known to interfere with the pharmacokinetics of cyclosporin; a history of epilepsy, drug or alcohol abuse; pregnancy, lactation or risk of pregnancy without medically approved contraception; hypertension (diastolic blood pressure > 95 mmHg); serum creatinine, potassium or uric acid above the upper normal limits; bilirubin or liver enzymes more than twice the upper normal limit.

### Design of study and randomization

The study was a randomized, prospective comparison of cyclosporin (Sandimmun<sup>®</sup>) 4 mg kg<sup>-1</sup> daily with identical-appearing soft gelatin capsules containing placebo over 4 weeks following a 1-week assessment period during which patients started (or continued) cetirizine 20 mg daily (UCB Pharma Ltd, Watford, U.K.) and completed baseline assessments of urticaria activity. Skin tests and pre-entry blood tests were done at week - 1. Sera were stored in sterile aliquots at - 70 °C for repeat skin testing and *in vitro* histamine release studies. A clinical assessment, blood count and biochemical profile were done at weeks 0 and 2. Responders at week 4 were entered into the follow-up phase of the study and reviewed at 2-week intervals for a month, then monthly until either relapse, discontinuation at the patient's request, or reaching the maximum study duration of 6 months. Non-responders at week 4 were offered open-label cyclosporin and followed in the same way. Cetirizine was given during the baseline and placebo phases because of the severity of the urticaria and was maintained throughout the study for comparability of the urticarial activity assessments. There are no known interactions between cetirizine and cyclosporin.

Randomization codes were generated using a randomization schedule generator written in SAS<sup>®</sup> by Novartis AG using the SAS Macro facility. The macro utilized information on the number of centres, number of patients per centre, preferred block size, number and type of treatments and treatment ratios to produce the randomization schedule. Once generated, the code was sent to the Research and Development Department in Horsforth, U.K. for the production of the drug labels and code break envelopes. The code break envelopes were only to be opened if the health of the patient was threatened or the future management would be affected, and this was not the case for any of the patients recruited into the study.

### Dose modification and withdrawals

The protocol specified a 25% dose reduction of cyclosporin for the following events: increase of serum creatinine 30% above baseline value, serum potassium above the normal range, increase in total serum bilirubin or liver enzymes by > 100% or to twice the normal ranges, or diastolic blood pressure > 95 mmHg on two consecutive visits. A further 25% dose reduction was applied if the abnormality persisted.

Withdrawal from the study was occasioned by a rise of serum creatinine to above twice the upper normal limit, occurrence of any event specified under 'Exclusions', lack of response or clinical relapse. Patients who left the study for other reasons were classed as discontinued.

#### *Assessments and criteria for response and relapse*

Patients completed a daily record for the preceding 24 h of small (diameter < 3 cm) and large (> 3 cm) weal numbers, scored as follows: 0, < 10 small weals; 1, 10–50 small weals or < 10 large weals; 2, > 50 small weals or 10–50 large weals; 3, almost covered. Severity of itch was scored as 0, none; 1, mild; 2, moderate; 3, severe. The possible weekly aggregate urticaria activity score (UAS) therefore ranged from 0 to 42. Patients also completed a 10-cm visual analogue score (VAS) at each visit indicating the overall severity of their urticaria over the previous 2 weeks from 0 (none) to 10 (worst ever).

Response was defined as a reduction of the weekly UAS to < 25% of baseline and relapse as a return of the UAS to > 75% of baseline.

#### *Skin tests*

Cetirizine was discontinued at least 48 h before skin testing. Fifty-microlitre aliquots of autologous serum, saline and histamine (10 µg mL<sup>-1</sup> histamine base in saline) were injected intradermally into clinically uninvolved volar forearm skin. A positive ASST was defined as a 30-min pink weal of diameter ≥ 1.5 mm than a saline control skin test. A positive response provides evidence of histamine-releasing activity (HRA) in the serum.<sup>7</sup> Histamine served as a positive control.

All patients had a positive ASST as a condition of entry for the study. Only 19 were skin tested with freshly drawn serum at baseline (week - 1). The others were tested with serum stored at - 70 °C from an earlier venesection due to an unplanned protocol difference between the two centres. The median interval between taking blood and skin testing at baseline in these patients was 6 weeks (range 1–28). Only those skin tested with fresh sera at baseline were included in the pre- and post-treatment comparisons in case the levels of serum HRA had changed during the storage interval.

ASSTs were performed with stored baseline serum on the last day of cyclosporin administration (week 4, or week 8 for open-label treatment), and the results

compared with the week - 1 skin test response to look for any changes in skin mast cell 'releasability'. They were repeated 2 weeks later (when cyclosporin was expected to have been eliminated from the skin) with stored baseline serum and freshly drawn serum, to look for changes in HRA during treatment.

#### *Histamine release assays*

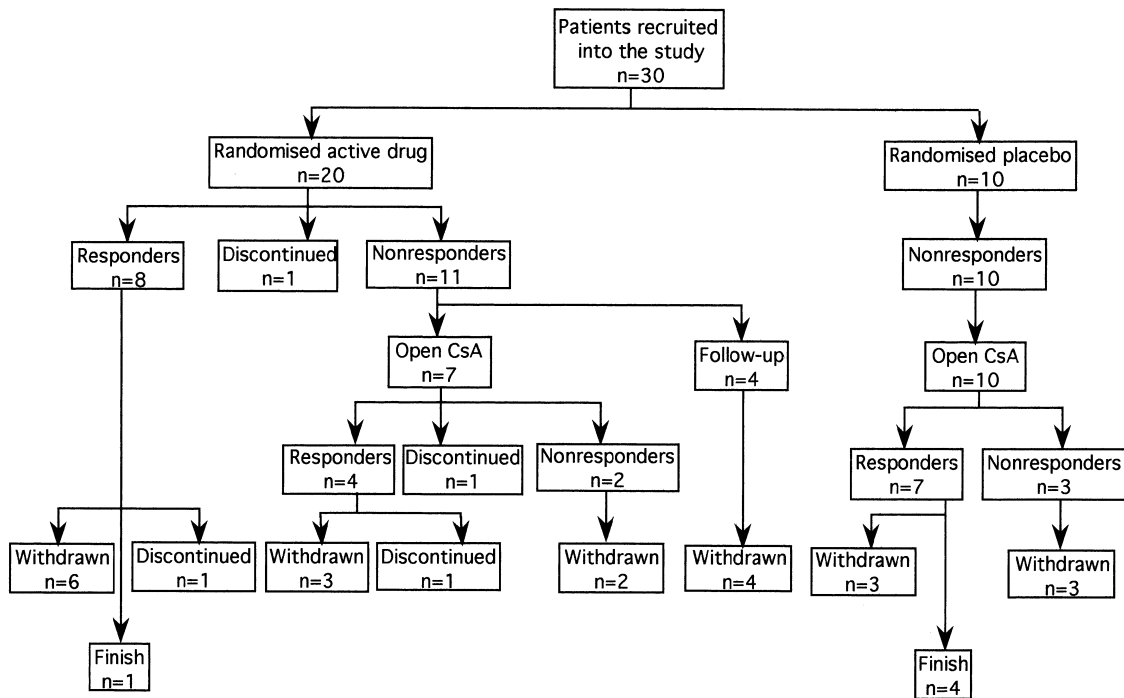
Sera were assayed for HRA on the well-characterized basophils of two donors, as described previously.<sup>1</sup> Basophils from these donors were selected on the basis of their responsiveness to anti-FcεRI and anti-IgE autoantibodies. Maximum histamine release was used for analysis of pre- and post-treatment serum HRA. Histamine release > 5% was considered positive. Assays were done on baseline sera, 2 weeks after finishing cyclosporin, and during follow-up in selected cases. They were not done on sera taken while patients were on cyclosporin in case basophil histamine release was inhibited.<sup>8</sup>

#### *Routine laboratory investigations*

Baseline investigations in all patients included a full blood count, erythrocyte sedimentation rate (ESR), biochemical profile, antinuclear antibody (Hep 2 assay) and C4 component of complement (as a screen for C1 esterase inhibitor deficiency). Blood count and biochemistry were repeated at each visit until the follow-up phase of the study. Plasma cyclosporin levels were measured at weeks 4 and 6 for responders to the trial medication and at weeks 8 and 10 for non-responders treated with open-label cyclosporin, to check compliance with medication and residual levels at the time of skin testing. Normal therapeutic ranges were 80–160 µg L<sup>-1</sup> at the Norfolk and Norwich Hospital, and 70–180 µg L<sup>-1</sup> at the St John's Institute of Dermatology. The results were not available to clinicians or patients when the decision was taken to give open-label cyclosporin to non-responders on completion of the 4-week randomized trial medication.

#### *Statistical analysis*

The main analysis of efficacy was restricted to the first 4 weeks when all subjects were on randomized blinded trial medication. Analysis of covariance employed a correction for age, sex and baseline activity.<sup>14,15</sup> The number of patients needed to be treated (NNT) to achieve one response in 4 weeks was calculated using



**Figure 1.** Randomization and progress summary flow chart showing withdrawals and discontinuations.

standard methods.<sup>16,17</sup> A Kaplan–Meier survival curve was used to show the proportion of patients not achieving a reduction of weekly UAS to <25% of baseline at each assessment up to 10 weeks. Frequency of responses was analysed with  $\chi^2$  using Yates’s correction. Differences in VAS and pre- and post-treatment data on ASSTs and serum HRA were analysed by Student’s *t*-tests after checking for normal distribution of data.

*Ethics approval*

The study was approved by the ethics committees of the West Lambeth Health Authority and the Norwich Health District. All patients gave written informed consent.

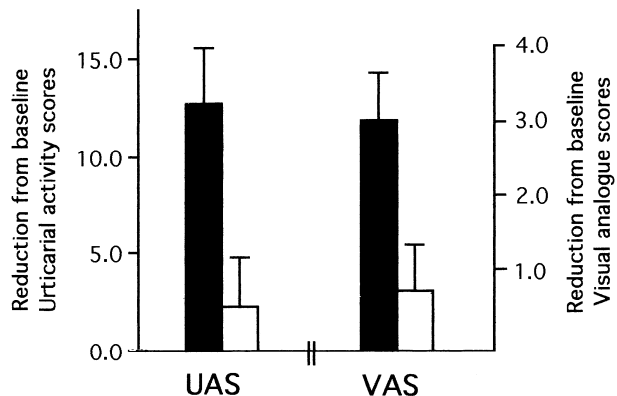
**Results**

*Clinical response to randomized trial medication (weeks 0–4)*

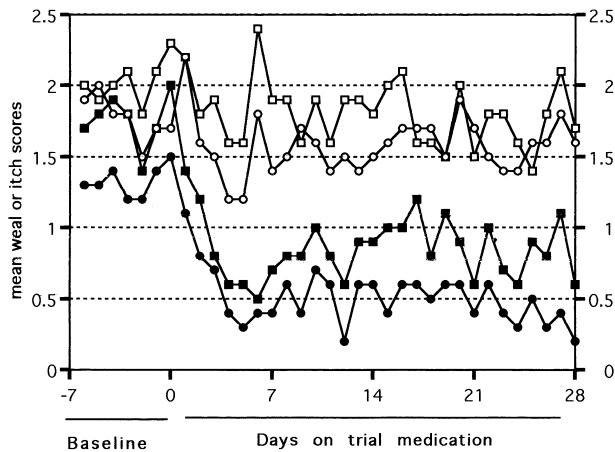
Twenty-nine patients completed the randomized 4-week trial medication and were followed up (Fig. 1). Eight of 19 subjects who received active therapy responded at 4 weeks whereas none of the 10 placebo subjects did so ( $P < 0.05$ ). Three additional patients

receiving active drug met the criterion for response at 2 weeks but not at 4 weeks. One of these had low plasma cyclosporin levels at week 4 and subsequently responded to open-label cyclosporin, so may have complied poorly with the trial medication.

Mean reduction in UAS from baseline at 4 weeks was 12.7 (95% confidence interval, CI 6.6–18.8) for patients randomized to active medication and 2.3 (95% CI – 3.3 to 7.9) for placebo (Fig. 2) ( $P = 0.005$ ). The reduction in VAS at 4 weeks for active (mean 3.0, 95%



**Figure 2.** Mean  $\pm$  SEM reduction in urticaria activity score (UAS) and visual analogue score (VAS) on randomized cyclosporin or placebo at 4 weeks. ■, cyclosporin; □, placebo.



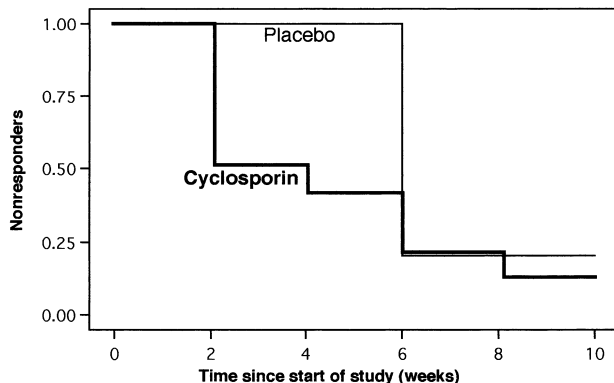
**Figure 3.** Mean daily scores for itch and weal numbers at baseline and during the randomized trial medication. □ placebo: itch; ○ placebo: weals; ■ cyclosporin: itch; ● placebo: weals.

CI 1.5–4.5) and placebo (mean 0.7, 95% CI –0.9–2.3) was also significant ( $P = 0.026$ ). Mean weal numbers and itch fell within 5 days of starting active and placebo capsules, and this improvement was sustained during active treatment (Fig. 3). Urticarial activity ceased within as little as 48 h in six patients.

The number of chronic urticaria patients (as defined in this study) who would need treatment (NNT) with cyclosporin to achieve one response at 4 weeks was 2.4 (95% CI 1.6–5.0). For a response at 2 weeks, the NNT was 1.7 (95% CI 1.2–2.8).

#### Clinical response to open-label cyclosporin (weeks 4–8)

Seventeen non-responders (seven originally randomized to active and 10 to placebo) received open-label



**Figure 4.** Survival analysis curve showing time to remission in patients randomized to cyclosporin or placebo followed by open-label cyclosporin in non-responders (weeks 0–10).

cyclosporin for 4 weeks and 11 (four active, seven placebo) responded.

#### Overall response to randomized and open-label cyclosporin (weeks 0–8)

The overall response rate to randomized and/or open-label cyclosporin was 19 of 29 (65%). Survival analysis for time to first response showed a large difference between active and placebo treatments in the first 4 weeks of the study, followed by convergence as non-responders were put on open-label cyclosporin (Fig. 4). Five of the 19 responders (26%) were still clear or almost clear at 6 months.

#### Withdrawals, discontinuation and dose reduction

As shown in Figure 1, one patient on active medication discontinued the study after 2 weeks. This was because she felt unwell and her urticaria had not responded. She was excluded from the subsequent analysis. Six of the eight active trial drug responders relapsed after stopping therapy (two within 2 weeks, two within 4 weeks and two within 6 weeks) and were withdrawn. One active trial drug responder discontinued the study at her own request after 4 weeks. One responder to open-label cyclosporin discontinued the study at 10 weeks while still in remission because she moved abroad; another failed to complete the open-label cyclosporin. A 25% dose reduction was made for hypertension in two patients, severe paraesthesiae in one and hypoglycaemic episodes in an insulin-dependent diabetic.

#### Side-effects

Side-effects during cyclosporin treatment were common but not severe enough to require withdrawal from the study. Twenty-nine of the 30 patients reported symptoms which were probably or definitely drug-related: tingling of the fingers, feet or lips ( $n = 15$ ); gastrointestinal upset ( $n = 11$ ); headache ( $n = 12$ , severe in three); feeling 'light headed' ( $n = 2$ ); tiredness ( $n = 9$ ); general malaise ( $n = 2$ ); 'flu-like symptoms' ( $n = 3$ ); upper respiratory tract infections ( $n = 2$ ); arthralgia ( $n = 4$ ); backache ( $n = 2$ ); leg cramps ( $n = 2$ ); swollen or bleeding gums ( $n = 3$ ); hypertrichosis (six women: two, upper lip; two, face; two, face and body); and one each with loin pain, breast tenderness, exacerbation of scalp hair loss, and possible increase in growth rate of scalp hair. Five patients noted side-effects during

**Table 2.** Pretreatment serum histamine-releasing activity of patients randomized to cyclosporin or placebo. Results expressed as mean  $\pm$  SD

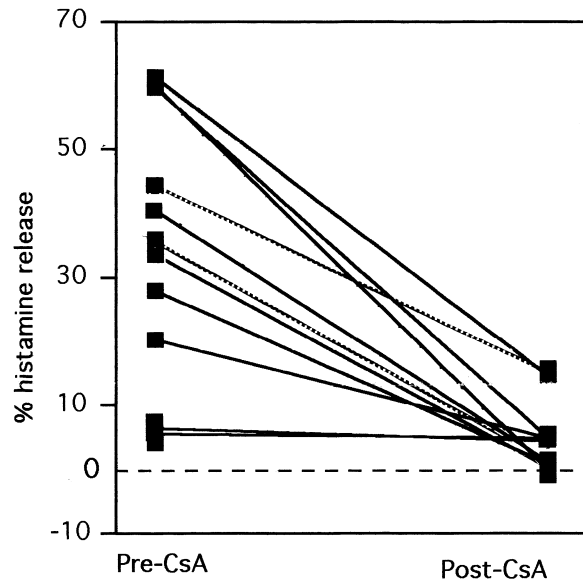
	Active	Placebo
Autologous serum skin test		
No. tested with week - 1 sera	13	6
Serum response at week - 1 (mm)	3.5 $\pm$ 1.8	4.3 $\pm$ 2.6 <sup>a</sup>
Basophil histamine-releasing activity		
No. of baseline sera tested	17	10
No. releasing > 5% histamine	8	6
Mean histamine release (%) (basophil donor 1 or 2)	18.9 $\pm$ 25.6	20.6 $\pm$ 20.7 <sup>a</sup>

<sup>a</sup> Not significant ( $P > 0.05$ ).

placebo treatment (mild gastrointestinal upset in three, dry mouth in one and lethargy in one).

*Routine laboratory tests*

Blood abnormalities were generally mild and not clinically important. Baseline ESR was raised in seven patients (18–36 mm in the first hour) and antinuclear antibody titre was weakly positive (1 : 10) in three, but all other screening tests were normal or negative. Renal and liver function tests remained normal in all patients. Cyclosporin assays confirmed that all but one patient (randomized to active trial drug) taking cyclosporin had levels within or above the therapeutic range. Cyclosporin was below the limit of detection ( $< 20 \mu\text{g L}^{-1}$ , Norfolk and Norwich Hospital;

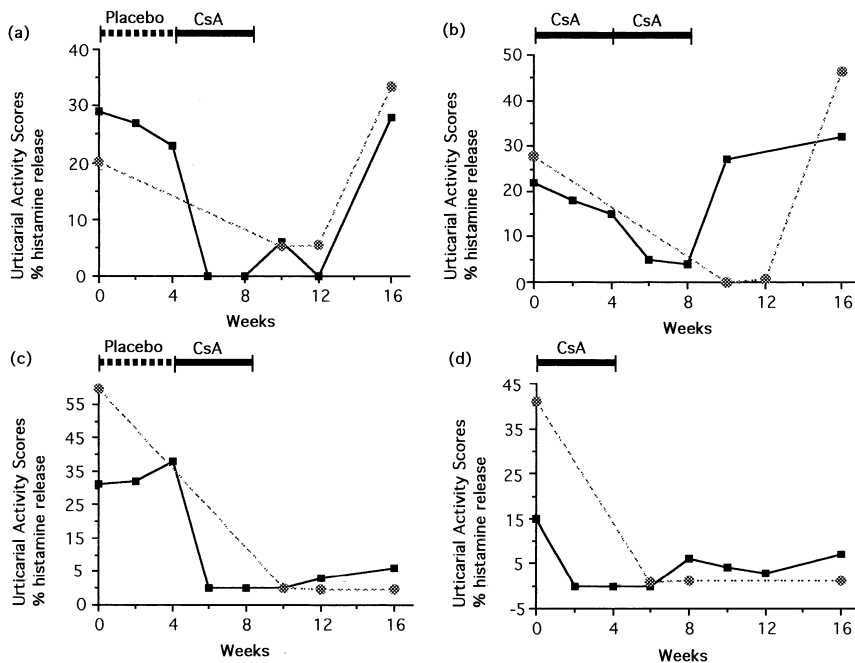


**Figure 5.** Reduction in histamine-releasing activity of paired sera from 11 patients taken before and after cyclosporin (CsA) treatment ( $P < 0.0001$ ).

$< 25 \mu\text{g L}^{-1}$ , St John’s Institute of Dermatology) 2 weeks after stopping it in all except two patients (33 and  $59 \mu\text{g L}^{-1}$ ).

*Skin tests*

Of the 19 patients in whom baseline ASSTs were performed with fresh sera, 13 received active



**Figure 6.** (a–d) Serial urticaria activity scores (solid lines) and serum histamine-releasing activity (dotted lines) in four patients over 16 weeks. The scores show a reasonably close relationship. CsA, cyclosporin.

medication and six placebo. There was no significant difference in baseline serum responses or histamine weal diameters between the two groups (Table 2). The response to fresh serum skin-tested 2 weeks after stopping cyclosporin was significantly lower than the response to stored pretreatment serum skin-tested on the same day (2.1 mm, 95% CI 1.0–3.3, vs. 4.8 mm, 95% CI 2.4–7.2,  $P = 0.04$ ,  $n = 13$ ), consistent with a reduction in serum HRA. However, the response to serum skin-tested at week – 1 and the response to the same (stored) serum after 4 weeks on cyclosporin showed no statistical difference, suggesting that cyclosporin had no effect on skin mast cell 'releasability'.

#### *Basophil histamine release assays*

Baseline sera were available for *in vitro* analysis from 27 subjects. The mean highest histamine release of these sera was 20.4% (95% CI 10.8–29.7), of which 14 released > 5% histamine (mean 36.7%). There was no significant difference between HRA of sera randomized to the active vs. the placebo groups (Table 2). Paired pre- and post-treatment sera were available for analysis in only 11 of the 14 patients with positive HRA. They showed a highly significant fall in mean HRA from 36% (95% CI 22–49%) to 5% (95% CI 1–8%) ( $P < 0.0001$ , Fig. 5).

#### *Relationship between basophil histamine release and clinical response*

Thirteen of 18 clinical responders to cyclosporin in whom baseline serum HRA was available for assay were positive (> 5%) compared with one of nine non-responders ( $P < 0.01$ ). All 11 patients included in the analysis of pre- and post-treatment paired sera were clinical responders. Their mean UAS fell from 23.6 (baseline) to 1.2 (post-treatment). The relationship of clinical activity to serum HRA is shown for four patients who responded to cyclosporin and were followed for 16 weeks (Fig. 6a–d). UAS and HRA corresponded quite closely during relapse (Fig. 6a,b) and sustained remission (Fig. 6c,d).

## Discussion

This study provides strong evidence that cyclosporin may bring about clinical improvement in chronic ordinary urticaria patients with a positive ASST. Disease control was achieved in about two-thirds of

patients and long-term improvement in a quarter of these. Three of the five responders who completed the study without meeting the criteria for relapse continued to have mild disease, which suggests either that cyclosporin can, in some instances, reset urticaria to a lower level of activity, or that the patients underwent spontaneous improvement. The 68% overall response rate to open cyclosporin reported by Toubi *et al.*<sup>11</sup> is similar. They used 3 mg kg<sup>-1</sup> daily of Sandimmun® for 6 weeks followed by 2 mg kg<sup>-1</sup> daily for 3 weeks, then 1 mg kg<sup>-1</sup> daily for 3 weeks. Eleven of 13 responders remained in remission 3 months later. Barlow *et al.* used 2.5–3.5 mg kg<sup>-1</sup> daily of open Sandimmun® for 4 weeks, with a response rate of 75%.<sup>10</sup> Seven of nine responders had some beneficial effects at least 1 month later. Similar results have been obtained by Vena *et al.*<sup>12,13</sup> The presence of a positive ASST response offers a marker for histamine-releasing autoantibodies, but does not appear to be a prerequisite for a good clinical response to cyclosporin, as 10 patients with a positive ASST did not respond in this study and seven of the responders reported by Toubi *et al.* had negative pretreatment serum skin tests;<sup>11</sup> however, the *in vitro* HRA of their sera was not reported.

Fewer adverse events might have been encountered with a smaller dose of cyclosporin. Toubi *et al.* reported only mild side-effects in two of 19 patients (slight increase of creatinine in one and agitation with sleeplessness in another), using a starting dose of 3 mg kg<sup>-1</sup> daily.<sup>11</sup> The optimal dose and duration of cyclosporin in chronic ordinary urticaria still needs to be established. Treatment with the new microemulsion formulation of cyclosporin (Neoral®, Novartis Pharmaceuticals) might allow lower doses to be given, as a comparison between Neoral® and Sandimmun® in chronic psoriasis showed similar disease control with an overall 10% dose reduction on Neoral®.<sup>18</sup>

The low levels of cyclosporin detected in two patients 2 weeks after finishing the prescribed medication were unexpected because cyclosporin should be effectively cleared within five half-lives of stopping treatment (6–20 hours). It is possible that they did not adhere strictly to the prescribed dose of trial medication or that detectable levels were due to slow elimination. One of the two patients relapsed at week 8, while the other was still in remission at the close of study (week 24).

The reduction in *in vitro* serum HRA after cyclosporin in the responders and the reduced ASST responses to post-treatment sera indicate that histamine-releasing autoantibodies may be directly involved in disease pathogenesis, and support the



concept of autoimmune urticaria. The rate of fall is not known because serial measurements of serum HRA were not made during cyclosporin treatment.

It is possible that the very early cessation of wealing in some patients (within 48 h) was due to other factors, such as stabilization of histamine release, which has been shown *in vitro* for healthy human basophils<sup>8</sup> and skin mast cells<sup>9</sup> pretreated with cyclosporin and stimulated with anti-IgE. Our study showed no evidence of a reduced skin test response to stored serum in the presence of cyclosporin, just as Munro *et al.* found no reduction in allergen-induced wealing in atopic eczema patients treated with cyclosporin,<sup>19</sup> suggesting that cyclosporin does not suppress the acute manifestations of cutaneous mast cell degranulation *in vivo*. Evidence from the mouse indicates that cyclosporin can inhibit IgE-dependent tumour necrosis factor (TNF)- $\alpha$  secretion from skin mast cells and can reduce the responsiveness of target cells to TNF- $\alpha$ , leading to inhibition of neutrophil accumulation after degranulation.<sup>20</sup> Cyclosporin also inhibits the release of cytokines and granular proteins from eosinophils<sup>21</sup> that are often present in lesional urticaria biopsies.

## Acknowledgments

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