

Cyclosporine-A in severe chronic urticaria: the option for long-term therapy

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Abstract

Background: The treatment of severe chronic urticaria (CU) remains a difficult goal to achieve. Many patients do not respond to anti-histamine therapy, even when off-label doses are given. Thus, cyclosporine-A (CsA) becomes a good therapeutic option for severe patients and for some, long-term therapy is required. We evaluated the effectiveness and safety of low-dose CsA, when treatment cannot be discontinued and long-term CsA therapy is needed to maintain severe CU in remission.

Methods: Among 2000 patients with CU who were referred to our outpatient clinic, 120 patients who suffered from a very severe CU began treatment with CsA 3 mg/kg. A clinical and laboratory followup was performed during this period of treatment.

Results: In 20 patients, CsA was discontinued within 2–15 days after initiation because of side-effects. Among 62 of the remaining 100 patients (62%), CsA was administered for a period of 3 months with a highly beneficial outcome. In another 20 patients (20%), CsA was considered beneficial; however, it was required for a longer period of time, 5–10 years for some of the cases. In all cases, CsA was well tolerated and most important, it was safe. For 18 patients (18%), CsA therapy was reported as failed.

Conclusion: A low dose of CsA is a good option for patients who suffer from especially severe CU. In most cases, this therapy regimen is considered effective and safe. For a small group of patients, long-term therapy is needed, and until now it is considered safe.

The major concept of chronic urticaria (CU) is that it is of an autoimmune origin and is based on the finding of pathogenic IgG autoantibodies that are directed against the anti-IgE receptor on mast cells in 30–40% of patients suffering from CU (1). However, subsequent research has characterized CU in the broader context of an immune-mediated disorder rather than a focused autoimmune event. In this respect, a polyclonal activation of B cells and the presence of unrelated autoantibodies such as anti-thyroid antibodies were reported in patients with CU (2). Also, CD4⁺ T cells were found to be in an 'activated state' as evidenced by the over-expression of CD40L on their surface in association with disease severity (3). In addition, we later reported on the elevation of MMP-9 in the plasma of patients with severe CU (4).

In practice, however, most specialists who deal with this disabling disorder are mainly concerned with the management of patients who suffer from severe form of CU. In a study where 562 patients with CU were followed, mild to

moderate CU responded well to H1 antihistamines. However, 46% (most of whom were defined as severe) were considered nonresponders to H1 blockers (5). This impression was confirmed by others, where 40–50% of patients with a severe form of CU did not respond sufficiently well to H1-blockers and therefore needed more aggressive therapy (6). When treatment is discussed, one should consider the issue of CU duration. In this respect, the duration was assessed in a follow-up study among 220 patients with CU. Whereas CU was resolved within 1 year in only 35% of the patients, for 29%, the symptoms gradually decreased after 1 year, however, among 40–50% CU persisted for more than 1 year (7). In this respect, we also reported continuing CU for 3 years in 50% of the patients who experienced a very severe onset of urticaria (8). Thus, when CU is severe and long lasting, defined as nonresponding to H1-blockers and short courses of corticosteroids are repetitively required, low-dose cyclosporine-A (CsA) turns to be an optional therapeutic choice.

In 1991, Fradin et al. was the first to give CsA 6 mg/kg for a period of 3–9 weeks to three patients suffering from severe CU. Despite its beneficial effects, CsA was discontinued in all the three patients because of its undesirable side-effects (9). Two years later, Barlow RJ et al. treated 12 patients who suffered from severe CU with low-dose CsA (3 mg/ml) for 1 month, and reported on both its safety and beneficial effect (10). In 1997, our group described a modified protocol for CsA administration over a 3-month period, with an initial dose of 3 mg/kg that was gradually reduced. One-third of the patients with CU were cured and another third experienced reduced symptom severity (11). Notably, in one-third of the patients in full remission, urticaria relapsed 6–12 months after CsA was discontinued, and longer CsA therapy was needed.

During the last decade, CsA was widely administered by many centers mainly for patients with very severe CU. Although there is agreement that it is a drug with evidence-based benefit and short-term safety, only a few studies posed the question of how long CsA could be administered to patients who need it for longer periods. In most of the previously mentioned studies, CsA was administered for 1–3 months and in many of them, urticaria relapsed upon CsA discontinuation and longer therapy was considered. In this regard, we reported on a longer CsA therapy for a small group of patients as being efficient and safe (12).

In this study, we summarize our long-term experience with CsA therapy over more than a decade. We focus on the issues of its beneficial effect, its safety and mainly on the option of administering CsA for a long time period. We discuss the question of whether patients on long-term CsA therapy should fear malignancy.

Methods

Between 1997 and 2009, 2000 patients suffering from CU were followed in our outpatient clinic (a referral center for CU). Among these patients, 120 patients who were considered to be especially severe and nonresponders to conventional therapy for at least 6 months were initiated on 3 mg/kg CsA. Patients with pure physical urticaria, presumed chronic infection, food or food additive intolerance were not included in the study.

The decision of giving CsA was undertaken when these patients were considered as nonresponders to high doses of anti-histamines, or to the addition of H2 blockers, singular, or when their quality of life was altered because of the sedative side-effects of high (off-label) doses of anti-histamines. We preferred low-dose CsA therapy over the need of administering recurrent short courses of corticosteroids. Low alternate day doses of prednisone were sufficient to control severe urticaria in only few number of patients. All patients in whom CsA therapy was well tolerated and was continued for at least 3 months were closely evaluated every 4–6 weeks for their urticaria status. Blood pressure and routine laboratory analysis including: cell blood count (CBC), serum electrolytes, glucose, cholesterol, uric acid and creatinine were closely observed every 6–8 weeks. Because of the fact that serum creatinine does

not increase until glomerular filtration rate (GFR) is below 50% of normal, we calculated GFR according to the modified Cockcroft-Gault GFR formula (13). Later, whether still on CsA for longer periods or discontinued, patients were evaluated every 3 months for a period between 3 and 10 years.

Urticaria score

All patients were scored on a four-point scale as formerly described by Breneman et al. Briefly, this scale takes into consideration the number of lesions, number of separate episodes, average size of lesions, average duration of lesions and pruritus as follows: 0 = no symptoms; 1 = mild urticaria (1–4 points); 2 = moderate urticaria (5–9 points); 3 = severe urticaria (10 points). The urticaria score was performed at baseline before starting CsA and during follow up (14).

The mode of cyclosporine-A therapy

When patients responded and sufficiently tolerated the treatment, they continued with 3 mg/kg CsA for 2 months; then their dosage was gradually decreased to 2 and the 1 mg/kg during the following month. Patients were then followed to assess whether remission was long lasting or if they needed H1 blockers if urticaria was still persistent though in a milder form. When urticaria was severe and CsA therapy could not be discontinued, patients continued with a minimal CsA dose (1–1.5 mg/kg) and were closely followed.

Long-term safety

All patients with severe CU who received CsA therapy for a period of 3 months or longer were followed for a period of 3–10 years. During this period of time, we were able to monitor their general health status and looked for possible related malignancies, especially among those who were treated for 5–10 years.

Results (See Fig. 1)

Of 120 patients in whom CsA was begun, treatment was discontinued for 20 patients (16.5%) because of severe side-effects. In nine patients, treatment was stopped after 2 days of therapy because of severe gastrointestinal side-effects (abdominal pains and/or diarrhea). In another 11 patients, CsA was discontinued after 10–15 days because of the persistence of peripheral neuropathy or severe headaches. Among 100 patients who tolerated CsA well (free of all side-effects mentioned clinically), treatment was continued for at least 3 months (for some much longer). This enabled us to evaluate them during the course of therapy and then for a variable period of time between 3 and 10 years.

Among these patients, 30 (30%) achieved full remission (urticaria score 0) and CsA was discontinued after 3 months. Those patients who remained in remission for at least 3 years had their follow-up discontinued. In another 32 patients (32%), CsA was considered moderately beneficial (urticaria score 1–2), the severity of urticaria was declined to a degree

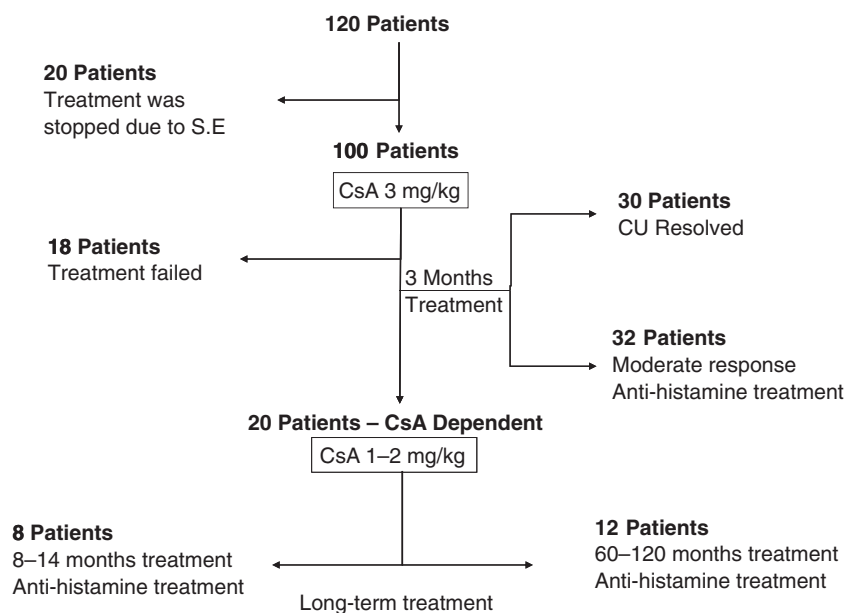


Figure 1 Among 120 patients with chronic urticaria who were treated with cyclosporine-A (CsA) (3 mg/kg/day), treatment for 20 patients was stopped because of side-effects. From the remaining 100 patients, after 3 months of treatment, the urticaria resolved in 30 patients and became milder in another 32 patients. In eighteen patients, the treatment was failed. In 20 patients, severe urticaria

reappeared after stopping treatment and, therefore, 1–2 mg/kg CsA was continued. In eight of these 20 patients, CsA was continued for 8–14 months and then discontinued. In another 12 patients, owing to the impossibility of discontinuing CsA, a very low dose of CsA (1–1.5 mg/kg) was continued for longer periods between 5–10 years.

in which maintenance with anti-histamine therapy was sufficient, and the patients' quality of life was satisfactory. Thus, CsA was summarized as variably beneficial in 62 (62%) patients, and they were able to discontinue therapy after 3 months. In 20 patients, CsA was highly beneficial and complete or almost complete remission was achieved; however, when CsA was discontinued or the dosage was reduced below 1 mg/kg, severe urticaria and angioedema reappeared (urticaria score 3) and, therefore, 1–2 mg/kg CsA was continued.

In eight patients, CsA was continued for 8–14 months and then discontinued, enabling patients to maintain a reasonable quality of life with anti-histamine therapy only (urticaria score 1–2). In another 12 patients, and because of the impossibility of discontinuing CsA, a very low dose of CsA (1–1.5 mg/kg) was continued for variable periods between 5–10 years. These patients tolerated CsA well (there was no blood pressure elevation or laboratory abnormalities).

In all 20 patients on long-term CsA therapy, GFR was assessed: At baseline, a mean of 106 ± 11 GFR ml/min was measured. After 1 year in some, and 5–10 years in the others, a mean of 99 ± 14 GFR was measured. None of them had GFR below the normal.

Careful evaluation (although in a small group of patients) did not raise any clues for possible malignancy development. Finally, in 18 patients where CsA was administered for at least 1 month was considered as a total failure and therefore discontinued.

The accepted nontoxic serum level of CsA is reported to be in the range between 75–325 ng/ml. However, this range

was adjusted for transplanted patients; however, it was never evaluated for other diseases. It is important to note, in all of our treated patients' sera, measured levels of CsA did not exceed 100 ng/ml, although most patients where CsA was maintained between 1–1.5 mg/ml, serum levels were approximately 50 ng/ml.

Discussion

When severe CU continues and conventional doses of both first generation and nonsedative antihistamines are not effective, patients become disabled and their quality of life turns to be unbearable. At this stage, higher doses of antihistamines such as Fexofenadine and Desloratadine are considered and there are many reported on their additive value in improving urticaria (15). However, 40–50% of patients with extremely severe CU who could tolerate high doses of sedative antihistamines or off-label doses of nonsedative antihistamines remained unresponsive and complained of a lower quality of life, thus requiring a more aggressive therapy (6).

During the last decade, many studies pointed to the importance of assessing health-related quality of life (HRQoL) in patients with severe CU. In these studies, health status scores in patients with CU were comparable to those of patients with ischemic heart disease. Others, being aware of assessing HRQoL, described a higher incidence of sleep disorders, work disability and psychiatric morbidity among patients with CU. The quality of life decreases among those patients

where higher and continuous doses of H1-blockers may cause tiredness or lowered concentration during work time (16, 17).

When patients did not respond to anti-histamine therapy, even when off-label doses were administered, short courses of corticosteroids for a period of 2–3 weeks were administered, sometimes in addition to leukotrein antagonists. In many of these cases, the attenuation of CU severity allowed a reasonable quality of life. However, when urticaria was extremely severe and longer corticosteroid therapy was the only option, we then considered low-dose CsA to be a better option for a long-lasting and severe CU (18).

During the last decade, CsA was reported to be beneficial in 27 original studies, some of which were double-blind controlled studies (19, 20). In six of them, the dose of CsA was between 4–5 mg/kg, whereas a low dose (2–3 mg/kg) was given in the other studies including our study. When higher doses were administered, side-effects, such as hypertension, peripheral neuropathy and increased serum creatinine, were reported in 20–30% of the patients. In most patients, they were transient or improved following dose decrease, and therapy discontinuation of therapy was rare. However, when a low dose of CsA was administered (2–3 mg/kg), most studies reported on a very low incidence of side-effects (mostly gastrointestinal or peripheral neuropathy) (11, 20, 21).

In this prospective cohort, 20 patients (16.5%) developed rapid onset severe side-effects, and CsA therapy had to be discontinued. However, when CsA doses were below the range of 3 mg/kg, mild side-effects such as peripheral neuropathy or abdominal discomfort were transient, and treatment was always tolerated. We also recommend that patients on long-term low-dose CsA should undergo periodically GFR examination, to prevent even mild CsA nephrotoxicity.

The main issue of this study is to discuss the need for long-term therapy (5–10 years) with low-dose CsA that was administered to 12 of our patients, who insisted on continuing this highly beneficial therapy regimen. The major concern in this report is the fear of malignancy that may possibly appear in patients who are maintained on long-term CsA therapy. The safety of giving low-dose CsA in severe CU over a long time period should be further evaluated in a larger group of patients. Moreover, the effectiveness of low-dose CsA in some patients with extremely severe CU and for those who must take this therapy regimen as their only option for maintaining a good quality of life must be continued until additional safety data are available. The incidence and risk of malignancy is reported to be elevated in solid organ transplant recipients (mainly those on immunosuppressive therapy) compared with the general population (22). As proof of the relationship between immunosuppressive therapy and posttransplant malignancy, epidemiological data reveal

that the length of exposure to immunosuppressive therapy and the intensity of therapy are clearly related to the development of malignancy. The incidence of posttransplant lymphoproliferative disorder was reported to be 1.6% with onset occurring more than 5 years after transplantation especially when CsA was administered at doses of more than 5 mg/ml. Indirectly, immunosuppressive drugs greatly increase the posttransplant risk of malignancy by impairing cancer surveillance and facilitating the action of oncogenic viruses. Thus, both the higher dose of CsA therapy and the higher incidence of oncogenic viral infections such as cytomegalovirus (CMV) and Epstein-Barr virus (EBV) in these patients are the main risk factors that contribute to the development of posttransplant malignancies (23).

The issue of the autonomous cellular mechanism for CsA and tacrolimus in promoting malignancy was proposed in animal models only. In this respect, tumor progression developed in T-, B-, and NK cell-deficient severe combined immunodeficiency (SCID)-beige mice but not in normal mice. It is also believed (as reported previously) that malignancy is probably related to CsA dosage, suggesting that low doses are safe (24).

Nonmelanoma skin cancers (NMSCs) that were reported to be associated with immunosuppression have been mostly reported in solid organ transplant patients, particularly in renal transplant patients (25, 26). Although the two most important risk factors for NMSCs in the transplant population are the amount of sun exposure and age at transplantation, the duration of immunosuppressive drug therapy has been considered to be a risk factor predisposing to NMSCs (27). Therefore, one should consider the recommendation to avoid sun exposure in patients with CU who are on long-term CsA therapy.

In our case, a follow-up study that was conducted 8–10 years after patients who were administered CsA for only 3 months and then discontinued, or in patients where long-term therapy was administered (although to a small cohort of patients) does not show any cases of malignancy or any increase in the incidence of infections. Thus, our data suggest that when low-dose CsA is used in patients with CU (who are otherwise normal) and where the rate of CMV or EBV infections is definitely no higher than that of normal, individuals are probably safe.

Finally, we believe that the chance of malignancy is much lower when serum CsA levels do not exceed 50 ng/ml (a very low serum level). In conclusion, when CsA is required for longer periods, the goal should be to keep the dosage between 1–1.5 mg/ml. However, further studies with a larger number of patients with CU are required to establish this concept.

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