

biopsy specimen from the finger showed thickened collagen bundles in the dermis. A third biopsy from the forearm showed edematous dermis with slightly thickened collagen bundles in the lower dermis. Although detailed examination denied pulmonary, renal and esophageal involvement, the symptoms of the patient fulfilled the 2013 classification criteria of systemic sclerosis proposed by American College of Rheumatology/European League against Rheumatism.<sup>1</sup> Oral prednisolone (PSL) (30 mg/day) was started along with intravenous administration of alprostadil. The ulcer was epithelialized six months later. Thereafter, PSL was gradually tapered, and in turn, dapson (50 mg/d) was started. He is well-controlled under 8-10 mg/d oral PSL, without recurrence of ulcers.

Lupus erythematosus profundus (LEP) is a subtype of chronic cutaneous LE with or without systemic lupus erythematosus (SLE). Additionally, LEP is rarely seen in patients with connective tissue diseases other than SLE. Association between LEP and systemic sclerosis (SSc) is extremely rare, and only a few cases have been reported to date.<sup>2</sup> Association with LEP and SSc is extremely rare, and thus the etiology of the present case is unclear. The present case suffered from SSc, and detailed examination denied SLE and mixed connective tissue disease (MCTD). However, it was interesting to observe overlapping conditions of scleroderma and LEP in our case. He developed sclerosis of the upper extremities, but without organ involvement. LEP was developed on the forehead, scalp, and upper extremity. A recent report reviews 20 cases of lupus panniculitis of the scalp, which involved the parietal (70%), frontal (45%), temporal (40%), occipital (30%), and vertex (10%) regions.<sup>3</sup> Ulcer was observed in 10%.

To date, only a few cases of ulcerative LEP have been reported,<sup>4,5</sup> and microangiopathic processes such as segmental fibrinoid vascular necrosis, small vessel thrombosis, and dense angiocentric lymphocyte infiltrates have been suggested. Ishiguro et al. speculated that intractable ulcers occurred as a result of necrobiotic changes in the subcutaneous tissues caused by vascular changes.<sup>5</sup> On the other hand, xanthomatous reaction was detected in the fibrotic tissue of LEP.<sup>6</sup> In the present case, vasculitis was not observed but foam cells were detected in the dermis as well as within the blood vessels. It was speculated that xanthomatous cells were induced by phagocytosis of lipid peroxides caused by macrophage-derived oxygen radicals following destruction of sebaceous glands initiated by immune complex deposition,<sup>7</sup>

which may have induced circulation abnormalities and also tissue damages. Moreover, cellular infiltrates were observed not only in the subcutaneous tissues but also in the muscle layers, and thus those tissue damages may have led to the ulceration of LEP in this case.

## References

1. van den Hoogen F, Khanna D, Fransen J, Johnson SR, Baron M, Tyndall A, et al. 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis Rheum.* 2013;65:2737-47.
2. Oka H, Tanikawa A, Matsuda F, Tanaka M, Nishikawa T. Systemic sclerosis with unusual panniculitis and overlying discoid lupus erythematosus-like lesions. *J Dtsch Dermatol Ges.* 2005;3:627-9.
3. Lueangarun S, Subpayasarn U, Tempark T. Distinctive lupus panniculitis of scalp with linear alopecia along Blaschko's lines: a review of the literature. *Int J Dermatol.* 2019;58:144-50.
4. Martens PB, Moder KG, Ahmed I. Lupus panniculitis: clinical perspectives from a case series. *J Rheumatol.* 1999;26:68-72.
5. Ishiguro N, Iwasaki T, Kawashima M, Kawakami M. Intractable ulceration in a patient with lupus erythematosus profundus successfully treated with cyclosporine. *Int J Dermatol.* 2012;51:1131-3.
6. Ishikawa O, Akimoto S, Sato M, Okugi Y, Takeuchi Y, Miyachi Y. Xanthomatous reaction in lupus panniculitis. *Acta Derm Venereol.* 1996;76:411-2.
7. Arai H, Ito A, Hashimoto A, Eto H, Nishiyama S. Normolipemic xanthoma developed on alopecia lesion on a SLE patient: histological study. *Jpn J Dermatol.* 1991;101:427-37 [in Japanese].

T. Mori,\* T. Ito, N. Kikuchi, T. Yamamoto

*Department of Dermatology, Fukushima Medical University, Fukushima, Japan*

\* Corresponding author.

*E-mail address: mtatsu@fmu.ac.jp (T. Mori).*

<https://doi.org/10.1016/j.adengl.2021.05.021>

1578-2190/ © 2021 Published by Elsevier España, S.L.U. on behalf of AEDV. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

## Ciclosporin: An Old Ally in the Treatment of Chronic Spontaneous Urticaria<sup>☆</sup>



### Ciclosporina: una vieja amiga en el tratamiento de la urticaria crónica espontánea

*Dear Editor:*

Since the introduction of omalizumab for the treatment of chronic spontaneous urticaria (CSU), it has been possi-

ble to control the disease in a high percentage of patients who had been refractory to treatment with high doses of antihistamines<sup>1</sup>. According to the most recent European guidelines<sup>2</sup>, treatment with ciclosporin is indicated in cases where omalizumab has already failed. In this indication, it is prescribed off-label, although it has traditionally been used for treatment of CSU<sup>3</sup>. Published data are scarce, and only 2 randomized clinical trials involving no more than 16 weeks<sup>4</sup> and 8 weeks<sup>5</sup> of treatment have been performed. Nevertheless, there are cohorts and case series of patients treated with this drug at low doses for longer periods (i.e., up to 10 years)<sup>6</sup>. We performed the present study to improve our knowledge of ciclosporin for treatment of CSU in patients whose therapy with omalizumab had already failed.

We designed an observational, longitudinal, prospective study of patients diagnosed with CSU and treated with ciclosporin at our center. Previous treatment with omalizumab had failed. We recorded epidemiological and clinical data and assessed the severity of urticaria using the 7-day

<sup>☆</sup> Please cite this article as: Pinilla Martín B, Tous Romero F, Ortiz de Frutos FJ. Ciclosporina: una vieja amiga en el tratamiento de la urticaria crónica espontánea. *Actas Dermosifiligr.* 2021;112:768-769.

**Table 1** Results From Our Series

	Sex	Age at onset, y	Baseline UAS24 h	Baseline UAS7 d	Baseline dose, mg/kg	UAS24 h at 1 mo	UAS7d at 1 mo	Final dose	Duration of treatment, mo	Duration of follow-up, mo
Patient 1	Female	42	6	42	3.85	0	0	0.68	12	6
Patient 2	Female	44	5	41	3.15	0	3	0.6	14	4
Patient 3	Female	60	2	24	3.8	1	6	0.46	5	2

Urticaria Activity Score (UAS7d). We also recorded the dose of ciclosporin at different points during treatment (baseline, maximum dose, end of treatment), duration of treatment and follow-up, and adverse effects observed.

Of a total of 38 patients who had received treatment with omalizumab, 3 (7.9%) did not respond to the biologic and were switched to ciclosporin (Table 1). The UAS7d score at initiation of treatment with ciclosporin was 24, 41, and 42. Ciclosporin was started at 3.8, 3.15, and 3.85 mg/kg/d, respectively. The disease was controlled (UAS7d < 7) in all 3 patients at the first month of treatment, thus making it possible to gradually taper the dose of ciclosporin without flare-ups before suspending it altogether after 5, 14, and 12 months, with doses ranging from 0.46 and 0.68 mg/kg/d. We recorded no recurrences of urticaria in any of the patients. Similarly, no relevant adverse effects were reported during follow-up.

While ciclosporin has traditionally been used for treatment of CSU, no definitive regimens have been established. A meta-analysis published in 2017<sup>7</sup> analyzed various studies from the literature, including 2 clinical trials<sup>4,5</sup>. The results indicate that ciclosporin is an effective treatment for CSU, although they are difficult to extrapolate to real life, since candidates for this approach have long-standing CSU that does not respond to omalizumab and often requires cycles of oral corticosteroids. We must go back to articles published before approval of omalizumab if we are to find regimens for affected patients in the medium term, without inducing the feared adverse effects of ciclosporin. Kessel and Toubi<sup>6</sup> performed a prospective study of 20 patients with CSU that could not be controlled with ciclosporin at 3 mg/kg/d for 3 months who received the drug at 1-2 mg/kg/d continuously until control was achieved. In 8 cases, the drug could be discontinued after 8-14 months of treatment; the remaining 12 patients continued to receive ciclosporin for 60-120 months without adverse effects.

Boubouka et al.<sup>8</sup> reported similar results from their prospective study, in which a cohort of 30 patients with CSU received treatment with ciclosporin at doses ranging from 1.5 to 2.5 mg/kg/d depending on symptoms for 5 months. The disease was controlled in 88% of cases with a final dose of 0.55 mg/kg/d.

Our experience indicates that ciclosporin is an option for treating CSU after failure of omalizumab. In our opinion, the most appropriate regimen (i.e., fewer adverse effects with the same efficacy) is an initial dose of 3-4 mg/kg/d until the disease is controlled, followed by gradual tapering to very low doses (<1 mg/kg/d).

izumab treatment in adolescent and adult patients with chronic idiopathic (spontaneous) urticaria: a meta-analysis of "Real-world" evidence. *JAMA Dermatol.* 2019;155:29, <http://dx.doi.org/10.1001/jamadermatol.2018.3447>.

- Zuberbier T, Aberer W, Asero R, Abdul Latiff AH, Baker D, Ballmer-Weber B, et al. The EAACI/GA<sup>2</sup>LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticarial. *Allergy.* 2018;73:1393–414, <http://dx.doi.org/10.1111/all.13397>.
- Ciclosporina UR. 25 mg/50 mg/100 mg cápsulas blandas EFG [información folleto]. Las Matas (Madrid, España): GERMED FARMACÉUTICA, S.L.; 2012.
- Vena GA, Cassano N, Colombo D, Peruzzi E, Pigatto P. Cyclosporine in chronic idiopathic urticaria: a double-blind, randomized, placebo-controlled trial. *J Am Acad Dermatol.* 2006;55:705–9, <http://dx.doi.org/10.1016/j.jaad.2006.04.078>.
- Grattan CE, O'Donnell BF, Francis DM, Niimi N, Barlow RJ, Seed PT, et al. Randomized double-blind study of cyclosporin in chronic 'idiopathic' urticaria. *Br J Dermatol.* 2000;143:365–72, <http://dx.doi.org/10.1046/j.1365-2133.2000.03664.x>.
- Kessel A, Toubi E. Cyclosporine-A in severe chronic urticaria: the option for long-term therapy. *Allergy.* 2010;65:1478–82, <http://dx.doi.org/10.1111/j.1398-9995.2010.02419.x>.
- Kulthanan K, Chaweekulrat P, Komoltri C, Hunnangkul S, Tuchinda P, Chularojanamontri L, et al. Cyclosporine for chronic spontaneous urticaria: a meta-analysis and systematic review. *J Allergy Clin Immunol Pract.* 2017;6:586–99, <http://dx.doi.org/10.1016/j.jaip.2017.07.017>.
- Boubouka C, Harissi C, Kouimintzis D, Kalogeromitros D, Stavropoulos P, Katsarou A, et al. Treatment of autoimmune urticaria with low-dose cyclosporin a: a one-year follow-up. *Acta Derm Venereol.* 2011;91:50–4, <http://dx.doi.org/10.2340/00015555-0939>.

B. Pinilla Martín,\* F. Tous Romero, F.J. Ortiz de Frutos

*Servicio de Dermatología, Hospital Universitario 12 de Octubre, Madrid, Spain*

\* Corresponding author.

E-mail address: [belenpinillamartin@gmail.com](mailto:belenpinillamartin@gmail.com)

(B. Pinilla Martín).

<https://doi.org/10.1016/j.adengl.2021.07.002>

1578-2190/ © 2021 Published by Elsevier España, S.L.U. on behalf of AEDV. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

## References

- Tharp MD, Bernstein JA, Kavati A, Ortiz B, MacDonald K, Denhaerynck K, et al. Benefits and harms of omal-