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Cyclosporine and omalizumab together: a new option for chronic refractory urticaria

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Short title: Cyclosporine and omalizumab for chronic refractory urticaria.

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Clinical implications:

In patients with chronic refractory urticaria who do not achieve improvement with the treatment recommended in the international guidelines (antihistamines, omalizumab OR cyclosporine), the combined use of antihistamines, omalizumab AND cyclosporine is a useful and safe alternative to achieve clinical control.

To the editor:

Chronic spontaneous urticaria (CSU) is a disease with high personal and social impact. Following the steps recommended in international guidelines for pharmacological treatment (antihistamines, omalizumab or cyclosporine) (1), most patients achieve satisfactory control (2). However, several studies show that between 10% and 30% of patients with CSU do not achieve adequate control of symptoms despite the use of these therapies (3).

Some treatments such as methotrexate, azathioprine, and autologous serum have been used as alternative methods of treatment in refractory patients. An increase in the monthly dose of omalizumab has also been proposed (4). Although all these measures have been shown to be effective in some patients, the cost factor is substantially increased with the use of omalizumab in high doses and the safety and efficacy of the other therapies have been little studied in CSU.

Given that omalizumab and cyclosporine are two of the most studied treatments for CSU, another alternative treatment could be the use of both therapies at the same time. At the moment, most of the guidelines recommend the use of these treatments in a step-by-step sequence (1), but there is little information on the combined use of antihistamines, omalizumab and cyclosporine (5). Hypothetically, because both therapies have independent mechanisms of action, it is possible that together they will achieve better

clinical control. Although omalizumab and especially cyclosporine may have recognized adverse effects (6), it has been observed that in patients with CSU, the frequency of side effects is quite low at the dose of 200mg per day for cyclosporine and 300 mg per month for omalizumab (7). In this cross-over comparative study conducted in two allergy services from Medellín, Colombia, we evaluated the efficacy and safety of these therapies in combination.

Over a period of 12 months, patients 18 years of age or older and uncontrolled urticaria (UAS7>14) despite use of high dose antihistamines (x 4 for at least 2 months) and omalizumab (300 mg/month) or cyclosporine (3 mg/kg/day) for at least four months, were recruited. Patients with urticaria vasculitis, pregnancy and lactation, hepatitis or renal disease were excluded, as well as patients receiving other therapies (e.g., methotrexate) that could interfere with the evaluation of the response to the intervention of interest.

The selection of starting with either cyclosporine or omalizumab was according to medical discretion. In patients without clinical response (UAS7 $\leq$ 6) after receiving one of these added therapies for at least 4 months, the other option was given sequentially (e.g., if the patient initially received omalizumab then cyclosporine was offered) with a period of two months of washout between each therapy. If after receiving the second immunomodulatory the patient had not reached a UAS7 <6 both omalizumab and cyclosporine were co-administered for 6 months in addition to continued antihistamine therapy. The overall study design is depicted in **Figure 1**.

All recruited patients signed an informed written consent endorsed by the ethics committee. Of 458 patients with CSU seen during the recruitment period, 126 patients had UAS7> 14 points after the use of antihistamines and 88 received omalizumab (48 patients) or cyclosporine (40 patients). Twelve patients with omalizumab and 15 from the cyclosporine group were still uncontrolled after four months according to UAS7; five patients who received omalizumab after cyclosporine and one who received cyclosporine after omalizumab achieved clinical control with the added therapies.

The 21 patients who did not reach clinical control with the use of each one of these therapies started the two therapies together. After four months, 16 patients reached a UAS7 <6 points (**Figure 2**) and had no relapses during the follow-up period. Out of the 63 patients who received omalizumab, 9 reported headaches and 6 cramps on the day of application; however, none of them discontinued therapy. Of the 52 patients who received cyclosporine, 4 had a transient increase in blood pressure and 6 had a 10% decrease in leukocytes; however, none of them presented serious adverse events that justified discontinuation of therapy. Among the 21 patients who received the two therapies together, we did not observe a significant increase in the frequency of adverse events or the need to suspend any of the therapies.

According to our results the combined use of omalizumab and cyclosporine seems to be a safe and effective step-up option for those unable to achieve control with individual immunomodulatory therapy. Our study has the characteristics of a cross-over study in that the evaluation of different interventions in the same subject, and among its disadvantages is that there may be an carryover effect that alters the evaluation of each intervention. It is important to note that effect of omalizumab and cyclosporine can extend more than two months, which was the time we gave for washout between each intervention. However, the clinical measures (UAS, Urticaria control test, Dermatology Life Quality Index) showed had no significant variations at the beginning of each of these therapies in any of the groups and the improvement among patients who responded to the joint therapy was rapid. Therefore, we consider that at least most of the clinical effect observed was due to their joint use and not due to the residual effect of their use separately.

The use of cyclosporine and omalizumab has more evidence than any other therapy in the management of CSU, so their joint use offers advantages over other therapies that although they may also be useful, have been less studied. Additionally, it is cheaper than increasing the dosage of omalizumab and possibly more effective if we compare our results with the percentage of control achieved with 600mg of omalizumab in other

studies (4); nevertheless, the immunomodulators used in tandem must be compared directly to high dose (600 mg) omalizumab.

In conclusion, our study suggests that the use of omalizumab in tandem with cyclosporine could be an effective step-up therapy in patients with uncontrolled urticarial despite the addition of an individual immunomodulator.

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FIGURES

Figure 1. Study design

Figure 1. Clinical control was considered to be when patients have at least 2 months with UAS7 <6. A total of 21 patients received both therapies.

Figure 2. Patients with clinical control.

Figure 2. Kaplan-Meier curve of patients with UAS7 >7 points. After 4 months, five out of twenty-one patients had UAS7 >7 points.



