Title:

Are antihistamines still used during the omalizumab treatment in chronic spontaneous urticaria?

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ABSTRACT

Background: The guidelines of chronic spontaneous urticaria (CSU) recommend adding omalizumab in non-controlled patients with 4-fold doses of second-generation antihistamines (AH). On the contrary, some studies revealed that omalizumab was effective without concomitant AH and several authors suggest to taper them off when CSU is controlled with omalizumab.

Objectives: The aim of our study is to evaluate the use of AH during the treatment with omalizumab in patients with CSU in real clinical practice.

Materials and Methods: This is a multicenter cross-sectional and observational study conducted by the Catalan and Balearic Chronic Urticaria Network (XUrCB) in a cohort of 298 CSU patients treated with omalizumab.

Results: 23.5% of our patients decided for themselves to stop taking AH during omalizumab treatment. The ratio of patients with CSU without concomitant inducible urticaria and also the percentage of patients with a good response to omalizumab (UAS7≤6 and/or UCT ≥12) were higher in those who significantly stopped taking AH.

Conclusion: More studies are required to identify the phenotypic characteristics of patients responding to omalizumab in monotherapy in order to avoid overtreating with AH. Our study suggests that the patients with CSU without concomitant inducible urticaria and the patients who achieve a good response to omalizumab tend to be controlled by omalizumab without AH. There is a lack of evidenced based studies in order to provide a guideline about how to stop AH.

KEYWORDS

Antihistamines, Chronic spontaneous urticaria; Chronic urticaria

MANUSCRIPT

Introduction

The guidelines of chronic spontaneous urticaria (CSU) recommend adding omalizumab in non-controlled patients with 4-fold doses of second-generation antihistamines (AH)[1]. Conversely, some studies revealed that omalizumab is effective without concomitant HA in some patients.

Objectives

The aim of our study is to evaluate the use of AH during the treatment with omalizumab in patients with CSU in real clinical practice.

Methods

This is a multicenter cross-sectional and observational study conducted by the Catalan and Balearic Chronic Urticaria Network (XUrCB) in a cohort of 298 CSU patients treated by at an initial dose of 300mg every 4 weeks, whose dose could change during follow-up. A patient anonymous survey to evaluate the use of AH during treatment with omalizumab was carried out and informed consent was obtained. Multivariate logistic regression analysis was performed. The variables analyzed: age, sex, gender, presence of angioedema, the association to concomitant inducible urticaria and the response to omalizumab (considering a responder patient when UAS7≤6 and/or UCT ≥12). The alpha was set as usual (0.05). The software was IBM-SPSS (V26.0).

Results

Out of 298 patients included in this study, 208 (69,8%) were female and the mean age was 51 years [15-87]. 76.5% continued taking AH (34.6% unchanged doses and 41.9% with a lower dose) during omalizumab treatment. Most of them used it continuously (78.4%) compared to of 21,6% of patients who confirmed that they took it on demand. Moreover, when we asked how long these patients took AH, 69.6% of them stated they took AH during the entire treatment with omalizumab. Nevertheless, 30.4% of these patients confirmed they used AH only at the beginning of the treatment. The standard dose was the most prevalent (35.7%) followed by the double dose (22.7%). The majority of patients did not combine different types of AH (86.2%), 10.6% of patients used two

types of AH concomitantly and 3.1% of them took 3 types at the same time. The most commonly used AH were ebastine (29.3%) and rupatadine (28.4%) and a 7% of our patients used first-generation AH.

On the other hand, 23.5% (IC95% 18.7%-28.3%) of our patients responded on the survey that they decided for themselves to stop its use. The patients answered in the survey that they mainly stopped AH due to a subjective good response to the anti-IgE therapy (67.1%), 10% of them did not take AH because they did not feel comfortable with so many pills and 7.1% because they forgot to take them. In the multivariate statistical study, we did not observe differences by gender, age or reported angioedema (Table 1-3). According to the criteria mentioned (UAS7≤6 and/or UCT ≥12), 87,2% of all patients presented a good response to omalizumab. The percentage of patients with a good response to omalizumab was higher in those who significantly decreased the dose of AH (91,9%) or stopped taking them altogether (90.6%) compared with the patients who continued AH (79.8%) (P = .037). Independently, the ratio of patients with isolated-CSU was higher in those who significantly stopped taking AH comparing with patients also affected by inducible urticaria (75% vs 24.5%) (P = .037). Limitations of this study should be considered based on the sample size and the fact that the information was obtained through a patient survey. Furthermore, we did not evaluate the dose of omalizumab and the baseline UAS unfortunately, which are also limitations.

Discussion

In our country, AH and omalizumab in any dose or regimen that the physician considers are financed by the public health system. In our region, it is advisable to follow the CSU guidelines which recommend adding omalizumab in non-controlled patients with 4-fold doses of second-generation AH[1]. Omalizumab starting dose is always 300 mg every 4 weeks and depending on the control of the disease we can increase or decrease the dose of omalizumab as recommended by Spertino et al[2], but usually in addition to AH. Although this consensus, in our study only 76.5% of patients continued under AH. We believe that one of the drawbacks of the patient survey is that the results may be biased in favor of intake AH because the patients wish to please their physician, and the proportion of patients who continued taking AH could be even lower. It should be noted that against the recommendations, 13.8% of patients combined different types of AH and surprisingly 7% of them used first-generation AH. Even so, there is no evidence of

efficiency differences between second-generation AH[3]. While AH continue being the mainstay of treatment of urticaria, a review of 16 studies revealed that omalizumab was effective without concomitant AH in up to 60% of patients[4], a higher percentage than has been observed in other studies [5,6,7,8] as well as in our study (23.5%). Based on this rational, some authors suggest to taper them off when CSU is controlled with omalizumab although guidelines recommend taking AH during entire omalizumab treatment[9,10]. A recent Brazilian report shows an increased number of patients who stop AH over time (27.2%)[7]. Interestingly, they also concluded that the patients who discontinued AH treatment before starting omalizumab had a longer duration of CSU[7]. Similarly to our findings, any relation between the AH use and the presence of angioedema was relevant [7, 11] and as Salman et al report no differences in age or gender were observed[8]. In addition, Türk *et al,* found that the patients with higher baseline IgE levels presented less effectivity to second-generation AH as-needed[11]. Moreover, Ensina *et al* did not find evidence of differences between the use of AH in fast and slow responders[7]. Furthermore, some studies stated that baseline UAS7 scores were not associated with taking AH[7,8]. In related omalizumab response, Cubiró *et al*[5] showed how the proportion of patients who continued taking AH was lower in the group that achieved a complete response (UAS7=0) at week 24. Also, similarly to our results, Salman A *et al* observed higher rates of complete response (UAS7=0) and well-controlled activity (UAS7 1-6) in patients treated with omalizumab monotherapy compared to a combination with AH[8]. Finally, we observed that patients with isolated-CSU stopped taking AH in a higher percentage, which suggests that this phenotype of patients has a good control with omalizumab in monotherapy, compared to patients with CSU with concomitant inducible urticaria. Different behavior and AH requirements probably reflect how the differences in the mechanism of drugs induce an independent therapeutic response. More studies are needed to investigate these underlying mechanisms.

In conclusion, more studies are required to identify the phenotypic characteristics of patients responding to omalizumab in monotherapy in order to avoid overtreating with AH. Although there is not enough evidence to establish a recommendation, our study suggests that the patients with CSU without concomitant inducible urticaria and also the patients who achieve a good response to omalizumab (UAS7≤6 and/or UCT ≥12) tend to be controlled by omalizumab without AH regardless of the presence of angioedema. There is a lack of evidenced based studies that allowed maid any suggestion or

recommendation about the use of AH in CSU patients well controlled by omalizumab in order to provide a guideline about how to stop AH and its relation to the omalizumab dosing.

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TABLES

Table 1. Taking AH while on omalizumab and the relation by gender

	Male	Female	Total *P=.2*
Continue AH	31,1%	68,9%	100%
Continue AH but lower dose	33,6%	66,4%	100%
Stop AH	22,9%	77,1%	100%

Table 2. Taking AH while on omalizumab and the relation by age

	Mean age
Continue AH	53.6
Continue AH but lower dose	51.4
Stop AH	48.7

Table 3. Taking AH while on omalizumab and the presence of angioedema

	Angioedema	No angioedema	Total *P*=.25
Continue AH or continue AH but lower dose	66,7%	33,3%	100%
Stop AH	58%	42%	100%