



The impact of home treatment and self-administration of omalizumab on chronic urticaria

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ABSTRACT

Background: Patients suffering from Chronic Spontaneous Urticaria (CSU) may be recalcitrant to treatment with high dose second-generation antihistamines. These patients are, according to international guidelines, eligible to treatment with omalizumab. Treatment with omalizumab has proven to be very effective for this group of patients. Until 2018, when the self-administration of omalizumab was approved, patients have had to visit an outpatient clinic to receive the treatment.

Methods: In this study we performed a survey among 75 CSU patients who had changed their treatment from administration at an outpatient clinic to self-administration at home.

Results: None of the patients experienced decreased effect of the treatment with omalizumab, whereas 41.4% reported improved effect of the treatment during self-administration. The most common reported benefits for the patients were decreased travel time and the ability to choose dosing time at the day of treatment, whereas the most reported concern was fear of performing the injection.

Conclusions: Patients are very content with self-administration of omalizumab. There has been no decreased effect of the treatment, and as discussed in this paper, there might be other societal benefits from self-administration. Thus, self-administration at home of omalizumab should be standard of care when using this treatment.

Keywords: Chronic spontaneous urticaria, Omalizumab, Self-administration, Home-treatment, Patient satisfaction

BACKGROUND

Chronic Spontaneous Urticaria (CSU) is a disease with an immense impact on patients' quality of life. It is characterized by an intense, sudden itch along with characteristic hives and/or angioedema all of

which contribute to the deterioration of the patient's quality of life. One of the most debilitating features of CSU is the unpredictability of the disease, which leaves the patients frustrated and anxious, as they never know when the disease will

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flare up. The disease is often caused by autoantibodies of either IgG- or IgM-type, directed against the IgE receptor (FcεRI) or membrane bound IgE on the surface of mast cells, or IgE-type directed against self-antigens.¹ Many patients suffering from CSU also suffer from chronic inducible urticaria (CIndU). CIndU can be caused by physical stimuli such as pressure, heat, cold, sunlight, or vibration. CIndU can be controlled through avoidance strategy. However, this is not always possible or feasible for the patients if they want to maintain a normal life with a job or leisure time activities, for example.² Further, CSU patients have increased risk of other co-morbidities including atopic and autoimmune diseases.³

First line treatment of CSU is licensed dose second-generation non-sedating antihistamines. In case of treatment failure, the dosage should be increased up to fourfold. If symptoms persist, current guidelines recommend add-on therapy of omalizumab, an IgG anti-IgE-antibody with high efficacy in this subgroup of patients.⁴ Omalizumab is administered as subcutaneous injections from prefilled syringes and is currently not available as an auto-injector. For some patients, it has proven difficult to administer the subcutaneous injections themselves, and until 2018 when the European Medicines Agency (EMA) approved omalizumab for self-administration, the label of the drug stated that the injection should be supervised by health-care personnel.⁵ Thus, the patients would need to attend either an outpatient clinic or a healthcare center to have omalizumab administered, and self-administration and home treatment would be off-label. For some patients, this would both require traveling long distances and taking time off from work.

During the COVID-19 pandemic, limitations of hospital visits were part of the strategy to limit the transmission of COVID-19 and spurred a more widespread use of home treatment.⁶ However, even before the COVID-19 pandemic, long distances to the centers administering omalizumab treatment, and a large number of patients receiving the treatment, made it necessary to employ home treatment. This has been performed without any reports of decreased treatment efficacy and without an increase in side effect or serious adverse events.^{7,8} Finally, the use of home administration of omalizumab has

also been demonstrated more cost efficient than administration at the hospital.⁹

UCARE (Urticaria Center of Reference and Excellence) is a network under the GA²LEN (Global Allergy and Asthma European Network) CORE (Centers of Reference and Excellence) initiative to improve and provide excellence in management of *hard-to-treat* urticaria, as well as increase knowledge, research, and education on this disease. In our UCARE center, home treatment with omalizumab has been standard since 2018. Over a period of 6 months in 2019, we conducted a survey among patients receiving omalizumab home treatment. We hypothesized that home treatment, when compared to hospital treatment, would not have any deteriorating effect on treatment efficiency, that patients are fully capable of regulating the treatment intervals themselves, and that home treatment would lead to a higher degree of patient satisfaction. Furthermore, we also wanted to explore whether the patients had any reservations regarding home treatment and how these were handled.

METHODS

We developed a questionnaire which covered: demographics including age; distance to treatment (in the hospital); educational level; number and age of children; and urticaria characteristics including duration, treatment(s) before omalizumab, duration of omalizumab treatment, presence of angioedema, and physical inducers of urticaria (CIndU). In the questionnaire, the patients were specifically asked whether pressure, heat, cold, exercise, or scratching induced their urticaria. For the statistical analysis, a "yes" to one or more of these options was registered as CIndU positive. Regarding home treatment and self-administration, the questionnaire addressed reasons for refusing home treatment, if this was the case. In addition, the patients were asked about side effects, change in effect, treatment satisfaction and fears, if any, with regards to home treatment and self-administration. The questionnaire was administered as a written questionnaire. The questionnaire was tested and evaluated by 10 random patients treated with omalizumab before being applied and changed according to their suggestions.

Characteristics	n = 75 ^a
Gender	
Female	86.11% (62)
Male	13.89% (10)
Age (years)	42.67 ± 13.85 (75)
Education level	
Primary and lower secondary school	12.86% (9)
General upper secondary education	10.0% (7)
Short-cycle higher education	15.71% (11)
Professional bachelor's degree	10.0% (7)
Vocational upper secondary education	31.43% (22)
Bachelor's degree	5.71% (4)
Master's degree	14.29% (10)
Number of children	2 ± 1.06 (62)
0	12.90% (8)
1	9.67% (6)
2	48.39% (30)
3	22.59% (14)
4	6.65% (4)
Time since diagnosis of CSU (years)	9.46 ± 9.78 (73)
Travel distance to hospital (km)	76.63 ± 61.67 (75)
Home self-administration of omalizumab (years)	0.83 ± 0.56 (67)

Table 1. Demographics and characteristics. ^a% or mean ± SD (n, from whom information was possible)

Patients

As patients visited the outpatient clinic for medical follow-up by a doctor, patients were consecutively recruited from the UCARE urticaria clinic in the period August 2019 to March 2020 (when the COVID-19 pandemic caused a general lockdown in Denmark). Inclusion criteria were ongoing treatment with omalizumab for CSU, age 18 years or older, and willingness to participate. No ethical approval was needed according to Danish law because it was not a biomedical experiment, and the questionnaires were anonymous. At the initiation visit for self-administration of omalizumab, patients were taught how to administer omalizumab by a specialist nurse and were invited to a follow up visit after 3–4 months. Subsequently, patients were followed up every 6 months in the outpatient clinic.

Statistics

Descriptive statistics were used to describe the cohort. The data were analyzed using chi-square test, t-test and Fisher's exact test.

RESULTS

Patient characteristics

A total of 75 patients answered the questionnaire. The patients were recruited consecutively among patients seen in or urticaria clinic coming for omalizumab treatment. Very few patients refused to participate and only due to time constraints. Refusals were not registered. The overall demographic characteristics are shown in [Table 1](#). Female patients comprised 86.1% and male patients, 13.9% ($p < 0.05$ when compared to the general population). The average age was 42.7 (±13.9) years. The distribution of educational level and the mean number of children, which was 2 (±1.06), both reflected those of the general population.¹⁰

The mean duration of urticaria since diagnosis was 9.46 years, although the variability was high. The mean duration of home treatment was 0.83 (±0.56) years. The mean duration from CSU diagnosis until initiation of omalizumab treatment was 7.7 (±9.69) years for females and 6.88 (±10.42)

	Total ^a	Female ^b (n = 62)	Male ^b (n = 10)	p ^c
Angioedema ^e				
Yes	54	75.80% (47)	77.78% (7)	0.735
No	17	24.19% (15)	22.22% (2)	
CIndU ^d				
Yes	53	84.21% (48)	71.43% (5)	0.691
No	11	15.79% (9)	28.57% (2)	
Time from diagnosis of CSU to initiation of omalizumab treatment (years)	69	7.70 ± 9.69 (60)	6.88 ± 10.42 (9)	0.817
Time from initiation of omalizumab treatment to conversion to home self-administration (years)	64	1.42 ± 1.87 (56)	1.05 ± 1.21 (8)	0.594
Side effects				
Yes	40	67.86% (38)	22.22% (2)	0.026
No	25	32.14% (18)	77.78% (7)	

Table 2. Disease and treatment characteristics. ^aNumber of patients for whom information was available. ^b% or mean ± SD (N). ^cRefers to Fisher's exact test or t-test estimating a two-tailed p-value. ^dChronic inducible urticaria. Respondents were asked if they had experienced wheals induced by pressure, scratch, cold, heat or exercise. ^eAngioedema on one or more of the following areas; lips, eye area, hands, feet and genitals

years for males (Table 2). Angioedema was reported in 75.7% and CIndU in 83.6% of the patients. There was no significant difference between male and female patients. Among females, 67.9% experienced side effects to omalizumab, whereas only 22.2% of males experienced any of these problems. No serious adverse effects were reported (Table 4).

Home treatment with omalizumab

Improved effect of treatment, after initiation of home treatment, was reported in 41.4% of patients, and 58.6% reported no change in treatment efficacy. There were no reports of decreased efficacy.

When comparing the patients with improved effect, after initiating home treatment, with those who experienced no change in effect statistically significant differences were found for: the total duration of omalizumab treatment and the time from omalizumab treatment in the hospital was initiated to home treatment of omalizumab started (Table 3). Both time intervals were significantly shorter among the patients who experienced improved effect of self-administration at home.

Concerning treatment satisfaction, the patients were asked about the benefits of home treatment. Among 53 responders to this question, 83 responses were recorded (patients could give more than one answer). The two most common benefits were "no transportation or waiting time" (n = 48) and "the ability to choose dosing time of the day" (n = 18) (Fig. 1a). Among the responders, the greatest concerns regarding home treatment were "fear of injections" and "whether the injections were performed correctly" (Fig. 1b).

DISCUSSION

The patients in this study were recruited consecutively from a UCARE urticaria outpatient clinic among patients being treated with omalizumab and who were asked to fill in the questionnaire.

The average time from diagnosis of CSU until treatment with omalizumab was 7.70 and 6.88 years for females and males, respectively. This is a very long delay compared to other studies, in which the time is less than a year.¹¹ There might be 2 explanations for this. As noted, there is a high variability on the time from diagnosis until treatment in our study, which may be due to patients' delay as well as doctors'

	N ^a	Improved effect ^b (n = 24)\1	Unchanged effect ^b (n = 34)	p ^c
Overall	58	41.38% (24)	58.62% (34)	
Gender				
Female	48	86.96% (20)	84.85% (28)	0.856
Male	8	13.04% (3)	15.15% (5)	
Age (years)	58	39.58 ± 14.77 (24)	45.15 ± 12.33 (34)	0.125
Travel distance (km)	58	79.71 ± 64.95 (24)	71.38 ± 64.36 (34)	0.631
Number of children	49	1.94 ± 1.14 (17)	2.06 ± 1.05 (32)	0.710
Angioedema ^d				
Yes	43	62.50% (15)	84.85% (28)	0.106
No	14	37.50% (9)	15.15% (5)	
CIndU ^e				
Yes	42	90.91% (20)	73.33% (22)	0.215
No	10	9.09% (2)	26.67% (8)	
Total duration of Omalizumab treatment (years)	57	1.70 ± 1.26 (24)	2.71 ± 2.21 (33)	0.048
Duration of home self-treatment (months)	52	9.43 ± 5.25 (22)	12.23 ± 6.45 (30)	0.101
Time from omalizumab treatment was initiated to home self-treatment was started (years)	52	0.86 ± 1.06 (22)	1.82 ± 2.15 (30)	0.039
Previous CSU medication				
No	7	12.50% (3)	12.12% (4)	0.729
Yes	50	87.50% (21)	87.88% (29)	
Side effects				
No	21	41.67% (10)	39.29% (11)	0.914
Yes	31	58.33% (14)	60.71% (17)	

Table 3. Characteristics of patients with improved and unchanged effect of home treatment and self-administration. *p* < 0.05 in bold. ^aNumber of patients for whom information was available. ^bPatients were categorized according to their answer to the question; "Does your omalizumab treatment have a better effect when it is home self-administrated?" Patients answering "yes" were categorized as "improved effect", patients answering "no" were categorized as "unchanged effect". Values presented are % or mean SD (N). ^cRefers to Fisher's exact test or t-test estimating a two-tailed p-value. ^dAngioedema on one or more of the following areas; lips, eye area, hands, feet and genitals. ^eChronic inducible urticaria. Respondents were asked if they had experienced wheals induced by pressure, scratch, cold, heat or exercise

delay in general practice and among private practicing dermatologists. Furthermore, very recent evidence suggests that even in tertiary centers, the guidelines for the diagnosis and treatment of urticaria are not sufficiently adhered to.^{12,13}

Effect of home therapy

None of the patients reported decrease of the effect of omalizumab after initiating home therapy, whereas 41% experienced increased effect and 59% experienced no change in effect. The only

AE	Injection site reaction	Leg or arm pain	Headache	Sinusitis	Sore throat	Dizzines	Nausea	Hair loss
Yes	4	3	29	3	2	1	2	1
No	71	72	46	72	73	74	73	74

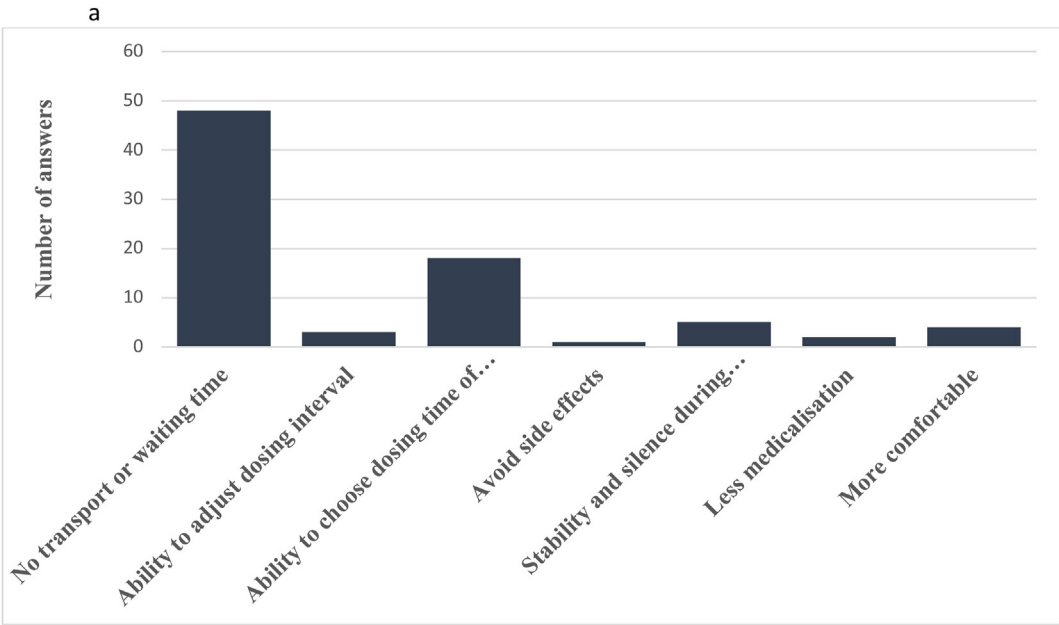
Table 4. Reported adverse events. Adverse events where registered according to those described for the drug. Headache was the most prevalent AE, yet none led to discontinuation of omalizumab treatment

significant differences between these two groups (increased effect and no change) were total time in omalizumab treatment, and time from omalizumab was initiated in the hospital until home treatment started; both being shorter in the group who experienced improvement in effect. This is in line with what has been reported previously.^{7,14} These results probably reflect that those, who experienced increased effect after home therapy was initiated, were patients who had not yet achieved full effect in the hospital, and, if these patients had remained in outpatient treatment, they probably would have experienced the improvement there rather than during home treatment. And those in optimal treatment might have changed to home treatment faster. We would have expected that the number of children could have made a difference in the sense that having more children would increase the satisfaction of home therapy leaving the patients more time at home, but this was not the case.

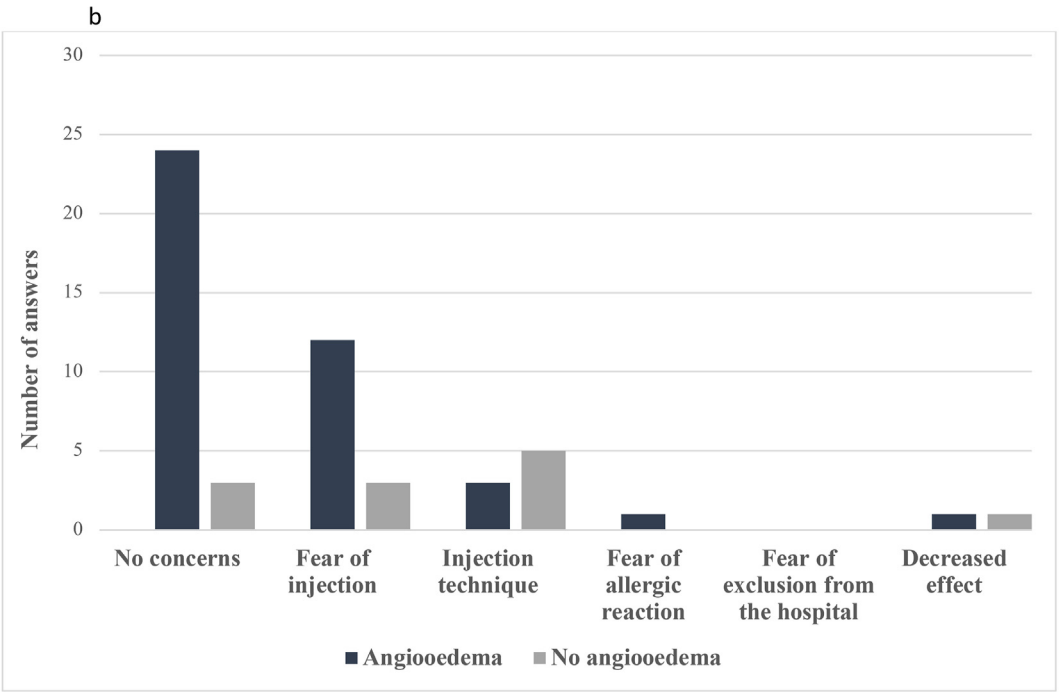
Patient satisfaction

Patient satisfaction was high, and the main benefits reported by the patients were decreased travel time and flexibility for time of administration during the day. Others have reported the same benefits for the patients.¹⁴ In the United States, it has even been postulated that home administration may decrease fatal automobile accidents by 14.6 per 1 million person years, as well as increase the cost effectiveness by \$500,648,430.⁹

In our study population a rather large proportion of the patients suffered from angioedema (75.7%) and CIndU (83.6). In the ASSURE study, it was reported that 40.8% of patients with CSU also suffered from angioedema,¹⁵ whereas the number was only 5% in a recent Swedish registry study.¹⁶ The differences in these numbers may be explained by the method through which the results were obtained. The ASSURE study was an observational study in which the investigator extracted data from the patients’ medical records and the patients’ own report on whether or not they had angioedema. This study may underestimate the prevalence since misaligned reporting constituted a large part (32.8%).¹⁵ In the Swedish study, the data are from the general population and are stored in a database that



Benefits of Omalizumab Self-administration reported by the patients.



Main concerns reported by the patients

Fig. 1 a). Benefits of omalizumab self-administration reported by the patients. b) Main concerns reported by the patients

collects data on all publicly subsidized healthcare provided in Stockholm. Consequently, it is not a highly selected patient population, resulting in the inclusion of many less severe cases of

urticaria. Also, the ICD-10 diagnosis for angioedema may be underreported, since the urticaria diagnosis is reported as the authors of the study suggest. In conclusion, the proportion of

angioedema patients in our study is high, but as the recruitment of patients was from a highly specialized UCARE center, this may indicate a highly selected patient population.

CIndU

CIndU has been reported to affect 25% of all patients with CSU in the observational Scandinavian AWARE study.¹⁷ In a study from Columbia, 75% of patients reported a physical trigger of their urticaria, but only 36% of patients displayed a positive provocation test.² In the Swedish study, however, only 11% of patients had CIndU.¹⁶ In our study, 83.6% of patients reported CIndU. In the registry study, it is very likely that there was an underrepresentation of CIndU cases caused by misregistration of the ICD-10 diagnoses combined with the above mentioned less severe urticaria cases. We did not perform provocation testing for physical stimuli in this study, thus there may be an overrepresentation of CIndU cases in our material.

LIMITATIONS

This study was performed in a population of patients treated in a tertiary hospital in a UCARE urticaria clinic. Patients who have attended this clinic received face to face training in Xolair injection techniques and might thus be better prepared for home therapy than in other settings. This may have resulted in patients a higher degree of patient satisfaction. Furthermore, we did not include any objective measurements from the patients e.g. UAS7 or UCT, and thus we have only asked for patients opinion and experience.

CONCLUSION

In conclusion, home therapy with omalizumab is safe and offers the patients greater autonomy regarding administration of the treatment. There does not seem to be any benefit in terms of treatment results from home treatment, however others have shown a large potential for the cost effectiveness of home treatment versus treatment in the hospital. The greatest concerns for the patients were related to the actual administration of the medication, such as fear of the injection itself

and whether they were able to perform the injection correctly. These concerns need to be addressed, and patients must be educated and reassured in the procedure, when they are prescribed home treatment with omalizumab. The cohort that we studied deviated somewhat from the general urticaria population in which 68.5% are women³ with a higher proportion of females and a much higher proportion of patients with angioedema and CIndU. Yet, this probably reflects a population of antihistamine refractory CSU treated in a tertiary urticaria referral center very well.

Abbreviations

CIndU, Chronic inducible Urticaria; CSU, Chronic Spontaneous Urticaria; EMA, European Medicines Agency; GA²LEN-CORE, Global Allergy and Asthma European Network -Centers of Reference and Excellence; ICD-10, International Classification of Diseases 10th revision; UCARE, Urticaria Center of Reference and Excellence.

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Data availability

All data are available on file.

Contributions to this work

ACW Analysis of data, authoring the paper, collecting data, MAKW, authoring the paper, collection of the data, analysis of the data, SH designing the survey collecting the data, authoring the paper ASF, Analysis of the data, authoring the paper, JAS authoring the paper and critically reviewing the results, MD Authoring the paper and critically reviewing the results, SFT authoring the paper and critically reviewing the results, CV Authoring the paper and critically reviewing the results designing the study.

Consent

All the authors consent to publication of this work.

Ethics statement

The study performed in the manuscript entitled "The impact of home treatment and self-administration of omalizumab on urticaria patients' treatment satisfaction in a UCARE clinic", by Anne Christine Wiuff et al has been performed as an anonymous collection of surveys. Due to the anonymous nature of this study no ethics approval nor approval by the Danish Data protection agency is needed.

Declaration of competing interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.waojou.2022.100725>.

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