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ORIGINAL ARTICLE

Atopic Dermatitis, Urticaria and Skin Disease

Omalizumab is effective and safe in chronic inducible urticaria (CIndU): Real-world data from a large multi-national UCARE study

R. Soegiharto[1] | M. Alizadeh Aghdam[1] | J. A. Sørensen[2] | E. van Lindonk[3] | F. Bulut Demir[4] | N. Mohammad Porras[5] | Y. Matsuo[6] | L. Kiefer[7,8] | A. C. Knulst[1] | M. Maurer[7,8] | C. Ritchie[9] | M. Rudenko[10] | E. Kocatürk[7,11] | R. F. J. Criado[12] | S. Gregoriou[13] | T. Bobylev[14] | A. Kleinheinz[14] | S. Takahagi[6] | M. Hide[6,15] | A. M. Giménez-Arnau[5] | A. Salman[4,16] | R. Oztas Kara[17] | B. S. Dikicier[17] | M. B. A. van Doorn[3,18] | S. F. Thomsen[2] | J. M. P. A. van den Reek[19] | H. Röckmann[1]

Correspondence
Reineke Soegiharto, Department of Dermatology, University Medical Centre Utrecht Heidelberglaan, 100, 85500, 3584 CX, Utrecht, Netherlands.
Email: r.soegiharto@umcutrecht.nl

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Abstract

Background: Long-term data on the effectiveness and safety of omalizumab for chronic inducible urticaria (CIndU) in large populations are lacking.

Objective: To evaluate the effectiveness, safety, estimated omalizumab treatment duration and its predictors, as well as differences between CIndU subtypes, in a large long-term CIndU cohort.

Methods: A multinational multicenter study was conducted at 14 specialized urticaria centres (UCAREs), including all CIndU patients ever treated with omalizumab from 2009 until July 2022. Kaplan–Meier survival and regression analyses were performed.

Results: Across 234 CIndU patients (55% female; mean age 37 years), 76% ($n = 178$) had standalone CIndU and 24% ($n = 56$) had predominant CIndU plus minor CSU, with an observation period up to 13 years. Most CIndU patients (73%, $n = 145/200$ with available data on response) had complete/good response to omalizumab treatment, without significant differences between CIndU subtypes. Sixty-two (26%) patients discontinued omalizumab; due to well-controlled disease (47%, $n = 29$), ineffectiveness (34%, $n = 21$), side effects (3%, $n = 2$), combination of ineffectiveness and side effects (3%, $n = 2$) and other reasons (13%, $n = 8$). The median estimated omalizumab treatment duration exceeded 5 years (54% drug survival at 5 years) and was mostly determined by well-controlled disease. Higher age predicted a lower chance to discontinue omalizumab due to well-controlled disease (HR 0.969, 95%CI 0.945–0.995).

Abbreviations: AE, angioedema; CIndU, chronic inducible urticaria; CSU, chronic spontaneous urticaria; CU, chronic urticaria; IQR, interquartile range; RCT, randomized controlled Trial; SD, standard deviation; UAS7, urticaria activity score; UCARE, urticaria centers of reference and excellence; UCT, urticaria control test.

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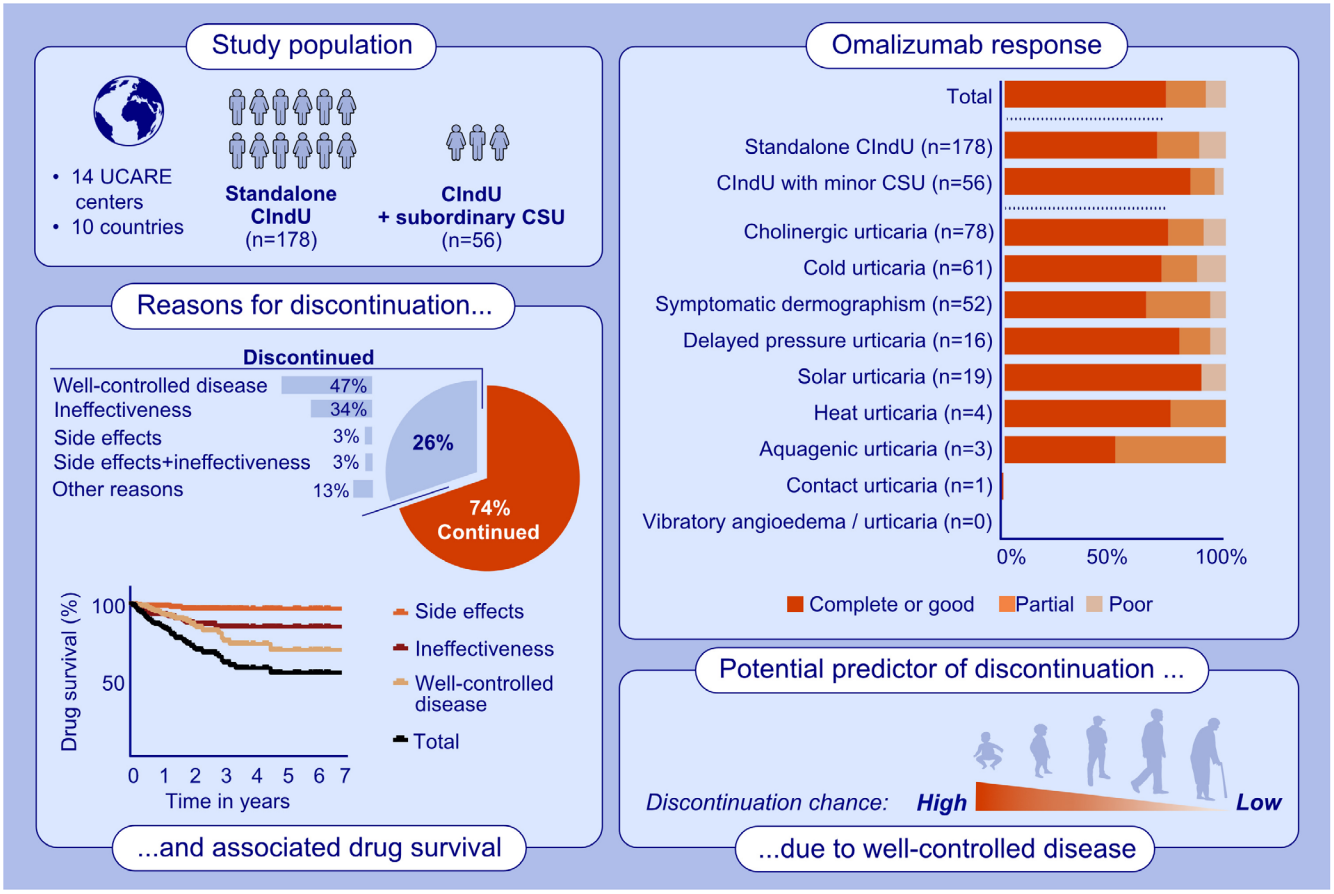
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CIndU subtype and presence of minor CSU were not related to response and time until omalizumab discontinuation for any reason.

Conclusion: Omalizumab is highly effective and safe in CIndU patients, with long estimated treatment duration mainly reflecting long disease duration. Our data show omalizumab's high potential as treatment in any subtype of CIndU and support its clinical use for these patients.

KEYWORDS
angioedema, chronic inducible urticaria, drug survival, omalizumab, predictor



GRAPHICAL ABSTRACT

Among 234 CIndU patients, 73% had complete/good response to omalizumab, without significant differences between CIndU subtypes. Twenty-six percent of CIndU patients discontinued omalizumab, mostly due to well-controlled disease and ineffectiveness, resulting in an estimated omalizumab treatment duration exceeding 5 years. Higher age predicted lower chance of discontinuation due to well-controlled disease; CIndU subtype and presence of minor CSU were not associated with omalizumab discontinuation.

Abbreviations: CIndU, chronic inducible urticaria; CSU, chronic spontaneous urticaria; UCAREs, urticaria centres of reference and excellence.

1 | INTRODUCTION

Chronic urticaria (CU) is characterized by recurrent, severely itching wheals, angioedema (AE), or both, for longer than 6 weeks, and is categorized into two subtypes: chronic spontaneous urticaria (CSU) and chronic inducible urticaria (CIndU).[1] In CIndU, signs and symptoms only occur upon exposure to definite eliciting triggers that are specific for each CIndU subtype (e.g., friction in symptomatic dermographism; cold in cold urticaria, or physical exercise in cholinergic urticaria). When symptomatic treatment is required, the international urticaria guideline recommends using a nonsedating antihistamine followed by omalizumab in case of insufficient response to antihistamine treatment, following the same treatment algorithm for CSU.[1,2] However, omalizumab is currently only licensed for CSU and

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not for CIndU. Consequently, it is often not reimbursed and/or available for CIndU patients.

To date, only three randomized controlled trials investigated the effectiveness and safety of omalizumab in patients with CIndU. In these studies, patients with symptomatic dermographism ($n=55$)[3] or cold urticaria ($n=31$)[4] received three administrations of omalizumab, and cholinergic urticaria patients ($n=22$) received 12 administrations.[5] Complete/good response was observed in 58%, 78%, and 31% of patients with symptomatic dermographism, cold urticaria, and cholinergic urticaria, respectively. With regards to safety, no patients in these trials discontinued omalizumab treatment due to side effects.[3–5] Further evidence for the effectiveness and safety of omalizumab in CIndU comes from case reports, case series, and small daily practice cohort studies. Here, omalizumab was reported to be effective in the majority (53%–100%) of CIndU patients, with fast response in 25%–44% of patients,[6,7] and to be safe and well tolerated, with no or only mild side effects reported.[6–15] However, all previous studies were performed in small CIndU populations ($n=12$–80).[6–15] Also, in many of them, the duration of omalizumab treatment was limited to a maximum of three to six months,[3,4,6,7,8,11] emphasizing the need for studies in larger CIndU populations with long-term follow-up. Knowledge about the long-term effect of omalizumab, the estimated treatment duration and its predictors in CIndU, and potential differences between CIndU subtypes could improve expectation management and shared decision-making.

To address this unmet need, we investigated the long-term effectiveness and safety of omalizumab in patients with CIndU in a large multinational multicenter real-world cohort using the global network of urticaria centers of reference and excellence (UCARE).[16] Furthermore, we assessed the estimated treatment duration with omalizumab, and reasons and predictors of omalizumab discontinuation in these CIndU patients.

2 | METHODS

2.1 | Patient population, data collection, and study conduct

This study is a retrospective, multinational, multicenter daily practice cohort study performed in 14 international certified centers specialized in urticaria care (Urticaria Centers of Reference and Excellence; UCAREs)[16] from 10 different countries. Informed consent was not required and the study was approved by the Ethical Committee Utrecht, The Netherlands (18/862) and the ethics committees of participating UCAREs as required. All patients with CIndU as major CU diagnosis, that is, standalone CIndU and patients with a combination of CIndU and clearly subordinary CSU symptoms, who have ever received at least one omalizumab administration until center specific data lock were included (latest data lock July 2022, Table S1). Patients with standalone CSU, or a combination of predominant CSU and minor CIndU symptoms were excluded. All patients were treated according to their local treatment protocol mainly based on the international guideline.[1,2] Omalizumab was fully or partially reimbursed for CIndU patients in three and eight centers, respectively (Table S1). Centre specific treatment protocols were assessed by a questionnaire as they may differ in relevant details such as interval prolongation strategy, access to higher than standard-dosed omalizumab and availability of self-administration.

All data were obtained from hospital medical records, with exception of one center (C4), which retrieved the specific data on treatment characteristics and treatment response (as described below) from a questionnaire sent to patients with a response rate of 22%. All data were collected and stored in a Castor-database[17] and included the following:

1. *Patient characteristics*: age; sex; any concomitant autoimmune disease as described in patient history; time of disease onset; type of CIndU; presence of concomitant minor spontaneous wheals and/or angioedema (CSU).
2. *Treatment characteristics*: antihistamine use during omalizumab treatment; use of immunosuppressive drugs at start and during omalizumab treatment; time between start, stop and (if applicable) restart of omalizumab; occurrence of side effects; maximum omalizumab dosage; reasons for discontinuation.
3. *Disease control*[18]: Urticaria Control Test (UCT) at baseline, second administration (i.e., 4 weeks after first injection, T_2), and end of treatment (T_{end}). T_{end} was defined as date of treatment discontinuation or in case of continuous treatment the last visit before data lock or lost to follow-up.

2.2 | Treatment response

Treatment response was classified as "complete" (UCT = 16), "good" (UCT 12–15),[19] "partial" (UCT 3–11 and improvement ≥3)[20] or "no response" (UCT 0–11 and improvement of <3) and was evaluated at T_2 and T_{end}. Fast response was defined as UCT≥12 within 4 weeks after first injection (T_2). In case of missing UCT scores, (onset of) treatment response was determined based on the physicians' description in the patients' medical records and categorized as complete/good (symptom-free/satisfied with minor symptoms only), partial (insufficient) or no/lack of response.

2.3 | Statistical analyses

The estimated omalizumab treatment duration (i.e., 'drug survival', expressed as 'omalizumab survival rates') was assessed with Kaplan–Meier survival analysis and was calculated as time between start and treatment discontinuation, or in case of continuous treatment the last visit before data lock or lost to follow-up. Omalizumab discontinuation was defined as an interruption of ≥90 days and was differentiated by reason for discontinuation: any reason (I), well-controlled disease (i.e., being symptom-free; II), side effects

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(III) or ineffectiveness (IV). When patients discontinued due to both ineffectiveness and side effects, they were considered to have discontinued in both sub-analyses (III and IV). When patients discontinued for other reasons, they were considered to have discontinued in the overall drug survival analysis (I) but were censored in the sub-analyses (II, III, IV). Patients who continuously used omalizumab at time of data lock or lost to follow-up were analysed until their last contact and censored thereafter.

To identify predictors of time until omalizumab discontinuation (reflecting estimated omalizumab treatment duration), a univariate Cox regression analysis was performed on all patient characteristics that were present at baseline and center specific treatment protocol aspects that were deemed clinically relevant (access to higher than standard-dosed omalizumab, a maximum dosing interval of >12 weeks and availability of self-administration). Potential predictors with a *p*-value ≤.2 were entered into a multivariate Cox regression model with manual backward selection omitting the variable with the highest *p*-value in each step. In the multivariate Cox regression model, variables with a *p*-value ≤.05 were considered statistically significant. Prior to the analysis of predictors of time until omalizumab discontinuation, we noted missing values in potential predictors. As only analyzing patients without missing values (i.e., complete case analysis) may have resulted in bias and loss of statistical power, we used the multiple imputation method.[21,22] The missing data were imputed with a fully conditional specification with predictive mean matching for continuous variables and logistic regression for binary variables. Based on the percentage of missing data, 30 imputed datasets were constructed, thereafter, manual backward analysis was performed on the pooled results. Statistical analyses were performed in SPSS IBM SPSS Statistics 27 (IBM, Armonk, NY, U.S.A.). Graphs were made using GraphPad Prism 8.3.

3 | RESULTS

3.1 | Patient and treatment characteristics

A total of 234 patients (mean ± SD age 37 ± 16 years; 55% female) with CIndU who have ever received omalizumab between June 2009 and July 2022, were investigated. Seventy-six percent (*n* = 178) had standalone CIndU, and 24% (*n* = 56) had predominant CIndU with minor CSU. Characteristics of patients with standalone CIndU did not significantly differ from those of CIndU patients with minor CSU (Table 1). The three most common CIndU subtypes were cholinergic urticaria (35%, *n* = 82), cold urticaria (28%, *n* = 66) and symptomatic dermographism (27%, *n* = 62, Table 1 and S2). Uncommon CIndU subtypes such as heat urticaria and aquagenic urticaria were also present in this cohort (2% (*n* = 4) and 1% (*n* = 3), respectively). One in ten patients (11%, *n* = 22) had concomitant autoimmune disease, and 59% (*n* = 131) were diagnosed with CIndU more than two years prior to the start of omalizumab treatment.

At the start of omalizumab treatment, a minority of CIndU patients (7%, *n* = 14) used immunosuppressive co-treatment (Table 1). During omalizumab treatment, almost all CIndU patients (90%, *n* = 178) used antihistamines, half of them (50%, *n* = 98) at higher than standard dose. Most patients (72%, *n* = 136) were treated with standard-dosed omalizumab, and 28% (*n* = 53) used higher than standard-dosed omalizumab. Only eight patients (3%) used immunosuppressive co-medication during omalizumab treatment (Table 1).

3.2 | CIndU patients show high rates of response to omalizumab treatment

Disease control before the start of omalizumab treatment was poor, with a median baseline UCT of 5 (IQR 2–7). Based on UCT or physician's assessment, 73% (*n* = 145/200) of patients had complete or good response to omalizumab. Specifically, 34/84 (41%) and 31/84 (37%) of patients assessed by UCT achieved complete control (UCT 16) and well-controlled disease (UCT 12–15), respectively. Of the total 200 patients with available UCT or physician's assessment, 18% (*n* = 35) had partial response, and 10% (*n* = 20) were non responders at T_{end} (Table 1). Fast response (UCT≥12 within 4 weeks after first injection) was achieved in 38% (*n* = 76) of patients.

3.3 | The CIndU subtype or presence of minor CSU does not influence the response to omalizumab

Response rates of all CIndU subtypes of our cohort, including the most uncommon forms, were investigated and compared (Table S2). A non-significant trend (*p* = .153) towards higher overall complete/good response rates at T_{end} was observed in solar urticaria (89%, *n* = 16/18), delayed pressure urticaria (79%, *n* = 11/14), heat urticaria (75%, n = 3/4), cholinergic urticaria (74%, *n* = 52/70) and cold urticaria (71%, *n* = 35/49) compared to symptomatic dermographism (64%, *n* = 27/42) and aquagenic urticaria (50%, *n* = 1/2). No significant differences in the rates of patients with fast response were seen between CIndU subtypes. Another trend was observed towards a higher complete/good response rate (85% vs. 69%, *p* = .117) and fast response rate (48% vs. 35%, *p* = .125) in CIndU patients with minor CSU compared to patients with standalone CIndU (Table 1). Additionally, we investigated whether the CIndU subtype and presence of minor CSU were associated with treatment response using univariate and multivariate logistic regression analyses. Both patient characteristics were not statistically significantly associated with response at T_{end}.

3.4 | Well-controlled disease is a major reason for omalizumab discontinuation

The majority of CIndU patients (74%, *n* = 172/234) used omalizumab continuously within the study period (lost to follow-up: 18%, *n* = 41) with a maximum omalizumab treatment duration of 12.4 years. Most

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TABLE 1 Patient and treatment characteristics, and response of patients with CIndU as major CU diagnosis.

	Total $N = 234$	Standalone CIndU $N = 178$ (76%)	CIndU with minor CSU $N = 56$ (24%)	p-value[a]
Female	128 (55%)	95 (53%)	33 (59%)	0.466
Age at start omalizumab (SD; min-max)	37 (16;8–79)	37 (17; 8–79)	36 (14; 14–64)	0.709
Age at start omalizumab < 18 years	18 (8%)	15 (8%)	3 (5%)	0.452
Disease duration >2 years prior to omalizumab treatment [I]	131 (59%)	99 (59%)	31 (57%)	0.814
Autoimmune disease [II]	22 (11%)	18 (12%)	4 (8%)	0.457
CIndU subtype[b]				
• Cholinergic urticaria	82 (35%)	65 (37%)	17 (30%)	0.359
• Cold urticaria	66 (28%)	48 (27%)	18 (32%)	0.453
• Symptomatic dermographism	62 (27%)	47 (26%)	15 (27%)	0.913
• Delayed pressure urticaria	20 (8%)	11 (6%)	9 (16%)	*0.033*
• Solar urticaria	19 (8%)	16 (9%)	3 (5%)	0.386
• Heat urticaria	7 (3%)	6 (3%)	1 (2%)	0.544
• Aquagenic urticaria	5 (2%)	5 (3%)	0 (0%)	0.205
• Contact urticaria	1 (0.4%)	1 (0.6%)	0 (0%)	0.574
• Vibratory angioedema/urticaria	0 (0%)	0 (0%)	0 (0%)	-
Disease control scores at baseline				
• UCT (median, IQR) [III]	5 (2–7)	6 (3–8)	4 (2–6)	0.068
Treatment characteristics at start of omalizumab treatment				
Immunosuppressive co-treatment [IV]	14 (7%)	9 (6%)[V]	5 (10%)	0.337
• Prednisolone	7 (3%)	5 (3%)	2 (4%)	0.577
• Ciclosporin	7 (3%)	5 (3%)	2 (4%)	0.577
• Other	2 (0.9%)	1 (0.6%)	1 (1.8%)	0.649
Treatment characteristics during omalizumab treatment				
• Antihistamine use [V]	178 (90%)	136 (91%)	42 (86%)	0.467
• Fourfold dose [V]	98 (50%)	71 (48%)	27 (55%)	0.340
• Omalizumab standard dose [VI]	136 (72%)	103 (71%)	33 (73%)	0.937
• High Dose [VI]	53 (28%)	41 (29%)	12 (27%)	0.814
• Immunosuppressive co-treatment [VII]	8 (4%)	6 (4%)	2 (4%)	0.943
• Prednisolone	4 (2%)	2 (1%)	2 (4%)	0.429
• Ciclosporin	4 (2%)	4 (2%)	0 (0%)	0.429
Omalizumab response (n/available)				
Fast response[α]	76/201 (38%)	55/157 (35%)	21/44 (48%)	0.125
Response at T_{end}[β]	145/200 (73%)	107/155 (69%)	38/45 (84%)	0.117
Partial response at T_{end}[γ]	35/200 (18%)	30/155 (19%)	5/45 (11%)	
Poor response at T_{end}[δ]	20/200 (10%)	18/155 (12%)	2/45 (4%)	

Note: Definition response: α Fast response: UCT > 11 at T2; β Response at Tend: UCT 12–16; γ Partial response at Tend: UCT 3–11 and improvement of ≥3; δ Poor response at Tend: UCT 0–11 and improvement of <3. In case of missing UCT scores, (onset of) treatment response was determined based on the physicians' description in the patients' medical records and categorized as complete/good (symptom-free/satisfied with minor symptoms only), partial (insufficient) or no (lack of) response. Tend was defined as date of treatment discontinuation or in case of continuous treatment the last visit before data lock or lost to follow-up. Missings: I $n = 10$; II $n = 39$; III 98; IV $n = 38$; V $n = 36$; VI $n = 44$; VII $n = 38$.

Abbreviations: CIndU, Chronic inducible urticaria; CSU, Chronic spontaneous urticaria; IQR, interquartile range; UCT, Urticaria Control test;

[a]Comparisons between patients with standalone CIndU and patients with CIndU and minor CSU were made using the chi-squared test in case of categorical variables, continuous variables were tested by *t*-test.

[b]The total of CIndU subtypes present in this table exceeds the total number of patients, as $n = 24$ patients had a combination of 2 or 3 CIndU subtypes.

of the continuously treated patients with at least 6 months of omalizumab treatment (81%, $n = 97/120$ with available data) had complete/good response at T_{end}.

Twenty-six percent of patients ($n = 62$) discontinued omalizumab, mostly due to well-controlled disease in 47% ($n = 29$) or ineffectiveness in 34% ($n = 21$) of patients, and less frequently due to

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side effects (3%, $n=2$), a combination of ineffectiveness and side effects (3%, $n=2$), or other reasons (13%, $n=8$). The reported side effects that led to treatment discontinuation were arthralgia, increased perspiration, peeling skin and worsening of urticaria related symptoms. No anaphylactic reactions were reported in this CIndU population.

The 1-year, 2-year and 5-year overall omalizumab survival was 86%, 73%, and 54%, respectively (Figure 1; Table S3), indicating that the median estimated treatment duration exceeds 5 years. The estimated omalizumab treatment duration was mostly determined by well-controlled disease, as this was the most frequent reason for discontinuation (47%). Omalizumab survival rates associated with well-controlled disease were 95% and 69% at 1 and 5 years, respectively (Figure 1; Table S3). The 1-year, 2-year and 3-year omalizumab survival associated with ineffectiveness was 93%, 88% and 85%, respectively. Omalizumab survival rates associated with side effects were 99%, 97% and 97% after 1, 2 and 3 years, respectively. This indicates that no patients in this cohort discontinued omalizumab due to ineffectiveness or side effects after 3 and 2 years of treatment, respectively.

After discontinuation, 26% ($n=16/62$) started a second omalizumab treatment period after a median treatment-free period of 6 months (IQR 4–11). Most ($N=11$) of them were continuously treated until data lock with a median treatment duration of 14 months (IQR 7–20). Five patients also discontinued this second omalizumab treatment period after a median of 5 months (IQR 3–6). Two patients started a third and one patient a fourth omalizumab treatment period due to seasonal treatment of cold urticaria.

3.5 | Discontinuation of omalizumab due to well-controlled disease is predicted by age

The univariate cox regression analysis is presented in Table 2. The multivariate cox regression analysis showed only the patient characteristic higher age as a statistically significant predictor of a lower chance of omalizumab discontinuation (long estimated treatment duration) due to well-controlled disease (HR 0.964, 95% CI 0.938–0.990) (Figure 2); inversely, younger patients had a higher chance to stop treatment because of well-controlled disease. Time to discontinuation due to well-controlled disease was not predicted by the presence of minor CSU symptoms or CIndU subtype. Of note, due to the low number of discontinuations per CIndU subtype, predictive analysis was only performed with the three most prevalent subtypes in this cohort. Of the center specific treatment protocol aspects, "access to higher than standard-dosed omalizumab" predicted a lower chance to stop (long estimated treatment duration) due to well-controlled disease (HR 0.241, 95% CI 0.088–0.658).

For discontinuation due to ineffectiveness, no patient characteristics were identified as potential predictors by univariate and multivariate Cox regression analysis. The treatment protocol aspect "access to higher than standard-dosed omalizumab" predicted a lower chance of discontinuation (long estimated treatment duration) due to ineffectiveness (HR 0.338, 95%CI 0.115–0.998).

Since only a few CIndU patients ($n=4$) discontinued omalizumab due to side effects, no predictors of discontinuation due to this reason were analyzed.

4 | DISCUSSION

This long-term multinational multicenter daily practice cohort study investigated the largest CIndU population treated with omalizumab to date. We found that almost 75% of patients had complete/good response to omalizumab. Eight different CIndU subtypes were analysed and no significant differences in treatment response were found. We observed an overall omalizumab survival rate of 54% at 5 years, indicating a median estimated treatment duration exceeding 5 years. The estimated omalizumab treatment duration was mostly determined by well-controlled disease as this was the major reason for discontinuation. Treatment discontinuation due to side effects was very rare with no reports of anaphylactic reactions. Higher age at the start of omalizumab treatment predicted a longer time until discontinuation due to well-controlled disease, which has not been observed in CIndU patients before. Interestingly, CIndU subtype and presence of minor CSU symptoms had no influence on omalizumab discontinuation for any reason nor response.

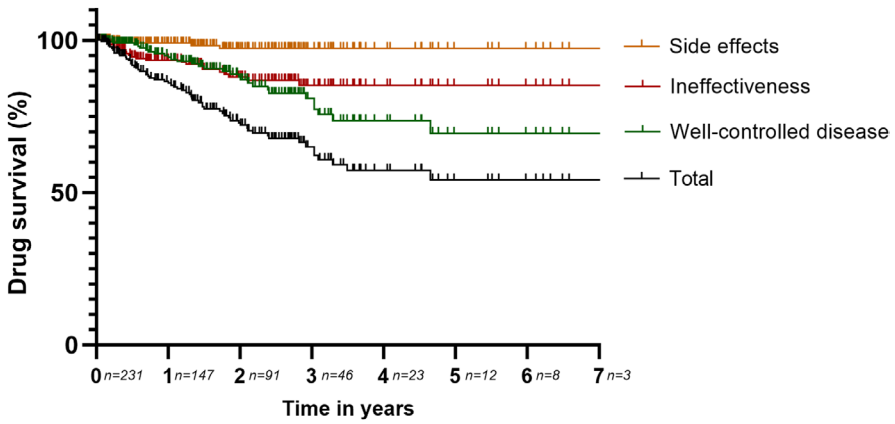


FIGURE 1 Estimated omalizumab treatment duration (drug survival) in CIndU patients differentiated per reason for discontinuation. The overall estimated omalizumab treatment duration (total) and differentiated per reason for discontinuation: Well-controlled disease, side effects and ineffectiveness. The numbers in *italic* represent the number of active patients on omalizumab at that specific time point.

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TABLE 2 Univariate analysis of potential predictors of time to discontinuation due to well-controlled disease and ineffectiveness, respectively.

	Well-controlled disease		Ineffectiveness	
	p-value	Hazard ratio (95% CI)	*p*-value	Hazard ratio (95% CI)
Patient characteristics				
CIndU subtype				
Cholinergic urticaria	**.179**	**1.641**	.796	0.884
Cold urticaria	.267	**(0.796–3.383)**	.269	(0.349–2.244)
Symptomatic dermographism	.675	0.603 (0.247–1.472)	.750	1.604 (0.694–3.707)
		0.826 (0.339–2.017)		1.163 (0.458–2.953)
CSU as minor symptom	.273	0.622 (0.266–1.454)	.281	0.552 (0.187–1.628)
Disease duration >2y prior to OMA	.433	0.749 (0.363–1.545)	.219	1.854 (0.693–4.958)
Higher age	**.018**	**0.969 (0.945–0.995)**	.216	1.014 (0.990–1.039)
Female sex	.760	1.118 (0.546–2.287)	.656	0.830 (0.366–1.882)
Fast response [I]	.942	0.972 (0.453–2.087)		
Autoimmune disease	.905	1.075 (0.327–3.538)	.588	0.607 (0.100–3.701)
Immunosuppressive co-treatment at start of OMA	.449	0.166 (0.002–17.558)	.982	0.978 (0.145–6.607)
Protocol aspects				
Access to higher than standard-dosed OMA [II]	**.025**	**0.333 (0.127–0.872)**	**.050**	**0.338 (0.115–0.998)**
Self-Administration Available [III]	.395	1.387 (0.652–2.951)	.471	1.387 (0.570–3.375)
Maximum dosing interval >12 weeks [IV]	.249	1.691 (0.693–4.130)	.518	1.428 (0.486–4.197)

Abbreviations: CIndU, chronic inducible urticaria; CSU, chronic spontaneous urticaria; OMA, omalizumab.

Note: Variables with a *p*-value ≤.2 (bold) in univariate cox regression analysis were included as potential predictors in the multivariate cox regression analysis. Due to few ($n=4$) discontinuations for side effects, no predictors thereof were analyzed. I Response within 4 weeks after first administration (T2); II The treating physician in a particular center was allowed to prescribe a dose higher than 300 mg; III Patients were allowed to administer omalizumab out of hospital (e.g., by themselves, home-nurse); IV Omalizumab was stopped after a symptom-free treatment interval of >12 weeks was reached.

Our study demonstrates the high long-term effectiveness of omalizumab in CIndU, consistent with prior smaller daily practice studies (53%–100%, $n=12$–80).[6–15] Moreover, this study presents data on eight different CIndU subtypes, enabling the comparison of omalizumab treatment response among some of the rarest forms of CIndU, that is, heat urticaria and aquagenic urticaria. Previous studies inconsistently found differences in omalizumab effectiveness among CIndU subtypes with some reporting higher response rates in delayed pressure urticaria (89%–100%), symptomatic dermographism (83%) and cold urticaria (78%–80%) compared to cholinergic urticaria (33%–57%),[7,11] while others found higher response rates in solar (82%), and cholinergic urticaria (90%) compared to symptomatic dermographism (46%).[10] Although not statistically significant, we observed a slight trend towards higher response rates in solar urticaria (89%), delayed pressure urticaria (79%), heat urticaria (75%), cholinergic urticaria (74%) and cold urticaria (71%) compared to the other subtypes. The response rates reported by previous studies might vary due to differences in population size, variation in included CIndU subtypes or treatment duration. Long-term prospective studies with a balanced representation of all CIndU subtypes are needed to compare omalizumab response between the various CIndU types. Nonetheless, these high response rates and the observation that CIndU subtype or presence of minor CSU symptoms were not associated with treatment response, suggest that omalizumab is a very effective treatment option in most patients with antihistamine-refractory CIndU of any subtype on the long-term. This is even more

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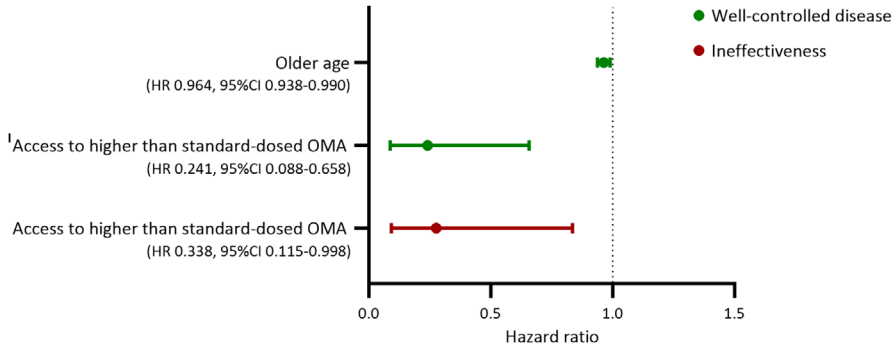


FIGURE 2 Predictors of omalizumab discontinuation due to well-controlled disease and ineffectiveness. OMA, omalizumab; max, maximum. All variables with a *p*-value ≤.2 in the univariate cox regression analysis were included in the multivariate cox regression analysis. The outcome of the multivariate cox regression analysis is presented in this figure. Due to few ($n=4$) discontinuations for side effects, no predictors thereof were analysed. I The treating physician in a particular center was allowed to prescribe a dose higher than 300 mg.

important given the currently limited alternatives with no effective add-on therapy licensed for this indication.

Interestingly, while the response rate was high over the course of omalizumab treatment, only 38% of CIndU patients showed fast response (UCT≥12 within 1 month after first administration), which is lower compared to the overall CU population (49%–70%).[23–25] The observed percentage of fast responders is in line with two other CIndU cohort studies, that observed fast response in 25% ($n=15/59$) and 44% ($n=26/59$) of CIndU patients, respectively.[6,7] One of these studies reported an increase in response rate when treatment continued over 24 weeks.[7] Altogether, these results could indicate a slower response to omalizumab in CIndU patients compared to CSU patients and may suggest a difference in underlying pathophysiological mechanisms. The general good response to omalizumab in CIndU patients suggests the involvement of the high affinity receptor (FcεRI), as supported by a previous study.[26] However, FcεRI stimulation in CIndU may occur via autoallergic as well as autoimmune mechanisms, similar to CSU. Differences in treatment response and time to response between CIndU and CSU, and possibly underlying mechanisms should be investigated in future studies.

In addition to confirming the high effectiveness of omalizumab in CIndU patients, this study also confirmed its safety by demonstrating that only a limited number of patients ($n=4/234$) discontinued treatment due to this reason, none of them due to anaphylaxis. As treatment discontinuation because of side effects was rare, predictive analysis for discontinuation due to this reason could not be performed. Of note, discontinuation of omalizumab due to side effects and ineffectiveness occurred up until after 3 and 2 years, respectively, but not beyond these time points. Thus, in some patients, acceptance of side effects or suboptimal effect due to the current absence of an effective and safe alternative treatment cannot be excluded.

Another objective of this study was to investigate the reasons for omalizumab treatment discontinuation and the estimated omalizumab treatment duration in CIndU patients. The proportion of patients who discontinued omalizumab treatment (26%) was relatively small and the estimated treatment duration (median exceeding 5 years) was relatively long when compared to the discontinuation rate (38%–47%) and the median overall estimated treatment duration (1.1–2.4 years) in the general CU population.[12,27] Of note, 26% of patients that discontinued, required retreatment with a long subsequent treatment duration, accentuating the long overall treatment duration in CIndU patients. Since omalizumab is considered a non-disease modifying treatment,[28] the relatively long estimated treatment duration with omalizumab may reflect a longer disease duration in CIndU patients compared to CSU patients, which has been observed before (3.5 years and 2.5 years, respectively).[29,30] At the same time, while the estimated treatment duration of CIndU is relatively long, patients rarely discontinue treatment due to ineffectiveness, indicating well-controlled disease during omalizumab treatment. This is confirmed by the high response rate (81%) seen in patients who had at least 6 months of omalizumab treatment and were continuously treated until the end of the study period. Altogether, these results confirm that CIndU is a more chronic disease, with good effect of omalizumab treatment.

Longer estimated treatment duration was predicted by age; with every additional year of age, CIndU patients were less likely to stop treatment because of well-controlled disease. However, higher age was not associated with worse treatment response. This implies a longer disease duration in older patients with subsequent longer, but probably effective, treatment. This has not been described in CIndU patients before, but current literature is contradictory about the role of age in the duration of CU in general. One retrospective cohort study ($n=4552$) observed no influence of age on time to CU remission.[31] Other studies report longer time to remission[32] and higher rate of omalizumab retreatment after discontinuation,[33,34] reflecting longer treatment duration associated with higher age, supporting our finding. This might be attributable to immunosenescence, meaning that patients become more susceptible to autoimmune diseases with higher age, which is also observed in asthma patients who exhibit a reduced response to omalizumab.[35] A similar mechanism could play a role in CIndU patients and should be investigated in future studies.

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As this study reflected daily practice, missing data were inevitable, which could be considered as a limitation. However, to maintain statistical power for predictor analysis, missing data were imputed. Information on provocation tests, which could have added to the objectiveness of the response, was not collected.

In conclusion, we confirmed the high effectiveness and safety of omalizumab in CIndU patients by demonstrating high response rates and low risk of discontinuation due to ineffectiveness in a large multinational CIndU cohort. We showed that CIndU patients generally require long-term treatment, possibly reflecting long disease duration, which was predicted by higher age. Our data suggests that omalizumab is beneficial in CIndU patients regardless of CIndU subtype, and should be widely available for patients that remain symptomatic after treatment with escalated dosages of antihistamines.

AUTHOR CONTRIBUTIONS

All authors have made substantial contributions to conception, design or data acquisition of this study and have been involved in drafting or revising the manuscript. All authors have given final approval of the version to be published and agreed to be accountable for all aspects of the work. R. Soegiharto has full access to all the data in the study and takes responsibility for the integrity of the data. R. Soegiharto takes full responsibility for the accuracy of the data analysis.

AFFILIATIONS

[1]Department of Dermatology/Allergology, University Medical Centre Utrecht, Utrecht, Netherlands
[2]Department of Dermato-Venereology and Wound Healing Centre, University of Copenhagen, Bispebjerg Hospital, Copenhagen, Denmark
[3]Department of Dermatology, Erasmus MC, Rotterdam, Netherlands
[4]Department of Dermatology, Marmara University School of Medicine, İstanbul, Turkey
[5]Department of Dermatology, Hospital del Mar Research Institute. Universitat Pompeu Fabra de Barcelona, Barcelona, Spain
[6]Department of Dermatology, Graduate School of Biomedical and Health Sciences, Hiroshima University, Hiroshima, Japan
[7]Urticaria Center of Reference and Excellence (UCARE), Institute of Allergology, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany
[8]Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Immunology and Allergology, Berlin, Germany
[9]Secciones Alergia Adultos y Pediátrica, Hospital Italiano de Buenos Aires Perón, Ciudad Autónoma de Buenos Aires, Argentina
[10]London Allergy and Immunology Centre, London, UK
[11]Department of Dermatology, Koç University School of Medicine, Topkapi Istanbul, Turkey
[12]Department of Dermatology, faculdade de medicina do ABC, Santo André, Brazil
[13]First Department of Dermatology and Veneorology, National and Kapodistrian University of Athens A Syggros Hospital, Athens, Greece
[14]Clinic for Dermatology, Elbe Klinikum Buxtehude, Buxtehude, Germany
[15]Department of Dermatology, Hiroshima City Hiroshima Citizens Hospital, Hiroshima, Japan
[16]Department of Dermatology, Acibadem Mehmet Ali Aydinlar University School of Medicine, Istanbul, Turkey
[17]Department of Dermatology, Sakarya University Faculty of Medicine, Sakarya, Turkey
[18]Centre for Human Drug Research, Leiden, Netherlands
[19]Department of Dermatology, Radboud University Medical Centre, Nijmegen, Netherlands

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CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

R. Soegiharto https://orcid.org/0000-0002-1942-2508
M. Alizadeh Aghdam https://orcid.org/0000-0003-3584-9250
M. Maurer https://orcid.org/0000-0002-4121-481X
R. F. J. Criado https://orcid.org/0000-0003-2482-3047
A. M. Giménez-Arnau https://orcid.org/0000-0001-5434-7753
A. Salman https://orcid.org/0000-0002-6407-926X

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SUPPORTING INFORMATION

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