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1 Omalizumab drug survival in chronic urticaria: a retrospective multicentric French study

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53 (Novartis)

54 The study was registered with ClinicalTrials.gov (NCT04584190).

55 Abstract

56 **Background :**

57 Omalizumab (OMA) dramatically improves disease control and quality of life in patients
58 with chronic urticaria (CU).

59 **Objective :**

60 We aimed to evaluate the discontinuation patterns of OMA and their determinants in a
61 cohort of French patients with CU.

62 **Methods :**

63 We conducted a retrospective multicenter study in nine French tertiary referral hospitals.
64 All patients diagnosed with either spontaneous (CSU) and/or inducible (CIndU) CU who
65 received at least one injection of OMA between 2009 and 2021 were included. We
66 analyzed OMA drug survival and investigated possible determinants using Kaplan-Meier
67 curves and log-rank tests.

68 **Results**

69 A total of 878 patients were included in this study; 48.8% had CSU, 10.1% CIndU, and
70 41.1% a combination of both. OMA was discontinued in 408 patients but the drug was
71 later reintroduced in 50% of them. The main reason for discontinuing treatment was the
72 achievement of a well-controlled disease in 50% of patients. Half of the patients were still
73 being treated with OMA 2.4 years after the initiation of treatment. Drug survival was
74 shorter in patients with CIndU and in those with an autoimmune background. In atopic
75 patients, OMA was discontinued earlier in patients achieving a well-controlled disease. A
76 longer OMA drug survival was observed in patients with a longer disease duration at
77 initiation.

78 **Conclusion**

79 In French patients with CU, the drug survival of OMA appears to be longer than that
80 observed in previous studies conducted elsewhere, highlighting discrepancies in
81 prescription and reimbursement possibilities. Further studies are warranted to develop
82 customized OMA treatment schemes based on individual patterns.

83 **Key words:** chronic urticaria ; real-life study; omalizumab ; drug survival

84 **Highlight box:**

85 *1. What is already known about this topic?*

86 - Omalizumab is effective and well-tolerated in antihistamine-resistant chronic spontaneous
87 urticaria.

88 - Relapses after omalizumab discontinuation are frequent; however, retreatment with
89 omalizumab is usually effective.

90 - Omalizumab discontinuation modalities differ significantly worldwide.

91 *2. What does this article add to our knowledge?*

92 - In France, where omalizumab is fully reimbursed without a time limit, half of the patients with
93 chronic urticaria were still treated with omalizumab 2.4 years after initiation.

94 - Patients with a longer disease duration had a longer duration of omalizumab treatment.

95 - Patients with atopic background discontinued omalizumab earlier when they achieved well-
96 controlled disease.

97 - Patients with chronic inducible urticaria or an autoimmune background discontinued
98 omalizumab earlier due to its ineffectiveness.

99 *3. How does this study impact current management guidelines?*

100 - This study emphasizes the need to optimize omalizumab treatment schemes to reduce
101 medico-economic costs and improve patients' quality of life.

102 - There are unmet needs for the treatment of chronic inducible urticaria; some patients, but not
103 all, may benefit from omalizumab.

104 [Abbreviations](#)

105 CU: chronic urticaria

106 CSU: chronic spontaneous urticaria

107 CIndU: chronic inducible urticaria

108 CSUp: combination of CSU and CIndU with CSU predominantly affects patients' quality of life

109 CIndUp: combination of CSU and CIndU with CIndU predominantly affects patient quality of life

110 HR: hazard ratio

111 OMA: omalizumab

112 Introduction

113 Chronic urticaria (CU) affects approximately 1% of the population (1). It is characterized by itchy
114 wheals and/or angioedema that recur for at least six weeks. CU can occur without any identified
115 trigger (chronic spontaneous urticaria, CSU) or can be strictly inducible (CIndU) by various stimuli
116 such as cold contact and pressure. Some patients may have a combination of CSU and CIndU, or
117 several concomitant CIndUs. International guidelines (2) recommend the use of second-
118 generation antihistamines as the first-line of therapy, if necessary. Omalizumab (OMA), a first-in-
119 class IgG1 monoclonal antibody targeting IgE, has been used in France as a second-line therapy
120 in CSU patients since 2015 (3) with a good efficacy and safety profile both in pivotal and real-life
121 studies, but it remains off-label for CIndU. In real-life studies, 53.8% to 83.1% of CSU patients are
122 refractory to up-dosed antihistamines, and although omalizumab is recommended for these
123 patients, it is only prescribed to a third of them (4–6). A major uncertainty regarding OMA in CU
124 management is the lack of a defined optimal treatment duration (2,7), partially because CSU can
125 resolve spontaneously within 5 years in most patients (8). OMA discontinuation patterns vary
126 significantly among physicians due to differences in reimbursement regimens between countries
127 and varying practices within a given country. In France, the reimbursement regimen for OMA
128 allows for continuous treatment of CSU, raising concerns about its long-term costs. Further, the
129 off-label use of OMA for CIndU is frequent in French tertiary referral centers, particularly when
130 dealing with a combination of CSU and CIndU. Thus, we aimed to evaluate the drug survival of
131 OMA in patients with CSU, CIndU or both, in a retrospective multicenter French cohort and to
132 investigate its potential determinants. Drug survival depends on a series of parameters including
133 efficacy, tolerance, patient preferences and physicians' preferences. Drug survival analysis is a
134 common procedure in assessing therapies in chronic skin diseases (9).

135 Population and methods

136 In this retrospective, multicenter study, data collection was carried out between January 30th,
137 2020, and data lock January 30th, 2021, in 9 French tertiary referral centers, all of which are
138 members of the urticaria study group of the French Dermatology Society, with three centers also
139 being members of the GA2LEN Urticaria Centers of Reference and Excellence.

140 All patients, with no restrictions on gender or age, who were diagnosed with CSU and/or CIndU
141 according to the EAACI definition (1) and received at least one OMA injection since December
142 2009 (time of first injection in the selected centers) were included. Data from medical records
143 were collected until data lock or until the patient was lost to follow-up.

144 Patients with an unknown date of OMA initiation and discontinuation, and those treated with
145 OMA for conditions other than CU were excluded.

146 Using a standardized questionnaire and in collaboration with the corresponding physician in
147 charge at each center, a single reviewer collected the following data: demographic
148 characteristics, type of CU, and the predominant subset impacting patients' quality of life in the
149 case of CSU/CIndU combination, presence of an atopy background, autoimmunity background
150 (defined as any mentioned autoimmune condition or presence of (a)symptomatic antinuclear or
151 antithyroid antibodies), systemic symptoms (fever, arthralgia, abdominal pain), history of
152 previous medications, modalities of OMA use including time of initiation and discontinuation
153 pattern, if applicable (time and underlying reason), dosage, tolerance and efficacy (Online
154 Repository Text). The evaluation of disease severity, response to treatment, and impact on
155 patients' quality of life was performed by a single reviewer in collaboration with the
156 corresponding physician in charge at each center and was based on various scores according to
157 their availability at the time of evaluation. Specifically, data regarding disease activity and OMA
158 (dis)continuation were collected for up to five years after OMA initiation. Patient-reported

159 outcome measures (PROMs) were not available in all files, especially before translation into
160 French. Accordingly, the following scores were collected: the modified Physician Global
161 Assessment (PGA) (10,11), urticaria control test (UCT), and urticaria activity score (UAS7). A
162 complete response to OMA was defined as an improvement of more than 90% (PGA 0 or 1)
163 and/or $UCT \geq 12$ and/or $UAS7 \leq 6$. A partial response was defined as an improvement of 30-90%
164 (PGA 2, 3, 4) and/or $UCT \leq 11$ and/or $UAS7 > 6$ but significant improvement of UCT and/or UAS7
165 of at least 3 and 10 points, respectively (12). The absence of response was defined as an
166 improvement of less than 30% (PGA 5) and/or $UCT \leq 11$ and/or $UAS7 > 6$ with no significant
167 improvement of UCT or UAS7. Disease activity was defined as follows: well-controlled disease
168 (WCD) in cases of $>90\%$ disease control (PGA 0 or 1), and/or $UCT \geq 12$ and/or $UAS7 \leq 6$; mild to
169 moderate disease in cases of disease control between 30-90% (PGA 2, 3, 4) and/or $UCT 8-11$
170 and/or $7 < UAS7 < 27$; and uncontrolled disease in cases of $<30\%$ disease control (PGA 5) and/or
171 $UCT \leq 7$ and/or $28 < UAS7 < 42$ (13). PGA 6 was defined as worsening disease. The reasons
172 underlying OMA discontinuation were formalized as follows: achievement of a well-controlled
173 disease, ineffectiveness, occurrence of limiting adverse events, pre-treatment contraindications
174 to OMA continuation (desired or ongoing pregnancy, incompatible intercurrent illness), and
175 personal and organizational reasons. In cases with multiple reasons for discontinuation, we
176 prioritized adverse events over well-controlled disease, and ineffectiveness over adverse events.
177 The study protocol was approved by the institutional review board (2019_IRB-MTP_07-13).
178 Patients did not object to the use of their clinical data for this study. The study was registered
179 with ClinicalTrials.gov (NCT04584190).

180 [Statistical analysis](#)

181 Categorical variables were presented as numbers and percentages. We used mean and standard
182 deviation for normally distributed continuous variables, and median and interquartile ranges for

183 non-normally distributed continuous variables. The groups under focus were compared with χ^2
184 or exact Fisher test for categorical variables and with Wilcoxon-Mann-Whitney test for
185 quantitative variables. Holm-Bonferoni procedures were used to account for multiple
186 comparisons when comparing individual subsets of CU.

187 Overall drug survival was defined as the time interval during which patients continued to be
188 treated with OMA, with the “event” being the first OMA discontinuation. Patients who were still
189 receiving OMA at the end of follow-up period were censored. The probability of continuing
190 treatment with OMA was analyzed using Kaplan-Meier survival curves. Drug survival was
191 evaluated for each reason for discontinuation using the (1 – cumulative incidence) function,
192 taking into account that discontinuation of treatment for a reason other than the one being
193 studied acted as a competitive risk (14).

194 For the overall analyses, five potential determinants of drug survival (CU subset, angioedema,
195 autoimmunity, systemic steroids, and disease duration) were analyzed using Kaplan-Meier curves
196 and log-rank tests. Crude and adjusted hazard ratios (HR) and their 95% confidence intervals
197 were estimated using univariate and multivariate Cox models. We then stratified analyses of drug
198 survival determinants according to reason for discontinuation (“well-controlled disease” versus
199 “other reasons for discontinuation”). Crude and adjusted sub-distribution-HRs and their 95%
200 confidence intervals were estimated using univariate and multivariate Fine and Gray models (15),
201 considering discontinuation of treatment for a reason other than the one under focus as a
202 competitive risk. Multivariate analyses were adjusted for sex, age, disease duration, CU subsets,
203 angioedema, atopy/autoimmune background, presence of systemic symptoms, and previous
204 medications. To avoid the loss of statistical power and selection bias related to missing data in
205 multivariate analyses (less than 5% for each explanatory variable), 15 imputed datasets were
206 created using the multiple imputation method. Missing values for covariates considered in the

207 analysis were replaced by values generated using the Fully Conditional Specification (FCS)
208 method and the PROC MI procedure of SAS version 9.2. Each imputed dataset was analyzed as
209 complete, and hazard ratios (HRs) and their CI were compiled using the PROC MIANALYZE
210 procedure (16).

211

212 Results

213 Patients' characteristics and treatment

214 Out of the 972 patients' medical files reviewed (Figure 1), 878 (mean age 38.3 +/-17 years, f/m
215 sex ratio 2.4) were included in the final analysis. The baseline characteristics of the population
216 (Table 1) were consistent with those reported in previous real-life studies: predominance of
217 middle-aged women, high frequency of atopy or autoimmunity background in CSU patients, and
218 lower frequency of angioedema in CIndU patients (17–19). CSU was present in 89.9% of patients,
219 and CIndU in 51.2% of patients, while a combination of CSU and CIndU was observed in 41.1% of
220 patients. Patients were followed up at the participating centers for an average of 2.3 years (range,
221 3 months-10 years). OMA was prescribed in combination with various dosages of first- or second-
222 generation antihistamine drugs, especially when OMA was initiated before the 2014
223 international guidelines. No other concomitant therapies were reported in the patients' files. Due
224 to missing data regarding antihistamine drugs, their adherence and dosage were not specifically
225 analyzed. In patients with CSU or combined CSU/CIndU, OMA was prescribed according to its on-
226 label use in France for CSU, *i.e.* 300 mg subcutaneously every 4 weeks. In the 89 patients with
227 CIndU only, OMA was introduced later in the disease course compared to CSU patients (7.1
228 versus 4.8 years), with the same dosage as prescribed for CSU, although in an off-label setting.

229 Response patterns to omalizumab

230 The complete response rate reached 75.5% after six months of OMA treatment (Table 2), which
231 is also in line with previous real-life studies (20). The presence of CIndU and/or autoimmune
232 background negatively influenced the response and its delay, while there was no difference in
233 response rates according to sex, disease duration, atopy background, presence of angioedema,
234 systemic symptoms, or previous therapies (data not shown). Also in line with previous real-life
235 studies, disease activity data assessed one and five years after OMA initiation showed a stable
236 majority of patients with well-controlled disease (66.7 and 69.2%, respectively) and a slightly
237 decreasing minority of patients with uncontrolled disease (5.6 and 3.1%, respectively). Regarding
238 OMA dosage (Figure E1), the percentage of patients treated with standard-dose OMA (300 mg
239 every 4 weeks subcutaneously) decreased over time, reaching 25.5% after five years. Conversely,
240 the percentage of patients treated with lower-than-standard-dosed OMA (longer intervals
241 between OMA injections and/or reduced individual OMA dosage per injection) increased over
242 time, reaching up 61.8% after 5 years, with a mean maximal interval between OMA injections of
243 7.6 ± 4.1 weeks (range, 2-52). Almost 50% (39/80) of patients receiving higher-than-standard OMA
244 doses (shorter intervals between OMA injections and/or increased individual OMA dosage per
245 injection) achieved a well-controlled disease after 1 year. Forty-eight percent (n=196) of the 408
246 patients who discontinued OMA at any time point during follow-up were subsequently retreated
247 after a median time of 4.4 months after discontinuation (range 2-42; Q1-Q3: 2.6-9.3), with a
248 similar or better efficacy in 75% of them (n=147). Only 12% (6.1%) patients reported a lower
249 efficacy upon rechallenge, and data was missing for the remaining 37 patients. No difference in
250 rechallenge frequency was observed according to CU subset, atopy or autoimmune background,
251 or presence of systemic symptoms, but the size of the corresponding subsets was limited.

252 Drug survival of omalizumab and reasons for discontinuation

253 After 2.4 years, 50% of patients were still receiving OMA (Figure 2) (66 and 33.7% after 1 and 5
254 years, respectively). During the period under scope, a total of 408 (46.5%) patients discontinued
255 OMA, which was due to the achievement of a well-controlled disease in 203 (23.1%) patients
256 (16.2% and 35.7% after one and five years of treatment, respectively). Conversely, treatment
257 failure led to OMA discontinuation in 88 (10.0%) patients, mostly during the first year of
258 treatment. In these refractory CU patients, data regarding the potential interest in OMA up-
259 dosing schemes were missing for the majority (75/88) of patients. Adverse event occurrence was
260 the least frequent reason for discontinuation, reported in only 23 (2.6%) patients and involving
261 1.9% of patients during the first year of OMA treatment versus 4.1% after 5 years. Of note,
262 adverse events were reported in 104 (11.9%) patients. In line with previous real-life studies and
263 clinical trial data (20,21), headaches and arthromyalgia were reported in 4.3 and 3.9% of the
264 patients, respectively. The former led to discontinuation in only 15.8% of the cases versus 41.2%
265 due to the latter. Other adverse events are listed in Table E1; however, no previously unknown
266 adverse events were reported in this large cohort. Other reasons for discontinuation accounted
267 for less than 10% and remained stable over time. The per-treatment occurrence of
268 contraindications involved 44 (5.0%) patients, who were generally younger than those
269 discontinuing OMA due to good disease control, treatment failure or any adverse events (mean
270 32.7 ± 15.7 versus 38.3 to 42.8 years in these 3 latter subgroups, $p=0.038$) and more often
271 involved women (14.5% vs 1.9% of men ($p=0.014$)). Planned or ongoing pregnancies accounted
272 for 77.3% of the contraindications. Other contraindications included malignancy or other severe
273 noncutaneous conditions. Eventually, thirty-five (4.0%) patients discontinued OMA due to
274 alleged personal and organizational motives; these patients were younger than those
275 discontinuing OMA due to a well-controlled disease, treatment failure or any adverse events
276 (mean 33.5 ± 14.8 versus 38.3 to 42.8 years in the 3 latter subgroups, $p=0.038$). Fifteen (1.8%)

277 patients discontinued OMA due to unknown reasons. The distribution of reasons for
278 discontinuation did not seem to be influenced by disease duration, CU subset, atopy or
279 autoimmune background, presence of angioedema or systemic symptoms, or previous therapies.
280 However, a lack of statistical power due to the small size of the subgroups cannot be ruled out.

281 Determinants of the drug survival of omalizumab

282 In the overall study population, CIndU (HR 2.19, IC95 [1.56-3.06], $p < 0.0001$), autoimmune
283 background (HR 1.45, IC95 [1.11-1.9], $p = 0.01$) or prior treatment with hydroxychloroquine,
284 salazopyrin, colchicine, or dapsone (HR 1.87, IC95 [1.35-2.58], $p = 10^{-4}$) were significantly
285 associated with a shorter OMA survival. Conversely, longer drug survival was observed in patients
286 with longer disease duration at baseline (Figures 3 and 4).

287 In the specific subset of patients who discontinued OMA owing to a well-controlled disease, an
288 atopy background (HR 1.38, IC95 [1.02-1.87], $p = 0.036$) or previous therapy with
289 hydroxychloroquine, salazopyrin, colchicine, or dapsone (HR 2.09, IC95 [1.37-3.21], $p = 7.10^{-4}$)
290 were significantly associated with a shorter OMA survival. In patients who discontinued OMA for
291 other reasons, female gender (HR 1.51, IC95 [1.05-2.18], $p = 0.026$), CIndU (HR 2.3, IC95 [1.37-
292 3.87], $p = 0.002$) and autoimmunity background (HR 1.61, IC95 [1.10-2.35], $p = 0.014$) were
293 significantly associated with a shorter OMA survival (Figure 4).

294

295 Discussion

296 In this large real-life study with a protracted follow-up, OMA demonstrated a satisfactory
297 efficacy/safety ratio in CSU patients and, to a lesser extent, in CIndU patients. Regarding OMA
298 drug survival, 50% of the 878 included patients were still receiving OMA after 2.4 years.
299 Discontinuation due to treatment failure remained rare after 1 year of treatment, suggesting that
300 secondary resistance to OMA is uncommon. These results differ from the study by Hasal et al.

301 (22), which reported only 2.8% of patients still receiving OMA after 24 months, but they are
302 consistent with two major previous studies by Spekhorst et al. (13) and Ghazanfar et al. (10),
303 reporting 56% and 77% of patients still being treated with OMA after 1 year, respectively. These
304 discrepancies may reflect the differences in OMA prescription modalities and reimbursement
305 regimens between countries. In this study, the overall drug survival of OMA was longer in patients
306 with a longer disease duration at OMA initiation, which indirectly supports the findings by Hasal
307 et al., showing that patients with a shorter disease duration at OMA initiation were more likely
308 to achieve well-controlled disease (22). Indeed, the main reason for OMA discontinuation in our
309 study was the achievement of a well-controlled disease in 23.1% of patients, which is in line with
310 previous studies by Spekhorst et al. (13) and Ghazanfar et al. (10) (15 and 29% of patients,
311 respectively). The other reasons for discontinuing OMA in our study were also consistent with
312 these previous reports (8.1 and 13% of discontinuation due to ineffectiveness and 1.2% and 5.8%
313 due to adverse events, respectively).

314 In our study, achievement of well-controlled disease was associated with shorter OMA survival
315 in patients with atopy background. This finding indirectly aligns with previous studies that
316 reported higher rates of rapidly achieved complete response in patients with elevated total IgE
317 levels (23). Similarly, the achievement of a well-controlled disease resulted in earlier
318 discontinuation of OMA in patients previously treated with non-immunosuppressive drugs such
319 as hydroxychloroquine or colchicine, therapies not currently recommended in CSU management,
320 but widely used among French practitioners before OMA became available. This result may also
321 reflect a coincidental spontaneous remission of CU after a period of no response to these drugs.
322 Among patients who discontinued OMA for reasons other than well-controlled disease, patients
323 with exclusive CInDU discontinued OMA earlier. This contradicts the findings of Spekhorst et al.
324 This discrepancy, however, may be explained by the different classifications of patients with

325 CIndU, mainly combining CSU and CIndU (13). In our study, OMA drug survival was similar
326 between patients with combined CSU/CIndU and CSU patients. The previously observed lower
327 rate of good response in the CIndU group may have prompted patients with exclusive CIndU to
328 discontinue off-label OMA earlier in our study. Moreover, 29.2% of the latter had cholinergic
329 urticaria, which seems to have the lowest rate of a good response to OMA (24,25). Higher-than-
330 standard-dosed OMA could have been beneficial to non-responder CIndU patients, as previously
331 suggested (26), but data regarding an updose of OMA were only available for a minority of these
332 patients and therefore were not analyzed.

333 In the same setting (OMA discontinuation for reasons other than achieving well-controlled
334 disease), patients with an autoimmune background also discontinued OMA earlier. In the
335 literature, the impact of an autoimmune background on the response to OMA is unclear, and
336 various definitions of autoimmunity are not consistent (23,27–30). In our study, an autoimmunity
337 background negatively influenced the initial response after 6 months of OMA treatment. As
338 recommended by Grattan et al. (31), these patients may have been switched to cyclosporin A
339 earlier, but this data was not available in the patients' records.

340 In patients discontinuing OMA for reasons other than a well-controlled disease, OMA was
341 interrupted earlier in women compared to men. More specifically, 77.2% of the 44 patients who
342 discontinued OMA due to the occurrence of contraindications during treatment were women,
343 primarily because of planned or ongoing pregnancy. At the time of the study, OMA was not
344 recommended in pregnant women with CU owing to limited data regarding its safety and the
345 non-lethality of CU (32,33).

346 A number of methodological limitations are to be acknowledged in this survey, which are mainly
347 related to its retrospective design. The single-reviewer extraction of information, the absence of
348 systematically collected PROMs and the non-standardized use of validated scores to evaluate the

349 quality of disease control are likely to result in significant bias in data interpretation. For instance,
350 the “mild to moderate disease” subset is likely to be heterogeneous, mixing partial responses,
351 dissociated responses in combined CSU/CInDU and perhaps ‘end-of-OMA-dose’ effects.
352 Additionally, a significant number of missing data are to be highlighted, especially regarding the
353 dosage of antihistamine drugs used either prior to or in combination with OMA.

354 In our opinion, OMA discontinuation or at least a progressive tapering in search of the minimal
355 effective dosage should always be considered since spontaneous remissions are possible, and
356 rechallenge is most often effective (24,34–37), especially considering that OMA is an expensive
357 treatment (38). In our survey, OMA discontinuation modalities varied, but most French
358 practitioners opted for stepping down OMA with increasingly longer time intervals between
359 injections. Very different durations of long-term remission upon discontinuation have been
360 reported in the literature, ranging from 7% (10) to 83% (39), and some authors have suggested
361 systematically planning OMA discontinuation after 6 months in patients with well-controlled
362 disease. However, the relapse rate is high, reaching 50% in the overall population in our study,
363 which is in line with previous data ranging from 44% to 79.1%. The mean time to relapse ranged
364 from 4.7 weeks to 3.2 months (10,24,25,34,39–42) after OMA discontinuation. Thus, patients
365 who achieve a high-quality remission after 6 months of treatment with OMA could be eligible for
366 treatment interruption and on-demand rechallenge, thus defining an optimal interval between
367 further injections of OMA. The optimal initial duration of OMA is still not known, but it is worth
368 noting that the initial OMA treatment duration does not appear to be related to the risk of relapse
369 in the X-TEND study (25). Other risk factors for relapse are still being debated (43,44).

370 [Conclusion](#)

371 In France, OMA drug survival in CU seems to be longer than previously reported. Prospective
372 studies comparing and evaluating various methods of OMA discontinuation when remission is

373 achieved are warranted to optimize customized treatment regimens and ensure a protracted
374 response in patients with CSU, CIndU or both.

375 Acknowledgement to B. Ducotterd for providing data from Grenoble University Hospital.

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500 patients. *J Eur Acad Dermatol Venereol* 2019;33:918- 24.

501 Tables and figures legends

502 Figure 1. Flow chart of the study

503 OMA omalizumab, N number

504 *other conditions included mast cell disorder, neutrophilic urticaria, pruritus sine materia,
505 aquagenic pruritus, urticarial vasculitis, atopic dermatitis, dermatomyositis, melanoma,
506 contact dermatitis, bullous pemphigoid, isolated asthma, food or venom immunotherapy,
507 unspecified diagnosis

508

509 Figure 2 : Drug survival of omalizumab

510 Overall drug survival was analyzed using Kaplan-Meier curves. Drug survivals for each reason to
511 discontinuation were analysed using 1 – cumulative incidence functions with all other reasons
512 considered as competitive risks.

513

514 Figure 3 : Analyses of overall drug survival of omalizumab according to subset of chronic
515 urticaria (A), presence of an autoimmunity background (B), disease duration at omalizumab
516 initiation (C), presence of angioedema (D) and previous medication with corticosteroids (E).

517 Overall drug survivals were analyzed using Kaplan-Meier curves and Log-rank test

518 CU chronic urticaria, CSU chronic spontaneous urticaria, ClndU chronic inducible urticaria, CSUp
519 combination of CSU and ClndU with CSU predominantly impacting the patients' quality of life,
520 ClndUp combination of CSU and ClndU with ClndU predominantly impacting the patients'
521 quality of life, CS corticosteroids

522

523 Figure 4 : Analyses of the determinants of the drug survival of omalizumab in overall population
524 (A) and in subgroup of patients who discontinued for having achieved a well-controlled disease
525 (B) or for any other reason (C)

526 CU chronic urticaria, CSU chronic spontaneous urticaria, CIndU chronic inducible urticaria, CSUp
527 combination of CSU and CIndU with CSU predominantly impacting the patients' quality of life,
528 CIndUp combination of CSU and CIndU with CIndU predominantly impacting the patients' quality
529 of life, HR hazard ratio

530 *These HR differed significantly from reference groups ($p < 0.05$). Reference groups for age,
531 disease duration and subset of CU were: age <25years old, disease duration <1year, CSU. HR were
532 estimated using multivariate Cox models (A) and Fine and Gray models (B)(C), and mutually
533 adjusted for all variables presented.

534

535 Table 1 : Population characteristics at baseline

536 CU chronic urticaria, CSU chronic spontaneous urticaria, CIndU chronic inducible urticaria, CSUp
537 combination of CSU and CIndU with CSU predominantly impacting the patients' quality of life,
538 CIndUp combination of CSU and CIndU with CIndU predominantly impacting the patients' quality
539 of life, SD standard deviations, n number

540 ^{a,b,c,d} groups with the same letter are not significantly different after adjustment for multiple
541 comparison (Holm-Bonferoni procedure)

542 *other previous therapies included colchicine, dapsone, salazopyrin and hydroxychloroquine

543

544 Table 2 : Characteristics of the patients' response 6 months after omalizumab initiation

545 CU chronic urticaria, CSU chronic spontaneous urticaria, CIndU chronic inducible urticaria, CSUp
546 combination of CSU and CIndU with CSU predominantly impacting the patients' quality of life,
547 CIndUp combination of CSU and CIndU with CIndU predominantly impacting the patients' quality
548 of life, SD standard deviations, n number

549 *A rapid complete response was defined as a complete response achieved before the second
550 injection of omalizumab.

551

552 Figure E1 : Omalizumab dosages at 1 to 5 years in patients still treated with omalizumab

553 Standard dosage: 300mg every 4 weeks, lower-than-standard dosage: intervals between
554 injections were longer than 4 weeks and/or OMA dosage was < 300mg per injection, higher-than-
555 standard dosage : intervals between injections were shorter than 4 weeks and/or OMA dosage
556 was > 300mg per injection

557 N = number of patients still treated by omalizumab after 1 to 5 years, WCD well-controlled
558 disease.

Table 1: Population characteristics at baseline

| | Total population n=878 | CSU n=428 | CSUp n=299 | CIndU n=89 | CIndUp n=62 | p-value |
|--|------------------------------|---------------------------|---------------------------|----------------------------|-----------------------------|----------------------------|
| Subsets of CIndU (n) | | | | | | |
| <i>Cold contact urticaria</i> | 53 | - | 4 | 44 | 5 | |
| <i>Cholinergic urticaria</i> | 75 | | 32 | 26 | 17 | |
| <i>Dermographism</i> | 248 | | 221 | 9 | 18 | |
| <i>Solar urticaria</i> | 11 | | 4 | 5 | 2 | |
| <i>Delayed pressure urticaria</i> | 110 | | 87 | 4 | 19 | |
| <i>Vibratory urticaria</i> | 6 | | 5 | 1 | 0 | |
| <i>Aquagenic urticaria</i> | 5 | | 4 | 0 | 1 | |
| Mean age at CU onset, years (SD) | 38.3 (±17) | 42.1 (±16.8) ^a | 36.9 (±16.6) ^b | 29.4 (± 16.9) ^c | 32.2 (±16.1) ^{b,c} | <0.001 |
| Female patients, n (%) | 621 (70.7) | 311 (72.7) ^a | 217 (72.6) ^a | 48 (53.9) ^b | 45 (72.6) ^{a,b} | <0.004 |
| Clinical features, n (%) | | | | | | |
| <i>Atopy background</i> | 345 (39.3) | 166 (43.2) | 123 (44.4) | 32 (43.2) | 24 (42.9) | 0.990 |
| <i>Autoimmunity</i> | 127 (14.5) | 67 (17.2) | 46 (16.3) | 7 (9.1) | 7 (11.9) | 0.271 |
| <i>Angioedema</i> | 402 (45.8) | 231 (54.0) ^a | 145 (48.5) ^{a,b} | 9 (10.1) ^c | 17 (27.4) ^d | <0.000001 |
| <i>Systemic symptoms</i> | 163 (18.6) | 88 (23.1) ^a | 57 (20.8) ^{a,b} | 6 (8.1) ^b | 12 (20.3) ^{a,b} | 0.037 |
| Previous therapies, n (%) | | | | | | |
| <i>Antihistamines and Leukotriene receptor antagonists</i> | 868 (98.9) | 421 (98.4) | 298 (99.7) | 88 (98.9) | 61 (98.4) | 0.274 |
| <i>Corticosteroids</i> | 278 (31.7) | 149 (34.8) ^a | 106 (35.5) ^a | 12 (13.5) ^b | 11 (17.7) ^b | 3.9 10⁻⁴ |
| <i>Bradykinin inhibitors</i> | 14 (1.6) | 8 (1.9) | 5 (1.7) | 1 (1.1) | 0 (0) | 0.940 |
| <i>Non-immunosuppressive drugs</i> | 78 (8.9) | 31 (7.2) | 25 (8.4) | 13 (14.6) | 9 (14.5) | 0.056 |
| <i>Immunosuppressive drugs</i> | 65 (7.4) | 31 (7.2) | 17 (5.7) | 9 (10.1) | 8 (12.9) | 0.172 |
| Mean disease duration, years (SD) | 5.4 (±7.3) | 4.8 (±7.1) ^a | 5.2 (±6.7) ^a | 7.1 (±7.3) ^b | 8.0 (±8.8) ^b | <0.001 |

Table 2: Initial response evaluated 6 months after the first injection of omalizumab

| | Complete response (quick) <i>n (%) or mean(SD)</i> | Complete response (late) <i>n (%) or mean(SD)</i> | Partial response <i>n (%) or mean(SD)</i> | No response <i>n (%) or mean(SD)</i> | Worsening disease <i>n (%) or mean(SD)</i> | p-value |
|------------------------------|---|--|--|---|---|---------|
| Total | 530 (62.9) | 107 (12.7) | 123 (14.6) | 73 (8.8) | 10 (1.2) | |
| Age in years at introduction | 38.8 (±16.6) | 41.1 (±18.82) | 35.2 (±17.0) | 34.5 (±18.9) | 50.3 (±12.6) | 0.008 |
| <i>Type of CU</i> | | | | | | 0.010 |
| ClndU | 49 (56.3) | 9 (10.3) | 13 (14.9) | 16 (18.4) | 0 | |
| CSU | 266 (65.4) | 53 (13.0) | 48 (11.8) | 33(8.1) | 7 (1.7) | |
| ClndUp | 33 (53.2) | 6 (9.7) | 17 (27.4) | 5 (8.1) | 1 (1.6) | |
| CSUp | 182 (63.4) | 39 (13.6) | 45 (15.7) | 19 (6.6) | 2 (0.7) | |
| <i>Autoimmunity</i> | | | | | | 0.035 |
| yes | 65 (51.6) | 17 (13.5) | 25 (19.8) | 18 (14.3) | 1 (0.8) | |
| no | 419 (64.4) | 81 (12.4) | 92 (14.1) | 51 (7.8) | 8 (1.2) | |

Figure 1. Flow chart of the study

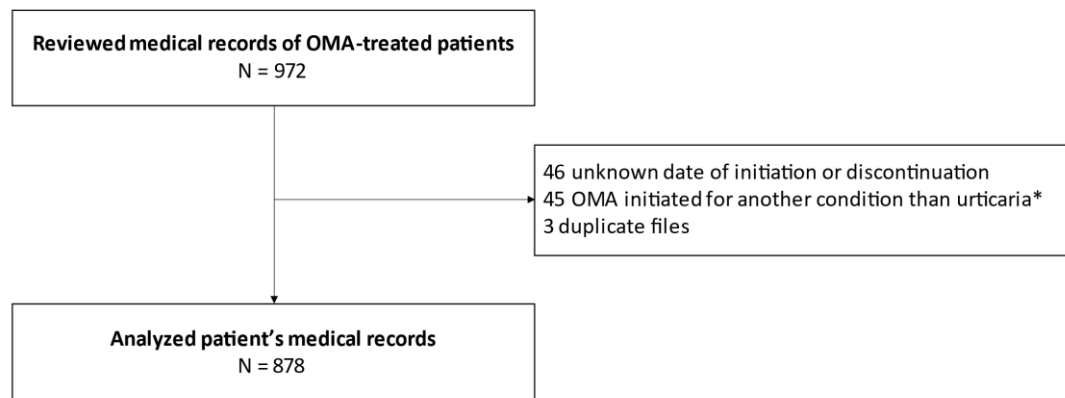


Figure 2: Drug survival of omalizumab

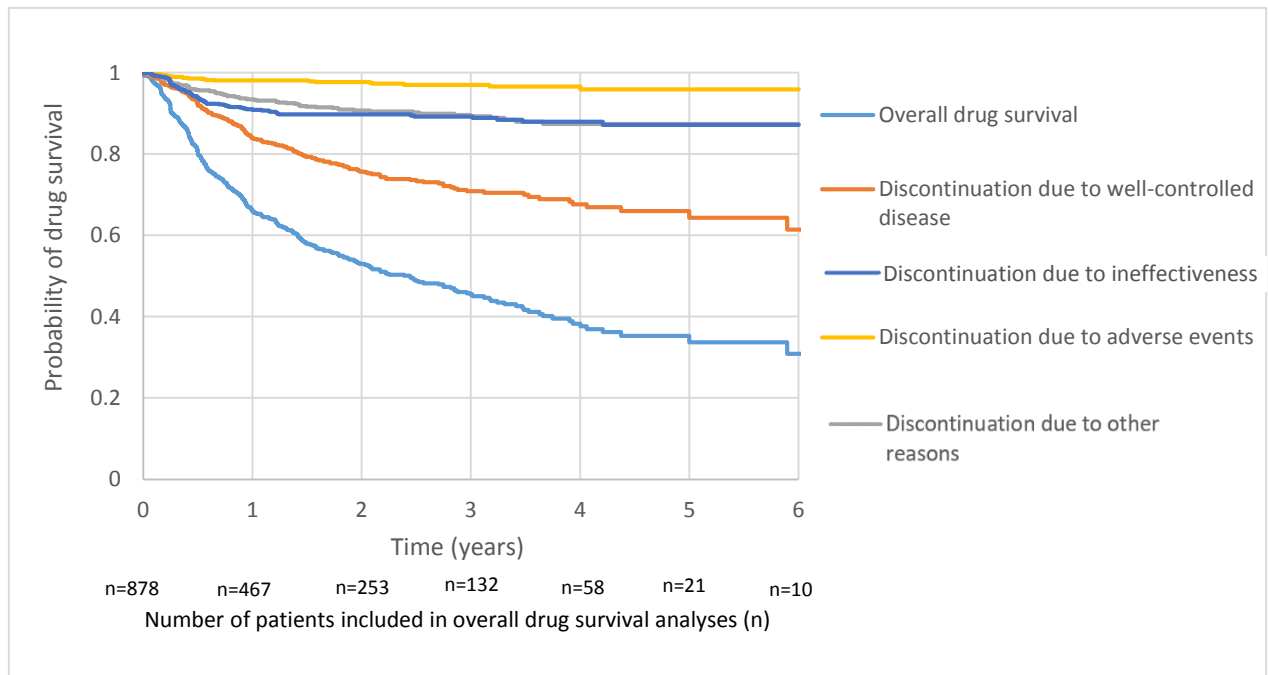
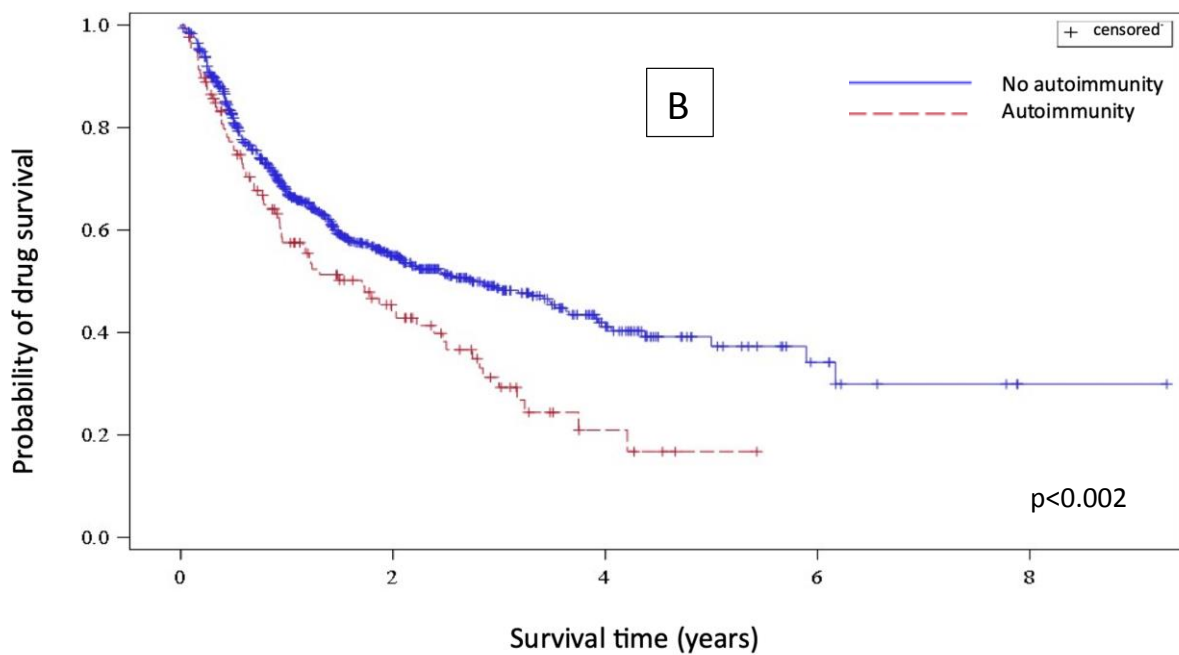
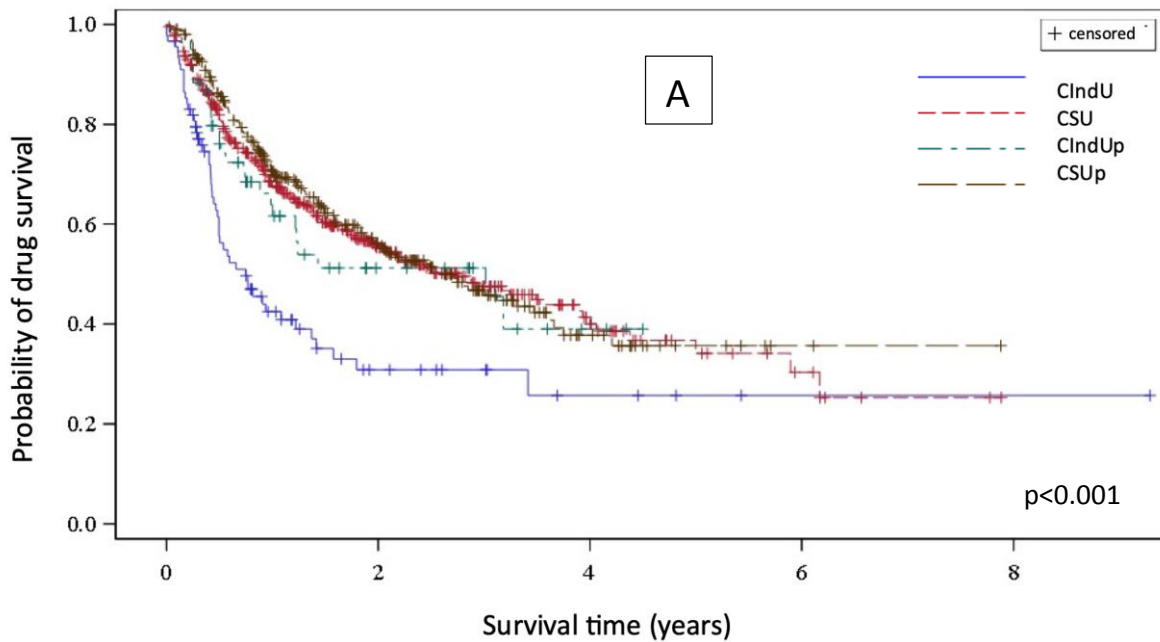
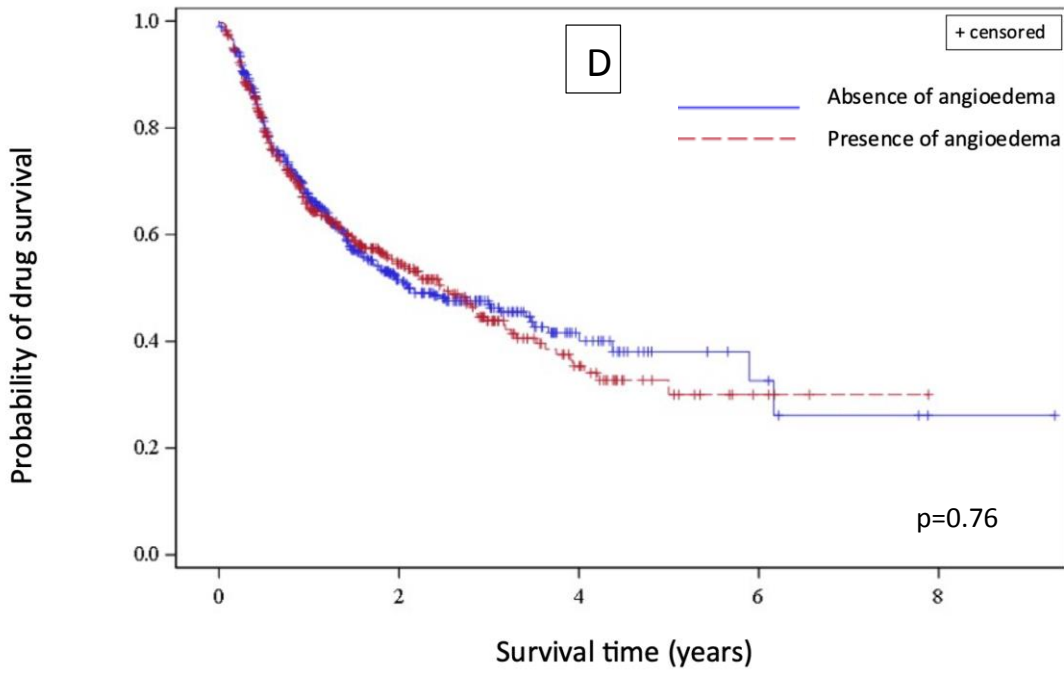
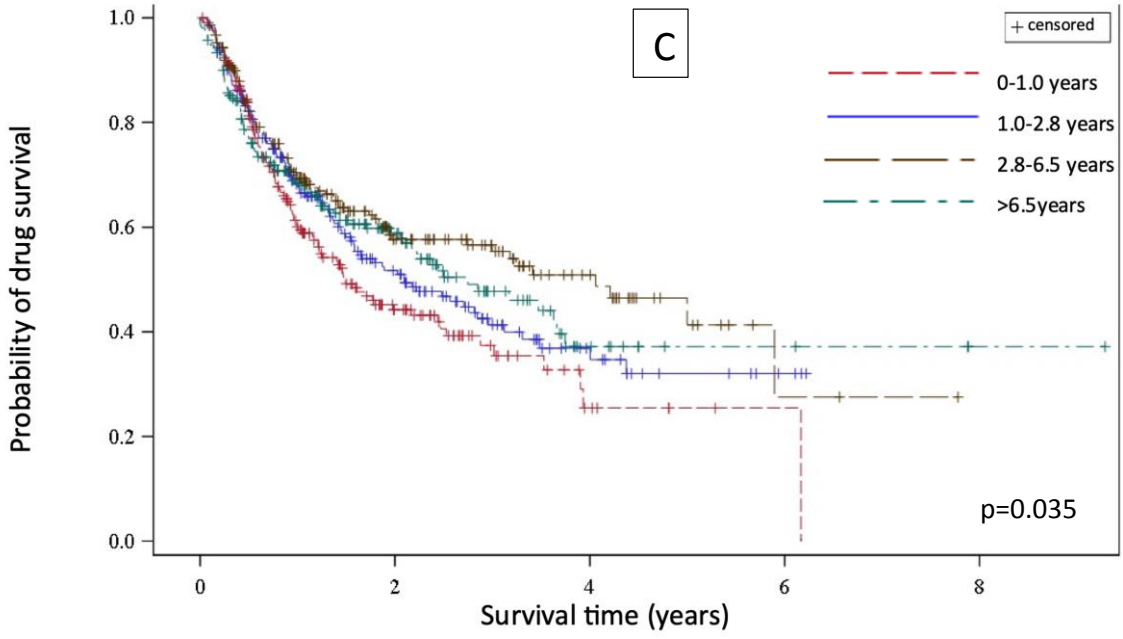


Figure 3: Analyses of overall drug survival of omalizumab according to subset of chronic urticaria (A), presence of an autoimmunity background (B), disease duration at omalizumab initiation (C), presence of angioedema (D) and previous medication with corticosteroids (E)





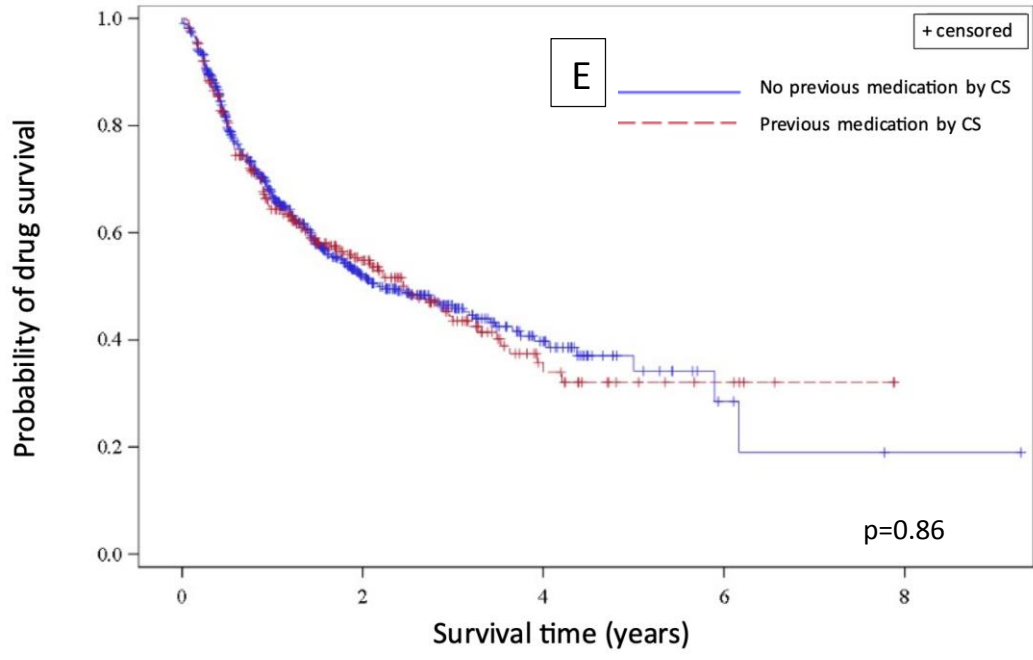
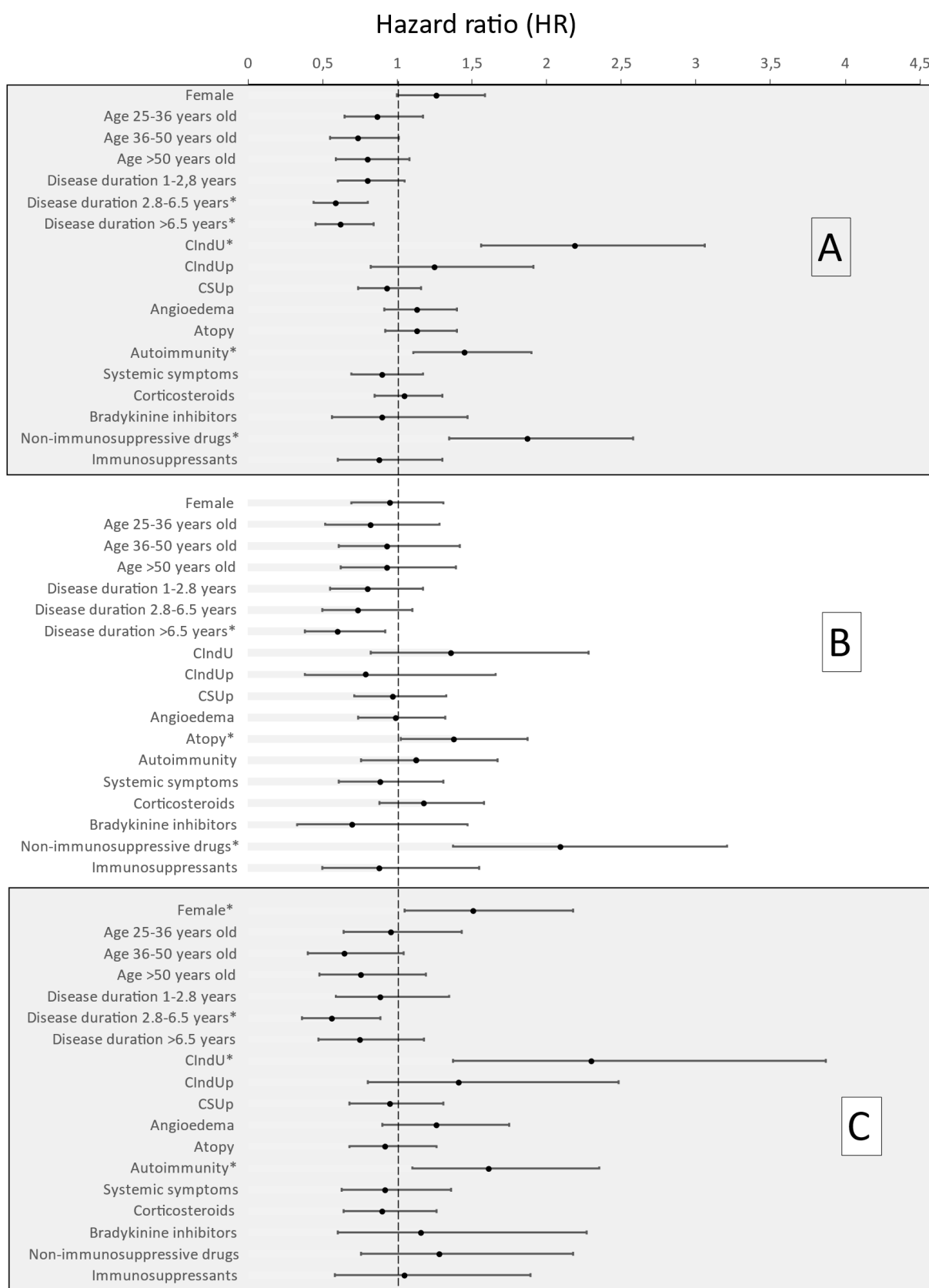


Figure 4: Analyses of the determinants of the drug survival of omalizumab in overall population (A) and in subgroup of patients who discontinued for having achieved a well-controlled disease (B) or for any other reason (C)



Repository text:

Data recorded were the following: age, gender, type of CU, presence of angioedema, atopy background (asthma, allergic rhinitis, atopic dermatitis, food allergies), autoimmunity background (autoimmune comorbidity or detection of asymptomatic antinuclear or antithyroid antibodies), systemic symptoms (arthralgia or digestive symptoms), previous medications (antihistamines, corticosteroids, bradykinin inhibitors, non-immunosuppressive drugs such as hydroxychloroquine, colchicine, dapsone, salazopyrin immunosuppressants such as methotrexate, ciclosporin, mycophenolate mofetil, azathioprine, leflunomide), date of CU onset, date of introduction, discontinuation and rechallenge of omalizumab, initial response to omalizumab (using PGA, UCT, UAS7 scores), reason to discontinuation, adverse events, omalizumab status and disease activity (using PGA, UCT, UAS7 scores) after 1 to 5 years of follow-up

Figure E1 : Omalizumab dosages at 1 to 5 years in patients still treated with omalizumab

Standard dosage: 300mg every 4weeks, lower-than-standard dosage: intervals between injections over 4 weeks and/or dose injected < 300mg, higher-than-standard dosage : injections of more than 300mg and/or intervals between injections <4weeks

N = number of patients still treated by omalizumab after 1 to 5 years, WCD well-controlled disease.

Table E1: Most frequently reported adverse events, leading or not to discontinuation of omalizumab.

| | Number of adverse events occurrences n (%) | Number of adverse events leading to discontinuation n (%) |
|-------------------------------|---|--|
| Headache | 38 (4.3) | 6 (15.8) |
| Arthromyalgia | 34 (3.9) | 14 (41.2) |
| Asthenia | 23 (2.6) | 8 (34.8) |
| Injection point skin reaction | 13 (1.5%) | 5 (38.5%) |
| Digestive disorder | 13 (1.5%) | 4 (30.8%) |
| Weigh gain | 9 (1.0%) | 2 (22.2%) |

Figure E1: Omalizumab dosages at 1 to 5 years in patients still treated with omalizumab

