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Étude de survie de l'omalizumab dans l'urticaire chronique : une étude française rétrospective, multicentrique

Julie Litovsky

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UNIVERSITE DE MONTPELLIER
FACULTE DE MEDECINE MONTPELLIER-NIMES

THESE

Pour obtenir le titre de

DOCTEUR EN MEDECINE

Présentée et soutenue publiquement

Par

Julie LITOVSKY

Le 20 septembre 2021

XO-DS

**Etude de survie de l'omalizumab dans l'urticaire chronique :
Une étude française rétrospective, multicentrique.**

Directeur de thèse : Dr Aurélie DU-THANH

JURY

Président :

Pr DEMOLY Pascal (PU-PH)

Assesseurs :

Dr DU-THANH Aurélie (MCU-PH)

Dr MARIA Alexandre (PH)

Dr HACARD Florence (PH)

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Partie 1 : Avant-propos

L'urticaire chronique est une maladie dermatologique fréquente qui atteint environ 1 % de la population(1,2). Elle associe des papules ou plaques érythémateuses migratrices et prurigineuses et/ou des angioœdèmes qui persistent au minimum 6 semaines. Elle peut être spontanée (CSU) et/ou induite par différents stimuli (CIndU), par exemple : la friction (dermographisme), les vibrations, l'exposition solaire, le froid, la chaleur, l'activité physique (urticaire cholinergique), la pression, l'eau(3). Si la majorité des urticaires se résout en moins de 5 ans, il existe de grandes variations inter-individuelles et certaines peuvent durer jusqu'à plusieurs dizaines d'années(4–6).

Les lésions d'urticaire résultent d'une activation des mastocytes cutanés et des basophiles entraînant la libération de médiateurs inflammatoires tels que l'histamine, les leucotriènes, les prostaglandines, le facteur d'activation plaquettaire ou diverses autres cytokines. Ces médiateurs provoquent l'activation de nerfs sensitifs, une vasodilatation et une extravasation de plasma. Tous les signaux activateurs des mastocytes ne sont pas bien définis et les voies d'activation sont probablement hétérogènes(3). Environ la moitié des patients avec une CSU ont des auto-anticorps dirigés soit contre les IgE soit contre leur récepteur de haute affinité FcεRI, présent sur les mastocytes et basophiles. D'autres patients auraient une dérégulation non-immunologique de voies de signalisation intracellulaire des mastocytes et basophiles(7,8). On note également une basopénie périphérique et des taux élevés de basophiles dans les lésions d'urticaire suggérant leur recrutement cutané(9).

Bien qu'il n'existe pas de risque vital, l'urticaire chronique peut induire une surconsommation de soins médicaux et avoir un retentissement majeur sur la qualité de vie. En effet, une perturbation des activités quotidiennes, une altération de la productivité au travail (présentéisme ou absentéisme), des troubles du sommeil, une majoration de l'anxiété et des troubles de l'humeur ont été largement rapportés(10–12).

Le traitement repose en première intention sur la prise d'antihistaminiques anti-H1 (AH1) de 2^{ème} génération à la dose usuelle (1 comprimé par jour), qui peut être augmentée en 2^{ème} intention jusqu'à 4 doses par jour en cas de réponse insuffisante ou d'échec thérapeutique. En 3^{ème} intention, les recommandations internationales de 2018 préconisent l'utilisation additionnelle d'omalizumab (XOLAIR®) avec une très bonne efficacité et tolérance (3,13). Il s'agit d'un anticorps monoclonal humanisé de type IgG1 dirigé contre les IgE qui a l'autorisation de mise sur le marché

depuis 2014 pour l'urticaire chronique et coûte environ 700€/mois. La posologie autorisée (AMM) en Europe est de 300mg par voie sous-cutanée toutes les 4 semaines(14).

Le mécanisme exact de l'omalizumab reste mal compris. Il se lie à la fraction constante des IgE, inhibant sa liaison avec son récepteur FcεRI. Il en résulte une augmentation du taux d'IgE totales mais une diminution du taux d'IgE libres, ce qui induit une régulation négative des récepteurs FcεRI au niveau des basophiles et mastocytes(7). Une hypothèse mécanistique est la modification du comportement des basophiles par l'omalizumab avec une diminution de la densité des FcεRI et IgE sur les basophiles, affectant possiblement leur migration dans la peau(15,16).

Si les recommandations européennes sont claires sur les indications de l'omalizumab (échec ou réponse insuffisante avec des antihistaminiques à dose augmentée), il n'existe pas de recommandation sur les modalités d'arrêt.

En France, contrairement à d'autres pays européens, il est possible de prescrire l'omalizumab sans restriction de durée. De fait, les pratiques des différents prescripteurs (dermatologues, pneumologues, pédiatres, internistes) paraissent très variables en termes d'interruption de l'omalizumab : certains espacent les injections ou diminuent les doses avant arrêt, d'autres non.

L'objectif de ce travail était d'évaluer les modalités d'utilisation et d'interruption de l'omalizumab en vie réelle dans des centres spécialisés français de prise en charge de l'urticaire chronique depuis la mise à disposition de ce traitement dans cette indication.

Nous avons recueilli les données de l'étude concernant 878 patients, via le Groupe thématique Urticaire de la Société Française de Dermatologie (GUS) et grâce à la participation des praticiens en charge des consultations spécialisées dans l'urticaire chronique de 9 centres hospitalo-universitaires (Bordeaux, Grenoble, Lille, Lyon, Montpellier, Nantes, Paris, Rouen, Saint-Etienne). Une analyse de type « *drug-survival* » a été menée avec ces données.

Partie 2 : Article

I. Introduction :

Chronic urticaria (CU) is defined as itchy and fleeting wheals and/or angioedema (AE) that persist during at least 6 weeks and result of the activation of skin mast cells (3). Overall life-time prevalence of chronic urticaria is estimated at 1.4% [0.8-2.2] with geographic, sex and age variations (1)(2). Alteration of daily activities and work productivity (through absenteeism or presenteeism), sleep disturbances, associated anxiety and depression, medical cost were widely reported(10–12).

Cutaneous lesions result from the activation of skin mast cells and basophils and the release of inflammatory mediators such as histamine, platelet activating factor (PAF) and various cytokines leading to sensory nerve activation, vasodilatation, and plasma extravasation. Mast-cells activation signals are not well defined and are probably heterogenous(3).

Two major mechanisms are evoked. First is non autoimmune dysregulation of intracellular signalling pathways within mast cells and basophils that leads to defects in trafficking or function of these cells. Second involves the presence of auto-antibody directed against either IgE or FcεRI, their high affinity receptor on basophils and mast cells(7,8). Role of basophils is also suggested by the high levels of basophils observed in skin lesions and the increase of basophil counts in peripheral blood from patients treated with omalizumab(9).

Chronic urticaria can be spontaneous (CSU) or inducible (CIndU) whenever urticaria appears in response to a specific trigger, for instance cold, heat, water, friction, sun, vibration, pressure, exercise. In both forms, first line therapy involves avoidance of eliciting factors, if known, and antihistamines administration up to four-fold the standard dose. When CSU is refractory to up-dosed antihistamines, which can occur in 53.8% to 83.1% cases(17), omalizumab can be prescribed according to the 2018 European recommendations, before cyclosporin A(3).

Omalizumab is available since 2014 in this indication and commercialized since 2005 for asthma in Europe. It is an IgG1 monoclonal antibody targeting IgE. Licensed dose is 300mg in Europe and 150 or 300mg in the US administered every 4 weeks subcutaneously(14,18). Cost approaches 700€/months excluding nurse fees. The real-life observational study AWARE found out that a third of antihistamine refractory CSU patients will be treated with omalizumab(17).

Efficacy and safety have already been demonstrated for CSU in clinical studies (13,19,20) and real-life large cohorts of patients (21–29). Even though it is not approved for ClndU, case series have also shown some efficacy in this indication(30). A 6-month-treatment duration is proposed before evaluating the efficacy and discontinuing the treatment in the absence of response(3,31). Although CU can resolve spontaneously in most patients within 5 years(4–6), disease duration can widely vary between patients. Known prognostic factors of longer disease are the following: associated or isolated ClndU, angioedema, late onset, long disease duration at the time of diagnosis(5,32,33).

Exact mechanisms of omalizumab efficacy are still unclear though. It binds to the constant region of the IgE molecule, inhibiting its binding to FcεRI. As a result, total IgE levels in peripheral blood increase but free IgE are reduced to very low levels, thus down regulating FcεRI on basophils and mast cells(7). A proposed mechanism of action is that omalizumab may lower the density of FcεRI and IgE on basophils, possibly affecting their migration(15,16).

Optimal duration of treatment with omalizumab is unknown and not discussed in European recommendations(3). Therefore, discontinuation modalities differ between physicians.

We aimed to evaluate the drug survival of omalizumab in patients treated for CU in a multicentric French cohort and explore its potential determinants. Drug-survival analysis combines the evaluation of efficacy, tolerance, patients' and doctors' preferences and is commonly used to assess therapies in chronic skin disease(34).

II. Materials and methods

We performed a retrospective, multicentric, observational study. Data collection was carried out in 9 French centres (Bordeaux, Grenoble, Lille, Lyon, Montpellier, Nantes, Paris, Rouen, Saint-Etienne) between January 30th, 2020, and January 30th, 2021. They are all referral centres and members of the urticaria study group of the French dermatology society (GUS, groupe urticaire de la société française de dermatologie).

Patients diagnosed between 2005 and 2020 with CSU and/or CIndU according to the EAACI recommendations and who received at least one injection of omalizumab were included. The first omalizumab injection occurred in December 2009. There were no restrictions on gender or age. Exclusion criteria included: lack of data (unknown initiation and discontinuation date of omalizumab and no data at follow-up), other diseases (vasculitis, aquagenic pruritus sine urticaria, neutrophilic urticaria, hereditary AE), omalizumab initiated for another indication (asthma or tolerance induction).

Screening was performed day-to-day through consultations follow-up or by informatic research using the keywords “urticaria AND omalizumab” or “urticaria AND Xolair”.

We collected available data in patients’ medical records regarding age, gender, type of CU, presence of AE, atopy (asthma, allergic rhinitis, atopic dermatitis, food allergies), autoimmunity (autoimmune comorbidity or detection of asymptomatic antinuclear or antithyroid antibodies), systemic symptoms (arthralgia or digestive symptoms), previous medications, date of CU onset, date of introduction, discontinuation and rechallenge of omalizumab, initial response to omalizumab, reason to discontinuation, adverse events, omalizumab status and disease activity after 1 to 5 years of follow-up.

Types of CU were divided in 4 categories: chronic spontaneous urticaria (CSU), chronic inducible urticaria (CIndU), and when both subsets were present, designated as either predominant CSU (CSUp) or predominant CIndU (CIndUp).

Previous medications were recorded in 5 categories: (i) antihistamines and leukotrienes receptor antagonists (AH/LTRAs); (ii) corticosteroids (CS), either occasional or long-term use; (iii) bradykinin antagonists and tranexamic acid (BA); (iv) immunomodulators (IM) including hydroxychloroquine, dapsone, colchicine, salazopyrin; (v) immunosuppressive therapies (IS) including methotrexate, ciclosporin, mycophenolate mofetil, azathioprine, leflunomide.

Validated tools to evaluate dermatological diseases, such as the modified Practitioner Global Assessment (PGA)(29,35), and specific urticaria evaluation tools, such as urticaria control test (UCT) and urticaria activity score (UAS7)(3,36,37), were used to evaluate initial response to omalizumab and disease activity at 1 to 5 years follow-up.

As recommended by experts' opinion(38) and reported in pivotal studies(13,19,20), response to omalizumab was evaluated at 6 months and defined as complete response (CR), partial response (PR), no response (NR). We added Worsening Disease (WD) which was reported in daily practice. CR was defined as an improvement of more than 90% (PGA 0 or 1), and/or $UCT \geq 12$ and/or $UAS7 \leq 6$. PR was defined as an improvement of 30-90% (PGA 2, 3, 4) and/or $UCT \leq 11$ and/or $UAS7 > 6$ but significant improvement of UCT (≥ 3 points) and/or $UAS7 (\geq 10$ points)(22). NR was defined as an improvement of less than 30% (PGA 5) and/or $UCT \leq 11$ and/or $UAS > 6$ and no significant improvement of UCT or UAS7. Worsening disease (WD) was defined as disease aggravation (PGA 6) or significant aggravation of UCT and/or UAS7. Patients were classified as quick or late responders (QR, LR) if CR was obtained before or after the 2nd injection of omalizumab, respectively.

Likewise, disease activity was classified as well-controlled disease (WCD) in case of $>90\%$ disease control (PGA 0 or 1), and/or $UCT \geq 12$ and/or $UAS7 \leq 6$; Mild to moderate disease (MD) in case of disease activity between 30-90% (PGA 2, 3, 4) and/or $UCT 8-11$ and/or $UAS7 7-27$; Uncontrolled disease (UD) in case of $<30\%$ disease control (PGA 5) and/or $UCT \leq 7$ and/or $UAS7 28-42$ (39).

Omalizumab status at 1 to 5 years of follow-up was recorded as follow: (i) standard dose (300mg every 4 weeks); (ii) optimized dose defined as up dosing each dose or narrowing the injection intervals; (iii) spaced dose defined as more than 4 weeks between each injection; (iv) diminished dose and (v) diminished and spaced dose defined as a decreased dose under 300mg every 4 or more weeks; (vi) unknown dosage.

Reasons to discontinuation were divided in: (i) well-controlled disease, (ii) inefficacy, (iii) adverse events, (iv) apparition of contraindication, (v) personal and organisational motives. Apparition of contraindication included pregnancy (desired or ongoing) and intercurrent illness. In case of multiple reasons to discontinuation, we prioritized inefficacy over adverse events and adverse events over well-controlled disease for categorizing patients.

Numbers and percentages were used to describe qualitative data. Means, standard deviations, minimum and maximum were used to describe quantitative data. Chi² and Fisher tests were used

to compare qualitative data and Wilcoxon and Mann-Whiney tests were used for quantitative data.

Overall drug survival was performed using Kaplan-Meier survival curves. The event was the first discontinuation of omalizumab. Drug-survivals for each reason of discontinuation (well controlled disease, inefficacy, adverse events, and others) were analysed using cumulative incidence functions that consider other motives of discontinuation as competitive risks.

We identified the following candidate determinants of drug survival: sex, age, disease duration in quartiles, type of CU, AE, atopy, autoimmunity, systemic symptoms, and previous therapies.

Determinants of overall drug survival were analysed using Kaplan-Meier curves and compared using Logrank test. Hazard ratio and confidence intervals were determined in a univariate and multivariate Cox model.

Determinants of drug survival in discontinuation due to well-controlled disease and discontinuation due to other reasons were estimated considering competitive risks and compared using Gray's test. Subhazard ratio and confidence intervals were estimated in univariate and multivariate Fine and Gray model.

The study protocol was approved by institutional review board (2019_IRB-MTP_07-13). Patients did not object to the use of their clinical data for this study. The study is registered with ClinicalTrials.gov (NCT04584190).

III. Results

1. Population

Out of the 1021 screened patients, 878 were retained for analyses (Figure 1). Baseline characteristics are reported in Table 1. CSU was the only or main form of CU in 82.8% patients. 10.1% were isolated CIndU. CIndU patients were significantly more often males (53.9% versus 27.3%) and younger than CSU (mean age 29.4 versus 42.1 years old). On the contrary, AE, presence of systemic symptoms and previous CS administrations were more often observed in CSU patients; respectively 54.0%, 23.1% and 34.8% versus 10.1%, 8.1% and 13.5% for CIndU. Omalizumab was introduced more rapidly after the onset in CSU patients (4.8 versus 7.1 years in CIndU). Demographic characteristics of CSUp and CSU patients were alike. CIndUp patients were like CIndU in terms of younger age at onset and longer disease duration before introduction of omalizumab, but sex ratio and presence of systemic symptoms were rather like CSU patients. CIndUp had more AE and more previous CS than CIndU but less than CSU. The presence of a background of atopy or autoimmunity did not differ between the types of CU. CIndU patients and CIndUp tend to be more often treated by immunomodulators ($p=0.056155$).

CIndU ($n=89$) included 44 patients with cold contact urticaria, 26 with cholinergic urticaria, 9 with symptomatic dermographism, 5 with solar urticaria, 4 with pressure urticaria and 1 with vibratory urticaria. CIndUp ($n=62$) included mostly pressure urticaria ($n=19$), symptomatic dermographism ($n=18$) and cholinergic urticaria ($n=17$). CSUp ($n=299$) were more often associated with symptomatic dermographism ($n=221$), pressure urticaria ($n=87$) and cholinergic urticaria ($n=32$). (Supplementary data – Fig 9S)

2. Initial response to omalizumab

Six months after the 1st injection of omalizumab, 75.6% patients had a complete response (CR) with 62.9% quick response (QR) and 12.7% a late response (LR); 14.6% of the patients had a partial response (PR), 8.7% no response (NR), and 1.2% a worsening disease (WD). The latter were significantly older (50.3 versus 34.5 to 41.1 years old for the other categories, $p=0.008$).

Initial response rate differed between CU subtypes ($p=0.0103$). A higher rate of QR along with CR was observed in CSU and CSUp versus CIndU and CIndUp (63.4 and 65.4% versus 53.2 and 56.3%, respectively). The highest rate of NR was observed in CIndU (18.4% versus 6.6 to 8.1%) and the highest rate of PR was observed in CIndUp (27.4 versus 11.8 to 15.7%). Patients with autoimmunity had less CR (65.1% vs 76.8%) and less QR (51.6% vs 64.4%). ($p=0.0350$) (Table 2). CR did not differ between patients with or without AE (72.3% versus 78.2%, $p=0.3129$). There

was no difference in response rates based on gender, time to introduction of omalizumab, atopy, systemic symptoms, or previous therapies.

In CIndU patients, 25 patients out of 44 with cold urticaria had a QR/CR, versus 12 out of 26 with cholinergic urticaria, 4 out of 9 with symptomatic dermatographism and 8 out of 10 with other CIndU subtypes. (Supplementary data – Fig 10S)

3. Discontinuing omalizumab: reasons and drug-survival

In total, 408 (46.5%) patients discontinued omalizumab during the study time. Main reason for discontinuation was well-controlled disease (WCD) in 203 (23.1%) patients, followed by inefficacy in 88 (10.0%) patients, apparition of contraindication in 44 (5.0%) patients, personal and organisational motive in 35 (4.0%), patients and adverse events in 23 (2.6%) patients. Reason to discontinuation did not differ based on disease duration, type of CU, presence of AE, history of atopy, autoimmunity or systemic symptoms, previous therapies. Women discontinued because of apparition of contraindication more often (14.5% versus 1.9% in men, $p=0.014$). Patients who discontinued omalizumab due to personal and organisational motives or apparition of contraindication were younger than those discontinuing for WCD, inefficacy or adverse events, respectively 33.5 (± 14.8) and 32.7 (± 15.7) years old versus 38.3 to 42.8 years old ($p=0.038$).

Respectively, 66%, 53%, 45.4%, 38.3%, 33.7% and 30.9% patients were still receiving omalizumab at 1, 2, 3, 4, 5 and 6 years. Most discontinuations because of inefficacy occurred during the first year (9.1% versus 3.8% during all the following years combined). For adverse events, discontinuation was slightly more regular with 1.9% discontinuation during 1st year and 0.4 to 0.7% during following years. (Figure 2)

Shorter drug-survival (DS) was associated with CIndU, autoimmunity and IM whereas longer DS was associated with longer disease duration in both univariate and multivariate overall analyses. (Figure 3, 4, 5, 6) Patients aged between 36-50 years old had a longer DS in univariate analysis only (HR 0.7 [0.5-0.9], $p = 0.0199$). There was no difference of overall DS based on gender, AE, atopy, systemic symptoms, and previous therapy by CS, BA or IS.

Shorter DS was associated with atopy (HR 1.4 [1.0 – 1.9], $p=0.0406$) and previous IM (HR 2.2 [1.4-3.5], $p=0.0007$) in patients who discontinued because of WCD. Shorter DS was found in CIndU (HR 2.5 [1.4 – 4.5], $p=0.0034$), autoimmunity (HR 1.5 [1.0-2.3], $p=0.0429$) and females (HR 1.5 [1.0-2.2], $p=0.0469$) in the patients who discontinued because of other reasons. (Figure 6)

There was a non-significant trend of longer DS when disease duration was over 6.5 years (HR 0.6 [0.4 – 1.0], p=0.05) in patients who discontinued because of WCD. Longer DS was found in patients with disease duration between 2.7-6.5 years (HR 0.5 [0.3-0.8], p=0.0063) when omalizumab was discontinued because of other reasons. (Figure 6)

In sub analyses based on reason to discontinuation, there were no difference of DS based on age, AE, systemic symptoms, previous therapy by CS, BA or IS.

4. Retreatment

Out of the 408 patients who discontinued omalizumab, 196 (48.0%) were further retreated. There was no difference in retreatment occurrence based on the type of CU, atopy, autoimmunity, systemic symptoms. Initial response to omalizumab influenced retreatment (p<0.000001) with a decreasing chance of retreatment in case of QR/CR (62.5%), PR (47.1%), LR/CR (31.9%), NR (12.7%) or WD (0%). Disease duration before 1st injection of omalizumab was higher in patients who further needed retreatment (5.2 ±5.9 versus 4.8 ±7.7 years, p <0.004).

Mean time to retreatment was 7.4±7.7 months (min 2; max 42 weeks) with similar efficacy in at least 144 (73.1%) of the patients, even better efficacy in 3 (1.5%) patients and lower efficacy in 12 (6.1%) patients. Data was missing for other patients. In CIndU and CIndUp patients further retreated with omalizumab (n=45), efficacy was similar or even better in 71.1% patients.

Among patients with initial NR, 8 were further retreated. They had had a shorter duration of initial treatment with omalizumab (less than 6 months) and had never undergone optimized dosage. Two of them had cholinergic urticaria associated with CSU and had a PR after omalizumab was re-challenged at optimized dose. Two of them had symptomatic dermographism associated with CSU and did not improve after re-treatment. Another patient had discontinued omalizumab before the 6th injection because of pregnancy and retreatment after childbirth was effective. Lastly, retreatment in 3 other patients did not prove effective.

5. Follow-up

Follow up ranged from 3 months to 10 years (mean 2.3years). Disease activity was consistent over time during the 5 years follow-up: well-controlled disease (WCD) represented 66.1% to 69.2% of the patients, mild to moderate disease (MD) 17.1% to 20.1% and uncontrolled disease (UD) 2.5% to 5.5%.

The rate of patients undertaking standard dosage decreased from 40.9% to 25.5% whereas the rate of patients treated with spaced doses increased from 35.7% to 54.5%. A minority of patients

had a diminished dose of omalizumab over the years (2.4% to 5.4%). Patients receiving standard dose, spaced dose, reduced dose with or without spacing mostly had WCD (70% or more). Patients with optimized dose of omalizumab had more often a MD from 40% at 1 year to 75% at 5 years. (Figure 3) The mean maximal spacing in patients receiving spaced doses during several years was 7.6 ± 4.1 weeks (min 2 weeks; max 52 weeks).

Most patients with WCD received standard (35.8% to 20.0%) or spaced dose, but the latter increased over the years (35.3% to 57.8%), similarly to overall analyses. (Supplementary data – figure 11S)

Patients with MD appeared to be a heterogenous population with no significant predominance in patients treated with standard dose, spaced dose, optimized dose and discontinued omalizumab. (Supplementary data – figure 12S).

Most UD did not receive omalizumab at time of evaluation (>75% during year 1 to 4). The effectives in this population were small (n= 40 after 1 year and n= 16 after 3 years): those patients either discontinued omalizumab due to inefficacy (42.5% after 1 year and 12.5% after 3 years) or had an initial complete response and a subsequent relapse at discontinuation (27.5% after 1 year and 43.8% after 3 years). (Figure 4)

In the group of 88 patients which discontinued omalizumab due to inefficacy, data regarding the subsequent treatments were available in 41 patients: 16 (39.0%) received cyclosporin A; 25 (61.1%) received methotrexate and 4 (9.8%) received colchicine. Cyclosporin A was effective in 4 patients and methotrexate was effective in 9 patients.

6. Adverse events

Adverse reactions were reported in 104 (11.9%) patients. The most frequently reported adverse event was headache (4.3%) which rarely led to discontinuation (15.8%). On the contrary, arthromyalgia (3.9%) often led to discontinuation (41.2%). Adverse events reported in >1% of the patients were asthenia, injection point reaction, digestive disorders, and weight gain. (Table 3) Other adverse events reported in <1% patients were dizziness, alopecia, hypotension, flushes, sensation of chest oppression. No anaphylactic event was reported.

IV. Discussion

1. Population

Our population had similar demographic characteristics to previous studies with a predominance of middle-aged women, associated atopy or autoimmunity and less AE in ClndU(40–42).

We chose to categorize patients into four distinct groups, namely CSU, CSUp, ClndU and ClndUp, because it seemed relevant in clinical practice. In the end, it appears that CSUp finally seemed to be like CSU in terms of demographic characteristics. However, contrary to previous observations (40,43), female patients did not prevail in ClndU. This could be explained by the choice we made to separate ClndU from ClndUp. In ClndU, main subsets were cold contact urticaria and cholinergic urticaria. In cold contact urticaria, female predominance is not as important as in CSU with a mean proportion of women of 62%, ranging from 33% to 91% in up to 1379 patients from 28 previous studies (44). In cholinergic urticaria, previous studies showed a male predominance(45–50). On the contrary, ClndUp, mainly symptomatic dermographism and delayed pressure urticaria, differentiated from ClndU by a higher female/male ratio. ClndUp also had more often systemic symptoms and more AE than ClndU but less autoimmunity and AE than CSU. Effectives of ClndU and ClndUp remained small, classification of spontaneous or inducible predominance was declarative and we did not record diagnostic methods of ClndU (based on interrogation or standardized tests).

Compared to a large previous real-life study, we found a higher rate of ClndU (10.1% versus 5.1%) and concomitant CSU and ClndU (41.1% of ClndUp/CSUp versus 24,9% ClndU+CSU).(40) This could be explained by our recruitment in expert centres with trained practitioners and thorough investigations for ClndU including provocation tests, as suggested in a recent survey among GUS experts(51).

French specialists agreed to avoid CS prescriptions as much as possible and only 23% declared to exceptionally prescribe short course of CS(51). Patients in this study seemed to have been prescribed CS more often (35%), but it could reflect prescriptions made prior the referral to specialized centres. Higher prescriptions of CS in CSU and CSUp compared to ClndU was also found in previous studies(29).

Response rate to up-dosed AH in ClndU has previously been estimated at 60%. (50) If the use of omalizumab in antihistamine-resistant ClndU is growing, alternatives such as hydroxychloroquine, immunoglobulins, or tranexamic acid were alternately proposed in case of

antihistamine resistant CIndU(52). Approval of omalizumab in CSU rather than CIndU might have led to quicker use of omalizumab in CSU and more use of alternatives in CIndU, explaining the trend to more previous treatment by IM in CIndU and CIndUp. Earlier use and approval in CSU may also explain the shorter disease duration before omalizumab introduction, similarly to Sperkhorst et al.'s findings(39).

2. Initial response to omalizumab

Our findings are consistent with a meta-analysis by Tharp et al. of “real-world” evidence of articles published between January 1st 2006 and January 1st 2018. 67 articles were included combining around 1200 patients in total. CR occurred in 72.2% patients, PR in 17.8% patients and NR in 7% patients(21). Real-life experiences published after 2018 also showed similar response rates(22–24,53).

Previous studies found that omalizumab at 300mg can be effective in reducing AE and burden disease in CSU patients(54,55). Higher proportions of CR was found in patients without AE but difference was not significant in neither studies which is consistent with our findings(29,56).

Contrary to Sperkhorst et al.(39), response to omalizumab differed between sub-groups of CU. As for demographic characteristics, CSUp had similar response to CSU but CIndUp had more PR and CIndU had more NR than CSU/CSUp. Even though effectives were small, some studies suggested poorer response to omalizumab in cholinergic urticaria (30,57), which could explain the high NR rate in CIndU. For CIndUp, a PR could be explained by a dissociative response between CSU and CIndU. One study found a good overall response in 58/80 CIndU patients with a significant poorer response in symptomatic dermographism and late response in cholinergic urticaria. The authors note that up dosing might benefit non-responding patients (58). The dose of omalizumab at 6 months in CIndU was not recorded and poor response observed in our study may result from lack of up dosing.

A trend of better efficacy of omalizumab in older patients was described by Ghazanfar et al. (29) and, in a larger population, the difference was significant in our study. It can correlate to CSU patients being older than CIndU and better response rate observed in CSU. They also found a trend of better efficacy of omalizumab in case of shorter disease duration which was not found in our patients. However, longer disease duration has been previously described as predictive of longer time to remission and more severe disease(59–61).

Impact of autoimmunity on response to omalizumab is not clear, high levels of anti-tissue factor IgE and IgG have been previously linked to rather late response(62). Patients with anti-TPO IgE antibodies seemed to experience quicker response whereas late responders were thought to have IgG antibodies against FcεRI(8,63,64). Another study found no difference between patients with or without thyroid autoimmunity in terms of quick or late response (65). In our study, patients with autoimmunity, defined as an autoimmune comorbidity or asymptomatic presence of antinuclear or antithyroid antibodies, do not respond as well to omalizumab. However, the definition of autoimmunity and diagnostic methods in previous studies are not consistent.

Previous studies found that patients with baseline IgE levels <43 UI/L, no increase in baseline/4weeks IgE levels, lower baseline FcεRI and IgE density on basophils and mast cells and very low absolute number of circulating basophils, high plasma C3 levels, high protein C reactive, associated obesity or HTA may be prognostic markers of poor response to omalizumab. Positive tests detecting auto-antibodies (Basophil Histamine Release Assay or Autologous Serum Skin Test) seem to correlate with slower response to omalizumab(7,66,67).

3. Discontinuing omalizumab

Our findings regarding drug-survival are consistent with previous studies with 56 and 77% of patients still receiving omalizumab at 1 year(29,39,68). Treatment failure after initial good response is scarce with few discontinuations due to inefficacy after 1 year.

Contrary to Spekhorst et al. who found CIndU to be predictive of longer DS in CSU, (39) CIndU patients in our study had shorter DS. This could be explained by a population mainly composed of CSU (93%) in their study with 24% associated CIndU whereas our population of CIndU with shorter DS are CIndU only. We found a poorer response to omalizumab in CIndU explaining a shorter DS. In our population, CSUp DS did not significantly differ from CSU.

We identified new factors linked to DS. Longer disease was associated with longer DS. Autoimmunity was associated with shorter DS in overall analysis and discontinuation due to other reasons which could be explained by the poorer response we observed. Females was associated with shorter DS in discontinuation due to other reasons only, probably linked to the desired or ongoing pregnancies. Atopy and previous IM were associated with shorter DS in patients who discontinued due to WCD, suggesting that atopic patients and patients who previously received IM are more likely to discontinue because of WCD.

Previous studies found reasons to discontinuation in the overall population to be WCD in 15 to 29%, inefficacy in 8.1 to 13% and adverse events in 1.2 to 5.8% (29,39,69) which is consistent

with our findings. We also categorized two new reasons: personal/organizational motives and apparition of contraindications, which included significantly younger patients and more females. This can be explained by pregnancy being the main contraindication occurrence because of limited data available to date. (70) Though the EXPECT pregnancy registry showed no evidence of an increase of major congenital anomalies among 250 pregnant women with asthma exposed to omalizumab so far(71). To be noted, even though data remain limited and further investigations are needed, the European recommendations regard omalizumab as a therapeutic option to be discussed during pregnancy in patients with CU(3,70).

A high relapse rate, ranging from 44% to 79.1% has been widely reported after direct discontinuation of omalizumab(29,69,72–76). Quick relapse is described with a mean ranging from 4.7 weeks to 3.2 months(20,57,69,75). Sussman et al. did not find patients treated with 150mg to have a higher relapse rate compared to those treated with 300mg but Ferrer et al. found more severe relapse in patients treated with 150mg only(75,77). The X-TEND study found similar relapse rate in patients who discontinued after 24 or 48 weeks suggesting some patients should be treated beyond 48 weeks(76). Lower relapse rate and longer time to relapse have been reported after a 2nd cycle of discontinuation, in Turkey and Italy, where omalizumab is prescribed in 6months cycles(69,73,74).

We found wide ranges of long-term remission from 7% in Ghazanfar et al. to 83% after 3 cycles of treatment in Di Bona et al.(29,73). Di bona et al. discussed the contribution of planned discontinuation after a 6-months therapy which allowed to identify up to 50% of patients with rapid and sustained response. They found higher relapse rate in case of positive ASST(73).

Higher probability of rapid relapse after omalizumab discontinuation was noted in patients with high baseline UAS7, with longer duration disease and with slower initial response(77,78). Although IgE levels previously did not impact relapse rate, Ertas et al. found faster relapse in patients with baseline total IgE levels over 100ku/l(73,79). There seemed to be different patients' profiles after discontinuation of omalizumab, according to the short or long delay to relapse or the absence of relapse at follow-up(79).

4. Retreatment

A high relapse rate led to recurrent questioning of retreatment modalities and efficiency. Over 80% efficacy at retreatment was reported in previous studies(75,80). Retreatment was mainly evaluated in patients who achieved complete symptom control whereas 24 patients in this study with a PR at 6 months were also retreated with similar, but no better, efficacy. Mean time to

response after omalizumab re-introduction was similar to that observed with initial treatment (75) or quicker in some smaller cohorts (81). Only two studies evaluated retreatment in CIndUs patients and also found good efficacy (57,82). Likewise, 71.1% of the 45 retreated patients with CIndU or CIndUp, alleged good efficacy in our study. In our study, a longer disease duration was associated with higher chances of retreatment which is an indirect marker of relapse rate but not of the delay to relapse.

5. Follow-up

During follow-up, we noted a stable proportion of WCD which contradicts the AWARE study in which patients obtained better control over the years : patients with uncontrolled disease (UCT<12) dropped from 78% to 28.7% after 2 years (40). Same control was obtained with lower doses of omalizumab (more spaced dosed and less standard dose). When WCD is achieved, further continuation or tapering of omalizumab is not consensual. Most practitioners in our study chose to lengthen dose intervals over reducing dosage or direct discontinuation in WCD. When recorded, range of maximal spacing was very wide, up to 1-year intervals in a patient with cold urticaria raising the possibility of on demand omalizumab in some patients. When maximal dose interval is obtained, or in case of poor tolerance of omalizumab, lowering dose could also be considered, as 150mg/4 weeks seems effective and sufficient in some patients(13,83).

Patients we classified in the PR group need more characterization in our opinion because this is a very heterogenous group, representing CSUp patients with dissociated response (WCD for their CSU but not for their CIndU), and/or patients with early relapse (end-of-dose effect) and/or patients with CU only partially improved with omalizumab. Likewise, UD patients seemed to regroup omalizumab resistant patients and patients with early or late relapse at omalizumab discontinuation.

6. Adverse events

Adverse events were specifically studied in 335 patients in pivotal study GLACIAL (20): the incidence and severity of adverse events were similar in omalizumab and placebo groups. The rates of adverse events were similar in the GLACIAL study and our study, respectively 11.1% and 11.9%. Discontinuation of omalizumab due to related adverse events remained scarce though they seemed higher in our study (5.8% versus 1.2% in GLACIAL). This may be related to a longer follow-up of patients in our study, to its real-life nature including unselected patients with possibly more comorbidities and to our choice of favouring adverse events above WCD while categorizing several simultaneous alleged reasons to discontinuation of omalizumab. Our

retrospective collection of data may have biased the recording of rather more severe adverse events which more often led to discontinuation. On the contrary, if not severe, some adverse events may not have been registered in this study: for instance, upper respiratory tract infections were significantly more frequent in the omalizumab group versus placebo in the GLACIAL study, while no such adverse events were reported in this larger series.

Most frequent adverse events reported by Tharp et al. were headaches, fatigue and injection site reactions which are consistent with our 4 more frequent reported adverse events. In 1314 patients, anaphylaxis was reported in 3 patients and adverse events rate was estimated at 4% (1 to 7%) with significant heterogeneity across studies(21). No previously unknown adverse events were declared in this large cohort.

7. Strengths and limitations

This study is a large real-life experience with a long follow-up involving trained specialists in referral centres across France, probably allowing a rather comprehensive insight of french CU patients referred to these centres for the initiation and follow-up of omalizumab treatment. Despite its off-label use in this indication, this study showed a significant number of patients with CIndU, for whom large series of treatment with omalizumab are rarely reported. To our knowledge, this is also the first time that predominant CSU or CIndU, when both forms are present, were distinguished beside “pure” CSU and CIndU. We believe this classification to be both valid because the diagnosis was made in referral centres mostly via provocation tests and relevant in clinical practice. Recording the background of atopy was also believed to be valid in such centres.

The main limitation in this retrospective study was the accuracy of the evaluation of the disease control, due to various available scores in medical records. For instance, UAS7 is a patient-oriented score which is not performed during visits, contrary to UCT or PGA or CU-Q2oL, and data related to UAS7 were frequently missing; UCT was first published in 2014, not immediately available in french, and thus rarely used during the first years of this study. Compared to other studies evaluating retreatment efficacy, we could not evaluate symptom control precisely but only PGA. Classification of autoimmunity is probably different in our study and in literature because we focused on the diagnosis of autoimmune diseases rather than performing ASST test.

This study underlines that the optimal pattern of omalizumab discontinuation to avoid further relapses is yet to be determined, because no valuable and affordable prognostic factors could be validated so far. After 6 months of standard dose treatment, several regimens should be

compared and evaluated in appropriate studies. (i) Discontinuing omalizumab followed by, in case of relapse, subsequent 6-month courses of omalizumab at standard dose could help to quickly identify patients entering long-term remission. (ii) Lengthening intervals between omalizumab administrations or tapering the dose of each administration could help to determine the individual optimal dose. (iii) Discontinuing omalizumab and using the delay to relapse to determine the appropriate length between two injections at retreatment could help to determine both patients entering long-term remission and individual optimal dose. In this aim, prospective studies comparing different discontinuation methods are needed.

Cost-effectiveness of omalizumab has already been assessed (84) but more medico-economic investigations of different discontinuation patterns would be beneficial for an optimal use of expensive monoclonal antibodies.

V. Conclusion

In this large and long-time follow-up real-life study, efficacy and safety of omalizumab were confirmed in CSU and to a lesser extent in CIndU. Drug-survival analyses showed that most discontinuation of omalizumab occurred in patients with well-controlled disease. Shorter drug-survival was noted in patients with CIndU, autoimmunity and previous treatment by immunomodulators. Longer drug-survival was associated with longer disease duration. Atopic patients were more likely to stop omalizumab sooner for well-controlled disease.

In this study, most French practitioners chose to taper omalizumab through lengthening the dose interval before interruption. In view of good efficacy at retreatment, drug cost and high natural remission rates in chronic urticaria, trying to discontinue omalizumab appears reasonable even though relapse rate remains high, reaching 50%. Further studies are needed to better identify predictive factors of relapse as well as strategies to minimize them.

Partie 3 : commentaire

Dans cette large cohorte de 878 patients, nous avons pu confirmer l'efficacité et la bonne tolérance de l'omalizumab dans l'urticaire chronique spontanée et, dans une moindre mesure, dans l'urticaire chronique inducible.

L'étude de survie a montré que la majorité des arrêts avait lieu à la suite d'un bon contrôle de l'urticaire. La durée de traitement était plus courte chez les patients avec une urticaire chronique inducible, une auto-immunité associée et un traitement antérieur par immunomodulateurs. Les patients atopiques arrêtaient plus rapidement que les non-atopiques pour bon contrôle de l'urticaire. Au contraire, une maladie plus longue à l'introduction de l'omalizumab était associée à une durée plus longue de traitement.

En cas d'arrêt, 48 % des patients ont dû reprendre l'omalizumab avec une efficacité similaire dans plus de 70 % des cas, à la fois dans les formes spontanées et inducibles. Beaucoup de praticiens ont choisi d'espacer les injections d'omalizumab au cours du suivi.

Contrairement à d'autres maladies dermatologiques telles que l'eczéma ou le psoriasis où l'arrêt des biothérapies semble difficile après introduction, essayer d'arrêter l'omalizumab dans l'urticaire chronique paraît justifié devant le taux élevé de rémission spontanée de l'urticaire, le coût du traitement et sa bonne efficacité en cas de reprise.

Après un traitement de 6 mois à la dose AMM, différentes stratégies peuvent être envisagées :

- (i) Un arrêt avec, en cas de rechute précoce, reprise de l'omalizumab par cures courtes de 6 mois à dose AMM permettrait d'identifier les patients en rémission prolongée.
- (ii) L'espacement des injections ou la diminution des doses d'omalizumab permettraient de déterminer la dose individuelle optimale.
- (iii) Un arrêt avec, en cas de rechute précoce, reprise de l'omalizumab avec un espacement des injections basé sur le délai de rechute permettrait d'identifier les patients en rémission prolongée et la dose individuelle optimale.

Ces différentes stratégies et leurs coûts mériteraient d'être comparés dans des études adaptées. Approfondir la recherche de facteurs prédictifs de rechutes et de stratégies pour les minimiser semble également nécessaire.

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Annexes

1. Figures et tableaux

Table 1: Population characteristics in the defined four subsets of chronic urticaria

	CSU	CSUp	CIndU	CIndUp	p-value
Number (%)	428 (48.8)	299 (34.1)	89 (10.1)	62 (7.1)	
Age at CU onset (SD) (years)	42.1 (\pm 16.8)	36.9 (\pm 16.6)	29.4 (\pm 16.9)	32.2 (\pm 16.1)	<0.001
Female – No (%)	311 (72.7)	217 (72.6)	48 (53.9)	45 (72.6)	0.003677
Angioedema – No (%)	231 (54.0)	145 (48.5)	9 (10.1)	17 (27.4)	<0.000001
<i>Clinical features – No (%)</i>					
Atopy	166 (43.2)	123 (44.4)	32 (43.2)	24 (42.9)	0.990528
Autoimmunity	67 (17.2)	46 (16.3)	7 (9.1)	7 (11.9)	0.271557
Systemic symptoms	88 (23.1)	57 (20.8)	6 (8.1)	12 (20.3)	0.036861
<i>Previous therapies – No (%)</i>					
AH/LTRA	421 (98.4)	298 (99.7)	88 (98.9)	61 (98.4)	0.274245
CS	149 (34.8)	106 (35.5)	12 (13.5)	11 (17.7)	0.000039
AB	8 (1.9)	5 (1.7)	1 (1.1)	0 (0)	0.940261
IM	31 (7.2)	25 (8.4)	13 (14.6)	9 (14.5)	0.056155
IS	31 (7.2)	17 (5.7)	9 (10.1)	8 (12.9)	0.172413
Time to omalizumab introduction (SD) (years)	4.8 (\pm 7.1)	5.2 (\pm 6.7)	7.1 (\pm 7.3)	8.0 (\pm 8.8)	<0.001

Legend: CU = chronic urticaria, CSU = chronic spontaneous urticaria, CIndU = chronic inducible urticaria, CSUp = predominant CSU, CIndUp = predominant CIndU, AH/LTRA = antihistamines and leukotriene receptor antagonists, CS = corticosteroids, AB = bradykinin inhibitors, IM = immunomodulators, IS = immunosuppressants, No = numbers, SD = standard deviations

Table 2: Initial response to omalizumab

	QR/CR	LR/CR	PR	NR	WD	p-value
Number (%)	530 (62.9%)	107 (12.7)	123 (14.6)	73 (8.77)	10 (1.2)	
Age at introduction (SD) (years)	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 – No (%)</i>						0.0103
CIndU	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)	
CIndUp	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 – No (%)</i>						0.0350
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)	

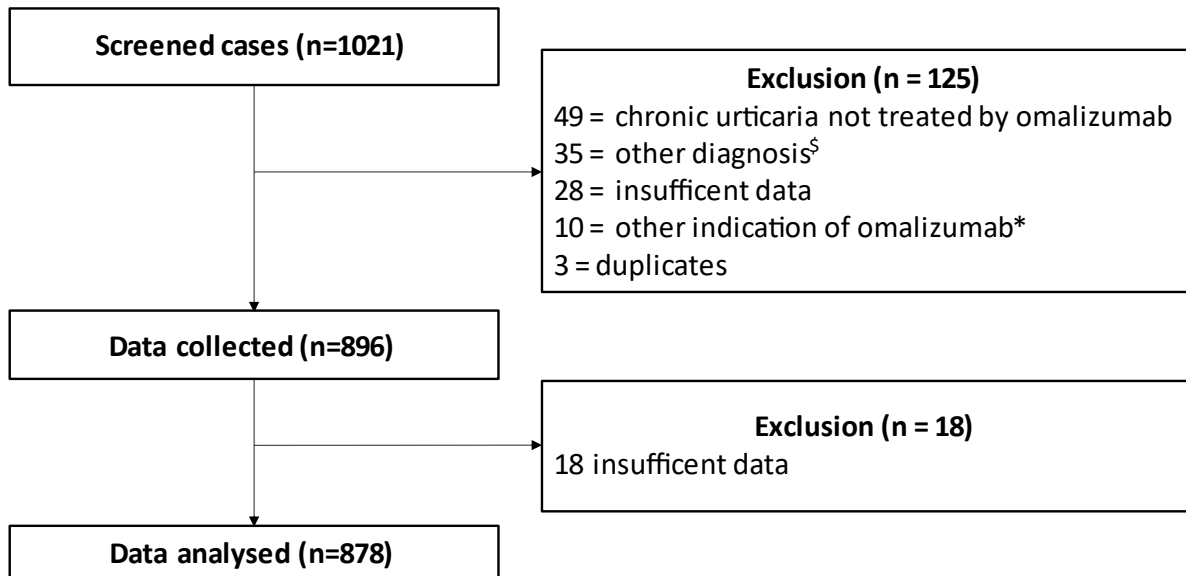
Legend: CU = chronic urticaria, CSU = chronic spontaneous urticaria, CIndU = chronic inducible urticaria, CSUp = predominant CSU, CIndUp =predominant CIndU, QR/CR = Quick and complete response, LR/CR = Late and complete response, PR = Partial response, NR = No response, WD = Worsening disease, No = numbers, SD = standard deviations

Table 3: Most frequently reported adverse events, leading or not to discontinuation of omalizumab.

	Number of adverse events occurrences No (%)	Number of adverse events leading to discontinuation No (%)
Headache	38 (4.3)	6 (15.8)
Arthromyalgia	34 (3.9)	14 (41.2)
Asthenia	23 (2.6)	8 (34.8)
Injection point reaction	13 (1.5%)	5 (38.5%)
Digestive disorder	13 (1.5%)	4 (30.8%)
Weigh gain	9 (1.0%)	2 (22.2%)

Legend: No number.

Figure 1: Flow-chart



[§]5 mast cell disorder, 6 neutrophilic urticaria, 2 pruritus sine materia, 4 aquagenic pruritus, 5 urticaria vascularitis, 2 atopic dermatitis, 1 dermatomyositis, 1 melanoma, 2 contact dermatitis, 1 bullous pemphigoid, 6 unspecified diagnosis

*asthma, food or venom immunotherapy

Figure 2: Overall drug-survival and drug-survival based on reasons to discontinuation of omalizumab

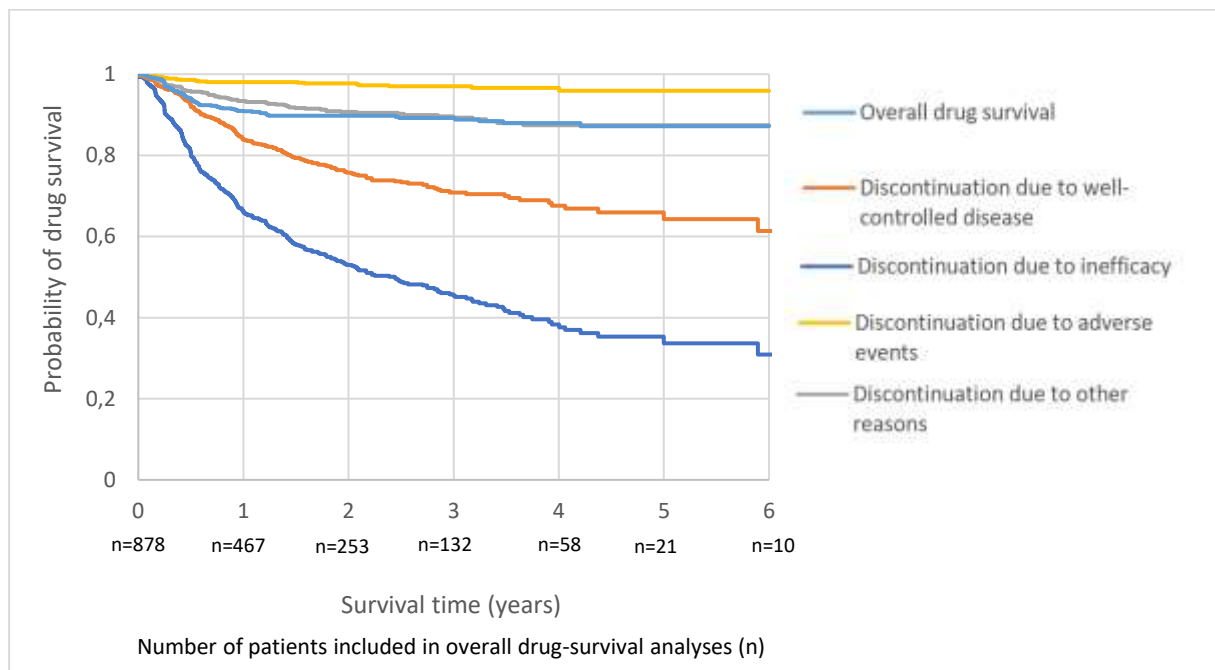
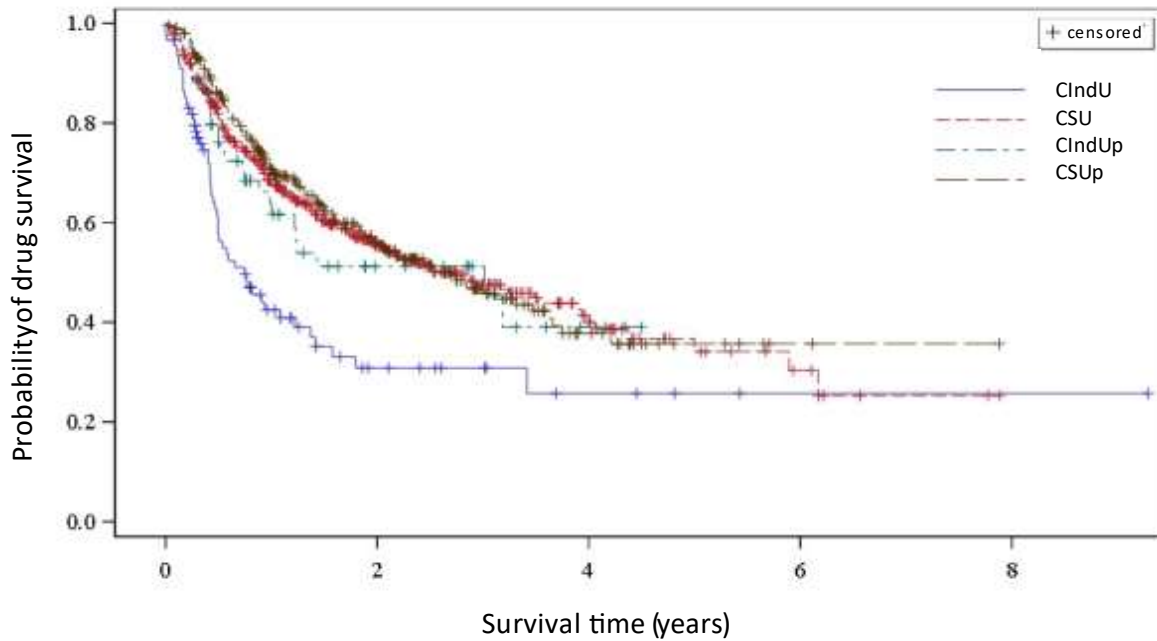


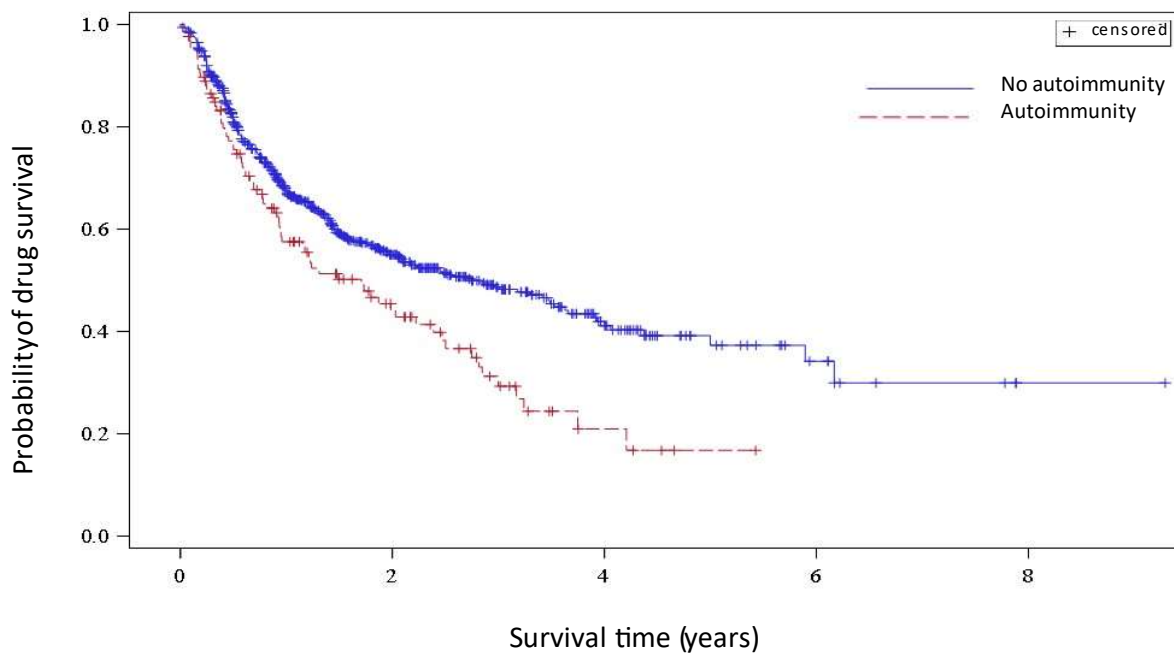
Figure 3: Drug-survival based on subtype of chronic urticaria



Legend: CSU = Chronic spontaneous urticaria, CIndU = Chronic inducible urticaria, CIndUp = predominant chronic inducible urticaria, CSUp = predominant chronic spontaneous urticaria

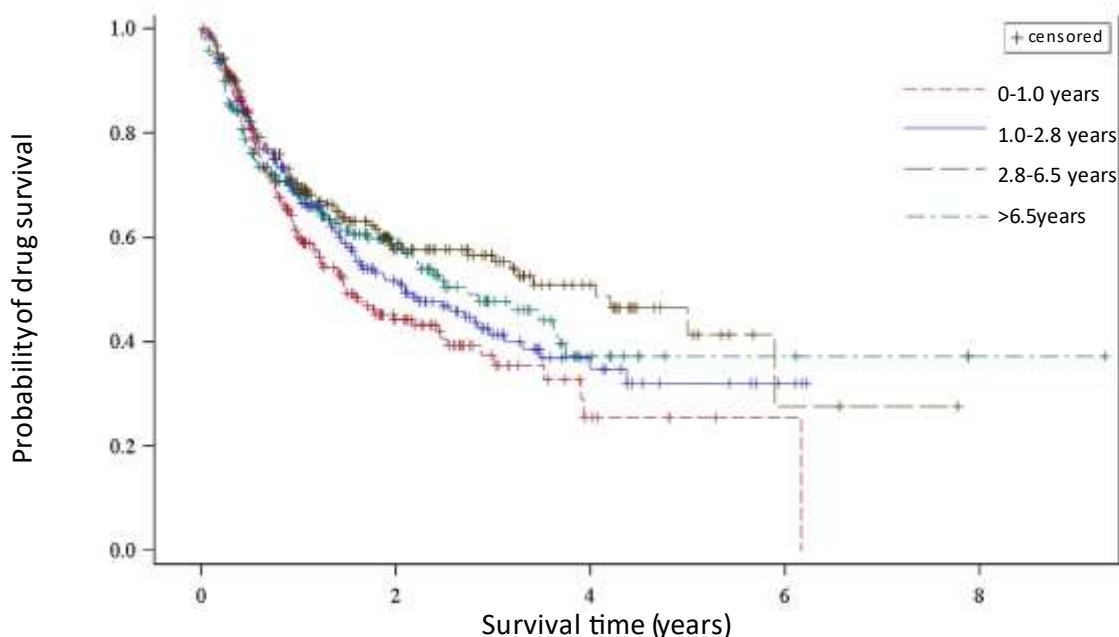
**Hazard ratio for CIndU compared to CSU in overall multivariate analyse (HR[IC95], p-value) :
HR=1.9 [1.3-2.8], p=0.0012**

Figure 4: Drug-survival based on autoimmunity



**Hazard ratio for autoimmunity in overall multivariate analyse (HR[IC95], p-value):
HR 1.4 [1.0-1.8], p=0.0307**

Figure 5: Drug survival based on disease durations



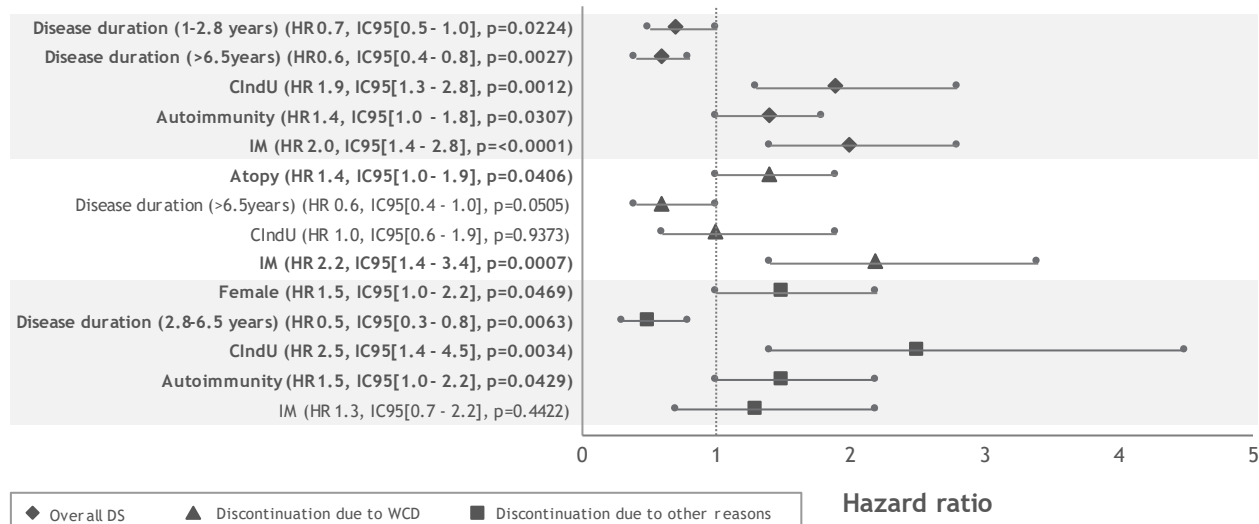
Hazard ratio for disease duration in overall multivariate analyse (HR [IC95], p-value):

Disease duration 1-2.8 years: HR= 0.7 [0.5-1.0], p=0.0224

Disease duration 2.8-6.5 years: HR= 0.6 [0.4-0.8], p=0.0011

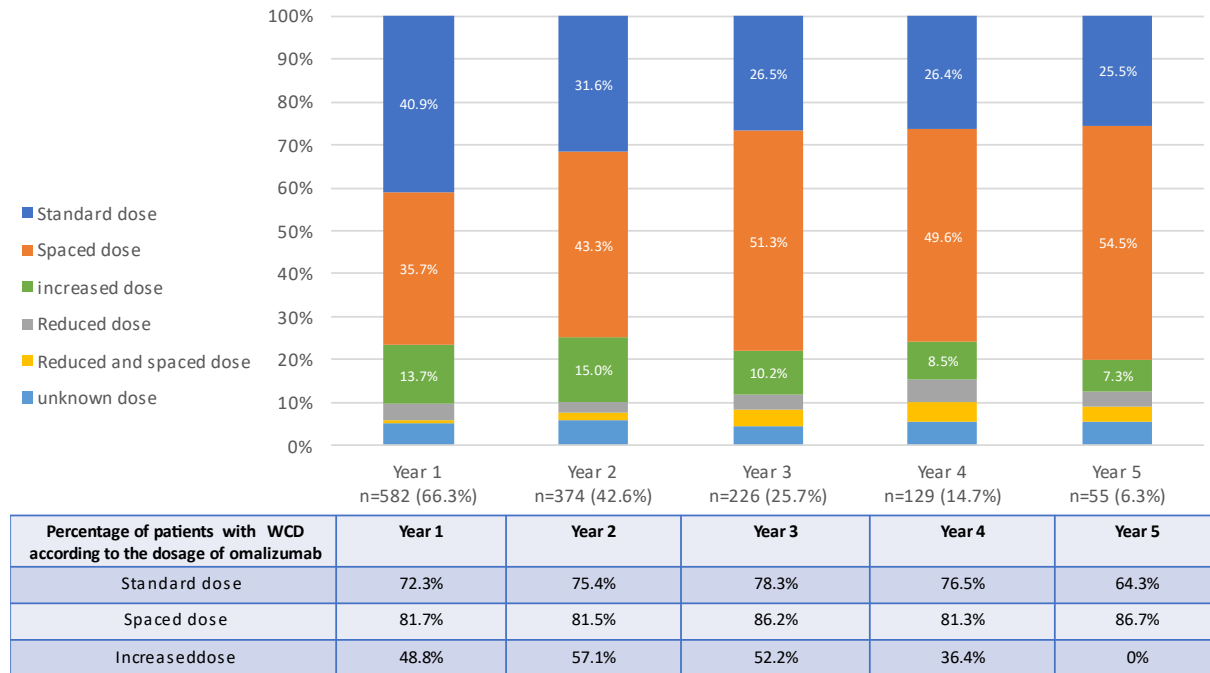
Disease duration >6.5 years: HR= 0.6 [0.4-0.8], p = 0.0027

Figure 6: Hazard ratio for predictive factor of drug survival for overall analyse, discontinuation for well-controlled disease and discontinuation for other reasons



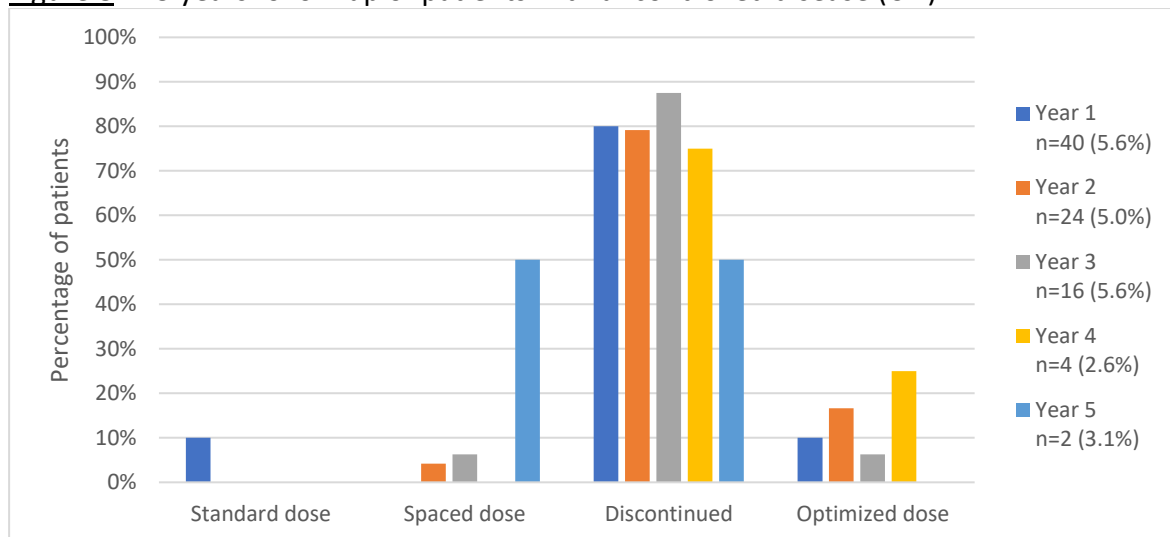
Legend: HR = hazard ratio, IC95 = confidence interval of 95%, p = p-value, CIndU = chronic inducible urticaria, CSU = chronic spontaneous urticaria, IM = previous therapy by immunomodulators. HR for disease duration was compared to disease duration <1year.

Figure 7: 1-5 years follow-up of patients still treated with omalizumab



Legend: n number of patients treated by omalizumab at 1 to 5 years post introduction; the percentage is calculated with the overall number of patients. WCD = well-controlled disease

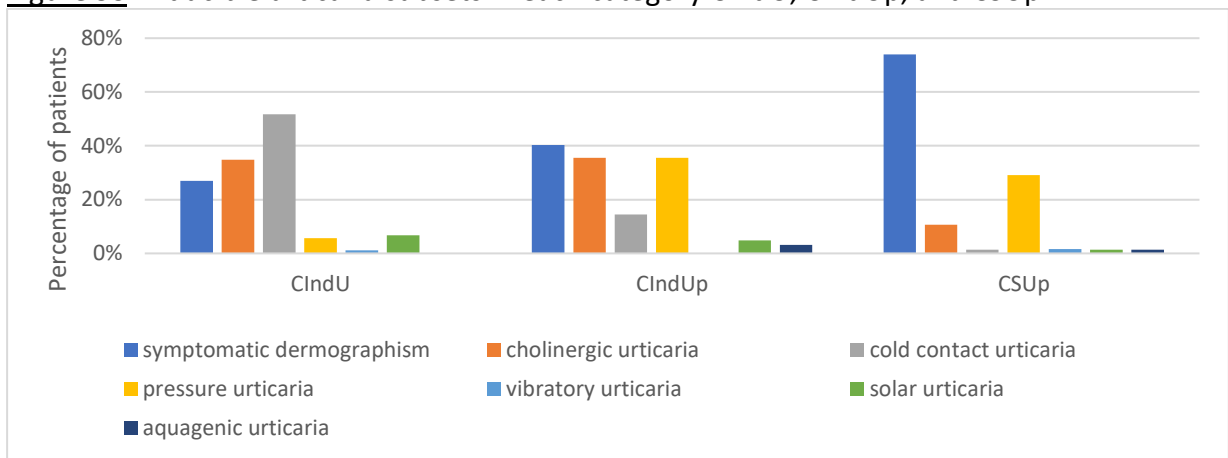
Figure 8: 1-5 years follow-up of patients with uncontrolled disease (UD)



Legend: n number of patients with an uncontrolled disease at 1-5 years of follow-up; percentages were calculated over the number of patients still followed at 1-5 years of follow-up.

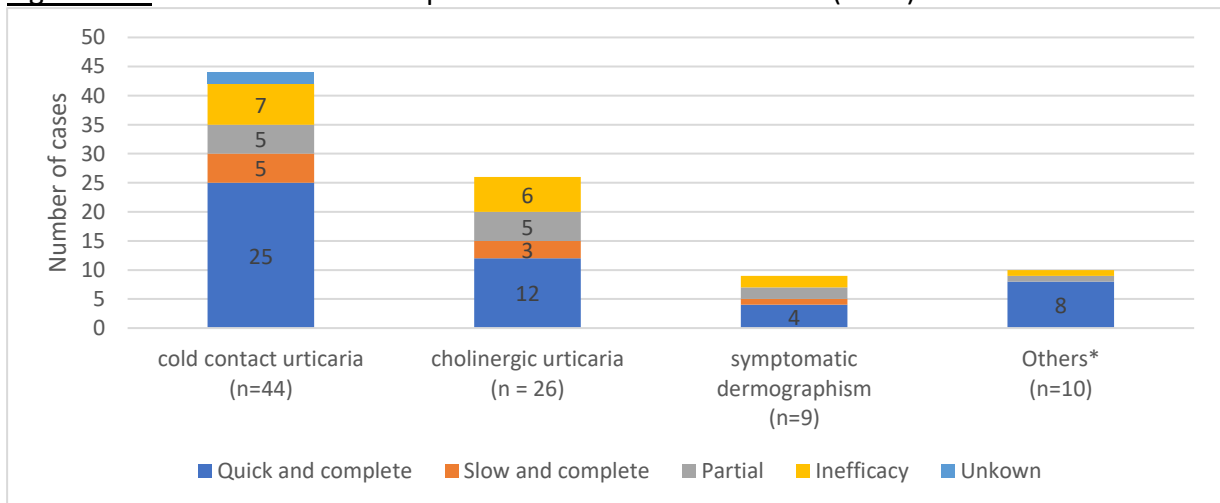
Supplementary data:

Figure 9S: Inducible urticaria subsets in each category CIndU, CIndUp, and CSUp



Legend: CIndU = chronic inducible urticaria, CIndUp = predominant CIndU, CSU = predominant chronic spontaneous urticaria

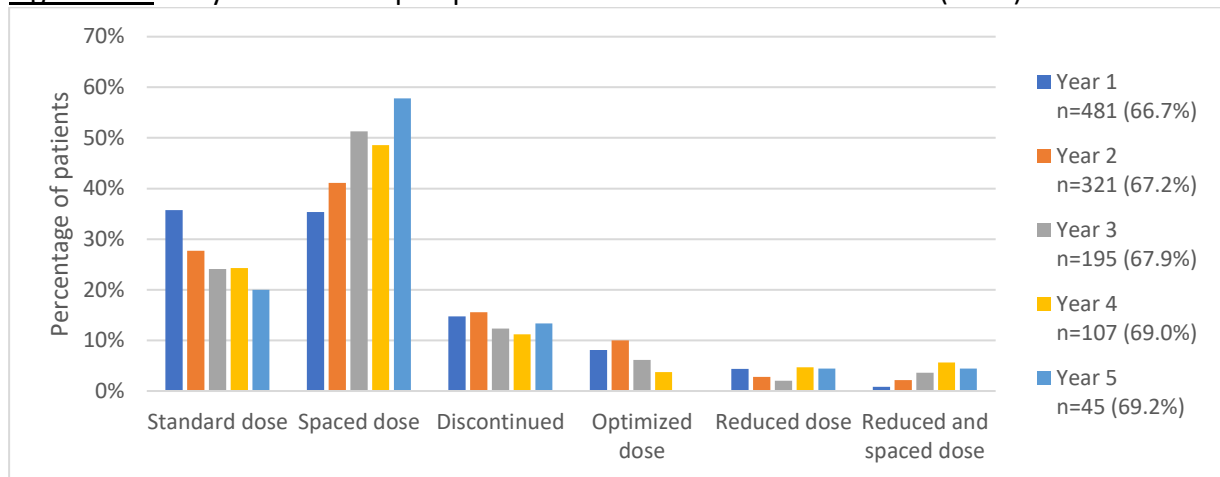
Figure 10S: Evaluation of the response to omalizumab in CIndU (n=89)



Legend: CIndU = chronic inducible urticaria

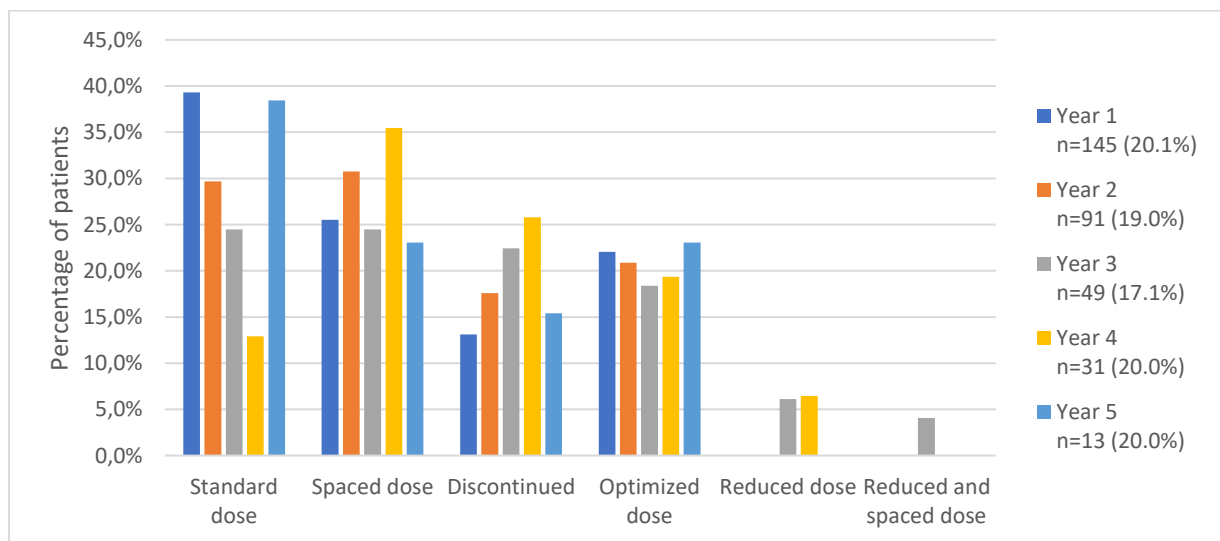
*Includes 5 patients with solar urticaria, 4 with pressure urticaria and 1 with vibratory urticaria

Figure 11S: 1-5 years follow-up of patients with well-controlled disease (WCD)



Legend: n= number of patients with a well-controlled disease at 1-5 years of follow-up; percentages were calculated over the number of patients still followed at that time. Unknown doses were excluded from this chart.

Figure 12S: 1-5 years follow-up of patients with mild to moderate disease (MD)



Legend: n= number of patients with a partially controlled disease at 1-5 years of follow-up; percentages were calculated over the number of patients still followed at that time. Unknown doses were excluded from this chart.

2. Abréviations

AE : angioedema

AH/LTRA : antihistamines and leukotrienes receptor antagonists

AMM : autorisation de mise sur le marché

BA : bradykinin antagonists and tranexamic acid

CS : corticosteroids

CU : chronic urticaria

CR : complete response

CSU : chronic spontaneous urticaria

CIndU : chronic inducible urticaria

CSUp : predominant CSU

CIndUp : predominant CIndU

DS : drug-survival

HR : Hazard ratio

IM : immunomodulators

IS : immunosuppressants

LR : late responder

MD : mild disease

NR : no response

PGA : practician global assessment

PR : partial response

QR : quick responder

SD : standard deviation

UC : uncontrolled disease

WCD : well-controlled disease

WD : worsening disease

SERMENT

- *En présence des Maîtres de cette école, de mes chers condisciples et devant l'effigie d'Hippocrate, je promets et je jure, au nom de l'Être suprême, d'être fidèle aux lois de l'honneur et de la probité dans l'exercice de la médecine.*
- *Je donnerai mes soins gratuits à l'indigent et n'exigerai jamais un salaire au-dessus de mon travail.*
- *Admis (e) dans l'intérieur des maisons, mes yeux ne verront pas ce qui s'y passe, ma langue taira les secrets qui me seront confiés, et mon état ne servira pas à corrompre les mœurs, ni à favoriser le crime.*
- *Respectueux (se) et reconnaissant (e) envers mes Maîtres, je rendrai à leurs enfants l'instruction que j'ai reçue de leurs pères.*
- *Que les hommes m'accordent leur estime si je suis fidèle à mes promesses. Que je sois couvert (e) d'opprobre et méprisé (e) de mes confrères si j'y manque.*

Abstract:

Introduction: Chronic urticaria (CU) affects about 1% of the population and impacts quality of life. Since 2018, omalizumab is recommended as third-line therapy in CSU when up-dosed antihistamines are poorly tolerated or inefficient. We aimed to describe the real-life use and discontinuation modalities of omalizumab in chronic urticaria referral centres since its commercialization in this indication.

Methods: We performed a retrospective, multicentric, observational French study including patients with chronic spontaneous (CSU) and/or inducible (CIndU) urticaria, treated with omalizumab at least once between 2005 and 2020. Drug survival analyses were performed, and determinants of drug survival were analysed.

Results: 878 patients were included with 82.8% CSU or predominant CSU and 10.1% CIndU. Complete response (CR) was obtained in 75.6%. CR was lower in CIndU. 66% patients were still receiving omalizumab at 1 year and 30.9% at 6 years. Main reason to discontinuation was well-controlled disease. Shorter drug-survival was noted in patients with CIndU, autoimmunity and previous treatment by immunomodulators. Longer drug-survival was associated with longer disease duration. Atopic patients were more likely to stop omalizumab sooner for well-controlled disease. 48% of patients who discontinued omalizumab were further retreated with >70% similar efficacy in CSU and in CIndU patients. Many practitioners chose to lengthen dose interval during follow-up.

Conclusion: In view of good efficacy at retreatment, drug cost and high natural remission rates in chronic urticaria, trying to discontinue omalizumab appears reasonable. Further studies are needed to identify predictive factors of relapse as well as strategies to minimize them.

Key words: chronic spontaneous urticaria, chronic inducible urticaria, omalizumab, drug-survival, real life, discontinuation, retreatment, relapse

RESUME

Introduction : L'urticaire chronique atteint environ 1 % de la population et a un retentissement majeur sur la qualité de vie. Depuis 2018, l'omalizumab est recommandé comme traitement de 3^e ligne en cas de mauvaise tolérance ou d'inefficacité des antihistaminiques à dose augmentée. Notre objectif était d'évaluer les modalités d'utilisation et d'interruption de l'omalizumab en vie réelle dans des centres spécialisés de prise en charge de l'urticaire chronique depuis la mise à disposition de ce traitement dans cette indication.

Méthode : Une étude multicentrique, observationnelle, rétrospective a été menée dans 9 centres français, incluant des patients atteints d'urticaire chronique spontanée (CSU) et/ou induite (CIndU) entre 2005 et 2020. Une analyse de survie a été réalisée et les facteurs influençant la durée de traitement ont été recherchés.

Résultats : 878 patients ont été inclus avec 82,8 % de CSU seule ou prédominante et 10,1 % de CIndU. Une réponse complète a été obtenue dans 75,6 % des cas avec une moins bonne réponse chez les patients CIndU. A 1 an et 6 ans respectivement, 66 % et 30,9 % des patients étaient toujours sous omalizumab. Le principal motif d'arrêt était le bon contrôle de l'urticaire. L'omalizumab était arrêté plus précocement chez les patients avec une CIndU, une auto-immunité associée et un traitement antérieur par immunomodulateurs. Les patients atopiques arrêtaient plus rapidement que les non atopiques pour bon contrôle de l'urticaire. Une durée d'évolution plus longue de l'urticaire à l'introduction de l'omalizumab était associée à une durée plus longue de traitement. En cas d'arrêt, 48 % des patients ont dû reprendre l'omalizumab avec une efficacité similaire dans plus de 70 % des cas, à la fois pour les CSU et les CIndU. La majorité des praticiens ont choisi d'espacer les injections d'omalizumab au cours du suivi.

Conclusion : Devant l'efficacité maintenue à sa reprise, son coût et le taux élevé de rémission spontanée de l'urticaire chronique, une tentative d'arrêt systématique de l'omalizumab paraît justifiée. Il semble également nécessaire d'approfondir la recherche de facteurs prédictifs des rechutes et de stratégies pour les minimiser.

Mots clés : urticaire chronique, urticaire chronique spontanée, urticaire induite, omalizumab, survie, vraie vie, arrêt, rechute, retraitement