OMALIZUMAB IMPROVES ANGIOEDEMA-RELATED QUALITY OF LIFE (QOL) IMPAIRMENT IN PATIENTS WITH CHRONIC IDIOPATHIC/CHRONIC SPONTANEOUS URTICARIA (CIU/CSU): RESULTS FROM THE X-ACT STUDY

Karsten Weller,[1] Petra Staubach,[2] Martin Metz,[1] Nadine Chapman-Rothe,[3] Christian Sieder,[4] Matthias Bräutigam,[4] Marcus Maurer[1]

[1]Charité – Universitätsmedizin Berlin, Berlin, Germany; [2]University Medical Center Mainz, Mainz, Germany; [3]Novartis Pharma AG, Basel, Switzerland; [4]Novartis Pharma GmbH, Nuremberg, Germany

INTRODUCTION

- Chronic idiopathic/spontaneous urticaria (CIU/CSU) is defined as the repeated occurrence of spontaneous wheals (hives) and/or angioedema for at least 6 weeks without a specific external trigger[1,2]
- Between 33% and 67% of patients with CIU/CSU are reported to experience hives and angioedema; 1%–13% experience only angioedema[3]
- Angioedema is a major driver of quality of life (QoL) impairment in patients with CIU/CSU;[4] owing to the unpredictable development of disfigurement and/or functional impairment, angioedema episodes can have a significant impact on daily activities and social interactions[5]
- Omalizumab is approved as an add-on therapy in patients with CIU/CSU refractory to H_1-antihistamines.[6] Subcutaneous omalizumab (300 mg) has been shown to reduce the frequency and severity of angioedema in H_1-antihistamine-refractory CIU/CSU, as well as reducing QoL impairment[7]

OBJECTIVE

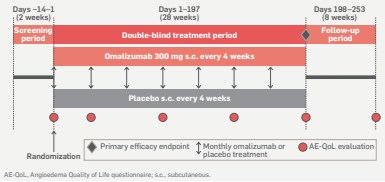
- To examine the effect of omalizumab treatment on angioedema-related QoL, including patient fear of a life-threatening angioedema (swelling) episode, in the X-ACT study (NCT01723072)

METHODS

Study design

- The X-ACT (Xolair Effects on Angioedema in Chronic Spontaneous Urticaria Treatment) study was a Phase 3, randomized, double-blind, placebo-controlled, multicenter study conducted in Germany[7]
- Patients were randomized 1:1 to receive subcutaneous omalizumab 300 mg or placebo every 4 weeks for 28 weeks, with an 8-week follow-up period (**Figure 1**)

Figure 1. X-ACT study design



AE-QoL, Angioedema Quality of Life questionnaire; s.c., subcutaneous.

Study population

- Key inclusion criteria for the X-ACT study included:
  - Age 18–75 years
  - Moderate-to-severe CIU/CSU with frequent angioedema episodes (≥4 episodes within the last 6 months before study enrollment)
  - Medically confirmed diagnosis of CIU/CSU that is refractory to treatment with 2–4 times the approved dose of second-generation H_1-antihistamines

Patient-reported outcomes: QoL, disease activity, and psychological well-being

- Outcomes reported in this poster were measured using the following assessments:
  - **AE-QoL:** Angioedema Quality of Life questionnaire; 17 items that include four subdomains (functioning, fatigue/mood, fears/shame, and food). Scores range from 0 to 100, with higher scores indicative of higher impairment to QoL
  - **Weekly AAS (AAS7):** Angioedema Activity Score; scores range from 0 to 105, with higher scores indicating higher disease activity
  - **WHO-5:** World Health Organization Well-being Index; a 5-item questionnaire with a maximum score of 25. Values lower than 13 indicate signs of depression

Statistical analysis

- In the full analysis set (FAS; all those randomized who received ≥1 dose of study drug), patients were analyzed according to the treatment to which they were randomized
- Treatment group comparisons of change in AE-QoL scores were performed using an analysis of covariance (ANCOVA) model with treatment and center as factors, and baseline score as a covariate. The analysis was conducted in the FAS by using observed values for AE-QoL scores[5]
- The AAS7 and WHO-5 results were analyzed analogously to the AE-QoL as a mean difference from baseline to Week 28 in an ANCOVA conducted on the FAS by using observed cases[5]
- The WHO-5 assessment and the question regarding fear of a life-threatening swelling episode were regarded as exploratory endpoints
- Pearson correlation coefficients were computed to explore the correlations between different endpoints[5]

RESULTS

Patients

- A total of 91 patients were randomized, with 68 (omalizumab, n=35; placebo, n=33) completing the 28-week treatment period
- Patient demographics and baseline disease characteristics are shown in **Table 1**
  - Female patients had higher AE-QoL total scores at baseline compared with male patients (P=0.001) and a tendency toward higher disease activity (higher AAS7 scores, P=0.086)

Table 1. Patient demographics and baseline disease characteristics

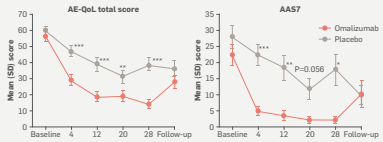
	Omalizumab (n=44)	Placebo (n=47)
Age, years, mean (SD)	44.9 (13.7)	41.1 (10.6)
Female, n (%)	30 (68.2)	33 (70.2)
BMI, mean (SD) kg/m^2	27.3 (6.3)	29.0 (5.9)
AAS7, mean (SD)	22.5 (20.6)	28.1 (24.1)
Angioedema-burdened days, mean (SD)*	2.7 (2.3)	3.5 (2.4)
AE-QoL total score, mean (SD)	56.2 (18.7)	59.9 (19.2)
DLQI total score, mean (SD)	14.6 (5.7)	16.6 (7.3)

*At Week 1 during the 2-week screening period.
AAS7, weekly Angioedema Activity Score; AE-QoL, Angioedema Quality of Life questionnaire; BMI, body mass index; DLQI, Dermatology Life Quality Index; SD, standard deviation.

Angioedema-related QoL and disease activity

- Improvement in angioedema-related QoL correlated with reduced angioedema activity (Week 12: 0.526, P<0.001; Week 28: 0.501, P<0.001; Pearson correlation coefficient)
- After treatment discontinuation, both angioedema-related QoL impairment and angioedema activity approached placebo levels (**Figure 2**)
  - Least squares (LS) mean difference (95% confidence interval [CI]) in AE-QoL score for omalizumab versus placebo at: Week 4, −17.6 (−26.9, −8.2); Week 12, −26.0 (−38.1, −13.9); Week 20, −16.3 (−27.6, −5.0); Week 28, −22.7 (−33.1, −12.2)
  - LS mean difference (95% CI) in AAS7 for omalizumab versus placebo at: Week 4, −15.6 (−22.7, −8.6); Week 12, −14.1 (−22.7, −5.5); Week 20, −7.0 (−14.1, 0.2); Week 28, −9.8 (−18.9, −0.7)

Figure 2. Angioedema-related QoL and disease activity



Omalizumab versus placebo: *P<0.05; **P<0.01; ***P<0.001.
AAS7, weekly Angioedema Activity Score; AE-QoL, Angioedema Quality of Life questionnaire; SD, standard deviation.

- As early as Week 4, patients in the omalizumab group had significantly greater improvements from baseline in three subdomains of the AE-QoL compared with the placebo group (**Figure 3**)

Figure 3. Change from baseline in AE-QoL subdomain scores at Week 4

Change versus placebo: *P<0.05; **P<0.01; ***P<0.001.
AE-QoL, Angioedema Quality of Life questionnaire; SD, standard deviation.

Fear of life-threatening swelling episode

- At baseline, when patients were asked if they were afraid of a life-threatening swelling episode, 67% responded 'occasionally', 'often', or 'very often'. At Week 28, this decreased to 13.6% in the omalizumab group versus 41.7% in the placebo group
- Similarly, 49% of patients at baseline were 'occasionally' to 'very often' afraid that 'they could suffocate due to swelling episode'. At Week 28, this decreased to 4.5% in the omalizumab group versus 25.1% in the placebo group
- Reduced fear of life-threatening swelling episodes was evident from as early as 4 weeks after starting omalizumab treatment, but increased upon discontinuation of treatment
  - At Week 28, 63.6% of patients in the omalizumab group were 'never' afraid of life-threatening swelling episodes compared with 29.2% in the placebo group. During the follow-up period, these proportions were 37.5% and 35.7% in the omalizumab and placebo groups, respectively (**Table 2**)

Table 2. Patient fear of a life-threatening swelling episode (baseline to follow-up at Week 36)

	Baseline		Week 4		Week 12		Week 28		Follow-up	
	Omalizumab (n=44)	Placebo (n=46)	Omalizumab (n=43)	Placebo (n=45)	Omalizumab (n=37)	Placebo (n=34)	Omalizumab (n=22)	Placebo (n=24)	Omalizumab (n=32)	Placebo (n=28)
'Were you afraid of a life-threatening swelling episode?'										
Never	7 (15.9)	6 (13.0)	19 (44.2)	15 (33.3)	20 (54.1)	11 (32.4)	14 (63.6)	7 (29.2)	12 (37.5)	10 (35.7)
Rarely	11 (25.0)	6 (13.0)	11 (25.3)	7 (15.6)	6 (16.2)	9 (26.5)	5 (22.7)	7 (29.2)	10 (31.3)	4 (14.3)
Occasionally	11 (25.0)	16 (34.8)	3 (7.0)	16 (35.6)	9 (24.3)	6 (17.6)	3 (13.6)	7 (29.2)	6 (18.8)	10 (35.7)
Often	8 (18.2)	11 (23.9)	7 (16.3)	6 (13.3)	1 (2.7)	3 (8.8)	0 (0.0)	1 (4.2)	3 (9.4)	2 (7.1)
Very often	7 (15.9)	7 (15.2)	3 (7.0)	1 (2.2)	1 (2.7)	5 (14.7)	0 (0.0)	2 (8.3)	1 (3.1)	2 (7.1)

Data presented as n (%).

Psychological well-being

- Omalizumab treatment, but not placebo, increased the mean WHO-5 total score to levels above the depression threshold (indicating no signal for depression) (**Figure 4**)

Figure 4. WHO-5 index total scores

Omalizumab versus placebo: *P<0.05, ***P<0.001.
SD, standard deviation; WHO-5, 5-Item World Health Organization Well-being Index.

CONCLUSIONS

- Omalizumab 300 mg treatment led to a rapid and sustained reduction of angioedema-related QoL impairment
  - This is correlated with decreased angioedema activity
- Omalizumab rapidly improved AE-QoL subdomain scores for functioning, fatigue/mood, and fear/shame
  - Numerical improvements in the food subdomain were observed but did not reach statistical significance
- Discontinuation of omalizumab treatment resulted in the return of angioedema symptoms
- Symptom-related fears of suffocation and life-threatening episodes in the omalizumab group decreased versus those in the placebo group, supporting the benefit of omalizumab treatment in patients with CIU/CSU with H_1-antihistamine-refractory angioedema and decreased QoL
- General psychological well-being improved with omalizumab treatment, as indicated by increased mean WHO-5 scores to levels above the depression threshold

ACKNOWLEDGMENTS

Medical writing in the development of this presentation was provided by Novartis Ireland Ltd. Editorial assistance was provided by Heather St Michael of Fishawack Communications Ltd, Abingdon, UK, and this service was supported by Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA.

The scientific content of this poster was originally presented orally at the 36th Annual Congress of the European Academy of Allergy and Clinical Immunology, June 17–21, 2017, Helsinki, Finland.

FUNDING

This study was supported by Novartis Pharma GmbH, Germany.

DISCLOSURES

In relation to this presentation, we declare the following real or perceived conflicts of interest:
KW has received honoraria for educational lectures (Dr R. Pfleger, Essex Pharma [now MSD], Moxie, Novartis, UCB, Uriach); has received honoraria for consulting (Novartis); was involved in clinical research projects (Dr R. Pfleger, Essex Pharma [now MSD], Faes, Novartis, Uriach). **PS** has received research funding and/or fees for consulting and/or lectures (AbbVie, Astellas, Celgene, CSL Behring, Dr R. Pfleger [now MSD], Genentech, Janssen, Karrer, LEO, Leti, Lilly, MSD, Novartis, Pfizer, Shire, Sobi, UCB). **MMetz** has received honoraria as a speaker (Bayer Pharma, Dr R. Pfleger [now MSD], Essex Pharma, LEO, Merck, Moxie, Novartis, Recordati Pharma, Sanofi, Shire, UCB, Uriach). **NC-R** is an employee of Novartis Pharma AG. **CS** and **MB** are employees of the study sponsor, Novartis Pharma GmbH. **MMau** has received research funding and/or fees for consulting and/or lectures (Faes, Genentech, GSK, Moxie, MSD, Novartis, UCB, Uriach).

CONCLUSIONS

- Omalizumab 300 mg treatment led to a rapid and sustained reduction of angioedema-related QoL impairment
  - This is correlated with decreased angioedema activity
- Omalizumab rapidly improved AE-QoL subdomain scores for functioning, fatigue/mood, and fear/shame
  - Numerical improvements in the food subdomain were observed but did not reach statistical significance
- Discontinuation of omalizumab treatment resulted in the return of angioedema symptoms
- Symptom-related fears of suffocation and life-threatening episodes in the omalizumab group decreased versus those in the placebo group, supporting the benefit of omalizumab treatment in patients with CIU/CSU with H_1-antihistamine-refractory angioedema and decreased QoL
- General psychological well-being improved with omalizumab treatment, as indicated by increased mean WHO-5 scores to levels above the depression threshold

REFERENCES

1. Zuberbier T, *et al. Allergy.* 2014;69:868–87.
2. Grattan C. *Clin Med.* 2012;12:164–7.
3. Maurer M, *et al. Allergy.* 2011;66:317–30.
4. Choi WS, *et al. Korean J Intern Med.* ePub ahead of print Jun 1, 2016. DOI: 10.3904/kjim.2015.195.
5. Staubach P, *et al. Allergy.* ePub ahead of print Oct 23, 2017. DOI: 10.1111/all.13339.
6. McCormack PL. *Drugs.* 2014;74:1693–9.
7. Staubach P, *et al. Allergy.* 2016;71:1135–44.