Be AWARE: learnings from real-world evidence

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Ligelizumab is an investigational drug in development for the treatment of CSU and has not received marketing authorization
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Disclosures

In relation to this talk, Ana Giménez-Arnau declares the following, real or perceived conflicts of interest:

- Medical Advisor for Uriach Pharma, Genentech, Novartis, FAES, GSK, Sanofi–Regeneron, Amgen, Thermo Fisher Scientific
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International urticaria guidelines have undergone numerous revisions and updates

ESDR Symposium ‘Urticaria 2000’
2nd International Consensus Meeting Urticaria 2004
3rd International Consensus Meeting Urticaria 2008
Systematic review* & Consensus Meeting 2012
4th International Consensus Meeting Urticaria Planned 2016

Consensus reports 2001\(^1,2\)
EAACI/GA\(^2\)LEN/EDF Guideline 2006\(^3,4\)
EAACI/GA\(^2\)LEN/EDF/WAO Guideline 2009\(^5,6\)
EAACI/GA\(^2\)LEN/EDF/WAO 2013 revision & update (published 2014)\(^7\)
EAACI/GA\(^2\)LEN/EDF/WAO 2017 revision and update (published 2018)\(^8\)

The 2017 guidelines are the result of a systematic literature review using a modified version of GRADE and outcomes from a consensus conference on 1 December 2016 in Berlin, Germany with >250 participants

*Using GRADE (Grading of Recommendations Assessment, Development and Evaluation)
EAACI, European Academy of Allergy and Clinical Immunology; EDF, European Dermatology Forum; ESDR, European Society for Dermatological Research; GA\(^2\)LEN, Global Allergy and Asthma European Network; WAO, World Allergy Organization
The EAACI/GA²LEN/EDF/WAO urticaria guideline provides a full diagnosis algorithm.
Treatment objective of the guideline is to achieve rapid and complete symptom relief

- Identification and elimination of underlying causes,
- Avoidance of eliciting factors, tolerance induction, and/or
- Symptomatic pharmacological treatment by reducing mast cell mediator release and/or the effect of these mediators at the target organ\(^1,2\)

- Acute urticaria is self-limited and treatment is usually focused on symptomatic relief.
Omalizumab is recommended as third-line treatment.

**First line**

Second-generation AH1

- Consider referral to a specialist

**Second line**

Increasing dosage up to fourfold second-generation AH1

- Should be performed under the supervision of a specialist

**Third line**

Add on to second line: Omalizumab

- After 2–4 weeks or earlier if symptoms are intolerable

**Fourth line**

Add on to second line: Ciclosporine A

- Control inadequate after 6 months or earlier if symptoms are intolerable

Other treatments are available

Short course (max 10 days) of corticosteroids may also be used at all times if exacerbations demand it.

AH1, H1-antihistamine

Zuberbier T et al. The EAACI/GA²LEN/EDF/WAO Guideline for the Definition, Classification, Diagnosis and Management of Urticaria. Allergy 2018;73:1393-1414
A World-wide Antihistamine-Refractory Chronic Urticaria Patient Evaluation

- Guidelines are clear and practical
- What about real life?
- Be AWARE
**AWARE Study**

**World-wide Antihistamine-Refractory chronic urticaria patient Evaluation**

A program of prospective, non-interventional studies of patients with chronic urticaria (CU) refractory to at least 1 approved dose of a H₁-antihistamine¹,²

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*Aforementioned data as of 29 January 2018*

AWARE: Overall Objectives

Europe & Central - Latin America studies
To assess the impact of treatment over 24 months (± 6 weeks) on PROs in patients who failed ≥ H₁-antihistamine treatment in the real-life clinical setting.

Asia-Pacific, Middle East and Northern Africa study
To describe clinical outcomes, treatment patterns, healthcare resource utilization and quality of life for patients with H₁-antihistamine-refractory CU including both CSU and CIndU, treated under current real-life medical practice.
Learnings from Baseline Results

- Mean (SD) age was 46.3 (15.6) years and the majority of the patients were female (70%).
- The mean (SD) time since CSU diagnosis was 4.8 (7.2) years.
- 46.1% were classified as CSU with angioedema and 2.9% as angioedema without wheals.
- 76% had CSU and 24% had CSU concomitantly with CIndU.
- Only 57.6% of patients had received treatment for CSU at baseline: 46.3% second-generation H1-antihistamines; 9.1% first-generation H1-antihistamines and 15.8% received corticosteroids.
Learnings from Baseline Results

- The mean (SD) UCT score was 7.9 (4.3)
- The majority of patients (77.5%) showed signs of uncontrolled urticaria (UCT score <12)
- 27% of patients had taken sick leave because of urticaria
- Angioedema average intensity was rated as severe by 31.3%, as moderate by 46.4% and as mild by 20.5%
- The mean DLQI score was 8.3 – 32.8% of CSU patients had a very large or extremely large impact on their QoL
- The most severely impaired subdomains of the CU-Q_2oL were itching/embarrassment (mean 48.2), sleep (mean 45.2) and the mental status (mean 41.4)
What happens when we follow these patients up for 2 years

**Study type**  
Phase IV, observational, non-interventional, multicenter study

**Aims**  
Evaluate prospectively and under conditions of daily living the disease burden, current treatment schedule and use of clinical resources by patients with H<sub>1</sub>-antihistamine refractory chronic urticaria as a function of the administered therapy

**Study design**  

| Follow up period (24 months) | V1 Baseline | V2 Quarterly visit | V3 Quarterly visit | V4 Annual visit | V5 Quarterly visit | V6 Annual visit | V7 Quarterly visit | V8 Annual visit | V9

**Key end points**  
- PROs in relation to medication used: DLQI, CU-Q<sub>2</sub>oL, WPAI, UCT, UAS7/CIndU tracker  
  - In case of angioedema AE-QoL/AAS  
- Utilization of medical facilities  
- Previous and current medication

AAS, Angioedema Activity Score; AE-QoL, Angioedema Quality of Life score; CIndU, chronic inducible urticaria; CU-Q<sub>2</sub>oL, Chronic Urticaria Quality of life questionnaire; DLQI, Dermatology Life Quality Index; UAS7, weekly Urticaria Activity Score; UCT, Urticaria Control Test; WPAI, Work Productivity and Activity Impairment.

AWARE Data on File.
UCT scores improved over time but proportion of patients with uncontrolled disease remained substantial.

- At Month 24, CSU was controlled (UCT≥12) in 71.3% (n/N=667/936) of patients, however, in 28.7% (n/N=269/936) of patients CSU was still uncontrolled (UCT<12)
Quality of life improved over time

CSU, Chronic spontaneous urticaria; CU-QoL, chronic urticaria-quality of life questionnaire; DLQI, dermatology life quality index; N, total patients; n, patients included

Moderate to Extremely Large Effect on DLQI was Observed in More Patients with Angioedema with Wheals

- Patients with angioedema and wheals showed higher mean (SD) DLQI scores 8.9 (7.4) compared with angioedema only patients 5.5 (6.2)

DLQI, Dermatology Life Quality Index; QoL, quality of life; SD, standard deviation

*Data was available for 1,768 of the ‘angioedema’ population and 75 of the ‘angioedema without hives’ population.

Maurer et al. Poster presented at FCDC, 18–21 October 2018, Las Vegas, USA
The percentage of patients with CSU, CIndU and CSU+CIndU achieving DLQI=0-1 increased from 17.4%, 15.1% and 12.5% at baseline, respectively, to 57.7%, 39.6% and 50.3%, respectively, by Visit 9.
Treatment escalation was frequent in some countries

Other third line treatment options* and sedating antihistamines were used infrequently

- With regard to medication groups, 17.3% of CSU patients were treated with approved doses of nsAH and 23.2% of these patients had poorly controlled disease (UCT<12) at month 24
- Non-recommended use of ‘on demand’ nsAH increased from 3.1% before enrollment to 12.8% (n/N=163/1278) at month 24

* Defined in the 2014 EAACI/GA²LEN/EDF/WAO guidelines

CSU, chronic spontaneous urticaria; nsAH, non-sedating antihistamines; UCT, urticaria control test

Real-world clinical practice is not consistent with recommendations for managing CSU in international guidelines.

CSU remains undertreated despite the availability of effective treatment options.

In many patients, CSU remains uncontrolled despite treatment.

CSU has a substantial impact on QoL.

Angioedema is underreported and has a negative impact of QoL in patients with CSU.
Overall conclusions

Current guidelines for the treatment of CSU offer clear and practical recommendations for the diagnosis and management of CSU.

Real-world evidence from the AWARE study shows that CSU remains undertreated and poorly controlled in many patients, with a substantial negative impact on quality of life.

Treatments like omalizumab have improved patient management, but new therapeutic options are still required for many patients to achieve the goal of complete symptomatic control.

Several drugs are currently under development for the treatment of CSU.