Targeting complete CSU control: current state of the art and future perspectives

EADV 2021 virtual symposium
Friday 1 October 2021
13:00–14:00 CEST
Introduction

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Universitat Pompeu Fabra
Barcelona, Spain
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Faculty

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Hospital del Mar, Parc de Salut Mar Universitat Autònoma, Spain
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Prof Romi Saini
Johns Hopkins University School of Medicine, USA
Professor Saini is a Professor of Medicine at the Johns Hopkins University School of Medicine, and Training Program Director for the Allergy and Clinical Immunology Fellowship Program at Johns Hopkins

Dr John Reed
Churchill Hospital, Oxford University, UK
Dr Reed is a Clinical Lead, Consultant Dermatologist, and Honorary Senior Lecturer at Oxford University
Learning objectives

• To review the burden of disease and unmet needs in CSU
• To discuss the importance of achieving complete control and the need to follow treatment guidelines
• To provide an overview of current and potential future treatments for CSU
## Agenda

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<td>Welcome and introduction</td>
<td>Ana Maria Giménez-Arnau (Spain)</td>
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<td>The patient journey in CSU: The challenges we face</td>
<td>Ana Maria Giménez-Arnau (Spain)</td>
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<td>Romi Saini (USA)</td>
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<td>Live Q&amp;A</td>
<td>All faculty</td>
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The patient journey in CSU: The challenges we face

Ana M Giménez-Arnau
Dermatology Hospital del Mar
Universitat Autónoma
Universitat Pompeu Fabra
Barcelona, Spain
Ana M 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, Almirall, Leo Pharma

- Research Grants supported by Uriach Pharma, Novartis, Grants from Instituto Carlos III-FEDER

- Educational activities for Uriach Pharma, Novartis, Genentech, Menarini, LEO PHARMA, GSK, MSD, Almirall, Sanofi-Regeneron, Avene
Dermatology team
The patient journey in CSU: the challenges we face

- Burden of the disease
- Treatment guidelines update
- Unmet needs in the patient journey
- Pathophysiology and treatment targets for CSU
CU is a common disease across the world

Overall lifetime chronic urticaria prevalence 4.4%; point prevalence 0.7%

CU, chronic urticaria.
Patients experience long delays in diagnosis and correct treatment

<table>
<thead>
<tr>
<th>CANADA</th>
<th>USA</th>
<th>WESTERN EUROPE</th>
<th>JAPAN</th>
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<tbody>
<tr>
<td>24 months for diagnosis</td>
<td>&gt;6 weeks to see a physician for 45% of patients</td>
<td>2–4 years for diagnosis</td>
<td>One month from onset of urticaria to consult an allergist/dermatologist for 85% patients</td>
</tr>
</tbody>
</table>

Although the diagnosis is simply based on the clinical history, patients receive unnecessary testing or incorrect/frustrating messages and strategic management plans.
Delays in diagnosis and treatment impact the burden of CU comorbidities and concomitant diseases

- **Concomitant autoimmune diseases**
  - Thyroid autoimmunity, 4–37.1%
  - Systemic lupus erythematosus, 26.7 times increased risk in female patients
  - Type diabetes mellitus, 1.8%
  - Vitiligo, 0.4%
  - Coeliac disease and rheumatoid arthritis, 0.6%

- **Concomitant atopy, 16.9%**

- **Psychiatric comorbidities, >30%**
  - Anxiety
  - Depression
  - Somatoform disorders

- **Other comorbidities and concomitant conditions**
  - Hypertension and obesity, >20%
    - Hyperlipidemia
    - Metabolic syndrome
  - Headaches, particularly in children
  - Infectious diseases, Helicobacter pylori, parasitic infections or acute and chronic viral infections
  - Others, rarely papillary thyroid, lung and hematologic malignancies

RWE study AWARE demonstrates that quality of life is often impaired in patients with CSU

Note: Proportions are presented based on the denominator for patients who had available DLQI data at visit 1 (baseline).
CSU, chronic spontaneous urticaria; DLQI, Dermatology Life Quality Index.
What is the goal of treating patients suffering chronic urticaria?

Absence of symptoms
“Treat the disease until it is gone”

We recommend aiming at complete symptom control in urticaria considering, as much as possible, the safety and the quality of life of each individual patient.

Complete disease control is associated with the least impact of disease on QoL

In patients at Week 20 of the Phase IIb QGE031C2201 study.

DLQI, Dermatology Life Quality Index; LS mean, least squares mean; QoL, quality of life; SE, standard error; UAS7, seven days urticaria activity score.

# Omalizumab in chronic spontaneous urticaria: A meta-analysis of randomized controlled trials

Omalizumab 300 mg complete responders

<table>
<thead>
<tr>
<th>Study</th>
<th>Omalizumab Events</th>
<th>Omalizumab Total</th>
<th>Placebo Events</th>
<th>Placebo Total</th>
<th>Weight</th>
<th>M-H. Fixed. 95% CI</th>
</tr>
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<tbody>
<tr>
<td>ASTERIA I</td>
<td>29</td>
<td>81</td>
<td>7</td>
<td>80</td>
<td>15.4%</td>
<td>4.09 [1.90, 8.80]</td>
</tr>
<tr>
<td>ASTERIA II</td>
<td>35</td>
<td>79</td>
<td>4</td>
<td>79</td>
<td>8.8%</td>
<td>8.75 [3.26, 23.46]</td>
</tr>
<tr>
<td>GLACIAL</td>
<td>85</td>
<td>252</td>
<td>4</td>
<td>83</td>
<td>13.2%</td>
<td>7.00 [2.65, 18.49]</td>
</tr>
<tr>
<td>MOA</td>
<td>1</td>
<td>17</td>
<td>0</td>
<td>8</td>
<td>1.5%</td>
<td>1.50 [0.07, 33.26]</td>
</tr>
<tr>
<td>MYSTIQUE</td>
<td>9</td>
<td>25</td>
<td>0</td>
<td>21</td>
<td>1.2%</td>
<td>16.08 [0.99, 260.85]</td>
</tr>
<tr>
<td>X-ACT</td>
<td>18</td>
<td>44</td>
<td>3</td>
<td>47</td>
<td>6.4%</td>
<td>6.41 [2.03, 20.26]</td>
</tr>
<tr>
<td>XCUISITE</td>
<td>5</td>
<td>7</td>
<td>1</td>
<td>22</td>
<td>1.1%</td>
<td>15.71 [2.19, 112.84]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>505</td>
<td>340</td>
<td></td>
<td></td>
<td>47.5%</td>
<td>6.55 [4.17, 10.28]</td>
</tr>
<tr>
<td>Total events</td>
<td>182</td>
<td></td>
<td>19</td>
<td></td>
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</tbody>
</table>

Heterogenity Chi²=3.83, df=6 (P=0.70); I²=0%
Test for overall effect: Z=8.18 (P<0.00001)

CI, confidence interval; M-H, Mantel-Haenszel.
Therapeutic options and rational treatment

First-line: Second generation AH₁
After 2–4 weeks or earlier if symptoms are intolerable

Second-line: Increase dosage up to fourfold of 2nd generation AH₁
After 2–4 weeks or earlier if symptoms are intolerable

Third-line: Add on to 2nd generation AH₁: omalizumab
If inadequate control after 6 months or earlier if symptoms are intolerable

Fourth-line: Add on to 2nd generation AH₁: ciclosporin A

Consider referral to a specialist
Should be performed under the supervision of a specialist
Other treatments are available

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

AH, antihistamines.
## What have we learned about omalizumab in CSU?

<table>
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<tr>
<th>Topic</th>
<th>References</th>
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<tbody>
<tr>
<td></td>
<td>Kocatürk E, et al. Int Arch Allergy and Immunology. 2018;21:1-5</td>
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CSU, chronic spontaneous urticaria.
New proposed algorithm

General Practitioner
Consider referral to a specialist

Second generation AH₁
Increase dosage up to fourfold of 2nd generation AH₁
After 2–4 weeks or earlier if symptoms are intolerable

Add on to 2nd generation AH₁: omalizumab
Increase the dose and/or shorten interval
If inadequate control after 6 months or earlier if symptoms are intolerable
2nd- and 3rd-line treatments apply just for CU a. 300 mg every 4 weeks b. Up to 600 mg every 2 weeks

Add on ciclosporin A
only if AH₁ and omalizumab fails

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

AH, antihistamines; CU, chronic urticaria.
Antihistamine-resistant CSU remains uncontrolled in a proportion of patients after 2 years

Patients enrolled in Europe (N=3741)

Belgium: 80
Denmark: 82
France: 95
Germany: 2,247
Greece: 145
Italy: 249
Norway: 50
Portugal: 76
Russia: 141
Spain: 277
Sweden: 28
UK: 261

AWARE was a multicenter, prospective non-interventional study that followed patients with CU for 2 years, who were inadequately controlled with at least one approved dose of H1-antihistamine.

Symptom control (wheals and angioedema) and Disease control after 2 years in AWARE

**HIVES**

- Baseline: 2706
- Month 3: 2058
- Month 12: 1570
- Month 24: 1241

**ANGIOEDEMA**

- Baseline: 2706
- Month 3: 2042
- Month 12: 1555
- Month 24: 1232

**UCT GROUPS**

- Baseline: 2727
- Month 3: 2174
- Month 12: 1647

**AAS**

- Baseline: 2727
- Month 3: 2174
- Month 12: 1647

AAS, angioedema activity score; CSU, chronic spontaneous urticaria; CU, chronic urticaria; H1, histamine; UCT, urticaria control test.

Antihistamine-resistant CSU remains uncontrolled in a proportion of patients after 2 years

Patients enrolled in Europe (N = 3741)

AWARE was a multicenter, prospective non-interventional study that followed patients with CU for 2 years, who were inadequately controlled with at least one approved dose of H₁-antihistamine.

Symptom control (wheals and angioedema) and Disease control after 2 years in AWARE

<table>
<thead>
<tr>
<th>Country</th>
<th>N</th>
</tr>
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<tbody>
<tr>
<td>Belgium</td>
<td>80</td>
</tr>
<tr>
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AAS, angioedema activity score; CSU, chronic spontaneous urticaria; CU, chronic urticaria; H₁, histamine; UCT, urticaria control test.

Approximately a third of antihistamine-resistant patients received omalizumab

Other treatment options were rarely used

Prior to AWARE enrollment, Ciclosporin was prescribed in 2.6% (n=71) of patients, which reduced to 0.3% (n=4)

Montelukast was prescribed for 3.6% (n=97) of patients and prescriptions reduced to 1.9% (n=24)

Non-recommended sAH were similarly rarely prescribed, with 4.1% before enrollment reduced to 3.0% (n=38)

Despite the use of omalizumab, 29% of patients had uncontrolled CSU (UCT<12) at 2 years

Percentage of poorly-controlled (UCT<12) and well-controlled (UCT ≥12) patients receiving different treatments at each visit

*Not currently approved for treatment. CSU, chronic spontaneous urticaria; H₁, histamine; UCT, urticaria control test.
There are still a number of unmet needs in the CSU patient journey

- Many patients experience delays in receiving a diagnosis and appropriate treatment.
- In the absence of diagnosis and appropriate treatment, comorbidities and concomitant diseases can develop/worsen, further impacting on the patient’s quality of life.
- Failure to achieve complete control of CSU symptoms means quality of life remains poor.
- A large proportion of patients with CSU have uncontrolled disease, even when treatment guidelines are followed.

CSU, chronic spontaneous urticaria.
CSU is a mast cell-driven disease

Images used with permission from Giménez-Arnau A et al, Hospital del Mar.
Many therapeutic targets can be found in the mast cell

Free IgE
- Omalizumab*\(^a\)
- Ligelizumab\(^b\)
- UB221\(^b\)
- LP0201 (FB-825)\(^b\)
- GI-301\(^b\)

Receptor-bound IgE
- Ligelizumab\(^b\)

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*Omalizumab is approved for the treatment of CSU. \(^a\)Currently available, \(^b\)under investigation, \(^c\)hypothetical

BTK, Bruton’s tyrosine kinase; CRTH2, Prostaglandin D\(_2\) receptor; CSU, chronic spontaneous urticaria; C5, complement 5; FcεRI, high-affinity IgE receptor; H1-AH, H\(_1\)-antihistamines; IgE, immunoglobulin E; IgG, immunoglobulin G; IL, interleukin; MRGPRX2, Mas-related G Protein-coupled receptor-X2; NK, neurokinin; PAF, platelet-activating factor; TSLP, thymic stromal lymphopoietin.

Infiltrating cells also play a role in wheal pathophysiology

Images used with permission from Giménez-Arnau A et al, Hospital del Mar.
CSU has a complex pathophysiology, with many potential therapeutic targets.
Novel treatments, targets and approaches


BTK, Bruton’s tyrosine kinase; CRTH, Prostaglandin D2 receptor; H1/4R, histamine 1/4 receptor; Ig, immunoglobulin; IgE, immunoglobulin E; IL, interleukin; FcεRI, high-affinity IgE receptor; LTR, leukotriene receptor; NK, neurokinin; C5, complement 5; PI3 K, phosphoinositide 3-kinase; S1P, sphingosine-1-phosphate; SHIP, SH2-containing inositol phosphatase 1; SYK, spleen tyrosine kinase; TSLP, thymic stromal lymphopoietin. *Currently available, †under investigation, ‡hypothesised

Conclusions

Many patients experience a delay in diagnosis or do not receive optimal treatment, despite the recommended treatment algorithm for CSU.

This can lead to a high burden of disease and impact on quality of life.

It is recommended to aim for complete symptom control with CSU, with the goal of treatment being to “treat the disease until it is gone.”

CSU, chronic spontaneous urticaria
Optimizing patient outcomes in CSU: Could new biologics help achieve this?

Sarbjit S. Saini, MD
Professor of Medicine
Johns Hopkins University School of Medicine
Disclosures

- Research Interests – NIH, Novartis, Sanofi, Regeneron
- Other Interests – Consultant to Allakos, Genentech, Medimmune, Novartis, Ono, Regeneron, Gbio
- Organizational interests – *UptoDate*, ABAI, AAFA, AAAAI
Today we will discuss:

- The role of IgE in CSU
- Omalizumab in the treatment of CSU
- The potential to further improve outcomes for patients with CSU
- Novel biologics in development
International guidelines recommend $H_1$-antihistamines as first-line treatment for CSU

**US-AAAAI/ACAAI Guidelines**

- **Step 1**: 2nd generation AH$_1$ monotherapy
- **Step 2**: One or more of the following:
  - Increase 2nd generation AH$_1$ (up to 4x)*
  - Add alternative 2nd generation AH$_1$
  - Add a H$_2$-antagonist*
  - Add a 1st generation AH$_1$ at night*
- **Step 3**: Add or dose advance a potent AH$_1$ (i.e. doxepin or hydroxyzine)
- **Step 4**: Add omalizumab, ciclosporin or other anti-inflammatories, immunosuppressants or biologics

**EAACI/WAO Guidelines**

- **Step 1**: 2nd generation AH$_1$ monotherapy
- **Step 2**: Increase 2nd generation AH$_1$ dose (up to 4x)*
- **Step 3**: Add omalizumab to 2nd generation AH$_1$
- **Step 4**: Add ciclosporin to 2nd generation AH$_1$

*Not currently licensed for treatment of CSU.

AAAAI/ACAAI, American College of Allergy, Asthma, and Immunology; AH, antihistamine; CSU, chronic spontaneous urticaria; EAACI, European Academy of Allergology and Clinical Immunology; WAO, World Allergy Organization.

However, many patients are refractory to treatment with $H_1$-antihistamines

- CSU
  - $\sim 1.6 \text{ M to } \sim 3.5 \text{ M patients}^{1,2}$
  - $\sim 80\%$ inadequate response to labeled dose of $H_1$-antihistamines$^3$

- $H_1$-antihistamine refractory (1x)
  - $\sim 1.3 \text{ M to } \sim 2.8 \text{ M patients}^2$
  - $\sim 50\%$ inadequate response to increased dose of $H_1$-antihistamines$^4,5$

- $H_1$-antihistamine refractory (up to 4x)
  - $\sim 800 \text{ K to } \sim 1.75 \text{ M patients}^2$

Numbers calculated using a US population.
CSU, chronic spontaneous urticaria; $H_1$, histamine 1 receptor
Omalizumab is recommended for treatment of CSU in patients that do not respond to antihistamines.
IgE plays a central role in the pathogenesis of CSU

Ba, basophil; CSU, chronic spontaneous urticaria; Eos, eosinophil; FcεRI, high-affinity IgE receptor; IgE, immunoglobulin E; MrgX2, mas-related gene X2; PgD2, prostaglandin D2; TH2, T helper 2.
Phase III studies showed more patients on omalizumab achieved complete control (UAS7=0) versus placebo.

Across the three studies, the safety profile for omalizumab was consistent with the established safety profile observed with asthma and previous CSU studies.

~40% patients had UAS7=0 after 12 and 24 weeks

*P<0.05 and **P<0.001. Omalizumab 75 mg is not licensed for CSU; omalizumab 150 mg is not licensed for CSU in some countries. Data are for mITT population; p values are vs placebo.

CSU, chronic spontaneous urticaria; OMA, omalizumab; mITT, modified intention to treat; UAS7, seven days Urticaria Activity Score.

More patients on omalizumab achieved well-controlled disease (UAS7≤6) versus placebo.

Across the three studies, the safety profile for omalizumab was consistent with the established safety profile observed with asthma and previous CSU studies.

~60% patients had UAS7≤6 after 12 and 24 weeks.

*P<0.05 and **P<0.001. Omalizumab 75 mg is not licensed for CSU; omalizumab 150 mg is not licensed for CSU in some countries. Data are for mITT population; p values are vs placebo.

CSU, chronic spontaneous urticaria; OMA, omalizumab; mITT, modified intention to treat; UAS7, seven days Urticaria Activity Score.

Predictors of poor response to omalizumab

- Low serum IgE\(^1\)–\(^4\)
- Low basophil IgE receptors\(^5\)
- Presence of serum activity inducing Baso CD203c, ASST, histamine releasing activity\(^6,\)\(^7\)
- Presence of autoantibodies to Fc\(\varepsilon\)RI, resulting in basopenia\(^8\)
- Altered basophil IgE functional phenotype\(^9\)

ASST, autologous serum skin test; Baso, basophil; CD203c, ectonucleotide pyrophosphatase and/or phosphodiesterase; Fc\(\varepsilon\)RI, high-affinity IgE receptor; IgE, immunoglobulin E.

Serum BHRA or ASST+ predicts slow response to omalizumab in CSU

Complete Response
UAS7<6

N=56 subjects

ASST, autologous serum skin test; BHRA, basophil histamine release assay; UAS7, seven days Urticaria Activity Score.
How might we further improve outcomes in CSU – a more effective anti-IgE?
IgE binds two IgE-receptors, which have different roles in disease

**FcεRI**
- **1–3** (high-affinity receptor)
- Mast cells, basophils
  - Mediator release
  - Skin reaction, bronchoconstriction
- **CSU, CIndU, food allergy**

**FcεRII/CD23**
- **1,3** (low-affinity receptor)
- Antigen-presenting cells
  - Th2 cytokine production
  - Inflammation (pulmonary eosinophilia)
- **Allergic asthma**

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CIndU, chronic inducible urticaria; CSU, chronic spontaneous urticaria; FcεRI, high-affinity IgE receptor; FcεRII/CD23, low-affinity IgE receptor; IgE, immunoglobulin E; TH, T-helper.

Ligelizumab has a different inhibition profile to omalizumab

- **IgE binding affinity**
  Ligelizumab > omalizumab

- **Dissociation rate**
  Ligelizumab < omalizumab

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QGE031C2201 was a Phase IIb randomized, double-blind dose-finding study for ligelizumab

Screening
Wk -2

Core study
Treatment
Wk 12
Wk 20

Follow-up
Wk 32
Wk 44

Ligelizumab 240 mg q4w (n=85)
Ligelizumab 72 mg q4w (n=84)
Ligelizumab 24 mg q4w (n=43)
Omalizumab 300 mg q4w (n=85)
Ligelizumab 120 mg SD
Placebo q4w (n=42)\(^a\)
Placebo (n=43)

Eligible to enroll in the extension study from Wk 32 onwards, if UAS7≥12\(^b\)

\(^a\)The 120 mg single-dose (SD) arm was chosen to characterize the PK/PD. Data from this arm assesses the duration of response and correlates this with the concentration of drug in serum at the time when symptoms reappear; \(^b\)Patients who remained in the follow-up period for at least 12 weeks and had active disease (UAS7≥12), could enter the extension study from Week 32 onwards.

Ligelizumab provided more rapid disease control vs omalizumab

*Analysis performed on as observed data. N, total number of patients in each arm at that time point.
q4w, every 4 weeks; UAS7, weekly Urticaria Activity Score, complete response: UAS7=0.

All doses of ligelizumab were well-tolerated. The percentages of patients who experienced at least one adverse event were similar across the ligelizumab, omalizumab and placebo treatment groups.
Higher rate of complete CSU control with ligelizumab vs omalizumab, sustained after treatment discontinuation

Patients considered completely controlled
(HSS7=0, ISS7=0, AAS7=0)

Patients considered CSU free
(HSS7=0, ISS7=0, AAS7=0, DLQI=0–1)

All doses of ligelizumab were well-tolerated. The percentages of patients who experienced at least one adverse event were similar across the ligelizumab, omalizumab and placebo treatment groups.

AAS7, seven days Angioedema Activity Score; DLQI, Dermatology Life Quality Index; HSS7, seven days Hives Severity Score; ISS7, seven days Itch Severity Score.

Other targets are being evaluated for the treatment of CSU

C5αR1, complement component C5α receptor; CD4, cluster of differentiation 4; CD200, cluster of differentiation 200; CDX-0159, KIT inhibitor; cKIT, tyrosine-protein kinase KIT; FcεRI, high-affinity IgE receptor; GI-301, anti-IgE biologic; IgE, immunoglobulin E; IL, interleukin; MRGPRX2, mas-related G protein-coupled receptor X2; SCF, stem cell factor; TSLP, thymic stromal lymphopoietin; TSLPR, thymic stromal lymphopoietin receptor.

Conclusions

Omalizumab is an anti-IgE that is recommended to treat patients who do not respond to \(H_1\)-antihistamines

Novel biologics in development may have the potential for more complete disease control

Phase II data shows that treatment with ligelizumab results in more rapid and sustained control of CSU vs omalizumab

CSU, chronic spontaneous urticaria; IgE, immunoglobulin E.
Exploring novel pathways in the journey to complete CSU control

Dr John Reed PhD FRCP
Consultant Dermatologist, Churchill Hospital, Oxford
Disclosures

- Novartis – speaker & advisory board role in product development, education & trial design
CSU: a predominantly autoimmune disease?

BTK, Bruton’s tyrosine kinase; CSU, chronic spontaneous urticaria; IgE, immunoglobulin E; IgG, immunoglobulin G; IL, interleukin; FcεRI: high affinity IgE receptor; S1P, sphingosine-1-phosphate; SHIP-1, src homology 2-containing inositol phosphatase; Syk, protein tyrosine kinase; TNF, tumor necrosis factor.

Eosinophils and CSU

Auto-allergic CSU

Auto-immunological CSU

Mast cell

Lymphocyte

Eosinophil

Dermal fibroblast

Basophil

Autoantigen

IgG-anti-IgE

IgG-anti-FcεRI

IL-5

Eotaxins

MCP3

RANTES

CCL24

Eotaxins

IL-4, IL-13

Endothelial cells

CCL24, CC-motif chemokine ligand 24; CSU, chronic spontaneous urticaria; IgE, immunoglobulin E; IgG, immunoglobulin G; IL, interleukin; FcεRI: high affinity IgE receptor; MCP, mast cell protease; RANTES, regulated on activation, normal T-cell expressed and secreted.

Extrinsic coagulation pathway in CSU

TF: VIIa, Xa, IIa; activated coagulation factors

BA, basophils; C5α, complement component 5α; C5αR, C5α receptor; EC, endothelial cells; Eo, eosinophils; H1R, histamine 1 receptor; IL, interleukin; LPS, lipopolysaccharide; MC, mast cell; PAF, platelet activating factor; PAR, protease activated receptor; TLR4, toll-like receptor 4.

CSU has a complex pathophysiology, with many potential therapeutic targets.

Image adapted from Kocaturk E, et al. 2017

BTK, Bruton's tyrosine kinase; CD5, complement 5; CD20, cluster of differentiation 20; CRTH2, Prostaglandin D2 receptor; H1/4R, histamine 1/4 receptor; Ig, immunoglobulin; IgE, immunoglobulin E; IL, interleukin; LTR, leukotriene receptor; KIT, growth factor tyrosine kinase receptor; NK, neurokinin; P3K, phosphoinositol-3-kinase; S1P, sphingosine-1-phosphate; SHIP, SH2-containing inositol phosphatase 1; Syk, spleen tyrosine kinase; TNF, tumor necrosis factor; TSLP, thymic stromal lymphopoietin.

*Currently available, †under investigation, ‡hypothetical

Introduction to Bruton’s tyrosine kinase

BTK is a member of the TEC family of tyrosine kinases\(^1,2\)

It is expressed in select immune cells including B cells, macrophages, mast cells, basophils and thrombocytes\(^1,3,4\)

BTK is crucial for signaling in the mast cell\(^4\)

BTK is also active on the BCR\(^3,4\)

BCR, B cell antigen receptor; BTK, bruton tyrosine kinase; TEC, tyrosine-protein kinase

BTK is crucial for the FcεRI signalling that leads to mast cell degranulation.


BTK, bruton tyrosine kinase; FcεRI, high affinity IgE receptor; Ig, immunoglobulin.
Bruton’s tyrosine kinase (BTK) inhibitors

Ibrutinib & acalabrutinib

✓ Licensed for treatment of B-cell malignancy
✓ Binds covalently to cysteine residue 481 of BTK
✓ Limited selectivity leading to off-target activity: reacts with other kinases

BTK, Bruton’s tyrosine kinase.
**Remibrutinib is a novel oral BTK inhibitor**

**Remibrutinib** binds to BTK\(^1,2\), blocking mast cell degranulation, regardless of FcεRI activation mechanism\(^3\).

Inhibiting BTK on BCR may also lead to lower secretion/production of antibodies\(^3,4\).

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**BCR, B cell antigen receptor; BTK, Bruton tyrosine kinase; CSU, chronic spontaneous urticaria; FcεRI, high affinity IgE receptor; Ig, immunoglobulin.**

Remibrutinib – a highly selective covalent BTK inhibitor

Binds to BTK in the inactive conformation

High selectivity for BTK over other kinases

Covalent binding leads to sustained BTK occupancy

BTK, Bruton's tyrosine kinase; FcεRI, high affinity IgE receptor
Gabizon R and London N. J Med Chem. 2020;63:5100-1
Remibrutinib: Phase IIb study design

Multicenter, randomized, double-blind, placebo-controlled Phase IIb dose-finding study to investigate the efficacy, safety and tolerability of remibrutinib in adult CSU patients inadequately controlled by 2nd generation H1 receptor antagonists.

**Background therapy:** 2nd gen. H1 antihistamine

**Rescue therapy:** alternative 2nd gen. H1 antihistamine

**Randomization**

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<th>Week</th>
<th>Day</th>
<th>-14 to -10</th>
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<th>57</th>
<th>85</th>
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</tr>
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**Screening**

- Low-dose remibrutinib QD (n=44)
- Medium-dose remibrutinib QD (n=44)
- High-dose remibrutinib QD (n=44)

**Double-blind treatment period**

- Low-dose remibrutinib BID (n=44)
- Medium-dose remibrutinib BID (n=44)
- High-dose remibrutinib BID (n=44)

**Follow-up**

- Placebo BID (n=44)

Fenebrutinib in AH-refractory CSU

Double-blind, placebo-controlled Phase II study

No SAEs; transient increased ALT occurred in 150 mg OD and 200 mg BID groups

*Significant improvement

AH, antihistamine; ALT, alanine aminotransferase; BHRA, basophil histamine release assay; BID, twice daily; CSU, chronic spontaneous urticaria; OD, once daily; UAS7, seven days urticaria activity score.

Anti-Siglec-8: Lirentelimab (AK002)

- Sialic acid-binding immunoglobulin-type lectins
- Transmembrane proteins: regulate intra- & intercellular signaling
- Siglec-8 is expressed on mast cells and eosinophils
  - induces eosinophil apoptosis
  - inhibits FcεRI-mediated mast cell histamine & PGD2 release

CSU, chronic spontaneous urticaria; FcεRI, high affinity IgE receptor; MC, mast cell; PGD2, prostaglandin D2; UAS7, seven days urticaria activity score.
C5αR and avdoralimab

• C5α augments mast cell activation in CSU
  – effects of mast cell-activating IgG antibodies in type IIb autoimmunity in part mediated by C5αR activation
  – C5α also generated by extrinsic coagulation pathway

• Avdoralimab
  – specific C5αR inhibitory binding
  – evaluated in CSU and pemphigoid

C5α, complement component 5a; C5αR, C5α receptor; CSU, chronic spontaneous urticaria; MC, mast cell.
Summary of potential targets in CSU

- BTK, Bruton's tyrosine kinase
- C5α, complement component 5a
- C5αR, C5α receptor
- CRTH2, Prostaglandin D2 receptor
- CD200, cluster of differentiation 200 receptor
- CD300a, inhibitory receptor protein 60
- FcεRI, high-affinity IgE receptor
- FcγRIIB, low-affinity IgG receptor
- H1/4R, histamine 1/4 receptor
- IL, interleukin
- KIT, growth factor tyrosine kinase receptor
- LTR, leukotriene receptor
- NK, neurokinin
- OSMRβ, oncostatin M receptor
- PI3 K, phosphoinositide 3-kinase
- S1P, sphingosine-1-phosphate
- SHIP, siglec-8, sialic acid-binding Ig-like lectin 8
- SH2-containing inositol phosphatase
- SYK, spleen tyrosine kinase
- TNF, tumor necrosis factor
- TSLP, thymic stromal lymphopoietin

**Currently available,** **under investigation,** **hypothetical**


Summary

CSU has a complex pathophysiology, with many potential therapeutic targets.

BTK is crucial for FcεRI receptor signaling that leads to mast cell degranulation, resulting in CSU symptoms.

Remibrutinib is currently in Phase IIB of development, and has a unique covalent binding property and high selectivity for BTK.

Exploring novel treatment pathways may have the potential to provide complete disease control for more patients with CSU.

BTK, Bruton's tyrosine kinase; CSU, chronic spontaneous urticaria; FcεRI, high affinity IgE receptor.
Live Q&A

All faculty
Thank you for your participation

We would appreciate your feedback on this symposium, please fill out the evaluation form on the EADV platform