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GUIDELINES

EAACI Biologicals Guidelines—Omalizumab for the treatment of chronic spontaneous urticaria in adults and in the paediatric population 12–17 years old

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Abbreviations: ADA, anti-drug antibodies; AE, adverse events; AIS, activity impairment score; ASST, autologous serum skin test; BHRA, basophil histamine release assay; BTs, basophil tests; CI, confidence interval; CIU, chronic idiopathic urticaria; CSU, chronic spontaneous urticaria; CU-Q2oL, Chronic Urticaria Quality of Life Questionnaire; DARPins, Designed Ankyrin Repeat Proteins; DLQI, Dermatology Life Quality Index; EAACI, European Academy of Allergy and Clinical Immunology; ECs, Endothelial cells; EMA, European Medicine Agency; EtD, evidence to decision; FcεR1, high-affinity IgE receptor; FcεRI, high-affinity receptors for IgE; FDA, Food and Drug administration; GDG, Guideline Development Group; GPCRs, G protein-coupled receptors; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HCP, healthcare professionals; Ig, immunoglobulin; IL, interleukin; IRR, incidence rate ratios; ISS, itch severity score; ITAMs, immunoreceptor tyrosine-based activation motifs; mAb, monoclonal antibodies; MCs, mast cells; MD, mean difference; MID, minimal important difference; MMP, metaloproteinase; MRGPRX2, Mas-related G protein-coupled receptor X2; PICO, population, intervention, comparator, and outcomes; QoL, quality of life; RCT, randomized controlled trial; ROB, risk of bias; RR, risk ratio; RWE, real-world evidence; SAE, serious adverse events; SC, subcutaneous; SOF, summary of findings; SR, systematic review; SYK, spleen tyrosine kinase; TSLP, thymic stromal lymphopoietin; UAS, urticaria activity score; UCT, urticaria control score; WIS, work impairment score; WPAI, work productivity and activity impairment.

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Abstract
Chronic spontaneous urticaria (CSU) imposes a significant burden on patients, families and healthcare systems. Management is difficult, due to disease heterogeneity and insufficient efficacy of classical drugs such as H_1R-antihistamines. Better understanding of the mechanisms has enabled a stratified approach to the management of CSU, supporting the use of targeted treatment with omalizumab. However, many practical issues including selection of responders, the definition of response, strategies to enhance the responder rate, the duration of treatment and its regimen (in the clinic or home-based) and its cost-effectiveness still require further clarification. The EAACI Guidelines on the use of omalizumab in CSU follow the GRADE approach in formulating recommendations for each outcome. In addition, future therapeutic approaches and perspectives as well as research priorities are discussed.

KEYWORDS
chronic spontaneous urticaria, GRADE, guidelines, omalizumab

1 | INTRODUCTION

1.1 | The current landscape of chronic spontaneous urticaria

1.1.1 | Definition and burden

Chronic spontaneous urticaria (CSU) is a condition which persists for more than 6 weeks and where itchy wheals, angioedema, or both occur in the absence of definite and specific triggers.[1] CSU is as common in children as it is in adults and more in women than in men, with a peak occurrence in the third to fifth decades of life. The prevalence and incidence of CSU are not truly known. In the general population, it is estimated at 0.5 to 5%, while the annual incidence is reported around 1.4%.[1,2] The Chronic Urticaria Registry (CURE) is expected to provide more precise data, improve our scientific understanding, the clinical treatment and healthcare planning for chronic urticaria patients.[3] An international observational study assessed a cohort of 673 adult patients with CSU whose symptoms persisted for ≥12 months despite treatment. Almost 50% of patients had moderate-to-severe disease activity as reported by Urticaria Activity Score (UAS) and had significant impairment in their quality of life (QoL), including significant interference with sleep and daily activities. More than 20% of patients reported ≥1 h per week of missed work, while productivity impairment was 27%. These effects increased with increasing disease activity.[4] More than 25% of cases are resistant to H_1R-antihistamines, even at higher than licensed doses, and third- and fourth-line therapies (omalizumab and ciclosporin) control the disease only in two-thirds of H_1R-antihistamine-resistant patients.[5] Significant healthcare resources and costs are needed to manage CSU.[4,5]

1.1.2 | Phenotypes and endotypes—practical implications for management

CSU results from pathogenic activation of skin mast cells (MCs), which gives rise to the release of proinflammatory mediators that support the generation of itchy wheals, angioedema or both.[6]

Activation of the high-affinity IgE receptor, FcεR1, is an important step in the development of CSU.[7] This receptor is composed of an α-, β- and two γ subunits.[8] Whereas the α-subunit binds to the Cε3 constant region of the IgE molecule, the β- and γ-subunits contain cell immunoreceptor tyrosine-based activation motifs (ITAMs) which, when phosphorylated, promote activation of spleen tyrosine kinase (SYK) and downstream recruitment of a host of secondary molecules including those involved in the phosphoinositide-3 kinase (PI3K) pathway. This series of events is responsible for degranulation of mast cells and can predispose to pathologic mast cell activation when inappropriately upregulated. SYK is recruited to the

FcεR1 upon antigen stimulation, and inhibition of this protein has been shown to inhibit mast cell degranulation, production of lipid mediators and cytokines.[9] Mast cells from the blood of CSU patients with active urticarial disease were found to release significantly more histamine in vitro than their healthy counterparts.[10] Yet when these CSU patients were further subdivided into responders vs. non-responders based on their ability to degranulate in response to anti-IgE (with responders showing >10% degranulation activity), SYK levels were shown to be higher in the responder group than in the non-responder group, suggesting that this protein is a major determinant of predilection towards spontaneous degranulation. SYK expression is highly variable among the general population and is thought to correlate with the degree of IgE-mediated degranulation. Intriguingly, the presence of autoantibodies to FcεRIα or IgE does not predispose to upregulation of basophil SYK expression.[11]

Accordingly, FcεRI has emerged as a viable target for the development of biologicals that act to inhibit or attenuate the activation of mast cells and basophils. At the forefront of these strategies are as follows: (a) omalizumab and ligelizumab, anti-IgE monoclonal antibodies that bind IgE and reduce FcεRI surface expression; (b) designed Ankyrin Repeat Proteins (DARPins) inhibiting FcεRI-IgE activation through protein-protein interactions; (c) and fusion proteins to co-aggregate FcεRI with the inhibitory FcγRIIb.[12-18]

Recent evidence points towards an autoimmune aetiology in up to 50% of patients with CSU, due to MCs activating autoantibodies and an autoallergic aetiology, in more than 50% of patients, due to IgE autoantibodies to autoallergens. These two different autoimmune mechanisms are held to be responsible for MC activation in most patients with CSU: in the majority of patients, type I autoimmunity ('autoallergy') is present, that is an auto-IgE-mediated immediate reaction against an autoantigen, an endogenous allergen. In a smaller proportion of CSU patients, type IIb autoimmunity is present, in which IgG and IgM antibodies are directed against cellular structures on MCs, for example the IgE receptor FcεRI, leading to MC activation.[19,20] IgG-anti-thyroperoxidase may also be present and is held to be a marker for type IIb autoimmune CSU.[21,22] Autoreactive IgE and IgG often co-exist.[23] The presence of MC activating autoantibodies can be screened by the autologous serum skin test (ASST) and basophil tests (BTs), either basophil activation test or basophil histamine release assay (BHRA), as well as immunoassays. Many CSU patients are positive in only one of these tests, and they show divergent results in about 1/3 of the cases. The authors advance the hypothesis of autologous skin signals modulating MC degranulation.[24]

Characterization of this endotype in the clinic is important as it seems to be more severe and less responsive to the targeted intervention with omalizumab. The assessment of basophil FcεRI levels might also be relevant in predicting response to anti-IgE treatment.[7] Patients who have a positive BHRA (~ 20% of all CSU patients) are not only more likely to have an overall more severe and prolonged CSU, but also respond significantly worse to therapy with omalizumab, which is otherwise very successful in CSU.[25] Interleukin 24 (IL-24) has been identified as an IgE autoallergen in CSU.[26] These patients seem to respond to autologous serum therapy.[27] The epithelial derived cytokines IL-25, IL-33 and thymic stromal lymphopoietin (TSLP) have previously been shown to promote T2 inflammation which in turn activates MCs thus can contribute to the pathogenesis of CSU.[28] Both IL-4 and IL-5 contribute to the survival of MCs, and they can enhance FcεRI-mediated degranulation.[29,30]

Another CSU endotype might be driven by dysregulation of MCs surface receptors or the intracellular signalling pathways within mast cells and basophils that lead to defects in trafficking or function of these cells. MCs express numerous G protein-coupled receptors (GPCRs) that lead to activation and degranulation of MCs. These include the complement C5a receptor (C5aR, CD88), to which the anaphylatoxin C5a binds, and the Mas-related G protein-coupled receptor X2 (MRGPRX2), both preferentially expressed by the skin MCs.[31-34] MRGPRX2 is a receptor that is activated by substance P, major basic protein, and eosinophil peroxidase and by various external triggers.[35] A small group of MC receptors mediates inhibitory signals. Two of these inhibitory MC receptors are Siglec-8 and CD200R.[36,37]

Endothelial cells (ECs) and eosinophils contribute importantly to key features of CSU. Several markers of EC activation have been reported, from adhesion molecules, tissue factor and P-selectin to D-dimers, MMP-9, endostatin, heat shock proteins, cleaved high molecular weight kininogen and adipokines.[38] As for eosinophils, histologic studies have reported eosinophils in CSU skin lesions and peripheral blood eosinopenia, and treatments that reduce eosinophil recruitment, such as mepolizumab, reslizumab, benralizumab and lirentelimab, have been reported benefit patients with CSU.[39]

1.1.3 | Current management

The therapeutic goal in the treatment of CSU is to achieve complete freedom of symptoms, to 'treat the disease until it is gone'. The current guideline for the treatment of CSU recommends second-generation non-sedating H_1R antihistamines in standard doses as the first step. If control is not adequate (after 2–4 weeks or earlier, if symptoms are intolerable), the antihistamines dose should be increased up to fourfold. Individual tolerance and a possible increase in sedative effects at higher doses should be considered. If this does not result in sufficient control, omalizumab is additionally administered. If there is no therapeutic success after six months of treatment with omalizumab, the guidelines recommend off-label use with cyclosporine A in addition to existing therapy with H1 antihistamines. Recommended dosages of cyclosporine A are 3–5 mg/kg/day. In case of acute exacerbations, treatment with sufficient doses of oral glucocorticoids can be given for a short period (up to a maximum of ten days) to reduce the duration and activity of the disease. A medium-high dose of prednisolone of 20–50 mg/day for a maximum of ten days is recommended in adults. Long-term treatment with systemic glucocorticoids or frequent 'acute interventions' should be avoided at all costs due to the high rate of side effects.[1,19] Management of triggering factors and of co-morbidities improves disease control. The assessment of the disease burden, defined as disease activity plus quality of life and disease control, supports the decision whether therapy is successful or should be escalated if necessary.

1.2 | Biologicals

Biologic products (biologicals) include a wide range of products such as vaccines, blood and blood components, allergen vaccines, somatic cells, gene therapy, tissues and recombinant therapeutic proteins. They are isolated from a variety of natural sources—human, animal or microorganism—and may be produced by biotechnology methods and other cutting-edge technologies. For the purpose of this guideline, we refer to monoclonal antibodies (mAb) as biologicals. In contrast to chemical compounds and small-molecule agonists or antagonists, biologicals bind a specific determinant, for example, a cytokine or receptor. Owing to this selectivity, biologicals are ideal for 'personalized' or 'precision' medicine.[40]

Omalizumab inhibits the interaction between IgE and its high-affinity receptor FcεRI, thus preventing mast cell and basophil activation, and blocks IgE binding to its low-affinity receptor (CD23) on B cells and antigen-presenting cells. Omalizumab has also the ability to dissociate pre-bound IgE from mast cells and basophils, resulting in a reduction of proximal phosphorylation-mediated signalling events and in a decrease in degranulation.[41] The crystal structure of the complex between an omalizumab-derived Fab and IgE-Fc with one Fab bound to each Cε3 domain was recently described.[13] Free IgE-Fc adopts an acutely bent structure, but in the complex, it is only partially bent, with large-scale conformational changes in the Cε3 domains that inhibit the interaction with FcεRI. CD23 binding is inhibited sterically due to overlapping binding sites on each Cε3 domain. Studies of omalizumab Fab binding in solution demonstrate the allosteric basis for FcεRI inhibition and, together with the structure, reveal how omalizumab may accelerate dissociation of receptor-bound IgE from FcεRI, exploiting the intrinsic flexibility and allosteric potential of IgE.[42] Its use in CSU is supported by the key role of IgE and its high-affinity receptor, FcεRI, in the degranulation of skin mast cells that drives the development of the signs and symptoms of CSU, itchy wheals and angioedema.

1.3 | Purpose of the EAACI Guidelines

Delivering high-quality clinical care is a central priority for allergists, dermatologists, paediatricians, internal medicine and other specialities caring for patients with CSU. The European Academy of Allergy and Clinical Immunology (EAACI) develops and updates each year's resources to help healthcare professionals (HCP) and researchers to design the best interventions, deliver high standard care and to assess their actions and decisions for purposes of quality improvement and/or reporting.

EAACI guidelines include recommendations for the management of patients with particular conditions or diseases. Guidelines are developed using a systematic process, and are based on available evidence and the clinical experience and expertise of all interested stakeholders. Following the rapid accrual of evidence for omalizumab in CSU together with an advancement of guideline development methodologies, a guideline focused on the use of omalizumab in CSU was therefore needed.

The current EAACI guideline for the use of omalizumab in CSU is focussed only on treatment with omalizumab for CSU. It does not address any topics related to CSU diagnosis, concurrent treatment or monitoring adherence.

The EAACI Guideline for the use of omalizumab in CSU is not intended to impose a standard of care. Instead, it provides the framework for rational decisions for the use of omalizumab in CSU by HCPs, patients, third-party payers, institutional review committees and other stakeholders. Statements regarding the underlying values and preferences as well as qualifying remarks accompanying each recommendation are an integral part of the Guidelines and aim to facilitate more accurate interpretation. They should never be omitted or ignored when quoting Guidelines recommendations.

1.3.1 | Target audience

The target audience includes all HCPs involved in the management of CSU, patients and caregivers, basic scientists involved in biologicals development, regulatory authorities and policymakers.

1.3.2 | Biologicals included—rationale for choosing

This EAACI guideline provides recommendations for the use of omalizumab in patients with CSU. Omalizumab is currently the only biological with regulatory approval for the treatment of CSU.

Additional comments are provided for the biologicals and other targeted interventions currently tested and not yet approved and for doses/routes not approved by regulatory authorities.

2 | METHODS

This EAACI guideline followed the GRADE methodology (available at www.gradeworkinggroup.org). Training was conducted with all members of the guidelines development group (GDG) to prepare them for their roles, including specific sessions on the GRADE methodology.

2.1 | The Guideline Development Group

A Core Leadership Team (Table S1) supervised the project and was responsible for defining the project scope, drafting the clinical question to be addressed by the guideline, coordinating the search and drafting the manuscript together with the Voting Panel (Table S1). The project was led by three chairs with both content and methodologic expertise. The Core Leadership Team received support from a methodologist team, who advised on the process and provided input on the GRADE summary of findings (SOF) tables. The methodologist team conducted the systematic literature review (SR) for the clinical question, graded the quality of evidence, developed the SOF tables and provided the evidence reports. Narrative reviews were conducted by different content specialist subgroups for each topic to be covered to complement the SR.

The Voting Panel, composed of content experts, decided which clinical questions are to be asked and which outcomes are critical, important and of low importance, and voted for the final recommendations after reviewing the evidence provided by the methodology team and the narrative reviews. The Voting Panel included specialists with expertise and clinical experience in treating CSU, biologists and clinical immunology experts, as well as patient representatives.

In accordance with EAACI policy, everyone who was intellectually involved in the project (ie considered for guideline authorship) disclosed all potential conflict of interest (COIs) in writing at the beginning, middle and end of the project. The Guideline Oversight Committee (Table S1) was responsible for developing and implementing rules related to COIs.

2.2 | Definitions

The GDG framed the clinical question as '*Is the treatment with omalizumab efficacious and safe for patients with CSU*?' (Table 1). For the purpose of the SR, the population was defined as patients 12 years or older with a diagnosis of CSU inadequately controlled by H1-antihistamine treatment.

For the recommendations, the population was defined as in the clinical trials that informed the regulatory approval.

2.3 | Systematic review question and prioritization of outcomes

Clinically relevant interventions and comparators were developed balancing comprehensiveness with feasibility (Table 1). The most challenging decision in framing the question was how broadly the patients and intervention should be defined. The underlying biology of CSU suggested that across the range of patients and interventions it is plausible that the magnitude of effect on the key outcomes is different; thus, the GDG defined subpopulations based on age (12–17 years old, >18 years old) and on omalizumab dose (150 mg vs. 300 mg).

As required by the GRADE approach, CSU-related outcomes were prioritized in a first step by the GDG using a 1 to 9 scale (7–9 critical; 4–6 important; and 1–3 of limited importance). The critical outcomes were weekly urticaria activity score (UAS)-7, the weekly itch severity score (ISS)-7 and safety (drug-related adverse events and serious adverse events). Important outcomes were as follows: QoL (assessed with Dermatology Life Quality Index (DLQI) and the Chronic Urticaria Quality of Life Questionnaire (CU-Q2oL)); resource utilization (assessed with work productivity and activity impairment (WPAI), with two sub-scales separately, work impairment score (WIS) and activity impairment score (AIS)); and rescue medication use (assessed with number of tablets of diphenhydramine per week) (Table 2). After reviewing the evidence, the prioritization of the outcomes was reassessed to ensure that important outcomes that were not initially considered are included and to reconsider the relative importance of outcomes in light of the available evidence. All CSU-related relevant outcomes were addressed simultaneously.

The GDG also defined and addressed clinical questions not covered by the systematic review (Table 3).

2.4 | Minimal important difference

To evaluate the imprecision for each outcome, their minimal important difference (MID) thresholds were considered: 9.5 to 10.0 points for UAS-7,[43-48] 4.5 to 5 points for ISS-7[45,46,48] and 2.24 to 3.10 for DLQI.[49] Of note, licensing studies used a different scoring system for UAS-7 (twice daily average wheals (UAS-7 TD)) rather than once daily retrospective estimate over 24 hours, used most widely in clinical practice). The two scoring systems give very similar but not identical scores.[44] In this paper, the reported MID was 11 for the UAS7 (smallest detectable change (SDC) = 12) and 12 for the UAS7TD (SDC = 11).

TABLE 1 Structured clinical question: Is the treatment with omalizumab efficacious and safe for patients with CSU

Population	Intervention	Comparison	Outcomes
Patients 12 years or older with a diagnosis of CSU inadequately controlled by H1-antihistamine treatment.	Omalizumab sc 150 or 300 mg every four weeks	Standard of care	**Critical**: • Urticaria activity score (UAS)7 • Itch severity score (ISS)7 • Safety (adverse events)[a] **Important**: • Quality of life (DLQI; CU-Q2oL) • Rescue medication use • Resource utilisation (WIS, AIS)

[a]Only drug related adverse events and severe adverse events were considered.

TABLE 2 GRADE scoring of CSU related outcomes

Outcome	Importance
Urticaria activity score (UAS)7; Itch severity score (ISS)7; Safety (AE and SAE)	Critical (7-9)
Quality of life[a] Rescue medication use[b] Resource utilization[c]	Important (4-6)
-	Low importance (1-3)

[a]Assessed with Dermatology Life Quality Index (DLQI) and the Chronic Urticaria Quality of Life Questionnaire (CU-Q2oL)
[b]Assessed with number of tablets of diphenhydramine per week
[c]Assessed with work productivity and activity impairment (WPAI), reporting two sub-scales separately, work impairment score (WIS) and activity impairment score (AIS)

TABLE 3 Clinical questions not covered by the systematic reviews

1. Relevance of clinical trial population for real-world patients
2. Efficacy and safety in the paediatric population
3. Safety in pregnancy
4. Safety long term
5. At home administration
6. Risk factors for adverse events
7. Immunogenicity
8. Anti-drug antibodies (ADA)
9. Joint treatment of co-morbidities
10. Biomarkers/predictors of response
11. Continuation/discontinuation criteria
12. Defining efficacy; definition of responder, partial responder (dissociated outcome), non-responder
13. Treatment duration
14. Health economics data

2.5 | The GRADE approach (search, appraisal of the evidence)

Key principles and provisions, key terms, descriptions, drug categories, PICO (population, intervention, comparator, and outcomes) questions, search methodology and evidence reporting used in the guideline development process were predefined.

A systematic review was conducted to inform the recommendations.[50] A GRADE SOF table was provided for the PICO question. The quality of evidence was evaluated based on GRADE quality assessment criteria by two independent reviewers and discordance resolved by consensus. Quality assessment includes the risk of bias (ROB) of included trials, the likelihood of publication bias, inconsistency between trial results, indirectness of the evidence (eg differences between populations, interventions or outcomes of interest in the group to whom the recommendation applies versus those who were included in the studies referenced) and imprecision (wide confidence intervals, usually due to a small number of patients or events, or those situations where clinical decision-making would differ at the extremes of the confidence interval).[51-53] The quality of evidence for each outcome was rated as high, moderate, low or very low. In the absence of any data, the level of evidence was rated as very low, based on clinical experience only. Search results were pooled in an evidence report as SOF tables and accompanied by a qualitative summary of the evidence for the PICO question. The Content Panel reviewed the drafted evidence report to address evidence gaps prior to presentation to the Voting Panel.

2.6 | Additional evidence

In support of formulated recommendations, the GDG performed narrative reviews collecting evidence on phase IV, observational, real-world trials and registries and on clinical questions not addressed by the SR (Table S2).

2.7 | Consensus building and formulating recommendations

After reviewing the evidence report and the additional evidence, the Voting Panel discussed and consented by voting in a hybrid meeting (face-to-face and online) in January 2020 on the final recommendations of this Guideline. Due to the COVID-19 pandemic, the publication was delayed by one year. For each outcome, the Voting Panel heard an oral summary of the evidence and voted on the wording, direction and strength of the related recommendation. A 70% consensus threshold was reached for all recommendations presented below. The recommendations follow the data included in the evidence-to-decision (EtD) tables and take into consideration the balance of desirable and undesirable consequences, the quality of evidence, patients' values and preferences, feasibility, and acceptability of various interventions, use of resources paid for by third parties, equity considerations, impacts on those who care for patients and public health impact.[51-53] A strong recommendation was made in favour of an intervention when the GDG was certain that the desirable consequences outweighed the undesirable consequences. A conditional recommendation was provided if there were reasons for uncertainty on the benefit-risk profile, especially for low or very low quality of evidence. The underlying values and preferences played a key role in formulating recommendations. As the key target audience of this EAACI Guideline are HCPs and the patients they treat, the perspective chosen when formulating recommendations was mainly that of the HCPs and of the patient, although the health system perspective was also evaluated, as per WHO recommendations for guidelines development.[54] Recommendations are formulated separate by outcome. The recommendations formulated in this guideline should be used following the GRADE interpretation (Table 4). These recommendations should be reconsidered when new evidence becomes available and an update of this guideline is planned for 2025.

TABLE 4 Interpretation of GRADE recommendations

Implications	Strong recommendation	Conditional (weak) recommendation
For patients	Most individuals in this situation would want the recommended course of action and only a small proportion would not. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	The majority of individuals in this situation would want the suggested course of action but many would not.
For clinicians	Most individuals should receive the intervention. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.	Recognise that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful helping individuals making decisions consistent with their values and preferences.
For policy makers	The recommendation can be adapted as policy or performance measure in most situations.	Policy making will require substantial debate and involvement of various stakeholders. Documentation of appropriate (e.g. shared) decision-making processes can serve as performance measure.

Where no evidence was available, the GDG formulated expert-based recommendations.

The Guideline was available on the EAACI website for two weeks (26 May–8 June 2021) for public comment, and it underwent external peer-reviewed. All comments received were carefully reviewed by the GDG and incorporated where applicable.

2.8 | Final review and approval of the guideline by EAACI

In addition to journal and external peer review, the EAACI Scientific Committee and Executive Committee reviewed the manuscript. These EAACI over-sight groups did not mandate that certain recommendations be made within the guideline, but rather serve as peer reviewers.

2.9 | Key recommendations

Accumulating experience with omalizumab treatment for CSU confirmed its effectiveness and safety, by reducing the signs and symptoms and burden of CSU, improving QoL, and decreasing the use of reliever medication, both in the paediatric population 12–17 years old and in adults.[55-65]

2.10 | Omalizumab 150 mg

The summary of the supportive evidence is presented in Table S3. Recommendations for adults and the 12- to 17-year-old paediatric population are based on the evidence-to-decision Table 5.

Recommendations are formulated together for the adult and 12- to 17-year-old population included in the SR (Box 1).

2.10.1 | Justification

Omalizumab 150 mg every 4 weeks did not result in a clinically meaningful reduction of disease activity as assessed by use of the UAS7 (MD −5; 95% CI −7.75 to −2.25; high certainty of evidence). It also failed to achieve a clinically meaningful reduction of ISS7 values (MD −2.15; 95%CI −3.20 to −1.10, high certainty of evidence), thus the GDG formulated a conditional recommendation for decreasing disease activity. Compared to standard of care, omalizumab 150 mg did not meaningfully reduce DLQI values (MD −1.95; 95%CI −3.06 to −0.83; moderate certainty of evidence), and thus, the GDG formulated a conditional recommendation for improving QoL. As it decreased the use of rescue medication with moderate certainty of evidence: MD −1.68 (95%CI −2.95 to −0.40), the GDG formulated a conditional recommendation.

As omalizumab 150 may increase the risk of drug-related AE with low certainty of the evidence: RR 1.40 (95%CI 0.63 to 3.13), the GDG formulated a conditional recommendation for a good safety profile advising periodical monitoring of AEs.

2.11 | Omalizumab 300 mg

The summary of the supportive evidence is presented in Table S4. Recommendations for adults and the 12- to 17-year-old paediatric population are based on the evidence-to-decision Tables 6 and 7.

Recommendations are formulated together for the adult and 12- to 17-year-old population included in the SR (Box 2).

2.11.1 | Justification

Omalizumab 300 mg every 4 weeks led to a clinically meaningful decrease in UAS-7 (MD −11.05; 95% CI −12.87 to −9.24) and in the ISS-7 (MD −4.65; 95%CI −5.41 to −3.89), both with moderate certainty

TABLE 5 Evidence to decision table supporting recommendations for omalizumab 150 mg every 4 weeks in adults and the 12-17 paediatric population with CSU for its efficacy in reducing disease activity, rescue medication, improving QoL and its safety (drug-related AEs and SAEs)

	Judgement						
Problem (importance)	**No**	**Probably no**	**Probably yes**	**Yes**		**Varies**	**Don't know**
Desirable Effects	Trivial	Small	Moderate	Large		Varies	Don't know
Undesirable Effects	Large	Moderate	Small	Trivial		Varies	Don't know
Certainty of evidence	Very low	Low	Moderate	High			No studies included
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	no important uncertainty or variability			
Balance of effects	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
Certainty of evidence of required resources	Very low	Low	Moderate	High			No studies included
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No studies included
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
Acceptability	No	Probably no	Probably yes	Yes		Varies	Don't know
Feasibility	No	Probably no	Probably yes	Yes		Varies	Don't know

BOX 1 Recommendation for omalizumab as add-on treatment in adults and in the paediatric population 12–17 years old with uncontrolled CSU

1. Omalizumab 150 mg is recommended in adults and adolescents with chronic spontaneous urticaria* uncontrolled under antihistamines to:	Reduce disease activity as reflected by UAS-7 and ISS-7	Conditional recommendation
	Improve quality of life	Conditional recommendation
	Reduce rescue** medication	Conditional recommendation
2. Omalizumab has demonstrated a good safety profile; however, drug-related AEs should be periodically monitored		Conditional recommendation

* Population: CSU refractory to antihistamines.** Rescue refers to 'on demand'.

of evidence; thus, the GDG formulated a strong recommendation for decreasing disease activity. It also reduced DLQI values (MD −4.01; 95%CI −4.94 to −3.08), with an improvement in QoL above the MID with high certainty of evidence. This was paralleled by a significant decrease in CU-Q2oL scores (MD −15.34; 95%CI −24.84 to −5.84); consequently, a strong recommendation for improving QoL was formulated. There was moderate certainty for reducing rescue medication (MD −2.04 (95%CI −3.19 to −0.88)); thus, a conditional recommendation was formulated. Compared to standard of care, omalizumab 300 mg improved WIS (MD −24.24; 95%CI −35.74 to −12.74) and AIS (−26.59; 95% CI −37.36 to −15.72) at 24 weeks.[64] However, as data come from only one RCT, a conditional recommendation was formulated.

Omalizumab 300 mg slightly increased drug-related AEs (RR 1.37 (95%CI 0.67 to 2.82) with low certainty and decreased with moderate certainty drug-related SAEs (RR 0.77; 95% CI 0.20 to 2.91)), although results are inconclusive due to the small RR. One study reported a single anaphylactic episode during the open-label phase of the study.[63] The GDG formulated a conditional recommendation for a good safety profile advising periodical monitoring of AEs and SAEs.

2.12 | Subgroups: stratified by co-morbidities

The GDG evaluated the evidence for omalizumab efficacy in CSU associated with other co-morbidities not included in the SR (Table S2) and formulated a conditional recommendation, expert opinion based on the efficacy of omalizumab in patients with CSU and other co-morbidities (Box 3).

2.13 | Biomarkers predicting response

For asthma, pre-treatment-free (non-Omalizumab bound) IgE levels in serum are a measure of effective omalizumab dosing. However, determining non-Omalizumab bound IgE levels is not available as routine technique. Recent years findings point to a possible role of total IgE as a marker of CSU disease activity, endotypes and responses to treatment.[66-69] A review of 141 publications showed that up to 50% CSU patients had elevated total IgE serum levels, but normal or very low total IgE levels also occurred. High total IgE may be linked to disease activity, longer disease duration, high chance of responding to omalizumab treatment, quick relapse after stopping omalizumab and lower chance of responding to cyclosporine. Low IgE, in contrast, may suggest Type IIb autoimmune CSU, poor and slow response to treatment with omalizumab and a better chance to benefits from cyclosporine treatment. Furthermore, IgE in different CSU cohorts may have different physicochemical properties that could explain differences in treatment responses to IgE-directed therapies.[70]

In support of the EAACI guideline recommendation a SR was performed, including all published studies evaluating the following predictive biomarkers for omalizumab efficacy: IgE and IgG autoantibodies to high- and low-affinity IgE receptors (FcεRI and FcεRII), total IgE levels, thyroid autoimmunity (IgE and IgG autoantibodies against thyroperoxidase and/or thyroglobulin), eosinopenia, basopenia, eosinopenia associated with basopenia, IgE and IgG autoantibodies to tissue factor, autologous serum skin test, basophil activation test, basophil histamine release assay positivity, high D-dimer, high CRP, high ESR and antinuclear antibodies (Tables S5-S42 and Figures S1-S6). For all biomarkers evaluated, the evidence is very uncertain. However, the GDG formulated a conditional recommendation, with low level of evidence, for high total IgE and stated that the other biomarkers evaluated need further exploration in prospective trials with prediction of response as primary end point.

2.14 | Implementation considerations

For omalizumab 300 mg every 4 weeks, the GDG formulated strong recommendations for the reduction in disease activity and for improving QoL and conditional recommendations for reducing rescue medication and resource use and for safety-related outcomes. For omalizumab 150 mg every 4 weeks, only conditional recommendations were formulated for all outcomes. According to GRADE for strong recommendations, most individuals should receive the intervention and the recommendation can be adapted as policy or performance measure in most situations (Table 4).

TABLE 6 Evidence to decision table supporting recommendations for omalizumab 300mg every 4 weeks in adults and the 12-17 paediatric population with CSU for its efficacy in reducing disease activity and improving QoL

	Judgement						
Problem (importance)	**No**	**Probably no**	**Probably yes**	**Yes**		**Varies**	**Don't know**
Desirable Effects	Trivial	Small	Moderate	Large		Varies	Don't know
Undesirable Effects	Large	Moderate	Small	Trivial		Varies	Don't know
Certainty of evidence	Very low	Low	Moderate	High			No included studies
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	no important uncertainty or variability			
Balance of effects	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
Certainty of evidence of required resources	Very low	Low	Moderate	High			No included studies
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
Acceptability	No	Probably no	Probably yes	Yes		Varies	Don't know
Feasibility	No	Probably no	Probably yes	Yes		Varies	Don't know

TABLE 7 Evidence to decision table supporting recommendations for omalizumab 300mg every 4 weeks in adults and the 12-17 paediatric population with CSU for its efficacy in reducing rescue medication and resource use and its safety (drug-related AEs and SAEs)

	Judgement						
Problem (importance)	**No**	**Probably no**	**Probably yes**	**Yes**		**Varies**	**Don't know**
Desirable Effects	Trivial	Small	Moderate	Large		Varies	Don't know
Undesirable Effects	Large	Moderate	Small	Trivial		Varies	Don't know
Certainty of evidence	Very low	Low	Moderate	High			No studies included
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	no important uncertainty or variability			
Balance of effects	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
Certainty of evidence of required resources	Very low	Low	Moderate	High			No studies included
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No studies included
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
Acceptability	No	Probably no	Probably yes	Yes		Varies	Don't know
Feasibility	No	Probably no	Probably yes	Yes		Varies	Don't know

BOX 2 Recommendation for omalizumab 300 mg as add-on treatment in adults and in the paediatric population 12–17 years old with uncontrolled CSU

1. Omalizumab 300 mg is recommended in adults and adolescents with chronic spontaneous urticaria* uncontrolled under antihistamines to:	Reduce disease activity as reflected by UAS-7 and ISS-7	Strong recommendation
	Improve quality of life	Strong recommendation
	Reduce rescue** medication	Conditional recommendation
	Decrease resource utilization	Conditional recommendation
2. Omalizumab has demonstrated a good safety profile; however, drug-related AEs and SAEs should be periodically monitored		Conditional recommendation

* Population: CSU refractory to antihistamines** Rescue refers to 'on demand'

However, the GDG cautions on several unsolved key pillars supporting the implementation of these recommendations, such as independent high-quality cost-effectiveness studies, selection of responders, documentation of the disease-modifying effect together with long-term safety data, studies addressing a priori CSU together with its co-morbidities. The cost-effectiveness of omalizumab based on real-world treatment patterns is largely unknown. Including broader evidence on treatment, discontinuation, caregiver burden, and rescue medication and resource use reduction from real-world studies and CSU registries may better reflect the effects and value of biologicals for all healthcare stakeholders.[3] Last but not least the value of the recommendations depends also on the setting in which the current guideline will be implemented, as recommendation suitable for resource-rich environments might change from strong to conditional in resource-poor environments (Box 5).

3 | PRACTICAL APPROACH

3.1 | Definition of response: continuation and stopping rules

Disease control is a major treatment aim in CSU (Box 6). UAS-7 has become the standard for assessing CSU disease activity in clinical studies and the routine management of patients, but it does not evaluate disease control per se. The urticaria control test (UCT) is a 4-item questionnaire about physical symptoms, QoL, treatment effects and urticaria control over the previous 4 weeks.[70] Responder rates using UCT score of greater than or equal to12 and UAS value of 6 or less yielded very similar results.[71] As of now, there is no agreement on the interval when CSU activity and control should be evaluated after the initiation of omalizumab treatment. Approximately 30% of patients remain symptomatic at licensed doses of omalizumab 150 mg and 300 mg, even after a treatment period of over 6 months. In the recent years, there have been several studies on up-dosing omalizumab until 600 mg once or twice a month, suggesting that an individualized approach for urticaria treatment with omalizumab is useful. Real-world data mainly show that up-dosing/dose adjustment evaluated with the assessment of disease activity (UAS-7) and control (UCT) achieves better clinical response to omalizumab with a good safety profile in a subgroup of patients with CSU.[72]

In addition, adherence to background treatment and to avoidance of CSU triggers should be evaluated before deciding to stop omalizumab due to lack of efficacy.

Results suggest that high baseline UAS7 and low UAS7 area above curve (slow decrease of symptoms) indicate a higher probability of rapid symptom return.[73]

3.2 | Monitoring treatment

3.2.1 | Adverse events

Use of omalizumab is associated with reported side effects ranging from local skin inflammation at the injection site to systemic anaphylaxis. Omalizumab binds to the constant region of free IgE only and, therefore, does not cause mast cell degranulation. However, omalizumab has been reported to cause anaphylaxis in <0.1% of patients, with reactions being delayed in some cases.[74-76] To date, the mechanisms through which omalizumab induces adverse reactions are still unknown. Treatment with omalizumab results in a markedly increased sensitivity of basophils to IgE-mediated stimulation in terms of the number of IgE molecules required to produce a given response.[77] Another explanation might be that omalizumab binds IgE-Fc-FceRI without disrupting IgE. On the contrary, ligelizumab removes IgE-Fc fragments.[41] In a recent experimental model, it was shown that omalizumab can induce skin inflammation and anaphylaxis by engaging FcγRs, and demonstrated that Fc-engineered versions of the mAb could be used to reduce such adverse reactions without compromising efficacy.[78] A non–IgE-mediated anaphylactic response to the polysorbate excipient might also be involved.[79]

In pre-marketing clinical trials in patients with asthma, anaphylaxis was reported in 3 of 3,507 (0.1%) patients. In post-marketing spontaneous reports, the frequency of anaphylaxis attributed to omalizumab use was estimated to be at least 0.2% of patients based on an estimated exposure of about 57,300 patients from June 2003 through December 2006. The risk factors for these anaphylactic reactions were uncertain given the limitations of spontaneous reports and the lack of control

BOX 3 recommendation for omalizumab in adults and 12- to 17-year-old patients with both CSU associated with other co-morbidities

Omalizumab may be of particular benefit in adults and 12- to 17-year-old patients with CSU associated with other co-morbidities (chronic inducible urticaria, allergic asthma, allergic rhinitis)	Conditional recommendation, expert opinion based

BOX 4 recommendation for biomarkers in prescribing omalizumab in adults and 12- to 17-year-old patients with CSU

High total IgE* may indicate a higher chance of responding to omalizumab treatment	Conditional recommendation, low level of evidence

* Different thresholds are reported depending on the measurement method[70]

BOX 5 Factors impacting the implementation of recommendations for the use of omalizumab in CSU (adults and 12–17 years old)

1. Cost-effectiveness, especially independent real-world evidence
2. Long-term safety data
3. Immune modulation/disease-modifying effect
4. Stratification* based on biomarkers**
5. Patient's preference
6. Availability of resources

* Stratification—safety and efficacy** Biomarkers include both clinical and laboratory features

BOX 6 Recommendations for practical use of omalizumab in adults and 12- to 17-year-old patients with CSU

The evaluation of response should be done after 4–6 months of treatment	Conditional recommendation, expert opinion based
As there are no validated criteria for defining response to omalizumab in CSU the GDG recommends a composite end point combing evaluation of disease activity (UAS-7 and ISS-7), disease control (UCT), and with measures of QoL	Conditional recommendation, expert opinion based
A pre-established cut-off reached through shared decision-making with the patient should be used	Conditional recommendation, expert opinion based
For insufficient response up-dosing may be considered	Conditional recommendation, low quality evidence

data. Due to this increase in the rate of anaphylaxis, a black box warning was added to the omalizumab label in 2007. To understand the risk factors associated with anaphylaxis among omalizumab-treated patients, a pharmacosurveillance data repository (Q4458g, X-PAND) was initiated in early 2009 as a post-marketing commitment. Data collected included clinical histories, immunogenicity assessment and an optional allergy skin test. Thirty cases of anaphylaxis and 120 controls were considered to give 79% power to detect a fourfold increase in the risk for an anaphylactic reaction assuming a 10% prevalence for an identified risk factor and a 5% type I error (2-tailed). Prespecified potential clinically meaningful risk factors (eg presence of food allergy, pre-omalizumab IgE levels, asthma severity, sex and age) were assessed for effect on the frequency of anaphylaxis. Most cases of anaphylaxis (24 of 30; 80%) included symptoms categorized as cutaneous/subcutaneous/mucosal (ie lips, tongue, palate and uvula) and respiratory (ie nose, laryngeal and lung). Most (70.0%) events occurred within 1 hour of omalizumab dosing (only 1 event occurred after 2 h [ie at 3.5 h]). Median (range) time from the last dose of omalizumab to the anaphylactic event was 30 (0–210) minutes. Eleven of 28 (39.3%) patients in whom the number of previous doses had been recorded experienced anaphylaxis within the first 3 doses of omalizumab; anaphylaxis occurred after 4–20 doses in 8 (28.6%) cases and after more than 20 doses in 9 (32%) cases (1 case after >60 injections). None of the anaphylactic events resulted in disability or death. Anaphylactic events were considered life-threatening in 12 of 30 (40.0%) cases and required hospitalization in another 6 (20.0%) cases. Treatment of anaphylaxis included the use of antihistamines (23 of 30; 76.7%), epinephrine (21 of 30; 70.0%), systemic corticosteroids (19 of 30; 63.3%) and inhaled β-agonists (13 of 30; 43.3%). Bivariate conditional logistic regression analysis indicated that among omalizumab users, a history of anaphylaxis to food, medication, or other causes increased the subsequent risk of anaphylaxis associated with omalizumab use (OR, 8.1; 95% CI, 2.7–24.3). The US Food and Drug Administration examined this information and advised including it in an updated Xolair US package insert. Total number of omalizumab doses, food allergies, female sex, presence of urticaria/hives and race also were identified as potential risk factors for anaphylaxis associated with omalizumab. The absolute risks for anaphylaxis may be estimated on the basis of overall risks of 0.1% (based on clinical trial data) or 0.2% (based on post-marketing reports) of users. Assuming an overall 0.2% risk, the absolute increase in risk can be indirectly estimated from the OR, and it would be approximately 0.62% for patients with a history

BOX 7 Recommendations for managing anaphylaxis under omalizumab treatment for CSU

The occurrence of anaphylaxis following treatment with omalizumab in CSU is an event of special interest that should be reported appropriately in order to improve the post-marketing surveillance data	Conditional recommendation, expert opinion based
The first 3 doses should be administered in a setting with experience in managing anaphylaxis; an observation period of 30 min post-administration is recommended. Thereafter, post-administration observation is at the discretion of the healthcare provider	Conditional recommendation, expert opinion based
Consultation with an allergist is encouraged if risk factors for anaphylaxis are present	Conditional recommendation, expert opinion based
As most cases are mild/moderate and respond well to anaphylaxis treatment omalizumab should not be discontinued (shared decision between clinician and patient)	Conditional recommendation, expert opinion based
Home administration is an option starting with the 4th dose with the condition that the patient has been provided with an anaphylaxis action plan and proper education	Conditional recommendation, expert opinion based

of anaphylaxis and 0.08% for patients with no history of anaphylaxis, resulting in a risk difference (ie attributable risk) of 0.54%.[80] As part of this study, an assay that could detect antibodies of IgE isotype to omalizumab was developed. Using this assay, there was no apparent correlation between either anaphylaxis or skin test reactivity and the presence of antibodies of IgE isotype to omalizumab.[81] As a result of this study, FDA withdrew the black box warning. Furthermore, as the reported incidence of anaphylaxis continues to be low, in several countries omalizumab was licensed in several countries for home administration. The guideline panel formulated recommendations on how to tackle the risk of anaphylaxis under omalizumab (Box 7).

While elevated serum IgE is generally associated with allergic/atopic conditions, very low or absent IgE may hamper antitumour surveillance, indicating the importance of a balanced IgE-mediated immune function.[82] The Epidemiologic Study of Xolair Evaluating Clinical Effectiveness and Long-Term Safety in Patients with Moderate to Severe Asthma (EXCELS), a 5-year observational cohort study was conducted in patients 12 years or older with moderate-to-severe asthma to evaluate the long-term safety of omalizumab, primarily the risk of malignancy.[83] The authors conclude that the results 'suggest that omalizumab is not associated with an increased risk of malignancy'. However, the potential for unmeasured/uncontrolled confounding, the selection biases introduced by the enrolment of 'prevalent users' (previously exposed to omalizumab) and the initial exclusion of patients with a history of cancer or a premalignant condition, and the high study discontinuation rate significantly limit the ability of the study to rule out a malignancy risk with omalizumab treatment. A systematic review and meta-analysis of intervention and observational studies evaluated whether prolonged treatment with omalizumab influences development or progression of solid epithelial cancer in patients with atopic asthma or CSU. Only 12 studies reported outcomes of interest and none included CSU. There was insufficient evidence to determine whether long-term treatment with omalizumab influences development or progression of solid epithelial cancer in these patient populations.[84] Of note, EXCELS showed a higher rate of cardiovascular and cerebrovascular events.[85]

3.2.2 | Routine laboratory monitoring

Given the good safety profile, no routine laboratory monitoring is recommended under omalizumab (Box 8).

3.2.3 | Infections and response to vaccination

Omalizumab reduces inflammation by blocking proinflammatory cytokines and may even have antiviral effects. It affects mast cells, blocking the release of inflammatory agents such as histamine and protease in addition to proinflammatory cytokines including IL-1, IL-6 and IL-33 and has been shown to increase antiviral immunity through downregulation of the high-affinity IgE receptor on plasmacytoid dendritic cells.[86] In inner-city asthmatic children aged 6–17 years, preseasonal omalizumab treatment prevented the viral exacerbations in the fall, while increasing IFN-α responses to rhinovirus.[87] Treatment with omalizumab was effective and safe in patients with ABPA, regardless of comorbid chronic respiratory tract infections (chronic *Pseudomonas aeruginosa* or nontuberculous mycobacterial infection of the lower respiratory tract).[88] There was no safety signal from RCTs or RWE data on the use of omalizumab and increased risk of bacterial, viral or fungal infections, nor on the use of anti-infectious vaccines.

BOX 8 Recommendation for routine laboratory monitoring for omalizumab treatment for CSU

No routine laboratory monitoring is recommended for omalizumab in CSU	Conditional recommendation, moderate-quality evidence

BOX 9 Recommendation for management of infections and vaccinations under omalizumab treatment for CSU

Omalizumab should not be discontinued in case of cutaneous or non-cutaneous bacterial, viral or fungal infections or in case a vaccination is required; however, an unexpected outcome such as serious infection or vaccination failure should be reported appropriately in order to improve the post-marketing surveillance data	Conditional recommendation, moderate-quality evidence
Pre-treatment screening for geohelminths is recommended for patients where this infection is endemic	Conditional recommendation, expert opinion based
A 7-day window between the vaccine and omalizumab administration is recommended to unequivocally assign adverse events to either of the interventions	Conditional recommendation, expert opinion based

Although the role of IgE in immunity against helminth parasites is unclear, there was concern that omalizumab may be unsafe in subjects at risk of helminth infection. In an exploratory study of allergic subjects at high risk of helminth infections, omalizumab therapy appeared to be safe and well tolerated, but may be associated with a modest increase in the incidence of geohelminth infection (OR adjusted for study visit, baseline infection status, gender and age = 2.2 (0.94–5.15); one-sided $p = 0.035$). Infection severity and response to helminths appeared to be unaffected by omalizumab therapy.[89] The European Society of Clinical Microbiology and Infectious Diseases recommends that pre-treatment screening for *Strongyloides stercoralis* and other geohelminths should be considered in patients who come from areas where these are endemic who are receiving IgE-targeted agents.[90]

Several recommendations were formulated by the guidelines panel for the management of infections and vaccinations under omalizumab treatment for CSU (Box 9).

4 | OTHER BIOLOGICALS AND SMALL MOLECULES TESTED FOR CSU

4.1 | Targeting the IgE pathway: ligelizumab, quilizumab, GI-310

A high-affinity monoclonal anti-IgE antibody, ligelizumab, has recently been developed to overcome some of the limitations associated with the clinical use of omalizumab. Ligelizumab shows superior inhibition of IgE binding to FcεRI, basophil activation, IgE production by B cells and passive systemic anaphylaxis in an in vivo mouse model. However, ligelizumab was less potent in inhibiting IgE:CD23 interactions than omalizumab.[41] Overall, ligelizumab has ~50 times higher affinity for IgE than omalizumab. The results of a recently published multicentre, randomized, controlled phase II study show that ligelizumab is a highly effective therapy for CSU, with a higher rate of complete responders as compared with omalizumab, and with a very rapid and effective response and a longer lasting effect.[15] In the SR conducted for the EAACI guidelines, the certainty of evidence for ligelizumab in decreasing UAS-7 was categorized as low as the decrease was below the MID (−2,28; 95%CI −7,72 to −3,16). However, ligelizumab showed a good safety profile as it may decrease drug-related adverse events (risk ratio 0.72; 95%CI 0.50 to 1.05) (Table S43). Phase 3 trials in adults and adolescents with CSU are currently ongoing and have yet to confirm these results (NCT03580369, NCT03580356).

Quilizumab, a humanized, afucosylated, monoclonal IgG1 antibody, binds membrane IgE at the M1-prime segment, which is absent in soluble IgE. In animal studies, quilizumab bound membrane IgE on IgE-switched B cells and plasmablasts and depleted them through apoptosis and antibody-dependent cell-mediated cytotoxicity.[91] In the QUAIL study (NCT01987947), although quilizumab reduced median serum IgE level by approximately 30% in patients with CSU, it did not cause clinically meaningful improvements in the ISS-7 or the UAS-7.[92] A similar failure to achieve a significant clinical effect was encountered in asthma,[93] and the quilizumab development programme was discontinued.

GI-301 (GI-Innovation) is a novel long-acting IgE trap-Fc fusion protein that, like omalizumab and ligelizumab, binds circulating IgE. Similar to ligelizumab GI-3012 has higher and more durable binding to IgE than omalizumab.[94]

UB-221 (United Biopharma) is a humanized IgG1 mAb that targets IgE and leads to both neutralize-free IgE and down-regulate IgE synthesis via CD23 on B cells.[95,96] As described of the manufacturer's website, it neutralizes free IgE more effectively than omalizumab with a binding affinity eightfold higher.

4.2 | Targeting the T2 pathway: dupilumab, benralizumab, mepolizumab, reslizumab

Recently, a small case series suggested that dupilumab, an anti-IL-4Rα antibody, may be effective in adult patients with CSU.[97] The efficacy of dupilumab in urticaria is currently being investigated in several clinical trials, in CSU, cholinergic urticaria (NCT03749135, NCT03749148 and NCT04180488) and primary acquired chronic inducible cold urticaria (NCT04681729).

Mepolizumab and reslizumab have been successfully used in the treatment of individual patients with CSU.[98,99] Positive results of smaller controlled trials with benralizumab were recently published.[100,101] Benralizumab and mepolizumab are currently in clinical trials to test their efficacy in CSU (NCT04612725 and NCT03494881).

4.3 | Targeting mast cell receptors

Lirentelimab, an anti-Siglec-8 monoclonal antibody, was recently shown to inhibit MC activation and lead to extensive depletion of eosinophils. Lirentelimab has been successfully tested in an open-label phase IIa pilot study in patients with omalizumab-naïve and omalizumab-refractory CSU, as well as in patients with symptomatic dermographism or cholinergic urticaria.[102] However, larger controlled studies to confirm the safety and efficacy of the drug in the treatment of CSU are still pending. Initial findings on the safety of lirentelimab were gathered in a study on eosinophilic gastritis and duodenitis.[103]

The monoclonal antibody LY3454738 directed against CD200R was tested in a randomized, controlled phase 2 trial in patients with CSU (NCT04159701). Clinical development in CSU was terminated for lack of efficacy after an interim analysis was performed.

Preliminary results from a phase 1 study in 32 healthy volunteers with the anti-Kit antibody CDX-0159 suggest that treatment leads to a substantial reduction of MCs. A single intravenous dose-dependent administration led to an almost complete reduction of basal tryptase in the blood after only a few days. In the two higher doses, there was a sustained suppression of tryptase until the end of the observation period of 71 days.[104] CDX-0159 is currently in ongoing clinical trials for CSU.

4.4 | Targeting complement

Avdoralimab (IPH5401) is a therapeutic antibody that specifically binds and blocks C5a receptors (C5aR1) expressed on subsets of myeloid-derived suppressor cells. According to the company website, the product is tested in investigator-sponsored trials in CSU.

4.5 | Targeting epithelial cytokines

Due to its ability to activate ILC2, Th2 cells, dendritic cells and B cells TSLP might prove a good target in CSU. Tezepelumab is currently tested in a phase 2 trial in CSU (NCT04833855).

5 | DISCUSSION

5.1 | Relevance of the EAACI guideline in relation to existing CSU guidelines

The EAACI Guidelines recommendations for the use of omalizumab in CSU are formulated per outcome and per dose. The GRADE approach was used to rate the certainty of the evidence. The outcomes included were prioritized beforehand and the minimal important difference was considered when available for all CSU-related outcomes. Besides judging the risk of bias, the recommendations considered all relevant aspects related to the certainty of evidence like heterogeneity, indirectness or imprecision of the results. A critical appraisal of the evidence not included the SR provided additional support for the GDG in formulating recommendations. The recommendations follow the data included in the evidence-to-decision tables and take into consideration the balance of desirable and undesirable consequences, quality of evidence, cost-effectiveness, patients' values and preferences, feasibility, and acceptability of various interventions, use of resources paid for by third parties, equity considerations, impacts on those who care for patients and public health impact.

The EAACI/GA²LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria recommends adding on omalizumab 300 mg for the treatment of patients with CU unresponsive to 2nd-generation H1R-antihistamines, mentioning that omalizumab has high-quality evidence, high cost, very good safety profile and very good efficacy. It also acknowledges the preventive effect on angioedema in CSU.[1] However, the recommendation is formulated on the basis of >90% consensus, and there are no separate recommendations for different outcomes (disease activity, QoL, rescue use and safety), nor a strength of the recommendation. EAACI guidelines also offer a conditional recommendation for the 150 mg dose.

The 2014 Joint Task Force on Practice Parameters mentions omalizumab (together with cyclosporine) under Annotation 4 (Add an immunosuppressant or biologic agent) as having the greatest published experience documenting efficacy in patients with CU compared with all other alternative agents. Besides being recommended in step 4, together with immunosupressants, there is no other specific recommendation in CSU besides the fact that omalizumab should be considered for refractory CU if this is favourable from the standpoint of balancing the potential for benefit with the potential for harm/burden and cost and the decision to proceed is consistent with patients' values and preferences.[105]

The Italian Society for Pediatrics, the Italian Society for Allergy and Immunology, and the Italian Society for Pediatric dermatology convened a multidisciplinary panel that prepared clinical guidelines for diagnosis and management of chronic urticaria in childhood.[106] The panel recommends omalizumab in children 12 years of age and older with CSU added to second-generation H1-antistamines as a second-line therapy when second-generation H_1R-antistamines alone do not give adequate relief. (Level of evidence I. Strength of recommendation A). Again, there are no separate recommendations per outcome or per dose.

The KAAACI/KDA Evidence-Based Practice Guidelines for CSU in Korean Adults and Children recommends omalizumab for patients with CSU that do not respond to H1R-antihistamines (strong recommendation, moderate-quality evidence).[107] The guidelines follow the GRADE approach and are based on a SR conducted specific for these guidelines but similar to the previous guidelines is does not provide specific recommendations per outcome or per dose. However, these guidelines offer an additional recommendation for omalizumab for patients with CU if not controlled with H_1R-antihistamines and immunomodulators (conditional recommendation, very low-quality evidence).

5.2 | Future perspectives, barriers and facilitators

5.2.1 | Precision medicine using endotyping and multiple upstream targets

The separation into type I and type IIb autoimmunity and further validation of biomarkers is of utmost importance to select responders to omalizumab.[19,25,108-110] In addition, a better understanding of the 'non-canonical' mechanisms of action of omalizumab, such as effects on mast cell releasability or the coagulation cascade or targeting membrane-IgE in IgE+B cells, reducing IL4R expression and IgE synthesis and decreasing the number of these cells, possibly by causing B-cell anergy, should be further prioritized.[111,112] Targeting of epithelial derived cytokines or the GPCRs of MCs and MCs silencing and depletion are attractive pathways for endotype-driven management of CSU.[113]

5.2.2 | The disease-modifying effect

The 'crowning achievement' for the use of biologicals in CSU is to validate their disease-modifying potential. One RCT assessed worsening in UAS7 (≥12 points for ≥2 consecutive weeks) and DLQI worsening (≥3 points increase) for omalizumab 300 mg after stopping the treatment.[63] Patients in the placebo group were at higher risk for UAS7 worsening (RR 2.88; 95%CI 1.79 to 4.63) and had higher likelihood of DLQI worsening (RR 3.34;95% CI 2.07 to 5.40) as compared to the omalizumab 300 mg group. This result may suggest an 'extended' effect of omalizumab; however, currently omalizumab did not demonstrate a convincing disease-modifying effect in CSU, as the efficacy is lost a few weeks or months after the treatment is stopped.

5.2.3 | Long-term safety

Omalizumab has evidence for long-term safety above 5 years for the treatment of severe asthma, both in the adult and in the paediatric population.[114-116] However, there are no data on the long-term use in CSU. Thus, post-marketing surveillance, especially collected through structured registries like CURE, is of utmost importance.

5.2.4 | Considerations for the paediatric population

Despite being approved for severe asthma in children 6 years and older, there are only case series and case reports of efficacy and safety of omalizumab in children <12 years old with CSU[117,118]; thus, large and well-designed RCTs are needed.

Data on the efficacy and safety of omalizumab in the 12- to 17-year-old CSU patients are limited, and evidence for long-term use (>1 year) is lacking. The development of new drugs for the treatment of paediatric CSU proves difficult due to the limited availability and high heterogeneity of the paediatric population to enter randomized placebo-controlled trials in combination with the stringent requirements of the Paediatric Investigational Plan (EMA) or Paediatric Study Plan (FDA). Registries and large-scale international consortia evaluating paediatric CSU could help to overcome this major unmet need in the field of omalizumab for CSU.

5.2.5 | Efficacy versus effectiveness in a real-world setting

Several retrospective real-life cohorts and CSU registries report similar impact of omalizumab on CSU severity as in RCTs with an acceptable safety profile (Table S2).

5.2.6 | Cost-effectiveness

To determine the cost-effectiveness of omalizumab relative to standard of care (up to four times the daily dose of H1R-antihistamines) in the Netherlands from a societal perspective, a Markov model was used which consisted of five health states based on UAS-7 with a 10-year time horizon. The incremental cost-effectiveness ratio (ICER) of omalizumab versus standard of care was €17,502 per quality-adjusted life-year (QALY) gained. Productivity costs played an important role in the value of the ICER as by discarding productivity costs resulted in an ICER of €85,310 per QALY.[119] In a similar model applied in the UK with a deterministic ICER of £3183 in the base case, omalizumab use was associated with both increased costs and benefits relative to standard of care.[120] Both studies were considered by the GDG in the EtD tables for formulating recommendations.

5.2.7 | Additional major unmet needs and research priorities

The GDG proposed several key areas of interest both for the clinician and the basic researcher and from the healthcare point of view (Box 10). Unmet needs have been assessed from the perspectives of different stakeholders.

6 | CONCLUSION

The addition of omalizumab for the treatment of patients with chronic spontaneous urticaria not controlled by antihistamines

BOX 10 **Gaps in evidence for the use of omalizumab in CSU and plan to address**

Gaps in evidence	Plan to address	Priority
Standardizing the use in clinical practice 1. Criteria for responders and suboptimal response (early stopping rules) 2. Switching rules 3. Duration of treatment in responders (late stopping rules) 4. Long-term treatment regimen in responders: longer interval, down-dosing, possibility of stopping treatment, switch to strategies like topical application, etc. 5. Identification of factors related to failure 6. Routine measurement of anti-drug antibodies (ADA)	Prospective trials testing the clinical question followed by validation in independent population	High
Implementation of guidelines for the use of biologicals in clinical practice	In-depth education of HCPs on CIU pathogenic mechanisms and in recognizing the endotype	High
Improving evaluation by combining clinical and molecular outcomes	Multidimensional endotyping validating skin and systemic biomarker profiles	High
Long-term safety data (>5 years)	Well-structured post-marketing surveillance using CSU registries	High
Assess the long-term efficacy/disease-modifying effect (after treatment cessation)	Identify biomarkers related to the course of CSU Well-designed RCT and real-life studies focusing on long-term efficacy Mechanistic studies at a single cell level	High
Efficacy and safety data in the paediatric population	RCT and RWE trials/registries focused primarily on the paediatric population	High
Efficacy and safety in selected populations (pregnancy,) and in high-risk populations	RCT and RWE trials/registries focused primarily on these populations	High
Cost-effectiveness	Sectoral and generalized cost-effectiveness analysis, including the real-word perspective Long-term perspective as disease-modifying intervention and thereby influence long-term cost	High
Use of biomarkers for stratification	Proof of concept studies evaluating patient selection based on biomarkers	High
Impact of multi- morbidities	Studies evaluating the global effect of biologicals on multi-morbidities	High
Fair accessibility to CSU correct diagnosis and optimal targeted treatment	Reorganization of CSU care Implementation of the patients' perspective from research to models of care Implementation of management pathways/clinical decision systems	High
Comparison between biologicals available for CSU (approved and currently tested)	Independent head-to-head comparison between biologicals, ideally with cross-over design	High
Alignment of studies (including RWE) with guidance from regulatory bodies.	Work in partnership with regulatory bodies to continuously review trial methodology and outcomes.	Medium
The impact of age/race/ethnicity on the short and the long-term effects (efficacy and safety)	Well-designed RCT, example for personalized medicine	Medium
Does 'resistance' occur as in antibiotic or anti-cancer therapy and what are the underlying molecular mechanisms?	Well-designed RCT, example for personalized medicine	Medium
Validation of different regimens: shorter or longer intervals ('pulse-wise') rather than as a chronic ('maintenance') therapy (eg to prevent resistance)?	RCTs and real-life studies testing different approaches in terms of dose, duration and route	Medium
Combination of omalizumab with other immune modulation interventions (eg small molecules)	RCTs and real-life studies	Medium

is supported by improved understanding of disease mechanisms and has proved so far efficacious and safe in adults and the 12- to 17-year-old population.

There are several critical points that need further evaluation, from the effectiveness in real-world settings to the sustainability by healthcare systems, especially if long-term administration is warranted.

This EAACI Guideline on the use of omalizumab for chronic spontaneous urticaria offers a desk reference tool for healthcare providers, patients, regulators and healthcare systems based on a critical appraisal of the current evidence and a structured approach in formulating recommendations in alignment with the key principles of personalized medicine and implementation science.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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