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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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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.

Key words: chronic spontaneous urticaria, GRADE, guidelines, omalizumab

Abbreviations

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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
FDA = Food and Drug administration
FcεRI = high affinity receptors for IgE
GDG = Guideline Development Group
GPCRs = G protein-coupled receptors
GRADE = Grading of Recommendations Assessment, Development and Evaluation
HCP = healthcare professionals
Ig = immunoglobulin
IL = interleukin
ISS = itch severity score
IRR = incidence rate ratios
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

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QoL = quality of life
PICO = population, intervention, comparator, and outcomes
RCT = randomised 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

I. Introduction

a. The current landscape of chronic spontaneous urticaria

i. 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 hour 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

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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).

ii. 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 toward 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 do 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: 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

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activation through protein-protein interactions: c) and fusion proteins to co-aggregate FcεRI with the inhibitory FcγRIIb (12,13,14,15,16,17,18).

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, i.e., 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).

Characterisation 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,

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CD88), to which the anaphylatoxin C5a binds, and the Mas-related G protein-coupled receptor X2 (MRGPRX2), both preferentially expressed by the skin MCs (31,32,33,34). 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).

iii. *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 4-fold. Individual tolerance as well as 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 to 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.

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b. 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 'personalised' 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 (42). 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 (43). 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.

c. 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.

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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.

i. 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 policy makers.

ii. 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.

II. 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.

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a. 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 (i.e., 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.

b. 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.

c. 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

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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 prioritised in a first step by the GDG using a 1 to 9 scale (7 to 9 critical; 4 to 6 important; 1 to 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: QoL (assessed with Dermatology Life Quality Index (DLQI) and the Chronic Urticaria Quality of Life Questionnaire (CU-Q2oL)); resource utilisation (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 prioritisation 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).

d. 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 (44,45,46,47,48,49), 4.5 to 5 points for ISS-7 (46,47,49) and 2.24 to 3.10 for DLQI (50). 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 (45). In this paper the reported MID was 11 for the UAS7 (smallest detectable change (SDC) = 12) and 12 for the UAS7TD (SDC = 11).

e. 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 (51). 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 (e.g.,

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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) (52,53,54). 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.

f. 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).

g. 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 (52,53,54). 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 systems perspective was also evaluated, as per WHO recommendations for guidelines development (55).

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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.
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.

h. 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.

III. 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 (56,57,58,59,60,61,62,63,64,65,66).

a. Omalizumab 150 mg

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

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

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	Reduce disease activity as reflected by UAS-7 and ISS-7	Conditional recommendation
	Improve quality of life	Conditional

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adults and adolescents with chronic spontaneous urticaria* uncontrolled under antihistamines to:		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”

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), 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.

b. Omalizumab 300 mg

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

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

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 utilisation	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

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 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

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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 (65). 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 (64). The GDG formulated a conditional recommendation for a good safety profile advising periodical monitoring of AEs and SAEs.

c. 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).

Box 3: recommendation for omalizumab in adults and 12-17 years old patients with both CSU associated with other co-morbidities

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

d. 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 (67,68,69,70). A review of 141 publications showed that up to 50% CSU patients had elevated total IgE serum levels, but

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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 (71).

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 thyro-peroxidase 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, 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.

Box 4: recommendation for biomarkers in prescribing omalizumab in adults and 12-17 years 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 (71)

e. 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

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intervention and the recommendation can be adapted as policy or performance measure in most situations (table 4).

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).

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

IV. Practical approach

a. 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 (71). Responder rates using UCT score of greater than or equal to12 and UAS

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value of 6 or less yielded very similar results (72). 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 (73).

Box 6: Recommendations for practical use of omalizumab in adults and 12-17 years 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

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 (74).

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b. Monitoring treatment

i. 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 (75,76,77). 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 (78). 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 (79). A non–IgE-mediated anaphylactic response to the polysorbate excipient might also be involved (80).

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 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 4-fold 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 (e.g., 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,

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uvula) and respiratory (i.e., nose, laryngeal, lung). Most (70.0%) events occurred within 1 hour of omalizumab dosing (only 1 event occurred after 2 hours [i.e., at 3.5 hours]). 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 to 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 of anaphylaxis and 0.08% for patients with no history of anaphylaxis, resulting in a risk difference (i.e., attributable risk) of 0.54% (81). 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 (82). 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 the risk of anaphylaxis under omalizumab (box 7).

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	Conditional recommendation, expert opinion

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data	based
The first 3 doses should be administered in a setting with experience in managing anaphylaxis; an observation period of 30 minutes 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

While elevated serum IgE is generally associated with allergic/atopic conditions, very low or absent IgE may hamper anti-tumour surveillance, indicating the importance of a balanced IgE-mediated immune function (83). 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 (84). 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

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development or progression of solid epithelial cancer in these patient populations (85). Of note, EXCELS showed a higher rate of cardiovascular and cerebrovascular events (86).

ii. Routine laboratory monitoring

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

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

iii. 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 (87). In inner-city asthmatic children aged 6 to 17 years preseasonal omalizumab treatment prevented the viral exacerbations in the fall, while increasing IFN-α responses to rhinovirus (88). 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) (89). 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.

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

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omalizumab therapy (90). 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 (91).

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

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

V. Other biologicals and small molecules tested for CSU

a. 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 multicenter, randomized, controlled phase II study show that ligelizumab is a highly effective therapy for CSU,

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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 categorised 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 (92). In the QUAIL study (NCT01987947), although quilizumab reduced median serum IgE level approximately 30% in patients with CSU, it did not cause clinically meaningful improvements in the ISS-7 or the UAS-7 (93). A similar failure to achieve a significant clinical effect was encountered in asthma (94) 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 (95).

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 (96,97). As described of the manufacturer's website it neutralizes free IgE more effectively than omalizumab with a binding affinity 8-fold higher.

b. 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 (98). The efficacy of dupilumab in urticaria is currently being investigated in several clinical trials, in CSU, cholinergic urticaria (NCT03749135, NCT03749148, NCT04180488) and primary acquired chronic inducible cold urticaria (NCT04681729).
Mepolizumab and reslizumab have been successfully used in the treatment of individual patients with CSU (99,100). Positive results of smaller controlled trials with benralizumab were recently

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published (101, 102). Benralizumab and mepolizumab are currently in clinical trials to test their efficacy in CSU (NCT04612725, NCT03494881).

c. 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 (103). 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 (104).

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 (105). CDX-0159 is currently in ongoing clinical trials for CSU.

d. 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.

e. 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).

VI. Discussion

a. Relevance of the EAACI guideline in relation to existing CSU guidelines

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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 prioritised 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 with 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, 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 (106).

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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 (107). 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 of evidence) (108). 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 of evidence).

b. Future perspectives, barriers and facilitators

i. 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 (19,25,109,110,111). 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 prioritised (112, 113). Targeting of epithelial derived cytokines or the GPCRs of MCs and MCs silencing and depletion are attractive pathways for endotype-driven management of CSU (114).

ii. 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 (64). Patients in the placebo group were at higher risk for UAS7 worsening (RR 2.88;

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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.

iii. Long-term safety

Omalizumab has evidence for long-term safety above 5 years for the treatment of severe asthma, both in the adult and the paediatric population (115, 116,117). 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

iv. 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 (118,119), thus large and well-designed RCTs are needed.

Data on the efficacy and safety of omalizumab in the 12-17-years 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 randomised 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.

v. 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).

vi. 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

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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 (120). 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 (121). Both studies were considered by the GDG in the EtD tables for formulating recommendations.

vii. 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 health-care point of view (box 10). Unmet needs have been assessed from the perspectives of different stakeholders.

Box 10: Gaps in evidence for the use of omalizumab in CSU and plan to address

Gaps in evidence	Plan to address	Priority
Standardising 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 recognising 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	High

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	surveillance using CSU registries	
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 generalised 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	Reorganisation 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	Medium

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	continuously review trial methodology and outcomes.	
The impact of age/race/ethnicity on the short and the long-term effects (efficacy and safety)	Well-designed RCT, example for personalised medicine	Medium
Does 'resistance' occur as in antibiotic or anti-cancer therapy and what are the underlying molecular mechanisms?	Well-designed RCT, example for personalised medicine	Medium
Validation of different regimens: shorter or longer intervals ('pulse-wise') rather than as a chronic ('maintenance') therapy (e.g. 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

VII. Conclusion

The addition of omalizumab for the treatment of patients with chronic spontaneous urticaria not controlled by antihistamines is supported by improved understanding of disease mechanisms and has proved so far efficacious and safe in adults and the 12-17 years 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 offer 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 personalised medicine and implementation science.

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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) * **Important**: • Quality of life (DLQI; CU-Q2oL) • Rescue medication use • Resource utilisation (WIS, AIS)

*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* Rescue medication use** Resource utilization***	Important (4-6)
-	Low importance (1-3)

*Assessed with Dermatology Life Quality Index (DLQI) and the Chronic Urticaria Quality of Life Questionnaire (CU-Q2oL)

** Assessed with number of tablets of diphenhydramine per week

***Assessed with work productivity and activity impairment (WPAI), reporting two sub-scales separately, work impairment score (WIS) and activity impairment score (AIS)

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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

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

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		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.

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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

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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

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	Probably no important uncertainty	no important uncertainty			

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		or variability	or variability	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

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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

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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

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Table S1: The EAACI Guidelines for Biologicals in Chronic Idiopathic Urticaria – Guideline Development group

The Guideline Development Group is composed of the Core Leadership Team and the Voting Panel. The Methodology team provided support for the systematic review

Core Leadership Team	Voting Panel	Oversight Committee managing COI	Methodology Team
Chairs: Ioana Agache (Romania), Oscar Palomares (Spain), Marek Jutel (Poland)	Mubeccel Akdis, Switzerland Knut Brochow, Germany Ana Giménez-Arnau, Spain Jan Gutermuth, Belgium	Chair: Barbara Rogala, Poland Maria Beatrice Bilo, Italy Joanna Gluck, Poland	Lead: Pablo Allonso Coello Jessica Beltran Claudio Calderón
Cezmi Akdis, Switzerland Tomas Chivato, Spain Stefano Del Giacco, Italy Thomas Eiwegger, Canada Kilian Eyerich, Germany Liam O'Mahony, Ireland Jurgen Schwarze , UK	Emma Guttman-Yassky, US Marcus Maurer, Germany Graham Ogg, UK Peck Ong, US Amena Warner, UK (patient representative) Thomas Werfel, Germany	Johannes Ring, Germany Glenis Scadding, UK	Carlos Canelo Margarita Posso Ivan Sola Yang Song

Table S2: evidence for questions not included in the systematic review

Question	References/major outcome
Relevance of clinical trial population for real-world patients	Tharp MD, et al. JAMA Dermatol. 2019;155(1):29-38. Benefits and safety of omalizumab in the real-world treatment of CIU meet or exceed results from clinical trials. Lapeere H, et al. J Eur Acad Dermatol Venereol. 2020;34(1):127-134. Substantial improvements after 1 month of treatment. No anaphylaxis reported Eghrari-Sabet J, et al. Allergy Asthma Proc. 2018 May 7;39(3):191-200; Real-world use of omalizumab in patients with chronic idiopathic/spontaneous urticaria in the United States. Xuehua Ke, et al. J Manag Care Spec Pharm. 2018;24(7):598-606.The majority of CSU patients newly initiated with omalizumab were treated by allergists/immunologists, and approximately 60% of patients continued on therapy beyond 18 months. Concomitant medication use decreased after omalizumab initiation. Apalla Z et al. Eur J Dermatol. 2020 Dec 1;30(6):716-722. Five-year experience of omalizumab use in patients with refractory CSU in a real-world setting
Efficacy and safety in the pediatric population	Al-Shaikhly T, et al. Ann Allergy Asthma Immunol. 2019;123(2):208–210. Omalizumab for chronic urticaria in children younger than 12 years. Netchiporouk E, et al. Pediatr Allergy Immunol. 2015;26(6):585–588 Management of pediatric chronic spontaneous and physical urticaria patients with omalizumab: case series. Ari A, et al. Pediatr Dermatol. 2020;37(6):1051–1054 Efficacy of omalizumab treatment for pediatric chronic spontaneous urticaria: A multi-center retrospective case series. Passanisi S, et al. Dermatol Ther. 2020;33(4):e13489. Omalizumab in children and adolescents with chronic spontaneous urticaria: case series and review of the literature.

Safety in pregnancy	Pfaller B, et al Allergy. 2021;76(1):71-89. Systematic review on biologicals in pregnancy for indications of atopic diseases. Evidence in this field is scarce and mainly reserved to reports on the usage of omalizumab.
Safety long term	Nakamura M et al. Allergol Int. 2021;S1323-8930(21)00001-0; 104 weeks omalizumab treatment in children with severe asthma showed no safety signal
At home administration	Denman S, et al .Eur J Hosp Pharm. 2020;27(6):367-368. Home treatment with omalizumab for CSU is a safe and effective alternative to hospital administration. Shaker M, et al. J Allergy Clin Immunol Pract. 2020;8(2):565-572. For many patients, at-home administration of omalizumab may be a cost-effective strategy
Risk factors for adverse events	Lieberman PL et al. J Allergy Clin Immunol. 2016;138(3):913-915. 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). 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.
Immunogenicity/anti-drug antibodies (ADA)	Lieberman PL et al. J Allergy Clin Immunol. 2016;138(3):913-915 and Baker DL et al. AAPS J. 2016;18(1):115-23. No apparent correlation between either anaphylaxis or skin test reactivity and the presence of antibodies of IgE isotype to omalizumab
Joint treatment of CSU co-morbidities (asthma, AR, CINDU)	Dortas Junior S, et al. Ann Allergy Asthma Immunol. 2020;125(4):486-487 and Marcelino J et al. Eur Ann Allergy Clin Immunol. 2018;50(4):169-176 Efficacy of omalizumab in chronic spontaneous urticaria associated with chronic inducible urticaria. Boyce JA. Successful treatment of cold-induced urticaria/anaphylaxis with anti-IgE. J Allergy Clin Immunol. 2006;117(6):1415-8 Metz M, et al. Omalizumab is effective in cold urticaria-results of a randomized placebo-controlled trial. J Allergy Clin Immunol. 2017;140(3):864-867 Gastaminza, G., et al., Efficacy and Safety of Omalizumab (Xolair) for Cholinergic Urticaria in Patients Unresponsive to a Double Dose of Antihistamines: A Randomized Mixed Double-Blind and Open-Label Placebo-Controlled Clinical Trial. J Allergy Clin Immunol Pract, 2019. 7;5:1599-1609 Maurer, M., et al., Omalizumab is effective in symptomatic dermographism-results of a randomized placebo-controlled trial. J Allergy Clin Immunol, 2017.
Biomarkers/predictors of response	See S5 – S42
Continuation/discontinuation criteria	No study found
Defining efficacy; definition of responder, partial responder (dissociated outcome), non-responder	No study found
Optimal treatment duration	No study found
Health economics data	Kanters TA, et al. Br J Dermatol. 2018;179(3):702-708 and Graham J, et al Pharmacoeconomics.

	2016;34(8):815-27; Markov models showing the cost-effectiveness of omalizumab versus standard of care

Table S3. Summary of available evidence for the outcomes of interest for Omalizumab 150 mg compared to standard care for CSU

Patient or population: CSU 12-75 years old
Intervention: Omalizumab 150 mg
Comparison: standard care

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with standard care	Risk difference with Omalizumab
Weekly Urticaria Activity Score Assessed with: **UAS7** Scale from: 0 to 42	465 (3 RCTs) [1,2,3] 4 to 28 weeks	⊕⊕⊕⊕ HIGH [a]	-	Mean UAS7 0	**MD -5** (95% CI -7.75 to -2.25)
Weekly Itch Severity Score Assessed with: **ISS7** Scale from: 0 to 21	465 (3 RCTs) [1,2,3] 4 to 28 weeks	⊕⊕⊕⊕ HIGH [a]	-	Mean ISS7 0	**MD -2.15** (95% CI -3.2 to -1.1)
Any AE possibly related to study drug Assessed with: **Study personnel clinical follow-up**	479 (3 RCTs) [1,2,3] 4 to 28 weeks	⊕⊕◯◯ LOW [a,f,g]	**RR 1.40*** (0.63 to 3.13)	69 per 1,000	**+27 per 1,000** (95% CI -25 to +146)
Quality of Life Assessed with: **DLQI** Scale from: 0 to 30	305 (2 RCTs) [2,3] 4 to 28 weeks	⊕⊕⊕◯ MODERATE [a,d]	-	Mean DLQI 0	**MD - 2.01** (95% CI -3.22 to -0.81)
Rescue medication use Assessed with: **number of diphenydramine tablets/week**	321 (2 RCTs) [1,2] 4 to 28 weeks	⊕⊕⊕◯ MODERATE [a,e]	-	Mean rescue medication use 0	**MD -1.68** (95% CI -2.95 to - 0.4)

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; MD: Mean difference; RR: Risk ratio

GRADE Working Group grades of evidence
High certainty: High confidence that the true effect lies close to that of the estimate of the effect
Moderate certainty: Moderately confidence in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Limited confidence in the effect estimate : the true effect may be substantially different from the estimate of the effect
Very low certainty: Very limited confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. All studies were funded by industry, and all showed positive results in all outcomes. No industry-independent observational or randomized studies to support these results were found. Sponsorship industry bias was assessed as other bias as part of the RoB tool. The panel members considered that there were no major concerns about potential publication/sponsorship bias.
d. The minimal important difference (MID) for DLQI is 2.24 to 3.10 points

e. The lower limit of the confidence interval is not clinically relevant (less than 1 tablet)
f. Moderate heterogeneity (35%). The evidence was downgraded as effects favoured both intervention and placebo
g. The effect may be both harmful or beneficial.

References

1. Saini S, Bindslev-Jensen C, Maurer M, et al. Efficacy and safety of omalizumab in patients with chronic idiopathic/ spontaneous urticaria who remain symptomatic on H1 antihistamines: a randomized, placebo-controlled study. J Invest Dermatol. 2015;135(1):67-75
2. Maurer M, Rosén K, Hsieh HJ, et al. S, Omalizumab for the treatment of chronic idiopathic or spontaneous urticaria. N Engl J Med. 2013;368(10):924-935
3. Hide M, Park HS, Igarashi A, et al. Efficacy and safety of omalizumab in Japanese and Korean patients with refractory chronic spontaneous urticaria. J Dermatol Sci. 2017;87(1):70-78

Table S4. Summary of available evidence for the outcomes of interest for Omalizumab 300 mg compared to standard care for CSU

Patient or population: CSU 12-75 years old
Intervention: Omalizumab 300 mg
Comparison: standard care

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with standard care	Risk difference with Omalizumab
Weekly Urticaria Activity Score assessed with: **UAS7** Scale from: 0 to 42	610 (6 RCTs) [1,2,3,4,5,6] 4 to 28 weeks	⊕⊕⊕◯ MODERATE [a,b]	-	Mean UAS7 **0**	MD **-11.05** (95% CI -12.87 to -9.24)
Weekly Itch Severity Score Assessed with: **ISS7** Scale from: 0 to 21	628 (5 RCTs) [1,2,3,5,6] 4 to 28 weeks	⊕⊕⊕◯ MODERATE [a,c]	-	Mean ISS7 **0**	MD **-4.45** (95% CI -5.39 to -3.51)
AE possibly related to study drug Assessed with: **Study personnel clinical follow-up**	801 (4 RCTs) [1,2,3,7] 24 to 40 weeks	⊕⊕◯◯ LOW [a,f,g]	**RR 1.37** (0.67 to 2.82)*	85 per 1,000	**+32 per 1,000** (95% CI -28 to +156)
Serious AE possibly related to study drug Assessed with: **Study personnel clinical follow-up**	335 (1 RCT) [7] 24 to 40 weeks	⊕⊕⊕◯ MODERATE [f]	**RR 0.77** (0.20 to 2.91)*	36 per 1,000	**-8 per 1,000** (95% CI -29 to +69)
Quality of Life Assessed with: **DLQI** Scale from: 0 to 30	732 (4 RCTs) [2,3,4,6] 4 to 28 weeks	⊕⊕⊕⊕ HIGH [a]	-	Mean DLQI **0**	MD **-4.03** (95% CI -5.56 to -2.5)
Rescue medication use Assessed with: **number of diphenydramine tablets/week**	654 (3 RCTs) [1,2,7] 4 to 28 weeks	⊕⊕⊕◯ MODERATE [a,e]	-	Mean rescue medication use **0**	MD **-2.04** (95% CI -3.19 to -0.88)

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

Table S4. Summary of available evidence for the outcomes of interest for Omalizumab 300 mg compared to standard care for CSU

Patient or population: CSU 12-75 years old
Intervention: Omalizumab 300 mg
Comparison: standard care

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with standard care	Risk difference with Omalizumab

GRADE Working Group grades of evidence
High certainty: High confidence that the true effect lies close to that of the estimate of the effect
Moderate certainty: Moderately confidence in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Limited confidence in the effect estimate : the true effect may be substantially different from the estimate of the effect
Very low certainty: Very limited confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. All studies were funded by industry, and all showed positive results in all outcomes. No industry-independent observational or randomized studies to support these results were found. Sponsorship industry bias was assessed as other bias as part of the RoB tool. The panel members considered that there were no major concerns about potential publication/sponsorship bias
b. The minimal important difference (MID) for UAS7 is 9.5 to 10.5 points
e. The minimal important difference (MID) for ISS7 is 4.5-5 points
f. The lower limit of the confidence interval is not clinically relevant (less than 1 tablet)
g. The effect may be both harmful or beneficial.
h. Substantial heterogeneity (56%). The evidence was downgraded as effects favoured both intervention and placebo

References

1. Saini S, Bindslev-Jensen C, Maurer M, et al. Efficacy and safety of omalizumab in patients with chronic idiopathic/ spontaneous urticaria who remain symptomatic on H1 antihistamines: a randomized, placebo-controlled study. J Invest Dermatol. 2015;135(1):67-75
2. Maurer M, Rosén K, Hsieh HJ, et al. S, Omalizumab for the treatment of chronic idiopathic or spontaneous urticaria. N Engl J Med. 2013;368(10):924-935
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Table S5: studies included in the biomarker SR

Author Year	N, Mean age	Design	Population	Biological	Biomarker	Outcomes	Duration
Asero 2017	N=74, 49 years old ,(15-78)	Letter to editor, retrospective cohort	Adults with severe CSU unresponsive to second-generation antihistamines at up to 4 times licensed dose	Omalizuamb , 300 mg, q4w	D-dimer levels	-Omalizumab Responder -Correlation between D-dimer and time to response	3 months

			(urticaria activity score [UAS 7] > 30; mean disease duration 49 months; range 2-540 months) were studied.				
Asero 2019	N=161, 48 ± 16 years, range 15-80 years	Letter to editor, retrospective cohort	Adult patients with both active and severe CSU (baseline UAS-7 > 20) not responding to second-generation antihistamines at doses up to 4 times higher than the licensed dose and submitted to subcutaneous omalizumab treatment at a dose of 300 mg/ month for at least 3 months were studied	Omalizuamb, 300 mg, q4w	D-dimer levels	-Omalizumab Responder -Correlation between D-dimer and UAS-7;	3-7 days after first administration; 2-3 month; 3 shots of Omalizumab
Asero 2020	N=130, 50.6 years (range 13-89 years)	Letter to editor, retrospective cohort	Patients with severe CSU (UAS-7 > 30) unresponsive to second generation antihistamines at any dosage and successfully submitted to treatment with Omalizumab 300 mg/month for at least 3 months were studied.	Omalizuamb, 300 mg/month	Total IgE	-Omalizumab Responder	3 months
Endo 2020	N= 22, age range, 24 to 87 years	Prospective cohort	Consecutive patients with CSU who were receiving treatment with omalizumab were recruited for this study.	Omalizuamb, 300 mg, q4w, 3 months	Basophil activation test	-Urticaria activity score (UAS) 7 -Response to Omalizumab	3 months
Ertas 2017	N= 113, mean (SD)40.0 years (13.0)	Prospective cohort	CSU patients resistant to standard first-line treatments; that is, all patients were refractory to standard dosed and up to fourfold dosed sgAH treatment, and all had a UAS of 3 or more. Some patients	Omalizuamb, 300 mg, q4w, 12 weeks	Baseline IgE	-Omalizumab Responder - Correlation between baseline IgE and UAS, physician VAS, patient VAS, physician TES, and patient TES -Sensitivity -Specificity	12 weeks

			had treatments other than antihistamines before inclusion in this study. 83 of the patients included in this study were previously investigated for their response to omalizumab treatment and relapse after discontinuation of treatment.				
Ghazanfar 2018	N=117, 40.3 years (SD= 15.2, range 10-73 years)	prospective cohort	CUS patients who were refractory to high-dose antihistamines and who initiated treatment with add-on therapy of omalizumab (300 mg every four weeks) between January 2015 and May 2017 were included in this study	Omalizuamb, 300 mg, q4w. 6 months	Histamine release (HR) test Total IgE CRP levels Absolute neutrophil count	- UAS-7 between HR test yes and no groups - Correlation between change of UAS-7 score and Total IgE , CRP levels, Absolute neutrophil count	Measured at 3 months
Palacios 2016	N=41, 45.9 years (SD 17)	Letter to editor/ retrospective chart review	Consecutive adult patients with antihistamine-refractory CU seen at the University of Virginia outpatient allergy clinic between 2011 and 2013 to investigate the use of the basophil CD203c assay as a biomarker of responsiveness to omalizumab in CU.	Omalizuamb, 300 mg, q4w 3 months or more	CD203 cupregulating Activity positive	- Omalizumab Responder	3 months
Straesser 2018	N= 137, 45 (±15) years	Letter to editor Retrospective chart review	More than 12 years of age, with antihistamine-refractory CU; All subjects in the study were treatment-naïve to omalizumab, and 130 of 136 (95.6%) were not on other immunomodulatory medications for their chronic idiopathic urticaria at study	Omalizumab, 300mg/15mg, q4w, 4 months.	- IgE level - IgG thyroid autoantibodies - BAT	- Omalizumab Responder	4 months

			enrollment				
Syrigos 2018	N=20, 54.5 years (range 19–85 years)	Retrospective case series	Patients with refractory CSU, with persistent or recurrent symptoms despite use of high-dose H1-antihistamines and repeated courses of oral corticosteroids.	Omalizumab, 300mg, q4w, 3-25 months	ESR elevated CRP elevated IgE elevated	- Number of responders	Mean follow up 16.6 months (range: 3–26 months).
Uysal2018	N = 31, 56 years, range 21-93 years	Retrospective self-control study	Forty-seven subjects with the diagnosis of CIU/ CSU who had received at least 12 weeks treatment of omalizumab injections	Omalizumab, 300mg, q4w, 12 weeks	Baseline IgE (cut off: 31.35 IU/ mL)	- Number of responders	12 weeks
Viswanathan 2013	N = 19, 38.3 with a range of 8–69 years	Retrospective review	Patients with a diagnosis of CU who were treated with omalizumab between 2009 and 2012.	Omalizumab, 300mg, q2w/q4w, 1-16 months	Elevated IgE; Antinuclear antibody (ANA) positive; Antithyro globulin (ATG) positive; Antithyroperoxidase (ATPO) positive;	- Number of responders	1-16 months
Grieco_a 2020	N = 42, Mean age (range): 48.89 (19;83)	A monocentric observational study	Adult patients who had completed at least one course of treatment with omalizumab for CSU were enrolled in this study. The disease was diagnosed following the current criteria of the EAACI guidelines, requiring a history of spontaneous urticaria for 6 weeks or longer, with relative treatment.	Omalizumab, 300mg, q4w, 6 months	Serum IgE; D-dimer; basophil activation test; antinuclear antibodies (ANA); antithyroid peroxidase antibodies (ATPO); antithyroglobulin antibodies (ATG)	- Disease relapse - Responders to Omalizumab	Evaluated1 year
Grieco 2020	N = 8, Age mean $\pm$ SD [min;max] = 57 $\pm$ 4 [51;64] years	a pilot study with longitudinal design and a single intervention arm	Subjects with a diagnosis of CSU, refractory to first and second lines of treatment with second generation antihistamines, and candidates to	Omalizumab, 300mg, q4w, 6 months	IL-6; IFN-γ;	- Correlation between IL-6 and UAS score - Correlation between IFN-γ and UAS score	6 months

			treatment with omalizumab.				
Tamer 2019	N = 11, Age ranged between 19 to 59.	Retrospective records review	Eleven patients (2 male, 9 female) with chronic spontaneous urticaria treated with omalizumab between January 2014 and March 2017 were included in the study.	Omalizumab, 300mg, q4w, 4-146 months	Serum total IgE levels (IU/mL);	- Correlation between serum IgE and treatment outcome - Omalizumab responders	4 to 20 months
Aghdam 2020	N=30 median age 42 years (range 21-70)	Prospective cohort, single center, Netherlands	age ≥ 18 years, active diagnosis of CSU (weekly urticaria activity score [UAS7]) ≥ 16, in-clinic UAS ≥ 4 on the day of the first omalizumab administration, and insufficient response to a four-times daily administration of antihistamines	Omalizuamb 300 mg, q4w	-FcεRI -Total IgE	-Correlation between FcεRI bearing leucocytes and disease activity (UAS-7) -Response to omalizumab (UAS-7)	24 weeks
Altrichter 2014	N=39 (21 omalizumab, 18 placebo) Age NR	Letter to the editor, post-hoc analysis	patients with persistent symptoms for ≥6 weeks despite standard antihistamine therapy and a 7-day urticaria activity score (UAS7)6 of >7 were selected from a previous multicentre study (the X-CUISITE study)	Omalizumab 75–375 mg, q2-4w	IL-31 level (pg/mL)	-Response to omalizumab (UAS-7)	24 weeks
Baysak 2020	N=119 mean age 40.86 ± 13.59 years	Retrospective chart-review study, single center, Turkey	All the patients with a diagnosis of CSU who were continuously treated with omalizumab (300 mg/month) for at least 3 months between June 2016 and July 2019	Omalizumab 300 mg, q4w	-serum C-reactive protein (CRP) levels	-Correlation between CRP level UAS scores' -Response to omalizumab (UAS-7)	12 weeks
Castagna 2020	N=56 mean age (SD) 41.9 (16.7)	Letter to the editor, retrospective cohort, single center, France	All H1-antihistamine-refractory CSU patients treated with OMZ in the period February 2013 - December 2016	Omalizumab 300 mg, q4w	-BMI (>=30, <30) -Baseline D-dimer (>= 500, <500)	-Response to omalizumab (UAS-7)	6 months
Chen 2020	N=89 mean age	Letter to the editor,	NR	Omalizumab (dosis and	-Baseline total IgE levels	-Treatment efficacy (UCT)	6 months

	37.45±16.32 years.	retrospective cohort, Single center UCARE, China		frequency NR)			
Cildag 2018	N=41 mean age 45.65 ±11.79 years	Retrospective cohort, Single center, Turkey	Patients who started omalizumab treatment for refractory CSU	Omalizumab 300 mg, q4w	- IgE, IgA, IgM, or IgG levels - baseline eosinophil, neutrophil, lymphocyte or platelet levels	-Response to omalizumab (UAS-7)	12 weeks
Deza 2017	N=91 (47 CSU (median age 51 years (range 41–64)), and 44 HCs (median age 45 years (range 33–59))	Prospective cohort with control group, Single center, Spain	Consecutive adult patients controlled at the Urticaria Clinic of the Department of Dermatology of Hospital del Mar (Barcelona) with moderate-to-severe persistent and active CSU (7-days Urticaria Activity Score [UAS7] ≥16 and refractory to antihistamine therapy were included in the study during the period from January 2014 to December 2015.	Omalizumab 300 mg, q4w	- Total serum IgE levels at baseline (kU/l) - expression of the basophil FcεRI receptor at baseline	-Response to therapy (UAS7) -Sensititivity -Specificity	6 months
Deza 2018	N=44 Median age 49 (14-77)	Letter to editor, prospective cohort, Single center, Spain	patients with active CSU whose symptoms were not controlled with H1-antihistamines (even up to 4 times the recommended dose)	Omalizumab 300 mg, q4w	-baseline levels of basophil FcεRI receptor -Blood basophil count (x103/µL) -Total IgE levels at baseline (kU/L)	-Time to response to therapy (UAS7) (fast vs slow responders) -Correlation between levels of total serum IgE and baseline FcεRI expression	4 weeks
Gericke 2016	N=64 median age was 47 (range 23 – 85) years	Letter to editor, retrospective cohort, Single center, Germany	patients whose symptoms were not controlled with H1-antihistamines up to four times the recommended dose were treated with omalizumab at the Charité Department of Dermatology	Omalizumab 300 mg, q4w	- BMI - total IgE -ASST+1 -BHRA+1 -anti-FcεRI+1	-Complete response within 8 days	12 weeks
Nettis 2018	N=322 mean age 46.5 ± 14.3 years	Retrospective cohort, multicentric 23 Italian	Patients aged 12-85 years included in the study had a history of	Omalizumab 300 mg q4w	-ASST -IgE	-Response to omalizaumab (UAS7)	24 weeks

		centers	spontaneous urticaria for more than 6 weeks, not responding to treatment with licensed doses of non-sedating second-generation H1-antihistamines for at least four weeks, with a daily urticaria activity score (UAS) ≥4 assessed in clinic on one of the pre-treatment check-up days (days –14, –7, or 1), and a 7-day urticarial activity score (UAS7) >16 assessed during 7 days before first study treatment.				
Nazik 2019	N=136 Mean age 41.9 ±13.2 (14–85)	Restrospective cohort, Single center, Turkey	patients diagnosed with CU and AD, who received omalizumab treatment, from June 2014 to November 2017	Omalizumab 300 mg q4w	-IgE -% Eosinophils	-Response to omalizumab	6 months
Marzano 2018	N=470 median age (IQR) 49 (37–61)	Retrospective, Multicenter, 12 different Italian Dermatology and Allergology Units	only CSU patients resistant to standard first-line treatments, that is all patients were refractory to standard dosed and up to fourfold dosed second-generation antihistamine (sgAH) treatment, and all had a baseline UAS7 >16. Some patients had treatments other than antihistamines before inclusion in this study	Omalizumab 300 mg q4w	-IgE -D-dimer	-Response to omalizumab (UAS7)	24 weeks
Kolkhir 2019	N=1613 Median age (range) 43 (13-105)	Retrospective, 2 centers, Germany and Russia	patients with CSU	Omalizumab 300 mg q4w	-blood eosinophil -basophils -ASST + -BHRA +	-Response to omalizumab (UAS7)	8 weeks
Rijavec 2020	N=43 median age 48 (range, 22-81) years	Letter to the editor, prospective cohort, Single	patients with active CSU referred to the University Clinic of Respiratory	Omalizumab 300 mg q4w	-IgE -Absolute basophil count (cells/μL) -Absolute	-Response to omalizumab (UAS7)	12 weeks

		center, Slovenia	and Allergic Diseases Golnik (Slovenia), whose symptoms were not controlled with high doses of H1 antihistamines and were consequently treated with omalizumab.		lymphocyte count (cells/µL) -Absolute monocyte count (cells/µL)		

Table S6; risk of bias assessment (ROBINS-II: Cohorts studies)




Tamer 2019
Aghdam 2020
Altrichter 2014
Baysak 2020
Castagna 2020
Chen 2020
Cildag 2018
Deza 2017
Deza 2018
Gericke 2016
Nettis 2018
Nazik 2019
Marzano 2018
Kolkhir 2019
Rijavec 2020
Critical
Serious
Moderate
Low

Figure S1: Immunoglobulin E - Responders (defined by UAS score)

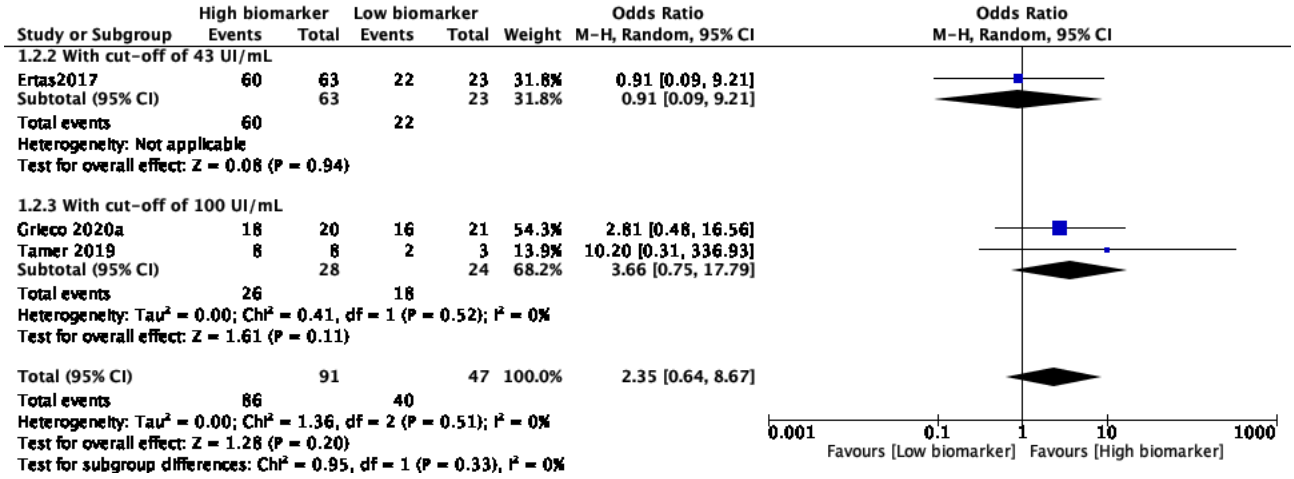


Figure S2: Immunoglobulin E - Responders (defined by symptoms)

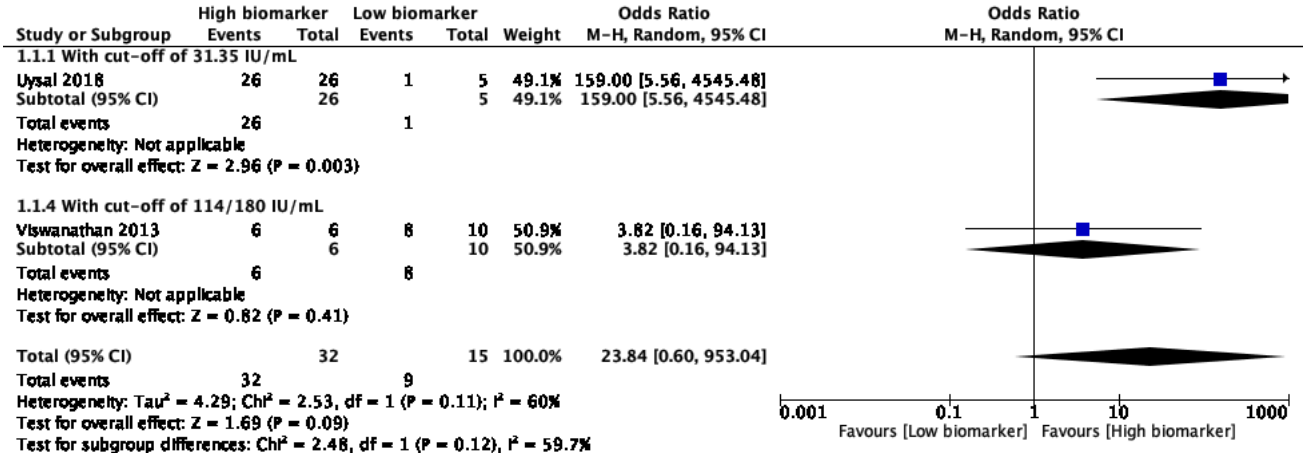
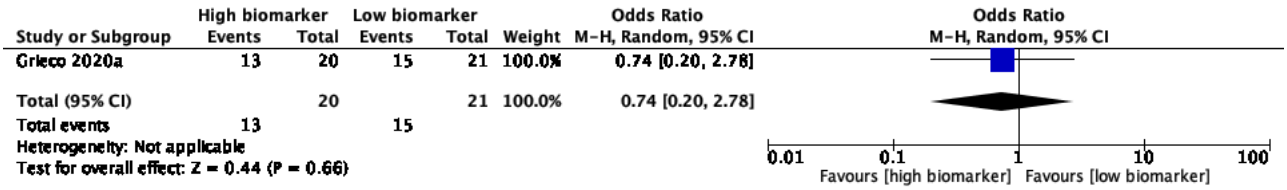


Figure S3: Immunoglobulin E - Responders according to clinical assessment

Study	Cut-off	Number of responder*/N		OR (95%CI)
		Biomarker High	Biomarker Low	
Straesser 2018	> 168 UI/mL vs. ≤ 15.21 UI/ mL	NR	NR	13.81 (3.58 to 48.45)
Straesser 2018	> 68.8 UI/ml vs. ≤ 15.21 UI/ mL	NR	NR	3.81 (1.94 to 7.46)
Straesser 2018	> 168 UI/mL vs. ≤ 68.8 UI/mL	NR	NR	3.46 (1.84 to 6.50)

Straesser2018: Clinical response to omalizumab was subjectively defined by documented clinical response to omalizumab by the prescribing provider and/or continuation of omalizumab beyond 4 months of therapy

Figure S4: Immunoglobulin E - Disease relapse (UAS score >16) evaluated with cut-off of 100 IU/mL



*Asero 2020 evaluated the prediction of early responder vs. late according to IgE cut off of 100 IU/ml, the odds ratio is 4.10 (1.24, 13.60).
*Syrigos 2018 evaluated prediction of early responder early responder vs. late according to IgE elevated and normal (no cut-off was provided), the odds ratio is 7.82 [0.35, 174.42]

Table S7: Correlation between IgE and efficacy outcome

Study ID	Efficacy outcome	Correlation coefficient (r)	Pvalue
Ertas 2017	UAS	-0.209	0.041
Ertas 2017	physician visual analog scale (VAS)	-0.185	>0.05
Ertas 2017	patient VAS	-0.187	>0.05
Ertas 2017	physician treatment score (TES)	0.099	>0.05
Ertas 2017	patient TES	0.179	>0.05

* Tamer 2019 reported the correlation narratively as "no correlation was observed between serum IgE levels and treatment outcome"
* Ghazanfar 2018 reported the association of the UAS-7 score and patients' IgE level, regression coefficient is
is 0.001 (-0.002 to 0.003), P=0.526.

Table S8: Differences in baseline IgE level between responders and non-responders

Study ID	Responders* Median (Range)	Non responder Median (Range)	Difference	Pvalue
Ertas 2017	73.7 IU/mL (19.5 to153.8)/14	17.9 IU/mL (17.0 to 55.0)/34	55.8	<0.05
Uysal2018	184.5 IU/mL(62 - 307)/27	25.6 IU/mL(10.8 - 30.2)/4	158.9	NR
Aghdam 2020	170.0 kU/L/15	81.9 kU/L/13	88.1	0.387
Chen 2020	98.0 kU/L /80	17.0 kU/L/9	81	0.003
Deza 2017	151 kU/l (66–311)/38	20 kU/l (5–59)/9	131	0.0003
Deza 2018	200 kU/L (17-1536)/33	66 kU/L (34-889)/11	144	0.067
Gericke 2016	239.2 ±250.6	130.0 ±155.0	109.2	0.104
Nazik 2019	250.6 IU/ml ±417.4/ 87	180.9 ±225.6/ 46	69.7	0.294
Marzano 2018	131.6 kUA/L (507)/ n = 425	42.1 kUA/L (299)/ 45	89.5	<0.0001
Rijavec 2020	87 kU/l (<1-1186)/ 36	20 kU/l (2-146)/ 9	67	.005

NR: not reported; * Responders were defined by UAS score in Ertas 2017, defined by relief of symptoms in Uysal 2018, defined by UAS7 score of 6 or lower in Aghdam 2020, defined by UCT in

Chen 2020, defined by UAS7 and UCT in Deza 2017, defined by UAS7 <=6 in Deza 2018, Gericke 2016, Marzano 2018, and Rijavec 2020
Cildag 2018: IgE, IgA, IgM, or IgG levels. No signifcant differences were observed in baseline levels between groups. Responder (n = 17) vs no responder (n = 24) p 0.48, 0.90, 0.58, 0.38.

Table S9- Antinuclear antibody (ANA); responders defined by UAS score (1 year)

Study	Cut-off	Number of responder*/N		OR (95%CI)
		Biomarker High	Biomarker Low	
Grieco 2020a	1:160	5/5	9/10	1.74 (0.06 to 50.43)

Table S10- Antinuclear antibody (ANA); Responders (defined by symptoms) (1-16 months)

Study	Cut-off	Number of responder*/N		OR (95%CI)
		Biomarker High	Biomarker Low	
Viswanathan 2013	Elevated (above respective upper limit)	6/7	28/34	1.29 (0.13 to 12.74)

Figure S5- Antinuclear antibody (ANA); Disease relapse (UAS score >16) evaluated with cut-off of 1:160

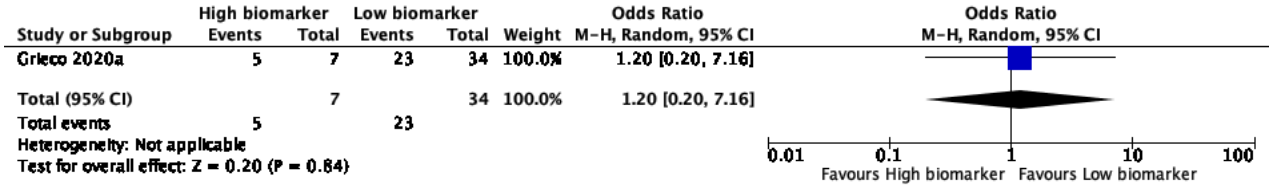


Table S11: Responder defined by UAS score - Antithyroglobulin (ATG) (1 year)

Study	Cut-off	Number of responder*/N		OR (95%CI)
		Biomarker High	Biomarker Low	
Grieco2020a	100 IU/mL	3/5	31/36	0.24 (0.03 to 1.83)

Responder defined by symptom - Antithyro globulin (ATG) (1-16 months)

Study	Cut-off	Number of responder*/N		OR (95%CI)
		Biomarker High	Biomarker Low	
Viswanathan 2013	Elevated (above respective	1/1	9/9	Not estimable

upper limit)

Table S12: Disease relapse (UAS score >16) - Antithyro globulin (ATG) (1 year)

Study	Cut-off	Number of responder*/N		OR (95%CI)
		Biomarker High	Biomarker Low	
Grieco2020a	100 UI/ml	4/5	24/36	2.00 (0.20, 19.91)

*Straesser 2018 evaluated responders and non responders for IgG thyroid autoantibodies positive group, n=32/39 (54%) and 7/39 respectively, p=0.187.

Palacios 2016 reported the correlation between thyroid autoantibodies and efficacy narratively as "no correlation was found".

Table S13: Responder defined by UAS score - Antithyroperoxidase (ATPO) (1 year)

Study	Cut-off	Number of responder*/N		OR (95%CI)
		Biomarker High	Biomarker Low	
Grieco2020a	16 IU/mL	7/9	27/32	0.24 (0.03 to 1.83)

Table S14: Responder defined by symptom - ATPO (1-16 months)

Study	Cut-off	Number of responder*/N		OR (95%CI)
		Biomarker High	Biomarker Low	
Viswanathan 2013	Elevated (above respective upper limit)	3/3	9/9	Not estimable

Table S15: Disease relapse (UAS score >16) - Antithyro globulin (ATPO) (1 year)

Study	Cut-off	Number of responder*/N		OR (95%CI)
		Biomarker High	Biomarker Low	
Grieco2020a	16 IU/ml	5/9	23/32	0.49 (0.01 to 2.25)

* Asero 2020 reported early and late responder according to ATPO cut off of 16 UI/ml, the odds ratio is 1.54 [0.41, 5.74], P=0.5215.

Marzano 2018 reported Positivity for antithyroglobulin or antithyroperoxidase autoantibodies in responders n (%): 106 (26.7) and not responders n (%) 15 (36.6), p= 0.1995.

Table S16: Basophil activation test (BAT) Responder defined by UAS score (1 year)

Study	Cut-off	Number of responder*/N		OR (95%CI)
		Biomarker High	Biomarker Low	
Grieco2020a	15	3/3	31/38	1.67 (0.08 to 35.84)

Table S17: Basophil activation test (BAT) - Responder defined by clinical response (3 months)

Study	Cut-off	Number of responder*/N		OR (95%CI)
		Biomarker High	Biomarker Low	
Palacios 2016	CD203 upregulating	9/18	20/23	0.15 (0.03 to 0.69)

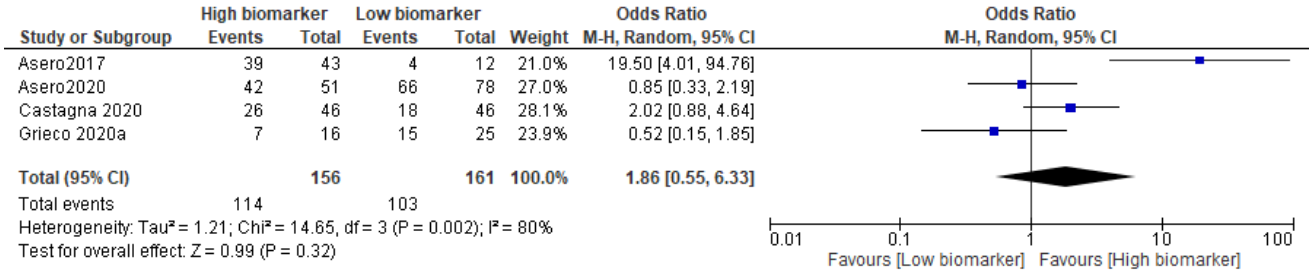
*Straesser 2018 evaluated responders for Positive (upregulation of CD203c), n=16/27.

Table S18: Basophil activation test (BAT) Disease relapse (UAS score >16) (1 year)

Study	Cut-off	Number of responder*/N		OR (95%CI)
		Biomarker High	Biomarker Low	
Grieco2020a	15 IU/ml	0/3	28/38	0.05 (0.00 to 1.11)

*Endo 2020 reported the UAS 7 score for BAT positive and negative group at 84 days, the median (range) is 16 (1-37) and 4(0-21), respectively. (data were extracted using WebPlotDigitizer)

Figure S6: D-dimer - Early responder vs. late/non responders (defined by UAS score reduction)



*Cut-off of D-dimer is 475 / 500 ng/mL; early response defined as reduction of UAS at 3-7 days; late/non-response was at 3 months or more.

Table S18: D-dimer - Disease relapse (UAS score >16) (1 year)

Study	Cut-off	Number of responder*/N		OR (95%CI)
		Biomarker High	Biomarker Low	
Grieco2020a	500 IU/ml	10/16	19/25	0.65 (0.17 to 2.47)

Box S1: Correlation between D-dimer and efficacy outcome

Asero 2019 reporetd "A significant correlation between D-dimer and UAS-7 at baseline was found (P = 0.014), whereas D-dimer levels used as a marker of the activation of the coagulation cascade and of its intensity were not able to predict the clinical response to omalizumab".

Asero 2017 reported correlation between D-dimer and time to response, Correlation coefficient (r) = -0.411, P=0.007.

Table S19: Difference on baseline D-dimer level between responders and non-responders

Study	Responders Mean (95%CI)/N*	Non responder Mean (95%CI)/N	Mean difference (95%CI)	Pvalue
Asero 2017	1536 (968-2104) ng/mL / 48	524 (316-732 ng/mL) ng/mL / 13	1012.00 (427.84 to 1596.16) ng/mL	<0.05
Asero 2019	826 (448-1203) ng/mL/28*	892 (439-1344) ng/mL /23	-66.00 (-625.13 to 493.13) ng/mL	0.8167
Marzano 2018	327.0 (874.1)	292.9 (689.6)		0.5560

*We used data evaluated at 3 months; Responders were defined as UAS score dection.
Asero 2017 reported the baseline D-dimer level mean (95%CI) for "late and partial responders" as 988 ± 1762 ng/mL, N=20.

Table S20: C-reactive protein (CRP); Early responder vs. late/non responders (UAS7 ≤ 6)

Study	Cut-off	Number of responder*/N		OR (95%CI)
		Biomarker High	Biomarker Low	
Syrlgos2018	CRP elevated	3/10	7/10	0.18 (0.03 to 1.24)

* Early responders means UAS score ≤ 6 within 3 months;

Box S2: Correlation between CRP level and UAS score

* Baseline CRP levels before the initiation of therapy were not correlated with treatment response at 12th or 24th week. (p=0,453, n = 45). High initial CRP levels were not associated with a higher decline in UAS and thus, better response to omalizumab therapy. Baysak 2020 reported the decline of CRP level was positively and strongly correlated with the decline of UAS, thus treatment response, (p=0.037) (Considered as a surrogate outcome).

Ghazanfar 2018 reported the association of the UAS-7 score and patients' CRP level, regression coefficient is -0.271 (0.62 to 0.74)/ n = 74, P=0.123.

Table S21: Erythrocyte sedimentation rate (ESR) - Early responder vs. late/non responders (UAS7 ≤ 6)

Study	Cut-off	Number of responder*/N		OR (95%CI)
		Biomarker High	Biomarker Low	
Syrlgos2018	ESR elevated	8/14	3/6	1.33 (0.20 to 9.08)

* Early responders mean UAS score ≤ 6 within 3 months;

Table S22: Basophil Histamine release (HR) test - UAS-7 score (3 months)

	UAS-7 change from baseline/N		
Study	Biomarker High (positive)	Biomarker Low (negative)	Mean difference (95%CI)
Ghazanfar 2018	18.67/12	17.23/102	1.44 (-7.20 to 10.08)

* Data were extracted using Web Plot Digitizer

Table S23: Baseline IL-31 levels of responders and non-responders (based on UAS-7 score)

Study	Responders*	Non responder	Pvalue
	Mean (95%CI)/N	Mean (95%CI)/N	
Altrichter 2014	70.9 pg/mL (0 to 3757)	690 pg/mL (0–30 to 691)	0.004

*disease activity was assessed by UAS7 (≤ 6)

Table S24: Basophil FcεRI receptor

Study ID	basophil FcεRI receptor cut-off	Number of responder*/N		OR (95%CI)
		Biomarker high	Biomarker low	
Deza 2017	5000 MFI	38/38	0/9	1463.00 [27.24, 78586.75]

*CSU achieved significant clinical improvement and were classified as "responders" (median value of UAS7
and UCT at 6 months: 0 and 14, respectively)

Table S25: Blood basophil count levels of responders and non responders

Study	Responders* Mean (95%CI)/N	Non responder Mean (95%CI)/N	P value
Deza 2018	Fast responders 0.03 (x103/µL) (0.01-0.09) / n = 33	Slow responders 0.04 (x103/µL) (0.01-0.11)/ n = 11	0.271
Rijavec 2020	Absolute basophil count (cells/µL) 8.6 (0.3-31.4)	Absolute basophil count (cells/µL) 0.2 (0.0-1.4)	< .0001

* Responders were defined by UAS7 (≤ 6) in Deza 2018 and Rijavec 2020
Ghazanfar 2018 reported the change of UAS score MD, 97% CI: 0.404 (-0.53; 1.34)

Table S26: Autologous serum skin test (ASST)

Study	Responders* N positive (%)	Non responder N positive (%)	Pvalue
Deza 2018	Positive ASST* *was only assessed in 37 patients (28 fast responders and 9 slow responders). 14 (50.0%) / N=33	Positive ASST* 7 (77.8%) / N=11	0.248
Gericke 2016	12/33 (36.4%)	11/13 (84.6%)	<0.01
Nettis 2018	Fast responders (Total=66) Positive 19 (28.8)	Slow responders (Total=69) Positive 44 (63.8)	<0.001

*Responders were defined by UAS7 ≤ 6 in all studies

Box S3. Eosinopenia

Kolkhir 2019 reported that nonresponders to second-generation H1-antihistamines or omalizumab had significantly lower eosinophils as compared with responders ($P < .05$ and $P < .01$, respectively). The combination of eosinopenia and basopenia is a better predictor of nonresponse to

secondgeneration H1-antihistamines than eosinopenia alone (odds ratio of 9.5 vs 4.8). Patients were divided into 3 groups according to their response to the treatment: nonresponders (a reduction of <30% in UAS7), partial responders (a reduction of 30%-89% in UAS7), and complete responders (a reduction of >90% from baseline in UAS7).

Table S27: Evidence Profile for IgE

Question: High level of baseline IgE compared to low level of baseline IgE for the prediction of Omalizumab usage for uncontrolled chronic urticaria

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High level of baseline IgE	low level of baseline IgE	Relative (95% CI)	Absolute (95% CI)		
Responders (Defined by UAS score) (follow up: mean 3 months; assessed with: with IgE cut off 43 IU/mL)												
1 [1]	observational studies	serious [a]	not serious [b]	not serious [c]	very serious [d]	none	60/63 (95.2 %)	22/23 (95.7 %)	**OR 1.00** (0.69 to 1.04)	**0 fewer per 1.000** (from 18 fewer to 2 more)	⨁◯◯◯ VERY LOW	
Responders (Defined by UAS score) (follow up: mean 3 months; assessed with: with IgE cut off is 100 IU/mL)												
2 [2,3]	observational studies	serious [e]	not serious	not serious	very serious [d]	none	26/28 (92.9 %)	18/24 (75.0 %)	**OR 3.66** (0.75 to 17.79) [f]	**167 more per 1.000** (from 58 fewer to 232 more)	⨁◯◯◯ VERY LOW	
Responders (defined by symptom) (follow up: mean 12 weeks; assessed with: IgE cut off is 31.35 IU/ml)												
1 [4]	observational studies	serious [a]	not serious	not serious	very serious [d]	none	26/26 (100.0 %)	1/5 (20.0 %)	**OR 159.00** (5.56 to 4545.48)	**775 more per 1.000** (from 382 more to 799 more)	⨁◯◯◯ VERY LOW	
Responders (defined by symptom) (follow up: range 1 months to 16 months; assessed with: IgE cut off is 114/180 IU/mL)												
1	observational studies	serious [e]	not serious	not serious	very serious [d]	none	6/6 (100.0 %)	8/10 (80.0 %)	**OR 3.82** (0.16 to 94.13)	**139 more per 1.000** (from 410 fewer to 197 more)	⨁◯◯◯ VERY LOW	
Disease relapse (Defined by UAS-7 score) (assessed with: relapse of symptoms (UAS7 > 16))												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High level of baseline IgE	low level of baseline IgE	Relative (95% CI)	Absolute (95% CI)		
1 [3]	observational studies	serious [e]	not serious	not serious	very serious [d]	none	13/20 (65.0 %)	15/21 (71.4 %)	**OR 0.74** (0.20 to 2.78)	**65 fewer per 1.000** (from 381 fewer to 160 more)	⊕◯◯◯ VERY LOW	
Correlation between IgE and UAS (follow up: mean 12 weeks)												
3 [1,2,5]	observational studies	serious [g]	not serious	not serious	very serious [h]	none	Ertas 2017 reported correlation coefficient (r) as -0.29, P = 0.041; Tamer 2019 reported the correlation naretively as “no correlation was observed between serum IgE levels and treatment outcome; Ghazanfar 2018 reported regression coefficient is 0.001 (-0.002 to 0.003), P=0.526.					⊕◯◯◯ VERY LOW	
Baseline IgE level of responders and non responders												
10 [1,4,6,7,8,9,10,11,12,13]	observational studies	serious [a]	not serious	not serious	very serious [d]	none	Ertas 2017 reported an absolute difference between responders and non responders os 55.8 IU/ml (p= <0.05), Chen 2020 difference 81 (p= 0.003) Deza 2017 131 (p= 0.0003), Marzano 2018 difference 89.5 (p = <0.0001) Rijavec 2020 difference 67 (p = .005)				⊕◯◯◯ VERY LOW	

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. There were concerns about risk of bias due to selection of participants and measurement of outcomes.
b. Serious heterogeneous was observed.
c. Outcome measurements are different across included studies.
d. There were a small number of events between groups. The estimated effects go from lower to increase risk
e. There were concerns about the risk of bias due to measurement of outcomes.
f. Staesser 2018 reported prediction of different level of IgE, the odds ratio (95%CI) for >168 UI/mL vs.≤ 68.8 UI/mL is 3.46 (1.84 to 6.50).
g. There were concerns about risk of bias due to selection of participants, deviations from intended interventions, and Measurement of outcomes.
h. The number of included participants in the analysis was below the optimal information size.

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12. Marzano, . Predictors of response to omalizumab and relapse in chronic spontaneous urticaria: a study of 470 patients. 2018.
13. Rijavec, . A very low number of circulating basophils is predictive of a poor response to omalizumab in chronic spontaneous urticaria. 2020.

Table S28: Evidence Profile for ANA

Question: High level of baseline Antinuclear antibody (ANA) for the prediction of Omalizumab usage for uncontrolled chronic urticaria

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High level of baseline (ANA)	low level of baseline (ANA)	Relative (95% CI)	Absolute (95% CI)		
Responders (Defined by UAS score) (follow up: mean 1 years; assessed with: cut off is 1:160)												
1 [1]	observational studies	serious [a]	not serious	not serious	very serious [b]	none	5/5 (100.0 %)	9/10 (90.0 %)	**OR 1.74** (0.06 to 50.43) [c]	**40 more per 1,000** (from 549 fewer to 98 more)	⨁◯◯◯ VERY LOW	
Responders (Defined by symptom score) (follow up: range 1 months to 16 months; assessed with: Cut off is defined according to respective upper limit)												
1 [2]	observational studies	serious [a]	not serious	not serious	very serious [b]	none	6/7 (85.7 %)	28/34 (82.4 %)	**OR 1.29** (0.13 to 12.74)	**34 more per 1,000** (from 446 fewer to 160 more)	⨁◯◯◯ VERY LOW	
Disease relapse (Defined by UAS-7 score) (assessed with: cut off is 1:160)												
1 [1]	observational studies	serious [a]	not serious	not serious	very serious [b]	none	5/7 (71.4 %)	23/34 (67.6 %)	**OR 1.20** (0.20 to 7.16)	**39 more per 1,000** (from 382 fewer to 261 more)	⨁◯◯◯ VERY LOW	

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. There were concerns about the risk of bias due to deviations from intended interventions, measurement of outcomes, and selection of reported results.

b. There were a small number of events between groups. The estimated effects go from lower to increase risk

c. Grieco 2020a defined cut off of 1:160; Viswanathan 2013 defined ANA cut-of as elevated (above respective upper límit).

References

1. Grieco T, Dies L, Sernicola A, Chello C,Gagliostro N,Carnicelli G,Paolino G.. . Potential clinical and serological predictors of chronic spontaneous urticaria relapse in patients under omalizumab treatment.. Immunotherapy; 2020.

2. Viswanathan RK, Moss MH, Mathur SK. Retrospective analysis of the efficacy of omalizumab in chronic refractory urticaria. Allergy Asthma Proc.; 2013.

Table S29: Evidence Profile for D-dimers

Question: High level of baseline D-dimer for the prediction of Omalizumab usage for uncontrolled chronic urticaria

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High level of baseline D-dimer	low level of baseline D-dimer	Relative (95% CI)	Absolute (95% CI)		
Early Responders (Defined by UAS score showing a dramatic reduction of UAS 7 to at least <14 as short as 3-7 days after the first administration) (follow up: range 1 weeks to 3 months; assessed with: with cut off around 500 IU/mL)												
4 [1,2,3,4]	observational studies	serious [a]	serious [b]	not serious [c]	serious [d]	none	114/156 (73.1 %)	103/161 (64.0 %)	**OR 1.86** (0.55 to 6.33)	**128 more per 1,000** (from 146 fewer to 279 more)	⨁◯◯◯ VERY LOW	
Disease relapse (Defined by UAS7 > 16) (follow up: mean 1 years; assessed with: cut off is 500 IU/mL)												
1 [3]	observational studies	serious [a]	not serious	not serious	very serious [d]	none	10/16 (62.5 %)	18/25 (72.0 %)	**OR 0.65** (0.17 to 2.47)	**94 fewer per 1,000** (from 416 fewer to 144 more)	⨁◯◯◯ VERY LOW	
Correlation between IgE and UAS (follow up: mean 12 weeks)												
2 [1,2]	observational studies	serious [a]	serious [b]	not serious	serious [e]	none	Asero 2019 reporetd "A significant correlation between D-dimer and UAS-7 at baseline was found (P = 0.014), whereas D-dimer levels used as a marker of the activation of the coagulation cascade and of its intensity were not able to predict the clinical response to omalizumab". Asero 2017 reported correlation between D-dimer and time to response, Correlation coefficient (r) = -0.411, P=0.007.			⨁◯◯◯ VERY LOW	

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. There were concerns about the risk of bias due to Selection of participants and measurement of outcomes.
b. Serious heterogeneous was observed.
c. Outcome measurements are different across included studies.
d. There were a small number of events between groups. The estimated effects go from lower to increase risk
e. The number of included participants in the analysis was below the optimal information size.

References

1. Asero R, Marzano AV,Ferrucci S,Genovese G,Cugno M. Baseline D-dimer plasma levels correlate with disease activity but not with the response to omalizumab in chronic spontaneous urticaria.. Allergy; 2019.
2. Asero R, Marzano AV,Ferrucci S,Cugno M.. Elevated baseline D-dimer plasma levels are associated with a prompt response to omalizumab in patients with severe CSU.. J Allergy Clin Immunol Pract; 2017.
3. Grieco T, Dies L,Sernicola A,Chello C,Gagliostro N,Carnicelli G,Paolino G.. . Potential clinical and serological predictors of chronic spontaneous urticaria relapse in patients under omalizumab treatment.. Immunotherapy; 2020.
4. Castagna, J.,Bernard,L.,Hacard,F.,Delcroix,F.,Darrigade,A. S.,Nicolas,J. F. Clinical predictive factors of unresponsiveness to omalizumab in patients with chronic spontaneous urticaria. British Journal of Dermatology.; 2020.

Table S30: Evidence Profile for baseline basophil activation test

Question: High level of baseline basophil activation test (BAT) for the prediction of Omalizumab usage for uncontrolled chronic urticaria

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High level of baseline basophil activation test (BAT)	low level of baseline basophil activation test (BAT)	Relative (95% CI)	Absolute (95% CI)		
Responders (Defined by UAS score) (follow up: mean 1 patient years; assessed with: cut of of BAT is 15)												
1 [1]	observational studies	serious [a]	not serious	not serious	very serious [b]	none	3/3 (100.0 %)	31/38 (81.6 %)	**OR 1.67** (0.08 to 35.84)	**65 more per 1,000** (from 554 fewer to 178 more)	⨁◯◯◯ VERY LOW	
Responders (Defined by clinical response) (follow up: mean 3 months; assessed with: cut off as CD203c up regulating)												
1 [2]	observational studies	serious [a]	not serious	not serious	very serious [b]	none	9/18 (50.0 %)	20/23 (87.0 %)	**OR 0.15** (0.03 to 0.69)	**370 fewer per 1,000** (from 703 fewer to 48 fewer) [c]	⨁◯◯◯ VERY LOW	
Disease relapse (Defined by UAS-7 score) (assessed with: relapse of symptoms (UAS7 > 16); assessed with: cut off is 15)												
1 [1]	observational studies	serious [a]	not serious	not serious	very serious [b]	none	0/3 (0.0%)	28/38 (73.7 %)	**OR 0.74** (0.20 to 2.78)	**62 fewer per 1,000** (from 378 fewer to 149 more)	⨁◯◯◯ VERY LOW	
UAS - 7 score (follow up: mean 3 months)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High level of baseline basophil activation test (BAT)	low level of baseline basophil activation test (BAT)	Relative (95% CI)	Absolute (95% CI)		
1 [3]	observational studies	serious [a]	not serious	not serious	very serious [d]	none	The median (range) for BAT positive and negative group are 16 (1-37) and 4(0-21), respectively. (data were extracted using WebPlotDigitizer)				⊕◯◯◯ VERY LOW	

CI: Confidence interval; **OR:** Odds ratio; **MD:** Mean difference

Explanations

a. There were concerns about the risk of bias due to selection of participants, measurement of outcomes, and selection of reported results.
b. There were a small number of events between groups. The estimated effects go from lower to increase risk
c. Straesser 2018 evaluated responders for Positive group (upregulation of CD203c), n=16/27.
d. The estimated effects go from reduce to increase. The number of included participants in the analysis was below the optimal information size.

References

1. Grieco T, Dies L,Sernicola A,Chello C,Gagliostro N,Carnicelli G,Paolino G.. . Potential clinical and serological predictors of chronic spontaneous urticaria relapse in patients under omalizumab treatment.. Immunotherapy; 2020.
2. Palacios T, Stillman L,Borish L,Lawrence M. Lack of basophil CD203c-upregulating activity as an immunological marker to predict response to treatment with omalizumab in patients with symptomatic chronic urticaria. J Allergy Clin Immunol Pract; 2016.
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Table S31: Evidence Profile for Thyroid autoimmunity

Question: High level of baseline Thyroid autoimmunity for the prediction of Omalizumab usage for uncontrolled chronic urticaria

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High level of baseline Thyroid autoimmunity	low level of baseline Thyroid autoimmunity	Relative (95% CI)	Absolute (95% CI)		
Responders (Defined by UAS score) (follow up: mean 1 years; assessed with: Predicted by Antithyro globulin (ATG), cut off is 100IU/mL)												
1 [1]	observational studies	serious [a]	not serious	not serious	very serious [b]	none	3/5 (60.0%)	31/36 (86.1%)	**OR 0.24** (0.03 to 1.83)	**263 fewer per 1,000** (from 704 fewer to 58 more)	⊕◯◯◯ VERY LOW	
Disease relapse (Defined by UAS score) (follow up: mean 1 years; assessed with: Predicted by Antithyro globulin (ATG), cut off is 100 IU/mL)												
1 [1]	observational studies	serious [a]	not serious	not serious	very serious [b]	none	4/5 (80.0%)	24/36 (66.7%)	**OR 2.00** (0.20 to 19.91)	**133 more per 1,000** (from 381 fewer to 309 more)	⊕◯◯◯ VERY LOW	
Responders (Defined by UAS score) (follow up: 3 months; assessed with: Predicted by Antithyroperoxidase (ATPO))												
1 [1]	observational studies	serious [a]	not serious	not serious	very serious [b]	none	5/9 (55.6%)	23/32 (71.9%)	**OR 0.49** (0.01 to 2.25)	**163 fewer per 1,000** (from 694 fewer to 133 more)	⊕◯◯◯ VERY LOW	
Disease relapse (Defined by UAS-7 score) (follow up: mean 3 months; assessed with: Predicted by Antithyroperoxidase (ATPO))												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High level of baseline Thyroid autoimmunity	low level of baseline Thyroid autoimmunity	Relative (95% CI)	Absolute (95% CI)		
1 [1]	observational studies	serious [a]	not serious	not serious	very serious [b]	none	5/9 (55.6%)	23/32 (71.9%)	**OR 0.49** (0.11 to 2.25)	**163 fewer per 1,000** (from 499 fewer to 133 more)	⨁◯◯◯ VERY LOW	

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. There were concerns about the risk of bias due to deviations from intended interventions, measurement of outcomes, and selection of reported results.

b. There were a small number of events between groups. The estimated effects go from lower to increase risk

References

1. Grieco T, Dies L,Sernicola A,Chello C,Gagliostro N,Carnicelli G,Paolino G.. . Potential clinical and serological predictors of chronic spontaneous urticaria relapse in patients under omalizumab treatment.. Immunotherapy; 2020.
erapy; 2020.

Table S32: Evidence Profile for CRP

Question: High level of baseline C-reactive protein (CRP) for the prediction of Omalizumab usage for uncontrolled chronic urticaria

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High level of baseline C-reactive protein(CRP)	low level of baseline C-reactive protein(CRP)	Relative (95% CI)	Absolute (95% CI)		
Early Responders (Defined by UAS score less/equal to 6 within 3 months) (follow up: range 3 months to 25 months; assessed with: cut off is elevated or normal)												
1 [1]	observational studies	serious [a]	not serious	not serious	very serious [b]	none	3/10 (30.0%)	7/10 (70.0%)	**OR 0.18** (0.03 to 1.24) [c]	**404 fewer per 1,000** (from 635 fewer to 43 more)	⊕◯◯◯ VERY LOW	
Correlation between IgE and UAS (follow up: mean 12 weeks)												
2 [2,3]	observational studies	serious [d]	not serious	not serious	very serious [e]	none	Baysak 2020 baseline CRP levels before the initiation of therapy were not correlated with treatment response at 12th or 24th week. (n = 45, P=0,453). Ghazanfar 2018 reported the association of the UAS-7 score and patients' CRP level, regression coefficient is -0.271 (0.62 to 0.74)/ n = 74, P=0.123				⊕◯◯◯ VERY LOW	

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. There were concerns about the risk of bias due to Selection of participants and measurement of outcomes.
b. There were a small number of events between groups. The estimated effects go from lower to increase risk
c. Biomarker was classified as elevated and normal, no definition was reported.
d. There were concerns about risk of bias due to selection of participants, deviations from intended interventions, measurement of outcomes, and selection of reported result.
e. The number of included participants in the analysis was below the optimal information size.

References

1. Syrigos N, Grapsa D,Zande M,Tziotou M,Syrigou E.. Treatment response to omalizumab in patients with refractory chronic spontaneous urticaria.. Int J Dermatol; 2018.
2. Baysak, S.,Kecici,A. S.,& Doğan,B.. Long-term follow-up effect of omalizumab in chronic spontaneous urticaria and its association with serum C-reactive protein levels.. Dermatologic Therapy; 2020.
3. Ghazanfar MN, Holm JG,Thomsen SF.. Effectiveness of omalizumab in chronic spontaneous urticaria assessed with patient-reported outcomes: a prospective study. J Eur Acad Dermatol Venereol; 2018.

Table S33: Evidence Profile for ESR

Question: High level of baseline Erythrocyte sedimentation rate (ESR) for the prediction of Omalizumab usage for uncontrolled chronic urticaria

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High level of baseline Erythrocyte sedimentation rate (ESR)	low level of baseline Erythrocyte sedimentation rate (ESR)	Relative (95% CI)	Absolute (95% CI)		
Early Responders (Defined by UAS score ≤ 6 within 3 months) (follow up: range 3 months to 25 months; assessed with: cut off is elevated or normal)												
1 [1]	observational studies	serious [a]	not serious	not serious	very serious [b]	none	8/14 (57.1%)	3/6 (50.0%)	**OR 1.33** (0.20 to 9.08) [c]	**71 more per 1,000** (from 333 fewer to 401 more)	⨁◯◯◯ VERY LOW	

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. There were concerns about the risk of bias due to Selection of participants and measurement of outcomes.
b. There were a small number of events between groups. The estimated effects go from lower to increase risk
c. Biomarker was classified as elevated and normal, no definition was reported.

References

1. Syrigos N, Grapsa D,Zande M,Tziotou M,Syrigou E.. Treatment response to omalizumab in patients with refractory chronic spontaneous urticaria.. Int J Dermatol; 2018.

Table S34: Evidence Profile for histamine release

Question: High level of baseline Histamine release (HR) test for the prediction of Omalizumab usage for uncontrolled chronic urticaria

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High level of baseline Histamine release (HR) test	low level of baseline Histamine release (HR) test	Relative (95% CI)	Absolute (95% CI)		
Early Responders (change of UAS) (follow up: mean 3 months; assessed with: HR test positive/negative)												
1 [1]	observational studies	serious [a]	not serious	not serious	very serious [b]	none	12	102	-	MD **1.44 score higher** (7.2 lower to 10.08 higher) [c]	⊕◯◯◯ VERY LOW	

CI: Confidence interval; **MD:** Mean difference

Explanations

a. There were concerns about the risk of bias due to Selection of participants, deviations from intended interventions, and measurement of outcomes.
b. There were a small number of events between groups. The estimated effects go from lower to increase risk
c. Biomarker was classified as elevated and normal, no definition was reported.

References

1. Ghazanfar MN, Holm JG,Thomsen SF.. Effectiveness of omalizumab in chronic spontaneous urticaria assessed with patient-reported outcomes: a prospective study. J Eur Acad Dermatol Venereol; 2018.

Table S35. Summary of main results Baseline Immunoglobulin E

Outcome	Effect size (95% CI)	Certainty	Plain language
Responders (defined by UAS), Cut off is 43 IU/mL	4 fewer per 1,000 (from 292 fewer to 39 more)	Very low	High baseline IgE may slightly identify patients likely to respond to omalizumab (UAS), but the evidence is very uncertain
Responders (defined by UAS), Cut off is 100 IU/mL	167 more per 1,000 (from 58 fewer to 232 more)	Very low	High baseline IgE may identify patients likely to respond to omalizumab (UAS), but evidence is very uncertain
Responders (defined by symptoms), cut off is 31.35 IU/ml	775 more per 1,000 (from 382 more to 799 more)	Very low	High baseline IgE may identify patients likely to respond to omalizumab (symptoms), but the evidence is very uncertain
Responders (defined by symptoms), cut off is 114/180 IU/mL	139 more per 1,000 (from 410 fewer to 197 more)	Very low	High baseline IgE may identify patients likely to respond to omalizumab (symptoms), but evidence is very uncertain
Disease relapse (Defined by UAS-7 score), Cut off is 100 IU/mL	65 fewer per 1,000 (from 381 fewer to 160 more)	Very low	High baseline IgE may slightly identify patients less likely to relapse after omalizumab is stopped (UAS), but the evidence is very uncertain

Table S35. Summary of main results Baseline Antinuclear antibody (ANA)

Outcome	Effect size (95% CI)	Certainty	Plain language
Responders (Defined by UAS score), cut off is 1:160	40 more per 1,000 (from 549 fewer to 98 more)	Very low	High baseline ANA may slightly identify patients likely to response to omalizumab (UAS), but evidence is very uncertain
Responders (Defined by symptom score), Cut off is defined as upper limit	34 more per 1,000 (from 446 fewer to 160 more)	Very low	High baseline ANA may slightly identify patients likely to response to omalizumab (symptom), but evidence is very uncertain
Disease relapse (Defined by UAS-7 score), cut off is 1:160	39 more per 1,000 (from 382 fewer to 261 more)	Very low	High baseline ANA may slightly identify patients likely to respond to omalizumab (UAS), but evidence is very uncertain

Table S36. Summary of main results Baseline D-dimer

Outcome	Effect size (95% CI)	Certainty	Plain language
Early Responders (UAS reduction at 3-7 days), cut off is 500 IU/mL	128 more per 1,000 (from 146 fewer to 279 more)	Very low	High baseline D-dimer may identify patients likely to response to omalizumab (UAS), but evidence is very uncertain
Disease relapse (Defined by UAS7 > 16), cut off is 500 IU/mL	94 fewer per 1,000 (from 416 fewer to 144 more)	Very low	High baseline D-dimer may identify patients less likely to relapse to omalizumab (UAS), but evidence is very uncertain

Table S37. Summary of main results Baseline basophil activation test (BAT)

Outcome	Effect size (95% CI)	Certainty	Plain language
Responders (Defined by UAS score), cut off is 15	65 more per 1,000 (from 554 fewer to 178 more)	Very low	High baseline BAT may slightly identify patients likely to response to omalizumab (UAS), but evidence is very uncertain
Responders (Defined by clinical response), cut off as CD203c up regulating	370 fewer per 1,000 (from 703 fewer to 48 fewer)	Very low	High baseline BAT may identify patients less likely to response to omalizumab (clinical response), but evidence is very uncertain
Disease relapse (Defined by UAS score), cut off is 15	62 fewer per 1,000 (from 378 fewer to 149 more)	Very low	High baseline BAT may slightly identify patients less likely to relapse to omalizumab (UAS), but evidence is very uncertain

Table S38. Summary of main results Baseline Thyroid autoimmunity - Antithyroid globulin (ATG)

Outcome	Effect size (95% CI)	Certainty	Plain language
Responders (Defined by UAS score), cut off is 100 IU/mL	263 fewer per 1,000 (from 704 fewer to 58 more)	Very low	High baseline ATG may identify patients less likely to response to omalizumab (UAS), but evidence is very uncertain
Disease relapse (Defined by UAS score), cut off is 100 IU/mL	133 more per 1,000 (from 381 fewer to 309 more)	Very low	High baseline ATG may slightly identify patients likely to relapse to omalizumab (UAS), but evidence is very uncertain

Table S39. Summary of main results Baseline Thyroid autoimmunity - Antithyroperoxidase (ATPO)

Outcome	Effect size (95% CI)	Certainty	Plain language
Responders (Defined by UAS score), cut off is 100 IU/mL	163 fewer per 1,000 (from 694 fewer to 133 more)	Very low	High baseline ATPO may identify patients less likely to response to omalizumab (UAS), but evidence is very uncertain
Disease relapse (Defined by UAS score), cut off is 100 IU/mL	163 fewer per 1,000 (from 499 fewer to 133 more)	Very low	High baseline ATPO may slightly identify patients less likely to relapse to omalizumab (UAS), but evidence is very uncertain

Table S40. Summary of main results Baseline C-reactive protein (CRP)

Outcome	Effect size (95% CI)	Certainty	Plain language
Early Responders (Defined by UAS score in 3 months), cut off is elevated or normal	404 fewer per 1,000 (from 635 fewer to 43 more)	Very low	High baseline CRP may identify patients less likely to response to omalizumab (UAS), but evidence is very uncertain

Table S41. Summary of main results Baseline Erythrocyte sedimentation rate (ESR)

Outcome	Absolute Effect size (95% CI)	Certainty	Plain language
Early Responders (Defined by UAS score in 3 months), cut off is elevated or normal	71 more per 1,000 (from 333 fewer to 401 more)	Very low	High baseline ESR may identify patients likely to response to omalizumab (UAS), but evidence is very uncertain

Table S42: Baseline
Histamine release (HR)

Outcome	Absolute Effect size (95% CI)	Certainty	Plain language
UAS 7 score, HR test positive/negative	MD **1.44 score higher** (7.2 lower to 10.08 higher)	Very low	High baseline HR may identify patients likely to response to omalizumab (UAS), but evidence is very uncertain

Table S43: evaluation of ligelizumab versus placebo

Outcome	Effect size (95% CI)	Certainty	Plain language
UAS7	-2,28 (-7,72 to -3,16)*	Low	May not reduce+
Drug-related AE	0.72 (0.50 to 1.05) **	Low	May decrease

* The mean difference of the change from baseline.
**RR: risk ratio
+ The decrease is below the MID