



# Expert consensus on the use of omalizumab in chronic urticaria in China

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## ABSTRACT

Chronic urticaria (CU) is a debilitating skin disease that lasts for more than 6 weeks with wheals and/or angioedema, including chronic spontaneous urticaria (CSU) and chronic inducible urticaria (CIndU). In China, the prevalence of this disease is high, more than 1%, and on the rise. CU has a major impact on the quality of life (QoL) of patients who frequently experience sleep disturbance, depression, and anxiety. Nearly one-third of patients with CSU, in China, are resistant to second-generation H<sub>1</sub>-antihistamines (sgAHs), even at a fourfold dose (second line; off-label). Omalizumab is approved for the treatment of CSU treatment in Europe and shows remarkable efficacy and safety. In China, regulatory approval for the use of omalizumab is pending, and its use in clinical practice varies widely. Consensus on omalizumab CU treatment in China is urgently needed. The aim of this article is to propose a practical omalizumab treatment algorithm for the management of antihistamine-resistant CSU and CIndU in adults and special population including children and adolescents, and pregnant or breast feeding women, to guide daily clinical practice in China. In the development of this consensus, an expert group including mainly dermatologists, allergists, but also pulmonologists, ENTs, immunologists, and pediatricians in Allergic Disease Prevention and Control Committee, Chinese Preventive Medicine Association, reviewed the existing evidence and developed consensus on the use of omalizumab in CU patients from China. The goal of this consensus is to assist clinicians in making rational decisions in the management of refractory CU with omalizumab. The key clinical questions covered by the treatment algorithm are: 1) Omalizumab treatment routine strategy in both CSU and CIndU patients; 2) Recommended dose and treatment duration for different age stratification; 3) Treatment duration for CU patients with other allergic comorbidities; 4) Recommendation on omalizumab stopping strategy.

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Full list of author information is available at the end of the article. <http://doi.org/10.1016/j.waojou.2021.100610>

Received 9 February 2021; Received in revised from 7 August 2021; Accepted 2 November 2021

Online publication date 5 December 2021

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**Keywords:** Chronic spontaneous urticaria, Chronic inducible urticaria, Treatment algorithm, Omalizumab, China

## INTRODUCTION

Chronic urticaria (CU) is a debilitating skin disease that lasts for more than 6 weeks with wheals and/or angioedema.<sup>1</sup> CU can be divided into chronic spontaneous urticaria (CSU) and chronic inducible urticaria (CIndU). CSU, the most frequent type, is usually not linked to external triggers, and autoimmunity rather than type I allergy is held to play a key role. CIndU can be further divided into symptomatic dermographism (SD), cold urticaria (ColdU), cholinergic urticaria (CholU), heat urticaria, solar urticaria, and other subtypes according to the relevant and specific triggers. CU is a global problem and affects people of all ages, with a worldwide prevalence estimated at 0.7%.<sup>2</sup> In China, the prevalence of this disease is high, above 1%, and it is increasing.<sup>3</sup> A recent study showed that the prevalence of CU among college freshmen in China was 4.2%.<sup>4</sup> Most studies have shown that CU mainly affects young adults, with the average age of onset between 25 and 50 years old.<sup>5</sup> However, a recent study in South Korea showed that children aged 0-9 and people aged 70-79 are also likely to suffer from CU.<sup>6</sup> In addition, CU has a major impact on the quality of life (QoL) of patients, who frequently experience sleep disturbance, sexual dysfunction, depression, and anxiety.<sup>7,8</sup> In short, CU comes with a heavy global burden for both patient and society.<sup>9,10</sup>

The etiology of CU is complex, and increasing evidence shows that IgE-dependent skin mast cell degranulation plays a key role. There are 2 types of autoimmune mechanisms in CSU.<sup>11</sup> Type I autoimmune CSU comes with IgE to autoantigens such as thyroid peroxidase and interleukin 24. Patients sensitized to these autoantigens (IgE-mediated autoimmunity/autoallergy) are held to experience whealing and angioedema due to the activation of skin mast cells via IgE. Type IIb autoimmune CSU comes with mast cell-targeting

and activating autoantibodies directed against IgE or its high affinity receptor (IgG-autoantibodies to IgE or FcεRI). The pathogenesis of CIndU remains unclear, however, IgE appears to be involved in many patients, and some studies suggest that the characterization of the role and relevance of IgE and mast cell has high priority.<sup>12</sup> The role and relevance of IgE and its receptor in the pathogenesis of CU provide a theoretical basis for immune-targeted therapy with anti-IgE.

The EAACI/GA<sup>2</sup>LEN/EDF/WAO guideline and Chinese Guideline for diagnosis and treatment of urticaria recommend that second-generation H<sub>1</sub>-antihistamines (sgAHs) are the first line treatment in CU and can be increased up to a fourfold dose (second line; off-label).<sup>1,13</sup> However, nearly one-third of CSU patients in China are refractory to sgAHs even at higher doses.<sup>14</sup> The use of omalizumab, a recombinant humanized anti-IgE antibody, has been recommended for these antihistamine-resistant patients. Omalizumab provides a remarkable advancement in the management of CU and is not linked to the wide array of side effects of immunosuppressive treatment including ciclosporin A.<sup>15,16</sup> The mechanisms of action of omalizumab in CU include its effects on IgE, lowering free IgE levels, and on the high affinity IgE receptor, FcεRI, lowering its expression on mast cells and basophils. The reduction of FcεRI levels is held to be the result of lowering IgE levels, as IgE bound to the receptor stabilizes its expression.<sup>17,18</sup>

Most studies on omalizumab in CU originate from Europe, Canada, South Korea, and the United States, where omalizumab is licensed for CSU in patients 12 years and older and that its use in CIndU and/or in patients younger than 12 years is off label.<sup>19</sup> In China, omalizumab has only recently been approved for the treatment of moderate-to-severe asthma in 2017. Omalizumab is still an off-label drug for CU in China. Although several

studies showed that Chinese patients with CU generally respond well to omalizumab,<sup>16,20,21</sup> most physicians in China rely on their own clinical experience and use the drug in different ways. They are unsure about how to start, adapt, and stop omalizumab therapy with respect to treatment dosing and intervals. Some physicians are reluctant to use omalizumab for lack of guidance. There is, therefore, an urgent need for a national consensus on the use of omalizumab for the treatment of CU. The establishment of such a consensus may also benefit countries that are similar to China in terms of the availability, approval, and reimbursement of CU treatments including omalizumab.

Here, we put forward a practical omalizumab treatment algorithm for the management of antihistamine-resistant CSU and CIndU in adults and special populations including children and adolescents, and pregnant and breast-feeding patients, to guide routine clinical practice in China. The algorithm has been structured so that primary care physicians (who see most CU patients in China) as well as specialists including dermatologists, pediatricians, and allergists can use it. It is intended to support evidence-based treatment guidelines available at both the international and national level.

## METHODS

We reviewed the literature on omalizumab and CU published in the last 10 years, combined with the results of recent research done inside and outside of China, and formulated the expert consensus described below after a collective discussion among the members of the expert group. The expert group includes mainly dermatologists, allergists, but also pulmonologists, ENTs, immunologists, and pediatricians in Allergic Disease Prevention and Control Committee, Chinese Preventive Medicine Association. Professor Zhao and Professor Maurer developed the initial draft of the practical algorithm for the use of omalizumab in CU patients from China. This was reviewed and modified with the other authors according to relevant expertise, local knowledge, guidelines, and literature.

## Clinical evidence for the treatment of antihistamine-resistant chronic urticaria

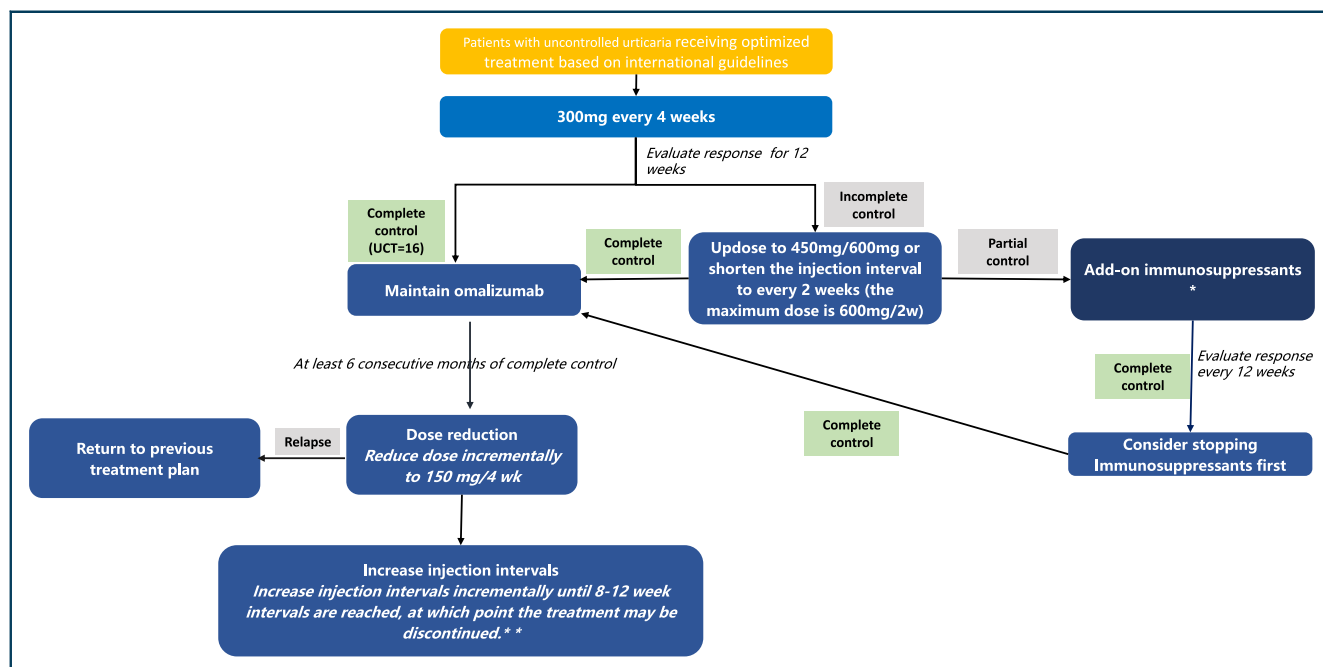
### Assessment of disease activity/severity, impact, and control in patients with chronic urticaria

The use of patient reported outcomes (PROs) is crucial when evaluating and monitoring CU disease activity/severity, QoL impairment, and disease control. All need to be evaluated at the first and every follow-up visit.

We recommend the use of urticaria-specific PRO measures to do so. The Urticaria Activity Score (UAS),<sup>22</sup> Urticaria Control Test (UCT),<sup>23,24</sup> and Chronic Urticaria Quality of Life Questionnaire (CU-Q<sub>2oL</sub>)<sup>25</sup> should be used in patients who predominantly suffer from whealing. The Angioedema Activity Score (AAS),<sup>26,27</sup> Angioedema Quality of Life Questionnaire (AE-QoL),<sup>28</sup> and Angioedema Control Test (AECT)<sup>29,30</sup> should be used in patients who predominantly suffer from angioedema. The generic, skin-specific QoL questionnaire Dermatology Life Quality Index (DLQI)<sup>31</sup> may be used to complement the results of these PRO measures. The Chinese version of UCT, CU-Q<sub>2oL</sub> and DLQI have also been validated.<sup>24,25,31</sup> Other assessment tools are available in English (<https://moxie-gmbh.de>).

In CIndU, the threshold of the eliciting factor(s) should be determined to assess disease activity and response to treatment. Examples include cold and heat urticaria, where a Peltier element-based provocation device (TempTest®)<sup>32</sup> is available, symptomatic dermographism for which dermographometers (eg, FricTest®) have been developed, and delayed pressure urticaria. The assessment routine should follow the consensus recommendations on the definition, diagnostic testing and management of CIndUs.<sup>33</sup>

UCT, which works in all types of CU, is the simplest tool with 4 items to assess the control of the disease under the treatment (poor-controlled: UCT <12, well-controlled: UCT ≥ 12, complete controlled: UCT = 16) (Fig. 1). In this consensus, we recommend to evaluate the on-treatment response with the UCT and to adjust dosing according to its outcome.



**Fig. 1 Omalizumab Treatment Paradigm and Recommendation on Omalizumab Stopping Strategy.** \*Options include cyclosporine A, methotrexate and cyclophosphamide. A short course (less than 1 week) of glucocorticosteroids may be considered in case of severe exacerbation. CSU: chronic spontaneous urticaria; UCT: urticaria control test. \*\* If control is lost (UCT<16) after adjustment of dose or interval, return patient to effective omalizumab dosing and treatment intervals and reevaluate after 3 months of complete control. CSU: chronic spontaneous urticaria; UCT: urticaria control test

## Omalizumab in chronic spontaneous urticaria

When to start omalizumab treatment in patients with chronic spontaneous urticaria

Most physicians use sgAHs as the first line treatment in CSU, as recommended. However, many patients continue to experience CSU signs and symptoms despite taking sgAHs, with as many as 60% of patients with CSU not achieving symptom control at approved doses. According to the current EAACI/GA<sup>2</sup>LEN/EDF/WAO guidelines for CU,<sup>1</sup> omalizumab is recommended as the only third-line treatment option in CSU patients refractory to sgAHs. We also recommend to start omalizumab in patients with CSU who failed sgAH treatment (combination 1st- and 2nd-generation H<sub>1</sub>-antihistamines as well as up to fourfold). Omalizumab is approved as add-on therapy for patients with inadequate response to H<sub>1</sub> antihistamine treatment; but real world data show that most patients with complete response to omalizumab do not need to continue their antihistamine treatment. In patients who start omalizumab treatment, we recommend continuing antihistamine treatment until complete response is achieved and to

consider stopping the antihistamine treatment once complete response has been reached for more than one month.

The clinical efficacy and safety of omalizumab in CSU has been shown in numerous clinical trials and real-life studies including several from China.<sup>16,20,33-38</sup> A real-world study from the Beijing Urticaria Center of Reference and Excellence (UCARE)<sup>39</sup> showed that 75.3% of CU patients achieved complete response with omalizumab therapy, and an additional 14.6% had partial response. Patients experienced substantial improvements of symptoms as early as after 1 month of omalizumab treatment and continued to benefit throughout the entire treatment period.<sup>16</sup> The therapeutic effect and speed of onset of effect for omalizumab were comparable between patients with CSU, CIndU, and both.<sup>20</sup>

How to start omalizumab treatment in patients with chronic spontaneous urticaria

The recommended starting dose of omalizumab in patients with CSU is 300 mg/4 weeks in adult and adolescent patients.<sup>1</sup> Responder rates in patients with

CSU started on 150 mg omalizumab reportedly range from 15% to 35%, lower than the responder rates of patients started on 300 mg omalizumab.<sup>40,41</sup> In addition, dosing at 150 mg/4 weeks was inferior in controlling angioedema episodes and improving QoL.<sup>35,42</sup> We recommend to start omalizumab treatment in adult and adolescent patients with CSU at 300 mg every 4 weeks (Table 1).

CSU patients with low IgE levels or a positive basophil activation test (BAT) tend to respond slowly and poorly to omalizumab.<sup>16,20</sup> Type IIb autoimmune mechanisms with mast cell-targeting and activating autoantibodies directed against IgE or its high affinity receptor may be relevant. Assessing patients for markers of type IIb autoimmune CSU such as low IgE and a positive basophil test can help to predict the outcome of omalizumab treatment.<sup>43</sup> If the patient is diagnosed with type IIb autoimmune CSU and CSU is poorly controlled (UCT<12) after 12 weeks of treatment, we recommend up dosing omalizumab to or shortening the injection interval to every 2 weeks instead of turning to another therapy immediately.

#### How to optimize omalizumab treatment in patients with chronic spontaneous urticaria

We recommend to evaluate patients started on omalizumab for their disease activity and control with the aim of optimizing treatment. The aim of treatment with omalizumab is complete control. After 12 weeks of omalizumab treatment a UCT should be performed. If CSU is poorly controlled (UCT<12), we recommend up dosing omalizumab to 450 or 600 mg

every 4 weeks or shortening the injection interval to every 2 weeks, as higher dosage and shorter injection intervals appear to result in better therapeutic effect in a subgroup of patients.<sup>44</sup> The maximum recommended dose is 600 mg every 2 weeks. The decision of increasing the dose or shortening injection interval will depend on provider discretion. In case of partial control ( $12 < \text{UCT} < 16$ ), we suggest to evaluate disease control at every visit to guide treatment optimization as needed (Fig. 1). After 24 weeks of treatment, if the patient has still not achieved complete control (UCT<16), add-on immunosuppressants should be considered. In CSU patients treated with omalizumab, the adjustment of dosage should be based on disease activity and disease control status.

Studies show that relapsed patients who underwent retreatment regain symptom control with a second course of treatment in the vast majority of cases indicating that retreatment with omalizumab is an effective therapy option for patients who discontinue omalizumab and previously benefited from this drug.<sup>45,46</sup>

#### When and how to stop omalizumab treatment in patients with chronic spontaneous urticaria

Omalizumab is not a curative or disease-modifying treatment in CSU. Therefore, instead of treating patients for a fixed length of time, omalizumab should be used until the disease is gone, until spontaneous remission. To this end, we recommend that CSU patients who achieve complete control are maintained on omalizumab

Age, in year	Recommended dose*(mg)	Treatment duration*, in month
0-3	75-150	6
3-6	75-150	6-12
6-12	150-300	6-12
12-18	150-300	6-12
18-65	300-600	6-12
>65	300-600	6-12

**Table 1.** Recommended dose and treatment duration for different age stratification \*It is suggested to adjust it according to clinical conditions. Recommendation for special age groups. Pediatric and adolescent population: In clinical studies enrolled children and adolescents, omalizumab is safe and has a similar incidence of adverse events as placebo. Whereas omalizumab is indicated for CSU in population 12 years of age and older both China<sup>16,20</sup> and worldwide.<sup>36</sup> Omalizumab should be administered with caution in children under 12 years of age, especially in children under 3 years of age. Elderly: There are limited data available on the use of Omalizumab in patients older than 65 years but there is no evidence that elderly patients require a different dose from younger adult patients

treatment for 6 to 12 months (Table 1) before treatment discontinuation is considered. In patients with completely controlled CSU (UCT = 16) for 6 to 12 months of treatment, we recommend following a stopping strategy, where first the dose is reduced to 150 mg every 4 weeks and then, if complete control is maintained, the dosing interval is incrementally increased to every 8-12 weeks. Patients who experience, during this tapering of omalizumab, loss of complete control of their CSU, should return to effective omalizumab dosing and treatment intervals and be reevaluated after 3 months of complete control (Fig. 1.)

Patients with higher baseline total IgE levels and longer disease duration are more likely to experience relapse after discontinuation of omalizumab treatment.<sup>20</sup> In a recent study from China, patients with disease relapse after omalizumab discontinuation had higher pre-treatment total IgE levels and longer disease duration than patients without disease relapse. High pre-treatment IgE levels are also linked to faster relapse in patients who experience relapse upon omalizumab discontinuation.<sup>47</sup> Assessing patients for pre-treatment IgE levels may help to guide decisions on when and how omalizumab should be stopped in complete responders.

Most relapse patients who are retreated with omalizumab regain symptom control. We recommend to reinitiate treatment with omalizumab in CSU patients who previously benefited from this drug and show relapse after stopping omalizumab.

## Omalizumab in chronic inducible urticaria

### When to start omalizumab treatment in patients with chronic inducible urticaria

Nearly half of CIndU patients are resistant to sgAHs up to fourfold doses, and this percentage is even higher when angioedema is present.<sup>48,49</sup> Omalizumab has been reported as an effective therapy in antihistamine-resistant CIndU, including SD, ColdU, CholU, solar urticaria, heat urticaria, as well as delayed pressure urticaria.<sup>50</sup> We recommend to start omalizumab in patients with CIndU who failed sgAHs. In CIndU, the omalizumab treatment plan should be individually designed for each patient based on CIndU type, activity, and control.

### How to start omalizumab treatment in patients with chronic inducible urticaria

The recommended starting dose of omalizumab in adult and adolescent patients with CIndU is 300 mg/4 weeks, the same as in CSU. There have been several randomized controlled trials comparing omalizumab and placebo. A randomized controlled trial in ColdU showed that both 150 mg and 300 mg of omalizumab significantly improved the symptoms after 3 subcutaneous injections at intervals of 4 weeks.<sup>51,47</sup> Similar efficacy was found in patients with SD and CholU.<sup>52,53</sup> Gastaminza et al observed that a progressive improvement in the rate of negative exercise challenge tests from 7.7% at 16th week to 31.3% with extending treatment duration for CholU at 300mg/4 weeks.<sup>53</sup> In the real-life study, the response of patients with CholU was significantly better than that of patients with SD at 300mg/4weeks.<sup>54</sup> We recommend to start omalizumab treatment in all types of CIndU in adult and adolescent patients at 300 mg every 4 weeks (Table 2).

As of yet, there are no reliable predictors of response to omalizumab treatment in CIndU. A history of atopy and higher baseline total serum IgE were linked to a faster response to omalizumab.<sup>54</sup> However, larger multi-centered studies in CIndU patients are needed to explore the factors that affect response to omalizumab.

### How to optimize omalizumab treatment in patients with chronic inducible urticaria

We recommend to evaluate patients with CIndU when they begin to use omalizumab for their disease control and on-treatment response with the aim of optimizing treatment. The aim of treatment with omalizumab is complete control. The initial 300mg/4 weeks of omalizumab should be used for 12 weeks.<sup>50</sup> After that if CIndU is well-controlled or completely controlled ( $12 < \text{UCT} \leq 16$ ), we recommend to maintain the previous treatment dose and interval. If CIndU is poorly controlled ( $\text{UCT} < 12$ ), We also recommend to adopt same adjustment strategy as CSU to increase the dose of omalizumab or reduce the dosing interval (Fig. 1). There is no preference toward increasing dose or increasing frequency first, and that the decision will depend on provider discretion. As for increasing the dose, we recommend increasing the dose to 450 mg/4w first, if it does not work,

Type of CIndU*	Recommended dose	Recommended treatment duration
Symptomatic dermographism	300 mg/4 week	At least 12 months, then the dose and treatment duration should be adjusted according to clinical needs
Cold urticaria		
Cholinergic urticaria		

**Table 2.** Recommended dose and treatment duration for adult and adolescent patients with different type of CIndU \*In clinical studies enrolled patients with CIndU, omalizumab is safe and has a similar incidence of adverse events as placebo. Omalizumab is indicated for symptomatic dermographism, cold urticaria, cholinergic urticaria in China and worldwide.<sup>50-52</sup> Due to limited clinical evidence for delayed pressure urticaria, vibratory angioedema, heat urticaria, contact urticaria or aquagenic urticaria, it is recommended to consider according to the clinical situation. Recommended dose and treatment duration for patients younger than 12 years old with different type of CIndU refer to Table 1. CIndU: chronic inducible urticaria

continue to increase the dose to 600 mg/4w, and the maximum dose is 600 mg/2w. If the urticaria has still not been completely controlled (UCT<16), add-on immunosuppressants should be considered.

Real-life studies in solar urticaria, ColdU, SD, CholU, delayed pressure urticaria, aquagenic urticaria, and heat urticaria found that rates of patients with well-controlled disease increased when the dose was increased to 450 mg or 600mg/4weeks in non-responders.<sup>54-56</sup> According to the evidence and our clinical experience in CIndU, we recommend that the dose of omalizumab for the 3 most common CIndU, ColdU, CholU, and SD, is 150-600 mg/4 weeks.<sup>56</sup> For solar urticaria, we recommend 150mg/4 weeks or higher dose according to clinical efficacy.<sup>16,20</sup> Due to limited clinical evidence for delayed pressure urticaria, vibratory angioedema, heat urticaria, contact urticaria, and aquagenic urticaria, we recommend omalizumab dosing and treatment duration be guided by the clinical situation (Table 2).

#### When and how to stop omalizumab treatment in patients with chronic inducible urticaria

Omalizumab, in CIndU, should be used until the disease is gone, until spontaneous remission. We recommend that the treatment duration of CIndU is at least 12 months. Complete control should be achieved before reducing the dose or prolonging the interval. If patients with completely controlled CIndU (UCT = 16) after 12 months of treatment, we recommend the same stopping strategy as CSU where first the dose is reduced to 150 mg every 4 weeks and then, if complete control is maintained, the dosing interval is incrementally increased to

every 8-12 weeks. If patients who experience relapse and cannot achieve complete control of their urticaria during the period of reducing the dose or prolonging the interval, should return to effective omalizumab dosing and treatment intervals and be reevaluated after 3 months of complete control (Fig. 1).

In addition, some evidence has shown that retreatment with omalizumab can also provide a rapid and significant improvement in CSU and CIndU patients who previously benefited and experienced relapse after discontinuation of treatment.<sup>45</sup>

#### Omalizumab in special populations

##### Omalizumab in children younger than 12 years old with chronic urticaria

Few data are available on the epidemiology of CU in children. In Europe, the prevalence of CU and CSU in children was reported to be 1.4% and 0.8%, respectively.<sup>57</sup> In pediatric populations, remission of CSU at 5 years from onset occurs in 38%-72% of patients.<sup>58</sup> CU in childhood is disabling and has a great impact on children's physical and psychological state, impairs their QoL, and affects performance at school.<sup>1</sup>

According to the EAACI/GA<sup>2</sup>LEN/EDF/WAO guidelines for CU,<sup>1</sup> a second-generation H<sub>1</sub>-antihistamine at approved dose is the first-line treatment for CU, and up dosing to up to 4 times the approved dose is the second-line treatment. However, many pediatric CU patients are resistant to antihistaminic treatment.<sup>59</sup> In a recent study, only 25 of 66 (38%) children with CU treated with a standard-dosed sgAH responded.<sup>60</sup>

Omalizumab is licensed for children with asthma 6 years or older at higher doses than in CSU, which also suggests that omalizumab is generally safe for the use for children. Based on the available evidence, although small, and our clinical experience, we suggest that omalizumab may be an effective and safe choice for children with antihistamine-refractory CU.<sup>21,61-63</sup>

We conducted a retrospective, observational study in Chinese patients under 16 years old with CU to investigate the efficacy and safety of omalizumab. Patients (n = 12) were treated with 150 or 300 mg of omalizumab every 4 weeks, and all of them including a 1-year-old child achieved well or completely controlled urticaria with the first four months of treatment.<sup>21</sup> In addition, a literature review of reports on omalizumab treatment in CU patients younger than 12 years old with 16 cases demonstrated that a 150- to 300-mg monthly dose of omalizumab achieved a complete response in 81% and a partial response in 19%.<sup>61</sup> Passanisi and coworkers reported on 6 pediatric CU patients treated with omalizumab, 2 of them younger than 12 years when started on omalizumab, had a clinically meaningful response, and added 4 cases with complete response to omalizumab on the basis of the former review.<sup>62</sup> A multi-center retrospective case series including 19 patients with CSU aged between 6 and 16.9 years, 9 of them <12 years old, also showed a response rate of 84% with omalizumab treatment.<sup>63</sup>

Up to now, although off-label, no adverse events have been reported in children with CSU treated with omalizumab. In summary, for the children younger than 3 years old, we recommend to treat with 75-150 mg/4 weeks for 6 months. The patients with age between 3 and 6 years old, we recommend to treat with 75-150 mg/4 weeks for 6 to 12 months. For patients younger than 12 years old but older than 6 years old, we recommend that to treat with 150-300 mg/4 weeks for 6 to 12 months (Table 1).

#### Omalizumab use in pregnant and lactating women

Based on previous evidence<sup>64-68</sup> and our clinical experience with using omalizumab in China, patients with CU who want to become pregnant, are pregnant, and are breastfeeding can be treated with omalizumab, weighing the benefits against possible risks.<sup>68</sup>

In addition to a large body of data on omalizumab treatment in pregnant and breast-feeding asthma patients, there are some reports on the use of omalizumab in pregnant or breastfeeding CU patients. In total, 11 CU patients receiving omalizumab during 13 pregnancies have been reported.<sup>64-68</sup> Updosing of omalizumab during pregnancy was only reported in one previous CU patient,<sup>69</sup> who was the first CU patient ever reported to receive omalizumab during pregnancy, disease activity decreased markedly with omalizumab 150 mg/4 weeks, and she achieved complete remission when intervals were shortened to every 2 weeks. All omalizumab treated CU patients gave birth to healthy children and no adverse effects have been reported. There were also no abnormalities observed in CU patients during lactation in the 6 breastfed children.<sup>64-68</sup> We reported two cases of pregnant women with CSU, both achieved complete controlled urticaria and did not have any adverse events.

Of note, omalizumab has been assigned pregnancy category-B risk status by the Food and Drug Administration (FDA)<sup>70</sup> and China Food and Drug Administration (CFDA).<sup>71</sup> Omalizumab is expected to cross the placental barrier and be present in human milk in small amounts.<sup>72</sup> In animal reproductive studies, no evidence of maternal toxicity, embryotoxicity, or teratogenicity was observed in *Cynomolgus* monkeys with subcutaneous doses of omalizumab up to approximately 10 times the maximum recommended human dose (MRHD) throughout the period of organogenesis. A large body of data on safety of omalizumab treatment in pregnant and breast-feeding asthma patients have been reported. In the EXPECT registry, a prospective cohort of pregnancy with asthma, this study compared 250 pregnant patients with an age-adjusted frequencies in a disease (asthma) matched external cohort of 1153 pregnant women without exposure to omalizumab, showed no increase in the rate of major birth defects or miscarriage.<sup>73</sup> In the cohort pregnancy exposure registry study of patients with asthma, compared with infants who were not breastfed, or infants who were breastfed without exposure to omalizumab, adverse events such as "infections and infestations" were not significantly increased



in breastfed infants who were exposed to omalizumab.<sup>72</sup> An increased rate of low birth weight was observed among registry infants, but difficult to determine whether it was due to omalizumab exposure or the disease severity.

In summary, if clinically needed, we recommend that the use of omalizumab may be considered during pregnancy and lactation (Table 1).

### Omalizumab in patients with multiple comorbid allergic diseases

Allergic diseases are often considered as a series of systemic disease which contain atopic dermatitis, asthma, allergic rhinitis, food allergy, allergic conjunctivitis, and so on. It is gradually accepted that these allergic diseases have common characteristics in the pathogenesis and may be different manifestations of atopic patients at different stages.<sup>74,75</sup> Similar to CSU and CIndU, patients with multiple comorbid allergic diseases may benefit from omalizumab. Omalizumab is a recombinant humanized monoclonal antibody which inhibits the binding of IgE to the high-affinity IgE receptor (FcεRI). This treatment approach also applies to other IgE-mediated diseases.

So far, omalizumab already received approval for treatment of chronic rhinosinusitis with nasal polyps (CRSwNP) by European Medicines Agency (EMA) and US Food & Drug Administration (FDA),<sup>76</sup> as well as severe seasonal allergic rhinitis in Japan.<sup>77</sup> For CSU patients with CRSwNP, it is recommended to follow the asthma medication table at a dose of 300 mg or higher for at least 6 months, and then adjust the dose and treatment duration according to clinical need.<sup>78</sup> For patients with CSU and allergic rhinitis, a dose of 300 mg or higher is recommended according to the asthma dosing table. The on-treatment response should be evaluated after 16 weeks. If the patient shows a good response, the treatment can continue for a year, after which re-evaluation should be considered.

In 2018, FDA granted Breakthrough Therapy Designation for omalizumab for the prevention of severe allergic reaction following accidental exposure to one or more foods in people with

allergies.<sup>76</sup> An on-going phase III study is exploring omalizumab alone or in combination with multi-allergen oral immunotherapy helping people with multiple food allergies to consume foods without dose-limiting symptoms.<sup>77</sup> For patients with CSU and food allergies, we recommend considering a dose of 300 mg or higher according to the asthma dose table. Efficacy should be evaluated after 16 to 20 weeks. If patients respond well to the treatment, omalizumab can be continued for up to 24 weeks (Table 3).

Four patients with allergic bronchopulmonary aspergillosis (ABPA) were treated with 375mg/2 week omalizumab for 1 year, an improvement in asthma control test symptom scores for both daytime and nighttime were found.<sup>79</sup> Different studies used various dosages of omalizumab ranging from 225 mg to 750 mg according to weight and serum IgE level, and dosing frequency ranged from once per week to once monthly while the most commonly used dose was 375 mg every 2 weeks.<sup>80</sup> The maximum recommended dose of 600 mg every 2 weeks for patient with a higher total IgE beyond the higher limit of 1500 IU/mL. For patients with ABPA and CSU, we recommend that patients can be treated with 375 mg every 2 weeks for at least 6 months, then the dose and treatment duration should be adjusted according to clinical needs (Table 3).

Researches on omalizumab for the treatment of patients with atopic dermatitis are rare. A systematic review including 15 studies showed that 43% of the patients with atopic dermatitis (AD) could achieve remarkable clinical response after omalizumab treatment.<sup>81</sup> The dosing regimens varied from 150 to 900 mg/month in the included studies. Serum IgE concentrations of less than 700 IU/mL may be more favorable clinical responses.<sup>81</sup> The pathogenesis of the diseases is remain unclear. Omalizumab has a higher therapeutic effect for those IgE-mediated diseases, while the pathogenesis of atopic dermatitis is otherwise complex, and IgE does not necessarily play a decisive role in pathogenicity. According to previous evidence and our clinical experience, we recommend that patient with CSU and AD can be

CSU with other allergic comorbidities	Recommended dose	Recommended treatment duration
CSU with CRSwNP <sup>76,78</sup>	300 mg or higher dose according to asthma dosing table	At least 6 months, then the dose and treatment duration should be adjusted according to clinical needs
CSU with food allergy <sup>77*</sup>	300 mg or higher dose according to asthma dosing table	For food allergy: evaluate response after 16 or 20 weeks treatment, continue to 24 weeks if good response
CSU with ABPA <sup>79,80*</sup>	375 mg/2 weeks	At least 6 months, then the dose and treatment duration should be adjusted according to clinical needs
CSU with allergic asthma <sup>81</sup>	300 mg or higher dose according to asthma dosing table	Evaluate response after 16 weeks, At least 12 months, then the dose and treatment duration should be adjusted according to clinical needs
CSU with allergic rhinitis <sup>81</sup>	300 mg or higher dose according to asthma dosing table	Evaluate response after 16 weeks, re-evaluate after 1-year treatment if good response
CSU with AD <sup>82*</sup>	150-450mg/2 week	Refer to Fig. 1 for stopping strategy

**Table 3.** Recommended dose and treatment duration for patients with other allergic comorbidities \*Limited clinical evidence, it is recommended to base treatment decision on the clinical situation. In cases where both the dose strength and frequency differ, result in the higher monthly dose is recommended. CSU: chronic spontaneous urticaria; CRSwNP: chronic rhinosinusitis with nasal polyps; ABPA: allergic bronchopulmonary aspergillosis; AD: atopic dermatitis

treated with 150-450mg/2 weeks (Table 3). The stopping strategy is similar to CSU (Fig. 1).

In conclusion, patients with multiple comorbid allergic diseases may benefit from omalizumab treatment according to limited clinical evidence. We recommend to consider the higher dosage according to the clinical situation for CU patients (both CSU and CIndU) with other comorbid allergic diseases (Table 3).

#### Other special populations

There have been no studies on the effect of impaired renal or hepatic function on the pharmacokinetics of omalizumab. Because omalizumab clearance at clinical doses is dominated by the reticuloendothelial system, it is unlikely to be altered by renal or hepatic impairment. While no dose adjustment is recommended for these patients, omalizumab should be administered with caution. No association between omalizumab and increase risk of malignancy has been demonstrated, Omalizumab can be used for the treatment of CSU in patients with comorbid malignancy.

#### Omalizumab treatment algorithm for antihistamine-resistant CU in China

The present consensus, as agreed by all authors, provides an omalizumab treatment algorithm for patients with antihistamine-resistant CU in China (Fig. 1). This algorithm follows a stepwise approach, brings on board other treatments as needed, and applies for adults and special populations of CSU patients including children, adolescents, and pregnant and breast-feeding women (Fig. 1, Tables 1-3).

#### CONCLUSIONS

CU is a major health issue, globally and in China. The risk/benefit profile of omalizumab supports its use in CU patients who do not achieve complete control with antihistamine treatment. Omalizumab is a well established, licensed and reimbursed treatment in many countries outside of China. Similar to other countries where omalizumab is available but off label and paid for by patients, Chinese physicians who treat patients with CU are in need for guidance on when, how, and for how

long to use omalizumab in this setting. This consensus document aims to provide this guidance. We encourage all urticariologists in China and in countries with similar settings to apply our recommendations in their routine clinical management of CU, report on the outcomes and help to improve them moving forward.

### Abbreviations

CU: chronic urticaria; CSU: chronic spontaneous urticaria; ClndU: chronic inducible urticaria; QoL: quality of life; sgAHs: second-generation H1-antihistamines; SD: symptomatic dermographism; ColdU: cold urticaria; CholU: cholinergic urticaria; UCARE: Urticaria Center of Reference and Excellence; UAS: Urticaria Activity Score; UCT: Urticaria Control Test; CU-Q2oL: Chronic Urticaria Quality of Life Questionnaire; AAS: The Angioedema Activity Score; AE-QoL: Angioedema Quality of Life Questionnaire; AECT: Angioedema Control Test; DLQI: Dermatology Life Quality Index; CRSwNP: chronic rhinosinusitis with nasal polyps; EMA: European Medicines Agency; FDA: Food & Drug Administration; ABPA: allergic bronchopulmonary aspergillosis; AD: Atopic Dermatitis; CRSwNP: chronic rhinosinusitis with nasal polyps; ABPA: allergic bronchopulmonary aspergillosis.

### Authors' contributions

Zuo-tao Zhao and Marcus Maurer have made substantial contributions to conception and study design; reviewed the article critically for important intellectual content. The other authors have drafted the manuscript. All authors were involved in the development of this consensus and final approval of the manuscript.

### Funding

None.

### Availability of data and materials

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

### Ethics statement

The authors declare that this manuscript complies with the ethics in publishing guidelines. The ethics approval and consent to participate is not applicable here.

### Submission declaration

We confirm that the manuscript is original, has not been published before, is not currently being considered for publication elsewhere. All authors agree to the publication.

### Declaration of competing interest

ZT Zhao has participated as Principal Investigator in clinical trials sponsored by Novartis, Pfizer. He has received consultancy/speaker honoraria from Novartis, Pfizer, Astellas, Galderma, Janssen, GSK, BAYER, LEO, MEDA Pharma (a Mylan Company), and has acted as scientific Advisory Board member for Pfizer, Novartis, Astellas, LEO, MEDA Pharma (a Mylan Company).

XH Gao has received consultancy/speaker honoraria from Novartis, Pfizer, Astellas, Galderma, Janssen, Sinofi, GSK, LEO, Lilly, MEDA Pharma (a Mylan Company), and has acted as scientific Advisory Board member for Novartis, Lilly, Sinofi, MEDA Pharma (a Mylan Company).

YS Guo has received consultancy/speaker honoraria from Novartis, Janssen, BAYER, AstraZeneca, Sanofi/Regeneron, ALK-Abello, Allergopharma, Takeda Pharmaceutical, MSD and Thermo Fisher Scientific.

H Long has received consultancy or speaker honoraria from Novartis, AbbVie, Lilly, Janssen, Astellas, GSK, BAYER, LEO, Menarini, Sanofi, BrightFuture, and CMS.

MM is or recently was a speaker and/or advisor for and/or has received research funding from Allakos, Amgen, Aralez, ArgenX, AstraZeneca, Celldex, Centogene, CSL Behring, FAES, Genentech, Gllnnovation, Gilead, Innate Pharma, Kyowa Kirin, Leo Pharma, Lilly, Menarini, Moxie, Novartis, Roche, Sanofi/Regeneron, Third HarmonicBio, UCB, and Uriach.

The rest of the authors declare that they have no relevant conflicts of interest.

### Acknowledgements

We thank Miao Yu and Xiaoting Song for expert help with formatting and revising the manuscript as well as its submission. We thank Jia Yu for her help in establishing communication between all authors.

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