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Chapter

The Use of Omalizumab in Chronic Urticaria: Available Data and Future Aspects of Anti-IgE Treatment

Young-Min Ye

Abstract

Chronic urticaria (CU) defined as repeatedly occurred itchy wheals and/or angioedema for at least 6 weeks. Due to the unpredictability, recurrent and disabling symptoms, and a considerably impaired quality of life, effective and tolerable treatment for CU patients is crucial. Almost a half of patients with CU are refractory to H1-antihistamines, even though the dose of antihistamines is increased up to 4-fold. Recently treatment modulating IgE levels and activities provides an efficient therapeutic approach. Omalizumab, the only approved anti-IgE treatment for chronic spontaneous urticaria (CSU) patients until now, with a strong evidence of the efficacy and safety, opened a new horizon in the care of the patients whose urticaria is not controlled with antihistamines. Recent international guidelines recommend omalizumab as the first choice of treatment for antihistamine-refractory CSU. However, as it is not curative neither disease-modifying agent, there is a subpopulation of CSU patients responding partly or never to omalizumab. The other things to be solved in the treatment of CU is that clinical evidence is still limited on chronic inducible urticaria (CIndU) and special populations. Thus, a new anti-IgE treatment, ligelizumab is actively evaluated in the efficacy compared with both placebo and omalizumab. Further understandings on the pathogenesis of CU can lead to the development of new mechanism-based therapeutics for CU patients.

Keywords: omalizumab, ligelizumab, IgE, urticaria, angioedema

1. Introduction

Symptomatic management to relieve itchy wheals has been recognized as the standard of care for chronic urticaria. However, around a half of patients with CU are refractory to recommended doses neither an increased doses of antihistamine. In these patients whose urticaria are not controlled with non-sedative antihistamines, more significantly impaired quality of life has been observed. Management guidelines for CU in past included omalizumab, cyclosporine, dapsone, hydroxychloroquine, methotrexate, montelukast, colchine, and phototherapy as alternative treatment for antihistamine-refractory CU [1, 2]. However, most of recent guidelines recommend omalizumab for the first of choice among various immunomodulating agents based on lots of study results [3, 4].

Omalizumab is the only biologics, approved for management of chronic spontaneous urticaria (CSU) in patients at age 12 years or older by Food and Drug Administration (FDA). It a recombinant humanized IgG1, monoclonal anti-IgE antibody. Although the pathophysiology of CU is not completely established, it is clear that mast cell activation is the key feature of CU. Omalizumab binds to free IgE at the Fc region and prohibits IgE from interacting with high-affinity receptor for Fc region of IgE (FcεRI) on mast cells, basophils and eosinophils [5, 6]. It has been shown to downregulate the expression of FcεRI on both mast cells and basophils [7]. This chapter reviews the current evidence of the efficacy, safety, and treatment response to biologics targeting IgE, including omalizumab, ligelizumab and quilizumab in CU patients.

2. Pivotal phase III trials with omalizumab in patients with CSU

The first successful use of omalizumab for CU was reported by Boyce in 2006 [8]. The 3 essential phase III multicenter, randomized, double-blinded studies that led to the FDA indication for CSU were the ASTERIA I [9] and II [10], and GLACIAL [11] trials. These trials included a total of 733 patients on omalizumab 75, 150, or 300 mg at 4-week intervals and 242 patients were allocated in the placebo groups. Clinical efficacy of omalizumab in randomized controlled trials including these 3 pivotal trials are summarized in **Table 1**.

ASTERIA I was a 40-week trial included patients receiving either omalizumab 75 mg, omalizumab 150 mg, omalizumab 300 mg, or placebo given in 4-week intervals for a 24-week treatment period with 16 weeks of follow-up [9]. The patients who had failed H1 antihistamine treatment at licenced doses were enrolled. All 3 doses of omalizumab met their primary efficacy endpoint of a reduction in weekly itch severity score (ISS) at 12 weeks compared with baseline (−6.46 with omalizumab 75 mg, −6.66 with omalizumab 150 mg, and − 9.40 with omalizumab 300 mg). The omalizumab 300 mg group achieved the minimally important difference in weekly ISS at a significantly shorter duration compared with the other omalizumab doses. However, urticaria symptoms returned to placebo levels after omalizumab was discontinued in all treatment groups during the follow-up period.

ASTERIA II was a 28-week trial that included 12 weeks of therapy with either omalizumab 75 mg, 150 mg, or 300 mg, or placebo in 4-week intervals with a 16-week follow-up period [10]. The patients having already failed treatment with approved doses of H1 antihistamines were included. The group of omalizumab 75 mg was failed to show significant difference in weekly ISS at 12 weeks compared with the placebo group. The omalizumab 150 mg and 300 mg groups reached significance for their primary end point of a mean change from baseline in weekly ISS at 12 weeks (−8.1 with omalizumab 150 mg and − 9.8 with omalizumab 300 mg), as compared with placebo. The proportion of patients who had complete symptom control was 16%, 22%, 44%, and 5% for omalizumab 75 mg, 150 mg, 300 mg, and placebo groups, respectively. During the 16-week follow-up period, the ISS for all omalizumab doses increased to levels similar to those of the placebo group.

GLACIAL trial included patients who had failed H1 antihistamines at up to 4 times the approved doses in addition to approved doses of leukotriene receptor antagonists or H2 antihistamines [11]. These patients were given either omalizumab 300 mg or placebo every 4 weeks for 24 weeks followed by a 16-week observation period. The weekly ISS at week 12 compared with baseline was significantly improved in the omalizumab 300 mg group compared with placebo (−8.6 with omalizumab 300 mg). All the other secondary efficacy end points also met

Trial name, Author, Year, Reference No.	**Population**	**Study design**	**Intervention**	**Mean change from baseline in UAS7 (mean, 95% CI or SD)**	**No. of complete responders (% of UAS7 = 0)**
MYSTIQUE Saini 2011 [12]	Patients aged 12–75 years with CU refractory to antihistamines.	Multicenter RDBPCT (N = 90; OMA75 = 23, OMA300 = 25, OMA600 = 21, placebo = 21)	Omalizumab 75, 300, 600 mg Single dose	Placebo: −6.9 (−11.5, 0.96) 75 mg: −9.8 (−17.77, −4.85) 300 mg: −19.9 (−25.4, −12.0) 600 mg: −14.6 (−22.5, −7.0) at 4 W	Placebo: 0% 75 mg: 4.4% 300 mg: 36.0% 600 mg: 28.6% at 4 W
XCUISITE Maurer 2011 [13]	Patients aged 18–70 years with a clinical diagnosis of moderate-to-severe CU.	Multicenter RDBPCT (N = 49; OMA = 27, placebo = 22)	Omalizumab 75 ~ 375 mg Q2W or Q4W based on the asthma dosing	Placebo: −7.9 300 mg: −17.8 at 24 W	Placebo: 4.5% 300 mg: 59.3% at 24 W
ASTERIA I Maurer 2013 [9]	Patients aged 12–75 years with moderate-to-severe CU who remained symptomatic despite H1AH.	Multicenter RDBPCT (N = 322; OMA75 = 82, OMA150 = 82, OMA300 = 79, placebo = 79)	Omalizumab 75, 150, 300 mg Q4W for 12 weeks	Placebo: −5.1 ± 5.6 75 mg: −5.9 ± 6.5 150 mg: −8.1 ± 6.4 300 mg: −9.8 ± 6.0 at 12 W	Placebo: 5% 75 mg: 16% 150 mg: 22% 300 mg: 53% at 12 W
ASTERIA II Saini 2015 [10]	Patients aged 12–75 years with a CU that remained symptomatic despite H1AH.	Multicenter RDBPCT (N = 318; OMA75 = 77, OMA150 = 80, OMA300 = 81, placebo = 80)	Omalizumab 75, 150, 300 mg Q4W for 24 weeks	Placebo: −8.01 ± 5.22 75 mg: −6.46 ± 6.14 150 mg: −6.66 ± 6.28 300 mg: −9.40 ± 5.73 at 12 W	Placebo: 8.8% 75 mg: 11.7% 150 mg: 15.0% 300 mg: 35.8% at 12 W
GLACIAL Kaplan 2013 [11]	Patients aged 12–75 years with a CU that remained symptomatic despite H1AH plus H2AH and/or LTRA.	Multicenter RDBPCT (post hoc analysis) (N = 336; OMA300 = 252, placebo = 84)	Omalizumab 300 mg Q4W for 24 weeks	Placebo: −8.5 (−11.1, −5.9) 300 mg: −19.0 (−20.6, −17.4) at 12 W Mean difference to placebo: −4.5 (−6.1, −3.0) at 24 W	34% vs. 5% at 12 W
X-ACT Staubach 2016 [14]	Patients aged 18–75 years with CSU and ≥ 4 episodes of angioedema who were symptomatic despite H1AH.	Multicenter RDBPCT (N = 91; OMA300 = 44, placebo = 47)	Omalizumab 300 mg Q4W for 24 weeks	Placebo: −6.5 ± 13.4 300 mg: −16.8 ± 14.8 Mean difference to placebo: −10.3 (−16.2, −3.9) at 28 W	50% vs. 10.6% at 28 W

Trial name, Author, Year, Reference No.	Population	Study design	Intervention	Mean change from baseline in UAS7 (mean, 95% CI or SD)	No. of complete responders (% of UAS7 = 0)
MoA Metz 2017 [15]	Patients aged 18–75 years with CU refractory to antihistamines.	Multicenter RDBPCT (N = 30; OMA300 = 20, placebo = 10)	Omalizumab 300 mg Q4W for 12 weeks	Placebo: −3.8 ± 6.63 300 mg: −11.4 ± 6.53 Mean difference to placebo: −14.82 at 12 W	NA
Jörg 2018 [17]	Patients aged 18–70 years with CSU refractory to H1AH.	Monocenteric RDBPCT Post hoc analysis (N = 30; OMA300 = 20, placebo = 10)	Omalizumab 300 mg Q4W for 16 weeks	NA	47.1% vs. 0% at 12 W 23.5% vs. 12.5% at 20 W
POLARIS Hide 2017 [19]	Japanese and Korean patients aged 12–75 years with CSU refractory to conventional H1AH at the randomization.	Multicenter RDBPCT (N = 218; OMA150 = 71, OMA300 = 73, placebo = 74)	Omalizumab 150, 300 mg Q4W for 12 weeks	Placebo: −13.9 150 mg: −18.8 300 mg: −22.4 at 12 W	Placebo: 4.1% 150 mg: 18.6% 300 mg: 35.6% at 12 W
XTEND-CIU Maurer 2018 [16] Casale 2019 [18]	Patients aged 12–75 years who remain symptomatic despite optimized H1AH treatment.	Multicenter RDBPCT (N = 134; OMA300 = 81, placebo = 53)	Omalizumab 300 mg Q4W for the 1st 24 W, and then randomized to OMA300 or placebo for additional 24 W	NA	36.8% at 12 W 52.0% at 24 W

Table 1.
Clinical efficacy of omalizumab in randomized controlled trials.

significance for the omalizumab group including change in weekly urticaria activity score (UAS7), Dermatology Life Qualirty Index, and proportion of patients who were itch and hive free. As with both ASTERIA trials, the effects of omalizumab appeared not to be permanent, and weekly ISS increased to placebo levels after discontinuing omalizumab treatment.

Recently, several systematic analyses based on various randomized controlled trials [9–19] to evaluate the effects of omalizumab for patients with CSU have been reported [3, 20–22]. These systematic reviews have provided high-quality of evidence on that omalizumab is effective in the treatment of antihistamine-refractory CSU independent of monthly dose [3, 22]. The dosage of 300 mg every 4 weeks is found to achieve better results in reductions of disease activity scores and in improvement of disease-specific quality of life. However, a recent meta-analysis analyzed minimal important differences in urticaria outcome measures, such as UAS7, ISS7, and quality of life demonstrated that omalizumab 300 mg resulted in clinically meaningful improvement of all the outcome measures, whereas

omalizumab 150 mg failed to prove clinically meaningful improvement in any of them as compared with standard of care [20].

3. Optimal dosing and interval of omalizumab treatment

In patients with allergic asthma, optimal dose of omalizumab is determined by serum total IgE levels and body weight of the patients. Unlike for allergic asthma, the FDA approved omalizumab for the management of CSU at doses independent of serum IgE levels or body weight. Based on the 3 pivotal trials, [9–11] the approved doses of omalizumab is 150 mg or 300 mg every 4 weeks. Doses lower than 150 mg did not consistently show a significant improvement in efficacy compared with placebo, and the higher dose of 300 mg dependably showed faster and more robust efficacy. Interestingly, higher doses of omalizumab at 600 mg were explored in the dose-ranging single omalizumab dose phase II MYSTIQUE trial [23, 24]. Although no significant difference in changes of UAS7 at week 4 from baseline between the omalizumab 600 mg and 300 mg groups, there was also no increase in adverse events [25–27]. Cases of patients requiring higher than approved doses, up to 600 mg, to reach complete remission have been reported [25, 27].

4. Proper duration of omalizumab treatment

As shown in all phase III trials, cessation of omalizumab resulted in an increase in weekly itch and wheal scores and returning to placebo levels within 16 weeks [9–11]. These results indicate that omalizumab is effective in controlling symptoms, but they do not provide evidence that omalizumab induces remission from CSU. Therefore, longer durations of treatment may be required for some patients. Omalizumab shows very good safety efficacious at therapeutic durations of more than 1 year [23, 24]. As soon as patients achieved complete control, antihistamines can be tapered off [4].

Several strategies have been proposed for weaning including reduction monthly doses or lengthening the time between doses [28]. A patient-tailored tapering protocol on the basis of a patient's UAS7 scores while on omalizumab treatment is needed. Increase the injection interval by 1-week intervals can be recommended when the patient achieved a complete response to omalizumab after 6 months of treatment [29]. If a patient can tolerate every 8-week injections over a 4-month period without increased activity, these patients can often have omalizumab discontinued. Fortunately, most of patients who have experienced relapsed urticaria after stopping omalizumab treatment, respond well to retreatment of omalizumab with previously effective dose and interval [30, 31].

5. Predictors of the response to omalizumab treatment

In patients with CU, omalizumab is not a disease-modifying or curative treatment. The treatment response to omalizumab in patients with CU is classified according to the onset and extent of the response. Fast or early response is defined when the onset of therapeutic response to omalizumab in CU patients starts within the first 4 weeks. On the other hand, the response appearing gradually by weeks 12–16 weeks is defined as slow or late response. The extent of therapeutic response to omalizumab is based on the UAS7. Complete response includes the patients

who achieve UAS7 = 0, no itch and wheal or UAS7 ≤ 6, well-controlled urticaria or have a significant improvement in UAS7 reduction from baseline (> 90%). Partial response is defined as UAS7 reduction between 30% and 90%. No response means that UAS7 reduction is less than 30% from baseline or the exacerbation of itchy wheals during omalizumab treatment [32, 33].

Around 70% of patients with CSU who benefit from omalizumab respond within the first week of treatment. From the results of 3 pivotal phase III trials, at week 4, well-controlled urticaria (UAS7 ≤ 6) was reported by 2 ~ 5%, 12 ~ 15%, 21 ~ 28%, and 37 ~ 51% of patients receiving placebo, 75, 150, 300 mg of omalizumab, respectively. And early response is linked to type I autoimmunity or IgE autoantibodies, such as IgE to thyroid persoxidase [13]. The proportion of well-controlled urticaria and complete responders during the 12-week of active treatment increased continuously. With continuous dosing of omalizumab 300 mg from 12 weeks to 24 weeks in ASTERIA I [9] and GLACIAL, [11] around a half of patients who did not respond at week 12 achieved complete response at week 24. The median time to complete response was also dependent on the dose of omalizumab. It was noted between 8 and 10 weeks for 300 mg of omalizumab, whereas fewer than 50% of patients in the 75 mg or 150 mg of omalizumab groups achieved complete response within the 12-week of treatment. However, around 40 ~ 50% of patients had partly or uncontrolled urticaria even with an active treatment of omalizumab for 24 weeks. Thus, before determining non-responders to omalizumab treatment and considering other therapeutics, use of omalizumab for at least 6 months is needed.

There are no markers to predict when their CSU will go into remission. Despite older and higher disease activity at onset, being female, and hypersensitivity to nonsteroidal anti-inflammatory drugs, comorbid CIndU, presence of angioedema, and thyroid disease were all reported to be associated with longer urticaria duration in CSU patients, [29] however, none on these markers guides to decide when to discontinue omalizumab.

Lower levels of serum total IgE at baseline (< 40 IU/mL) and decreased ratio of IgE levels at 4 weeks by baseline levels (<2.0) have been associated with higher risk of non-responder to omalizumab treatment in CSU patients [34]. Positive response to diagnostic tests for type IIb autoimmunity including basophil histamine releasibility assay, autologous serum skin test, and anti-FcεRI autoantibody in the sera from CSU patients are regarded as indicators for slow or poor response to omalizumab [34, 35].

Studies evaluating the efficacy of up-dosing of omalizumab to 450 mg or 600 mg in a month revealed a comparable benefit for CSU patients with partial or non-response to 300 mg of omalizumab [26, 27, 36]. There also reports that shortening the injection interval can lead to complete response inpatients with partial or no response to omalizumab 300 mg every 4 weeks. The most recent guidelines recommend cyclosporine add-on as a fourth-line treatment in CSU patients whose urticaria is not controlled with omalizumab treatment [3, 4, 37].

6. Omalizumab treatment for chronic inducible urticaria

As chronic inducible urticaria (CIndU), induced by common physical stimuli including exposure to cold or heat, skin friction or pressure, sunlight, and exercise, with longer duration, difficult to avoid the offending trigger, CIndU affects severely patients' quality of life. A recent study reported that up to 76% of CSU patients were found to have a concurrent CIndU and these patients have more severe

urticaria [38]. While omalizumab has been used to successfully treat CSU on the basis of strong evidence from randomized controlled trials, real-life studies, and meta-analyses, omalizumab is not yet licensed for CIndU.

A meta-analysis reported recently that omalizumab has substantial benefits in patients with various CIndUs [16]. Variation of omalizumab use was seen between the CIndU subtypes, with the strongest evidence available in patients with symptomatic dermographism (complete or partial response in 38/54 patients), cold urticaria (complete/partial response in 41/51 patients), and solar urticaria (complete/partial response in 28/36 patients). Little or no evidence was available on vibratory, aquagenic and contact urticaria.

A randomized, placebo-controlled trial involving 55 patients with symptomatic dermographism revealed that significant improvement in critical friction thresholds after 10 weeks of treatment with omalizumab 150 mg and 300 mg, compared with the placebo group [39]. No significant difference in efficacy was observed between omalizumab 150 mg and 300 mg groups. After 10 weeks of treatment, 6 (33%) of 18 receiving 150 mg of omalizumab and 8 (42%) of 19 patients receiving 300 mg of omalizumab did not respond at all compared with 15 (83%) of 18 in the placebo group. A retrospective observational study showed 86% of patients achieved a complete response [32].

Cold urticaria is the second most prevalent physical urticaria. A randomized, placebo-controlled trial including 31 patients with cold urticaria demonstrated significant clinical superiority of omalizumab versus placebo [40]. Mean changes in critical temperature threshold after 10 weeks of treatment were significantly higher in the omalizumab 150 mg and 300 mg groups compared with the placebo group. Improvements were seen by week 4. No significant dose-dependent response between the omalizumab 150 mg and 300 mg groups. After 10 weeks of treatment, 10% of 10 patients receiving omalizumab 150 mg and 22% of 9 patietns receiving 300 mg of omalizumab were non-responders compared with 75% of 12 patients in the placebo group.

Due to a longer symptomatic episode and a subtype of frequently accompanied in patients with CSU, delayed pressure urticaria was reported to result in a significant impairment of quality of life than other types of CIndU [41]. Furthermore, it is difficult to control delayed pressure urticatia with up-dosing of antihistamine treatment [16]. In a meta-analysis that found 11 publications of omalizumab treatment for patients with delayed pressure urticaria, favorable results were obtained [16]. Starting with 150 mg of omalizumab, 60% ~ 88% of patients with delayed pressure urticatia achieved complete control within 2 days.

There is sparse data on the efficacy of omalizumab for patients with cholinergic urticaria. Among retrospective analyses, one from the Germany [32] reported 62% of complete response and 25% of no response assessed by provocation test, whereas another study reported from Korean populations [42] showed relatively lower complete responders (4.8%, 1 of 21 patients).

Taken together, although evidence of the efficacy of omalizumab in CIndU has been accumulating, more data from randomized controlled trials are needed to establish the dose, injection interval, and treatment duration according to the type of CIndU. To date, while many studies proved a lower dose of 150 mg was enough to reach a good response, however as like in CSU patients, increasing dose of omalizumab in some patients with CIndU had better response. Most of studies found that CIndU patients achieved complete symptom control after the first injection of omalizumab, however, once discontinued, all patients got worse within 8 weeks after the last injection to need retreatment of omalizumab because antihistamines did not work for these patients [16].

7. Omalizumab treatment for angioedema

In X-ACT (Xolair Effects on Angioedema in Chronic Spontaneous Urticaria Treatment) study, a phase III, randomized, double-blind study involving selectively CSU patients with angioedema and wheals, omalizumab was superior to placebo in improving CU-Q2oL scores and reduction in angioedema-burdened days by three times during the 28-week of treatment [14, 43]. Angioedema was a prevalent symptom in patients with CSU in the three pivotal phase 3 studies of omalizumab and occurred in 44–53% of patients at baseline [9–11]. Treatment with 300 mg of omalizumab was efficacious in reducing patient-reported angioedema in patients with CIU/CSU who were symptomatic despite a variety of treatments [44]. Urgert et al. evaluated systematically the efficacy of omalizumab in CSU patients accompanying angioedema using 5 studies [21]. They provided high quality evidence of that the proportion of angioedema-free days were higher in the omalizumab group compared with placebo as well as use of rescue medications from baseline was significantly reduced in the omalizumab 300 mg group.

8. Omalizumab treatment for special populations

Although ASTERIA II [10] and GLACIAL [11] did include patients with 12 years and older, none of these larger trials addressed the use of omalizumab in the pediatric population below this age. Although significantly less common in the pediatric population, CU affects 0.1% to 0.3% of children with a similar morbidity profile as the adult population. A case series of the use of omalizumab for CU in the 4 patients in age from 4 to 16 years found that all 4 patients obtained complete response to omalizumab 150 mg monthly for the younger ones (age 4 and 5 years) and 300 mg monthly for the older patients at 10 and 16 years without any reported adverse events [45].

The EXPECT study evaluated the use of omalizumab during pregnancy [46]. In total, 191 pregnant women were included who had moderate to severe asthma and received at least 1 dose of omalizumab 8 weeks before conception or at any time during pregnancy. Based on the known outcomes of 169 pregnancies, there was no significant difference in spontaneous abortion, major congenital anomalies, prematurity, or low birth weight compared with a similar asthma population reported in previous studies [47, 48]. Because of the small number of patients in the study, it is difficult to draw any conclusions of safety on the use of omalizumab during pregnancy for CU [28]. Further studies are needed with larger sample sizes.

9. Safety issues of omalizumab

Safety was closely evaluated in all the randomized phase III trials [9–11]. ASTERIA II reported more headaches in the omalizumab 150 mg group compared with placebo but otherwise had no significant differences in adverse events. The GLACIAL study [11] showed no significant difference in adverse events between omalizumab group and placebo but did have some system-specific differences. In ASTERIA I, [9] headaches, arthralgia, and injection-site reactions were more common in the omalizumab groups but there was no significant difference in serious adverse events. No deaths, malignancies, or anaphylactic episodes were reported in these trials due to omalizumab.

Overall, omalizumab is very well tolerated and adverse reactions occurred in patients taking omalizumab were compatible with those on placebo in prospective, randomized trials for CU [3, 20, 49–51]. The most seriously considered adverse reaction is anaphylaxis-related to omalizumab that is defined as a combination of angioedema of the throat or tongue, bronchospasm, hypotension, syncope, and/or urticaria [52]. Omalizumab joint task force reviewed clinical trials and postmarketing surveillance data on omalizumab-induced anaphylaxis or anaphylactoid reactions [53]. They found a total of 35 patients with 42 episodes of anaphylaxis-related to omalizumab injection. Considering a total of 39510 patients who had exposed once to omalizumab, they estimated an anaphylaxis-reporting rate of 0.09% of patients [53]. The risk of anaphylaxis in patients with CU appears to be less than in those treated for asthma. In addition, there does not seem to be a dose-related effect on adverse events.

10. Anti-IgE therapeutics under development

10.1 Ligelizumab

Ligelizumab (QGE031) is a new promising humanizaed monoclonal anti-IgE antibody under development for the treatment of CSU patients. It has a 40-fold to 50-fold greater affinity to IgE compared with omalizumab [54]. In a phase 2b multicenter randomized placebo controlled trial, patients with antihistamine-refractory CSU were randomized to placebo, 300 mg of omalizumab, or 24, 72, or 240 mg of ligelizumab administered by subcutaneous injection with 4-week interval for 20 weeks [55]. Ligelizumab demonstrated rapid onset of action, dose-dependent efficacy, and superiority to omalizumab. At 12 week, a total of 30%, 51%, and 42% of the patients treated with 24 mg, 72 mg, and 240 mg of ligelizumab, respectivity, had complete control of urticaria, as compared with 26% of the patients receiving omalizumab 300 mg and none in the placebo group. More than 50% of patients taking 240 mg of ligelizumab were complete responders, a response rate twice than that seen in the omalizumab group. Furthermore, the mean time to relapse after the last injection was 4 weeks for omalizumab vs. 10 weeks for ligelizumab. Except higher rates of mild injection site reactions in the 240 mg of ligelizumab group, no difference in safety profiles of placebo, omalizumab, and ligelizumab was observed. The most frequently reported adverse events were viral upper respiratory tract infection and headache. No deaths or anaphylaxis events were reported in any of the trial groups. On the basis of favorable response of ligelizumab with a rapid onset of action, improved and sustained efficacy in antihistamine-refractory CSU patients over 300 mg of omalizumab treatment, now two phase III, multi-center, randomized, double-blind, active- and placebo-controlled, parallel-group studies (PEARL 1 and 2) are running. The primary outcome of these two trials will measure absolute change from baseline in UAS7 at Week 12 [56].

10.2 Quilizumab

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 [57]. In clinical trials, quilizumab reduced serum total and specific IgE levels in healthy volunteers and in patients with allergic rhinitis or mild asthma [58].

However, because quilizumab did not provide a significant differences in the clinical endpoints compared with placebo, it was indicated that ongoing IgE switching and stimulation of B-cell memory may not be key disease drivers [59].

11. Conclusion

Therapeutics modulating IgE levels and activities provide an efficient and very tolerable add-on treatment for patients with antihistamine-refractory CU. With a strong evidence of the efficacy and safety, omalizumab is recommended as the first choice of treatment for CSU patients who still suffered from urticaria with up-dosing antihistamine treatment in recent international guidelines. However, as it is not disease-modifying agent, there is a subpopulation of CSU patients responding incompletely or never to omalizumab. Moreover, clinical evidence on chronic inducible urticaria (CIndU) and special populations, such as children and older patients is still not enough. Thus, a new anti-IgE treatment, ligelizumab is actively evaluated in the efficacy compared with both placebo and omalizumab. Further understandings on the pathogenesis of CU can lead to the development of new mechanism-based therapeutics for CU patients.

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Conflict of interest

The authors declare no conflict of interest.

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