

Review



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The KAAACI/KDA Evidence-Based Practice Guidelines for Chronic Spontaneous Urticaria in Korean Adults and Children: Part 2. Management of H1-Antihistamine-Refractory Chronic Urticaria

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ABSTRACT

Quite a few patients with chronic spontaneous urticaria (CSU) are refractory to H₁-antihistamines, even though the dose of H₁-antihistamines is increased up to 4-fold. CSU that is not controlled with H₁-antihistamines results in increased disease burden. Several immunomodulators have been used to manage these patients. The guidelines reported herein are connected to Part 1 of the KAAACI/KDA Evidence-Based Practice Guidelines for Chronic Spontaneous Urticaria in Korean Adults and Children, and aimed to provide evidence-based recommendations for the management of H₁-antihistamine-refractory CSU. Part 2 focuses on the more commonly used additional treatment options for refractory CSU, including omalizumab, cyclosporine, leukotriene receptor antagonist, dapsone, methotrexate, and phototherapy. The evidence to support their efficacy, dosing, safety, and selection of these agents is systematically reviewed. To date, for patients with refractory CSU, the methodologically sound data to evaluate the use of omalizumab has been growing; however, the evidence of other immunomodulators and phototherapy is still insufficient. Therefore, an individualized stepwise approach with a goal of achieving complete symptom control and minimizing side effects can be recommended. Larger controlled studies are needed to elevate the level of evidence to select a rational therapeutic agent for patients with refractory CSU.

Keywords: Urticaria; antihistamine, treatment; guideline; evidence; leukotriene; IgE; cyclosporine

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INTRODUCTION

Chronic urticaria (CU) is a common skin disease characterized by repetitive wheals and pruritus with or without angioedema for at least 6 weeks.¹ Although CU is considered to be a non-serious and self-limiting disease, its unpredictable and long-term nature means that it has a substantial impact on quality of life and results in impaired productivity in terms of work or daily activity.²⁻⁶

Recent international guidelines recommend non-sedating, second-generation H₁-antihistamines as a first-line treatment for patients with CU.^{1,7,8} However, over 50% of patients remain symptomatic even with H₁-antihistamine treatment at approved doses.^{2,9} An increase in H₁-antihistamine dose has long been proposed as an effective treatment for CU patients whose symptoms are not controlled at an approved dose.^{1,8,10-12} This approach is supported by a recent meta-analysis, which showed that 63.2% of patients with chronic spontaneous urticaria (CSU) who were not responsive to standard doses, improved following up-dosing of antihistamines. However, although H₁-antihistamine up-dosing improved pruritus, it did not affect the number of wheals in these patients.⁹

In general, higher urticaria activity has a greater negative impact on quality of life, work performance, and healthcare resource use. According to the worldwide antihistamine-refractory CU patient evaluation study, patients with H₁-antihistamine-refractory CSU had high rates of angioedema and comorbid chronic inducible urticaria, leading to further impairment of quality of life.¹³ The burden of CSU was found to be substantial, with productivity impairment due to CSU being 27% and the rate of emergency department visit and hospitalization for CSU being 14.4% and 8.2%, respectively.¹⁴

Therefore, unmet clinical needs remain in patients with H₁-antihistamine-refractory CU and the addition of leukotriene receptor antagonists (LTRAs), immunomodulating agents (such as omalizumab, cyclosporine, dapsone, and methotrexate), and phototherapy has been evaluated and included in guidelines for the treatment of this patient group.^{1,7,8,15,16}

The objective of the present guideline was to focus on recommendations for the effective and safe treatment of Korean patients with H₁-antihistamine-refractory CU, based on a systematic review of the literature.

OMALIZUMAB

Background

Omalizumab is a humanized monoclonal antibody to immunoglobulin E (IgE) that plays an important role in the pathogenesis of urticaria. It binds to the Cε3 domain in the heavy chain of IgE and inhibits the binding of IgE to FcεRI on the surface of mast cells and basophils, leading to a decrease in FcεRI receptors on these cells.¹⁷ The efficacy and safety of omalizumab in the treatment of CU has been demonstrated in many studies to date.^{1,17-24} Omalizumab received US Food and Drug Administration approval as an add-on therapy for H₁-antihistamine-refractory urticaria in 2014. In Korea, it was approved as an additional therapy in this patient group by the Ministry of Food and Drug Safety in 2017, based on the results of 1 randomized controlled trial (RCT) conducted in Korea and Japan.¹⁸

In the 2013 revision and update of the EAACI/GA²LEN/EDF/WAO guidelines,¹² the addition of omalizumab, cyclosporine, or LTRA is recommended if a 4-fold increase in the dose of second-generation H₁-antihistamines is not effective. The 2014 US Joint Task Force on Practice Parameters guidelines first recommend a 4-fold increase in the dose of H₁-antihistamines, or the addition of H₂-antihistamines, LTRAs, and/or first-generation H₁-antihistamines if a standard dose of H₁-antihistamine is not effective. In addition, the introduction of omalizumab, cyclosporine, and other anti-inflammatory agents or immunomodulators is recommended if there is still no response. The joint guidelines for the management of CU, published by the European and US academic association in 2018, have recently been revised to first recommend omalizumab in patients with uncontrolled CU, despite a 4-fold increase in the dose of H₁-antihistamines.¹ However, there are still insufficient data on the efficacy of omalizumab in patients with CSU in Korea, and omalizumab treatment remains limited due to the high cost.

Therefore, a systematic literature review has been conducted to determine the therapeutic effects of omalizumab in patients with CSU who do not respond to H₁-antihistamines, and we have attempted to provide recommendations for 2 clinical questions.

Question 1. Is omalizumab useful in patients unresponsive to H₁-antihistamines?

Recommendation 1

We recommend omalizumab for patients with CSU that do not respond to H₁-antihistamines (strong recommendation, moderate quality of evidence).

Summary of evidence

We identified 2,031 potentially relevant studies, of which 1,297 were reviewed after excluding duplicates and 985 were excluded following review of information provided in the title and abstract of the publications. After excluding case series with <10 subjects; systematic reviews or meta-analyses; *post hoc* analysis of existing randomized, placebo-controlled clinical trials; and articles not related to the treatment effects of omalizumab for CSU or those for which pre- and post-treatment response cannot be evaluated, 34 full-text articles were assessed: 8 RCTs¹⁷⁻²⁴ for Recommendation 1 and 26 observational studies²⁵⁻⁵⁰ for Recommendation 2 (**Fig. 1**).

A meta-analysis was conducted using data from the 8 RCTs to derive Recommendation 1.^{1,17-24} These studies administered omalizumab or a placebo as an additional treatment while maintaining the initial antihistamine treatment initiated prior to randomization. The results of the meta-analysis showed significant improvement in urticaria as assessed by the urticaria activity score over 7 days (UAS7, which includes itch severity and hive count), compared with placebo in patients with H₁-antihistamine-refractory CSU after receiving omalizumab (mean difference, -7.87; 95% confidence interval [CI], -9.99, -5.75; $P < 0.001$; $I^2 = 68\%$; **Fig. 2**). In addition, significant improvement was observed with 300 mg compared with 150 mg omalizumab treatment, showing a dose-response relationship (mean difference, -4.54; 95% CI, -6.72, -2.35; $P < 0.001$; $I^2 = 0\%$; **Fig. 3A**).

Previous studies were primarily conducted in Western populations, with only one RCT conducted in Asian patients (Japanese and Korean).¹⁸ Therefore, additional analysis was conducted to determine whether the dose-dependent treatment effects observed in Western populations remained valid in Asian populations. The Asian population also showed a significant improvement when treated with omalizumab 300 mg compared with 150 mg (mean difference, -3.65; 95% CI, -7.16, -0.14; $P = 0.04$; $I^2 =$ not applicable; **Fig. 3B**). However,

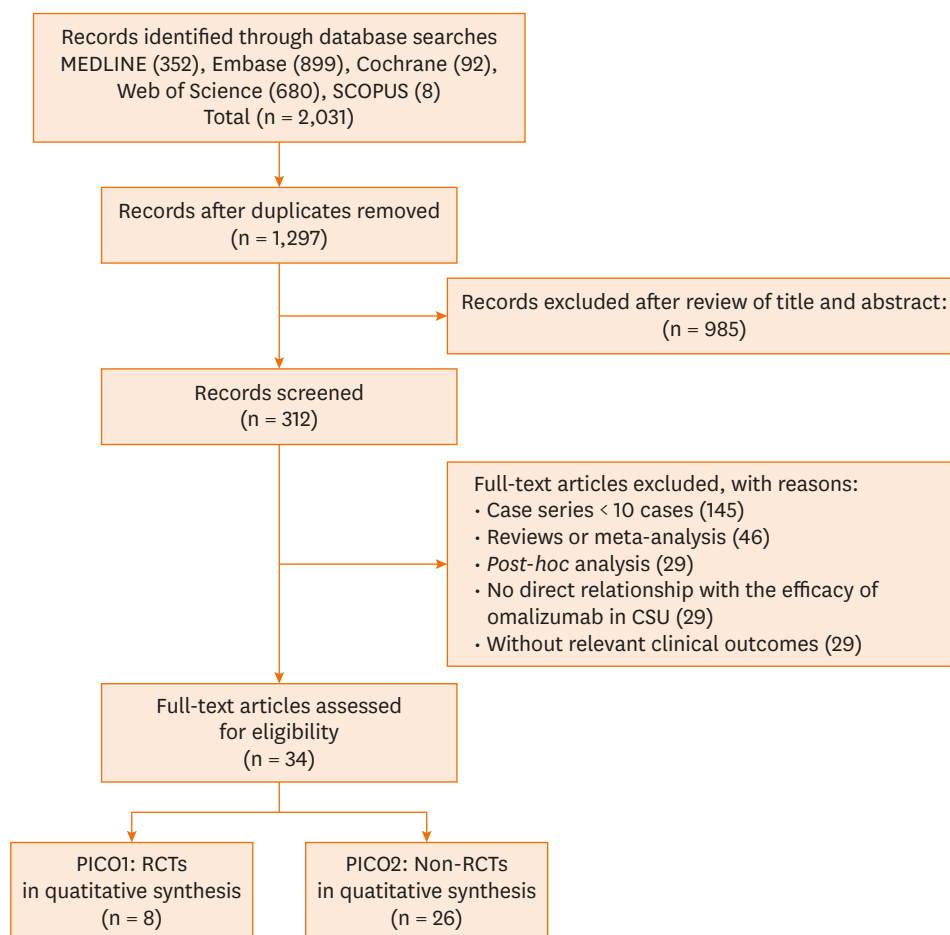


Fig. 1. Process of literature search relating to omalizumab treatment in patients with CSU. CSU, chronic spontaneous urticaria; RCT, randomized controlled trial.

the gap was smaller than that observed in the Western population (mean difference, -5.10 ; 95% CI, $-7.89, -2.31$; $P < 0.001$; $I^2 = 0\%$) and the clinical significance of this finding is unclear. Therefore, further research is necessary as only a small number of studies were included in the comparative analysis of dose versus treatment effect in Western and Asian populations. However, the risk of bias was assessed as low for most items, with the exception of 'other bias,' as most of the studies included in the meta-analysis were sponsored by pharmaceutical companies associated with omalizumab (**Fig. 4**).

Remark

In light of the evidence from the meta-analysis of 8 RCTs showing that omalizumab significantly improved urticaria in patients with H_1 -antihistamine-refractory CSU compared with placebo, the committee determined a strong recommendation for add-on therapy with omalizumab in patients with H_1 -antihistamine-refractory CSU. However, further research is required to determine the most appropriate dose for Asian patients because the cost of omalizumab is relatively high and the application for health insurance coverage is in progress. In addition, in the 2018 joint European and US Guideline on Urticaria Treatment, omalizumab is recommended over cyclosporine for the treatment of CSU unresponsive to H_1 -antihistamines, based on its superior safety profile in comparison with cyclosporine.¹

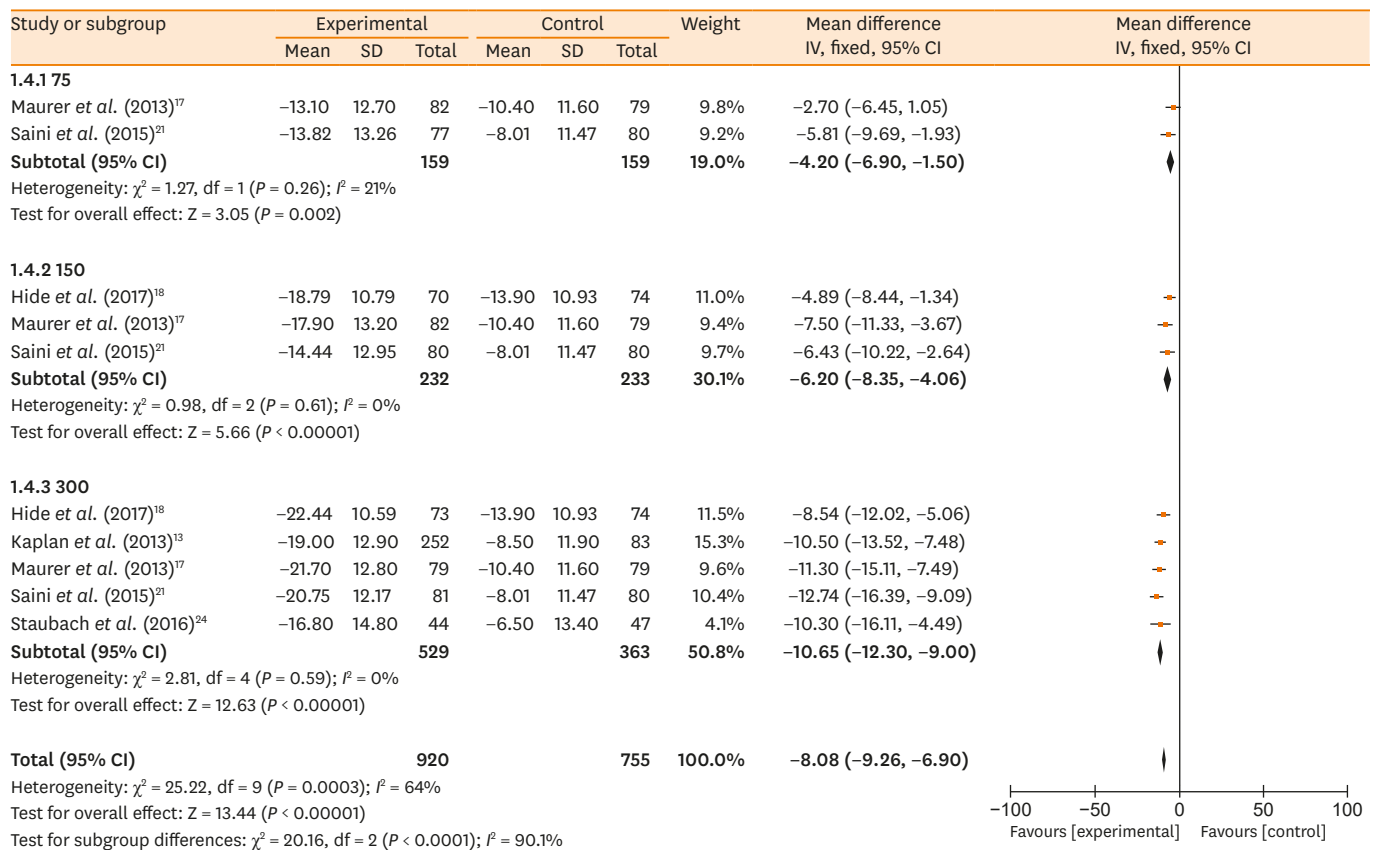


Fig. 2. Meta-analysis of UAS7 of 8 RCTs in comparison with UAS7 changes after omalizumab (75, 150, and 300 mg) and placebo in patients with CSU. UAS7, urticaria activity score 7; RCT, randomized controlled trial; CSU, chronic spontaneous urticaria; SD, standard deviation; CI, confidence interval.

However, it is important to consider that no study has directly compared cyclosporine and omalizumab in terms of safety, efficacy, and economic feasibility.

Question 2. Is omalizumab useful as an add-on therapy in patients unresponsive to H₁-antihistamines and other immunomodulators?

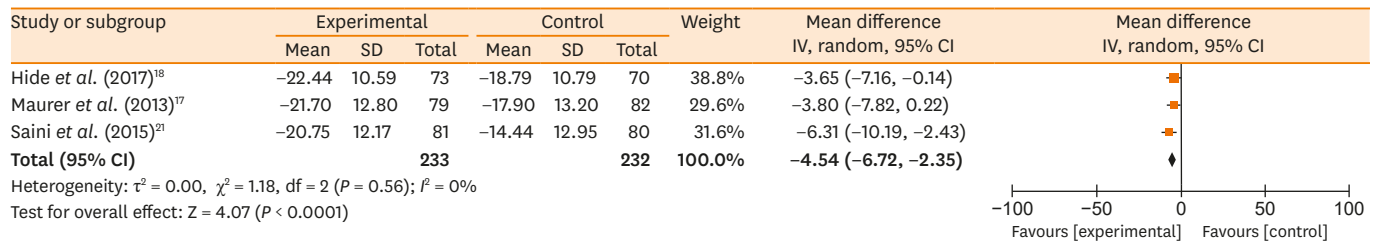
Recommendation 2

We suggest that an additional treatment with omalizumab should be considered for patients with CU that is not controlled with H₁-antihistamines and immunomodulators (conditional recommendation, very low quality of evidence).

Summary of evidence

A total of 26 studies (10 prospective observational studies²⁵⁻³⁴ and 16 retrospective observational studies³⁵⁻⁵⁰) were analyzed for the evidence of treatment response rates in patients with H₁-antihistamine-refractory CU that is not controlled by increasing the antihistamine dose or by treatment with immunomodulators, such as cyclosporine. The number of subjects ranged from 12 to 110, qualifying most as small-scale studies, and some included patients with chronic inducible urticaria, including cholinergic urticaria. The treatment response after the addition of omalizumab in CU patients with uncontrolled symptoms (despite an increased dose or combined use of antihistamines, or use of immunomodulators, such as cyclosporine, dapsone, methotrexate, and hydroxychloroquine)

A



B

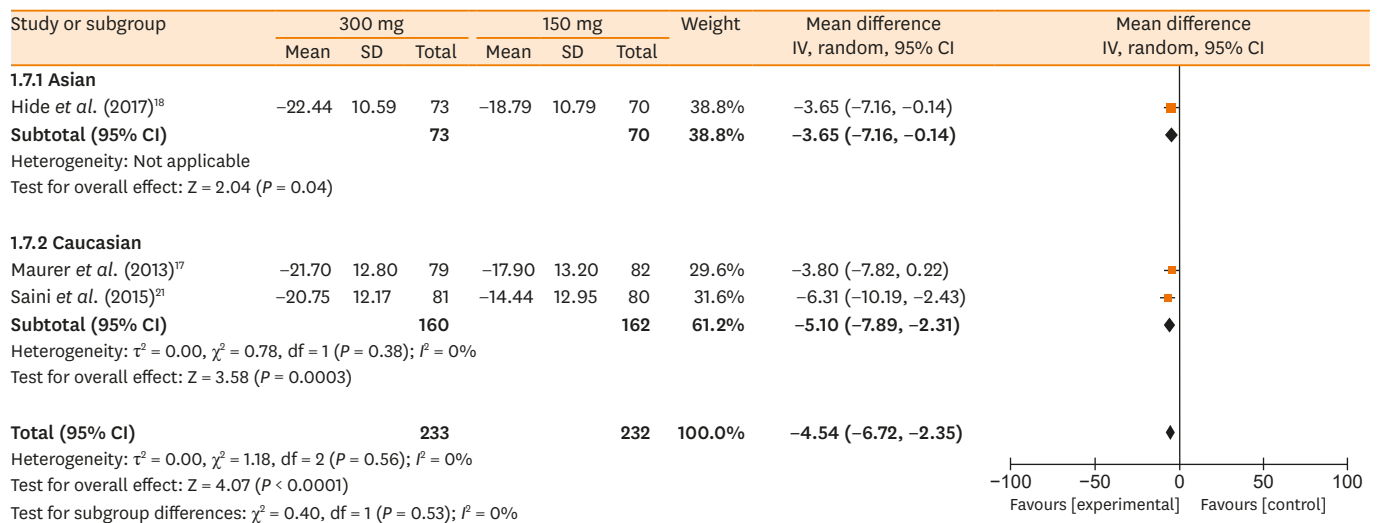


Fig. 3. (A) Meta-analysis of UAS7 of RCTs in comparison with UAS7 changes after treatment with 150 and 300 mg omalizumab. (B) Meta-analysis of UAS7 in comparison with UAS7 changes following 150 and 300 mg omalizumab treatment in Caucasian and Asian populations. UAS7, urticaria activity score 7; RCT, randomized controlled trial; SD, standard deviation; CI, confidence interval.

was defined as the percentage of patients who showed symptom improvement. Among the studies describing omalizumab dose-dependent treatment effect, 5 used 150 mg,^{33,38,40,45,49} 11 used 300 mg,^{25,27-32,35,36,39,40} and 9 were observational studies that included dose adjustments by increasing the dose from 150 to 300 mg when symptoms were uncontrolled or by decreasing the dose or increasing the administration interval if the condition was well controlled.^{26,34,37,41-44,46,47}

The results of the meta-analysis showed that the addition of omalizumab in patients with CU who did not respond to H₁-antihistamines and immunomodulators was associated with significant improvement in terms of treatment response rates (risk ratio, 54.39; 95% CI, 30.94, 95.59; $P < 0.001$, $I^2 = 0\%$). In addition, dose-dependent treatment response rates for omalizumab were analyzed. All comparisons showed significant increases in the percentage of patients showing improvement with the addition of omalizumab, with a risk ratio of 47.11 (95% CI, 13.64, 162.73; $I^2 = 0\%$, $P < 0.001$) in a comparative study of 150 mg; 53.00 (95% CI, 23.09, 121.63; $I^2 = 0\%$; $P < 0.001$) in a comparative study of 300 mg; and 53.89 (95% CI, 21.51, 135.01; $I^2 = 0\%$; $P < 0.001$) in a dose-modifying study. However, the level of evidence was evaluated as being very low due to several limitations: 1) All of the studies were observational and compared before and after treatment without intervention with other treatments in addition to omalizumab; 2) The results were assessed by confirming the percentage of patients who showed complete or partial response to omalizumab treatment without an

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Hide <i>et al.</i> (2017) ¹⁸	+	+	+	+	+	+	-
Kaplan <i>et al.</i> (2013) ¹³	+	+	+	+	+	+	-
Maurer <i>et al.</i> (2011) ²	+	+	+	+	+	+	-
Maurer <i>et al.</i> (2013) ¹⁷	+	+	+	+	+	+	-
Metz <i>et al.</i> (2017) ²⁰	?	?	+	+	+	+	-
Saini <i>et al.</i> (2011) ²²	+	+	+	+	+	+	-
Saini <i>et al.</i> (2015) ²¹	+	+	+	+	+	+	-
Staubach <i>et al.</i> (2016) ²⁴	+	+	+	+	+	+	-

Fig. 4. Risk of bias summary for each included study as determined by the Cochrane Collaboration's tool for assessing risk of bias.

objective tool for assessing the treatment response; 3) Some studies included patients with chronic inducible urticaria; 4) There were significant variations among individuals and studies in the duration of the observation period after treatment.

Remark

All of the RCTs evaluated for Recommendation 1 included patients who did not respond to standard doses of antihistamines. Considering the cost of omalizumab treatment in Korea, the addition of omalizumab is often concern in patients who do not respond to a 4-fold increase in antihistamine dose or whose symptoms persist despite additional treatment with immunomodulators (such as cyclosporine) in a clinical setting. Recommendation 2 was developed by analyzing 26 observational studies, which were likely to have been excluded from most meta-analyses due to qualitative problems. However, although omalizumab add-on has been shown to significantly increase treatment response rates in patients with CU who did not respond to antihistamines and immunomodulators, the committee concluded that this is a conditional recommendation due to various inherent limitations in the observational studies. Although they should be interpreted with caution, the results showed similar treatment response rates in patients maintained on 300 mg omalizumab and in those who received a modified dosage or administration interval, suggesting that appropriate doses and administration intervals need to be configured for individual patients. Further studies will be required to clarify these points.

CYCLOSPORINE

Background

Non-sedating H₁-antihistamines are recommended as a first-line treatment in patients with CSU. In patients with CSU not responding to the standard dose of H₁-antihistamines, up-dosing of these agents or a combination of different H₁-antihistamines can be helpful. However, there is a subset of patients who will remain unresponsive. Many studies have investigated immunomodulatory drugs as add-on therapies, and systematic analysis is required to determine the efficacy and safety profiles. Among various immunomodulatory drugs, cyclosporine has been most widely used for the treatment of H₁-antihistamine-refractory CSU. Cyclosporine is a calcineurin inhibitor that forms a complex with cyclophilins and inhibits the phosphorylation of nuclear factor of activated T cells and the subsequent transcription of IL-2. Cyclosporine inhibits the release of histamine from mast cells as well as the activation of T cells.^{51,52} In the present guideline, the committee analyzed the relevant evidence and aimed to provide a recommendation on the use of cyclosporine as an add-on therapy.

Question. Is cyclosporine useful as an add-on therapy in patients unresponsive to high doses of H₁-antihistamines or a combination of different H₁-antihistamines?

Recommendation

We suggest that cyclosporine be used as an add-on therapy in patients unresponsive to high doses of H₁-antihistamines or a combination of different H₁-antihistamines (conditional recommendation, low quality of evidence).

Summary of evidence

A search for RCTs that examined the efficacy and safety of cyclosporine treatment in addition to background therapy with antihistamine in patients with CSU unresponsive to antihistamine treatment identified 2 RCTs.^{53,54} However, these trials employed different efficacy measures, which precluded the use of a meta-analysis. Eight open-label prospective or retrospective studies that investigated the efficacy of cyclosporine in CSU⁵⁵⁻⁶² were excluded, as the question focuses on cyclosporine as an add-on therapy to H₁-antihistamines.

Grattan *et al.*⁵³ evaluated the efficacy of cyclosporine as an add-on therapy in 30 patients with CSU who responded poorly to antihistamines and showed a positive autologous serum skin test (ASST). Patients were randomized to cyclosporine 4 mg/kg/day (20 subjects) or placebo (10 subjects) for 4 weeks in addition to cetirizine 20 mg daily. A positive response (defined as a reduction to <25% of baseline UAS7) was significantly more common in the cyclosporine group (40%, 8 subjects) than in the placebo arm (0%) at 4 weeks. Non-responders from the cyclosporine and placebo arms received an additional open-label cyclosporine treatment; after 4 weeks, a positive response was seen in 57% and 70% of patients in each group, respectively. Side effects were common (96.7%) and included tingling sensation, gastrointestinal upset, and headache, but these were not sufficiently severe to require withdrawal from the study.

Vena *et al.*⁵⁴ assessed the response to cyclosporine treatment in 99 patients with persistent CSU during cetirizine treatment. In addition to background treatment with cetirizine 10 mg, patients received one of the 3 treatment regimens: cyclosporine for 16 weeks; cyclosporine for 8 weeks, followed by placebo for 8 weeks; or placebo for 16 weeks. Cyclosporine add-on therapy was associated with an 87% and 77.4% response rate in the 8-week and 16-

week treatment groups, respectively. Urticaria severity score (assessed by the Breneman scale) and dermatology life quality index at week 8 and 16 were significantly improved in both cyclosporine-treated groups compared with the placebo arm. Adverse events were experienced by 68.8% of cyclosporine-treated patients and 45.7% of placebo-treated patients. Although adverse events were common, only 6% of cyclosporine-treated patients discontinued the study as a result, including 2 patients (3%) with hypertension.

Remark

Cyclosporine has been widely used for the treatment of various skin disorders, such as atopic dermatitis and psoriasis, and can be effectively used for the treatment of CSU due to its action on mast cells, basophils, B cells, and T cells.^{51,52,63} Korean National Health Insurance approves the reimbursement of cyclosporine treatment for patients with CSU refractory to conventional therapy and who are positive for autoimmune antibodies. The quality of evidence supporting cyclosporine as an add-on therapy is low, based on only 2 RCTs^{53,54} using different outcome measures and limited patient numbers. However, the committee decided to issue a conditional recommendation because of the significant efficacy and tolerable safety profile. Careful and regular monitoring of patients receiving cyclosporine is required to identify any potential adverse events.^{8,64,65} Based on a recent meta-analysis, when hypertension, renal impairment, and other severe uncontrolled adverse reactions of cyclosporine occur in patients with CSU, the discontinuation of cyclosporine should be considered.⁶³ In the 2018 revision and update of the EAACI/GA²LEN/EDF/WAO guidelines, cyclosporine is recommended for patients with severe disease refractory to H₁-antihistamines and omalizumab because it is not licensed for urticaria and has an inferior side effect profile to omalizumab.¹ According to a recent meta-analysis and systematic review, the rate of adverse events was dose-dependent, and the pooled response rates were not significantly different between low (2–4 mg/kg/day) and moderate (4–5 mg/kg/day) cyclosporine doses, suggesting that low-dose cyclosporine is associated with a significant improvement in clinical symptoms and relatively low risk of adverse events.⁶³ Further studies are warranted to determine the optimal dosage and duration of treatment with cyclosporine.

LTRAs

Background

Leukotriene is a powerful inflammatory mediator involved in the pathophysiology of CU,^{66,67} and LTRAs have been shown to be effective in patients with asthma and allergic rhinitis. LTRAs are often used in patients with CU, either as a single therapy or in combination with other first-line treatments such as H₁-antihistamines. However, the efficacy of this approach remains controversial.⁶⁸

Question. Are LTRAs useful as add-on therapy in patients unresponsive to standard-dose H₁-antihistamines?

Recommendation

We suggest limited use of add-on LTRAs in patients with CU who are not controlled with standard doses of H₁-antihistamines (conditional recommendation, low quality of evidence).

Summary of evidence

We conducted a systematic literature review to evaluate the effect of the addition of LTRAs in CU patients who did not respond to a standard dose of H₁-antihistamines. One RCT and 1 double-

blind crossover study were identified.^{66,67} In the RCT performed by Bagenstose *et al.*,⁶⁹ 95 patients (aged ≥ 12 years) with CU, whose condition was not controlled with 10 mg cetirizine for 1 week, were randomly assigned to receive 10 mg cetirizine for 3 weeks, with the addition of either 20 mg zafirlukast or placebo twice daily. The results showed a significant improvement in the patient visual analog scale (VAS; 0 = no urticaria, 100 = urticaria throughout the body surface) in the zafirlukast add-on group ($n = 48$) compared with the cetirizine alone group ($n = 47$; 34.1 ± 27.6 vs. 44.5 ± 24.1 , respectively). However, the effect was only observed in patients who were positive to the ASST, suggesting that the addition of LTRA was only beneficial to patients with chronic autoimmune urticaria that does not respond to H₁-antihistamines.

In a double-blind, crossover study of 24 adults with CSU who did not respond to H₁-antihistamines, Kosnik *et al.*⁷⁰ compared the effects of adding 10 mg montelukast or placebo to an existing H₁-antihistamine regimen for 2 weeks with a 1-week washout period. The results showed that the symptom score assessed by the UAS (0–84) did not differ between the 2 groups (29.8 ± 21.2 vs. 30.1 ± 20.1 , respectively), and the superiority of montelukast treatment relative to placebo was only observed in the 5 most severe patients. Meta-analysis showed that the change in the urticaria severity index, as measured by VAS, or the degree of swelling after the addition of LTRA in CSU patients who did not respond to H₁-antihistamines, did not show a significant improvement compared with the addition of placebo (standard mean difference, -6.25 ; 95% CI, $-12.94, 0.44$; $P = 0.07$; $I^2 = 47\%$).

Remark

Despite the limited number of studies and the low level of evidence, the therapeutic effects reported in the literature suggest that LTRA as add-on therapy in H₁-antihistamine-refractory CU patients does not lead to any significant improvement. Although some patients with chronic autoimmune urticaria or severe CU may benefit from the addition of LTRAs, the number of patients included in the study was small, making it difficult to estimate the effect. The committee has drawn up a conditional recommendation based on the current evidence, cost-effectiveness, and the likelihood of adverse drug events.

METHOTREXATE

Background

Methotrexate is an anti-metabolite that has immunomodulatory and anti-inflammatory effects.^{74,75} A few case series and case reports have shown the benefits of methotrexate in patients with CU.^{71,73} Methotrexate has been described as an alternative agent that should be considered only in patients with CU refractory to anti-inflammatory, immunomodulatory, and other safe alternative agents,⁸ and it is not generally recommended as an add-on treatment option.¹ Therefore the committee aimed to provide a recommendation for methotrexate as an add-on therapy for patients with CU unresponsive to H₁-antihistamines.

Question. Is methotrexate useful as an add-on therapy in patients unresponsive to high doses of H₁-antihistamines or a combination of different H₁-antihistamines?

Recommendation

We suggest the limited use of methotrexate as an add-on therapy in patients unresponsive to high doses of H₁-antihistamines or a combination of different H₁-antihistamines (conditional recommendation, very low quality of evidence).

Summary of evidence

Only 1 RCT was identified.⁷⁴ Sharma *et al.*⁷⁴ evaluated the efficacy and safety of methotrexate in 29 patients with CSU who did not show >50% reduction in UAS following antihistamine treatment. Patients were randomized to receive oral methotrexate 15 mg or placebo weekly for 12 weeks, in addition to cetirizine 5 mg daily. In comparison with baseline, symptom improvement at week 12 was significant in each group but comparable between the methotrexate and placebo groups, with no statistically significant difference between the 2 groups. Although no serious adverse events were reported, 1 patient treated with methotrexate was withdrawn from the study due to severe nausea and vomiting. Two patients treated with methotrexate showed an increase in transaminase levels, which normalized over time.

Remark

In a retrospective case series study, 87% of patients (7 of 8) with CSU unresponsive to antihistamines achieved complete response with methotrexate; the duration of treatment until response was 4.6 ± 1.6 weeks.⁷¹ However, 1 RCT revealed that methotrexate did not provide any additional benefit over placebo.⁷⁴ The quality of evidence supporting the use of methotrexate as an add-on therapy was very low, and it is unclear whether the use of methotrexate is beneficial as an add-on therapy due to the limited evidence. Considering common and potentially severe adverse events, such as gastrointestinal discomfort and hepatotoxicity, the scarce evidence supporting the use of methotrexate led to a conditional recommendation. The committee decided to suggest the limited use of methotrexate as add-on therapy in patients unresponsive to high doses of H₁-antihistamines or a combination of different H₁-antihistamines.

DAPSONE

Background

Dapsone (4,4'-diaminodiphenylsulfone) is a sulfone antibiotic with anti-inflammatory and immunomodulatory effects. Its mechanism of action involves the down-regulation of prostaglandins, leukotrienes, and proinflammatory cytokines; the inhibition of lysosomal enzymes and neutrophil myeloperoxidase; and the suppression of neutrophil adhesion, recruitment, and activation.^{8,75} Dapsone has been used for the treatment of various chronic skin disorders characterized by the accumulation of neutrophils and/or eosinophils.⁷⁵ Dapsone can be considered for patients with antihistamine-refractory CSU.⁸ However, in the recent EAACI/GA²LEN/EDF/WAO guidelines, dapsone is no longer recommended in the algorithm due to the lack of evidence.¹ Here, we have summarized the current evidence regarding the efficacy and safety of dapsone as an add-on therapy in antihistamine-refractory CSU, and attempted to provide a recommendation for this alternative drug.

Question. Is dapsone useful as an add-on therapy in patients unresponsive to high doses of H₁-antihistamines or a combination of different H₁-antihistamines?

Recommendation

We suggest the limited use of dapsone as add-on therapy in patients unresponsive to high doses of H₁-antihistamines or a combination of different H₁-antihistamines (conditional recommendation, low quality of evidence).

Summary of evidence

A search of the literature and eligibility assessment identified 2 RCTs.^{76,77} The differences

in study design between the 2 studies did not allow further meta-analysis. Morgan *et al.*⁷⁶ conducted a double-blind, placebo-controlled crossover study to examine the benefit of dapsons in 22 patients with antihistamine-refractory CSU. Patients unresponsive to high doses of H₁-antihistamines or a combination of multiple H₁-antihistamines were randomized to receive 100 mg dapsons daily or placebo for 6 weeks. At 6 weeks, dapsons treatment was associated with a significant improvement over baseline in urticaria score, itch score, VAS, and Skindex-29, while the placebo arm showed no improvement in these outcomes. Significant improvement in itch and VAS was found in dapsons-treated patients when compared with placebo-treated subjects after 6 weeks.⁷⁶

Engin *et al.*⁷⁷ carried out a randomized, non-blinded study to evaluate the efficacy of dapsons 50 mg daily in addition to desloratadine 10 mg daily *vs.* desloratadine alone in 65 CSU patients. After 3 months, both groups showed significant and similar improvement over baseline in UAS and VAS. However, 3 months after treatment cessation, patients treated with dapsons and desloratadine showed a significant reduction in UAS and VAS compared with those treated with desloratadine alone, suggesting that dapsons treatment is associated with prolonged remission.⁷⁷

No patients were withdrawn from the 2 RCTs due to adverse events related with dapsons.^{76,77} Morgan *et al.*⁷⁶ reported mild nausea, vaginal candidiasis, mild neuropathy, and a decline in hemoglobin level that recovered after dapsons discontinuation. Engin *et al.*⁷⁷ reported a 13% incidence of adverse events in patients treated with dapsons in addition to antihistamine, while no patients in the control group experienced adverse events.

Remark

Dapsons was reported to produce significant improvements in patients with refractory CSU.^{76,77} However, the quality of evidence supporting the use of dapsons as an add-on therapy for refractory CSU is low. While dapsons treatment was well tolerated in these studies,⁷⁶⁻⁷⁸ it is associated with side effects such as anemia, methemoglobinemia, hepatotoxicity, and potentially serious hypersensitivity syndrome.^{8,75} Regular monitoring of laboratory tests, including complete blood count and liver function test, is recommended. In addition, the pre-treatment determination of the glucose-6-phosphate dehydrogenase level is recommended,^{8,75} although the prevalence of glucose-6-phosphate dehydrogenase deficiency is relatively low in Korea.⁷⁹ Therefore, we suggest the limited use of dapsons as an add-on therapy in patients unresponsive to high doses of H₁-antihistamines or a combination of different H₁-antihistamines.

PHOTOTHERAPY

Background

Phototherapy is the use of light to treat diseases and mainly employs the ultraviolet (UV) spectra. Phototherapy has been widely used for the management of a variety of chronic inflammatory skin disorders, such as psoriasis and atopic dermatitis.⁸⁰ Phototherapy may be effective for CU and some cases of physical urticaria.^{8,81-87} In the latest EAACI/GA²LEN/EDF/WAO guidelines, there is no recommendation regarding the use of phototherapy in the treatment of CU.¹ The mechanism of action for phototherapy in CU involves the reduced release of histamine and other proinflammatory mediators from mast cells, apoptosis of dermal mast cells, and the upregulation of anti-inflammatory IL-10.^{81,82}

The main modes of delivery reported for the treatment of CU are psoralen and UV-A (PUVA) photochemotherapy, and narrow-band UV-B (NBUVB). In Korea, PUVA phototherapy is not available due to a lack of the psoralen photosensitizer. Therefore, 311 nm NBUVB phototherapy is the main delivery mode in Korea. Systematic review is necessary to define the role of phototherapy as an add-on therapy in patients with H₁-antihistamine-refractory CU.

Question. Is phototherapy useful as an add-on therapy in patients unresponsive to H₁-antihistamines?

Recommendation

We suggest phototherapy (NBUVB) as add-on therapy in patients unresponsive to H₁-antihistamines (conditional recommendation, very low quality of evidence).

Summary of evidence

Only 1 RCT was identified that conformed to the PICO process.⁸⁵ Engin *et al.*⁸⁵ compared the efficacy of NBUVB in combination with H₁-antihistamine therapy *vs.* H₁-antihistamine treatment alone in 81 patients with CU. Patients were randomly allocated to receive NBUVB in addition to cetirizine 10 mg daily (n = 48) or H₁-antihistamine alone (n = 33). After 10 and 20 phototherapy treatment sessions, patients receiving NBUVB and antihistamine showed a significantly greater improvement in UAS than those receiving antihistamine alone, while both groups showed a significant improvement in UAS and VAS over baseline values. A significant improvement in VAS was maintained at 3 months post-treatment in the combination group when compared with the antihistamine alone group. Adverse events associated with phototherapy were transient erythema and pruritus, although these were not severe enough to require withdrawal from the study.⁸⁵

Remark

The quality of evidence supporting the use of phototherapy in antihistamine-refractory CU is very low due to the lack of well-designed, large-scale studies. NBUVB phototherapy has a more favorable long-term safety profile than PUVA photochemotherapy and no risk of gastrointestinal side effects from psoralen.⁸⁰ NBUVB phototherapy is a well-tolerated treatment modality that can be safely used in patients with systemic disorders, such as hepatic or renal diseases as well as pregnant women and children. NBUVB phototherapy can also be a useful approach for patients who are reluctant to agree to other systemic anti-inflammatory and immunomodulatory agents. It also has the additional benefit of increasing the production of vitamin D in deficient patients.

CONCLUSIONS

The prevalence of CU in Korea is comparable to that reported in other countries. However, many Korean doctors are still prescribing sedating H₁-antihistamines and systemic corticosteroids for the treatment of CU.⁸⁸ In addition, there is a considerable delay in referring patients with H₁-antihistamine-refractory CSU to specialists. Unnecessary evaluation and inadequate treatment in the real practice for patients with CU often result in increased medical cost and disease burden.

Based on growing evidence of the efficacy and safety of omalizumab in patients with CSU, we strongly recommend adding omalizumab to the treatment regimen of patients whose urticaria is refractory to H₁-antihistamines (**Table**). For other treatment options excluding omalizumab, there

Table. Summary of guidelines for the management of H₁-antihistamine-refractory chronic urticaria

PICO	Recommendation
Omalizumab	
1. Is omalizumab useful in patients unresponsive to H ₁ -antihistamines?	We recommend omalizumab for patients with CSU that does not respond to H ₁ -antihistamines (strong recommendation, moderate quality evidence).
2. Is omalizumab useful as an add-on therapy in patients unresponsive to H ₁ -antihistamines and other immunomodulators?	We suggest that additional treatment with omalizumab be considered for patients with CU that is not controlled with H ₁ -antihistamines and immunomodulators (strong recommendation, very low-quality evidence).
Cyclosporine	
1. Is cyclosporine useful as an add-on therapy in patients unresponsive to high doses of H ₁ -antihistamines or a combination of different H ₁ -antihistamines?	We suggest cyclosporine as an add-on therapy in patients unresponsive to high doses of H ₁ -antihistamines or combination of different H ₁ -antihistamines (conditional recommendation, low-quality evidence).
LTRAs	
1. Are LTRAs useful as an add-on therapy in patients unresponsive to standard dose H ₁ -antihistamines?	We suggest limited use of add-on of LTRAs in patients with CSU who are not controlled with standard dose H ₁ -antihistamines (conditional recommendation, low-quality evidence).
Methotrexate	
1. Is methotrexate useful as add-on therapy in patients unresponsive to high doses of H ₁ -antihistamines or a combination of different H ₁ -antihistamines?	We suggest the limited use of methotrexate as an add-on therapy in patients unresponsive to high doses of H ₁ -antihistamines or a combination of different H ₁ -antihistamines (conditional recommendation, very low-quality evidence).
Dapsone	
1. Is dapsone useful as add-on therapy in patients unresponsive to high doses of H ₁ -antihistamines or a combination of different H ₁ -antihistamines?	We suggest the limited use of dapsone as an add-on therapy in patients unresponsive to high doses of H ₁ -antihistamines or a combination of different H ₁ -antihistamines (conditional recommendation, low-quality evidence).
Phototherapy	
1. Is phototherapy useful as add-on therapy in patients unresponsive to H ₁ -antihistamines?	We suggest phototherapy (NBUVB) as an add-on therapy in patients unresponsive to H ₁ -antihistamines (conditional recommendation, very low-quality evidence).

CSU, chronic spontaneous urticaria; CU, chronic urticaria; LTRA, leukotriene receptor antagonist; NBUVB, narrow-band ultraviolet-B.

have been only a few clinical trials conducted on patients with CSU, while most of observational studies recruited CU patients without clear exclusion of patients with inducible urticaria. Thus, with little evidence of clinical efficacy and potential harms, we can recommend cyclosporine as an add-on therapy or limited use of other immunomodulators (including methotrexate and dapsone) in patients unresponsive to high doses of H₁-antihistamines or a combination of different H₁-antihistamines. Although there is very little evidence to support the efficacy of LTRAs and phototherapy, these approaches are recommended for limited use in H₁-antihistamine-refractory CU patients due to the good safety and tolerability profile (Fig. 5).

For each drug used in the treatment of patients with CU, the therapeutic effects and adverse reactions may vary depending on ethnic variations, comorbidities, concomitant medications, and the healthcare systems of each country. As the treatment guideline presented here is

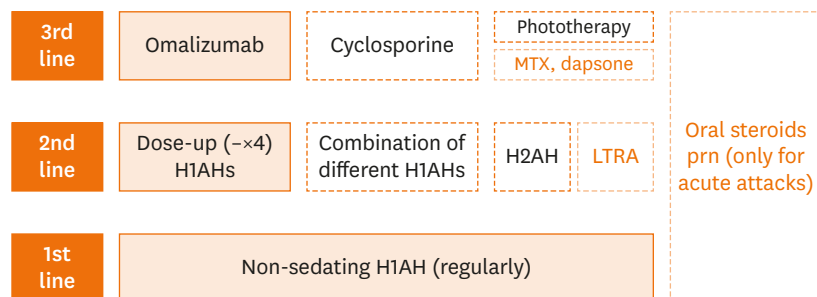


Fig. 5. Stepwise treatment for CSU patients. Solid lines indicate strong recommendations, and broken lines are conditional recommendations. The pale boxes are conditional and against current recommendations. CSU, chronic spontaneous urticaria; H₁AH, H₁-antihistamines; H₂AH, H₂-antihistamines; LTRA, leukotriene receptor antagonist; MTX, methotrexate.

based primarily on studies conducted in countries other than Korea, it will be important to promote further evaluation among Korean populations in order to determine any variations in therapeutic efficacy and safety. The efficacy of treatment may also vary according to phenotypes of CU, for example, CSU vs chronic autoimmune urticaria vs chronic inducible urticaria. Further studies comparing therapeutic efficacy in various phenotypes of CU are necessary. Therefore, the recommendations issued in this guideline should be updated regularly as new evidence emerges.

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