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Review

The KAAACI/KDA Evidence-Based Practice Guidelines for Chronic Spontaneous Urticaria in Korean Adults and Children: Part 1. Definition, Methodology and First-line Management

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ABSTRACT

Chronic spontaneous urticaria (CSU) is defined as the occurrence of spontaneous wheals, angioedema, or both for >6 weeks in the absence of specific causes. It is a common condition associated with substantial disease burden both for affected individuals and societies in many countries, including Korea. CSU frequently persists for several years and requires high-intensity treatment; therefore, patients experience deteriorations in quality of life and medication-associated complications. During the last decade, there have been major advances in the pharmacological treatment of CSU and there is an outstanding need for evidence-based guidelines that reflect clinical practice in Korea. The guidelines reported here represent a joint initiative of the Korean Academy of Asthma, Allergy and Clinical Immunology and the Korean Dermatological Association, and aim to provide evidence-based guidance for the management of CSU in Korean adults and children. In Part 1, disease definition, guideline scope and development methodology as well as evidence-based recommendations on the use of antihistamines and corticosteroids are summarized.

Keywords: Urticaria; guideline; disease management; therapeutics

INTRODUCTION

Urticaria is a common disease characterized by the sudden, unpredictable appearance of wheals, angioedema, or both. There are several subtypes of urticaria defined according to duration, triggers, and associated symptoms and signs. Chronic spontaneous urticaria (CSU) is a major disabling condition that is prevalent in the community and frequently

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persists for longer than 1 year, often requiring high-intensity treatment. The clinical practice guidelines reported here aim to address major clinical questions regarding the treatment of CSU in Korean adults and children. The guidelines reported here consist of 2 parts: Part 1 covers disease definition, guideline scope and methodology as well as evidence-based recommendations on the use of antihistamines and corticosteroids; Part 2 addresses treatment options for CSU patients who are refractory to first-line treatments. The guidelines are a joint initiative of the Korean Academy of Asthma, Allergy and Clinical Immunology (KAAACI) and the Korean Dermatological Association (KDA).

Definition

Chronic urticaria (CU) is defined as the occurrence of wheals, angioedema, or both for >6 weeks in both adults and children. Chronic urticaria can be divided into CSU and chronic inducible urticaria depending on specific eliciting factors. This guideline focuses on the treatment of CSU.

Epidemiology of CSU in Korea

Approximately 10%–20% of people experience urticaria at some stage in their lives.[1] The global prevalence of CSU is reported to range between 0.02% and 5.0%.[1-4] In the studies of Korean populations, the prevalence was seen to be 0.16%–2.3%, and it tends to increase each year.[5-9] The 10-year cumulative incidence rate of urticaria was calculated as 4.9% and that of chronic urticaria among patients with new-onset urticaria was 7.8% in the National Health Insurance Service-National Sample Cohort (NHIS-NSC) data in Korea.[10] In a recent analysis of the Korean Health Insurance Review and Assessment Service (HIRA) database, the median duration of CU was 591 days, and 61.9% of patients had urticaria symptoms that lasted for at least 1 year.[7] In adults with CSU, the remission rate (defined as no hospital visit with a diagnosis of urticaria for at least 1 year) was 21.5% at 1 year, but it was only 44.6% even after 5 years of follow-up.[11] In Korean children with CU, the mean duration to remission was 10.2 months and the remission rate at 24 months was 71.2%.[12]

Risk factors for CSU are largely unknown. In Korean nationwide population-based retrospective cohort studies using the Korean NHIS-NSC, CSU was positively associated with autoimmune thyroid diseases or obesity.[13,14] In a urban regional population study in Korea, the risk of chronic continuous urticaria was associated with living in a new residence and belonging to a family with high income.[8]

Although CSU is not a fatal condition, it restricts and disrupts many facets of patients' lives. Individuals commonly experience a serious deterioration in quality of life (QoL) due to severe itching, unpredictable occurrence and aggravation of symptoms, anxiety, fatigue, sleep disturbances, cosmetic problems, and the side effects of medication.[15-21] According to a Korean multicenter study, urticarial activity, dermographism, and emotional stress were strongly associated with QoL impairment.[16] It is commonly elicited by physical factors such as pressure or cold.[22] Psychiatric morbidity is also common in patients with CSU, such as obsessive-compulsive disorder or depression.[23] Due to the significant impact on daily life and activity, the socioeconomic burden of urticaria is also estimated to be substantial,[24] although there has been no direct estimation of the socioeconomic burden of CSU in Korea to date. In other countries, CSU has been associated with a significant reduction in work productivity and increased direct economic loss.[25]

Unmet patient needs in Korea

In our recent questionnaire-based survey of 100 Korean patients with CSU (unpublished data), treatment and diagnosis were the main reasons for medical consultations (93% and

53%, respectively). Major unmet clinical needs were seen to be a lack of previous treatment efficacy (61%), medical costs (21%), and medication side effects (16%). Patients reported that the following outcomes are important in treatment decision-making: better control of itching (76%), better control of wheals (62%), improvement of QoL (48%), fewer side effects (32%), and lower medical costs (29%).

Scope of the guidelines

These guidelines aim to provide evidence-based guidance for the management of CSU in Korean adults and children. The target audience is specialists (allergists and dermatologists) and primary care doctors who manage patients with CSU. Pharmacological and non-pharmacological treatment options are covered, while the diagnostic approach of CU, or treatment of other types of urticaria (acute urticaria or chronic inducible urticaria) is beyond the scope of the present guidelines.

How to use the guidelines

The present guidelines aim to provide the basis for rational, informed decision-making for patients, clinicians, and other healthcare professionals. The recommendations should not be viewed as dictates but rather as guidance for typical patients. They are not intended to address unique individual conditions.

METHODS

The guideline development committee consisted of clinicians from a range of specialties (allergy, dermatology, pediatrics, and family medicine) and clinical settings (referral hospitals and primary clinics). A methodology specialist (H.J.K.) coordinated and guided the committee members throughout the process of guideline development, including literature search, systematic review, evidence synthesis, and generation of recommendations. Methodological robustness was ensured according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach.[26] Committee members participated in discussions and arrived at a consensus to formulate key clinical questions to be addressed in the guidelines. They also participated in literature searches, data extraction, evidence synthesis, and formulating recommendations. All members were required to disclose any potential conflicts of interest. The population, intervention, comparison, and outcomes (PICO) format was used to construct the questions. Treatment efficacy (control of urticarial activity and improvement of QoL) and safety (drug side effects) were considered as important outcomes in decision-making.

Literature search

PubMed MEDLINE, Embase, Cochrane Central Register of Controlled Trials, Scopus, Web of Science, and KoreaMed databases were searched for relevant articles for each PICO question from inception until July 2017. Manual searches were performed for cross-referenced articles. Also, unpublished randomized controlled trials (RCTs) were retrieved from the ClinicalTrials.gov database. There were no language restrictions.

Study selection

Study eligibility was assessed using predefined criteria for each PICO question. Common eligibility criteria for inclusion were: 1) a population with CSU, 2) intervention (or investigation) and/or comparison relevant to each PICO question, and 3) outcomes related to

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urticaria. RCTs were considered as the primary source of evidence. However, where no RCTs were available, non-randomized trials were also considered. The eligibility of the retrieved studies was determined by at least 2 independent reviewers per PICO question, according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Briefly, the titles and abstracts of the retrieved studies were screened, and the full text was reviewed for potentially relevant papers. Reasons for exclusion were specified. Disagreements among reviewers were resolved by discussion and consensus within the committee.

Assessment of the risk of bias

The risk of bias was assessed using the Cochrane Collaboration's risk of bias tool for RCTs and the Risk of Bias in Non-randomized Studies (ROBINS-I) tool for non-randomized trials. Disagreements among reviewers were resolved by discussion and consensus within the committee.

Evidence synthesis

Data regarding baseline characteristics and core outcomes of each PICO question were extracted for analysis. The Mantel-Haenszel method or the inverse variance method with a random effects model was used to summarize treatment efficacy and safety. The meta-analysis was performed using RevMan software version 5.3 (Nordic Cochrane Centre, Copenhagen, Denmark) and Stata software version 13.1 (StataCorp LLC, College Station, TX, USA).

Grading the quality of evidence and strength of recommendations

The quality of evidence was rated for the important outcomes in each PICO question according to the GRADE approach.[26] Briefly, the evidence supported by RCTs was considered to be high quality, while that of observational studies was considered to be low quality. Five factors were considered to possibly down-grade the study (risk of bias, inconsistency, indirectness, imprecision, and publication bias), and 3 factors were considered to possibly up-grade the study (large effects, dose response, and all plausible residual confounders). The classification of evidence quality is shown in **Table 1**.

The committee members determined the direction and strength of recommendations based on the following considerations: balance of benefits and undesirable consequences of intervention, quality of evidence, patient values and preferences, and feasibility. Briefly, 1 of the 2 grades (strong or conditional) was assigned to describe the strength of recommendations. We used the words “we recommend” for strong recommendations and “we suggest” for conditional recommendations. The criterion for a strong recommendation was evidence that the desirable effects clearly outweighed the undesirable effects (or *vice versa*). The criterion for a conditional recommendation was evidence that the desirable effects likely or slightly outweighed the undesirable effects. **Table 2** shows the suggested interpretation of the strength of recommendations.

Table 1. Classification of evidence quality[27]

Quality of evidence	Definition
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
Very low	We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of the effect.

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Table 2. Interpretation of the strength of recommendations

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

The recommendations were first generated by the committee and then sent for a public hearing, where an agreement on the criteria was more than 70% of votes in favor. If no agreement was reached, the PICO question was further discussed by the committee for possible adjustment of the recommendation.

KEY QUESTIONS

The following 13 clinical questions were addressed by the systematic literature review and evidence-to-decision frameworks according to the GRADE approach. All recommendations in Part 1 are summarized in **Table 3** and **Figure**.

H1AH as the first-line therapy for CSU

Regimen	Recommendation (evidence level)
· **Non-sedating H1AH** (than sedating H1AH)	· **Strong (moderate)**
· **Up-dosing H1AHs up to 4-fold** (if not improved with standard dose H1AH)	· **Strong (low)**
· Combination of H1AHs (if not improved with standard dose H1AH)	· Conditional (very low)
· Regular use of H1AHs (than as needed use)	· Conditional (very low)

Add-on therapy (if not improved by H1AHs)

Drugs	Recommendation (evidence level)
· **Omalizumab**	· **Strong (moderate)**
· Cyclosporine	· Conditional (low)
· H2AHs	· Conditional (low)
· LTRAs	· Conditional, *against* (low)
· Dapsone	· Conditional, *against* (low)
· Methotrexate	· Conditional, *against* (very low)
· Phototherapy	· Conditional (very low)
· **Systemic corticosteroids**	· **Strong, *against* (very low)**

Figure. Treatment recommendations and evidence levels in the present guidelines for chronic spontaneous urticaria. Strong recommendations are highlighted in bold. Recommendations against the use are marked in italic and underlined.
CSU, chronic spontaneous urticaria; H1AHs, H_1-antihistamines; H2AHs, H_2-antihistamines; LTRA, leukotriene receptor antagonists.

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Table 3. Summary of recommendations in the present guidelines – Part 1. Antihistamines and corticosteroids

PICO	Recommendation
H_1-antihistamines	
1. Are non-sedating H_1-antihistamines to be preferred over sedating H_1-antihistamines as a first-line treatment of CSU?	We recommend non-sedating H_1-antihistamines as a first-line treatment in adults and children with CSU (strong recommendation, moderate quality evidence).
2. If there is no improvement following a standard dose of H_1-antihistamines, should the dose of H_1-antihistamines be increased?	We recommend up-dosing H_1-antihistamines up to 4-fold in patients with CSU not responding to a standard dose of non-sedating H_1-antihistamines (strong recommendation, low quality evidence).
3. If there is no improvement following a standard dose of H_1-antihistamines, should a combination of different H_1-antihistamines be used?	We suggest a combination of different H_1-antihistamines in patients with CSU not responding to a standard dose of non-sedating H_1-antihistamines (conditional recommendation, very low-quality evidence).
4. Should H_1-antihistamines be taken regularly or as needed?	We suggest non-sedating H_1-antihistamines be taken regularly by patients with CSU (conditional recommendation, very low-quality evidence).
H_2-antihistamines	
1. Are H_2-antihistamines useful as an add-on therapy in patients unresponsive to a standard dose of H_1-antihistamines?	We suggest a trial of H_2-antihistamines add-on therapy in patients not responding to a standard dose of H_1-antihistamines (conditional recommendation, low quality evidence).
Systemic corticosteroids	
1. Are systemic corticosteroids useful as an add-on therapy in patients unresponsive to H_1-antihistamines?	We do not recommend the routine use of systemic corticosteroids in patients not responding to H_1-antihistamines (strong recommendation, very low-quality evidence).

PICO, population, intervention, comparison, and outcomes; CSU, chronic spontaneous urticaria.

I. H_1-antihistamines
1. Are non-sedating H_1-antihistamines to be preferred over sedating H_1-antihistamines as a first-line treatment of CSU?
2. If there is no improvement after treatment with a standard dose of H_1-antihistamines, should the dose of H_1-antihistamines be increased?
3. If there is no improvement after treatment with a standard dose of H_1-antihistamines, should a combination of different H_1-antihistamines be used?
4. Should H_1-antihistamines be taken regularly or as needed?

II. H_2-antihistamines
1. Are H2-antihistamines useful as an add-on therapy in patients unresponsive to a standard dose of H_1-antihistamines?

III. Systemic corticosteroids
1. Are systemic corticosteroids useful as an add-on therapy in patients unresponsive to H_1-antihistamines?

IV. Leukotriene receptor antagonists
1. Are leukotriene receptor antagonists useful as an add-on therapy in patients unresponsive to a standard dose of H_1-antihistamines?

V. Omalizumab
1. Is omalizumab useful in patients unresponsive to H_1-antihistamines?
2. Is omalizumab useful as an add-on therapy in patients unresponsive to H_1-antihistamines and other immunosuppressants?

VI. Immunomodulators and others
1. Is cyclosporin useful as an add-on therapy in patients unresponsive to high dose H_1-antihistamines?
2. Is methotrexate useful as an add-on therapy in patients unresponsive to high dose H_1-antihistamines?
3. Is dapsone useful as an add-on therapy in patients unresponsive to high dose H_1-antihistamines?
4. Is phototherapy useful as an add-on therapy in patients unresponsive to high dose H_1-antihistamines?

I. H_1-antihistamines

Background

Urticaria is a mast cell-driven disease.[28,29] Histamine and other mediators released from activated mast cells lead to local sensory nerve activation, vasodilatation, extravasation, and

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inflammatory cell recruitment. The main features of urticaria, including itching and wheals, are mediated by histamine, and therefore H_1-antihistamines have been considered as the mainstay of treatment. Pharmacologically, they are inverse agonists with preferential affinity for inactive H_1histamine receptors, and H_1-antihistamines stabilize the receptors in this inactive status.[30] H_1-antihistamines have been available since the 1950s, and first-generation H_1-antihistamines have anticholinergic effects that may lead to undesirable side effects, such as rapid eye movement sleep disturbance, inattention, disorganized speech, or alterations in consciousness, which are more problematic in children and the elderly.[31] Second-generation H_1-antihistamines are largely free from anticholinergic side effects and are therefore generally considered in international guidelines to be the first choice for the management of CSU.[32] Generally, first generation H_1-antihistamines is referred to as sedating H_1-antihistamines and second generation H_1-antihistamines as non-sedating H_1-antihistamines.

However, some uncertainty and controversy remain over the use of H_1-antihistamines in the treatment of Korean patients with CSU, particularly in relation to drug selection, dose, and dosing intervals. According to a recent meta-analysis, the response rate to standard dose H_1-antihistamines in patients with CSU is only approximately 40%.[33] International practice guidelines[32] recommend up-dosing non-sedating H_1-antihistamines in patients who do not respond to a standard dose, and this is now also common practice in Korea. However, combining different H1-antihistamines is another common practice pattern in Korea and therefore the current guidelines include four major clinical questions regarding H_1-antihistamines drug selection, dosage, and regimen, which were considered to be important by the guideline committee members.

Question 1. Are non-sedating H_1-antihistamines to be preferred over sedating H_1-antihistamines as a first-line treatment of CSU?

- Recommendation 1: We recommend non-sedating H_1-antihistamines as a first-line treatment in adults and children with CSU (strong recommendation, moderate quality evidence).
- Summary of evidence: A total of 11 RCTs were identified.[34-44] In meta-analyses of urticarial activity outcomes, the efficacy of non-sedating H_1-antihistamines was slightly weaker, but not significantly different compared with sedating H_1-antihistamines (risk ratio [RR], 1.06; 95% confidence interval [95% CI], 0.99-1.13). However, adverse drug reactions were significantly less frequent with non-sedating H_1-antihistamines than with sedating H_1-antihistamines (RR, 0.53; 95% CI, 0.39–0.73). Common adverse events in the sedating H1-antihistamines treatment groups were somnolence, lethargy, fatigue, headache, nausea, dizziness, and dry mouth.
- Remark: Based on evidence regarding the safety profile of sedating H_1-antihistamines, the committee reached a consensus regarding a strong recommendation in favor of the use of non-sedating H_1-antihistamines over sedating H_1-antihistamines as the initial treatment of choice for patients with CSU. This view is in line with existing international guideline statements on the use of H_1-antihistamines in different allergic conditions.[31,32]

Question 2. If there is no improvement after treatment with a standard dose of non-sedating H_1-antihistamines, should the dose of H_1-antihistamines be increased?

- Recommendation 2: We recommend up-dosing non-sedating H_1-antihistamines up to 4-fold in patients with CSU not responding to a standard dose of H_1-antihistamines (strong recommendation, low quality evidence).
- Summary of evidence: Two RCTs,[45,46] were identified as directly relevant to the PICO

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question. In meta-analyses, 2-fold up-dosing of non-sedating H_1-antihistamines was seen to be significantly more effective in improving pruritus symptom scores compared with standard dose maintenance (standard mean difference [SMD], −3.30; 95% CI, −4.71 to −1.90). In an open label study of 21 patients poorly responsive to cetirizine 10 mg daily for 1 or 2 weeks, cetirizine 20 mg daily significantly improved urticarial activity scores for wheal, itch, duration, and total scores, compared with the 10 mg daily regimen.[45] In a double-blind, placebo-controlled cross-over trial of 20 patients refractory to conventional doses of second generation H_1-antihistamines (fexofenadine 60 mg twice daily), treatment with 120 mg fexofenadine twice daily significantly decreased pruritus visual analogue scale (VAS) scores and the urticaria severity index at 4 weeks.[46] None of these patients complained of fatigue or sleepiness in relation to the high dose treatment.[46]

In meta-analyses of clinical trials without placebo control (such as sequential dose escalation) or in trials without a strict requirement for refractoriness to previous standard dose H_1-antihistamines therapy in the patient selection criteria,[33] the beneficial effects of high dose non-sedating H_1-antihistamines (up to 2- or 4-fold) were also significant. The response rate to up-dosing in patients unresponsive to standard dose H_1-antihistamines was approximately 60%.[33]

Adverse effects increased with up-dosing of non-sedating H_1-antihistamines, although the findings were not consistent. Drowsiness was found in 20% of patients receiving cetirizine 20 mg daily, which disappeared after decreasing the dosage to 10 mg daily.[45] In a study involving 20 patients refractory to conventional doses of H_1-antihistamines, none of the patients receiving 240 mg fexofenadine per day complained of fatigue or sleepiness.[46] However, in a 4-week study comparing the efficacy and safety of different doses of rupatadine, somnolence was higher in the 20 mg rupatadine treatment group (21.43%) versus the lower intensity treatment groups (2.9% for placebo, 4.3% for 5 mg, and 5.4% for 10 mg rupatadine).[47]

- Remark: In terms of efficacy, current evidence suggests up-dosing (up to 2- or 4-fold) is likely to be helpful in many patients not responsive to the standard dose regimen. Meta-analyses showed that the response rate to standard dose H_1-antihistamines in patients with CSU is approximately 40%, whereas 60% of the unresponsive patients are likely to benefit from the up-dosing.[33] However, adverse reactions (such as somnolence) increase in a dose-dependent manner, and 4-fold up-dosing may be problematic in vulnerable populations, such as children or the elderly. Therefore, in terms of the balance of risk-benefit, 2-fold up-dosing may be suggested over 4-fold up-dosing. In patients tolerant to high dose H_1-antihistamines, a serial trial of 4-fold up-dosing may be considered. However, due to the relatively higher frequency of side effects, careful consideration of the risk-benefit balance is recommended when initiating 4-fold up-dosing therapy, particularly in children and the elderly.

Question 3. If there is no improvement following a standard dose of non-sedating H_1-antihistamines, should a combination of different H_1-antihistamines be used?

- Recommendation 3: We suggest a combination of different H_1-antihistamines in patients with CSU not responding to a standard dose of non-sedating H_1-antihistamines (conditional recommendation, very low-quality evidence).
- Summary of evidence: Only 1 study was identified. In a randomized study of 209 patients in China, a combination of mizolastine and ketotifen was superior to mizolastine alone in total efficacy rate (76.1% vs. 43.5%; $P < 0.05$) and recurrence rate (10.4% vs. 22.8%; $P < 0.05$) at 4 weeks. Adverse reactions were similar between the 2 treatment groups.[48]
- Remark: There is very little evidence of the efficacy and safety of a combination of

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different H_1-antihistamines in patients not responding to a standard dose of a single H_1-antihistamines. Given the additional benefits of H_1-antihistamines up-dosing (up to 4-fold), similar therapeutic gains may be expected from a combination regimen. However, the safety of this approach will depend on the safety profiles and possible drug interactions of the combined drugs. Due to uncertainties regarding the efficacy and safety of different drug combinations, a combination regimen is less preferable than the up-dosing of a single H_1-antihistamines. Therefore, the strength of this recommendation is considered conditional (i.e., weaker than that of up-dosing therapy).

Question 4. Should non-sedating H_1-antihistamines be taken regularly or as needed by patients with CSU?

- Recommendation 4: We suggest that non-sedating H_1-antihistamines be taken regularly by patients with CSU (conditional recommendation, very low-quality evidence).
- Summary of evidence: One RCT is directly relevant to this PICO question.[49] A total of 106 patients responding to desloratadine 5 mg daily for 4 weeks were randomized to receive desloratadine daily (daily desloratadine plus placebo rescue tablet) or only on days when urticarial wheals were present (daily placebo plus desloratadine rescue tablet) for an additional 8 weeks. At 4 and 8 weeks after randomization, subjects taking daily desloratadine showed a statistically significant improvement in QoL scores compared with those taking desloratadine as needed.[49]
  One trial has evaluated the efficacy of on-demand H_1-antihistamines to resolve existing wheals in patients with moderate-to-severe CSU. In this study, on-demand 5 mg desloratadine treatment significantly reduced the total hyperthermic skin area, but not wheal areas or volumes at 5 h compared with the group receiving no treatment.[50]
- Remark: Despite very low quality of evidence, the committee members agreed that the evidence is in line with clinical experience. As urticarial attacks are frequent and unpredictable in patients with active CSU, a preventive strategy would be preferred over an on-demand approach.

II. H_2-antihistamines

Background

H_2-receptors are primarily involved in the process of gastric acid secretion, but they also account for approximately 15% of all histamine receptors in the skin.[51] H_2-antihistamines are associated with a relatively good safety profile and have been used empirically as an add-on therapy for patients with CSU who are not adequately controlled by H_1-antihistamines; this approach was also recommended by some previous guidelines.[52,53] However, in the recent 2018 EAACI/GA^{2}LEN/EDF/WAO guidelines, the recommendation for H_2-antihistamines use was removed due to a lack of supporting evidence.[32,54] The purpose of this PICO question was to review the therapeutic benefits of H_2-antihistamines in patients unresponsive to H_1-antihistamines.

Question. Are H_2-antihistamines useful as an add-on therapy in patients unresponsive to a standard dose of H_1-antihistamines?

- Recommendation
  We suggest a trial of H_2-antihistamines add-on therapy in patients not responding to a standard dose of H_1-antihistamines (conditional recommendation, low quality evidence).
- Summary of evidence
  A total of 5 RCTs were identified.[55-59] Four studies reported that cimetidine use in addition to H_1-antihistamines (hydroxyzine, chlorpheniramine, or diphenhydramine) showed

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significant benefits in terms of urticarial symptom scores compared with placebo.[55,56,58,59] However, in an RCT of 32 patients with CSU, ranitidine as an add-on therapy to cetirizine failed to show any significant benefit over placebo in all measured efficacy outcomes, including urticarial activity score, chronic urticaria QoL questionnaire score, and patient-evaluated VAS scores.[57] There were no significant differences in adverse events related to H_2-antihistamines add-on therapy.[56-59]

- Remark
  A systematic review found very limited evidence mostly from a small number of older studies of cimetidine.[55,56,58,59] The only recent study of ranitidine use failed to show any significant benefit over placebo as an add-on therapy to cetirizine,[57] whereas the older studies of first-generation H_1-antihistamines plus cimetidine reported some benefit. Therefore, it is unclear whether H_2-antihistamines add-on may be beneficial in current management settings using newer generation H_1-antihistamines and H_2-antihistamines. However, H_2-antihistamines have a relatively good safety profile and degree of accessibility and, therefore, the committee agreed on a conditional recommendation for a trial of H_2-antihistamines add-on therapy in CSU patients not responding to standard dose H_1-antihistamines. However, it should be remembered that H_2-antihistamines add-on therapy is just one possible approach to add-on therapy, and it should be stopped if no improvement is seen within 1 or 2 months of the trial.

III. Systemic corticosteroids

Background

Systemic corticosteroids are often considered when urticaria symptoms are severe or poorly controlled by standard therapies. However, repeated use can be harmful as it can cause serious complications, including diabetes mellitus, hypertension, osteoporosis, or fractures.

Therefore, current international guidelines suggest that it is reserved for use only in patients with an acute exacerbation of urticaria.[32,52,54,60]

Question. Are systemic corticosteroids useful as an add-on therapy in patients unresponsive to H_1-antihistamines?

- Recommendation: We do not recommend a routine use of systemic corticosteroids in patients not responding to H_1-antihistamines (strong recommendation, very low quality evidence). A short-term use (within 10 days) may only be considered in limited circumstances, especially for relieving severe symptoms in patients with acute aggravation of CSU.
- Summary of evidence: Only 3 retrospective observational studies were identified.[61-63] In one retrospective study of 750 patients with H_1-antihistamine-refractory CSU, short-term (10 days) systemic corticosteroid treatment was helpful in controlling transient aggravation, and approximately 50% of the study population benefitted from a single dose of systemic corticosteroids; however, approximately 15% of patients still did not respond to systemic corticosteroids.[61] In a study of 641 Korean patients with CSU, the influence of initial treatment on the long-term control of urticaria was evaluated; in this study, the time to reach a controlled state did not differ between those who received H_1-antihistamines monotherapy vs. those treated with a combination of oral corticosteroids.[62] In a Japanese study of 386 patients with either acute or CSU, the use of systemic corticosteroids was not significantly associated with the remission of urticaria.[63]
- Remark: There is no good quality evidence (such as RCTs) to determine the efficacy of systemic corticosteroids in patients with refractory urticaria. However, observational

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studies suggest that while corticosteroids may be useful in relieving acute symptoms, this approach may not be helpful in modifying the long-term course of disease. Given the substantial side effects associated with chronic systemic corticosteroid exposure such as osteoporosis, fracture or diabetes mellitus, short-term use (within 10 days) only may be considered for acute symptom relief in patients with CSU flare-up.

CONCLUSIONS

CSU is a common condition associated with substantial disease burden. It frequently persists for several years and requires high-intensity treatment.[64] Patients may experience deterioration in QoL and medication-associated complications. During the last decade, there have been major advances in the pharmacological treatment of CSU. There is an outstanding need for clinical practice guidelines that reflect local circumstances and practice patterns in Korea, and this work is the first joint initiative of the KAAACI and the KDA to provide evidence-based guidance for the management of CSU in Korean adults and children. In Part 1 of the present guidelines, disease definition, guideline scope, and development methodology as well as recommendations on the use of antihistamines and corticosteroids were summarized. There is a strong consensus that non-sedating H_1-antihistamines are the first-line drug for patients with CSU, supported by quality evidence for its efficacy and safety profile. In patients not responding to a standard dose of H_1-antihistamines, up-dosing regimens are strongly recommended (up to 4-fold), but also a combination of different H_1-antihistamines or an addition of H_2-antihistamines may be considered. The routine use of systemic corticosteroids should be avoided due to substantial adverse effects, such as osteoporosis, fracture or diabetes mellitus; a short-term use (within 10 days) may only be considered in limited circumstances, especially for relieving severe symptoms in patients with acute aggravation of CSU. In Part 2 of this guideline, treatment options for patients with antihistamine-refractory CU are addressed.

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