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Letter to the Editor

Real-world clinical practices for spontaneous urticaria and angioedema in Japan: A nation-wide cross-sectional web questionnaire survey

Dear Editor,

Urticaria is characterized by wheals and/or angioedema, and causes substantial impairment of patients' QoL and economic impact on the health care system and society.^{1,2} These negative effects highlight the great need for appropriate management of the condition. In 2018, the Japanese Dermatology Association updated the guideline for the diagnosis and treatment of urticaria (the JDA-guideline).³ However, there has been no information on how much diagnostic work-up and treatment for urticaria recommended in the JDA-guideline are performed in clinical practices. Therefore, we conducted a web-based questionnaire in Japan to understand actual diagnostic and therapeutic procedures for urticaria by physicians who specialized in cutaneous allergic diseases (Supplementary Methods). This manuscript describes the results related to spontaneous urticaria and angioedema, which featured in the survey. Data were collected from 189 (15.6%) of 1209 physicians who were asked to participate (Supplementary Table 1).

With respect to diagnostic tests for chronic spontaneous urticaria (CSU), the JDA-guideline advises against routine screening tests and recommends the investigations for possible underlying causes only when the patient's history/physical manifestations suggested them.³ This study showed 57% of physicians performing no blood tests (Fig. 1a). Complete blood count, liver/kidney function test, C-reactive protein (CRP)/erythrocyte sedimentation rate (ESR), and total serum IgE were examined by one-third of physicians along with less frequency of antinuclear antibody and antigen specific IgE titer. This is in line with the recommendations of avoiding non-specific and comprehensive screening tests in the JDA-guidelines. The international EAACI/GA2LEN/EDF/WAO-guideline also recommends limited routine examinations and extended measures based on the patient's history.⁴ In previous surveys,^{5–7} prick tests and serum IgE measurements were undertaken by up to more than half of physicians. Moreover, differential blood count was examined by 60–80% of respondents, followed by CRP/ESR, thyroid hormones/autoantibodies, and antinuclear antibodies (35–70%). Our study suggests that diagnostic tests for CSU are performed less frequently in Japan than in other countries. For the assessment of disease activity and QoL in patients with CSU, 66% of physicians did not use any of the scales

recommended in the JDA-guideline (Fig. 1b), suggesting that more efforts to disseminate knowledge and use of the scales are needed even among specialists.

Regarding the pharmacological treatment of CSU, the JDA guideline describes the stepwise strategy and the avoidance of long-term (>4 weeks) administration of systemic corticosteroids.³ Second-generation antihistamines (sgAH) at the standard or double the dose are recommended as the first-line therapy. H2-antihistamines and antileukotrienes are added on for CSU refractory to sgAH, followed by omalizumab (OMA), ciclosporin A (CsA) or systemic corticosteroid as the third-line therapy. In this survey, 66% of participants did not use corticosteroids, and 29% did so in intractable cases, where antihistamines plus supplementary medications such as H2-antihistamines, antileukotrienes, and tranexamic acid were insufficient, in line with recommendations in the JDA-guideline (Fig. 1d). OMA was introduced prior to corticosteroids and CsA when antihistamine plus supplementary medications failed (46%) (Fig. 1e). This may be due to the potential severer adverse effects of corticosteroids and CsA than OMA. After obtaining complete response by OMA in patients with CSU, 34% of physicians discontinued OMA and 32% extended the interval with the same dose (Fig. 1f). Protocols for reducing the dose of, or discontinuation of, OMA have never been established, and should be explored in the future. In a recent multinational survey on the clinical practice of CSU,⁷ physicians who used urticaria guidelines for their clinical practices mainly administered the standard or up-dosed sgAH as the first-line therapy, followed by up-dosed sgAH (60%), H2-antihistamines (30%), montelukast (35%), or systemic corticosteroids (20–30%) as the second-line. It also reported that OMA was the major treatment (50%) along with less frequent use of montelukast (30%), CsA (23%), and corticosteroids (20–30%) as the third-line therapy. The EAACI/GA2LEN/EDF/WAO-guideline recommends adding on OMA before CsA for the treatment of CSU refractory to fourfold approved doses of sgAH dose.⁴ In this guideline, H2-antihistamines and antileukotrienes were mentioned as optional treatments. However, in real-world treatment procedures, there seems to be no significant differences in the use of corticosteroids, OMA, and supplementary medications such as H2-antihistamines and antileukotrienes between Japan and other countries.

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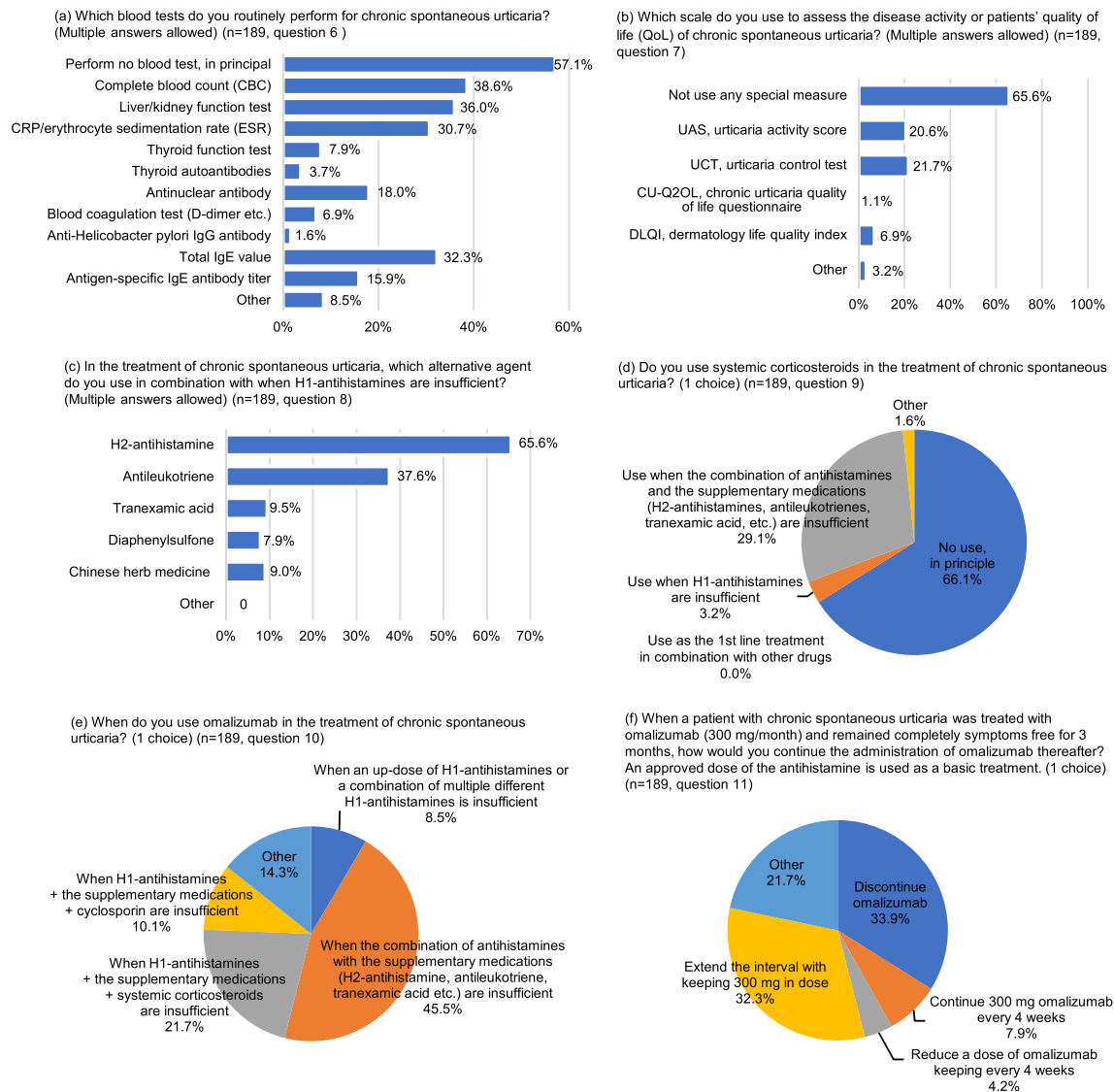


Fig. 1. The results of the questionnaire on chronic spontaneous urticaria (question 6–11).

In the treatment of acute spontaneous urticaria (ASU), this study showed that more physicians added systemic corticosteroids compared with CSU when the antihistamines were insufficient (24% vs 3%) (Fig. 1d, 2a). Although the efficacy of corticosteroids for ASU is still controversial,^{8,9} 23.8% of physicians in this survey used corticosteroids before or together with supplementary medications. It is known that a part of ASU is associated with bacterial infections,¹⁰ and nearly a half (45.0%) of physicians used antibiotics for ASU when fever and infectious lesions were found (Fig. 2b). However, only 11.1% physicians used antibiotics based only on fever, white blood cell count or CRP, suggesting a good adherence to both JDA- and EAACI/GA2LEN/EDF/WAO-guidelines. In the treatment of spontaneous angioedema (SAE) without wheals, 58% of physicians treated patients with prophylactic medications for attacks that developed more than once a month (Fig. 2c). When antihistamines were

insufficient, tranexamic acid (54% vs 10%) and corticosteroids (40% vs 3%) were used more often than those for CSU (Fig. 1c, d, 2d). Frequent and/or prolonged use of corticosteroids should be avoided because of their well-documented adverse effects and the lack of evidence for their efficacy in SAE.

A few studies in the literature have reported results of surveys exploring the actual clinical procedures for urticaria.^{5–7} However, approaches to the management of urticaria are affected by country-specific and regional features, due to differences in health care and insurance systems and the medications used in each country.⁷ In Japan, this is the first study to have clarified the actual clinical practices of urticaria conducted by physicians specializing in cutaneous allergic diseases, and showed that the management of spontaneous urticaria and angioedema seems to be performed mostly in line with recommendations of the JDA-guideline. It also suggests the necessity

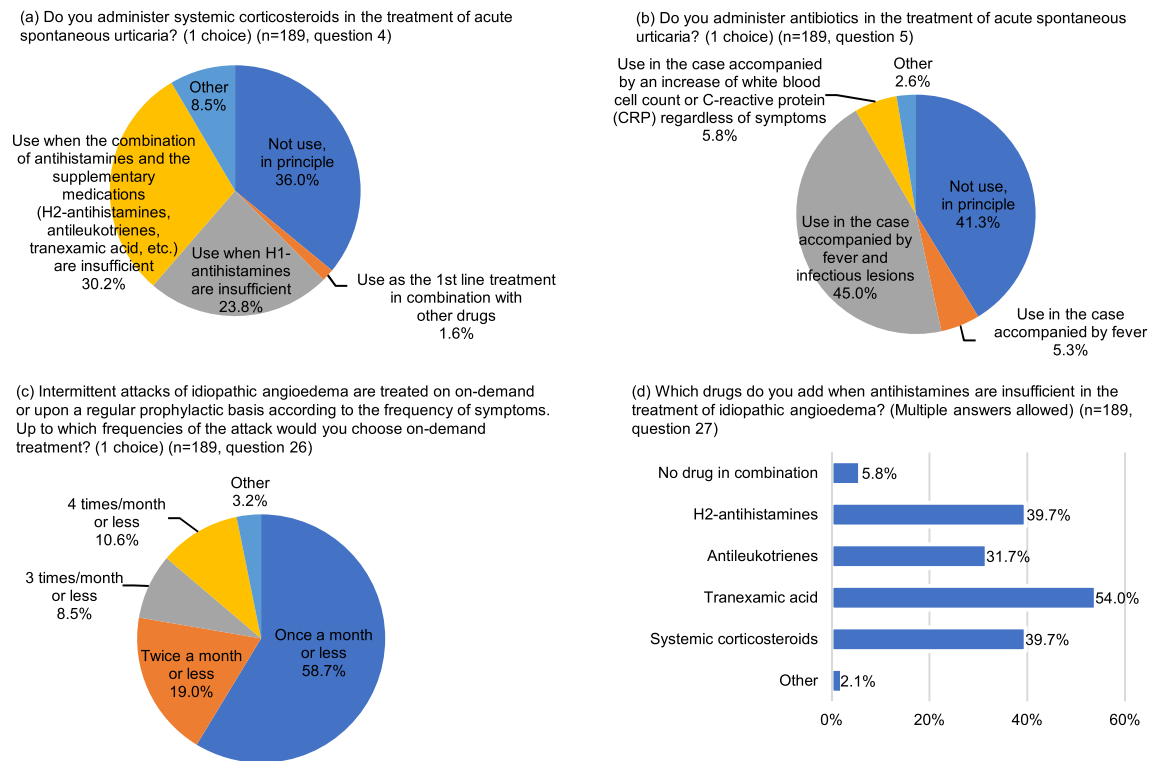


Fig. 2. The results of the questionnaire on acute spontaneous urticaria and spontaneous angioedema (question 4, 5, 26 and 27).

of establishing a protocol for discontinuation of OMA, disseminating knowledge and use of urticarial scales such as UAS or UCT, and avoiding often/prolonged use of systemic corticosteroids for ASU and SAE.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.alit.2019.10.003>.

Conflict of interest

MH reports speaker's fee from Taiho Pharmaceutical, Novartis Pharma and Mitsubishi-Tanabe. The rest of the authors have no conflict of interest. TN reports speaker's fee from Maruho Co., Ltd., and Sanofi, K.K., and belonging to the endowed division sponsored by Maruho Co., Ltd.. AF reports speaker's fee from Taiho Pharmaceutical and Novartis Pharma, and research funding from Taiho Pharmaceutical.

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Supplementary Table 1. Participants' characteristics (n=189, question 1, 2 and 3).

	n (%)
Work at	
University hospital	80 (42.3%)
National/public general hospital other than university hospital	23 (12.2%)
Hospital other than above	23 (12.2%)
Private clinic	63 (33.3%)
Other	0 (0.0%)
Total	189 (100%)
Length of clinical experience of dermatology	
Less than 3 years	4 (2.1%)
3-5 years	1 (0.5%)
6 to 10 years	14 (7.4%)
11 to 20 years	52 (27.5%)
Over 20 years	118 (62.4%)
Total	189 (100%)
Specialty	
Dermatology	183 (96.8%)
Pediatrics	1 (0.5%)
Allergy	4 (2.1%)
Unknown	1 (0.5%)
Total	189 (100%)

Supplementary Methods

Study survey & recruitment

From December 2018 to January 2019, we conducted a cross sectional survey study using a web-based questionnaire at the website equipped with Questant (MACROMILL Inc., Tokyo, Japan), a self-service questionnaire software (<https://questant.jp/en/>). The participants were physicians specialized in cutaneous allergic diseases and members of the Japanese Society for Cutaneous Immunology and Allergy (JSCIA). They were asked to participate in the survey via e-mail in reference to the member list of JSCIA. The e-mail contained a link (internet address) to the online questionnaire. This survey consisted of total 27 questions including several topics about spontaneous urticaria, spontaneous angioedema, chronic inducible urticaria, urticaria induced by type I allergy and aspirin-induced urticaria. They were single or multiple choice questions.

Web-based questionnaire items

Survey on diagnosis and management of urticaria in Japan

[Q1] Your name, affiliation and specialty:

[Q2] You work at (1 option):

- ☐ University hospital
- ☐ National/public general hospital other than University hospital
- ☐ Hospital other than above
- ☐ Private clinic
- ☐ Other

[Q3] Length of clinical experience of dermatology (years): (1 option).

- ☐ Less than 3 years
- ☐ 3-5 years
- ☐ 6 to 10 years
- ☐ 11 to 20 years
- ☐ Over 20 years

[Q4]-[Q11] Questions on spontaneous urticaria

[Q4] Do you administer systemic corticosteroids in the treatment of acute spontaneous urticaria? (1 choice)

- ☐ Not use, in principle
- ☐ Use as the 1st line treatment in combination with other drugs

- ☐ Use when H1-antihistamines are insufficient
- ☐ Use when the combination of antihistamines and the supplementary medications (H2-antihistamines, antileukotrienes, tranexamic acid, etc.) are insufficient
- ☐ Other

[Q5] Do you administer antibiotics in the treatment of acute spontaneous urticaria? (1 choice)

- ☐ Not use, in principle
- ☐ Use in the case accompanied by fever
- ☐ Use in the case accompanied by fever and infectious lesions
- ☐ Use in the case accompanied by an increase of white blood cell count or C-reactive protein (CRP) regardless of symptoms
- ☐ Other

[Q6] Which blood tests do you routinely perform for chronic spontaneous urticaria? (Multiple answers allowed)

- ☐ Perform no blood test, in principal
- ☐ Complete blood count (CBC)

- ☐ Liver/kidney function test
- ☐ CRP/erythrocyte sedimentation rate (ESR)
- ☐ Thyroid function test
- ☐ Thyroid autoantibodies
- ☐ Antinuclear antibody
- ☐ Blood coagulation test (D-dimer etc.)
- ☐ Anti-Helicobacter pylori IgG antibody
- ☐ Total IgE value
- ☐ Antigen-specific IgE antibody titer
- ☐ Other

[Q7] Which scale do you use to assess the disease activity or patients' quality of life (QoL) of chronic spontaneous urticaria? (Multiple answers allowed)

- ☐ Not use any special measure
- ☐ UAS, urticaria activity score
- ☐ UCT, urticaria control test
- ☐ CU-Q₂OL, chronic urticaria quality of life questionnaire
- ☐ DLQI, dermatology life quality index

☐ Other

[Q8] In the treatment of chronic spontaneous urticaria, which alternative agent do you use in combination with when H1-antihistamines are insufficient? (Multiple answers allowed)

☐ H2-antihistamine

☐ Antileukotriene

☐ Tranexamic acid

☐ Diaphenylsulfone

☐ Chinese herb medicine (please specify the name of the medicine)

☐ Other

[Q9] Do you use systemic corticosteroids in the treatment of chronic spontaneous urticaria? (1 choice)

☐ No use, in principle

☐ Use as the 1st line treatment in combination with other drugs

☐ Use when H1-antihistamines are insufficient

☐ Use when the combination of antihistamines and the supplementary medications

(H2-antihistamines, antileukotrienes, tranexamic acid, etc.) are insufficient

- ☐ Other

[Q10] When do you use omalizumab in the treatment of chronic spontaneous urticaria?

(1 choice)

- ☐ When an up-dose of H1-antihistamines or a combination of multiple H1-antihistamines is insufficient
- ☐ When the combination of antihistamines with the supplementary medications (H2-antihistamines, antileukotrienes, tranexamic acid etc) are insufficient
- ☐ When H1-antihistamines + the supplementary medications + systemic corticosteroid are insufficient
- ☐ When H1-antihistamines + the supplementary medications + cyclosporin are insufficient
- ☐ Other

[Q11] When a patient with chronic spontaneous urticaria was treated with omalizumab (300 mg/month) and remained completely symptoms free for 3 months, how would you continue the administration of omalizumab thereafter? An approved dose of the

antihistamine is used as a basic treatment. (1 choice)

- ☐ Discontinue omalizumab
- ☐ Continue 300 mg omalizumab every 4 weeks
- ☐ Reduce a dose of omalizumab keeping every 4-weeks
- ☐ Extend the interval with keeping 300 mg in dose
- ☐ Other

[Q12]-[Q17] Questions on urticaria induced by type I allergy

[Q12] Do you perform skin tests (prick test, intracutaneous test etc.) for diagnosis of urticaria induced by type I allergy? (1 choice)

- ☐ Yes (please proceed to [Q13])
- ☐ No, in principal (please proceed to [Q14])

[Q13] Which skin tests do you perform? (Multiple answers allowed)

- ☐ Prick test (using reagents commercially available for the test)
- ☐ Prick test (using suspected materials as is)
- ☐ Intradermal skin test
- ☐ Scratch test

☐ Other

[Q14] Do you perform provocation tests for diagnosis of urticaria induced by type I allergy? (1 choice)

- ☐ Yes, as needed (please proceed to [Q15])
- ☐ No (please proceed to [Q18])

[Q15] If 'yes' in [Q14], where do you carry out the provocation test? (1 choice)

- ☐ In the outpatient clinic
- ☐ Under hospitalization
- ☐ In the outpatient clinic or under hospitalization, depending on the case
- ☐ Other

[Q16] If 'yes' in [Q14], what amount of a causative agent do you start with for the provocation test? (1 choice)

- ☐ The amount that triggered episodes
- ☐ A half of the amount that triggered episodes
- ☐ One-fifth of the amount that triggered episodes

- ☐ One-tenth of the amount that triggered episodes
- ☐ Other

[Q17] If 'yes' in [Q14], which other department do you cooperate with to carry out the provocation test? (Multiple answers allowed)

- ☐ Do not cooperate with other departments
- ☐ Internal medicine
- ☐ Pediatrics
- ☐ Emergency medicine
- ☐ Otolaryngology
- ☐ Ophthalmology
- ☐ Surgery
- ☐ Other

[Q18]-[Q21]: Questions on aspirin-induced urticaria (NSAIDs intolerance)

[Q18] Do you perform tests for diagnosis of aspirin-induced urticaria (NSAIDs intolerance)? (1 choice)

- ☐ Yes (please proceed to [Q19])

- ☐ No (please proceed to [Q22])

[Q19] If 'yes' in [Q18], which tests do you perform for diagnosis of aspirin-induced urticaria? (Multiple answers allowed)

- ☐ Skin test (please specify tests) (please proceed to [Q22])
- ☐ Drug provocation test (please proceed to [Q20])
- ☐ Other

[Q20] If you perform a 'Drug provocation test' in [Q19], what dose do you start with?
(1 choice)

- ☐ The amount that triggered episodes
- ☐ A half of the amount that triggered episodes
- ☐ One-fifth of the amount that triggered episodes
- ☐ One-tenth of the amount that triggered episodes
- ☐ Other

[Q21] If you perform a 'Drug provocation test' in [Q19], do you conduct another provocation test to find a drug that can be safely taken, in addition to the identification

of the causative agent? (1 choice)

- ☐ Yes
- ☐ No
- ☐ Other

[Q22]-[Q25] Questions on physical urticaria/cholinergic urticaria

[Q22] Which types of the following urticarias have you made a diagnosis of, or seen patients with a diagnosis confirmed by other physicians? (Multiple answers allowed)

- ☐ Mechanical urticaria
- ☐ Localized cold urticaria
- ☐ Generalized cold urticaria
- ☐ Solar urticaria
- ☐ Heat urticaria (except cholinergic urticaria)
- ☐ Delayed pressure urticaria
- ☐ Aquagenic urticaria
- ☐ Cholinergic urticaria

[Q23] Do you perform a provocation phototest for diagnosis of solar urticaria? (1

choice)

- ☐ Yes (please proceed to [Q24])
- ☐ No (Please proceed to [Q25])

[Q24] If 'yes' in [Q23], which instruments do you use in the provocation test? (Multiple answers allowed)

- ☐ UVA lamp
- ☐ Broadband UVB lamp
- ☐ Narrow band UVB lamp
- ☐ Projector lamp
- ☐ Other

[Q25] To which points do you pay most attention when seeing patients with cholinergic urticaria? (Multiple answers allowed)

- ☐ Timing of wheal appearance
- ☐ Shape of wheals
- ☐ Subjective symptoms of wheals
- ☐ Presence or past history of atopic dermatitis

- ☐ Provocation test with sweating
- ☐ Presence of sweat allergy
- ☐ Presence of hypohidrosis
- ☐ Other

[Q26]-[Q27] Questions on idiopathic angioedema

[Q26] Intermittent attacks of idiopathic angioedema are treated on-demand or upon a regular prophylactic basis according to the frequency of symptoms. Up to which frequencies of the attack would you choose on-demand treatment? (1 choice)

- ☐ Once a month or less
- ☐ Twice a month or less
- ☐ 3 times/month or less
- ☐ 4 times/month or less
- ☐ 5 times/month or less
- ☐ Other

[Q27] Which drugs do you add when antihistamines are insufficient in the treatment of idiopathic angioedema? (Multiple answers allowed)

☐ No drug in combination

☐ H2-antihistamines

☐ Antileukotrienes

☐ Tranexamic acid

☐ Systemic corticosteroids

☐ Other