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

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Letter to the Editor

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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-antihisutamines and antileukotriens between Japan and other countries.

In the treatment of acute spontaneous urticaria (ASU), this study showed that more physicians added systemic

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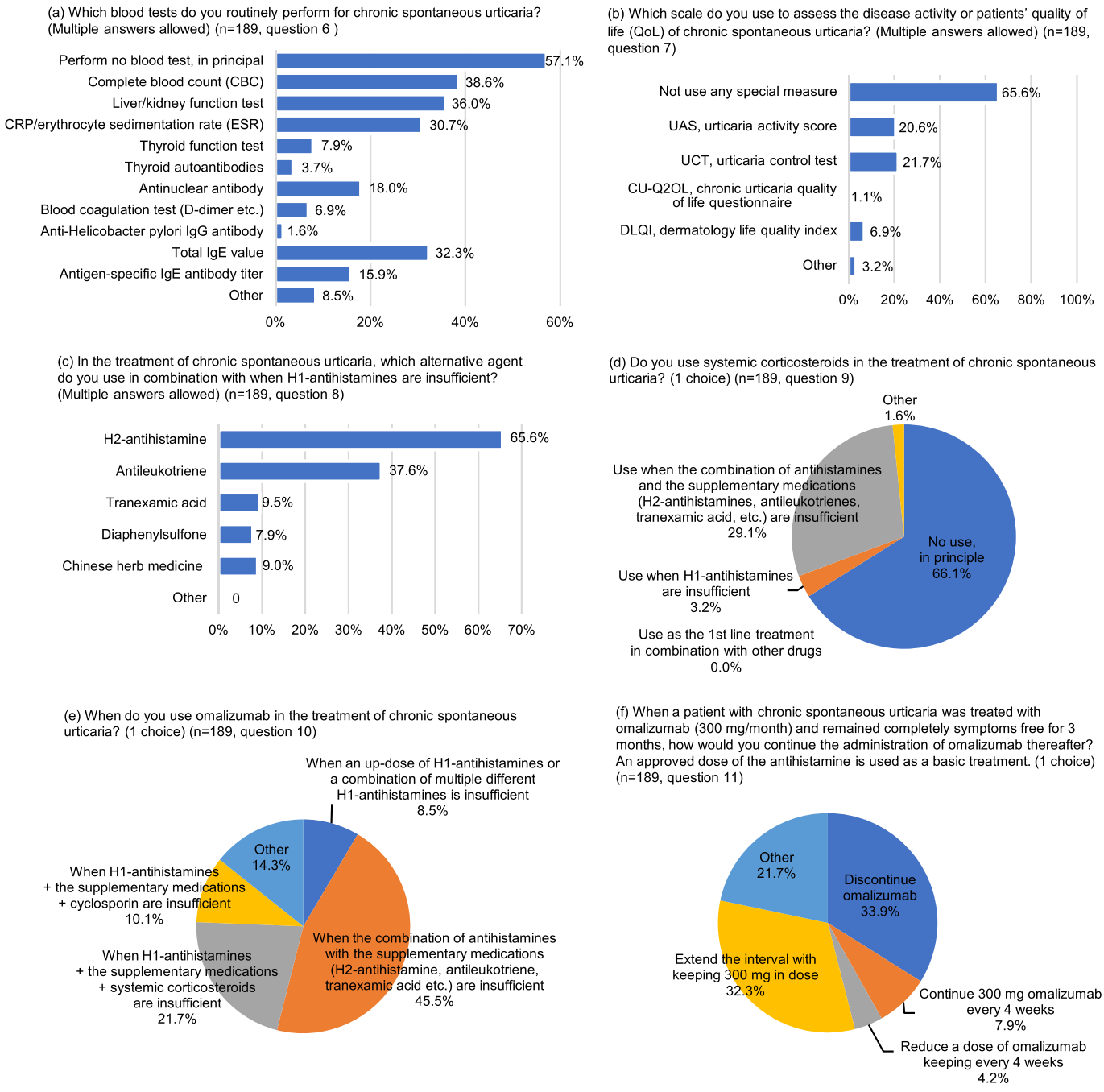

Fig. 1. The results of the questionnaire on chronic spontaneous urticaria (question 6–11).

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

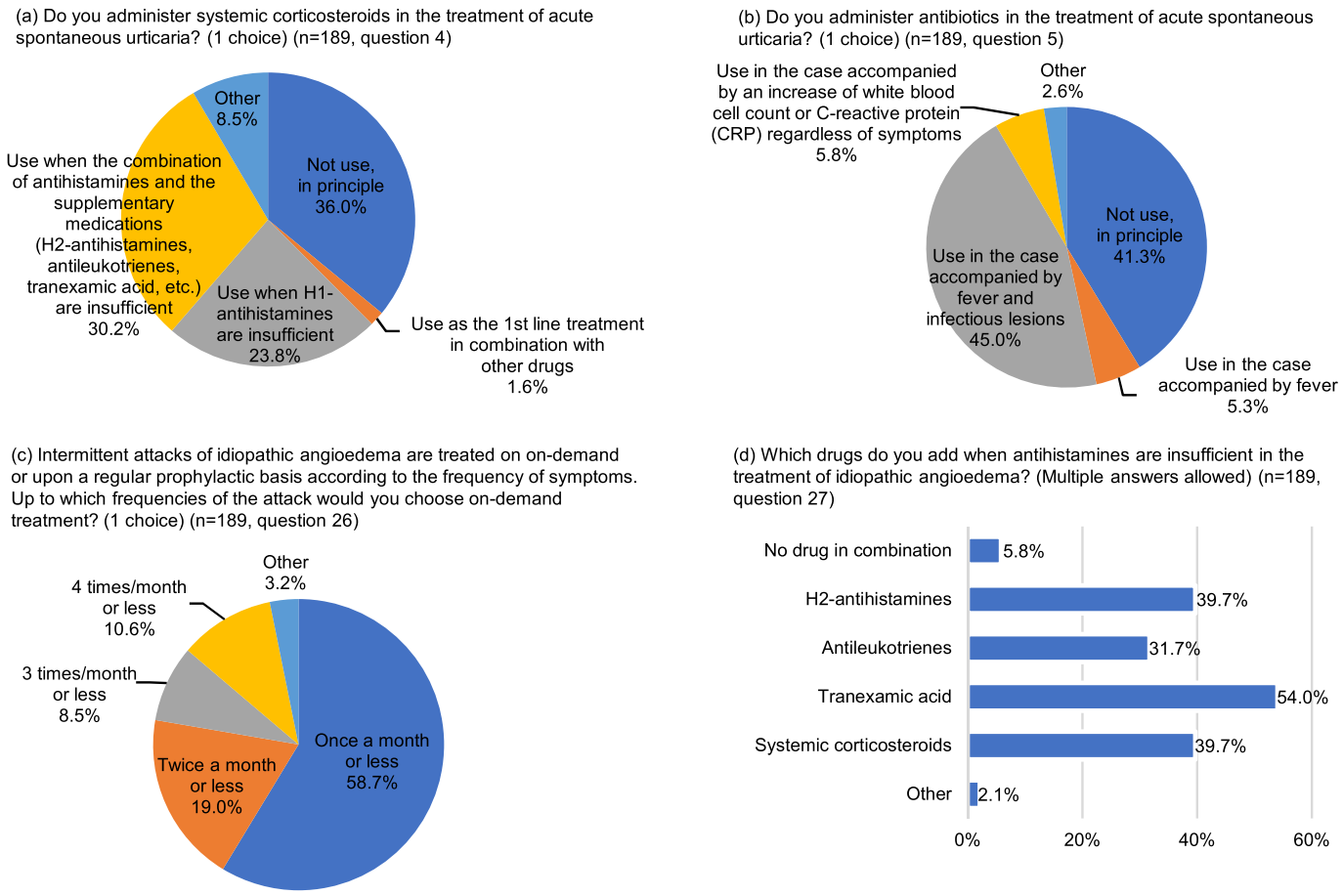

Fig. 2. The results of the questionnaire on acute spontaneous urticaria and spontaneous angioedema (question 4, 5, 26 and 27).

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

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