

## ORIGINAL ARTICLE

# Analysis of the long-term economic burden of omalizumab on patients with chronic spontaneous urticaria

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## ABSTRACT

Omalizumab (OMA) is highly effective for refractory chronic spontaneous urticaria (CSU), but its high cost exerts a great economic burden on patients and society. Current knowledge is lacking regarding the economic impact of long-term administration of OMA on patients with CSU in the real-world setting. We retrospectively investigated drug costs relevant to CSU treatment during the period before through to 12 months after starting OMA in actual clinical practice. This study involved 32 patients who received at least two injections of OMA (300 mg/4 weeks) and achieved good responses of urticaria control test score of 12 or more and/or weekly urticaria activity score of 6 or less within 12 weeks. Median drug costs of the overall patient cohort increased from ¥14 496/month to ¥104 522 after starting OMA, but reduced to ¥48 810 in 12 months along with reduced amount of OMA administration and concomitant medication use. In patients pretreated with antihistamine alone or plus alternative medicines such as H<sub>2</sub> blocker and antileukotriene prior to OMA, the increased drug costs by adding OMA decreased to approximately 30% in 12 months mainly due to the OMA dose reduction and interval extension of OMA. The drug cost reduction was also observed in patients pretreated with intensive multi-agents, due to discontinuation of expensive immunosuppressants. In conclusion, the introduction of OMA significantly increased the total drug costs relevant to CSU management, but the costs decreased to half in 12 months, along with dose-reduced and interval-extended OMA and discontinued concomitant drugs in patients with CSU who responded well to OMA.

**Key words:** chronic spontaneous urticaria, concomitant treatment, disease activity, drug cost, omalizumab.

## INTRODUCTION

Chronic spontaneous urticaria (CSU) is a common inflammatory skin disease in which pruritic wheals spontaneously appear for a period of 6 weeks or longer.<sup>1</sup> Its substantial impairment of patients' quality of life (QoL) highlights the great clinical need for its effective treatment.<sup>2</sup> The mainstay of the pharmacological treatment of CSU is non-sedating antihistamines, but treatment with licensed or even up-dosed antihistamines still does not effectively relieve symptoms in certain patients.<sup>2</sup> Recently, omalizumab (OMA), a humanized anti-immunoglobulin E antibody, has offered patients dramatic efficacy by achieving a weekly urticaria activity score (UAS7) of less than 6 and complete relief of symptoms in 50–65% and 35–45% of patients, respectively, in clinical trials of CSU refractory to antihistamines.<sup>3–6</sup> OMA also has been reported to show response rates as high as 85–90% in real-world clinical data.<sup>7,8</sup> Because of its high efficacy and safety, the EAACI/GA2LEN/EDF/WAO guideline recommends the use of OMA as

add-on treatment in patients unresponsive to high doses of antihistamines.<sup>1</sup>

Contrary to patients' relief from physical distress by its efficacy, the high cost of OMA exerts a great economic burden on patients and society. The Japanese guideline for the management of urticaria describes a stepwise treatment strategy for CSU, in which antihistamines are first-line therapy as in the EAACI/GA2LEN/EDF/WAO guideline.<sup>9</sup> It suggests adding H<sub>2</sub> antihistamines and/or antileukotrienes prior to the administration of OMA for cases refractory to antihistamines to avoid the economic burden placed on the patients and society related to OMA.<sup>9</sup> However, current knowledge is lacking regarding the actual economic impact of long-term administration of OMA for more than 3 months on patients with CSU in clinical practice. In this monocenter study, we retrospectively investigated drug costs relevant to CSU treatments before and after initiating OMA in the real-world setting in Japan, and further analyzed the relation of the drug cost to urticaria disease activity and concomitant treatments.

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## METHODS

### Patients

Fifty patients with CSU treated with OMA at Hiroshima University Hospital were observed from 29 March 2017 to 31 August 2019. Of these 50 patients, this study involved 32 subjects (male : female, 8:24; median age, 51.0 years; range 14–77) who received at least two injections of OMA (300 mg/4 weeks; a licensed dose for CSU in Japan) and achieved good clinical responses of urticaria control test (UCT) score of 12 or more and/or UAS7 of 6 or less within 12 weeks. As shown in the study protocol (Fig. 1), an analysis was performed on the data obtained from the observation period of a maximum of 12 months. In total, 19 patients completed the full 12-month follow up, while 13 patients were lost to follow up before completing the 12-month observation. Five of these 13 patients discontinued follow up due to changing hospital or achieving remission of the disease, and eight patients reached the end of the observation period before 6 ( $n = 2$ ) or 12 months ( $n = 6$ ). The dose and interval of OMA injection, drug costs, disease activity and concomitant treatments were retrospectively analyzed before and during the period of up to 12 months after starting OMA. The institutional review board of Hiroshima University Hospital approved the study protocol (approval no. E-1755).

### Administration of OMA

Omalizumab was initially introduced at the approved dose of 300 mg/4 weeks, followed by dose reduction and/or interval extension, or discontinuation. “Dose reduction” is defined as cases receiving OMA at least twice consecutively at a dose of at least 25% less than the initial dose, and “interval extension” as cases receiving OMA at the extended interval of 6 weeks or more at least twice consecutively. Cases where OMA was intentionally ceased after several injections without the dose reduction and the interval extension (Fig. 2) were referred to as “discontinuation”.

### Assessment of drug costs, disease activity and treatment steps

The price of each drug referred to the 2019 drug price list issued by the Japanese Ministry of Health, Labor and Welfare (e.g. omalizumab 75 mg/¥23 128).<sup>10</sup> Only drug costs relevant to the treatment for CSU were calculated and factored into the total amount of drug cost. CSU disease activity was evaluated using patient-reported outcome measures such as UAS7 and/or UCT as described elsewhere.<sup>1,11</sup> Treatments other than OMA were classified into five steps after the stepwise therapy suggested in the previous version of the Japanese guidelines for the management of urticaria with some modifications: step 0, no concomitant medicine; step 1, antihistamines at the approved dose; step 2, up-dosed antihistamines or combination of antihistamines; step 3, add-on alternative medicines such as  $H_2$  blockers, antileukotrienes and diaphenylsulfone; step 4, add-on systemic corticosteroid of 20 mg or less; and step 5, add-on other treatment options such as systemic corticosteroid of more than 20 mg, immunosuppressants and other experimental trial treatments.<sup>12,13</sup>

## RESULTS

### Administration of OMA

The protocol for OMA administration in each patient is shown in Figure 2, in which patients 1–15 and 16–32 are indicated to have been on treatment step 1, 2 or 3 (pretreatment step 1–3 group) and step 4 or 5 (pretreatment step 4–5 group), respectively, before initiating OMA. No adverse events causing withdrawal of OMA were observed, while discontinuation, dose reduction or interval extension of OMA treatment was intentionally performed along with the relief of urticarial symptoms. In seven (47%) of the 15 patients in the pretreatment step 1–3 group, but only three (18%) of the 17 patients in the pretreatment step 4–5 group, successfully discontinued OMA within 6 months after starting. During the observation period, only two (13%) of the 15 patients in the pretreatment step 1–3 group but four (24%) of the 17 patients in the pretreatment step 4–5 group still required OMA administration without dose reduction or interval extension.

### Drug cost of overall patient cohort

Median drug cost of the overall patient cohort was ¥14 496/month before the initiation of OMA. It amounted to ¥104 522 at the next month of introducing OMA, but followed by the gradual reduction to ¥48 810 after 12 months (Fig. 3a). The analysis of drug cost of the 19 patients who completed the full 12-month follow up showed similar trends; namely, a statistical analysis revealed that median drug cost of ¥15 516 before OMA amounted to ¥105 246 at the next month of introducing OMA, but reduced to ¥48 810 after 12 months (Fig. 3b). Hereafter, analyses were performed using data obtained from all 32 patients. Urticarial activity with high UAS7 score (median, 25) and low UCT score (median, 5) achieved dramatic improvements shortly after OMA initiation and was maintained under controlled conditions until the 12th month (Fig. 3c,d). As for concomitant treatments with OMA, more than half (53%) of the 32 patients had been treated with treatment step 4 or 5 before OMA, but most of the patients (91%) achieved clinical responses only on treatment step 0–3 by the 3rd month (Fig. 3e).

### Stratified analyses by prior treatments

In analyses stratified by pretreatments, the pretreatment step 1–3 group showed that median drug cost increased up to ¥103 359 at the next month of commencing OMA, but was followed by a dramatic decrease to ¥34 052 at the 12th month (Fig. 4a). In the pretreatment step 4–5 group, the increased drug costs reduced from ¥105 683 to ¥64 760 within 3 months; the reduction was larger than that in the pretreatment 1–3 group (Fig. 4b). However, no further apparent reduction of drug costs was observed after the 3rd month. As for the drug cost excluding OMA, the median drug cost before the introduction of OMA was ¥13 283 in the pretreatment step 1–3 group, but it decreased to ¥6429 by 50% reduction at the 3rd month after the OMA introduction (Fig. 4c). In the pretreatment step 4–5 group, the drug cost

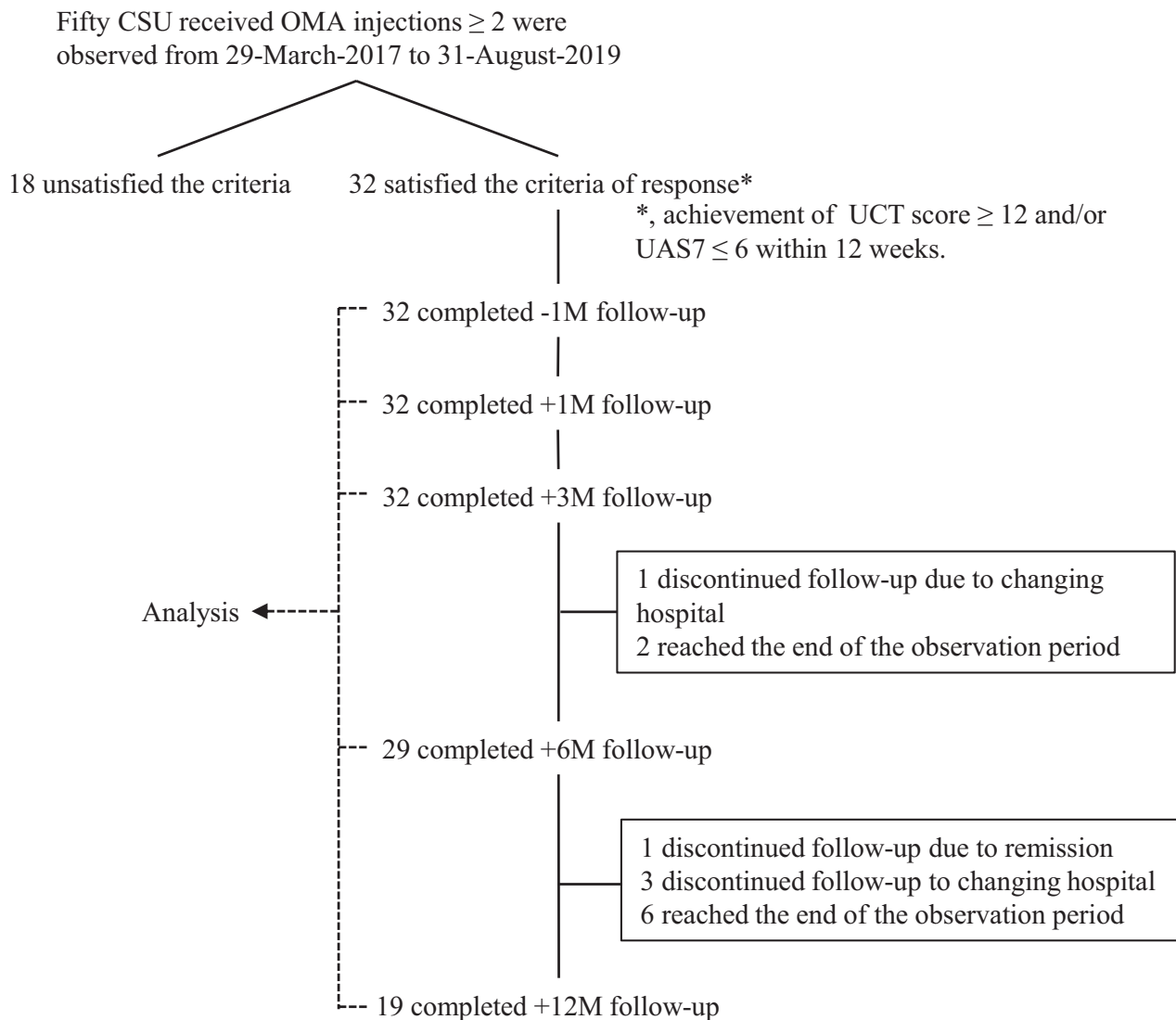


**Figure 1.** Study protocol. Analyzed data were acquired from patients' records reported during the defined observational period from 29 March 2017 to 31 August 2019. CSU, chronic spontaneous urticaria; M, months after starting OMA; OMA, omalizumab; UAS7, weekly urticaria activity score; UCT, urticaria control test.

before the administration of OMA was ¥21 705, and it decreased to ¥3687 by 80% reduction at the 3rd month after the administration of OMA (Fig. 4d). After 6 or more months of administration, no significant difference of the drug cost excluding OMA was found between both groups. Regarding concomitant treatments with OMA, 57% of patients in the pretreatment step 1–3 group stepped down treatment from step 3 to step 1 or 2 at the 3rd month, leading to six (67%) of nine patients in good condition on treatment step 0 or 1 at the 12th month (Fig. 4e). In the pretreatment step 4–5 group, 12 (80%) of the 15 patients withdrew systemic corticosteroid, immunosuppressants or other experimental trial treatments, and the step down to step 0 or 1 was achieved in eight (53.3%) of the 15 patients at the 6th month (Fig. 4f).

## DISCUSSION

In previous reports, the cost-effectiveness of OMA was analyzed by using the Markov model based on clinical trial data in the UK<sup>14</sup> and the Netherlands.<sup>15</sup> The results of these analyses indicate that OMA is more cost-effective from a socioeconomic point of view than conventional treatments such as up-dosed antihistamines, H<sub>2</sub> blockers and antileukotrienes. However, these analyses did not consider a variety of therapeutic procedures performed in real-world clinical practice, such as changing concomitant medications and reducing dose and/or extending the interval of OMA. Moreover, the cost-effectiveness of OMA in other countries cannot be directly applied to that in the actual clinical settings in Japan, because the cost of

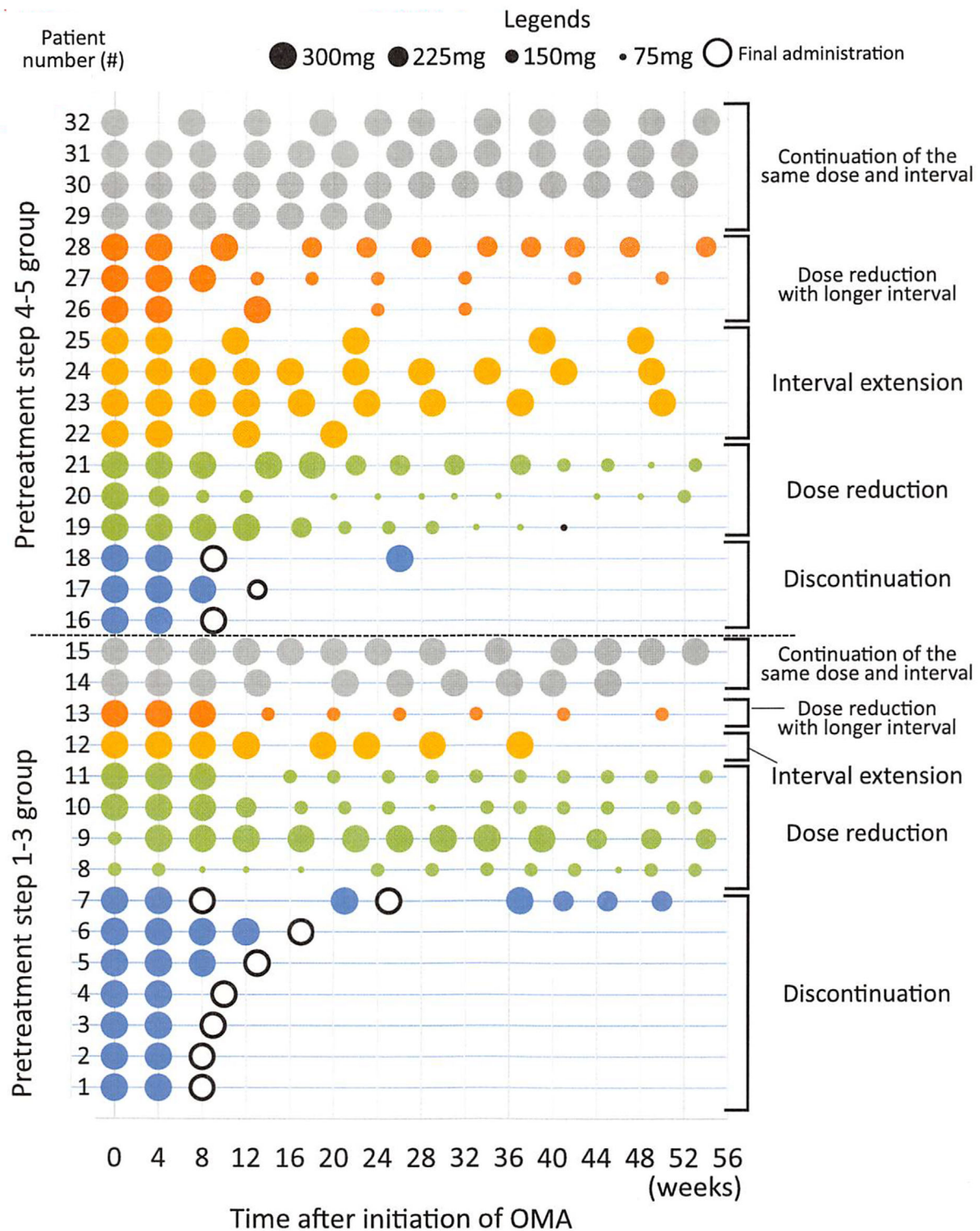


**Figure 2.** Protocol for the administration of omalizumab (OMA) in each patient. Circles indicate timing of OMA injection, and size of each circle corresponds to the dose. Open circles indicate the last administration of OMA by intentional withdraw, while closed circles show ongoing OMA.

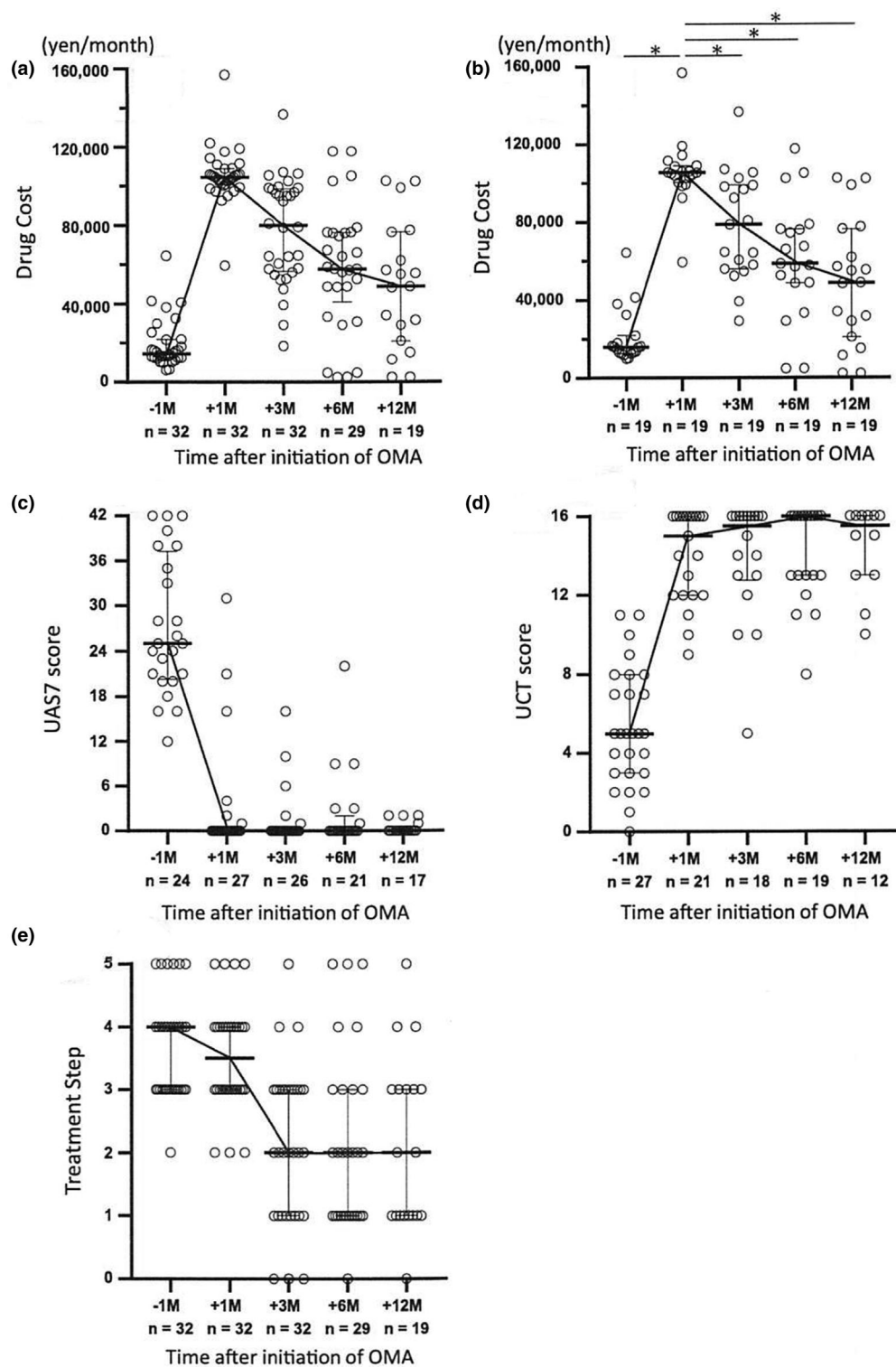


**Figure 3.** (a) Total drug cost, (c) weekly urticaria activity (UAS7), (d) urticaria control test (UCT) and (e) concomitant treatment in overall patient cohort during the period of the -1st month to the 12th month after introduction of omalizumab (OMA). (b) Total drug cost in 19 patients who completed the full 12 months of follow up during the observational periods. Data represent the median and interquartile range, and data in panel (b) were analyzed by Friedman's test. \* $P < 0.01$ . M, month.

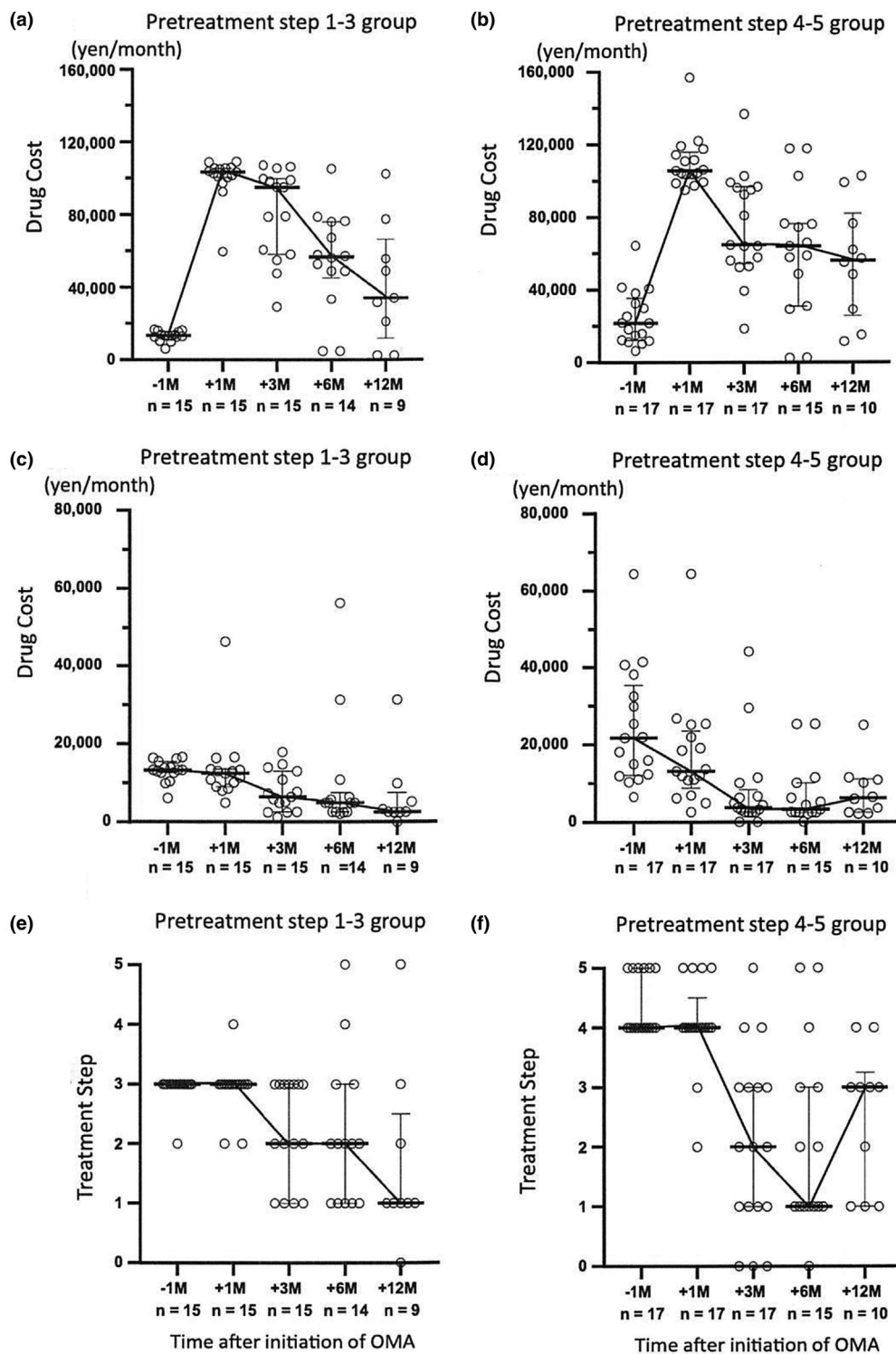


**Figure 4.** (a,b) Total drug cost in the pretreatment step 1–3 group or 4–5 group during the period of the –1st month to the 12th month after introduction of omalizumab (OMA). (c,d) Drug cost in the pretreatment step 1–3 group and that in the 4–5 group calculated by excluding the expense for OMA. (e,f) Concomitant treatment in the pretreatment step 1–3 group or 4–5 group. Data represent the median and interquartile range. M, month.

each drug and medical expenses related to treatments for CSU depends on each individual country's health-care system.

In this study, we analyzed the time course of the actual drug costs in patients with CSU treated by OMA based on real-world clinical data in Japan. As a result, the introduction of OMA caused significant increase of drug costs but which could be reduced to half in 12 months along with the prompt relief of urticarial symptoms. Particularly, patients in the pretreatment step 1–3 group showed that the drug costs in the 12th month after starting OMA decreased to one-third of those in the first month of OMA administration. In the pretreatment step 4–5 group, the drug costs decreased not as much as those of the pretreatment step 1–3 group at the 12th month, but concomitant drugs with potential serious adverse effects such as corticosteroids and cyclosporin were discontinued due to the improvement of urticarial symptoms by OMA.

A major factor contributing to decreased drug costs in 12 months after the introduction of OMA is the reduction of OMA administration. Especially in the pretreatment step 1–3 group, seven (47%) of the 15 patients discontinued OMA by the 6th month, and 13 of those (87%) achieved the discontinuation, dose reduction or interval extension of OMA during the observation period, resulting in a decrease in drug costs mainly in 6 months or later. Takahagi *et al.*<sup>16</sup> recently studied the actual use of OMA by physicians based on a nationwide cross-sectional web questionnaire survey in Japan. They reported that 34% of physicians discontinued OMA, 32% extended the interval and 4.2% reduced the dose after obtaining complete response. Other reports have also suggested the dose reduction or the interval extension of OMA after achieving relief of urticarial symptoms.<sup>17–20</sup> These dose reductions, interval extensions and discontinuation of OMA mainly contribute to reduce economic burden on patients and society.

Reduction of concomitant drugs played another role in decreasing drug costs. In the pretreatment step 4–5 group, the median drug cost decreased by 61% at the 3rd month despite only three (18%) of the 17 patients discontinuing OMA at the 3rd month after starting OMA. Meanwhile, 14 (82%) of these 17 patients reduced or discontinued relatively expensive immunosuppressants including cyclosporin during the same period. Notably, seven patients achieved the withdrawal of the concomitant drugs to step 0 (no concomitant medicine) or step 1 (antihistamines at the approved dose). Moreover, the drug cost excluding OMA after 3 months decreased more in the pretreatment step 4–5 group than in the pretreatment step 1–3 group. Therefore, the reduction of the drug costs at the 3rd month after the introduction of OMA partially depends on the dose reduction of expensive immunosuppressive medicines. Likewise, a previous study showed that 17% of patients with CSU were treated with cyclosporin before OMA while only 7% were still on cyclosporin in combination after initiating OMA.<sup>21</sup> Nevertheless, at the 6th month and later after starting OMA, the decrease in drug cost in the pretreatment step 4–5 group was not as much as that observed in the pretreatment step 1–3 group, because five (29%) of the 17 patients still continued OMA without dose reduction or interval extension. Thus, OMA is required to be continued in severe cases treated with step 4

or 5 treatment prior to OMA, but the reduction of immunosuppressants following relief of urticarial symptom by OMA can be achieved and thereby reduce patients' economic burden. Interestingly, the decrease of drug cost in the pretreatment step 1–3 group depends mainly on reducing OMA, while reduction of concomitant drugs also contributed to the early decrease of drug cost during the first 3 months in the pretreatment step 4–5 group.

The limitation of this study is that it focuses only on drug costs among various expenses relevant to the management of CSU. These expenses include medical expenses, such as drug prescription costs, laboratory costs, routine or emergency visit costs and inpatient costs, and social losses like reduction of salaries and work productivity while on leave for physician visits. However, a major driver of the medical expenses for this outpatient disease is drug cost,<sup>22</sup> which is thus highlighted in this study. In addition, this study could not reveal the value of cost-effectiveness of OMA compared with conventional treatments for CSU. The defined value of cost-effectiveness ought to be calculated from quality-adjusted life year based on the health-related QoL assessment.<sup>23</sup> In this study, the value of cost-effectiveness could not be analyzed because patients' QoL was not evaluated. Instead, both drug costs and the disease activity were assessed as an indicator of cost and effectiveness. In addition, this study is a non-interventional study in the real-world setting, reflecting real patients' treatments and drug costs in the clinical practice.

In conclusion, the introduction of OMA significantly increased the total drug costs relevant to the management of CSU, but these costs decreased to half in 12 months for patients with CSU who respond well to OMA. Thus, this study indicates that the prompt improvement of urticarial symptoms by OMA is expected to provide patients with subsequent reduction of economic burden compared with that at the time of starting OMA. In April 2020, the drug price of OMA in Japan was revised from ¥46 490 to ¥29 147/150 mg, contributing to further reduction of the economic burden placed on patients with CSU.

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