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Invited Review Article

Current status of sublingual immunotherapy for allergic rhinitis in Japan

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AIT, allergen immunotherapy;

SCIT, subcutaneous immunotherapy;

SLIT, sublingual immunotherapy;

AR, allergic rhinitis; JCP, Japanese cedar

pollen; JAU, Japanese allergy units;

JSA, Japanese Society of Allergology

ABSTRACT

Japanese cedar pollen (JCP) and house dust mite (HDM) are two major allergens that cause allergic rhinitis (AR) in Japan and the prevalence of AR is increasing. Pharmacotherapy is a commonly used treatment, but the level of patient satisfaction is very low. Allergen immunotherapy (AIT) is the only therapeutic modality that provides not only symptom relief but also quality of life improvement that leads to a high rate of satisfaction. In particular, sublingual immunotherapy (SLIT) is a safe and effective treatment for AR. Here we introduce a large-scale double-blind, placebo-controlled trial of SLIT in Japanese patients using JCP droplets or HDM tablets conducted in Japan. The immediate future of SLIT in Japan is also discussed.

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Introduction

Allergic rhinitis (AR) is the most common allergic disease in the world¹ that represents a global health problem. AR was estimated to affect nearly 40% of the Japanese population in a 2008 epidemiological study, which reported an increase in prevalence of about 10% compared with the same epidemiological study conducted in 1998.² In particular, the prevalence of Japanese cedar pollinosis (JCP) has increased more than other forms of AR caused by house dust mites (HDM) or pollinosis other than JCP, and continues to rise. AR is not a life-threatening illness; however, it can have a negative impact on quality of life,^{3,4} work productivity,⁵ learning ability,⁶ and sleep.⁷ In addition, the onset of AR has preceded the development of bronchial asthma (BA) in many patients according to a preliminary prospective small

study.⁸ Furthermore, recent reports suggest that AR in preschool children is a predictor for subsequent wheezing onset in school-aged children,⁹ and that AR in adults is also a risk factor for asthma in adults.¹⁰

JCP and HDM are the two major allergens in Japan. Other allergens commonly seen in allergic patients in Japan are cypress pollen, orchard grass, ragweed, mugwort, Birch, and Japanese Alder. The allergenicity of Japanese cedar and cypress allergens is homologous and nearly 70% of JCP-sensitized subjects also respond to cypress pollen.¹¹ Furthermore, JCP and HDM are a commonly seen combination of polysensitized allergens in allergic subjects, although patients polysensitized to more than three allergens were also recognized. Polysensitized and polyallergic patients are likely to have persistent rhinitis symptoms and their symptoms tend to become serious and intractable.

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Major allergens in Japan

Characteristics of pollinosis

In the spring, large amounts of JCP and cypress pollens disperse in Japan. Because JCP and cypress pollens disperse over several tens to thousands of kilometers, people living in urban areas also suffer from pollinosis. One epidemiological survey has indicated that 26% of the population suffers from seasonal allergic rhinitis caused by JCP and cypress pollen.² This is unique compared with other kinds of pollinosis around the world in that the Japanese cedars (JC) and cypress trees that disperse pollen in the spring in Japan are planted forests and not natural ones.

Nearly 70% of the land in Japan is forested, and about 40% of the forests are planted. Seventy percent of these comprise JC and cypress trees that disperse pollen in the spring. JC and cypress trees that were planted as the result of massive afforestation policies after World War II. These planted forests were not harvested because of competition from cheap imported wood.¹¹ As a result, JC and cypress trees that are 30 years old or over disperse a large amount of pollen every spring.

HDM allergens

HDMs are a major indoor allergen causing AR not only in Japan but also in other areas of the world. *Dermatophagoides pteronyssinus* (DP) and *Dermatophagoides farina* (DF) are commonly distributed HDM throughout the world; however, there is a higher density of HDM allergens in bedclothes in Japan, with a much higher concentration of *Dermatophagoides* species (Der 1) compared with the United States and Europe.¹² This indicates a large contribution of mite allergens to inducing perennial allergic rhinitis in Japan.

In addition, a longitudinal study suggested that HDM sensitization influences JCP sensitization, i.e., students who were positive for HDM sensitization in the JCP-negative groups in the first grade of primary school developed significantly higher JCP-specific IgE antibody levels compared with HDM-negative students over the 6 years of primary school.¹³ However, HDM sensitization did not affect the increase of JCP-specific IgE levels in the initially JCP-positive groups.

Treatment of AR

Management of AR consists of elimination and/or avoidance of environmental allergens, pharmacotherapy, allergen-specific immunotherapy (AIT) and surgical treatment.² Among these treatment modalities, AIT induces clinical tolerance, has long-term efficacy, and reduces the reliance on pharmacotherapy. In addition, AIT is the only form of therapy available that can alter the natural course of allergic diseases. As for AIT, subcutaneous immunotherapy (SCIT) has been used over the past century.² However, sublingual immunotherapy (SLIT) has been available very recently in Japan. This review article will discuss AIT, especially the current status of SLIT in Japan.

History of AIT in the world and Japan

AIT clinical research was begun more than a century ago by Leonard Noon.¹⁴ It was administered as a subcutaneous injection called SCIT until the sublingual trial was developed in 1986.¹⁵ In Japan, SCIT using non-standardized house dust crude allergen extract began in 1963 and continued until 2015, when the

Japanese Allergy Society (JSA) task force developed standardized mite allergen.¹⁶

JCP crude allergen has been also available since 1969 and was used in clinical practice until 1999. A standardized JCP allergen for SCIT became available in 2000 and has been used in general clinical practice ever since.

The use of SLIT was proposed following surveys describing SCIT-related deaths, leading to increased interest in the safety as well as the risks and benefits of SCIT. SLIT was first introduced in the EAACI guidelines in 1993¹⁷, and was then mentioned as a possible alternative to SCIT in a World Health Organization (WHO) position paper in 1998.¹⁸ SLIT was described as being as effective as SCIT and as having a better safety profile than SCIT in a WAO position paper in 2009.¹⁹ The ARIA guidelines (2001)²⁰ documented SLIT, and have consistently supported the effectiveness and safety of SLIT throughout subsequent updates. SLIT is currently available in many countries including those in Europe, North and South America, and Asia.

There is an urgent need in Japan to prepare guiding principles for the safe administration of SLIT. The Japanese Rhinologic Society task force prepared clinical questions concerning SLIT and searched literature published between January 2003 and December 2012. Qualifying studies were analyzed and the results evaluated, consolidated and codified. Finally, we presented evidence-based recommendations concerning SLIT in 2012.²¹

A phase III clinical trial on SLIT for JCP was conducted in 2011 and 2012.

A standardized JCP extract for SLIT, Cedartolen[®] has been available since October 2014. In addition, large-scale phase II/III clinical trials on SLIT tablets, produced by companies overseas, for Japanese patients with HDM-induced allergic rhinitis were conducted by two pharmaceutical companies separately. As a result, the Ministry of Health, Labour and Welfare approved two different SLIT tablets: Miticure[®] and Actair[®]. They have been available since June 2015. Consequently, one SLIT extract Cedartolen[®] for JCP and two SLIT tablets Miticure[®] and Actair[®] are available for HDM-induced allergic rhinitis in Japan.

Next, I introduce randomized, double-blind, placebo-controlled large scale trials of the JCP SLIT extract in adult Japanese JCP pollinosis patients and HDM SLIT tablet in Japanese HDM-induced AR, separately.

Efficacy and safety of SLIT extract in patients with JCP

Five hundred and thirty-one patients with JCP, aged 12–64 years, who had had symptoms of JCP for the previous 2 years and JCP-specific IgE levels (ImmunoCAP) of class 3 or higher, were randomized into a Cedartolen[®] group and a placebo group.²² Treatments were given for an average of 18 months from October 2010 to April 2012. Treatment began before the start of the pollen season in 2011 and continued to the end of the pollen season in 2012. The primary endpoint was the total nasal symptom and medication score (TNSMSs) during the peak symptom period in the second season. As a result, the TNSMSs during the peak symptom period were significantly lower in the SLIT group than in the placebo group (Fig. 1). There was a 30% reduction compared with the placebo group, suggesting clinically relevant efficacy. At least one adverse event (AE) occurred in 212 of the 266 subjects (79.7%) in the SLIT group and in 189 of the 265 subjects (71.3%) in the placebo group. The most common AEs were mouth edema, throat irritation, headache, oral pruritis and ear pruritis, and most of the AEs were mild and required no treatment. No anaphylactic reactions and no deaths occurred. Treatment-related AEs occurred in 36 subjects (13.5%) in the SLIT group and 14 (5.3%) in the placebo group (Table 1).

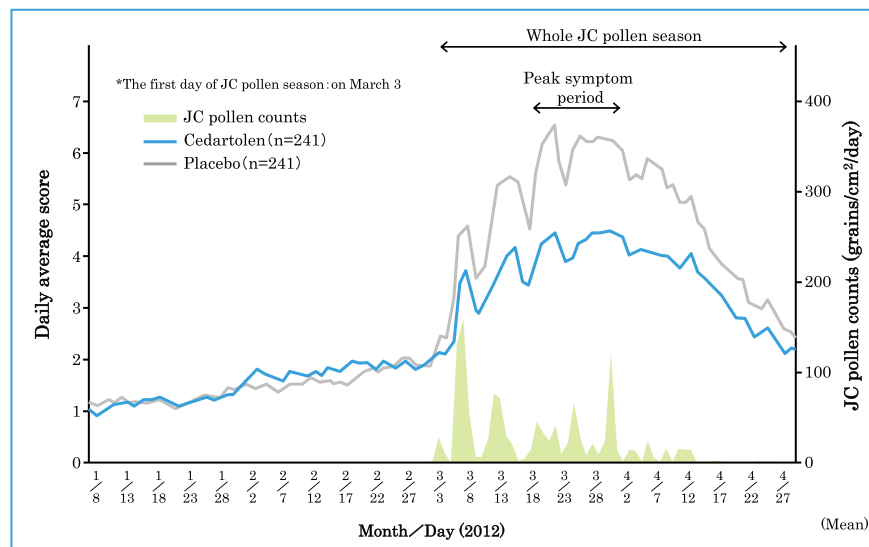


Fig. 1. Total Nasal Symptom Medication Score (TNSMS) in 2012. The placebo group is represented by the grey line, the SLIT group by the blue line, the JC pollen count by green shading. Adapted from Cedartolen® interview from Torii, Tokyo 2018 (in Japanese).²³

Table 1

Adverse events occurring in patients with JC pollinosis treated with JC pollen extract or placebo.

Summary of adverse events	JC pollen extract (n = 266)		Placebo (n = 265)	
	subjects, n (%)	events, n	subjects, n (%)	events, n
Total of adverse events	212 (79.7)	634	189 (71.3)	546
Treatment-related adverse events	36 (13.5)	52	14 (5.3)	27
Causal relationship				
Possible	11 (4.1)	15	1 (0.4)	2
Probable	29 (10.9)	37	13 (4.9)	25
Unlikely	207 (77.8)	582	187 (70.6)	519
Severity				
Mild	210 (78.9)	613	186 (70.2)	526
Moderate	16 (6.0)	19	18 (6.8)	20
Severe	2 (0.8)	2	0 (0.0)	0

Adapted from Okamoto *et al.*²² with permission.
JC, Japanese cedar.

Efficacy and safety of HDM SLIT tablet in Japanese adults and adolescents with HDM-induced AR

As mentioned previously, there are two HDM SLIT tablets available in Japan. Here I present the efficacy and safety of the SQ HDM tablet Miticure® in Japanese patients with HDM-induced AR.²⁴

A total of 946 subjects were randomly assigned to receive daily treatment with a SQ HDM SLIT tablet at a dose of 20,000 JAU (12 SQ) or 10,000 JAU (6 SQ) or a placebo. A nominal strength of 10,000 JAU has the same potency as 6 SQ-HDM (the unit used in Europe and the United States). Before reaching the maintenance dose, an up-dosing of 1 or 2 weeks was chosen. The subjects received treatment for 12 months. The primary endpoint was the total combined rhinitis score (TCRS), i.e., the sum of the rhinitis symptom and medication score during the last 8 weeks of the treatment period.

The differences in adjusted mean TCRS during the treatment period between the placebo and active groups tended to increase with increasing treatment period. The adjusted mean TCRS at week 12 in both active groups were significantly different from those in

the placebo group. This difference was maintained until the end of the treatment period. The primary endpoint was the TCRS during the last 8 weeks of the treatment period. The absolute differences in adjusted means TCRS to the placebo were 1.15 ($p < 0.001$) in the 10,000 JAU group and 0.09 ($p < 0.001$) in the 20,000 JAU group, respectively (Table 2). The relative differences to the placebo group were 22% and 19% in the 10,000 and 20,000 JAU groups, with 95% CI upper limits of 13% and 10%, respectively.

Adverse drug reactions (ADRs) were observed in 63.6% of the subjects in the active treatment groups (Table 3). No marked differences were seen between the two active treatment groups. The incidence of ADRs leading to interruption was higher in the active groups than in the placebo group, and most of the ADRs reported in either group were mild in severity. The most commonly observed ADRs were month edema, oral pruritus, and throat irritation. An anaphylactic reaction was reported in one subject in the placebo group.

In Europe, 12 SQ-HDM (20,000 JAU) was chosen as the marketed dose, as a more robust response with regard to key secondary endpoints was observed.

In Japan, 6 SQ-HDM (10,000 JAU) was chosen as the marketed dose, with the reason being that the differences in primary and secondary endpoints were modest.

As I have mentioned previously, another HDM tablet, Actair®, is also available in Japan. Here, I give a brief summary of the double-blind, placebo-controlled trial on the SLIT tablet Actair® for patients with HDM-induced AR in Japan.²⁵

A total of 968 subjects were randomized to receive 300 IR (the same potency as 57,000 JAU), 500 IR (95,000 JAU), or placebo groups. Before reaching the maintenance dose, an up-dosing of 2 weeks was chosen. The subjects received treatment for 52 weeks. The primary efficacy endpoint was the Average Adjusted Symptom Score (AASS) during the last 8 weeks of the treatment period.

The AASSs over week 44–52 in both active groups significantly improved compared with that in the placebo group. The mean absolute and relative differences in the AASSs (vs placebo) were 1.11 (18.2%) for the 300 IR group and 0.80 (13.1%) for the 500 IR group. The differences between the 300 IR and 500 IR groups was not statistically significant. The AASS in the 300 IR group was significantly improved at week 8–10, and this improvement was maintained until the end of the treatment.

Table 2

Analytic results on the primary end point (TCRS).

Analysis set	Treatment group	No.	Adjusted mean	Absolute difference from placebo (95% CI)	P value	Relative difference to placebo (95% CI)
FAS (LME)	Global null hypothesis (placebo = 10,000 JAU = 20,000 JAU)				<.001	–
	Placebo	285	5.14	–	–	–
	10,000 JAU	285	3.99	1.15 (0.64 to 1.65)	<.001	22% (13% to 31%)
	20,000 JAU	281	4.14	0.99 (0.48 to 1.50)	<.001	19% (10% to 28%)
ITT (MMRM)	All active treatment	566	4.07	1.07 (0.62 to 1.52)	<.001	21% (13% to 28%)
	Placebo	317	5.15	–	–	–
	10,000 JAU	304	3.95	1.19 (0.70 to 1.69)	<.001	23% (14% to 31%)
	20,000 JAU	307	4.14	1.00 (0.51 to 1.49)	<.001	19% (10% to 28%)
PPS (LME)	All active treatment	611	4.05	1.10 (0.68 to 1.52)	<.001	21% (14% to 28%)
	Placebo	276	5.12	–	–	–
	10,000 JAU	279	3.98	1.15 (0.64 to 1.65)	<.001	22% (13% to 31%)
	20,000 JAU	274	4.16	0.96 (0.45 to 1.48)	<.001	19% (9% to 27%)
	All active treatment	553	4.07	1.06 (0.61 to 1.51)	<.001	21% (13% to 28%)

Adapted from Okubo *et al.*²⁴ with permission.

TCRS, Total combined rhinitis score; FAS, Full analysis set; ITT, Intention-to-treat; PPS, Pre-protocol analysis set; LME, Linear mixed effect; MMRM, Mixed-model repeated model.

Table 3

Summary of safety.

Treatment group	Placebo (n = 319), no. (%)	10,000 JAU (n = 313), no. (%)	20,000 JAU (n = 314), no. (%)	All active treatment (n = 627), no. (%)	Overall, no. (%)
Serious AE	3 (0.9)	5 (1.6)	5 (1.6)	10 (1.6)	13 (1.4)
Serious ADR	–	–	–	–	–
AE					
All AEs	256 (80.3)	280 (89.5)	284 (90.4)	564 (90.0)	820 (86.7)
Mild	232 (72.7)	252 (80.5)	254 (80.9)	506 (80.7)	738 (78.0)
Moderate	24 (7.5)	27 (8.6)	30 (9.6)	57 (9.1)	81 (8.6)
Severe	–	1 (0.3)	–	1 (0.2)	1 (0.1)
ADRs					
All ADRs	54 (16.9)	199 (63.6)	200 (63.7)	399 (63.6)	453 (47.9)
Mild	51 (16.0)	192 (61.3)	191 (60.8)	383 (61.1)	434 (45.9)
Moderate	3 (0.9)	7 (2.2)	9 (2.9)	16 (2.6)	19 (2.0)
Severe	–	–	–	–	–
Significant AEs					
Anaphylactic reaction	1 [†] (0.3)	–	–	–	1 (0.1)
Asthma	3 (0.9)	3 (1.0)	2 (0.6)	5 (0.8)	8 (0.8)
AEs leading to discontinuation [‡]	9 (2.8)	7 (2.2)	5 (1.6)	12 (1.9)	21 (2.2)
ADRs leading to interruption	5 (1.6)	14 (4.5)	14 (4.5)	28 (4.5)	33 (3.5)

Adapted from Okubo *et al.*²⁴ with permission.

TCRS, Total combined rhinitis score; FAS, Full analysis set; ITT, Intention-to-treat; PPS, Pre-protocol analysis set; LME, Linear mixed effect; MMRM, Mixed-model repeated model.

[†] This subject is included in the serious AEs.[‡] Including serious AEs leading to discontinuation: 1 subject in the placebo group and 1 subject in the 20,000-JAU group; subjects with asthma leading to discontinuation: 2 subjects in the placebo group and 3 subjects in the 10,000-JAU group.

Adverse drug reactions (ADRs) were observed in 66.8% of the 300 IR group, 73.1% of the 500 IR group, and 18.6% of the placebo group. No marked differences were seen between the two active treatment groups. The incidence of ADRs leading to withdrawal was higher in the active group than in the placebo, and most of the ADRs were mild in severity. The most frequent ADRs were throat irritation, mouth edema, and oral and ear pruritis. No cases of anaphylactic shock were reported. Comparing between 300 IR and 500 IR, efficacy was almost the same; however, 300 IR tended to be slightly safer than 500 IR, and, consequently, 300 IR was chosen as the marketed dose.

Comparing the two RCT trials, it seems likely that the efficacy of Miticure[®] and Actair[®] is the same, although the strengths of the two HDM SLIT tablets were quite different according to the JAUs (10,000 and 57,000, respectively) assigned by JAS task force. The JAS task force selected measurement of Der 1 content as the surrogate in vitro assay for determining the potencies of HDM extracts.¹⁶ That is to say, Miticure[®] is 'low dose' and Actair[®] is 'high dose' in terms of Der 1 content. However, two tablets are different in formulation; fast-dissolving freeze-dried tablets (Miticure[®]) and compressed tablets (Actair[®]). Doi *et al.*²⁶ indicated that compressed tablets take

more time to release allergen contents and that longer sublingual holding time is needed for in vitro experimental studies. Doing so may result in roughly the same allergen bioavailability of the two tablets if used with the recommended sublingual holding time, and consequently the same efficacy. A report from a Task Force of the EAACI Immunotherapy Interest Group stated that "designation of lower and higher doses is only relevant for identical allergen preparations used within a given study".²⁷

The immediate future of SLIT in Japan

SLIT in children

Until recently, SLIT for JCP and HDM had been indicated for adults and adolescents aged 12 years and older in Japan. AIT induces not only clinical tolerance and has long-term efficacy, but it can also prevent sensitization and AR onset caused by other allergens. In other words, it can alter the natural course of allergic diseases. Accordingly, AIT may be a good treatment option for children whose symptoms are not adequately controlled with pharmacotherapy.

Efficacy and safety of SLIT tablet in Japanese children with JCP

Cedacure® (cedar pollen tablet) was developed by Torii, Pharmaceutical Co. Ltd., and a large-scale trial using with JCP subjects aged 5–64 years was carried out in 2015. The trial included children aged 5–11 years.

In this placebo-controlled randomized trial, subjects received 2000 JAU, 5000 JAU, or 10,000 JAU cedar pollen tablet, or placebo. After 1 year treatment, total nasal score and medication score was significantly improved in the active groups compared with the placebo during the peak pollen season. In addition, TNSMSs with subjects receiving 5000 JAU and 10,000 JAU were significantly lower than those of 2000 JAU. However, similar improvement of TNSMSs between subjects receiving 5000 JAU and 10,000 JAU was observed. As for safety, no anaphylactic reactions or deaths were observed. The efficacy and safety between subjects aged 5–17 years and 18–64 years showed the same profile. Consequently, 5000 JAU cedar pollen tablet was chosen as an appropriate marketed dose considering its efficacy and safety.²⁸ Cedacure® obtained manufacturing approval in September 2017, and it is anticipated to be available in clinical practice in the near future.

Efficacy and safety of HDM SLIT tablet in Japanese children with HDM-induced AR

A large-scale randomized, double-blind, placebo-controlled trial was conducted at various sites within Japan from July 2015 to November 2016. Japanese children aged 5–17 years were randomized to either the Japanese marketed dose of 10,000 JAU Miticure® or placebo.²⁹ The subjects received treatment for about 1 year. The total combined rhinitis score (TCRS) during the last 8 weeks of the treatment period was significantly improved compared with placebo. No serious ADRS were reported. All ADRS were mild or moderate and recovered early. No anaphylactic reactions were observed. Local reactions (mouth swelling, stomatitis, and throat irritation) were the reasons for the interruption in most of the subjects.

The efficacy and safety of Actair® tablet for pediatric patients with HDM-induced AR were also observed in a large scale randomized, double-blind placebo controlled trial.³⁰

In February 2018, the Ministry of Health, Labour and Welfare approved the HDM tablets Miticure® and Actair® for use in pediatric patients. A tablet for JCP is expected to be its approved for use in pediatric patients and adults. Thus, it is likely that the Japan market will have tablets available to treat JCP- and HDM-induced AR in the near future.

Sequential SLIT treatment

In order for SLIT to be useful for many poly-allergic patients, especially both JCP- and HDM-sensitized AR patients, it is necessary to clear its safety for both forms of administration. We tried sequential SLIT with JCP droplets and HDM tablet and observed their safety profiles.³¹

Patients were treated with JCP droplets for 4 weeks followed by sequential SLIT treatment where the JCP droplets and HDM tablets were administered with a 5-min interval for 24 weeks. Most of the AEs were mild and sequential SLIT was well tolerated. It is important to examine the efficacy and safety of sequential SLIT tablets (Cedacure® and Miticure®) when the JCP tablet is available.

In addition, it is likely that a combination of SLIT tablet, with JCP and cypress pollen tablet, is likely to be the desired treatment, because 70–80% of seasonal AR patients with JCP are also sensitive to cypress pollen.

Conclusion

SLIT in Japan is still in its infancy. As for SCIT, it has been performed in a limited number of facilities because of the occurrence of anaphylaxis. However, every doctor who attends an e-learning for allergen immunotherapy and passed the test can prescribe the SLIT droplet and tablet. Furthermore, as its drug adverse reactions are mild compared with SCIT, it is easy to introduce SLIT.

However, before introducing SLIT, a correct diagnosis of JCP-or HDM-induced AR is necessary, and the appropriate indication for SLIT must be considered carefully.²¹ Adequate informed consent from patients with regard to the administration schedule of SLIT and local AE frequently observed during the early time of the introduction of SLIT is also required. Doctors need to prepare for AEs when necessary even if they are few and mild. This could improve both patient adherence and the efficacy of SLIT. The increased use of SLIT will depend upon appropriate treatment circumstances and education of patients with regard to the disease and immunotherapy.

Conflict of interest

KM received lecture fees from Torii and Shionogi. TM received research funding from Torii. AK has no conflict of interest.

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