Safety of Dual Sublingual Immunotherapy with Japanese Cedar Pollen and SQ House Dust Mite SLIT-Tablets in Children, Adolescents and Adults

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Rationale

In Japan, many patients with allergic rhinitis (AR) are sensitized to both Japanese cedar pollens (JCP) and house dust mites (HDM). The ratio of HDM and JCP co-sensitized patients is estimated at 30 to 50 % based on our previous SQ-HDM or JCP SLIT tablet clinical trials in Japanese adult and adolescent. The fast-dissolving freeze-dried JCP sublingual immunotherapy (SLIT) -tablets and SQ HDM SLIT-tablets are available with no limitation of age in Japan. We conducted a post-marketing clinical trial to investigate the safety of dual SLIT-tablet administration and showed the treatment was well tolerated. This analysis examined the safety across subgroups of children, adolescents, and adults.

Methods

This was a multicenter, open-label randomized, parallel-group trial (Figure 1).

A total of 109 patients aged 5-64 years with both JCP and HDM AR were treated with either JCP tablets (JCP-first group; n=55) or SQ HDM SLIT-tablets (HDM-first group; n=54) solely for 4 weeks, followed by co-administration of the two tablets for 8 weeks.

These patients were divided into two groups

- JCP-first group (N= 55): 1st administration was JCP SLIT tablet
- HDM-first group (N=54): 1st administration was SQ HDM SLIT tablet

During co-administration period, each tablet was placed under the tongue for 1 minute prior to swallowing, second tablet was administered within 5 minutes after swallowing first tablet.

The subgroup analyses were conducted by age of these patients: 5-11 years (children, n= 34), 12-17 years (adolescents, n= 24) and 18-64 years (adults, n= 51).

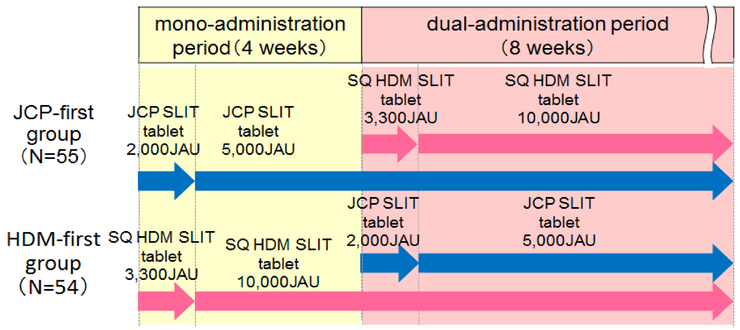

Figure 1: Trial design

Results

98.2% (N=54) in JCP-first group and 96.3% (N=52) in HDM-first group completed the study.

The overall occurrence of adverse drug reactions (ADRs) were 78.2% in JCP-first group and 74.1% in the HDM-first group . No serious ADRs occurred. Most ADRs were mild: 99% in the JCP-first group, and 100% in the HDM-first group.

There was no increase in intensity of ADRs following the start of dual SLIT. The occurrence of ADRs in the 4 weeks of mono JCP SLIT was 63.6%, and the 8 weeks of dual SLIT was 69.1%. The occurrence of ADRs in the 4 weeks of mono SQ HDM SLIT was 64.8%, and the 8 weeks of dual SLIT was 52.8% (Figure 2).

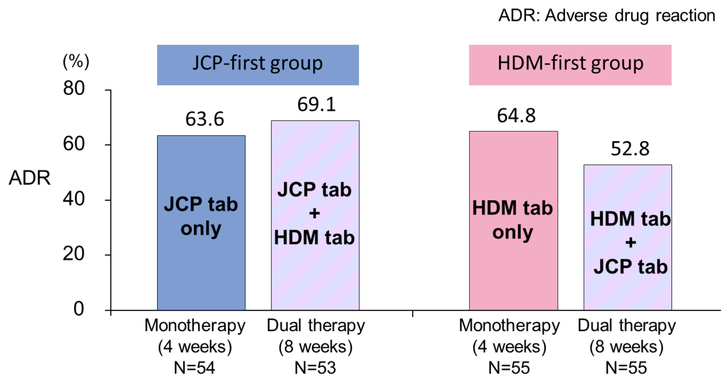

Figure 2: Occurrence of ADRs in each of period

The incidence of ADRs in the subgroups were 79.4% (5-11 years) , 83.3% (12-17 years) and 70.6% (18-64 years), respectively. No obvious differences of the incidence of ADRs were seen among subgroups by age (Table 1).

Table 1: Occurrence of ADRs in each of period for age subgroups

	Treatment period（12 weeks）				Monotherapy（4 weeks）				Dual SLIT therapy（8 weeks）			
	N	ADR			N	ADR			N	ADR		
		E	N	%		E	N	%		E	N	%
5-11 years	34	140	27	79.4	34	60	22	64.7	34	80	21	61.8
12-17 years	24	108	20	83.3	24	36	19	79.2	23	72	18	78.3
18-64 years	51	124	36	70.6	51	58	29	56.9	51	66	27	52.9

E, number of events; N, number of patients; %, percentage of patients with ADRs

Most ADRs were local reactions, such as mouth swelling, oral pruritus and throat irritation in all age groups (Table 2).

The local reactions occurred within first week mostly and tended to decrease in and after two weeks in both mono- and dual-administration periods of both groups. These local reactions were mild and recovered without discontinuation of JCP and SQ HDM SLIT-tablets.

Table 2: The preferred terms of the 5 most common ADR

MedDRA / JPT	5-11 years（N=34）			12-17 years（N=24）			18-64 years（N=51）			Total（N=109）		
	E	N	%	E	N	%	E	N	%	E	N	%
Mouth swelling	12	8	23.5	9	6	25.0	18	14	27.5	39	28	25.7
Oral pruritus	16	9	26.5	11	3	12.5	18	12	23.5	45	24	22.0
Throat irritation	14	8	23.5	4	4	16.7	10	8	15.7	28	20	18.3
Rhinorrhea	9	6	17.6	11	8	33.3	3	3	5.9	23	17	15.6
Oropharyngeal discomfort	6	4	11.8	6	6	25.0	7	6	11.8	19	16	14.7

E, number of events; N, number of patients; %, percentage of patients with ADRs

Disclosure of presenting author: Y.Okamoto was an investigator on this trial.

Funding: The SQ HDM SLIT tablets (Torii, Tokyo, Japan; manufactured by ALK-Abelló, Hørsholm, Denmark) and JCP SLIT tablets (Torii) are fast-dissolving freeze-dried tablets and were provided by Torii, the trial sponsor.

Conclusion

In this trial, no new safety concerns were identified moving from mono to dual SLIT-tablet regimens involving JCP and SQ HDM SLIT-tablets administered within 5 minutes apart.

It was also similar outcome by age group analysis.

The safety profiles were similar regardless of which SLIT-tablet was administered first.

Efficacy and safety of the ragweed SLIT-tablet across peak and entire season in children with allergic rhinoconjunctivitis

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Introduction

The ragweed sublingual immunotherapy (SLIT)-tablet improves symptoms and decreases symptom-relieving medication use in adults with allergic rhinitis with or without conjunctivitis (AR/C) during peak ragweed pollen season (RPS) when symptoms are most burdensome and throughout the entire season.[1,2] The efficacy and safety of the ragweed SLIT-tablet during the peak and entire season was evaluated in children in the largest pediatric SLIT-tablet trial conducted to date.

Methods

In an international, double-blind trial, children aged 5-17 years with ragweed AR/C with or without asthma were randomized to daily ragweed SLIT-tablet or placebo approximately 12 to 20 weeks before the RPS (NCT02478398). Treatment continued throughout the RPS (approximately 8 weeks). Symptom-relieving medication was provided to both treatment groups. The ragweed SLIT-tablet dose evaluated was the same as the dose approved for adults (12 Amb a 1-U).

The start of the RPS for each study site was defined as the first day of 3 consecutive recorded days with a pollen count of ≥10 grains/m^3, and the end of the RPS was defined as the last day of the last 3 consecutive recorded days with a pollen count ≥10 grains/m^3. Peak RPS for each study site was defined as the 15 consecutive recorded days within the RPS with the highest 15-day moving average pollen count.

Participants (or guardians) recorded allergy symptoms, symptom-relieving medication use, and asthma symptoms in an e-diary once-daily. Six rhinoconjunctivitis symptoms were measured on a scale of 0 to 3. The average total combined score (TCS; sum of rhinoconjunctivitis daily symptom score [DSS] and daily medication score [DMS]) was assessed for peak RPS (primary endpoint) and the entire RPS (key secondary endpoint). Other key secondary endpoints were DSS and DMS during peak RPS. DSS during the entire RPS was a tertiary endpoint. DMS during the entire RPS was analyzed post hoc. Adverse events (AEs) were monitored by questioning the participant at each trial visit and by the participant recording on a SLIT Report Card during the first 28 days of treatment.[3]

Results

In all, 1025 children were randomized, 1022 received treatment, and 952 completed the trial. Baseline characteristics were well balanced between treatment groups. The majority of participants were male (62.9%) and white (93.0%); the mean age was 12.1 years and 59.9% were aged 12 to 17 years. A history of asthma was reported in 42.7% of participants and 77.7% were polysensitized.

Mean pollen counts during peak RPS were approximately 186 grains/m^3/day and during the entire RPS were approximately 85 grains/m^3/day.

Relative TCS improvement with the ragweed SLIT-tablet versus placebo during peak RPS was 38.3% (95% CI, 29.7%, 46.0%; least square [LS] mean difference=2.73; P<0.001) and during the entire RPS was 32.4% (95% CI, 23.3%, 40.7%; LS mean difference=1.86; P<0.001; **Figure 1**). During peak RPS, DSS and DMS were improved with the ragweed SLIT-tablet versus placebo by 35.4% (95% CI, 26.1%, 43.2%; LS mean difference=1.40; P<0.001) and 47.7% (95% CI, 32.5%, 59.8; LS mean difference=1.84; P<0.001), respectively (**Figure 2**). During entire RPS, DSS and DMS were improved with the ragweed SLIT-tablet versus placebo by 30.4% (95% CI, 20.7%, 38.6%; LS mean difference=0.99; P<0.001) and 35.0% (95% CI, 22.4%, 38.6; LS mean difference=0.87; P<0.001), respectively (**Figure 2**).

Figure 1. Total combined score (TCS) during the peak and entire ragweed pollen season (RPS) (Full Analysis Set, observed data).

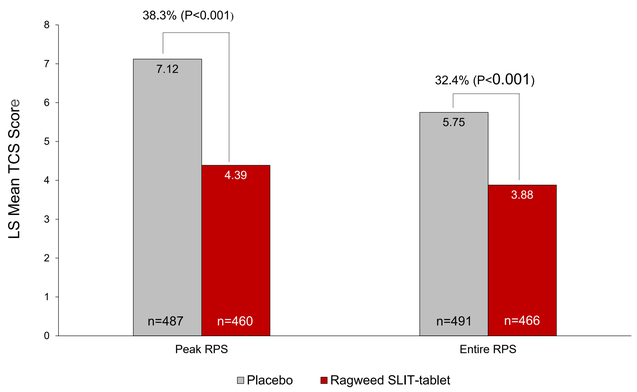
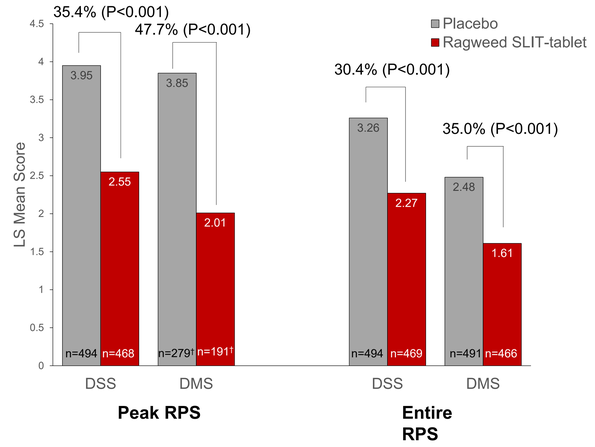


Figure 2. Daily symptom score (DSS) and daily medication score (DMS) during the peak and entire ragweed pollen season (RPS) (Full Analysis Set, observed data). During the peak RPS †269 participants on ragweed SLIT-tablet and 208 participants on placebo had no symptom-relieving medication use.



Treatment was well tolerated. No events of anaphylaxis, airway compromise, or severe treatment-related systemic allergic reactions were reported. The most common AEs related to ragweed SLIT-tablet were throat irritation, oral pruritus, and ear pruritus (**Table 1**). Discontinuation rates due to AEs were 3.9% with ragweed SLIT-tablet and 1% with placebo. Two systemic allergic reactions related to ragweed SLIT-tablet were reported (non-serious, mild skin pruritus and redness beginning on day 6 and serious moderate hypersensitivity [urticaria] on day 26). One additional participant experienced a serious AE related to ragweed SLIT-tablet (hospitalized on day 126 with severe laryngitis that resolved in 2 days). No participants treated with ragweed SLIT-tablet received intramuscular epinephrine.

Table 1. Treatment-related AEs reported by ≥5% of participants in either treatment group (all participants as treated).

Treatment-related AEs, n (%)	Ragweed SLIT-Tablet (n=513)	Placebo (n=509)
Throat irritation	249 (48.5)	92 (18.1)
Oral pruritus	244 (47.6)	59 (11.6)
Ear pruritus	174 (33.9)	32 (6.3)
Lip swelling	64 (12.5)	6 (1.2)
Glossodynia	63 (12.3)	12 (2.4)
Nausea	60 (11.7)	18 (3.5)
Oral pain	60 (11.7)	16 (3.1)
Pharyngeal edema	56 (10.9)	8 (1.6)
Swollen tongue	55 (10.7)	4 (0.8)
Upper abdominal pain	48 (9.4)	22 (4.3)
Stomatitis	33 (6.4)	5 (1.0)
Enlarged uvula	32 (6.2)	2 (0.4)

References

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3. Norquist J, et al. *Patient.* 2017;10:439-446.

Disclosure of presenting author: A.K. Ellis has participated in advisory boards for ALK Abello, AstraZeneca, Bausch Health, Circassia Ltd, GlaxoSmithKline, Kaleo, Merck, Mylan, Novartis, Nuvo, Pediapharm and Pfizer, has been a speaker for ALK, Aralez, AstraZeneca, Boehinger-Ingelheim, Meda, Mylan, Merck, Novartis, Pediapharm, Pfizer, Stallergenes-Greer, and Takeda. Her institution has received research grants from Bayer LLC, Circassia Ltd, Green Cross Pharmaceuticals, GlaxoSmithKline, Sun Pharma, Merck, Novartis, Pfizer, Regeneron and Sanofi.

The ragweed SLIT-tablet is effective and safe in children with AR/C during peak RPS when symptoms are greatest as well as throughout the entire RPS.

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