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ORIGINAL RESEARCH

Post-Marketing Surveillance of Adverse Events Following Vaccination with the Live-Attenuated Japanese Encephalitis Chimeric Virus Vaccine (Imojev®) in South Korea, 2015–2019

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ABSTRACT

Introduction: The live attenuated Japanese encephalitis chimeric virus vaccine (JE-CV; Imojev®) has been approved in South Korea for use in subjects aged ≥ 12 months since 2015. As part of the license agreement, a post-marketing surveillance study was undertaken to actively monitor the safety profile of JE-CV in the Korean population.

Methods: An observational, active safety surveillance study was conducted from 3 April 2015 through to 2 April 2019 at 12 centers in South Korea. Subjects aged ≥ 12 months who received a single dose of JE-CV (primary or booster) during a routine healthcare visit were recruited and followed up for solicited reactions (7 and 14 days for injection site and systemic reactions, respectively), non-serious unsolicited adverse events and serious adverse events within 42 days after vaccination.

Results: Overall, 810 subjects who received JE-CV were included in our analysis, the majority received the vaccine as a primary vaccination (94.9%; 769/810). There were 179 solicited reactions reported by 111 subjects; the majority of solicited reactions occurred within 0–3 days (80.4%; 144/179), were of 1–3 days' duration (79.3%; 142/179) and of grade 1 intensity (70.9%; 127/179). There were three grade 3 adverse reactions (irritability, pyrexia and malaise); all resolved within a few days. The incidence of solicited reactions were highest in those aged 12 to < 24 months (34.7% [52/150] subjects; 107 events) and 2 to < 10 years (17.8% [8/45] subjects; 14 events). All unsolicited adverse events (serious and non-serious) were unrelated to vaccination. There were no discontinuations due to adverse reactions/events.

Conclusion: JE-CV has a good safety profile under practice conditions in South Korea. No new safety issues were identified.

Trial registration: ClinicalTrials.gov identifier, NCT02933710

Keywords: Japanese encephalitis; Live-attenuated Japanese encephalitis chimeric virus vaccine; Safety; Vaccine

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Key Summary Points

Why carry out this study?

A post-marketing surveillance study was undertaken to actively monitor the safety profile of the live attenuated Japanese encephalitis chimeric virus vaccine (JE-CV; Imojev®) following its introduction in South Korea as part of the license agreement.

Subjects aged ≥ 12 months who received a single dose of JE-CV during a routine healthcare visit were followed up for solicited reactions, non-serious unsolicited adverse events and serious adverse events within 42 days after vaccination.

What was learned from the study?

This study supports the good safety profile of JE-CV when administered under real-life use in South Korea.

The safety profile of JE-CV described here is consistent with that reported in previous clinical studies in children and adults and another large phase IV, post-licensure study.

No new safety issues were identified with the introduction of JE-CV in the Korean population.

INTRODUCTION

The inactivated mouse brain-derived vaccine against Japanese encephalitis (JE) has been key in JE disease prevention in South Korea since its introduction in 1971 [1] and subsequent inclusion in the national childhood national immunization program in 1985 [1]. Since 2000, the mouse brain-derived JE vaccine has been administered as a three-dose primary series from age 12 months, with two subsequent boosters at 6 years and 12 years [2]. Yet despite high vaccination coverage, JE appears to have re-emerged in the last 2 decades in South Korea [1, 3, 4]; 118 cases were reported in the country between 2007 and 2017 [5]. Nonetheless, vaccination remains the best disease prevention strategy for JE disease control in endemic regions as there is currently no specific antiviral treatment.

In April 2015, the live attenuated JE chimeric virus vaccine (JE-CV; Imojev®) was approved by the Korean Ministry of Food and Drug Safety (MFDS) for use in subjects aged ≥ 12 months. In children and adolescents up to age 18 years the schedule consists of one primary dose followed by a booster 12–24 months later. In adults, a booster dose is not required for up to 5 years after the single vaccination dose. The use of JE-CV would thus reduce the number of doses required relative to the mouse brain-derived vaccine in the already crowded national childhood immunization program [6]. In addition, JE-CV could also potentially provide longer duration of protection.

As part of the license agreement, in accordance with Korean regulatory requirements for "Standards for Re-examination of New Drugs," a post-marketing surveillance study was required to actively monitor the safety profile of JE-CV specifically in the Korean population. Such surveillance is needed to help detect any new safety signals as the vaccine is introduced for wider use in a new region. Here we describe the safety profile of JE-CV during a multi-center, observational, active safety surveillance study undertaken in routine clinical practice in South Korea.

METHODS

Study Design

This post-marketing, observational, active safety surveillance study was conducted from 3 April 2015 through 2 April 2019 at 12 centers in South Korea (Clinical trials.gov: NCT02933710) in accordance with the Declaration of Helsinki (1964 and later amendments) and the Korean MFDS requirements for "Standard for Re-examination of New Drugs." The study protocol and

amendments were approved by the Institutional Review Board at the Hanil General Hospital study site (Seoul, South Korea); according to Korean MFDS guidelines ethical approval need only be obtained from one representative institution. Written informed consent was obtained from subjects aged ≥ 19 years or their parent(s) or other legal representative for those aged < 19 years.

Study Subjects

Subjects aged ≥ 12 months who received a single dose of JE-CV (either primary or booster dose) during a routine healthcare visit as immunization for the prevention of JE were recruited. Those participating or who planned to participate in another clinical study investigating a vaccine, drug, medical device or medical procedure during or in the 4 weeks preceding the present study period were excluded.

Safety Assessment

Subjects or parents/legally acceptable representatives were provided with diary cards, digital thermometers and flexible rulers (for measuring the size of injection site erythema and swelling) to record solicited injection site and systemic reactions as well as other unsolicited adverse reactions/events. Solicited injection site and systemic reactions were recorded daily for 7 and 14 days after vaccination, respectively. Solicited injection site reactions included pain/tenderness, erythema and swelling. Solicited systemic reactions in subjects aged < 24 months included fever, vomiting, crying abnormally, drowsiness, appetite loss and irritability. In subjects aged ≥ 2 years, solicited systemic reactions included fever, headache, myalgia and malaise. The intensity of the solicited reactions was graded on a three-point scale adapted to each age group (Supplementary materials, Tables S1–5). Body temperature was measured daily, with severity of each fever episode reported graded according to recorded highest body temperature during statistical analysis.

Unsolicited non-serious adverse events (assigned Medical Dictionary for Regulatory Activities [MedDRA] preferred term) were recorded for 42 days after vaccination. These were graded on a three-point scale as described above if included in the list of solicited reactions. Other unsolicited non-serious AEs were graded as follows: grade 1, no interference with activity; grade 2, some interference with activity; grade 3, significantly prevents daily activity. The actions taken to treat any adverse reactions or events were recorded on a five-point scale (0, none; 1, medication used; 2, healthcare provider contacted; 3, healthcare provider contacted and prescribed new medication; 4, hospitalized). Serious adverse events (defined according to the International Conference on Harmonisation E2A [ICH = E2A] guidelines for Industry [7]) were recorded throughout the study. The study sponsor assessed the causal relationship of each unsolicited adverse event to vaccination as related or unrelated.

Statistical Analyses

The sample size was predefined to ensure that there would be at least 600 safety evaluable subjects for the whole duration of the study in accordance with Article 6.3 of "Basic standard for re-examination of new drug" (Korean MFDS Notification No. 2011-60)." Assuming a 5% attrition rate, 632 subjects needed to be enrolled to ensure that the required number of subjects remained throughout the study. Subjects who received a dose of JE-CV according to approved local product labeling, and were followed-up for safety evaluation as per "Standards for Re-examination of New Drugs," were designated as the safety analysis set.

No statistical hypothesis was tested. The analysis was descriptive with numbers and percentages (95% confidence intervals [CIs]) of subjects with solicited and unsolicited adverse reactions/events and serious adverse events determined. The 95% CIs of percentages were calculated using the exact binomial distribution according to the Clopper-Pearson's method for proportions and using the normal approximation for quantitative data. Adverse reaction or

events were also analyzed by subject demographic characteristics; between group differences were assessed using Pearson's chi-square test or Fisher's exact test.

RESULTS

Subjects' Characteristics

A total of 823 subjects were enrolled: more subjects than planned were enrolled within a relatively short period after the study was expanded to include new participating sites. Of those recruited, 13 (1.6%) were excluded from the safety analysis set because of loss to follow-up (i.e., no further safety information provided after vaccination). The demographic characteristics of those included in the analysis are summarized in Table 1. Of 810 subjects who received JE-CV, the vast majority received it as a primary vaccination (94.9%; 769/810); the vaccine was injected in the upper arm in all subjects. There were no discontinuations due to adverse reactions or events in the study.

Safety Following Vaccination

Solicited Reactions

Solicited reaction reporting rates are summarized in Table 2. There were 179 solicited reactions reported by 111 subjects. The majority of solicited reactions occurred within 0–3 days (80.4%; 144/179), were of short duration (1–3 days) (79.3%; 142/179) and of grade 1 intensity (70.9%; 127/179). No action was required to treat symptoms for 91.1% (163/179) of the solicited reactions reported. There were three adverse reactions of grade 3 intensity: irritability in a 1-year-old girl who started on day 13 that lasted 2 days; pyrexia in a 2-year-old boy that started on day 7 and lasted 3 days; malaise in a 30-year-old woman that started on day 1 and lasted 4 days. The health care provider was contacted, and a prescription for new medication was received in the case of the grade 3 pyrexia, but no action was taken for the other two reactions. One reaction, pyrexia (grade 1) on day 1 in a 1-year-old girl, led to hospitalization; however, investigations revealed that this was a symptom of a urinary tract infection and reported as a serious adverse event unrelated to vaccination.

The incidence of solicited reactions by age group was highest in the 12 to < 24 month age group (34.67% [52/150] subjects; 107 events); however, the number and nature of solicited systemic reactions collected in this age group were considerably different from those collected in subjects aged ≥ 2 years. In the remaining age groups, the incidence of solicited reactions was highest in the 2 to < 10 year age group (17.8% [8/45] subjects; 14 events) and the 30 to < 40 year age group (9.3% [11/118] subjects; 22 events). The difference in the incidences of solicited reactions by age group was significant ($p < 0.0001$; chi-square test); the clinical significance of this difference is limited because of the higher number of reactions solicited in those aged 12 to < 24 months as already stated. In addition, there was a higher incidence of solicited reactions among subjects with concomitant medications/vaccination (29.9% [52/174] subjects, 111 events) than in those without (5.7% [36/636] subjects, 68 events) ($p < 0.0001$; chi-square test).

Unsolicited Non-Serious Adverse Events

Unsolicited non-serious adverse event reporting rates are summarized in Table 3. All non-serious adverse events were considered unrelated to vaccination. No unsolicited injection site reactions were reported. Overall, 172 non-serious systemic adverse events were reported by 98 subjects. The most frequently reported events were respiratory tract infections: 'bronchitis' (15.1%; 26/172 events), followed by 'nasopharyngitis' (14.0%; 24/172 events) and 'upper respiratory tract inflammation' (12.8%; 22/172 events). Most non-serious unsolicited adverse events occurred from day 8 onwards (75.6%; 130/172), were of 1–7-day duration (58.7%; 101/172) and were of grade 1 intensity (78.5%; 135/172). There was one adverse event of grade 3 intensity (pyrexia). The most common action taken regarding the unsolicited systemic events was to contact 'Health care provider and prescription of new medication' (93.0%; 160/172).

Table 1 Characteristics of subjects included in the analysis (safety analysis set)

Parameter	Number of subjects (*n* %)
Male	340 (41.98)
Female	470 (58.02)
Age group	
12 months < 24 months	150 (18.52)
24 months < 10 years	45 (5.56)
10 years < 20 years	17 (2.10)
20 years < 30 years	87 (10.74)
30 years < 40 years	118 (14.57)
40 years < 50 years	99 (12.22)
50 years < 60 years	118 (14.57)
≥ 60 years	176 (21.73)
Concomitant medication	
No	636 (78.52)
Yes	174 (21.48)
Alimentary tract and metabolism	53 (30.46)
Anti-infectives for systemic use	143 (82.18)
Blood and blood-forming organs	2 (1.15)
Cardiovascular system	14 (8.05)
Dermatologicals	4 (2.30)
Genitourinary system and sex hormones	1 (0.57)
Musculoskeletal system	62 (35.63)
Nervous system	51 (29.31)
Respiratory system	97 (55.75)
Sensory organs	1 (0.57)
Systemic hormonal (excluding sex hormones and insulins)	5 (2.87)

The incidence of unsolicited events was highest in the 2 to < 10 year age group (62.2% [28/45] subjects, 63 events), followed by the 12 to < 24 month age group (36.7% [55/150] subjects, 92 events) and the 30 to < 40 year age group (4.2% [5/118] subjects, 5 events). The difference in the incidences of unsolicited events by age group was significant ($p < 0.0001$; chi-square test across all ages groups). There was a higher incidence of unsolicited non-serious adverse events among subjects with concomitant medications/vaccination (55.8% [97/174] subjects, 171 events) than in those without (0.2% [1/636] subjects, 1 event) ($p < 0.0001$; chi-square test).

Table 2 Incidence of solicited reactions (safety analysis set)

	N	No. of subjects with events *n* (%)	95% CI (lower, upper)	No. of events
Solicited injection site reactions	810	51 (6.30)	(4.72, 8.20)	59
Injection site erythema	810	9 (1.11)	(0.51, 2.10)	9
Injection site pain	810	45 (5.56)	(4.08, 7.36)	45
Injection site swelling	810	5 (0.62)	(0.20, 1.43)	5
Solicited systemic reactions	810	60 (7.41)	(5.70, 9.43)	120
Assessed in subjects aged < 24 months only				
Crying	150	11 (7.33)	(3.72, 12.74)	11
Decreased appetite	150	16 (10.67)	(6.22, 16.74)	16
Irritability	150	10 (6.67)	(3.24, 11.92)	10
Somnolence	150	8 (5.33)	(2.33, 10.24)	8
Vomiting	150	7 (4.67)	(1.90, 9.38)	7
Assessed in subjects aged ≥ 2 years only				
Headache	660	7 (1.06)	(0.43, 2.17)	7
Malaise	660	14 (2.12)	(1.16, 3.53)	14
Myalgia	660	18 (2.73)	(1.62, 4.28)	18
Assessed in subjects of all ages				
Pyrexia	810	29 (3.58)	(2.41, 5.10)	29

Serious Adverse Events/Reactions

There were four serious adverse events reported by four subjects (all aged < 19 years), all unrelated to vaccination. These were all infections/infestations: pneumonia not otherwise specified, pneumonia due to respiratory syncytial virus, tonsillitis and urinary tract infection. All required hospitalization, and all subjects recovered.

DISCUSSION

Our post-marketing, observational, active safety surveillance study supports the good safety profile of JE-CV when administered under real-life use in South Korea. The safety profile of JE-CV described here is consistent with that reported in previous clinical studies in children and adults [8–13] and a large phase IV, post-licensure, safety study in children [14]. No new safety issues were identified. Solicited adverse reactions following vaccination were most frequently reported in the 12 to < 24 months age group, consistent with a previous clinical study that assessed single dose of JE-CV in both children and adults [12].

Our observational safety surveillance study has some limitations. Only one vaccination with JE-CV was assessed for each individual included. The decision to vaccinate was not controlled, which led to few subjects recruited in some age groups, particularly those aged 24 months to < 10 years and 10 years < 20 years. The low numbers in these age groups could be due in part to JE-CV not

Table 3 Incidence of unsolicited non-serious events (safety analysis set)

System organ class/preferred term	No. of subjects with events *n* (%)	95% CI (lower, upper)	No. of events *n*
Unsolicited non-serious events	98 (12.10)	(9.93, 14.55)	172
Gastrointestinal disorders	17 (2.10)	(1.23, 3.34)	18
Chronic gastritis	1 (0.12)	(0.00, 0.69)	1
Constipation	1 (0.12)	(0.00, 0.69)	1
Diarrhoea	2 (0.25)	(0.03, 0.89)	2
Dyspepsia	1 (0.12)	(0.00, 0.69)	1
Enteritis	6 (0.74)	(0.27, 1.61)	7
Fecaloma	1 (0.12)	(0.00, 0.69)	1
Gastric ulcer	1 (0.12)	(0.00, 0.69)	1
Gastritis	2 (0.25)	(0.03, 0.89)	2
Vomiting	2 (0.25)	(0.03, 0.89)	2
General disorders and administration site conditions	2 (0.25)	(0.03, 0.89)	2
Pyrexia	2 (0.25)	(0.03, 0.89)	2
Hepatobiliary disorders	1 (0.12)	(0.00, 0.69)	1
Hepatic function abnormal	1 (0.12)	(0.00, 0.69)	1
Immune system disorders	1 (0.12)	(0.00, 0.69)	1
Hypersensitivity	1 (0.12)	(0.00, 0.69)	1
Infections and infestations	76 (9.38)	(7.46, 11.60)	113
Acute sinusitis	2 (0.25)	(0.03, 0.89)	2
Bronchitis	24 (2.96)	(1.91, 4.38)	26
Bullous impetigo	1 (0.12)	(0.00, 0.69)	1
Cellulitis	1 (0.12)	(0.00, 0.69)	1
Conjunctivitis	2 (0.25)	(0.03, 0.89)	2
Croup infectious	1 (0.12)	(0.00, 0.69)	1
Cystitis	1 (0.12)	(0.00, 0.69)	1
Enterovirus infection	1 (0.12)	(0.00, 0.69)	1
Gastroenteritis	3 (0.37)	(0.08, 1.08)	3
Influenza	1 (0.12)	(0.00, 0.69)	1
Nasopharyngitis	23 (2.84)	(1.81, 4.23)	24
Otitis media	4 (0.49)	(0.13, 1.26)	4
Otitis media acute	1 (0.12)	(0.00, 0.69)	1

Table 3 continued

System organ class/preferred term	No. of subjects with events *n* (%)	95% CI (lower, upper)	No. of events *n*
Pharyngitis	5 (0.62)	(0.20, 1.43)	5
Pharyngotonsillitis	1 (0.12)	(0.00, 0.69)	1
Rhinitis	17 (2.10)	(1.23, 3.34)	17
Sinusitis	4 (0.49)	(0.13, 1.26)	4
Tonsillitis	2 (0.25)	(0.03, 0.89)	2
Upper respiratory tract infection	12 (1.48)	(0.77, 2.57)	14
Urinary tract infection	2 (0.25)	(0.03, 0.89)	2
Metabolism and nutrition disorders	1 (0.12)	(0.00, 0.69)	1
Decreased appetite	1 (0.12)	(0.00, 0.69)	1
Nervous system disorders	1 (0.12)	(0.00, 0.69)	1
Headache	1 (0.12)	(0.00, 0.69)	1
Respiratory, thoracic and mediastinal disorders	25 (3.09)	(2.01, 4.52)	29
Cough	2 (0.25)	(0.03, 0.89)	2
Epistaxis	1 (0.12)	(0.00, 0.69)	1
Rhinitis allergic	2 (0.25)	(0.03, 0.89)	2
Rhinorrhoea	2 (0.25)	(0.03, 0.89)	2
Upper respiratory tract inflammation	20 (2.47)	(1.51, 3.79)	22
Skin and subcutaneous tissue disorders	6 (0.74)	(0.27, 1.61)	6
Dermatitis atopic	1 (0.12)	(0.00, 0.69)	1
Rash	1 (0.12)	(0.00, 0.69)	1
Urticaria	4 (0.49)	(0.13, 1.26)	4

Coding dictionary: MedDRA version 19.0

currently being listed in the national immunization program; as such, it is possible that physicians may not have wished to switch to a new vaccine for the booster in these age groups. The higher numbers of participants recruited in the older age groups (age $\geq$ 30 years) are likely due to JE-CV being the only vaccine against JE approved for adults in South Korea.

The rate of unsolicited adverse events may reflect background rates for these events in the age groups recruited. Indeed, all unsolicited adverse events (serious and non-serious) were considered unrelated to vaccination. Subjects aged $<$ 2 years had more solicited reactions than those aged $\geq$ 2 years. However, the difference in the incidences of solicited reactions by age group observed could have been, in part, attributed to differences in the number and type of solicited reactions by age group. Although the study sample size was aligned with requirements of Korean regulatory authorities, it was not sufficient to allow for the investigation of rare or very rare adverse events.

CONCLUSION

In conclusion, JE-CV was shown to have a good safety profile under practice conditions in South Korea. No new safety issues were identified, and the safety profile was consistent with that reported in previous studies that assessed single-dose JE-CV administration in both children and adults.

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Compliance with Ethics Guidelines. This post-marketing, observational safety surveillance study was conducted from 3 April 2015–2 April 2019 at 12 centers in South Korea (Clinical trials.gov: NCT02933710) in accordance with the Declaration of Helsinki (1964 and later amendments) and the Korean MFDS requirements for "Standard for Re-examination of New Drugs." The study protocol and amendments were approved by the Institutional Review Board at the Hanil General Hospital study site; according to Korean MFDS guidelines ethical approval need only be obtained from one representative institution. Written informed consent was obtained from subjects aged $\geq$ 19 years or their parent(s) or other legal representative for those aged $<$ 19 years.

Data Availability. The datasets generated during and/or analyzed during the current study are not publicly available as these are in Korean language, but are available from the corresponding author on reasonable request.

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