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BRIEF REPORT

# Post-Marketing Surveillance of Hepatitis A Virus Vaccine (Avaxim® 160U) in South Korea from 2011 to 2015

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## ABSTRACT

***Introduction***: Hepatitis A, caused by hepatitis A virus (HAV), is one of the leading causes of acute hepatitis in South Korea. Avaxim® 160U is an inactivated hepatitis A vaccine that has been proven to be highly effective and well tolerated. It is licensed for use in more than 90 countries, and was approved for use in South Korea in 2011. Clinical trial and approval processes may not fully assess the safety and efficacy of a vaccine. Post-marketing surveillance (PMS) aims to provide a complete safety profile of a vaccine in a real-life setting. PMS trials are mandatory in South Korea to retain drug licensure.

***Methods***: This post-marketing observational study (NCT01838070) was conducted over 4 years at 16 centres in South Korea, and aimed to observe and record all types of adverse events (AE) occurring in an adult population after vaccination with Avaxim® 160U. This included solicited events, unsolicited non-serious events, unexpected events and serious events.

***Results***: Case report forms were collected from 614 vaccinees, all of whom completed 30 days of follow-up post-vaccination, of whom 36 (5.9%) experienced 53 solicited and unsolicited AEs, 17 (2.8%) experienced 22 of the solicited AEs, while there were no reports of AEs of severe intensity. A total of 31 unsolicited AEs were reported in 22 patients (3.6%), and no unexpected adverse drug reactions were reported.

***Conclusion***: No new safety issues were identified and the safety profile obtained from this study was comparable to that of previous studies for HAV vaccine.

***Trial Registration***: ClinicalTrials.gov identifier, NCT01838070.

***Funding***: Sanofi Pasteur.

**Keywords:** Avaxim; Hepatitis A; Safety; Tolerability; Vaccination

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## INTRODUCTION

Hepatitis A virus (HAV) is a major health issue worldwide and one of the most common global causes of acute hepatitis [1, 2]. It is primarily transmitted via the faecal/oral route, either by contact with an infectious person, or ingestion of contaminated food or water. Clinical manifestations depend on the age of the host: less than 30% of infected young children are affected by symptomatic hepatitis, while approximately 80% of infected adults develop severe

acute hepatitis as a result of HAV infection [3]. It has been estimated that, annually, over 100 million HAV infections resulted in significant morbidity and 15,000–30,000 deaths worldwide [4]. In South Korea, Moon et al. have reported that the incidence of HAV infection peaked in 2009 at over 15,000 reported cases, and has been decreasing since [5]. Most notably, between 2011 and 2013, the number of patients and incidence rate of HAV reported through the National Infectious Disease Surveillance System of Korean Centers for Disease Control and Prevention declined from 5521 to 867 [5], showing a continuous decline since 2011, the year when the HAV vaccine was approved for use in adults over the age of 16 years in South Korea [6], and the surveillance system in Korea was expanded to include every hospital.

Avaxim 160U (Sanofi Pasteur, Lyon, France) is an inactivated hepatitis A vaccine that is highly immunogenic and well tolerated [4]. Each dose contains 160 antigen-units of purified, formaldehyde-inactivated GBM strain HAV isolated from cultured human MRC-5 cells [7]. Vaccine efficacy was proven based on safety and immunogenicity assessments carried out in clinical studies, with more than 22,000 patients being exposed to HAV vaccine in clinical trials sponsored by Sanofi Pasteur [8–11]. It was first approved for vaccination of adult patients in 1996 in the UK, and is now available in more than 90 countries worldwide.

Pharmacovigilance aims to minimize the risks associated with drug administration by monitoring long-term drug safety in real-world settings. Standard clinical development and approval processes provide important information on drug safety and efficacy, but insights into drug safety may be incomplete due to the limitations of clinical trial design. For example, low patient numbers and the highly controlled conditions of drug exposure may all contribute to the need for further safety monitoring under real-life conditions. Therefore, post-marketing surveillance (PMS) provides important additional insights into drug safety, and can give a more comprehensive assessment of a drug's safety profile [12].

Here, we describe a post-marketing observational study assessing the safety of an inactivated Hepatitis A vaccine in adults $\geq$ 16 years, administered under routine clinical practice conditions.

## METHODS

This post-marketing observational study (NCT01838070) was conducted between 4 November 2011 and 3 November 2015 at 16 centres (one general hospital and 15 clinics) in South Korea. Participants were considered for inclusion if they were over the age of 16 years, considered healthy enough to have vaccinations based on local regulations, the study protocol, and product insert, and if they had been previously vaccinated with Avaxim 160U (Sanofi Pasteur). Patients were enrolled from a total of 16 sites, a mixture of hospitals and clinics with specialities ranging from a tertiary hospital, obstetrics and gynaecology units, paediatric units, an ear nose and throat unit and an internal medicine site, all of which provide vaccination services but are not vaccine-dedicated facilities. Vaccinations were administered on site, with age groups varying based on the site of injection, and data was collected according to the South Korean ministry of food and drug safety regulations. Recruitment continued until the objective of 600 evaluable patients had been achieved. A case report form (CRF) was filled out by trained nurses or principal investigators, during the surveillance period (30 days post-vaccination) and all patients whose CRFs were retrieved were included in the safety analyses set. Patients were also trained to use diary cards, and after the first visit these were to be brought back to the site by patients. Patients who did not return the diary card were then followed up by phone call.

There were no pre-specified or specific safety surveillance objectives; all adverse events (AEs) that occurred during the observation period were included, regardless of causal relationship to vaccination. This included solicited events, unsolicited non-serious AEs, unexpected AEs and serious AEs. A solicited AE was defined as an event that was listed in the CRF and occurred within 7 days of vaccination; these were

injection site pain, injection site erythema, fever, headache, myalgia, arthralgia, asthenia and gastrointestinal disorders. Due to their nature and timing, solicited AEs were considered to be adverse drug reactions (ADRs) that had a causal relationship with vaccination. An unsolicited AE was defined as an event that did not fulfil the conditions listed in the CRF in terms of symptoms or timing of onset; unsolicited AEs were assessed for 30 days after vaccination. Solicited AEs were classified according to severity into three grades: grade 1 (mild, regarded as having no interference with activity), grade 2 (moderate, regarded as having some interference with activity) and grade 3 (severe, regarded as significant and preventing daily activity) [13]. An unexpected AE was an unsolicited AE that was not listed in the Korean product information leaflet. Additionally, demographic characteristics, history of renal disease, hepatic disease, or allergies, recent vaccination history (defined as any vaccination within 4 weeks prior to recruitment) and concomitant medication/vaccination were documented.

No hypotheses were tested and all analyses were descriptive. The sample size of 600 evaluable patients was based on predefined criteria of the Korean Food & Drug Administration PMS guidelines. Safety data were analysed further using logistic regression modelilng to identify the factors (gender, age, medical history, allergy history, concomitant medication/vaccination) that may affect the safety of the study vaccine. All statistical analyses were carried out with SAS Software v.9.2 (Cary, NC, USA).

The trial was performed in accordance with the Good Epidemiological Practice guidelines, and the protocol was approved by the Ministry of Food and Drug Safety of Korea and Institutional Review Board of Yonsei University Severance Hospital. Informed written consent was obtained from all participants included in the study. All procedures performed in studies involving human participants were in accordance with IRB of Yonsei University Severance Hospital and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

# RESULTS

## Patients

A total of 614 CRFs were collected from vaccinees. All 614 completed 30 days of follow-up post-vaccination. Of these, 514 (83.7%) received HAV vaccine as a primary vaccination, and 100 (16.3%) received HAV vaccine as a booster vaccination. Demographic and baseline characteristics are presented in Table 1; 492,888 doses of study vaccination were distributed during the study period. None of the female patients included were pregnant during the

**Table 1** Demographics of patients

| Parameter | Value |
|---|---|
| Gender | |
| Male, *n* (%): female, *n* (%) | 228 (37.1): 386 (62.9) |
| Age | |
| Mean (SD), years | 32.19 (8.3) |
| Median, years | 32.0 |
| Minimum–maximum, years | 16–84 |
| 16–17 years, *n* (%) | 14 (2.3) |
| 18–19 years, *n* (%) | 31 (5.1) |
| 20–29 years, *n* (%) | 149 (24.3) |
| 30–39 years, *n* (%) | 338 (55.1) |
| $\geq$ 40 years, *n* (%) | 82 (13.4) |
| $<$ 65 years, *n* (%) | 610 (99.4) |
| $\geq$ 65 years, *n* (%) | 4 (0.7) |
| Body weight | |
| Number of patients | 223 |
| Mean (SD), kg | 64.36 (11.6) |
| Median, kg | 64.0 |
| Minimum–maximum, kg | 42.0–93.0 |

*SD* standard deviation

surveillance period. None of the patients had fever at the time of vaccination. None of the patients had a history of renal disease; however, 2.8% of patients were considered to have hepatic disease at study entry.

## Safety

Solicited and unsolicited AE reporting rates are described in Table 2. A total of 53 AEs were reported in 36 patients (5.9%), 17 patients reported a total of 22 solicited AEs (2.8%) and 22 patients reported a total of 41 unsolicited AEs (3.6%). Of the 22 solicited AEs, no remedial action was required for 19 events, and the patients' healthcare provider was contacted about the remaining three events. By the end of the observation period, 19 of the patients experiencing solicited AEs were classed as recovered and 3 as on-going. Solicited AEs were graded as being mild in intensity in 11 patients (1.8%), and moderate in 5 patients (0.8%). No severe AEs were reported (data was missing for one patient). A total of 31 unsolicited AEs were reported in 22 patients (3.6%). All of these unsolicited events were graded as mild in intensity. All unsolicited AEs were considered unrelated to vaccination.

In the patients with primary vaccination, AEs occurred in 6.4% (33/514) and, in the patients with booster vaccination, AEs occurred in 3.0% (3/100). There was no statistically significant differences in the AE incidence rate by vaccination dose ($p = 0.1829$) (data unavailable).

Unexpected AEs are described in Table 2. A total of 28 unexpected AEs were reported by 21 patients (3.4%); all were graded as mild and unrelated to the vaccination. There were no unexpected ADRs and no serious AEs reported by any of the patients.

Of the patients who were reported to have a history of hepatic disease, 2 reported AEs which were not associated to their chronic conditions.

## Concomitant Medication/Vaccination

A total of 180 patients (29.3%) received concomitant medication or vaccination. A total of

**Table 2** Incidence of solicited and unsolicited adverse events following vaccination

| | Adverse events | | |
|---|---|---|---|
| | **Patients with AEs, *n* (%)** | **95% CI (lower, upper)** | **No. of AEs** |
| Solicited adverse events[a] | | | |
| Injection site reactions | 11 (1.8) | (0.00, 4.07) | 12 |
| Pain | 9 (1.5) | (0.00, 3.54) | 9 |
| Erythema | 3 (0.5) | (0.00, 1.69) | 3 |
| Systemic reactions | 7 (1.1) | (0.00, 2.96) | 10 |
| Fever | 3 (0.5) | (0.00, 1.69) | 3 |
| Headache | 4 (0.7) | (0.00, 2.03) | 4 |
| Myalgia | 2 (0.3) | (0.00, 1.32) | 2 |
| Arthralgia | 0 (0.00) | (0.00, 0.00) | 0 |
| Asthenia | 0 (0.00) | (0.00, 0.00) | 0 |
| Gastro-intestinal disorders | 1 (0.2) | (0.00, 0.85) | 0 |
| Total solicited adverse events | 17 (2.8) | (0.00, 5.59) | 22 |
| Unsolicited adverse events | | | |
| Infections and infestations | 14 (2.3) | (0.00, 4.85) | 15 |
| Bronchitis | 4 (0.7) | (0.00, 2.03) | 4 |
| Pharyngitis | 4 (0.7) | (0.00, 2.03) | 4 |
| Nasopharyngitis | 3 (0.5) | (0.00, 1.69) | 3 |
| Influenza | 1 (0.2) | (0.00, 0.85) | 1 |
| Laryngitis | 1 (0.2) | (0.00, 0.85) | 1 |
| Vaginal infection | 1 (0.2) | (0.00, 0.85) | 1 |
| Vulvovaginal candidiasis | 1 (0.2) | (0.00, 0.85) | 1 |
| Gastrointestinal disorders | 5 (0.8) | (0.00, 2.35) | 5 |
| Dyspepsia | 2 (0.3) | (0.00, 1.32) | 2 |
| Gastrointestinal inflammation | 1 (0.2) | (0.00, 0.85) | 1 |

**Table 2** continued

| | Adverse events | | |
|---|---|---|---|
| | **Patients with AEs, *n* (%)** | **95% CI (lower, upper)** | **No. of AEs** |
| Stomatitis | 1 (0.2) | (0.00, 0.85) | 1 |
| Vomiting | 1 (0.2) | (0.00, 0.85) | 1 |
| General disorders and administration site conditions | 2 (0.3) | (0.00, 1.32) | 2 |
| Chest pain | 1 (0.2) | (0.00, 0.85) | 1 |
| Inflammation | 1 (0.2) | (0.00, 0.85) | 1 |
| Respiratory, thoracic and mediastinal disorders | 2 (0.3) | (0.00, 1.32) | 2 |
| Cough | 2 (0.3) | (0.00, 1.32) | 2 |
| Eye disorders | 1 (0.2) | (0.00, 0.85) | 1 |
| Conjunctival disorder | 1 (0.2) | (0.00, 0.85) | 1 |
| Musculoskeletal and connective tissue disorders | 1 (0.2) | (0.00, 0.85) | 1 |
| Back pain | 1 (0.2) | (0.00, 0.85) | 1 |
| Nervous system disorders | 1 (0.2) | (0.00, 0.85) | 1 |
| Dizziness | 1 (0.2) | (0.00, 0.85) | 1 |
| Reproductive system and breast disorders | 1 (0.2) | (0.00, 0.85) | 3 |
| Cervical ectropion | 1 (0.2) | (0.00, 0.85) | 1 |
| Uterine cervical erosion | 1 (0.2) | (0.00, 0.85) | 1 |
| Vulvovaginal pruritus | 1 (0.2) | (0.00, 0.85) | 1 |
| Skin and subcutaneous tissue disorders | 1 (0.2) | (0.00, 0.85) | 1 |
| Dermatitis contact | 1 (0.2) | (0.00, 0.85) | 1 |
| Total unsolicited events | 22 (3.6) | (0.39, 6.77) | 31 |
| Total events | 36 (5.9) | (1.82, 9.90) | 53 |

All solicited reactions and injection site adverse events were considered to be related to vaccination, and did not require the investigator's opinion on relationship. The incidence rates were calculated using the patient population

*AE* adverse event, *CI* confidence interval

[a] Solicited events that were ongoing after Day 7 were counted as "solicited events" only

72.2% (130/180 patients) received medication that fell within the category of 'allergy & immune system'; 111(61.7%) received vaccines, antisera and immunologicals and 25 (13.9%) received antihistamines and anti-allergics. A total of 23.3% (42/180 patients) received drugs pertaining to the 'gastrointestinal and hepatobiliary system', and an additional 20.0% (36/180 patients) received drugs used for treatment of the 'central nervous system'.

Controlling for other independent factors, concomitant medication/vaccination ($p < 0.0001$) as assessed by logistic regression analysis was the only factor found to have a statistically significant association with the adverse event occurrence rate. The rate of AEs in patients who had received concomitant medication/vaccination was 16.7% (30/180) and, in patients without concomitant medication/vaccination, the rate was 1.4% (6/434), resulting in an odds ratio of 12.13 (95% CI 4.72–31.16) in favour of concomitant medication/vaccination.

## DISCUSSION

The results of this study were consistent with pre-licensure studies for the more common adverse events, such as injection site and systemic reactions. During this period,

approximately 493,000 doses of Avaxim 160U were prescribed in South Korea. The safety profile of Avaxim 160U in this study appears to be similar to that observed in clinical studies undertaken in other regions [8, 9, 12]. However, it should be noted that the results of this study represent lower incidences of AEs compared with those reported from data gathered during clinical trials. When safety outcomes from eight clinical trials were assessed, the rate of solicited adverse events in patients vaccinated with intramuscular Avaxium 160U was approximately ten times greater than that reported here [14]. This suggests that safety outcomes may be under-reported in PMS studies.

The sample size used in PMS studies is predefined and not based upon the predicted risk of events, data collection methodology is not specified, there are no standards for monitoring data quality, and studies are not all conducted according to accepted international standards, such as Good Clinical Practice. Differences in methodology can lead to discrepancies in data, with previous studies reporting significant differences depending on the method of AE data collection (solicited vs. unsolicited, open questioning, etc.) even when assessing the same vaccine [15]. Similarly, it has been reported that data collection without the use of diary cards may result in under-reporting of relevant AEs and an over-reporting of AEs unrelated to vaccine treatment [16]. Diary cards were used in this study to improve the accuracy of data collection.

The European Medicines Agency (EMA) Post-Authorization Safety Studies (PASS) system has recently been strengthened in order to acquire more detailed information and, therefore, increase the reliability of post-marketing studies [12, 17]. The Korean PMS system aims to obtain more information regarding safety which was not sufficient from the result of clinical trials, and to identify new adverse events which may not have happened during the course of drug development, determine the status of these adverse events, and any factors affecting safety, to ultimately reflect the findings in approval for appropriate approval management. However, concern has been raised [17] over the possible misuse of the system and a failure to accomplish its objectives in real-world conditions. Although post-marketing observational studies are mandatory in South Korea as part of PMS activities in order to retain drug licensure, it is widely thought that changes will need to be made in order to ensure the reliability of the results [17].

The limitations of this study included small sample size and the method of recruitment of patients. A larger sample size would allow for the assessment of rare AEs. Additionally, the convenience sample used in this study may not be fully representative of the general Korean population. The use of patient completed diary cards to record AEs may also be associated with recall bias if not completed at the time of the reaction.

## CONCLUSION

No new or unexpected safety signals were observed, and no serious AEs were reported during the surveillance period. The rate of AEs observed was lower than in clinical trials, highlighting the potential need to improve the way in which PMS data are gathered in South Korea, including the quality of data gathering and analysis. Additionally, aligning the Korean system with GCP or other good standards of operation will ensure the integrity of the results of the Korean PMS system.

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***Disclosures.*** HeeSoo Kim is an employee of Sanofi Pasteur. Yongho Oh is an employee of Sanofi Pasteur. Yael Thollot is an employee of Sanofi Pasteur. Catherine Bravo is an employee of Sanofi Pasteur.

***Compliance with Ethical Guidelines.*** The trial was performed in accordance with the Good Epidemiological Practice guidelines, and the protocol was approved by the Ministry of Food and Drug Safety of Korea and Institutional Review Board of Yonsei University Severance Hospital. All patients provided written informed consent. All procedures performed in studies involving human participants were in accordance with IRB of Yonsei University Severance Hospital and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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



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