



Post-marketing Surveillance of a Quadrivalent Influenza Vaccine (Vaxigrip Tetra) in South Korea

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ABSTRACT

Introduction: In 2017, a quadrivalent inactivated split-virion influenza vaccine (QIV; Vaxigrip Tetra[®], Sanofi) was licensed in South Korea for active immunization against influenza A and influenza B viruses in individuals aged 3 years or older, which was subsequently extended to individuals aged 6 months or older in 2018. Post-marketing surveillance trials are mandatory in South Korea to retain drug licensure. Here, we assessed the safety of QIV in routine clinical practice in South Korea.

Methods: This was an open, multicenter, observational, active safety surveillance study conducted between 20 June 2017 and 19 June 2021 at 10 study sites in South Korea in individuals aged 3 years or older who received a single dose of QIV during a routine healthcare

visit. The participants or their legally acceptable representatives were instructed to record any adverse reactions (solicited events) and unsolicited non-serious adverse events (AE) in diary cards, and notify study investigators in case of serious adverse events (SAE).

Results: Overall, 663 participants were included in this study. There were no AEs leading to study termination, and no SAEs reported. Injection site pain (278 [41.9%]) was the most frequent solicited injection site reaction, with myalgia (250 [37.7%]) and malaise (236 [35.6%]) the most frequent solicited systemic reactions. Grade 3 solicited injection site and systemic reactions were reported by 8 (1.2%) and 13 (2.0%) participants, respectively; most participants with solicited reactions recovered without the need for further action. Overall, 39 (5.9%) participants experienced 49 unsolicited non-serious AEs with the most frequently reported being nasopharyngitis (19 [2.9%]). Grade 3 unsolicited non-serious adverse events were reported in 1 (0.2%) participant. None of the unsolicited non-serious AEs were considered to be related to QIV.

Conclusion: This post-marketing surveillance study confirms that QIV is well tolerated and has an acceptable safety profile in routine practice in South Korea. No unexpected safety concerns were identified.

Trial Registration: ClinicalTrials.gov identifier NCT05406180.

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Keywords: Safety; Quadrivalent inactivated split-virion influenza vaccine; Post-marketing surveillance study; South Korea; Vaxigrip Tetra; Influenza

Key Summary Points

Seasonal influenza is associated with significant morbidity and mortality in South Korea.

A quadrivalent inactivated split-virion influenza vaccine (QIV; Vaxigrip Tetra[®], Sanofi) was licensed in South Korea in 2017 for active immunization against seasonal influenza caused by influenza A and influenza B viruses.

A post-marketing safety surveillance study was carried out to characterize the safety of QIV when administered to participants aged ≥ 3 years in routine clinical practice in South Korea.

QIV was well tolerated and had an acceptable safety profile with no safety concerns identified, confirming its safety profile in routine practice in South Korea.

INTRODUCTION

Seasonal influenza causes significant morbidity and mortality in South Korea with an average of 2300–5300 excess deaths per year and an estimated mortality rate of 10.59 per 100,000 people, the majority of which occur in the elderly [1–3]. Annual influenza vaccination is the primary strategy used to limit the burden of influenza [4, 5] and annual vaccination is recommended by the World Health Organization (WHO) for high-risk groups including pregnant women, children aged 6–59 months, the elderly, and individuals with chronic health conditions [6]. The burden of disease is even higher when taking into consideration associated cardiovascular, diabetic, and renal complications; decreased activities of daily life; and

increased susceptibility to bacterial infections [7, 8]. Influenza infection is also a risk factor in the ongoing SARS-CoV-2 pandemic, as SARS-CoV-2 co-infection with influenza increases the risk of severe disease (need for invasive mechanical ventilation) and death [9]. Those at highest risk of severe outcomes following infection with SARS-CoV-2 or influenza viruses are the same, and include older people and residents of long-term care facilities and individuals with chronic comorbidities, including obesity [10–16].

The quadrivalent inactivated split-virion influenza vaccine (QIV; Vaxigrip Tetra[®], Sanofi), which includes two influenza A and two influenza B virus strains, was designed to offer broader protection against seasonal influenza than trivalent influenza vaccines [17]. QIV was initially approved for individuals aged 3 years or older in the European Union in 2016, with applications to lower the indicated age to 6 months or older approved in 2017. A study performed in South Korea demonstrated that QIV was highly immunogenic and well tolerated in adults aged 18–60 years and confirmed that the second B-lineage strain included should provide broader protection without affecting vaccine safety [18]. QIV was subsequently licensed in South Korea on 20 June 2017 for active immunization against seasonal influenza in individuals aged 3 years or older, and later extended to include individuals aged 6 months or older on 15 June 2018.

Post-marketing surveillance studies following approval of “New Drug Applications” are required in South Korea as part of post-licensure commitments to the “Standards on Re-examination of New Drugs” requested by the Ministry of Food and Drug Safety [19]. Such studies allow for a more comprehensive assessment than would be achieved in clinical studies of the drug’s safety profile during routine clinical practice in the wider population following initial licensure. Here, we describe a post-marketing safety surveillance study of QIV in South Korea.

METHODS

This was an open, multicenter, observational, active safety surveillance study conducted between 20 June 2017 and 19 June 2021 at ten study sites in South Korea. The study was conducted in accordance with the Good Epidemiological Practice guidelines. The protocol and amendments were approved by applicable independent ethics committees/institutional review boards (Hanil General Hospital, Seoul; HGH-2018-PMS-012) and the regulatory agency as per local regulations.

Individuals aged 3 years or older (as indicated in the approved local product labeling at the start of the study) and who had received a single dose of QIV (Vaxigrip Tetra[®], Sanofi) during a routine healthcare visit were enrolled. Individuals aged between at least 6 months and 3 years were enrolled in a separate ongoing post-marketing surveillance study (GQM15) in South Korea. Signed informed consent (or by the parent or legally acceptable representative for those aged 3–18 years) was required for enrollment in the study. All enrolled participants were followed up for 21(+ 7) days after vaccination; children aged 3–8 years may have received two doses of influenza vaccine, depending on their vaccination history, but were only followed up after one dose (either the first or second). Participation (within 4 weeks preceding enrollment) and planned participation in another study (while in the current study) were reasons for exclusion. No vaccine was provided as part of the study and participants were enrolled after routine vaccination.

The participants or their parent(s)/legally acceptable representative(s) were provided with digital thermometers, flexible rulers, and diary cards during visit 1 and were instructed to record solicited injection site (pain, erythema, swelling, induration, and ecchymosis) and systemic (fever, headache, malaise, myalgia, and shivering) reactions occurring up to 7 days after vaccination and any action taken to treat these. In addition, they were instructed to record in separate diary cards the occurrence of unsolicited non-serious adverse events (AEs) occurring up to 21(+ 7) days (visit 2) after

vaccination, and to notify study investigators in case of serious adverse events (SAEs) throughout the study. Safety information was collected during visit 2 at the study site and included a physical examination. The diary card provided by the investigator at visit 1 was reviewed by the investigator together with the participants or their parent(s)/legally acceptable representative(s), with the AEs reviewed including any reactions or solicited events that occurred from day 0 to day 7 as well as any unsolicited AEs and SAEs, along with concomitant medication used. A study termination record was completed if a participant did not turn up for visit 2 or if diary card information was not properly collected, with a follow-up phone call made in an attempt to collect the necessary information.

Solicited reactions were graded on a 3-point severity grade (Grade 1 to 3) in a similar manner previously described for adults (the ranges used for grading solicited injection site reactions [except pain] in children aged less than 12 years in the current study were half those described for adults) [18]. For the subjective reaction of pain, the participant's parent/legally acceptable representative recorded the severity grade in the diary card. For the measurable reactions of redness, swelling, hardening, and bruising, these were graded at the time of the statistical analysis in line with the measurements provided. Unsolicited non-serious AEs were graded in a similar manner to solicited reactions. The investigator assessed the causal relationship to QIV for each unsolicited non-serious AE and SAE as related or not related as per the South Korean Ministry of Food and Drug Safety post-marketing surveillance guidelines.

Statistical Analysis

Data analysis was descriptive. Since no statistical hypothesis was tested, the sample size was based on ensuring that at least 600 participants (600 vaccinations) would be evaluable in accordance with South Korean guidelines. Assuming a 10% attrition rate for loss to follow-up or for invalid or incomplete reports, we required 670 participants to be enrolled, which would provide a probability of approximately

95% of observing any AE (at least one occurrence) with a true incidence of 0.45% or more, using the rule of three.

For each safety endpoint, the number and percentage (with corresponding 95% CIs) of participants experiencing at least one of the corresponding events were described. The corresponding 95% CIs were calculated using the exact binomial distribution (Clopper–Pearson’s method) for proportions with the normal approximation for quantitative data. All analyses were done on the safety analysis set defined as participants who have received a dose of QIV regardless of their vaccination schedule. All statistical analyses were carried out using SAS version 9.2 or above (SAS Institute, Cary, NC, USA).

RESULTS

Study Participants

A total of 675 participants were enrolled, of which 12 (1.8%) were excluded from the safety analysis set. Reasons for exclusion included (more than one reason included) 11 (1.6%) due to inclusion/exclusion criteria violation, 5 (0.74%) loss to follow-up, and 4 (0.6%) due to prior receipt of influenza vaccine. Thus, 663 (98.2%) participants were included in this safety analysis. The demographics of participants included are presented in Table 1.

Safety

The overall incidence of unsolicited non-serious AEs, SAEs, and solicited reactions is summarized in Table 2. Injection site pain (278 [41.9%]) was the most frequent solicited injection site reaction, with myalgia (250 [37.7%]) and malaise (236 [35.6%]) the most frequent solicited systemic reactions. Nearly all solicited reactions were reported 0–3 days after vaccination. Grade 3 solicited injection site and systemic reactions were reported by 8 (1.2%) and 13 (2.0%) participants, respectively; these were due to pain at the injection site and malaise mainly and all participants recovered. There were 49

Table 1 Demographic characteristics: safety analysis set

| | Safety set (N = 663) n (%) |
|--|---|
| Gender | |
| Male | 138 (20.8) |
| Female | 525 (79.2) |
| Age groups* | |
| Children < 19 years | 150 (22.6) |
| Adults 19–64 years | 507 (76.5) |
| Elderly ≥ 65 years | 6 (0.9) |
| Concurrent disease | |
| No | 629 (94.9) |
| Yes | 34 (5.1) |
| Endocrine disorders | 2 (5.9) |
| Gastrointestinal disorders | 2 (5.9) |
| General disorders and administration site conditions | 1 (2.9) |
| Hepatobiliary disorders | 3 (8.8) |
| Infections and infestations | 17 (50.0) |
| Metabolism and nutrition disorders | 8 (23.5) |
| Musculoskeletal and connective tissue disorders | 3 (8.8) |
| Reproductive system and breast disorders | 2 (5.9) |
| Respiratory, thoracic, and mediastinal disorders | 10 (29.4) |
| Vascular disorders | 4 (11.8) |
| Concomitant medication | |
| No | 594 (89.6) |
| Yes | 69 (10.4) |
| Alimentary tract and metabolism | 16 (23.2) |
| Anti-infectives for systemic use | 24 (34.8) |
| Blood and blood-forming organs | 3 (4.4) |
| Cardiovascular system | 9 (13.0) |
| Dermatologicals | 1 (1.5) |

Table 1 continued

| | Safety set (<i>N</i> = 663) <i>n</i> (%) |
|---|---|
| Genitourinary system and sex hormones | 2 (2.9) |
| Musculoskeletal system | 14 (20.3) |
| Nervous system | 14 (20.3) |
| Respiratory system | 48 (69.6) |
| Sensory organs | 2 (2.9) |
| Systemic hormonal preparations, excl. sex hormones and insulins | 6 (8.7) |

*Mean 35.03 ± 17.96 years (median 39 years; range 3–75 years)

unsolicited non-serious AEs reported by 39 (5.9%) participants. The most frequently reported unsolicited non-serious AE was nasopharyngitis (19 [2.9%]), with all other unsolicited non-serious AEs reported by less than 1% of participants. One participant reported a Grade 3 unsolicited non-serious AE, pyrexia. None of the unsolicited non-serious AEs reported were considered related to QIV. There were no reported AEs leading to study termination, and no SAEs were reported.

DISCUSSION

This study confirms the safety of QIV in routine practice in South Korea, with no safety concerns identified. No SAEs were reported during the study period and no AEs leading to study discontinuation were reported. The most frequently reported solicited reactions were injection site pain, myalgia, and malaise. Overall, the QIV safety profile observed in our study appears generally similar or no worse than that reported from a clinical trial undertaken with QIV in adults in South Korea and other clinical trials conducted elsewhere, including countries in Asia across a range of age groups (though one small study did report much lower rates of myalgia and malaise [20]) [18, 20–22].

Table 2 Overall safety information: safety analysis set

| | <i>n</i> (%) | 95% CI | Number of events |
|--|--------------|--------------|------------------|
| Solicited injection site reactions | 280 (42.2) | (38.4, 46.1) | 357 |
| Injection site erythema | 36 (5.4) | (3.8, 7.4) | 36 |
| Injection site hemorrhage | 3 (0.5) | (0.1, 1.3) | 3 |
| Injection site induration | 8 (1.2) | (0.5, 2.4) | 8 |
| Injection site pain | 278 (41.9) | (38.1, 45.8) | 278 |
| Injection site swelling | 32 (4.8) | (3.3, 6.8) | 32 |
| Solicited systemic reactions | 312 (47.1) | (43.2, 50.9) | 585 |
| Chills | 37 (5.6) | (4.0, 7.6) | 37 |
| Headache | 56 (8.5) | (6.4, 10.8) | 56 |
| Malaise | 236 (35.6) | (32.0, 39.4) | 236 |
| Myalgia | 250 (37.7) | (34.0, 41.5) | 250 |
| Pyrexia | 6 (0.9) | (0.3, 2.0) | 6 |
| Unsolicited non-serious adverse events | 39 (5.9) | (4.2, 8.0) | 49 |
| Eye disorders | 1 (0.2) | (0.0, 0.8) | 1 |
| Conjunctivitis allergic | 1 (0.2) | (0.0, 0.8) | 1 |
| Gastrointestinal disorders | 1 (0.2) | (0.0, 0.8) | 1 |
| Stomatitis | 1 (0.2) | (0.0, 0.8) | 1 |
| General disorders and administration site conditions | 1 (0.2) | (0.0, 0.8) | 1 |
| Pyrexia | 1 (0.2) | (0.0, 0.8) | 1 |
| Infections and infestations | 31 (4.7) | (3.2, 6.6) | 32 |

Table 2 continued

| | <i>n</i> (%) | 95% CI | Number of events |
|--|--------------|------------|------------------|
| Bronchitis | 2 (0.3) | (0.0, 1.1) | 2 |
| Conjunctivitis | 1 (0.2) | (0.0, 0.8) | 1 |
| Gastroenteritis | 1 (0.2) | (0.0, 0.8) | 1 |
| Hordeolum | 2 (0.3) | (0.0, 1.1) | 2 |
| Nasopharyngitis | 19 (2.9) | (1.7, 4.4) | 19 |
| Pharyngitis | 1 (0.2) | (0.0, 0.8) | 1 |
| Rhinitis | 4 (0.6) | (0.2, 1.5) | 4 |
| Tonsillitis | 1 (0.2) | (0.0, 0.8) | 1 |
| Varicella | 1 (0.2) | (0.0, 0.8) | 1 |
| Metabolism and nutrition disorders | 2 (0.3) | (0.0, 1.1) | 2 |
| Hyperlipidemia | 1 (0.2) | (0.0, 0.8) | 1 |
| Vitamin D deficiency | 1 (0.2) | (0.0, 0.8) | 1 |
| Psychiatric disorders | 1 (0.2) | (0.0, 0.8) | 1 |
| Insomnia | 1 (0.2) | (0.0, 0.8) | 1 |
| Reproductive system and breast disorders | 2 (0.2) | (0.0, 1.1) | 2 |
| Dysmenorrhea | 1 (0.2) | (0.0, 0.8) | 1 |
| Erectile dysfunction | 1 (0.2) | (0.0, 0.8) | 1 |
| Respiratory, thoracic, and mediastinal disorders | 7 (1.1) | (0.4, 2.2) | 7 |
| Cough | 5 (0.8) | (0.3, 1.8) | 5 |
| Rhinitis allergic | 1 (0.2) | (0.0, 0.8) | 1 |
| Rhinorrhea | 1 (0.2) | (0.0, 0.8) | 1 |
| Skin and subcutaneous tissue disorders | 1 (0.2) | (0.0, 0.8) | 1 |
| Dermatitis contact | 1 (0.2) | (0.0, 0.8) | 1 |
| Vascular disorders | 1 (0.2) | (0.0, 0.8) | 1 |
| Essential hypertension | 1 (0.2) | (0.0, 0.8) | 1 |
| Serious adverse events | 0 (0.0) | (0.0, 0.6) | 0 |

Table 2 continued

| | <i>n</i> (%) | 95% CI | Number of events |
|---|--------------|------------|------------------|
| Adverse events leading to study termination | 0 (0.0) | (0.0, 0.6) | 0 |

A solicited reaction is an event that is pre-listed in the participant's diary card; the assessment of these AEs post-vaccination is mandatory. A solicited reaction is defined by a combination of symptom and time of onset post-vaccination. An unsolicited AE is an observed AE that does not fulfil the conditions pre-listed in the participant's diary card in terms of symptom and/or onset post-vaccination

The frequency of AEs in our study appears generally higher than those reported in passive surveillance studies conducted in Europe [23–25], due likely in part to the prospective soliciting of these events using diary cards in a manner similar to clinical trials in our study. Of note, the safety of QIV in clinical trials has been reported to be similar to that of the corresponding licenced trivalent influenza vaccines (TIV) [26].

The main limitation of our study was that the sample size used lacks the power to detect rare events and there was no comparator; as such, the background rate of the events reported in the population assessed is unknown. In addition, the number of elderly participants (aged 65 years or older) enrolled was very low, less than 1%, and as such our observations may not be representative for this key population targeted for influenza vaccination. Nonetheless, these results provide additional reassurance of the safety of QIV in South Korea, which showed that it is well tolerated and associated with predictable symptoms that are generally mild or moderate.

CONCLUSIONS

This post-marketing surveillance study confirms that QIV is well tolerated and has an acceptable safety profile in routine practice in South Korea.

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Disclosures. XL, OS, and MF are Sanofi employees and may hold shares and/or stock options in the company. SL reports no conflicts of interest.

Compliance with Ethics Guidelines. Signed informed consent (or by the parent or other legally acceptable representative for those aged 3–18 years) was required for participation in the study. This study was conducted in accordance with the Good Epidemiological Practice guidelines. The protocol and amendments were approved by applicable independent ethics committees/institutional review boards and the regulatory agency as per local regulations. The institutional review board responsible for approving this study was the Hanil General Hospital, Seoul (HGH-2018-PMS-012), which initially approved the study on 28 September 2018. All further modifications were approved by this institutional review board before the implementation of any changes.

Data Availability. The datasets generated and/or analyzed during the current study, including the raw data, are not publicly available in order to safeguard the privacy of participants and the confidentiality and protection of their data, as well as protect commercially sensitive information. Qualified researchers may request access to patient level data and related study documents including the clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan, and dataset specifications. Patient level data will be anonymized and study documents will be redacted to protect the privacy of our trial participants. Further details on Sanofi's data sharing criteria, including required permissions to access the data, eligible studies, and process for requesting access, can be found at <https://www.vivli.org/>.

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