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Adverse events following vaccination against coronavirus disease 2019

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To overcome the coronavirus disease 2019 (COVID-19) pandemic, large-scale vaccination is proceeding worldwide. As of December 23, 2021, 10 novel vaccines against COVID-19 had been validated for use by the World Health Organization (WHO), including BNT162b2 (Pfizer/BioNTech), mRNA-1273 (Moderna), AZD1222 (AstraZeneca), and Ad26.COV2.S (Janssen). These novel vaccines against COVID-19 showed acceptable safety profiles in randomized clinical trials. Most adverse events following immunization (AEFIs) associated with these novel vaccines ranged from mild to moderate and improved within a few days after administration. However, serious adverse events associated with vaccines that were not observed in the clinical trials were reported in real-world data. Adverse events of special interest include not only anaphylaxis or neurologic disorders (such as Guillain-Barré syndrome, transverse myelitis, or seizure) but also myocarditis or pericarditis associated with the messenger RNA (mRNA) vaccines and thrombosis with thrombocytopenia syndrome associated with the adenovirus-vector vaccines. Although several fatal cases of serious AEFIs that may have been related to vaccination have been reported, it is recommended to continue vaccination because the benefits of vaccines' preventive effects against COVID-19 outweigh the risks of rare serious adverse events. Long-term monitoring of various AEFIs and sharing of clinical experiences are necessary for safe and efficient large-scale vaccination.

Keywords: Adverse drug events; COVID-19; Vaccination

Introduction

On December 31, 2019, the first case of coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2, was reported in Wuhan City, China. Since then, the number of COVID-19 cases has continuously increased, reaching a total of 373,229,380 confirmed cases, including 5,658,702 deaths, reported to the World Health Organization (WHO) as of January 31, 2022 [1]. To overcome the pandemic, large-scale vaccination is implemented at an unprecedented rate worldwide. Until December 23, 2021, several novel vaccines against COVID-19 were validated for use by the WHO (Emergency Use Listing), as follows: BNT162b2 (Pfizer/BioNTech), AZD1222 (AstraZeneca), Ad26.COV2.S (Janssen), mRNA-1273 (Moderna), BBIBP-CorV (Sinopharm), CoronaVac (Sinovac), BBV152 (Bharat Biotech), and NVX-CoV2373 (Novavax) [2]. The three vaccines were approved for the prevention of COVID-19 by the

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U.S. Food and Drug Administration (FDA): BNT162b1 (Pfizer/BioNTech), mRNA-1273 (Moderna), and Ad26.COV2.S (Janssen) [3].

The adverse event following immunization (AEFI) is defined as any unexpected medical situation which follows immunization. It does not definitely have a causal relationship with the usage of the vaccine. It can either be truly resulting from vaccine or immunization process or coincidentally occurred caused by something other than the vaccine products, immunization error or anxiety [4]. Although randomized controlled trials have demonstrated the safety of these vaccines [5-8], several cases of severe AEFIs have been reported. To manage various AEFIs and assess the safety of novel vaccines, the government in each country monitors and discloses information about adverse events associated with vaccination [9-11]. Following the reported serious AEFIs associated with novel vaccines, strategies and policies of national vaccination have been changed; however, there are also people that still refuse to be vaccinated, concerned about serious adverse events. In this review, we consider the types and frequencies of AEFIs of four COVID-19 vaccines in use in the Republic of Korea: BNT162b2, mRNA-1273, AZD1222, and Ad26.COV.2.S.

BNT162b2 (Pfizer/BioNTech)

A total of 43,548 participants aged 16 years and over were enrolled in a randomized controlled trial to evaluate the safety and efficacy of BNT162b2 [7]. In the vaccinated group, mild-to-moderate pain at the injection site was the most commonly reported local AEFI, which was reported less frequently by older participants (>55 years of age) than by younger participants and more often after the first dose than the second. The most commonly reported systemic AEFIs were fatigue and headache after either dose in all the age groups. Systemic AEFIs, including fever, fatigue, headache, muscle pain, and joint pain, were reported more often by younger participants than by older participants and often after the second dose. In general, mild-to-moderate local and systemic AEFIs were observed within the first 1–2 days after vaccination and resolved shortly thereafter. In the vaccinated group, shoulder injuries related to vaccine administration, axillary lymphadenopathy, paroxysmal ventricular arrhythmia, and leg paresthesia were reported. Two vaccine recipients died during the study period, and no deaths were considered related to the vaccine [7,12]. In an ongoing trial with 6 months of follow-up after vaccination, BNT162b2 have had an acceptable safety profile. Nevertheless, new AEFIs attributable to the vaccine include decreased appetite, lethargy, asthenia, night sweats, and hyperhidrosis; no cases of myocarditis were noted in this trial [13].

Between December 14 and 23, 2020, the Centers for Disease Control and Prevention (CDC) and the FDA confirmed 21 cases of anaphylaxis reported through the Vaccine Adverse Event Reporting System after administration of 1,893,360 doses of BNT162b2 in the United States. The incidence of anaphylaxis was estimated to be 11.1 events per million doses. Most cases occurred within 30 minutes after administration. Four patients (19%) were hospitalized, and no deaths were reported. Seven out of 17 patients (41%) with a history of allergy had experienced anaphylactic reactions in the past, including reactions to vaccines. Polyethylene glycol (PEG), a component of BNT162b2 and mRNA-1273, has the potential to elicit allergic reactions [14]. PEG is frequently used as an excipient in various products, including bowel preparation medication, cosmetics, toothpaste, and contact lenses. Recently, a series of confirmed PEG allergies has been reported. PEG has then been described as an allergen hidden in drugs, which might be underdiagnosed [15]. Therefore, people who have experienced anaphylaxis associated with PEG are contraindicated in BNT162b2 vaccination.

It has been suggested that myocarditis and pericarditis may occur as cardiovascular adverse events associated with messenger RNA (mRNA) COVID-19 vaccines. Using national data from health care organizations in Israel, Barda et al. [16] reported that BNT162b2 vaccination was associated with an elevated risk of myocarditis (risk ratio, 3.24; 95% confidence interval [CI], 1.55–12.44); however, the risk of myocarditis was substantially increased after COVID-19 (risk ratio, 18.28; 95% CI, 3.95–25.12). In this study, the incidence of myocarditis was analyzed to be 2.2 events after vaccination and 10.3 events after COVID-19 per 100,000 persons (21/398,812 of vaccinated group vs. 19/183,710 of COVID-19 group). According to a systematic review of cardiac complications following mRNA COVID-19 vaccines, myocarditis and pericarditis were the most common adverse events among the 243 reported cardiac complications following mRNA COVID-19 vaccine administration up to September 25, 2021. Among them, 227 were diagnosed with

myocarditis. After receiving BNT162b2, 74.4% of myocarditis cases were reported after the second dose. The median age was 21 years (range, 12–70 years), and 92.1% of the patients were male. The most commonly reported symptoms were chest pain (96.1%), fever (38.2%), myalgia (18.8%), and shortness of breath (10.1%). Seven patients were diagnosed with pericarditis after BNT162b2 vaccination. The median age was 37 years (range, 21–80 years), and 71.4% of the patients were male. The most commonly reported symptom was chest pain (85.7%). Cardiac biomarkers (creatine kinase-myocardial band, troponin, and N-terminal prohormone of brain natriuretic peptide) and inflammatory markers (C-reactive protein and erythrocyte sedimentation rate) were elevated in most patients with myocarditis. However, all patients with pericarditis showed a normal range of troponin levels and elevated inflammatory markers. Cardiac magnetic resonance imaging the gold standard approach for diagnosing myocarditis, was abnormal in all patients diagnosed with myocarditis. Regarding transthoracic echocardiography, reduced left ventricular ejection fraction and pericardial effusion were commonly reported in myocarditis and pericarditis cases, respectively. Nonsteroidal anti-inflammatory drugs, colchicine, and steroids were commonly prescribed to manage both complications [17].

In Korea, according to the weekly report of adverse reaction after COVID-19 vaccination, 51st weeks published by Korea Disease Control and Prevention Agency reported by February 24, 2022, 319.8 adverse events and 12.7 serious adverse events were reported per 100,000 BNT162b2 vaccinations. Serious adverse events included death, anaphylaxis, admission of intensive care unit, critical ill condition, permanent disability and adverse event special interest. By February 20, 2022, 72,217,274 doses were administered. Five hundred and seventy-one cases of anaphylaxis were reported and 79.1% occurred after first dose of vaccination. Three hundred and sixty-one cases of myocarditis/pericarditis were reported. Among them, 61.5% were male and 70.9% were under the age of 40 which were similar to the reports from other countries [18].

mRNA-1273 (Moderna/NIAID)

According to a phase III randomized, observer-blinded, placebo-controlled trial conducted with 30,420 persons aged 18 years or older to evaluate the safety and efficacy of mRNA-1273, solicited local and systemic AEFIs was reported more often in the vaccinated group after both the first and second doses than in the placebo group [5]. In the vaccinated group, injection site pain was frequently reported after the second dose. Delayed injection site reactions with an onset from day 8 onwards, including erythema, induration, and tenderness, were reported to be 0.8% and 0.2% after the first and second doses, respectively, which resolved over the following 4–5 days. Systemic AEFIs, such as fatigue, myalgia, and headache, were more severe and frequent after the second dose than the first dose. Both local and systemic AEFIs were more common among the younger group aged under 65 years than the older group aged 65 years and over. The frequency of the serious adverse events was similar between the vaccinated and placebo groups. Hypersensitivity events and Bell's palsy were reported in 1.5% and <0.1% of the vaccinated groups, respectively, which was similar to the placebo group. Of the vaccinated participants, there were three cases of cerebrovascular accident (one in placebo), two of embolic stroke (none in placebo), one of transient ischemic attack (none in placebo), and two of deep vein thrombosis (none in placebo). However, none of these events were considered AEFIs by the investigator, as it was evident that all subjects had a significant medical history or increased risk for these events. No evidence of vaccine-associated death was reported [5,19].

According to the CDC's report of allergic reactions after administration of mRNA-1273, between December 21, 2020, and January 10, 2021, 4,041,396 doses of the vaccine were administered. Ten cases were diagnosed as anaphylactic reactions in the United States (2.5 per million of mRNA-1273 vaccines administered). Among them, six patients required hospitalization, and no deaths were reported [20].

According to a systematic review of cardiac complications following mRNA COVID-19 vaccines, the frequency of myocarditis was lower after administration of mRNA-1273 than after administration of BNT162b2 (25.6% and 74.4%, respectively) [17]. Patone et al. [21] reviewed COVID-19-vaccinated people aged 16 years or older between December 1, 2020, and August 24, 2021, in England to investigate the risk of cardiac AEFIs associated with COVID-19 vaccines on 1–28 days following vaccination (AZD1222, n=20,615,911; BNT162b2, n=16,993,389; mRNA-1273, n=1,006,191). The authors reported an extra 6 and 10 myocarditis events per 1 million people vaccinated with the first and second doses

of mRNA-1273, respectively. This number is much lower than the 40 myocarditis events per 1 million patients (95% CI, 38.0–41.0) following COVID-19. In the subgroup analysis, the risk of myocarditis following mRNA vaccination was the highest in those aged <40 years.

In phase III clinical trial, facial swelling was reported in two participants in the vaccinated group (one in placebo) and they received dermal filler injection prior to vaccination, which resolved within a week [19]. Rare cases of cutaneous reactions, such as erythematous and tender swelling, associated with hyaluronic acid dermal fillers and mRNA-1273 have been reported. These cases resolved spontaneously or were successfully managed with oral steroids. These may represent a delayed hypersensitivity reaction to an immunological trigger following vaccination [22-24].

In Korea, until February 20, 2022, 23,515,972 doses were administered. Adverse events and serious adverse events were reported at 461.4 and 9.9 per 100,000 mRNA-1273 vaccinations, respectively. One hundred and twenty-one cases of anaphylaxis were diagnosed; among them, 80.2% occurred after the first dose of vaccination and 51.2% were female. None of thromboembolic adverse event was reported after mRNA-1273 vaccination. One hundred and seventy-one cases of myocarditis/pericarditis were reported. Among them, 60.8% were male and 67.8% were under the age of 40. Compared with BNT162b2, the incidence of myocarditis/pericarditis in the under the age of 19 group was lower after mRNA-1273 vaccination (4.1% [7/171] vs. 28.3% [102/361], respectively) [18]. Currently, the ages at which BNT162b2 and mRNA-1273 can be administered are over 12 years old and over 18 years old, respectively [25]. Therefore, it is possible that the incidence of myocarditis/pericarditis after BNT162b2 vaccination was higher than after mRNA-1273 vaccination because administration rate of BNT162b2 was higher than mRNA-1273 in the age group under 19 years of age. No data could be found that the report of facial swelling related to mRNA-1273 vaccination after receiving dermal filler injection until February 2022, but continuous monitoring is needed.

AZD1222 (AstraZeneca/Oxford)

To evaluate the safety and efficacy of AZD1222, four ongoing blinded, randomized controlled trials were analyzed; COV001-phase I/II, COV002 phase II/III, COV003-phase III, and COV005-phase I/II [8,26-29]. Among the 12,021 recipients of AZD1222, the most commonly reported AEFIs were injection-site tenderness, headache, and fatigue. The AEFIs after the second dose were mild and less frequent than those after the first dose. AEFIs were reported less frequently in participants aged 65 years and older than in those aged 18–65 years. The frequency of serious AEFIs was 0.7% in the vaccinated group compared with 0.8% in the placebo group. Out of the reported 175 AEFIs, a case of transverse myelitis and fever higher than 40°C was considered to be related to AZD1222. Interestingly, adverse events of special interest (AESI) were reported less frequently in the vaccinated group than in the placebo group (0.8% and 1.1%, respectively). The definition of AESI is that a preidentified and predefined medically-significant event that has the potential to be causally associated with a vaccine product that needs to be carefully monitored and confirmed by further specific studies. AESI defined for COVID-19 vaccines include the following: vaccine-associated enhanced disease, multisystem inflammatory syndrome in children, acute respiratory distress syndrome, acute cardiovascular injury, coagulation disorder, acute kidney injury, generalized convulsion, Guillain-Barré syndrome (GBS), acute liver injury, anosmia/ageusia, chilblain-like lesions, single organ cutaneous vasculitis, erythema multiforme, anaphylaxis, acute aseptic arthritis, meningoencephalitis, acute disseminated encephalomyelitis, and thrombocytopenia [30]. In the vaccinated group, anaphylaxis (<0.1%), neurological events (0.5%), and thrombotic/thromboembolic events (<0.1%) were reported as AESI [8,26,27].

Although no related cases of anaphylaxis were reported in clinical trials, they also occurred. In Korea, as of January 23, 2022, 20,499,046 doses of AZD1222 had been administered, and 325 cases (1.6%) were reported suggesting anaphylactic reaction; 285 (87.7%) after the first dose and 39 (12.0%) after the second dose [10]. Polysorbate 80, an excipient of AZD1222, has been suggested as the cause of hypersensitivity reaction. Polysorbate is an excipient in hepatitis B, influenza, and human papillomavirus vaccines. PEG and polysorbate have the same structure and can represent cross-reactivity [31].

Thrombosis with thrombocytopenia syndrome (TTS) is a rare but serious adverse event associated with AZD1222. As of March 20, 2021, five patients presented with severe venous thromboembolism at unusual sites with thrombo-

cytopenia within 10 days after receiving the first AZD1222 dose. All these patients showed high levels of antibodies to platelet factor (PF)4-polyanion complexes [32]. As of April 7, 2021, 11 cases of thrombosis with thrombocytopenia following the first dose administration of AZD1222 were reported in Germany and Austria. Thrombotic events included cerebral venous thrombosis, splanchnic vein thrombosis, and pulmonary embolism, and six patients died. The serum obtained nine of 11 patients showed strong reactivity on the PF4-heparin enzyme-linked immunosorbent assay [33]. Initially, these cases were referred as vaccine-induced immune thrombotic thrombocytopenia, as their clinical features are similar with heparin-induced thrombocytopenia [32]. TTS was characterized by mainly occurring as cerebral venous sinus thrombosis or splanchnic vein thrombosis after 4 days to 2 weeks from AZD1222 administration, concomitant with thrombocytopenia without recent exposure of heparin. It was hypothesized that vaccine-induced antibodies lead to thrombosis through platelet activation [34]. The European Medicines Agency (EMA) registered TTS as a very rare adverse event of AZD1222 in the product description. However, the EMA and the Medicines and Healthcare products Regulatory Agency confirmed that the benefits of AZD1222 against COVID-19 continue to outweigh the risk of adverse events; therefore, continuous vaccination is recommended [35,36]. According to the Yellow Card Reports in the United Kingdom up to January 25, 2022 (24.9 million first doses, 24.2 million second doses), 436 cases of major thromboembolic events with thrombocytopenia following vaccination with AZD1222 were reported (88.8% after the first dose and 11.2% after the second dose). The overall case fatality rate was 18% [11].

GBS is a rare neurological disorder associated with infection or immunization. As of July 31, 2021, 833 cases of GBS were reported following AZD1222 vaccination, while approximately 592 million doses of AZD1222 were administered worldwide by July 25, 2021. Based on the assessment of these data, the EMA determined that a causal relationship between AZD1222 and GBS is at least a reasonable possibility. Therefore, GBS was added to the product information as a rare side effect of AZD1222 [37]. After AZD1222 vaccination, few cases of encephalitis or transverse myelitis have been reported, and they are still extremely rare (<1 report per 100,000 doses) [38,39]. In the case of serious neurological adverse events are reported after the first dose of AZD1222, administration of the second dose is not recommended.

Capillary leak syndrome (CLS) is a rare disorder associated with the recurrent episodes of extravasation of fluid and protein into the interstitial space from capillaries, resulting in swelling of arms and legs. The triad of hypotension, hemoconcentration, and hypoalbuminemia supports the diagnosis of CLS. Nevertheless, the exact pathophysiology of CLS remains unclear [40]. The EMA disclosed an estimated reporting rate of one case of CLS for more than 5 million doses of AZD1222. Although the causality between AZD1222 and CLS has not been fully demonstrated, the EMA concluded that CLS should be added to the product information of AZD1222 as an adverse event with unknown frequency. AZD1222 is contraindicated in patients who have previously experienced of CLS [37].

In Korea, until February 20, 2022, 20,348,850 doses were administered. Adverse events and serious adverse events were reported at 536.8 and 27.6 per 100,000 AZD1222 vaccinations, respectively. One hundred and eight cases of anaphylaxis were diagnosed; among them 95.0% occurred after the first dose of vaccination. Three cases of TTS were diagnosed, all occurring after the first dose of AZD1222 vaccination. One female in her seventies was diagnosed with deep vein thrombosis, two males in their thirties were diagnosed with cerebral vein thrombosis (CVT) and one died [18]. As a result, to reflect the risk of this fatal adverse event, the AZD1222 vaccination policy was revised to be recommended for those aged 50 and over as of July 2021 [41]. By February 18, 2022, 21 suspicious cases of GBS associated with COVID-19 vaccination were reviewed and 19 cases were reported after AZD1222 vaccination (first dose, 15 cases; second dose, 4 cases). In these 19 cases, there was a time probable relationship with vaccination and onset of adverse events, but it was determined that there were insufficient data of causal relationship between vaccine and adverse event. No case of CLS after AZD1222 vaccination was reported [18].

Ad26.COV2.S (Janssen)

A total of 39,321 participants who were subdivided into two age groups (18–59 years of age group and ≥60 years of age group) were enrolled in a randomized, double-blind, placebo-controlled, phase III trial to evaluate the safety and

efficacy of a single dose of Ad26.COV2.S vaccine [6]. Among them, 6,736 participants were included in the safety analysis during the 7 days after the administration of Ad26.COV2.S or placebo. The most commonly reported local and systemic AEFIs in the vaccinated group were injection-site pain and headache, respectively. More AEFIs were reported in the 18–59 years age group than in the ≥60 years of age group. The frequency of serious AEFIs considered related to the Ad26.COV2.S vaccine was similar between the vaccinated group and the placebo group (0.4% and 0.4%, respectively). In the vaccinated group, one patient had GBS, one pericarditis, two Bell's palsy, and one brachial radiculitis were reported. Notably, 11 cases of venous thromboembolism (three in placebo), four of seizure (one in placebo), and six of tinnitus (none in placebo) were reported in the vaccinated group. However, the authors could not determine a causal relationship between these events and Ad26.COV2.S. There were three deaths in the vaccinated group (16 in the placebo group), considered unrelated to the trial intervention [6]. In the final analysis of single-dose Ad26.COV2.S, one case of TTS was reported in the vaccinated group. No cases of CLS, myocarditis, or encephalitis have been reported [42].

From March 2 to April 21, 2021, in the United States, 12 cases of cerebral venous sinus thrombosis were reported among recipients of the Ad26.COV2.S vaccine. Similar to those of another adenovirus-vector vaccine, AZD1222, these events occurred primarily in females within 2 weeks of administration and were accompanied by thrombocytopenia. Eleven patients were confirmed positive for PF4-antibody, and three patients died [43]. As a result, vaccination of Ad26.COV2.S was temporarily paused in the United States, but it was resumed because the benefit of preventing COVID-19 was higher than the risk of a very rare adverse event [44]. Following the reports of updates on TTS following Ad26.COV2.S vaccination from March 2 to December 9, 2021 by CDC, 54 cases were reported and eight patients died. Most cases were women and under 50 years of age. The median time from vaccination to symptom onset was 9 days (range, 0–18 days). The CDC disclosed that the reporting rate of TTS following Ad26.COV2.S vaccination was 3.8 per million doses, and the proportion of TTS cases with death did not decrease after the vaccination pause on April 13, 2021 [45]. According to the results of an observational study in Europe using the EudraVigilance database, between January 1 and July 30, 2021, 761 cases of thrombotic events were reported (10,972,234 doses of Ad26.COV2.S administered). The reporting rate of CVT per 1 million person vaccinated-days was 11.48 (95% CI, 9.57 to 13.67) for Ad26.COV2.S., 21.60 (95% CI, 20.16–23.11) for AZD1222, 1.92 (95% CI, 1.71–2.12) for BNT162b2, and 5.63 (95% CI, 4.74–6.64) for mRNA-1273. Similar to the results of a report in the United States, the highest prevalence of CVT was observed in the under 65 years and female groups [46].

Transverse myelitis is an inflammation of parts of the spinal cord. By August 31, 2021, 11 cases of transverse myelitis were considered to have at least a possible or probable causal relationship with the Ad26.COV2.S vaccination (more than 33 million doses of the Ad26.COV2.S vaccine had been administered worldwide). Therefore, the EMA recommended the addition of inflammation of the spinal cord as a side effect with unknown frequency to the product information. GBS was also recommended to be added as a very rare side effect (it may affect up to 1 in 10,000 people) [47,48].

Similar to other adenovirus-vector vaccines (AZD1222), Ad26.COV2.S vaccines are not recommended for people who have previously had CLS. The EMA reviewed three cases of CLS following Ad26.COV2.S vaccination, and two of them died. Therefore, the Committee recommended that this vaccine should not be administered to people with a history of CLS, and healthcare professionals should be aware of the risk of CLS following vaccination, which can be fatal if untreated [49].

In Korea, until February 20, 2022, 1,508,231 doses were administered. Adverse events and serious adverse events were reported at 585.6 and 26.4 per 100,000 Ad26.COV2.S vaccinations, respectively. Thirty cases of anaphylaxis occurred and 66.7% were male; it may because the Ad26.COV2.S was primarily administered to Korean soldiers. No cases were reported with TTS or transverse myelitis. Two cases of GBS were reported after Ad26.COV2.S vaccination, which were determined that there were insufficient data of causal relationship between vaccine and GBS [18]. There was one case of fatal CLS after Ad26.COV2.S administration in patient with multiple myeloma [50]. This case was reviewed and finally demonstrated probably not related with vaccination because of the lack of data [18].

Conclusions

According to recent reports, the novel vaccines against

COVID-19 have an acceptable safety profile. Continuous vaccination is recommended, as the benefits outweigh the risks of rare serious adverse events. Long-term monitoring of various AEFIs and sharing clinical experience are necessary for safe and efficient large-scale vaccination.

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No potential conflict of interest relevant to this article was reported.

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