Vaxzevria® (COVID-19 vaccine AstraZeneca) and Guillain-Barré syndrome

Introduction

Vaxzevria®, produced by AstraZeneca (AZ), is a monovalent vaccine composed of a recombinant and replication-deficient chimpanzee adenovirus (ChAdOx1) vector encoding the spike glycoprotein of Sars-CoV-2, indicated for immunisation against Sars-CoV-2 virus causing COVID-19. Following intramuscular administration the spike glycoprotein is expressed locally, stimulating antibody and cellular immune response (1). In The Netherlands, Vaxzevria® has been used since February 2021, mainly used for immunisation of healthcare workers and people aged 60-65 and on demand for people > 65 years (2).

Guillain-Barré syndrome (GBS) is a rare and severe neurological disorder. GBS is an umbrella term for multiple types of immune-mediated acute paralysing neuropathies. The clinical presentation and disease course of GBS is heterogeneous with several clinical variants (e.g. sensorimotor, pure motor, Miller-Fisher) and electrophysiological subtypes (e.g. acute inflammatory demyelinating polyradiculoneuropathy [AIDP], acute motor axonal neuropathy [AMAN], and acute sensorimotor axonal neuropathy [AMSAN]). GBS often presents with progressive symmetrical muscle weakness and reduced reflexes. The symptoms usually progress over a period of 2 weeks. Muscle weakness can vary from mild to severe with respiratory failure requiring mechanical ventilation. In approximately two-thirds of GBS cases the disease is preceded by a respiratory-tract infection or gastroenteritis. It is thought that the infection evokes an autoimmune response that targets peripheral nerve components. Campylobacter jejuni is the most frequently identified pathogen. The first symptoms usually present 1-2 weeks after infection. GBS has been associated with vaccination as well (3, 4). For this reason, it is considered to be an Adverse Event of Special Interest (AESI) by EMA.(5) In a Dutch study from 2011, the background incidence rate was calculated by using the Integrated Primary Care Information (IPCI) database, a longitudinal observational database containing patient records of general practitioners in the Netherlands. The background incidence rate was found to be 1.14 per 100,000 person years (95% confidence interval [CI] 0.67-1.61). The incidence rate was significantly lower for people under 50 years compared to people older than 50 years. The highest incidence rate found was in the age group of 60-69 years (2.15 per 100,000 person years; 95%CI 0.04–4.25) (6). The study showed no significant difference in incidence rates between males and females, although literature suggest a higher incidence rate for males compared to females (4, 6).

Reports

Until June 28th, The Netherlands Pharmacovigilance Centre Lareb received 11 reports of GBS associated with Vaxzevria®. 7 reports were sent in by physicians, 3 by consumers or other non-health professionals and 1 by other health professionals. The 11 reports concern 7 females and 4 males. The youngest and eldest patients were 56 and 65 years old, respectively. The average age was 61 years. Time to onset varied from 7 days to 17 days with an average of 11.5 days. Details on the reported adverse drug reactions, complaints, course of the disease, treatment and diagnostics can be found in Table 1.

Table 1 **Reports of Guillain-Barré syndrome after Vaxzevria, until June 28th, 2021**

ID **sex** **age** **primary source**	**Drug (dose) and Time to onset**	**Reported ADRs** ***(description of complaints and course)***	**Treatment and Outcome**	**Diagnostics and reporter comments**
NL-LRB-00478813 male 61-70 Years Physician (Neurologist)	AZ (unknown) 11 days	Guillain Barré syndrome *(Initially cold hands, muscle weakness in legs and arms. During hospitalization: paresthesia hands and feet, progressive weakness in arms and legs, peripheral facial paralysis left, impaired swallowing, cough strength decreased. Patient needed a feeding tube. Due to an adverse effect of IVIG (posterior reversible encephalopathy syndrome with visual impairment) the patient was transferred to an academic hospital.)*	Intravenous Immunoglobulin (IVIG) After transfer: plasmapheresis Not Recovered	MRI cervical region, lumbar puncture, blood test: no abnormalities EMG: consistent with acute demyelinating polyneuropathy No signs of infection prior to complaints
NL-LRB-00517356 female 61-70 Years Physician (Neurologist)	AZ (1st) 14 days	Guillain Barré syndrome *(Ascending paresthesia, progressive loss of strength, 3 weeks after vaccination:*	IVIG Not Recovered	Lumbar puncture, blood test (unspecified), EMG: no results reported

		paraplegia, mild paresis of right arm and peripheral facial paralysis)		
NL-LRB-00532233 female 61-70 Years Physician (Neurologist)	AZ (unknown) 7 days	Guillain Barré syndrome *(Atypical course with no further details reported)*	Intensive care unit admission with mechanical ventilation, no further details provided Unknown	A number of causes still needed to be excluded (including: TBC, sarcoidosis, neuroborreliosis, malignancy)
NL-LRB-00518606 female 61-70 Years Physician (Neurologist)	AZ (1st) 9 days	Guillain Barré syndrome Facial paresis *(progressive pain complaints, sensory disorder, weakness of legs, peripheral facial paresis)*	IVIG Recovering	EMG, lumbar puncture: no results reported
NL-LRB-00542860 male 61-70 Years Physician (Neurologist)	AZ (1st) 8-13 days	Guillain Barré syndrome Facial paresis Myalgia Muscle weakness lower limb *(8 days after vaccination: diffuse muscle pain followed by vomiting. 13 days after vaccination: progressive bilateral peripheral facial paresis with fast progressive symmetrical weakness in arms and legs (proximal and distal), some autonomic dysfunction. After start treatment: muscle strength and facial paresis improved. Discharge from hospital after 8 days.)*	IVIG Recovering	Lumbar puncture: total protein 1.61 g/L, normal cell count CT brain: no abnormalities No signs of infection prior to complaints.
NL-LRB-00556367 male 51-60 Years Physician (Neurologist)	AZ (1st) 10-11 days	Guillain Barré syndrome Shoulder pain Neck pain *(10 days after vaccination: pain in shoulders and neck. 11 days after vaccination: start of muscle weakness in legs, after a number of days progressed to loss of strength in the arms, distal sensory disorders with paresthesia and areflexia. During hospitalization the patient also had swallowing difficulties.)*	IVIG + methyl-prednisolon Recovering	EMG: consistent with acute demyelinating polyneuropathy. Lumbar puncture: no abnormalities (negative for Borrelia and Lues, white blood cell count <5, glucose 4.4) Serology: negative for campylobacter, Borrelia, Lues COVID -19 test: negative
NL-LRB-00547285 male 61-70 Years Consumer or other non health professional	AZ (1st) 14 days	Guillain Barré syndrome *(Started with progressive myalgia with later paralysis of the legs first and then the arms. The patient had neuralgia as well.)*	IVIG + pregabaline Recovering	Diagnosis confirmed with EMG and lumbar puncture.
NL-LRB-00564792 female 51-60 Years Consumer or other non health professional	AZ (1st) 9 days	Guillain Barré syndrome Headache Malaise Pain in extremity Paresthesia of limbs *(2 hours after vaccination: malaise. 9 days after vaccination: headache, malaise, pain and paresthesia in arms and legs. The patient was consulted by a neurologist who diagnosed her with GBS. The patient did not describe the course but at the time of reporting (34 days after vaccination) she still had above mentioned symptoms, headache and fatigue.*	No treatment Not Recovered	Diagnostic tests not reported.
NL-LRB-00547865 female 61-70 Years Consumer or other non health professional	AZ (1st) 12 days	Guillain Barré syndrome Muscular weakness Generalized joint pain Paresthesia *(Symptoms started with tingling in the fingertips and soles of the feet, and later muscular weakness in the lower legs and 2 phalanges of the hands. Symptoms aggravated the first 3 weeks, but are slowly resolving. At the start of hospital admission, there were progressive symptoms, with the patient developing a mild foot drop in both feet (more on the right than left) and ascending*	No treatment Recovering	MRI, lumbar puncture: no abnormalities

		hypoesthesia of both legs. The patient mobilized safely with a walker under the supervision of the physiotherapist. During admission, the patient remained stable with no evidence of deterioration or improvement. The patient was discharged home after 4 days of hospitalization.)		
NL-LRB-00544798 female 51-60 Years Physician (Medical student)	AZ (1st) 18 days	Guillain Barré syndrome Chest pain Tetraparesis *(Started with pain between the shoulder blades and later paresthesia (first in the fingertips, then the tongue and later the right hand). Additionally, the patient had decreased muscular strength in her right hand. Before hospital admission the patient had muscular weakness in her legs which caused her fall and break her wrist. 2 days after treatment her symptoms improved: paresthesia decreased and mobility improved. Discharge after 11 days total.)*	IVIG Recovering	EMG: consistent with GBS Lumbar puncture: increased protein, no further abnormalities Antibody tests: Neuroborreliosis IgM and IgG negative. Anti-Borrelia IgM and IgG negative. Blood test: no abnormalities.
NL-LRB-00595612 female 61-70 years Other health professional (Medical student)	AZ (1st) 11 days	Guillain Barré syndrome *(Presented with pain in epigastric region. Developed bilateral facial paresis and sensory complaints. In the course of 4-7 days: extensive muscular weakness. No respiratory failure, no autonomic symptoms. GBS disability score after 2 weeks of admission: grade 4.)*	IVIG Recovering	Lumbar puncture: increased protein, total cell count normal to slightly increased.

Comparison with background incidence

Since GBS is a rare disease, the observed number of reported cases was compared to the expected number based on background incidence rates. However, it should be noted, that the results of the calculations should be interpreted with caution, since the rate of underreporting of GBS is unknown. To calculate the numerator of expected cases in the population, vaccination numbers based on estimated vaccinations involved in the vaccination campaign, were obtained (7). Unfortunately, these numbers are not stratified by age and gender. Background incidence rates for GBS in the Netherlands were chosen from the ACCESS project and from the aforementioned Dutch study by Van der Maas et al. (6, 8).

The formula used for calculating the number of expected cases is: $N_{Expected}$ = ($N_{Vaccine\_exposure}$ * (At risk period / 365) * 1/100,000) * Incidence rate. An O/E ratio of > 1 means that more cases were observed (reported) than were expected based on background incidence in a given period/ with corresponding given time-to-onset (9). Based on the outcome of calculated O/E ratios, the number of reported cases exceeds the number of expected cases in a 15-day or 30-day period following vaccination. See table 2.

Table 2 **Observed over expected analysis of Guillain-Barre syndrome after Vaxzevria®**

At risk period / TTO	**Number of reports (O)**	**Number of vaccinations**	**Incidence rate (per 100,000 person-years)**		**Expected cases (E)**	**O/E**
(days)			**Source**	**IR (95% CI)**	**E (95% CI)**	**O/E (95% CI)**
15	10	2,318,644	NL_PHARMO_HOSP	1.25 (1.04-1.51)	1.18 (0.98-1.43)	8.5 (7.0-10.2)
			Van der Maas, et al.	1.14 (0.67-1.61)	1.08 (0.63-1.52)	9.3 (6.6-15.8)
30	11	1,950,636	NL_PHARMO_HOSP	1.25 (1.04-1.51)	2.00 (1.67-2.42)	5.5 (4.5-6.6)
			Van der Maas, et al.	1.14 (0.67-1.61)	1.83 (1.07-2.58)	6.0 (4.3-10.2)

Other sources of information

SmPC

GBS is not included in the Summary of product characteristics (SmPC) of Vaxzevria® as an adverse drug reaction (1). GBS was however listed as an adverse event of special interest (AESI) in the European Union risk management plan for the vaccine (5). On July 9th the European Medicines Agency (EMA) announced that the Pharmacovigilance Risk Assessment Committee (PRAC) has recommended adding a warning for GBS to section 4.4 of the SmPC of Vaxzevria® to alert health care

professionals and vaccinated individuals. Based on European GBS cases and literature the PRAC could not confirm nor rule out a possible association between GBS and Vaxzevria® (10).

Other databases
In the WHO global database of individual case safety reports, VigiBase, a total of 1,224 GBS cases were recorded associated with all COVID-19 vaccines which was disproportionate reported (IC_{025} 1.1). 616 of the GBS cases were after Vaxzevria® (50.3%) which was considered to be disproportionate reported as well (IC_{025} 1.5) (11).
The Medicines and Healthcare products Regulatory Agency (United Kingdom) received 317 GBS cases, and variants of GBS, like 20 Miller Fisher syndrome cases (and 2 acute motor axonal neuropathy) cases until June 23rd with 24.5 and 20.7 million first and second doses of Vaxzevria® administered respectively (12). There were approximately 20 times more Vaxzevria® vaccinations administrated in the United Kingdom compared to The Netherlands (7).

Literature
A literature search on PubMed resulted in 7 research papers in English describing cases of newly developed GBS after a COVID-19 vaccination and 1 research paper describing an exacerbation of GBS after vaccination with a vector-based COVID-19 vaccine (13-20). 4 of the 7 papers described a total of 13 cases of GBS after vaccination with Vaxzevria® with all cases occurring post-marktering. (13-15, 18).

Discussion and conclusion

Case definition
The Netherlands Pharmacovigilance Centre Lareb received 11 reports of patients developing GBS after vaccination with Vaxzevria®. The degree of documentation of the diagnostics and symptoms varied. According to the clinical case definitions of the Brighton Collaboration, the following criteria are required for a level 1 diagnostic certainty (21):

- Bilateral and flaccid weakness of the limbs
- Decreased or absent deep tendon reflexes in weak limbs
- Monophasic illness pattern and interval between onset and nadir of weakness between 12h and 28 days and subsequent clinical plateau
- Electrophysiologic findings consistent with GBS
- Cytoalbuminologic dissociation (i.e. elevation of CSF protein level above laboratory normal value and CSF total white blood cell count <50 cells/µL)
- Absence of an identified alternative diagnosis for weakness

Additionally, for there to be an association between Vaxzevria® and GBS other more common causes such as a Campylobacter infection need to be excluded. None of the 11 cases meet the criteria for a level 1 diagnosis mostly due to missing information. However, the lack of information in the reports does not necessarily mean that the diagnoses are not certain, since all reporters were either sent in by a health care professional from a neurology department or sent in by consumers who were diagnosed by a neurologist.

O/E method limitations
The O/E analysis may be subject to a number of uncertainties. Firstly, as mentioned before the diagnoses are not all certain. Nonetheless, all reported cases were used in the analysis. Secondly, due to underreporting the exact number of cases of GBS after vaccination with Vaxzevria® is unknown. This could mean that the real total number of GBS cases could be higher than 11. However, even without taking underreporting into account the lower limits of the 95% CI of the O/E ratios were above 1. Thirdly, the data of the vaccination numbers were estimations and were not stratified by age and gender. As mentioned before, the incidence rate for GBS increases with age and is higher for males than females. Unfortunately, without stratified vaccination data available a stratified O/E analysis that is more accurate is not possible. Lastly, the background rates used in this analysis were from before the COVID-19 pandemic. With measures taken by governments to contain the spread of the virus, the incidence of other infectious and transmissible bacterial diseases were found to be significantly reduced during the pandemic (22). This may have led to a reduced incidence of GBS, since the disease is most often caused by infections.

GBS and other COVID-19 vaccines

Until June 28th the Netherlands Pharmacovigilance Centre Lareb received 4 reports of patients developing GBS after administration of Comirnaty® (Pfizer/BioNTech), 2 after the COVID-19 vaccine of Janssen Pharmaceutical Companies and 1 after Spikevax® (Moderna). Based on the number of administrated vaccines in The Netherlands and the related O/E analyses, the association with GBS stood out for Vaxzevria®. However, an association with the other COVID-19 vaccines cannot be ruled out and may be further investigated in the future.

GBS and COVID-19

Multiple cases reports describing a possible association between a COVID-19 infection and GBS were published as was illustrated in a recent systematic review of 73 cases. An abnormal immune response was suggested to be the underlying mechanism of GBS after a COVID-19 infection (23). However, an epidemiological study by Keddie et al. found no evidence for a causal relationship between COVID-19 and GBS in the UK. The study used the UK National Immunoglobulin Database (in which every intravenous immunoglobulin prescription is recorded) and compared the total GBS cases during the COVID-19 pandemic with numbers from before the pandemic. The number of GBS cases were found to be significantly reduced during the pandemic (24).

Conclusion

A causal relationship between GBS and Vaxzevria® seems possible based on the 11 cases of GBS and the results of the observed over expected analysis. This is in line with the PRAC assessment on GBS for Vaxzevria®. Further research is needed in order to assess the true risk of GBS after vaccination with Vaxzevria®.

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