**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 paralyzing 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**

<table>
<thead>
<tr>
<th>ID sex age primary source</th>
<th>Drug (dose) and Time to onset</th>
<th>Reported ADRs (description of complaints and course)</th>
<th>Treatment and Outcome</th>
<th>Diagnostics and reporter comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>NL-LRB-00478813 female 61-70 Years Physician (Neurologist)</td>
<td>AZ (unknown) 11 days</td>
<td>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.)</td>
<td>Intravenous Immunoglobulin (IVIG) After transfer: plasmapheresis Not Recovered</td>
<td>MRI cervical region, lumbar puncture, blood test: no abnormalities EMG: consistent with acute demyelinating polyneuropathy No signs of infection prior to complaints</td>
</tr>
<tr>
<td>NL-LRB-00517356 male 61-70 Years Physician (Neurologist)</td>
<td>AZ (1st) 14 days</td>
<td>Guillain Barré syndrome (Ascending paresthesia, progressive loss of strength, 3 weeks after vaccination: EMG: no results reported)</td>
<td>IVIG Not Recovered</td>
<td>Lumbar puncture, blood test (unspecified), EMG: no results reported</td>
</tr>
</tbody>
</table>

7/21/2021
<table>
<thead>
<tr>
<th>Case Number</th>
<th>Age</th>
<th>Gender</th>
<th>Profession</th>
<th>Onset</th>
<th>Duration</th>
<th>Symptoms at Onset</th>
<th>Diagnosis</th>
<th>Treatment</th>
<th>Outcome</th>
<th>Additional Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>NL-LRB-0053233</td>
<td>61-70 years</td>
<td>Female</td>
<td>Physician (Neurologist)</td>
<td>7 days</td>
<td></td>
<td>Guillain Barré syndrome</td>
<td>Intensive care unit admission with mechanical ventilation, no further details provided</td>
<td>Unknown</td>
<td>A number of causes still needed to be excluded (including, TBC, sarcoidosis, neuroborreliosis, malignancy)</td>
<td></td>
</tr>
<tr>
<td>NL-LRB-00518606</td>
<td>5 years</td>
<td>Female</td>
<td>Physician (Neurologist)</td>
<td>9 days</td>
<td></td>
<td>Guillain Barré syndrome</td>
<td>IVIG</td>
<td>Recovering</td>
<td></td>
<td>EMG, lumbar puncture: no results reported</td>
</tr>
<tr>
<td>NL-LRB-00542860</td>
<td>8-13 days</td>
<td>Male</td>
<td>Physician (Neurologist)</td>
<td></td>
<td></td>
<td>Guillain Barré syndrome</td>
<td>IVIG</td>
<td>Recovering</td>
<td></td>
<td>Lumbar puncture: total protein 1.61 g/L, normal cell count CT brain: no abnormalities No signs of infection prior to complaints.</td>
</tr>
<tr>
<td>NL-LRB-00547285</td>
<td>14 days</td>
<td>Male</td>
<td>Consumer or other non health professional</td>
<td></td>
<td></td>
<td>Guillain Barré syndrome</td>
<td>IVIG</td>
<td>Recovering</td>
<td></td>
<td>Diagnosis confirmed with EMG and lumbar puncture.</td>
</tr>
<tr>
<td>NL-LRB-00564792</td>
<td>9 days</td>
<td>Female</td>
<td>Consumer or other non health professional</td>
<td></td>
<td></td>
<td>Guillain Barré syndrome</td>
<td>No treatment</td>
<td>Not Recovered</td>
<td></td>
<td>Diagnostic tests not reported.</td>
</tr>
<tr>
<td>NL-LRB-00547865</td>
<td>12 days</td>
<td>Female</td>
<td>Consumer or other non health professional</td>
<td></td>
<td></td>
<td>Guillain Barré syndrome</td>
<td>No treatment</td>
<td>Recovering</td>
<td></td>
<td>MRI, lumbar puncture: no abnormalities</td>
</tr>
</tbody>
</table>
**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: $N_{expected} = \frac{N_{vaccine\_exposure} \times (At\_risk\_period \div 365) \times 100,000}{100,000} \times Incidence\_rate$. 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®

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

**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.
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\textsubscript{95} 1.1). 616 of the GBS cases were after Vaxzevria® (50.3%) which was considered to be disproportionate reported as well (IC\textsubscript{95} 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 23\textsuperscript{rd} 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-marketing. (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 administered 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®.

References

8. Vac4eu. Toolbox Dashboard Background rates of Adverse Events of Special Interest for COVID-19 vaccines. [cited 2021 June 30]. Available from: https://vac4eu.org/covid-

7/21/2021


This signal has been raised on July 21, 2021. It is possible that in the meantime other information became available. For the latest information, including the official SmPC’s, please refer to website of the MEB www.cbg-meb.nl