Vaxzevria® (COVID-19 vaccine AstraZeneca) and Transverse myelitis

Introduction

Vaxzevria® 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 COVID-19 by Sars-CoV-2 virus*. Following intramuscular administration the spike glycoprotein is expressed locally, stimulating antibody and cellular immune response [1]. Biodistribution studies in mice expressed highest levels of viral vector at injection site and in some samples only low levels in other tissues were found, although a study of biodistribution to the central nervous system is ongoing [2]. In The Netherlands, Vaxzevria® has been used since February 2021, mainly used for immunisation of healthcare workers and people aged 60-65 with and without a high risk of COVID-19 complications and on demand for people > 65 years [3].

Transverse myelitis (TM) is a rare acquired neuro-immune spinal cord disorder presenting with acute onset of weakness, sensory alterations and bladder or bowel dysfunction. It can occur independently or it can be part of other neuro-inflammatory disorders, such as acute disseminated encephalomyelitis, multiple sclerosis, myelin oligodendrocyte glycoprotein (MOG) antibody disease, neuromyelitis optica spectrum disorder (NMOSD), and acute flaccid myelitis (AFM). TM has been reported after infection and after vaccination, although a causal relationship could not always be established [4-6]. The incidence of TM in literature is estimated to be 1-8 new cases per million per year [4,6] However, registries used for estimating background incidence rates of Adverse Events of Special Interest (AESI's) in the ACCESS project (vACCine covid-19 monitoring readinESS) vary from 0.02 to 1.79 per 100,000 person-years, depending on country, type of registry and age [7,8].

During phase III clinical trials with the AstraZeneca/Oxford vaccine three people developed TM, of which one was possibly vaccination related and occurred 14 days after the second dose [9,10]. The trial was put on hold for a short period. Two other cases were considered unlikely to be related to the vaccination, since one (also in vaccine group) could be attributed to pre-existing multiple sclerosis and the other occurred in the control group after 68 days of the intervention, receiving the Meningococcal-ACWY vaccine. In this trial 12,021 subjects out of 23,745 participants received at least one dose of the AstraZeneca vaccine, based on the interim analysis [2,9].

Reports

Until June 15th, 2021, The Netherlands Pharmacovigilance Centre Lareb received four reports of transverse myelitis associated with Vaxzevria®, all reported by neurologists and reviewed by a clinical experts. They concern three women and one man. Time to onset varied from 6 to 20 days following the first administration. In three reports typical symptoms of inability to walk and urinate were reported and in one report also sensory disturbances of legs and hands were present. In all reports diagnostics were in favour of TM diagnosis in association with the vaccine: MRI with no abnormalities or demyelinating disorders (4), leucocytosis or pleocytosis in liquor (4), absence of bacterial/viral causative agents (3). In one report antibodies against Myelin Oligodendrocyte Glycoprotein (MOG), associated with neuromyelitis optica, were positive. However, this patient had not been diagnosed with this disease before and it did not become clear if vaccination could have triggered anti-MOG antibodies. None had had COVID-19 previously. Other details on the reports are shown in table 1. Two other reports were received with mRNA vaccines (one Comirnaty® and one Moderna), which are not included in this overview.

Table 1 **Reports of transeverse myelitis after Vaxzevria, until June 15th, 2021**

ID **sex** **age** **primary source**	**Vaccine** **(moment)** **Time to onset**	**Reported ADRs** ***(description of complaints)***	**Treatment** **Outcome**	**Diagnostics and reporter comments**
NL-LRB-00528704 **female** **60-70 years** **Physician (neurologist)**	AZ (1st) 10 Days	Myelitis transverse *(unable to walk and urinate indepently due to neurological loss)*	None Not Recovered	No other clear cause. MRI neuraxis with contrast: no abnormalities Liquor: 21 leukocytes, no bacterial or viral causative agent
NL-LRB-00528715 **female** **60-70 years** **Physician (neurologist)**	AZ (1st) 13 Days	Myelitis transverse *(progressive sensibility disorder in legs, unable to walk indepently and to urinate)*	None Not Recovered	For now, no other clear cause. MRI neuraxis with contrast: no abnormalities Liquor: 102 leukocytes; bacterial and virologic test results unknown
NL-LRB-00556881 **female** **30-40 years** **Physician (neurologist)**	AZ (1st) 20 Days	Myelitis transverse *(no description)*	Methyl-prednisolon Recovering	Patient was not previously diagnosed with optical neuromyelitis. Not clear if anti-MOG was triggered by vaccination. MRI myelum: myelitis transversa MRI brain: no signs of demyelinisation. Anti-MOG positive Anti-aquaporine 4 negative Lumbalpunctie: leukocytosis and increased protein, no bacterial and viral causative agents
NL-LRB-00559252 **male** **60-70 years** **Physician (neurologist)**	AZ (1st) 5 Days 6 Days 6 Days	Myalgia Myelitis transverse with Paraplegia *(Spinal cord injury; shortly after vaccination myalgia and neck pain, feeling of pressure in umbilical region after 8 days flu like symptoms and a little urine loss and since that evening unable to urinate, difficulty walking, tingling, after 10 days unable to walk, hyperesthesia of legs, bladder retention, tingling fingers and 13 days after vaccination paralysis of legs and little paresis of hands.)*	Methyl-prednisolon Not Recovered	MRI myelum and brain: no abnormalities; liquor: pleiocytosis, no bacteria etc. CRP 9.0 ANA negative Anti-dsDNA < 10 No signs of sarcoidosis on CT chest, no borreliosis/HIV/lues/virusses No auto-immune diseases Medical history: inguinal herna (13 years ago) with hernitomy with mesh implant

Comparison with background incidence

Since TM is a rare disease, the observed number of reported cases was compared to the expected number based on background incidence rates. However, the rate of underreporting is unknown. To define the numerator for the expected cases, vaccination numbers based on estimated vaccinations by all parties involved in the vaccination campaign, were obtained [11]. Unfortunately, these numbers are not stratified by age and gender. Background rates for TM from The Netherlands (lowest) and Denmark (highest) provided by the ACCESS project were chosen [8] and from literature [4, 6]

The formula used for calculating the number of expected cases is: $N_{Expected} = (N_{Vaccine\_exposure} * (\text{At risk period} / 365) * 1/100{,}000) * \text{Incidence rate}$. 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 [12].]. 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 transverse myelitis with 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) or range#	(95% CI) or range#	(95% CI) or range#
15	3	1,953,718	NL_PHARMO_HOSP	0.24 (0.16-0.37)	0.19 (0.13-0.29	15.6 (10.2-23.8)
			DK_DCE_PC	1.22 (0.97-1.55)	0.98 (0.77-1.24)	3.1 (2.4-3.9)
			Literature	0.5 (0.1-0.8)#	0.40 (0.08-0.64) #	7.5 (4.7-37.4) #
30	4	1,690,680	NL_PHARMO_HOSP	0.24 (0.16-0.37)	0.33 (0.78-1.33)	12.0 (3.0-5.1)
			DK_DCE_PC	1.22 (0.97-1.55)	1.70 (1.34-2.15)	2.4 (1.9-3.0)
			Literature	0.5 (0.1-0.8)#	0.69 (0.14-1.11) #	5.8 (3.6-28.8) #

Other sources of information

SmPC

Transverse myelitis is not labelled in the Summary of Product Characteristics of Vaxzevria [1]. It is mentioned in the Risk Management Plan as an Adverse Event of Special Interest (AESI), postulated with a risk estimate of less than one per million doses, if there is an association between TM and the vaccine [13].

Other databases

In VigiBase, the WHO global database of individual case safety reports (ICSRs), received 223 reports of transverse myelitis associated with all COVID-19 vaccines, of which 81 (36%) were related to the AstraZeneca vaccine. This association was reported disproportionate for both the AstraZeneca vaccine (IC_{025} 1.0) and for all COVID-19 vaccines (IC_{025} 1.2) [14].
The MHRA mentions 64 reports of transverse myelitis in its vaccine analysis print of the weekly summary of Yellow Card reporting (June 14th, 2021) with a total of 42.3 million first and second doses of AstraZeneca vaccine [15].

Literature

One case report about optic neuritis with longitudinal extensive transverse myelitis in a stable multiple sclerosis patient following vaccination with Vaxzevria® is described in literature. The authors made clear that the newly developed symptoms were not related to the existing disease or other infectious causative agents, but could be attributed to the recent vaccination [16].

Discussion and conclusion

Reporting rate

Based on the four reports, the reporting rate of TM with AstraZeneca vaccine in The Netherlands is 2 per million vaccine doses (number of vaccinations until May, 30th 20201). In the UK, the calculated reporting rate is 1.5 per million vaccine doses. These rates are within the same range of the estimated risk in the RMP, although the degree of underreporting is unknown [13].

TM and other vaccinations

TM has been reported following vaccination with various vaccines in children and adults, such as hepatitis B, measles-mumps-rubella (MMR), diphtheria-tetanus-pertussis (DTP), rabies and influenza vaccines [6]. There are various hypotheses about the mechanisms by which vaccines may induce transverse myelitis. It is postulated theoretically that antigens used for vaccination can induce autoimmunity like infectious agents, via molecular mimicry between infectious antigen and self-antigens, acceleration of ongoing auto-immune processes or the induction of autoimmunity by polyclonal activation of B lymphocytes or enhancing cytokine production [6].
Since many different vaccines are associated with development of TM, the role of adjuvants in inducing a more vigorous immune response and a possible genetic predisposition are not clear yet [6]. The mechanism in which way the adenovirus vector vaccine Vaxzevria can cause or trigger transverse myelitis is not known yet.

TM and COVID-19

Acute transverse myelitis is associated with COVID-19 as well, as was described by Roman et al. in a review of 43 case reports. Both a post-infectious neurological complication mediated by the immune response as well as a direct neurotropic effect of Sars-CoV-2 were postulated mechanisms [17]. However, none of our reports mentioned a concurrent COVID-19 illness.

Limitations O/E method

The exact number of cases of transverse myelitis following vaccination with Vaxzevria is unknown due to underreporting. Media attention can increase the number of reports. There was some media attention for TM since the phase three trial was put on hold for a short period. However there has been no specific media attention for transverse myelitis in during the vaccination campaign thus far. The accuracy of the calculation also depends on the quality of data used for vaccine exposure and background incidence rates. For vaccine exposure only estimated and non-stratified data could be used. Background rates differ between various sources. However, in any situation the number of reported (observed) cases exceeds that of expected cases in the given population size and risk periods.

Conclusion

Based on the reports of transverse myelitis and the lack of other potential causes as well as the outcomes of the observed over expected analysis, a causal relationship for transverse myelitis with Vaxzevria is considered possible.

References

1. EMA. Summary of Product Characteristics (SmPC) Vaxzevria. Via: https://www.ema.europa.eu/en/documents/product-information/vaxzevria-previously-covid-19-vaccine-astrazeneca-epar-product-information_en.pdf (accessed 17-6-2021)
2. EMA. Assessment report COVID-19 vaccine AstraZeneca. Via: https://www.ema.europa.eu/en/documents/assessment-report/vaxzevria-previously-covid-19-vaccine-astrazeneca-epar-public-assessment-report_en.pdf (version date 29-1-2021; accessed 17-6-2021)
3. Rijksoverheid. Vaccinatie tegen het coronavirus. Via: https://www.rijksoverheid.nl/onderwerpen/coronavirus-vaccinatie/volgorde-van-vaccinatie-tegen-het-coronavirus/volgorde-vaccinatie-voor-mensen-die-niet-in-de-zorg-werken (access date 16-6-2021)
4. Chitra Krishnan, MHS, Benjamin Greenberg, MD, MHS. Transverse myelitis, in: Uptodate (version date May 2021; accessed 16-6-2021)
5. Kinderneurologie.eu. Myelitis transversa. Via: https://www.kinderneurologie.eu/ziektebeelden/ontsteking/myelitis%20transversa.php (version date 30-1-2020; access date 16-6-2021)
6. Agmon-Levin N, Kivity S, Szyper-Kravitz M, Shoenfeld Y. Transverse myelitis and vaccines: a multi-analysis. Lupus. 2009 Nov;18(13):1198-204. doi: 10.1177/0961203309345730. PMID: 19880568. Via: https://pubmed.ncbi.nlm.nih.gov/19880568/
7. Encepp. Background rates of Adverse Events of Special Interest for monitoring COVID-19 vaccines. Via: http://www.encepp.eu/encepp/viewResource.htm?id=37274 (access date 16-6-2021)
8. Vac4eu. Toolbox Dashboard Background rates of Adverse Events of Special Interes for COVID-19 vaccines. Via: https://vac4eu.org/covid-19-tool/ (access date 16-6-2021)
9. Voysey M, Clemens SAC, Madhi SA, Weckx LY, Folegatti PM, …, Pollard AJ; Oxford COVID Vaccine Trial Group. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. Lancet. 2021 Jan 9;397(10269):99-111. doi: 10.1016/S0140-6736(20)32661-1. Epub 2020 Dec 8. Erratum in: Lancet. 2021 Jan 9;397(10269):98. PMID: 33306989; PMCID: PMC7723445.Via: https://pubmed.ncbi.nlm.nih.gov/33306989/
10. Knoll, M. D., & Wonodi, C. (2021). Oxford-AstraZeneca COVID-19 vaccine efficacy. Lancet (London, England), 397(10269), 72–74. https://doi.org/10.1016/S0140-6736(20)32623-4 Via: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7832220/
11. Rijksoverheid. Coronadashboard COVID-19 vaccinties. Via: https://coronadashboard.rijksoverheid.nl/landelijk/vaccinaties (accessed 16-6-2021)
12. Mahaux, O., Bauchau, V., & Van Holle, L. (2016). Pharmacoepidemiological considerations in observed-to-expected analyses for vaccines. Pharmacoepidemiology and drug safety, 25(2), 215–222. https://doi.org/10.1002/pds.3918 Via: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5063172/
13. EMA. European Union Risk Management Plan (EU RMP) for COVID-19 vaccine AstraZeneca. Via: https://www.ema.europa.eu/en/documents/rmp-summary/vaxzevria-previously-covid-19-vaccine-astrazeneca-epar-risk-management-plan_en.pdf (access date 18-6-2021)
14. Uppsala Monitoring Centre (UMC). VigiBase. Version date dataset 16-6-2021 (accessed 17-6-2021)
15. MHRA. Coronavirus vaccine - weekly summary of Yellow Card reporting. (version date 17-6-2021; access date 18-6-2021) Via: https://www.gov.uk/government/publications/coronavirus-covid-19-vaccine-adverse-reactions/coronavirus-vaccine-summary-of-yellow-card-reporting#annex-1-vaccine-analysis-print
16. Helmchen, C., Buttler, G.M., Markewitz, R. et al. Acute bilateral optic/chiasm neuritis with longitudinal extensive transverse myelitis in longstanding stable multiple sclerosis following vector-based vaccination against the SARS-CoV-2. J Neurol (2021). https://doi.org/10.1007/s00415-021-10647-x Via: https://link.springer.com/article/10.1007%2Fs00415-021-10647-x
17. Román, G. C., Gracia, F., Torres, A., Palacios, A., Gracia, K., & Harris, D. (2021). Acute Transverse Myelitis (ATM):Clinical Review of 43 Patients With COVID-19-Associated ATM and 3 Post-Vaccination ATM Serious Adverse Events With the ChAdOx1 nCoV-19 Vaccine (AZD1222). Frontiers in immunology, 12, 653786. https://doi.org/10.3389/fimmu.2021.653786 Via: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8107358/

This signal has been raised on July 7, 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