Covid-19 vaccine – Trigeminal neuralgia

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Summary

A preliminary safety signal was identified when a disproportionate case series of 48 reports of trigeminal nerve disorders following COVID-19 vaccination was identified in VigiBase, the WHO global database of individual case safety reports (ICSRs). The reports were from 14 countries up to 22 February 2021. A close temporal relationship with a median time-to-onset of one day (ranging from zero to 14) between vaccination and onset of symptoms was observed.

Trigeminal neuralgia (TN) is a neuropathic pain condition potentially causing one of the most severe pains to be experienced. Its management can require analgesic and corticosteroid treatment.

Several reports in the case series included risk or confounding factors, such as underlying multiple sclerosis (MS), previous episodes of TN, and concomitant herpes virus infections. Health care professionals should be aware of the possibility of TN following immunization with the novel COVID-19 vaccines and take appropriate measures as needed.

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Introduction

Trigeminal neuralgia

Trigeminal neuralgia (TN) is a chronic neuropathic pain condition affecting the fifth cranial (trigeminal) nerve. The aetiology of TN can be classified as idiopathic, classic, or secondary. Classic TN is associated with a compression of the nerve in the trigeminal root entry zone, potentially resulting in demyelination and dysregulation of the expression of voltage-gated sodium channels in the membrane. Secondary TN can be caused by underlying disease, such as multiple sclerosis (MS) or herpes virus infections[1,2]. Symptoms include extreme, sporadic, sudden burning or shock-like facial pain lasting from seconds up to two minutes and is usually a unilateral condition[3]. TN can occasionally occur with accompanying symptoms, such as lacrimation and/or redness of the eye[2]. TN is considered to cause one of the most severe types of pain a person can experience, heavily impacting a patient's quality of life[1]. The older age group was found to be at greater risk of the development of TN, with typical onset in patients of 50 years or older. Annual incidence of TN is estimated to be four to 13 per 100,000[2]. Furthermore, its incidence was observed to be sex-dependent, with more female than male patients suffering from it[1].

COVID-19 vaccines

Up to the date of the analysed case series (22 February 2021), 11 vaccines against the coronavirus SARS-CoV-2 had been authorized world-wide. Four are inactivated vaccines, each two vaccines use mRNA, an adenovirus-vector, or other non-replicating viral vectors, and one a peptide platform[4]. The aim of the vaccines is to provoke a long-lasting immune response by presenting virus antigens (namely the viral entry spike protein) to the immune system.

Reports from VigiBase

The combination "Covid-19 vaccine and trigeminal nerve disorders" was identified as a preliminary safety signal during a screening of VigiBase, the WHO global database of individual case safety reports (ICSRs) focussing on COVID-19 vaccines in February 2021.

Up to 22 February 2021, VigiBase contained 48 unique reports from 14 countries of TN-related PTs (Facial neuralgia, Trigeminal nerve disorder, Trigeminal nerve paresis, Trigeminal neuralgia, Trigeminal neuritis, Trigeminal palsy, and Vth nerve injury) following COVID-19 vaccination. The suspected vaccines were Pfizer/BioNTech in 46 cases, and AstraZeneca in two cases. Most were classified as not serious (n=32; 67%). Disproportionality in comparison with the entire database as background was observed especially for the Pfizer/BioNTech vaccine ('Facial neuralgia' IC_{025} = 2.7 (observed 27 vs expected 3), 'Trigeminal nerve disorder' IC_{025} = 0.79 (observed 6 vs expected 1), and 'Trigeminal neuralgia' IC_{025} = 0.74 (observed 34 vs expected 14)).

Patients were predominantly female (n=39; 81%), seven were male (15%), and for two the sex was unknown. The patients' median age was 47.5 years, ranging from 26 to 71. The Pfizer/BioNTech vaccine was reported as suspect in 46 cases (96%).

Median time-to-onset (TTO) between vaccination and the occurrence of TN was one day (range 0 to 14 days). In the 33 cases giving a TTO of zero or one day, detailed information on the TTO was available in eight, ranging from 0.5 to 10 hours (median three hours). The dose number was available in 26 cases. In 20 cases the reported TN occurred after administration of the first vaccine dose and in six cases after the second dose. Calculating the TTO divided by dose number, the reaction occurred at a median of one day after the first dose, ranging from zero to seven days and immediately after the second dose (ranging from zero to one day). However, in six cases (13, 22, 27,29, 34 and 46), patients receiving the first vaccine dose showed relevant medical history or concomitant conditions potentially favouring the occurrence of TN. In these six cases, TTO was observed to be slightly shorter with a median of zero days, ranging from zero to six days.

In eight reports there was information on which side of the body the symptoms occurred. The TN occurred on the same side as the vaccine was administered in six cases, and in two cases it was reported to have appeared on the opposite side. The outcome was reported as 'recovered' or 'recovering' in 30 cases, 'unknown' in five cases and 'not recovered' in 13 cases. Among the reports with outcome 'not recovered' the follow-up time is relatively short (median 7.5 days, ranging 0-20 days) and similar to cases with reported recovery (median 8.0 days, ranging 2-22 days), therefore there is no evidence for long-lasting disorders at this time. In 14 cases, information on the management of the reported

reaction was available. In 10 of these, symptoms were treated with NSAIDs, paracetamol, and/or other over-the-counter drugs, followed by symptom resolution in eight cases (two were 'not recovered'). In two other cases corticosteroids were administered, followed by a resolution of symptoms, and in the last two cases medication for pre-existing TN was increased with unknown outcomes.

Six patients had suffered from previous episodes of TN (cases 27, 30, 34, 41, 42, and 46) as suggested by the concomitant drugs and their indications (bold in Table 1). Furthermore, two patients suffered from underlying multiple sclerosis (MS) (cases 29 and 39) and one of them suspected the vaccine, or the vaccine-related fever, to have triggered a recurrence of MS symptoms causing the TN (case 39). For another patient topiramate was reported as a concomitant drug (case 17). Topiramate can be used for the treatment of TN, but in this case information on its indication was not given, leaving an underlying TN hypothetical.

In three cases, herpes zoster infections were co-reported with trigeminal neuralgia (cases 17, 31, and 44). One of these cases (44) mentioned 'Facial neuralgia' secondary to a previous herpes zoster infection which was suspected to have flared due to the COVID-19 vaccination. Another case (22) included the MedDRA PT 'Viral rash', without further specification.

The remaining co-reported reactions were mainly in line with the vaccines' expected adverse events, such as headache (n=16), pyrexia (n=11), and fatigue (n=7).

Table 1 gives an overview of the most important features of the 48 assessed cases.

Labelling and literature

Trigeminal neuralgia as a potential adverse drug reaction (ADR) is not labelled for the three EMA and FDA approved COVID-19 vaccines (AstraZeneca, Moderna, and Pfizer/BioNTech). However, the Summaries of Product Characteristics (SmPCs) of the two mRNA-based vaccines (Pfizer/BioNTech and Moderna) include acute facial paralysis (also known as Bell's palsy) as a rare ADR[5,6]. Furthermore, the risk management plan (RMP) of AstraZeneca's adenovirus vector-based vaccine includes nervous system disorders, including immune-mediated neurological conditions as an important potential risk[7]. As a reason for including this in the RMP, ongoing scientific discussions and inconclusive evidence regarding immune-mediated acute demyelinating events following viral vaccination were given[8,9].

Cranial neuropathies and COVID-19 infection

COVID-19 infection was observed to be associated with cranial neuropathies and facial nerve palsy[10,11]. A retrospective study in the Italian province of Reggio Emilia, for example, identified a more frequent occurrence of facial palsy during the first phase of the COVID-19 pandemic (27 February to 3 May 2020) in comparison with the same period in the previous year[11]. The mechanism of neurological injury remains unclear, but viral spike protein interaction with angiotensin-converting enzyme 2 receptors in nerves, muscles and the brain have been discussed[10]. Potential mechanisms are therefore neuro-invasion, infection of neurons and glia cells (neurotropism) inducing neurological disease (neurovirulence), or virus-induced autoimmunity[10]. Increasing evidence suggests that cranial nerve involvement in COVID-19 infections represents autoimmunity as observed in a case series of 11 patients experiencing COVID-19-related Guillain-Barré syndrome[12]. In the case series the virus itself was not detected in the cerebrospinal fluid, implying no direct root infection or intrathecal viral replication, but a post-viral-induced autoimmune disorder was suspected[12].

Discussion

Cranial neuropathies following immunization with viral vaccines have been the focus of scientific discussions for years[8]. Until now, evidence for a potential causal relationship is inconclusive. However, the involvement of potential autoimmune mechanisms as postulated by Dalakas[12] could shed a new light on this issue.

Up to 22 February 2021, there were 48 unique ICSRs reporting TN and related PTs in combination with COVID-19 vaccines. Furthermore, there were 44,965 ICSRs reporting PTs related to the system organ class (SOC) 'Nervous system disorders' in combination with COVID-19 vaccines. The most commonly reported reactions were 'Headache' (n=29,477), 'Dizziness' (n=7,075), and 'Paraesthesia' (n=3,563), but terms such as 'Facial paralysis' (Bell's palsy) (n=431), 'Guillain-Barré syndrome' (n=42), 'hearing loss'

(n=164), and 'Tinnitus' (n=367) could be observed as well[13].

The temporal relationship between COVID-19 vaccination and the occurrence of TN was consistently reported as close with a median TTO of one day.

Patients were mostly female with a median age of 48 years, which is in line with characteristics of TN patients independent of vaccination. A reason and potentially confounding factor for this observation could also be the prioritised vaccination of health care professionals (predominantly young and female). Indeed, 75% of the COVID-19 vaccine adverse reactions included in VigiBase concern females, and the median age is slightly over 40[14].

The presence of herpes zoster infections, previous episodes of TN, and underlying multiple sclerosis in eleven cases (23%) present further confounding or risk factors. Herpes zoster infection itself can cause trigeminal neuralgia. After an acute infection, herpes zoster viruses can persist in a latent form within the dorsal root ganglia neural cells. In a case of reactivation, symptoms can occur following the spread of the virus down the sensory nerve[2]. A case series published in 1999 described the reactivation of herpes zoster in three patients following vaccination against various non-herpetic viruses (case 1 – formaldehyde-inactivated hepatitis A vaccine, case 2 – trivalent influenza split vaccine, case 3 – rabies and Japanese encephalitis vaccine). In the last case, the herpes zoster developed in the second and third branches of the trigeminal nerve with a TTO of one day[15]. A possible mechanism for herpes infection reactivation following vaccination was discussed in a case published by Hassman and DiLoreto in 2016[16]. The patient experienced three episodes of herpes-related encephalitis and acute retinal necrosis after three distinct administrations of influenza vaccine. Interestingly, TTO was observed to be shorter after each re-exposure (ten days after the first vaccination, three days after the second, and only one day after the third)[16]. In the current case series a similar pattern could be observed in six patients developing TN immediately after vaccination with the first dose who suffered from underlying or concomitant conditions potentially favouring the occurrence of TN. Two immunological mechanisms were hypothesized: molecular mimicry, meaning immune response to a vaccine peptide could trigger demyelinating processes against resembling host proteins, or auto-inflammation[16]. Furthermore, a murine study showed reduced cerebral neurotropin levels in mice being intranasally infected with non-neurotropic influenza virus, resulting in a robust herpes virus replication[17]. Another hypothesis is the local immune response at the vaccination site resulting in a "distraction" of immunological surveillance mechanisms (e.g. guarding T-cells)[16].

In six cases, drugs potentially used for viral infections (e.g. aciclovir) or pre-existing TN (e.g. gabapentin, carbamazepine, or topiramate) were co-reported. To date some electronic reporting systems do not enable the inclusion of concomitant drugs since appropriate fields are missing. Therefore, it should be kept in mind that the assessed case series shows only a limited picture, and confounding factors could be underestimated.

Conclusion

The clinical review of TN related events following COVID-19 vaccination in VigiBase, submitted from 14 countries, showed a close temporal correlation between vaccination and the onset of symptoms. Although TN was experienced as intense severe pain, most of the patients recovered following intake of analgesics or treatment with corticosteroids. Healthcare professionals should be aware of the possibility of TN following immunization with the novel COVID-19 vaccines and take appropriate actions as needed. The potential benefit of the COVID-19 vaccines is considered to outweigh the possible associated risk of trigeminal neuralgia.

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Table 1. Overview of case reports on trigeminal neuralgia following COVID-19 vaccination in VigiLyze

Case	Age/ sex	Vaccine	Suspected (S), interacting (I) or concomitant (C) drugs*	Dose	Reactions (MedDRA PT)	Time-to-onset	Outcome	Additional information
1	37/F	Pfizer/BioNTech	Covid-19 vaccine (S)		**Trigeminal nerve disorder** Hypoaesthesia Lip swelling Swelling face	12 days	Not recovered	-
2	63/F	Pfizer/BioNTech	Covid-19 vaccine (S) Metoprolol (C)	2nd	**Facial neuralgia** Axillary pain Confusional state Ear discomfort Headache Myalgia Paraesthesia Pyrexia	0 days	Not recovered	-
3	37/-	Pfizer/BioNTech	Covid-19 vaccine (S)	-	**Trigeminal neuralgia** Chills Headache Vaccination site reaction	1 day	Unknown	-
4	67/M	Pfizer/BioNTech	Covid-19 vaccine (S)	-	**Trigeminal neuritis** Pain Pyrexia	1 day	Recovering	-
5	59/F	Pfizer/BioNTech	Covid-19 vaccine (S)	-	**Trigeminal neuralgia** Ear pain Hyperaesthesia Oropharyngeal pain Pain in extremity Pyrexia Stomatitis	0 days	Recovered	-
6	45/M	Pfizer/BioNTech	Covid-19 vaccine (S) Azathioprine (C)	-	**Facial neuralgia** Hyperpyrexia	0 days	Recovering	-

Case	Age/ sex	Vaccine	Suspected (S), interacting (I) or concomitant (C) drugs*	Dose	Reactions (MedDRA PT)	Time-to-onset	Outcome	Additional information
7	59/F	Pfizer/BioNTech	Covid-19 vaccine (S)	-	**Trigeminal neuralgia** Diarrhoea Headache Somnolence Vomiting	0 days	Recovering	-
8	61/F	Pfizer/BioNTech	Covid-19 vaccine, Hydrochlorothiazide; Nebivolol (S) Levothyroxine, Lormetazepam, Sertraline (C)	-	**Facial neuralgia** Fatigue Lymphadenopathy Oedema	1 day	Recovering	-
9	57/F	Pfizer/BioNTech	Covid-19 vaccine (S)	-	**Facial neuralgia**	0 days	Recovered	-
10	71/F	Pfizer/BioNTech	Covid-19 vaccine (S)	-	**Trigeminal neuralgia**	0 days	Not recovered	Medical history: Meningioma benign
11	47/F	Pfizer/BioNTech	Covid-19 vaccine (S)	2nd	**Trigeminal nerve disorder** Hypoaesthesia	0 days (1.5 hours)	Unknown	-
12	41/F	Pfizer/BioNTech	Covid-19 vaccine (S)	1st	**Facial neuralgia** Axillary pain Ear pain Muscular weakness Neck pain Pyrexia	0 days	Not recovered	Reaction on the same side as vaccination
13	49/F	Pfizer/BioNTech	Covid-19 vaccine (S)	1st	**Trigeminal nerve disorder** Erythema Limb discomfort	0 days (1 hour)	Recovered	Patient had **similar reactions to vaccines previously** (influenza in 2015 and 2020) Known reactions to penicillin and sulfa drugs
14	48/F	Pfizer/BioNTech	Covid-19 vaccine (S)	-	**Trigeminal neuralgia** Headache Heart rate increased Musculoskeletal stiffness Neck pain Presyncope	0 days (2 hours)	Recovered	-

Case	Age/ sex	Vaccine	Suspected (S), interacting (I) or concomitant (C) drugs*	Dose	Reactions (MedDRA PT)	Time-to-onset	Outcome	Additional information
15	34/M	Pfizer/BioNTech	Covid-19 vaccine (S)	2nd	**Trigeminal nerve disorder** Face oedema Toothache	1 day	Recovering	Reaction on the same side as vaccination
16	27/F	Pfizer/BioNTech	Covid-19 vaccine (S)	2nd	**Facial neuralgia** Chills Fatigue Hyperhidrosis Migraine Pyrexia	0 days	Recovering	-
17	42/F	Pfizer/BioNTech	Covid-19 vaccine (S) **Topiramate (C)**	-	**Trigeminal neuralgia** Facial paresis **Oral herpes** **Post herpetic neuralgia**	14 days	Recovering	-
18	51/F	Pfizer/BioNTech	Covid-19 vaccine (S)	1st	**Facial neuralgia** Cervical radiculopathy	3 days	Recovered	-
19	50/F	Pfizer/BioNTech	Covid-19 vaccine (S)	2nd	**Trigeminal neuralgia** Arthralgia Back pain Headache Lymphadenopathy Nausea Pyrexia	-	Recovering	-
20	32/F	Pfizer/BioNTech	Covid-19 vaccine (S)	1st	**Trigeminal nerve disorder** Paraesthesia Tongue oedema Vaccination site pain	0 days	Recovered	-
21	49/F	Pfizer/BioNTech	Covid-19 vaccine (S)	1st	**Trigeminal neuralgia** Asthenia Dysentery Myalgia Pyrexia	1 day	Recovered	-

Case	Age/ sex	Vaccine	Suspected (S), interacting (I) or concomitant (C) drugs*	Dose	Reactions (MedDRA PT)	Time-to-onset	Outcome	Additional information
22	47/F	Pfizer/BioNTech	Covid-19 vaccine (S)	1st	**Trigeminal neuralgia** Fatigue Headache Impaired work ability Insomnia Neuralgia Neuritis Rash **Viral rash**	1 day	Not recovered	Rash on the stomach, according to dermatologist viral exanthema (nos)
23	42/M	Pfizer/BioNTech	Covid-19 vaccine (S)	1st	**Facial neuralgia** Anaesthesia Paraesthesia	0 days	Recovered	Reaction on the same side as vaccination
24	52/F	Pfizer/BioNTech	Covid-19 vaccine (S)	2nd	**Facial neuralgia** Headache Pyrexia	0 days (a few hours)	Recovering	Reaction on the same side as vaccination
25	54/F	Pfizer/BioNTech	Covid-19 vaccine (S)	1st	**Facial neuralgia** Neuralgia	0 days	Recovered	Reaction on the opposite side of vaccination
26	46/M	Pfizer/BioNTech	Covid-19 vaccine (S)	1st	**Facial neuralgia** Face oedema Vision blurred	0 days (1 hour)	Recovering	Reaction on the same side as vaccination
27	49/F	Pfizer/BioNTech	Covid-19 vaccine (S) **Gabapentin (C)**	1st	**Trigeminal neuralgia** Headache Musculoskeletal pain Neck pain	0 days	Recovered	**Pre-existing trigeminal neuralgia**
28	30/M	Pfizer/BioNTech	Covid-19 vaccine (S)	-	**Trigeminal neuralgia** Pain	3 days	Not recovered	Bilateral pain
29	34/F	Pfizer/BioNTech	Covid-19 vaccine (S)	1st	**Trigeminal neuralgia**	6 days	-	Medical history: **Multiple Sclerosis** Concomitant conditions: **Ear infection**

Case	Age/ sex	Vaccine	Suspected (S), interacting (I) or concomitant (C) drugs*	Dose	Reactions (MedDRA PT)	Time-to-onset	Outcome	Additional information
30	52/F	AstraZeneca	Covid-19 vaccine (S) **Carbamazepine (C)**	-	**Trigeminal neuralgia** Asthenia Headache Hyperhidrosis Malaise Pain Pyrexia	1 day	Unknown	Carbamazepine for indication 'Head pain' secondary to brain tumor -> **pre-existing trigeminal neuralgia**
31	48/M	Pfizer/BioNTech	Covid-19 vaccine (S)	1st	**Trigeminal neuralgia** **Herpes zoster**	2 days	Recovering	-
32	44/F	Pfizer/BioNTech	Covid-19 vaccine (S)	1st	**Trigeminal neuralgia**	2 days	Not recovered	-
33	50/F	Pfizer/BioNTech	Covid-19 vaccine (S)	-	**Facial neuralgia** Erythema Fatigue Feeling hot Hypersensitivity Paraesthesia Pruritus Rash Swelling face	0 days (0.5 hours)	Recovered	-
34	35/F	Pfizer/BioNTech	Covid-19 vaccine (S)	1st	**Trigeminal neuralgia** Flank pain Hypoaesthesia Maternal exposure during breast feeding Pain	0 days	Not recovered	Medical history: Trigeminal neuralgia **Oral herpes**
35	37/F	Pfizer/BioNTech	Covid-19 vaccine (S)	1st	**Trigeminal nerve disorder** Hyperaesthesia Migraine	0 days (10 hours)	Recovered	-
36	57/F	Pfizer/BioNTech	Covid-19 vaccine (S)	-	**Facial neuralgia**	1 day	Not recovered	

Case	Age/ sex	Vaccine	Suspected (S), interacting (I) or concomitant (C) drugs*	Dose	Reactions (MedDRA PT)	Time-to-onset	Outcome	Additional information
37	54/F	Pfizer/BioNTech	Covid-19 vaccine (S)	-	**Facial neuralgia** Illness Influenza like illness Neuralgia	2 days	Recovered	-
38	30/F	Pfizer/BioNTech	Covid-19 vaccine (S)	-	**Trigeminal neuralgia** Nausea Paraesthesia oral Sensation of foreign body Vomiting	1 day (4 hours)	Not recovered	-
39	39/F	AstraZeneca	Covid-19 vaccine (S) **Amitriptyline**, Beclometasone, Omeprazole (C)	-	**Trigeminal neuralgia** Back pain Balance disorder Confusional state Decreased appetite Erythema Fatigue Headache Pyrexia Restless legs syndrome Sight disability Skin mass Skin warm Tremor	1 day (9.5 hours)	Recovering	Medical history: **Multiple Sclerosis**
40	35/F	Pfizer/BioNTech	Covid-19 vaccine (S)	1st	**Trigeminal neuritis**	2 days	Unknown	-
41	26/-	Pfizer/BioNTech	Covid-19 vaccine (S)	-	**Trigeminal neuralgia**	1 day	Not recovered	Medical history: Acephalgic migraine **Trigeminal neuralgia**
42	56/F	Pfizer/BioNTech	Covid-19 vaccine (S) Atorvastatin, **Carbamazepine**, Influenza vaccine, Lisinopril, Nebivolol (C)	-	**Trigeminal neuralgia** Facial pain	1 day	Recovering	Medical history: **Trigeminal neuralgia** (indication of carbamazepine)
43	52/F	Pfizer/BioNTech	Covid-19 vaccine (S)	1st	**Trigeminal neuralgia** Temporomandibular joint syndrome	2 days	Not recovered	Reaction on opposite side of vaccination

Case	Age/ sex	Vaccine	Suspected (S), interacting (I) or concomitant (C) drugs*	Dose	Reactions (MedDRA PT)	Time-to-onset	Outcome	Additional information
44	52/F	Pfizer/BioNTech	Covid-19 vaccine (S)	1st	**Facial neuralgia** **Herpes virus infection**	-	Recovering	Reporter's comment: "**trigeminal neuralgia probably secondary to herpes zoster infection**"
45	27/F	Pfizer/BioNTech	Covid-19 vaccine (S)	-	**Trigeminal neuralgia** Headache Tenderness	5 days	Recovered	Reaction at the same side of vaccination Recovered by day 7
46	48/F	Pfizer/BioNTech	Covid-19 vaccine (S) **Aciclovir**, Thiamine (C)	1st	**Trigeminal neuralgia** Arthralgia **Condition aggravated** Fatigue Tension headache	0 days	Recovering	**Pre-existing trigeminal neuralgia secondary to herpes zoster infection** until 4 days prior to vaccination Trigeminal neuralgia recurred on the same day of vaccination
47	42/F	Pfizer/BioNTech	Covid-19 vaccine (S)	-	**Trigeminal neuralgia** **Condition aggravated** Fatigue Headache Lymph node pain Vertigo	3 days	Recovered	Recovery after intake of corticosteroid
48	46/F	Pfizer/BioNTech	Covid-19 vaccine (S)	1st	**Facial neuralgia** Arthralgia Diarrhoea Headache Lymphadenopathy Malaise Myalgia Nausea Neck pain Pain in extremity Paraesthesia Paraesthesia oral Pharyngeal swelling Swelling face	7 days	Not recovered	-

*Substances marked in bold were found to be linked to pre-existing trigeminal neuralgia or herpes zoster infections

SIGNAL

WHO defines a signal as:

"Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously". An additional note states: "Usually more than one report is required to generate a signal, depending on the seriousness of the event and the quality of the information".*

A signal is therefore a hypothesis together with supporting data and arguments. A signal is not only uncertain but also preliminary in nature: the situation may change substantially over time one way or another as more information is gathered. A signal may also provide further documentation of a known association of a drug with an ADR, for example: information on the range of severity of the reaction; the outcome; postulating a mechanism; indicating an "at risk" group; a dose range which might be more suspect; or suggesting a pharmaceutical group effect or a lack of such an effect by a particular drug.

Signals communicated by UMC are derived from VigiBase, the WHO global database of individual case safety reports. This database contains summaries of individual case safety reports of suspected adverse drug reactions, submitted by national pharmacovigilance centres (NCs) that are members of the WHO Programme for International Drug Monitoring. More information regarding the status of this data, its limitations and proper use, is provided in the Caveat on the last page of this document.

VigiBase is periodically screened to identify drug-ADR combinations that are unknown or incompletely documented. Combinations of such interest that they should be further reviewed clinically are sent to members of the Signal Review Panel for in-depth assessment. The Signal Review Panel consists of experienced international scientists and clinicians, usually affiliated with a governmental or an academic institution. The expert investigates the clinical evidence for the reaction being related to the suspected drug.

The topics discussed in the signals represent varying levels of suspicion. Signals contains hypotheses, primarily intended as information for the national regulatory authorities. They may consider the need for possible action, such as further evaluation of source data, or conducting a study for testing a hypothesis.

The distribution of signals is currently restricted to NCs, regulatory authority staff and their advisers, participating in the WHO Programme. Signals are sent to the pharmaceutical companies when they can be identified as uniquely responsible for the drug concerned. UMC does not take responsibility for contacting all market authorisation holders. As a step towards increased transparency, since 2012 UMC signals are subsequently published in the WHO Pharmaceuticals Newsletter.

National regulatory authorities and NCs are responsible for deciding on action in their countries, including communicating the information to health professionals, and the responsible market authorisation holders, within their jurisdiction.

In order to further debate, we encourage all readers of signals to comment on individual topics.

* Edwards I.R, Biriell C. Harmonisation in pharmacovigilance. Drug Safety 1994;10:93-102.

Responses from industry

Signals on products under patent are submitted to patent holders for comments. Responses from industry are unedited. The calculations, analysis and conclusions are theirs, and should be given serious but critical consideration in the same way as any scientific document. The WHO and UMC are not responsible for their findings, but may occasionally comment on them.

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Caveat Document

Statement of reservations, limitations and conditions relating to data released from VigiBase, the WHO global database of individual case safety reports (ICSRs). Understanding and accepting the content of this document are formal conditions for the use of VigiBase data.

Uppsala Monitoring Centre (UMC) in its role as the World Health Organization (WHO) Collaborating Centre for International Drug Monitoring receives reports of suspected adverse reactions to medicinal products from National Centres in countries participating in the WHO Programme for International Drug Monitoring. The information is stored in VigiBase, the WHO global database of individual case safety reports (ICSRs). It is important to understand the limitations and qualifications that apply to this information and its use.

Tentative and variable nature of the data

Uncertainty: The reports submitted to UMC generally describe no more than suspicions which have arisen from observation of an unexpected or unwanted event. In most instances it cannot be proven that a specific medicinal product is the cause of an event, rather than, for example, underlying illness or other concomitant medication.

Variability of source: Reports submitted to national centres come from both regulated and voluntary sources. Practice varies: some national centres accept reports only from medical practitioners; others from a broader range of reporters, including patients, some include reports from pharmaceutical companies.

Contingent influences: The volume of reports for a particular medicinal product may be influenced by the extent of use of the product, publicity, the nature of the adverse effects and other factors.

No prevalence data: No information is provided on the number of patients exposed to the product, and only a small part of the reactions occurring are reported.

Time to VigiBase: Some national centres make an assessment of the likelihood that a medicinal product caused the suspected reaction, while others do not. Time from receipt of an ICSR by a national centre until submission to UMC varies from country to country. Information obtained from UMC may therefore differ from that obtained directly from national centres.

For these reasons, interpretations of adverse effect data, and particularly those based on comparisons between medicinal products, may be misleading. The data comes from a variety of sources and the likelihood of a causal relationship varies across reports. Any use of VigiBase data must take these significant variables into account.

Prohibited use of VigiBase Data includes, but is not limited to:

- patient identification or patient targeting
- identification, profiling or targeting of general practitioners or practice

Any publication, in whole or in part, of information obtained from VigiBase must include a statement:

(i) recording 'VigiBase, the WHO global database of individual case safety reports (ICSRs)' as the source of the information

(ii) explaining that the information comes from a variety of sources, and the probability that the suspected adverse effect is drug-related is not the same in all cases

(iii) affirming that the information does not represent the opinion of the UMC or the World Health Organization.

Omission of this statement may exclude the responsible person or organization from receiving further information from VigiBase.

UMC may, in its sole discretion, provide further instructions to the user, responsible person and/or organization in addition to those specified in this statement and the user, responsible person and/or organization undertakes to comply with all such instructions.

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