World Health Organization

WHO Pharmaceuticals NEWSLETTER

2022 No. 1

WHO Vision for Safety of Medicinal Products
No country left behind: worldwide pharmacovigilance for safer medicinal products, safer patients

The aim of the Newsletter is to disseminate regulatory information on the safety of medicinal products, based on communications received from our network of national pharmacovigilance centres and other sources such as specialized bulletins and journals, as well as partners in WHO.

The information is produced in the form of résumés in English, full texts of which may be obtained on request from:

Pharmacovigilance,
MHP/RPQ,
World Health Organization,
1211 Geneva 27, Switzerland,
E-mail address:
pvsupport@who.int

This Newsletter is also available at:
https://www.who.int/teams/regulation-prequalification

The WHO Pharmaceuticals Newsletter provides you with the latest information on the safety of medicinal products and legal actions taken by regulatory authorities around the world. It also provides signals based on information from the WHO global database of individual case safety reports, VigiBase.

In addition, this edition of the Newsletter includes a short article on the recent Advisory Committee on Safety of Medicinal Products (ACSoMP) meeting.

Contents

WHO Pharmaceuticals Newsletter No. 1, 2022

ISBN 978-92-4-004245-2 (electronic version)
ISBN 978-92-4-004246-9 (print version)

Table of Contents

Regulatory Matters

Safety of medicines

All the previous issues of the WHO Pharmaceuticals Newsletter can be accessed from our website at:

https://www.who.int/publications/i?healthtopics=c896df17-29f4-4e3a-b81f-302f999ed12d,9bc69cb6-e97e-4ae9-adf3-76d5b171ff08,5f7b6914-1953-48b6-aabe-9b997a16999e&publishingoffices=a511529e-adb5-49ea-bbde-546a3c26cba7&healthtopics-hidden=true&publishingoffices-hidden=true&regionscountries-hidden=true

Bisphosphonates, denosumab and romosozumab

Risk of atypical fracture in non-femur sites

Japan. The Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA) have announced that the product information for bisphosphonates, denosumab (Ranmark®) and romosozumab (Evenity®) should be revised to include the risk of atypical fracture in non-femur sites.

Bisphosphonates (including alendronate, ibandronate, etidronate, zoledronic, pamidronate, minodronic acid and risedronate), denosumab and romosozumab are indicated for the treatment of osteoporosis.

The MHLW and the PMDA reviewed reports of atypical fracture in non-femur sites (such as ulna or tibia) following administration of those products.

Reference:
Revision of Precautions, MHLW/PMDA, 20 June 2021 *(link to the source within www.pmda.go.jp/english/)*

(See WHO Pharmaceuticals Newsletter No.3, 2019: Risk of hypercalcaemia and multiple vertebral fractures for denosumab in UK)

Cefoperazone and sulbactam

Risk of acute coronary syndrome accompanying allergic reaction

Japan. The MHLW and the PMDA have announced that the product information for the products containing both cefoperazone and sulbactam (Sulperazon®) should be revised to include the risk of acute coronary syndrome accompanying allergic reaction.

Cefoperazone and sulbactam are indicated for the treatment of infectious diseases which are strains of genus susceptible to the substances.

The MHLW and the PMDA reviewed two cases of acute coronary syndrome accompanying allergic reaction in patients treated with the products reported in Japan.

Reference:
Revision of Precautions, MHLW/PMDA, 12 October 2021 *(link to the source within www.pmda.go.jp/english/)*

Chloral hydrate, cloral betaine

Restriction of paediatric indication

United Kingdom. The Medicines and Healthcare Products Regulatory Agency (MHRA) has announced that the paediatric indication for chloral hydrate (for children aged two years and older) and cloral betaine (children aged 12 years and older) has been restricted to short-term treatment (maximum two weeks) of severe insomnia only when the child or adolescent has a suspected or definite neurodevelopmental disorder and when the insomnia is interfering with normal daily life after treatment failure with other therapies (behavioural and pharmacological). The product information is being amended to clarify the restricted use.

Chloral hydrate (Welldorm Elixir®) and cloral betaine (Welldorm®) are indicated for severe insomnia that is interfering with normal daily life and where other therapies have failed, as an adjunct to non-pharmacological therapies. Chloral hydrate is licensed for use in adults and in children aged two years and older. Cloral betaine tablets are licensed for use in adults and adolescents aged 12 years and older.

The MHRA conducted a review of safety and efficacy data and sought independent expert advice including for paediatric sleep disorders. No new safety concerns were identified; however, in view of the carcinogenicity data in animals and the lack of long-term studies, a risk in humans for long-term use was not excluded. As such, the above restriction was recommended where the benefits of short-term use outweigh any potential risk, reflecting current clinical practice.

In addition, the maximum treatment period for these medicines in all patients has now been defined as two weeks in the product information because their prolonged use is associated with tolerance and the risks of dependence and abuse. Repeated courses are not recommended and can only be administered following medical specialist re-assessment. Following prolonged treatment, the dose should be slowly tapered before discontinuation

to avoid delirium.

Reference:
Drug Safety Update, MHRA, 6 October 2021 *(link to the source within www.gov.uk/mhra)*

COVID-19 vaccine NRVV Ad (ChAdOx1 nCoV-19)

Risk of immune thrombocytopenia (ITP)

Europe. The Pharmacovigilance Risk Assessment Committee (PRAC) has recommended a change to the product information for COVID-19 vaccine NRVV Ad (ChAdOx1 nCoV-19) (Vaxzevria®) to include a warning on immune thrombocytopenia (ITP) as an adverse reaction with an unknown frequency. ITP is a condition in which the immune system mistakenly targets platelets in blood.

COVID-19 vaccine NRVV Ad (ChAdOx1 nCoV-19) is a vaccine for preventing COVID-19.

The PRAC assessed cases of ITP reported following vaccination and evidence from the scientific literature.

Healthcare professionals should consider the risk of developing low platelet levels prior to administering the vaccine if an individual has a history of ITP and are recommended to monitor platelet levels following vaccination in individuals with a history of ITP.

Reference:
Patients and carers, EMA, 1 October 2021 *(link to the source within www.ema.europa.eu)*

COVID-19 vaccine NRVV Ad26 (JNJ 78436735)

1. Risk of venous thromboembolism (VTE)

Europe. The PRAC has recommended that thromboembolism (VTE) should be listed as a rare side effect in the product information for COVID-19 vaccine NRVV Ad26 (JNJ 78436735) (COVID-19 vaccine Janssen®). VTE is a condition in which a blood clot forms in a deep vein, usually in a leg, arm or groin, and may travel to the lungs causing a blockage of the blood supply, with possible life-threatening consequences.

COVID-19 vaccine NRVV Ad26 (JNJ 78436735) is indicated for preventing COVID-19.

The PRAC reviewed data form two large clinical studies and post marketing surveillance and concluded that there is a possible link to rare cases of VTE with COVID-19 vaccine NRVV Ad26 (JNJ 78436735).

The PRAC has also recommended to provide a warning to raise awareness among healthcare professionals and people taking the vaccine, especially those who may have an increased risk of VTE, and to assess a potential diagnosis of thrombosis with thrombocytopenia syndrome (TTS) when signs are present within three weeks after vaccination.

Reference:
Patients and carers, EMA, 1 October 2021 *(link to the source within www.ema.europa.eu)*

2. Risk of immune thrombocytopenia (ITP)

Europe. The PRAC has recommended a change to the product information for COVID-19 vaccine NRVV Ad26 (JNJ 78436735) (COVID-19 vaccine Janssen®) to include a warning on immune thrombocytopenia (ITP) as an adverse reaction with an unknown frequency. ITP is a condition in which the immune system mistakenly targets platelets in blood.

The PRAC assessed cases of ITP reported following vaccination and evidence from the scientific literature.

Healthcare professionals should consider the risk of developing low platelet levels prior to administering the vaccine if an individual has a history of ITP. They are recommended to monitor platelet levels following vaccination in individuals with a history of ITP.

Reference:
Patients and carers, EMA, 1 October 2021 *(link to the source within www.ema.europa.eu)*

3. Risk of dizziness and tinnitus

Europe. The PRAC has recommended that dizziness and tinnitus should be listed as adverse reactions in the product information of COVID-19 vaccine NRVV Ad26 (JNJ 78436735) (COVID-19 vaccine Janssen®). Tinnitus is ringing or other noises in one or both ears.

The PRAC assessed the available evidence including

cases of dizziness identified in spontaneous reports and cases of tinnitus identified in clinical trials and spontaneous reports and concluded that cases of dizziness and tinnitus are linked to the administration of COVID-19 vaccine NRVV Ad26 (JNJ 78436735).

Reference:
Patients and carers, EMA, 6 August 2021 *(link to the source within www.ema.europa.eu)*

Eperisone

Risk of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)

Republic of Korea. The Ministry of Food and Drug Safety (MFDS) has updated the product information for eperisone products (oral) to include the risk of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).

Eperisone is a centrally-acting muscle relaxant used for relieving painful muscle spasms or rigidity in musculoskeletal and neuromuscular disorders.

The Korea institute of Drug safety and Risk Management (KIDS) reviewed one report, which suggested a causal link between oral eperisone and SJS/TEN, and information from a foreign regulatory authority and a medical database.

Healthcare professionals should be aware of the signs and symptoms of SJS and TEN to allow early diagnosis and prompt treatment. Patients are advised to seek immediate medical attention if they experience these severe cutaneous symptoms.

Reference:
Based on the communication from MFDS and KIDS, November 2021

Erenumab

Risk of hypertension

Australia. The Therapeutic Goods Administration (TGA) has announced that the product information for erenumab (Aimovig®) has been updated with a warning statement about a potential causal relationship between the drug and hypertension.

Erenumab is indicated for prophylaxis of migraine in adults.

The TGA reviewed cases of the development of hypertension and worsening of pre-existing hypertension reported following use of the drug in the postmarketing setting internationally. Hypertension can occur at any time during treatment, but it was most frequently reported within seven days of dose administration. In the majority of cases, the onset or worsening of hypertension was reported after the first dose of erenumab.
Healthcare professionals should monitor patients treated with erenumab for new-onset hypertension or worsening of pre-existing hypertension. If hypertension is observed and evaluation fails to establish an alternative etiology, they should consider whether discontinuation of erenumab is warranted.

Reference:
Medicines Safety Update, TGA, 9 September 2021 *(link to the source within www.tga.gov.au)*

Fingolimod

Risk of liver injury

New Zealand. The Medsafe has announced that the product information for fingolimod (Gilenya®) has been updated to include the risk of liver injury, to require liver function monitoring during and after treatment, and to include criteria for stopping treatment to prevent serious drug-induced liver injury.

Fingolimod is an immunomodulating drug indicated for the treatment of relapsing multiple sclerosis.

Clinically significant liver injury and cases of acute liver failure requiring liver transplant have been reported in patients treated with fingolimod and the Centre for Adverse Reactions Monitoring (CARM) received four adverse reaction reports of increased hepatic enzymes where fingolimod was the suspected medicine.
Healthcare professionals are advised to check recent transaminase and bilirubin levels before initiation of treatment, to promptly measure transaminase and bilirubin levels if the patient treated with fingolimod reports signs and symptoms of liver injury, and not to resume the treatment unless a plausible alternative aetiology for the signs and symptoms of liver injury can be established.

Reference:
Prescriber Update, Medsafe, September 2021 *(link to the source within*

www.medsafe.govt.nz/)

(See WHO Pharmaceuticals Newsletter No.1, 2021: Risk of serious liver injury and herpes meningoencephalitis in UK)

Gadolinium-based contrast agents

Potential risk of stillbirth and neonatal death

Canada. Health Canada announced that it will work with the manufacturers of gadolinium-based contrast agents (GBCAs) to include the potential risks of stillbirth and neonatal death in their Canadian Product Monographs (CPMs) to raise awareness among healthcare professionals and encourage reporting of these potential safety issues.

GBCAs are used to make certain body tissues easier to see during a magnetic resonance imaging (MRI) or a magnetic resonance angiography (MRA) scan. Gadopentetate dimeglumine, gadobenate dimeglumine, gadodiamide, gadoxetate disodium, gadoterate meglumine, gadobutrol and gadoteridol are authorized as GBCAs.

Health Canada reviewed information from databases (Canada Vigilance database and VigiBase), where reports of stillbirths or neonatal deaths with the use of GBCAs during pregnancy are received, and literature and concluded that there is not enough information to rule out a link between the use of GBCAs during pregnancy and the risks of stillbirth and neonatal death. The measure will be taken as a precaution, given the potential for serious harm to fetuses and infants.

In the review process, case reports of congenital anomalies with the use of GBCAs were also assessed but no link was found between the use of GBCAs during pregnancy and the risk of congenital anomalies.

Reference:
Summary Safety Review, Health Canada, 22 September 2021 *(link to the source within www.hc-sc.gc.ca)*

Hydrocortisone

Risk of hypertrophic cardiomyopathy in neonates and infants

Japan. The MHLW and the PMDA have announced that the product information for hydrocortisone preparations (oral and injectable dosage forms) should be revised to include the risk of hypertrophic cardiomyopathy in neonates and infants.

Hydrocortisone preparations are used for various indications including endocrine and allergic diseases.

The MHLW and the PMDA reviewed cases of hypertrophic cardiomyopathy reported in neonates and infants treated with hydrocortisone preparations overseas.

Reference:
Revision of Precautions, MHLW/PMDA, 20 June 2021 *(link to the source within www.pmda.go.jp/english/)*

Ivermectin

1. Risk of disturbed consciousness

Japan. The MHLW and the PMDA have announced that the product information for ivermectin (Stromectol®) should be revised to include the risk of disturbed consciousness.

Ivermectin is indicated for the treatment of intestinal strongyloidiasis and scabies.

The MHLW and the PMDA reviewed four cases of disturbed consciousness reported in patients treated with ivermectin in Japan and other countries.

Reference:
Revision of Precautions, MHLW/PMDA, 12 October 2021 *(link to the source within www.pmda.go.jp/english/)*

2. Potential risk of encephalopathy

Saudi Arabia. The Saudi Food & Drug Authority (SFDA) has announced that healthcare professionals should be aware of the potential risk of encephalopathy associated with the use of ivermectin and to monitor any signs or symptoms in treated patients.

The SFDA reviewed eight case reports, of which two suggested possible association of encephalopathy with ivermectin and one case positive dechallenge reaction reported, as well as the literature.

Reference:
Safety Alerts, SFDA, 17 August 2021 *(link to the source within www.sfda.gov.sa)*

Magnesium sulfate

Risk of rickets-like bone lesion in neonates at birth

Japan. The MHLW and the PMDA have announced that the product information for magnesium sulfate (injection) indicated for eclampsia should be revised to include the risk of rickets-like bone lesion in neonates at birth with prolonged administration of this drug during pregnancy.

The MHLW and the PMDA reviewed cases of rickets-like bone lesion reported in neonates born to patients treated with magnesium sulfate in Japan and concluded that a causal relationship between the drug and event was reasonably possible in all the cases. The shortest duration of administration with magnesium sulfate (injections) to the mother was 18 days.

Reference:
Revision of Precautions, MHLW/PMDA, 20 June 2021 *(link to the source within www.pmda.go.jp/english/)*

(See WHO Pharmaceuticals Newsletter No.4, 2019: Risk of skeletal adverse effects in neonates in UK)

Methylphenidate

Potential risk of birth defects and malformations

Australia. The TGA has announced that the product information for methylphenidate products has been updated with new information about use in pregnancy. Updated safety information relating to birth defects and malformations is included and the pregnancy category has now been changed so that methylphenidate should not be prescribed for women of childbearing age unless, in the opinion of the physician, the potential benefits outweigh the possible risks.

Methylphenidate is a central nervous system stimulant. It is available in the forms of immediate-release tablets (Ritalin 10®), modified-release capsules (Ritalin LA®) and modified-release tablets (Concerta®) and is indicated for the treatment of ADHD.

The TGA reviewed large observational studies and observed a small increased occurrence of foetal cardiac malformations in women who received methylphenidate during the first trimester of pregnancy, compared with non-exposed pregnancies.

Reference:
Medicines Safety Update, TGA, 26 July 2021 (*link to the source within www.tga.gov.au*)

Minocycline

Risk of agranulocytosis

Australia. The TGA has announced that the product information for minocycline (Minomycin®, Akamin®) is in the process of being updated to include information about agranulocytosis, a rare but potentially life-threatening adverse event, where there is an extremely low number of granulocytes (a type of white blood cell) in the blood.

Minocycline is a tetracycline antibiotic used to treat bacterial infections.

The TGA reviewed four cases of agranulocytosis reported following treatment with minocycline. One case had a positive dechallenge while another was a fatal case reported as tetracycline-induced agranulocytosis. In the other two cases, minocycline-induced agranulocytosis could not be ruled out, as the cases were confounded by other medicines known to cause agranulocytosis.
Healthcare professionals should be aware of the potential risk of agranulocytosis associated with minocycline and the importance of early recognition and monitoring of full blood count and liver function tests during treatment. Prior to treatment with minocycline, patients should be made aware of the risk, including signs and symptoms, and what to do in the event of suspected agranulocytosis.

Reference:
Medicines Safety Update, TGA, 30 August 2021 *(link to the source within www.tga.gov.au)*

Nifedipine

Risk of pulmonary oedema when used in pregnancy

Australia. The TGA has announced that the product information for nifedipine products has been updated to provide new information about the risk of acute pulmonary oedema when used as a tocolytic agent (inhibiting myometrial smooth muscle contractions) for the treatment of preterm labor in pregnancy.

Nifedipine is a calcium channel blocker and indicated for the management of chronic stable angina pectoris and vasospastic

angina pectoris (Prinzmetal's angina, variant angina) due to coronary heart disease and the treatment of hypertension. Nifedipine is contraindicated in pregnancy and during lactation.

The TGA reviewed four adverse event reports involving off-label use of nifedipine in pregnancy. The risk was higher in cases of multiple pregnancy (twins or more), with an intravenous administration route or concomitant use of beta-2 agonists.

Reference:
Medicines Safety Update, TGA, 26 July 2021 *(link to the source within www.tga.gov.au)*

Ocrelizumab

Risk of late onset neutropenia

Australia. The TGA has announced that the product information for ocrelizumab (Ocrevus®) has been updated to include a warning and further information about late onset neutropenia.

Ocrelizumab is a recombinant humanised anti-CD20 monoclonal antibody (IgG1 subtype) that is indicated for patients with relapsing forms of multiple sclerosis and primary progressive multiple sclerosis.

The TGA reviewed four reported cases of neutropenia associated with ocrelizumab. Cases of late onset of neutropenia have been reported at least four weeks after the last Ocrevus infusion.

Healthcare professionals should be advised that late onset neutropenia is a serious safety concern and requires prompt recognition and treatment. Signs and symptoms of late onset neutropenia may not be apparent initially and can occur at least four weeks after the last administration of ocrelizumab.

Reference:
Medicines Safety Update, TGA, 26 July 2021 (*link to the source within www.tga.gov.au*)

Parenteral iron products

Risk of fetal bradycardia and Kounis syndrome

Australia. The TGA has announced that the product information for parenteral iron products has been updated class-wide to include information about fetal bradycardia and Kounis syndrome, which is the concurrence of acute coronary syndromes with conditions associated with mast cell activation. Both conditions can have serious clinical implications.

There are four parenteral iron products marketed in Australia: ferric carboxymaltose (Ferinject®) and ferric derisomaltose (Monofer®) are indicated for iron deficiency where oral administration is ineffective or contraindicated, or where there is a need to deliver iron rapidly; iron polymaltose (Ferrosig injection®) is for the treatment of iron deficiency anaemia when oral iron therapy is contraindicated, enteric absorption of iron is defective, or when patient non-compliance or persistent gastrointestinal intolerance makes oral therapy impractical; and iron sucrose (Venofer®) is for the treatment of iron deficiency anaemia in patients undergoing chronic haemodialysis and who are receiving supplemental erythropoietin therapy.

Hypersensitivity is a class effect that is well documented in the product information of all parenteral iron products. The TGA concluded that fetal bradycardia and Kounis syndrome are biologically plausible as a result of hypersensitivity reactions.

Reference:
Medicines Safety Update, TGA, 27 July 2021 *(link to the source within www.tga.gov.au)*

Pentosan polysulfate sodium

Potential risk of pigmentary maculopathy

Australia. The TGA has announced that the product information for pentosan polysulfate sodium (Elmiron®) has been updated with a warning about potential pigmentary maculopathy, especially after long-term use.

Pentosan polysulfate sodium is indicated for the treatment of bladder pain syndrome (interstitial cystitis).

The TGA reviewed rare cases of pigmentary maculopathy with the use of pentosan polysulfate sodium, especially after long-term use, reported in the literature. Visual symptoms could include complaints of difficulty to read and slow adjustment in low or reduced light environments.

Healthcare professionals should

be aware of this potential adverse event and advise patients receiving pentosan polysulfate sodium of the risks. All patients should have regular ophthalmic examinations for early detection of pigmentary maculopathy, particularly those on long-term use of pentosan polysulfate sodium.

Reference:
Medicines Safety Update, TGA, 11 October 2021 *(link to the source within www.tga.gov.au)*

(See WHO Pharmaceuticals Newsletter No.6, 2019: Rare risk of pigmentary maculopathy in UK)

Pregabalin

Risk of severe respiratory depression

Ireland. The Health Products Regulatory Authority (HPRA) has announced that the product information for pregabalin-containing medicinal products will be updated to include a warning on respiratory depression and to add it as a possible adverse reaction with unknown frequency, following the conclusions of the PRAC.

Pregabalin-containing medicinal products are indicated for the treatment of neuropathic pain in adults, as adjunctive therapy in adults for specific forms of epilepsy and for generalized anxiety disorder in adults.

The PRAC reviewed safety data and concluded that pregabalin is associated with reports of respiratory depression in the absence of concomitant therapy with opioids or other central nervous system (CNS) depressants, in patients with and without other risk factors for respiratory depression.

Healthcare professionals should be advised that patients with risk factors (compromised respiratory function, respiratory or neurological disease, renal impairment, concomitant use of CNS depressants and older age (> 65 years)) may be at higher risk of experiencing respiratory depression with pregabalin and dose adjustment may be necessary. Patients taking the medicine should be advised to contact their doctor if they experience trouble breathing or have shallow breaths and not to drink alcohol while taking pregabalin.

Reference:
Newsletters and Reports, HPRA, 16 September 2021 *(link to the source within www.hpra.ie)*

(See also WHO Pharmaceuticals Newsletter No.2, 2021: Risk of severe respiratory depression in UK)

Remdesivir

Potential risk of sinus bradycardia

Canada. Health Canada has announced that it will work with the manufacturer of remdesivir (Veklury®) to update the product information to include a warning on the potential risk of sinus bradycardia. Sinus bradycardia occurs when the heart beats slower than normal.

Remdesivir is indicated to treat COVID-19 in adults with pneumonia who require oxygen.

Health Canada assessed case reports of sinus bradycardia in patients receiving remdesivir in their database and in the literature and concluded that a link between the use of remdesivir and the risk of sinus bradycardia is possible.

Reference:
Summary Safety Review, Health Canada, 18 August 2021 *(link to the source within www.hc-sc.gc.ca)*

(See also WHO Pharmaceuticals Newsletter No.4, 2021: Risk of sinus bradycardia in Europe)

Sertraline

Potential risk of microscopic colitis

Singapore. The Health Sciences Authority (HSA) has announced that it is working with the manufacturers of sertraline-containing products to update the product information to include microscopic colitis as an adverse event. Microscopic colitis is a rare inflammatory disorder of the colon.

Sertraline is a selective serotonin reuptake inhibitor (SSRI) indicated for the treatment of depression, obsessive compulsive disorder, panic disorder, post-traumatic stress disorder, social phobia and pre-menstrual dysphoric disorder.

The HSA reviewed a case-control study, three case reports of microscopic colitis related to the use of sertraline and the decisions by other regulatory authorities.

Healthcare professionals should be advised to consider the possibility of microscopic colitis in patients on sertraline who

present with prolonged or severe diarrhoea. Diarrhoea is a common adverse drug reaction associated with the use of sertraline.

Reference:
Safety Alerts, HSA, 18 October 2021 *(link to the source within www.hsa.gov.sg)*

(See also WHO Pharmaceuticals Newsletter No.4, 2021: potential risk of microscopic colitis in Singapore)

Statins

Removal of contraindication for pregnant women

USA. The US Food and Drug Administration (FDA) has requested revisions to the information in the prescribing information for the entire class of statin medicines about use in pregnancy. These changes include removing the contraindication against using these medicines in all pregnant patients.

Statins are a class of medicines that have been used to lower low-density lipoprotein cholesterol (LDL-C) in the blood. Medicines in the statin class include atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin.

It was concluded that contraindicating these drugs in all pregnant women is not appropriate because the benefits of statins may include prevention of serious or potentially fatal events in a small group of very high-risk pregnant patients.

Healthcare professionals should discontinue statin therapy in most pregnant patients, or they can consider the ongoing therapeutic needs of the individual patient, particularly those at very high risk for cardiovascular events during pregnancy. Patients taking statins should notify their healthcare professionals if they become pregnant or suspect they are pregnant. Those who require statins after giving birth should not breastfeed and should use alternatives such as infant formula.

Reference:
MedWatch, US FDA, 20 July 2021 *(link to the source within www.fda.gov)*

Tetanus, diphtheria and pertussis (Tdap) vaccine

Risk of Guillain-Barré syndrome

Republic of Korea. The MFDS has updated the product information for tetanus, diphtheria and pertussis (Tdap) vaccine (Boostrix®) to include the risk of Guillain-Barré syndrome (GBS).

Tdap vaccine is indicated for booster immunization against tetanus, diphtheria and pertussis in individuals aged 10 years and older.

The KIDS reviewed one report, which suggested a causal link between Tdap vaccine administration and GBS, and other information from a foreign regulatory authority and a medical database.

Healthcare professionals should be aware of the signs and symptoms of GBS in patients with recent vaccination history.

Reference:
Based on the communication from MFDS and KIDS, November 2021

Tinidazole

Risk of fixed eruption

India. The National Coordination Centre – Pharmacovigilance Programme of India (NCC-PvPI), Indian Pharmacopoeia Commission (IPC) has advised the Central Drugs Standard Control Organization (CDSCO) to revise the prescribing information leaflet (PIL) for tinidazole to include fixed eruption as an adverse drug reaction.

Tinidazole is indicated for the treatment of intestinal amoebiasis, giardiasis, trichomoniasis and anaerobic infections.

NCC-PvPI, IPC reviewed 71 case reports of tinidazole associated fixed eruption and a strong causal relationship between them was found.

Reference:
Based on the communication from IPC, India, November 2021 *(ipc.gov.in)*

Tofacitinib, Baricitinib and Upadacitinib

Risk of serious heart-related events, cancer, blood clots, and death

1. USA. The US FDA has requested that the boxed warnings for tofacitinib (Xeljanz®/Xeljanz XR®),

baricitinib (Olumiant®) and upadacitinib (Rinvoq®), are updated to include the risk of serious heart-related events, cancer, blood clots, and death.

Tofacitinib, baricitinib and upadacitinib are janus kinase (JAK) inhibitors and are used to treat inflammatory conditions such as rheumatoid arthritis.

A review of safety data for tofacitinib was recently completed in USA. Based on this review increased risks of serious heart-related events, cancer, blood clots, and death were identified for tofacitinib compared with TNF blockers in the treatment of patients with rheumatoid arthritis.

Baricitinib and upadacitinib, also used for inflammatory conditions in the same class, are considered to have a risk similar to that of tofacitinib.

Healthcare professionals should consider the benefits and risks for individual patients prior to initiating or continuing therapy with these medicines. Patients should be advised to seek emergency medical attention if they experience signs and symptoms of a heart attack, stroke, or blood clot. Patients should tell their healthcare professional their history and risk factors for those events and seek emergency help immediately if they have any of those symptoms.

Reference:
MedWatch, US FDA, 1 September 2021 *(link to the source within www.fda.gov)*

2. United Kingdom. The MHRA has announced that the product information for tofacitinib will be updated with the information that tofacitinib should not be used in patients older than 65 years of age, people who are current or past smokers, or individuals with other cardiovascular (e.g., diabetes or coronary artery disease) or malignancy risk factors unless there are no suitable alternative treatments.

The MHRA reviewed the results of a clinical safety trial to evaluate the safety of tofacitinib compared with TNF blockers and identified these risk factors.

Reference:
Drug Safety Update, MHRA, 6 October 2021 *(link to the source within www.ema.europa.eu)*

3. Japan. The MHLW and the PMDA have announced that the package insert for tofacitinib should be revised to include the risk of cardiovascular events, such as myocardial infarction.

The MHLW and the PMDA reviewed the results of a clinical safety trial to evaluate the safety of tofacitinib compared with TNF blockers and identified these risk factors.

Reference:
Revision of Precautions, MHLW/PMDA, 12 October 2021 *(link to the source within www.pmda.go.jp/english/)*

(See also WHO Pharmaceuticals Newsletter No.4, 2021: Risk of cardiovascular events and cancer in Europe)

Topical corticosteroids

Risk of topical steroid withdrawal reactions

United Kingdom. The MHRA has warned that rare, severe adverse effects can occur on stopping treatment with topical corticosteroids, often after long-term continuous or inappropriate use of moderate to high potency products. Information about the risks and characteristics of topical steroid withdrawal reactions will be added to the product information for topical corticosteroid medicines.

Topical corticosteroids are used for treatments of skin conditions such as eczema, psoriasis, and atopic dermatitis. They are available in four different levels of potencies.

The MHRA reviewed 55 reports indicative of topical steroid withdrawal reactions, most of which were reported by patients, and information available in the literature and from other regulators and sought advice from clinical experts. Although it was not possible to estimate the frequency of these reactions, given the number of patients who use topical corticosteroids, it was understood that reports of severe withdrawal reactions were very infrequent.

To reduce the risks of these events, it is recommended that healthcare professionals should prescribe the lowest potency of topical corticosteroid needed and ensure patients know how to use it safely and effectively.

Reference:
Drug Safety Update, MHRA, 15 September 2021 *(link to the source within www.gov.uk/mhra)*

Tramadol

Risk of urinary retention

India. The NCC-PvPI, IPC has advised the CDSCO to revise the PIL for tramadol to include urinary retention as an adverse drug reaction.

Tramadol is indicated for the treatment of moderate to severe pain, diagnostic procedures and surgical pain.

NCC-PvPI, IPC reviewed seven reports of tramadol-associated urinary retention and a causal relationship between them was found.

Reference:
Based on the communication from IPC, India, November 2021 *(ipc.gov.in)*

Aflibercept

Potential risk of Fournier's gangrene

Saudi Arabia. The SFDA has released a potential safety signal concerning Fournier's gangrene associated with the use of aflibercept.

Aflibercept is indicated for the treatment of neovascular (wet) age-related macular degeneration and metastatic colorectal cancer.

The SFDA reviewed five case reports, two of which supported the association, and the literature.

Reference:
Safety Alerts, SFDA, 21 September 2021 *(link to the source within www.sfda.gov.sa)*

Atezolizumab

Potential risk of keratitis

Saudi Arabia. The SFDA has released a potential safety signal concerning keratitis associated with the use of atezolizumab.

Atezolizumab is a monoclonal antibody inhibiting PD-L1 and indicated for the treatment of locally advanced or metastatic urothelial carcinoma after prior chemotherapy or that are considered cisplatin ineligible.

The SFDA reviewed four case reports, one of which supported the association, and the literature.

Reference:
Safety Alerts, SFDA, 9 August 2021 *(link to the source within www.sfda.gov.sa)*

Bevacizumab

Potential risk of Fournier's gangrene

Saudi Arabia. The SFDA has released a potential safety signal concerning Fournier's gangrene associated with the use of bevacizumab.

Bevacizumab is a monoclonal antibody inhibiting VEGF-A and indicated for the treatment of non-small cell lung cancer and other cancers.

The SFDA reviewed 35 case reports, nine of which supported the association, and the literature.

Reference:
Safety Alerts, SFDA, 9 August 2021 *(link to the source within www.sfda.gov.sa)*

Cefuroxime

Potential risk of Kounis syndrome

Saudi Arabia. The SFDA has released a potential safety signal concerning Kounis syndrome associated with the use of cefuroxime.

Cefuroxime is cephalosporin antibacterial drug indicated for the treatment of infectious diseases caused by sensitive bacteria.

The SFDA reviewed 11 case reports, three of which supported the association, and the literature.

Reference:
Safety Alerts, SFDA, 21 June 2021 *(link to the source within www.sfda.gov.sa)*

Colchicine

Potential risk of pneumonia

Saudi Arabia. The SFDA has released a potential safety signal concerning pneumonia associated with the use of colchicine.

Colchicine is indicated for prophylaxis of gout flares in adults.

The SFDA reviewed 40 case reports, four of which supported the association, and the literature.

Reference:
Safety Alerts, SFDA, 9 August 2021 *(link to the source within www.sfda.gov.sa)*

Empagliflozin

Risk of ketoacidosis and Fournier's gangrene

New Zealand. The Medsafe has announced that empagliflozin is associated with the risk of ketoacidosis and Fournier's gangrene (necrotising fasciitis of the perineum).

Empagliflozin is a sodium glucose co-transporter 2 (SGLT2) inhibitors and is used for the treatment of type two diabetes mellitus.
The CARM received three reports of ketoacidosis and two reports of Fournier's gangrene following initiation of empagliflozin.

For the risk of ketoacidosis, healthcare professionals are advised to consider stopping empagliflozin temporarily during an acute illness, particularly if patients are unwell, febrile or vomiting and

not eating. Empagliflozin should also be temporarily stopped before undergoing medical procedures or surgery. For the risk of Fournier's gangrene, patients should be advised to seek immediate medical attention if they experience pain, tenderness, redness or swelling of the genital or perineal area, particularly with associated fever or malaise.

Reference:
Prescriber Update, Medsafe, September 2021 *(link to the source within www.medsafe.govt.nz/)*

(See WHO Pharmaceuticals Newsletter No.3, 2020: Risk of diabetic ketoacidosis for SGLT2 inhibitors in UK)

Finasteride

Potential risk of diabetes mellitus

Saudi Arabia. The SFDA has released a potential safety signal concerning diabetes mellitus associated with the use of finasteride.

Finasteride is a 5α-reductase inhibitor and indicated for the treatment of symptomatic benign prostatic hyperplasia (BPH) in men with an enlarged prostate.

The SFDA reviewed 62 case reports, two of which supported the association, and the literature.

Reference:
Safety Alerts, SFDA, 17 August 2021 *(link to the source within www.sfda.gov.sa)*

Infliximab

Potential risk of bursitis

Saudi Arabia. The SFDA has released a potential safety signal concerning bursitis associated with the use of infliximab.

Infliximab is a monoclonal antibody inhibiting the function of TNFα and indicated for the treatment of rheumatoid arthritis and other inflammatory diseases.

The SFDA reviewed 30 case reports, 18 of which supported the association and the literature.

Reference:
Safety Alerts, SFDA, 8 July 2021 *(link to the source within www.sfda.gov.sa)*

(See WHO Pharmaceuticals Newsletter No.4, 2018: Potential risk of linear IgA bullous dermatosis in Canada)

Octreotide

Risk of atrioventricular block

Australia. The TGA has announced that intravenous infusion of octreotide, which is used off-label in Australia, is linked to the risk of atrioventricular block.

Octreotide is an octapeptide that mimics natural somatostatin pharmacologically and is indicated for symptomatic control and reduction of growth hormone and IGF-1 plasma levels in patients with acromegaly etc. The approved route of administration for octreotide products is only subcutaneous injection for the registered indications, while one product (Sandostatin LAR®) may only be administered by deep intragluteal injection.

The TGA evaluated the risk of atrioventricular blocks associated with octreotide treatment using the product information in European Union and clinical guidelines in Australia.

Healthcare professionals should be advised of the identified risk of atrioventricular block in patients receiving off-label high doses of continuous infusion (100 micrograms/hour) of octreotide and in patients receiving bolus octreotide intravenously (50 micrograms bolus followed by 50 micrograms/hour continuous infusion).

Reference:
Medicines Safety Update, TGA, 25 October *2021 (link to the source within www.tga.gov.au)*

Propylthiouracil and carbimazole

Use in pregnancy

Australia. The TGA has announced that the pregnancy category for both propylthiouracil (PTU®) and carbimazole (Neo-Mercazole®) is being changed from being suspected of harmful effects on the human foetus by the pharmacological effects to the being associated with an increased incidence of human foetal malformations.

Propylthiouracil is an antithyroid drug indicated for the treatment of hyperthyroidism or prior to surgery or radioactive iodine therapy in these patients.

Carbimazole is also an antithyroid drug indicated for hyperthyroidism. It is used as a definitive therapy for the induction of a permanent remission in either primary or secondary thyrotoxicosis. It is also used in preparation for thyroidectomy before and after radioactive iodine treatment. The risks relating to congenital abnormalities in neonates are known for these medicines.

The TGA reviewed reported cases of congenital abnormalities for propylthiouracil and carbimazole in the postmarketing setting.

Healthcare professionals should be advised that propylthiouracil and carbimazole should not be prescribed for women of childbearing age unless, in the opinion of the physician, the potential benefits outweigh the possible risks.

Reference:
Medicines Safety Update, TGA, 15 September 2021 *(link to the source within www.tga.gov.au)*

(See WHO Pharmaceuticals Newsletter No.3, 2020: Potential risk of birth defects in Canada)

Selective serotonin reuptake inhibitors (SSRIs) and serotonin-noradrenaline reuptake inhibitors (SNRIs)

Increased risk of postpartum hemorrhage

Saudi Arabia. The SFDA has announced to healthcare professionals that there is a small increased risk of postpartum hemorrhage associated with use of selective serotonin reuptake inhibitors (SSRIs) and serotonin-noradrenaline reuptake inhibitors (SNRIs) antidepressants when used during the last month before delivery.

The SFDA reviewed the result from observational studies suggesting the risk.

Healthcare professionals are advised to carefully assess the safety of antidepressants use during pregnancy against the benefits, especially in later stages, and consider the patient's risk factors for bleeding or thrombotic events.

Reference:
Safety communication, SFDA, 29 July 2021 *(link to the source within www.sfda.gov.sa)*

(See also WHO Pharmaceuticals Newsletter No.4, 2021: Increased risk of postpartum haemorrhage in New Zealand)

A signal is defined by WHO as reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously. Usually more than a single report is required to generate a signal, depending on the seriousness of the event and the quality of the information. A signal is a hypothesis together with data and arguments and it is important to note that a signal is not only uncertain but also preliminary in nature.

The signals in this Newsletter are based on information derived from reports of suspected adverse drug reactions available in the WHO global database of individual case safety reports (ICSRs), VigiBase. The database contains over 27 million reports of suspected adverse drug reactions, submitted by National Pharmacovigilance Centres participating in the WHO Programme for International Drug Monitoring. VigiBase is maintained by the Uppsala Monitoring Centre (UMC) on behalf of WHO and periodic analysis of VigiBase data is performed in accordance with UMC's current routine signal detection process. International pharmaceutical companies, when identified as uniquely responsible for the drug concerned, are invited to comment on the signal text. Signals are thereafter communicated to National Pharmacovigilance Centres, before being published in this Newsletter. Signal texts from UMC might be edited to some extent by WHO and may differ from the original version. More information regarding the ICSRs, their limitations and proper use, is provided in the UMC caveat document available at the end of Signal (page 41). For information on the UMC Measures of Disproportionate reporting please refer to WHO Pharmaceuticals Newsletter Issue No. 1, 2012.

UMC, a WHO Collaborating Centre, is an independent foundation and a centre for international service and scientific research within the field of pharmacovigilance. For more information, on the UMC Measures of Disproportionate Reporting etc., visit www.who-umc.org. To leave a comment regarding the signals in this Newsletter, please contact: the Uppsala Monitoring Centre, Box 1051, SE-751 40 Uppsala, Sweden. E-mail: signals@who-umc.org.

Covid-19 vaccines and hearing loss and tinnitus

Christian Rausch, MD and Qun-Ying Yue, MD, Uppsala Monitoring Centre

Summary

A recent signal detection activity at the Uppsala Monitoring Centre (UMC) identified hearing loss (including sudden cases) and tinnitus following COVID-19 vaccination as a preliminary signal to be further assessed. Up to 22 February 2021[i], there were 164 unique individual case safety reports (ICSRs) which reported 'hearing losses' (MedDRA High Level Term, HLT), and 367 ICSRs which reported 'tinnitus' (Preferred Term, PT) with 'COVID-19 vaccine' in the WHO global database of ICSRs, VigiBase. The cases were from 10 countries, most had no co-morbidities. Time-to-onset varied between 0 and 19 days with a median of 1 day. Based on well-documented cases, alternative causes were not identified for most of the patients, although some may have had contributing morbidities (e.g., allergies, high blood pressure, prior hearing loss, auto-immune related disorders). The most common co-reported symptoms were tinnitus, followed by headache, dizziness and nausea, and many patients experienced quick recovery, while some needed steroid treatment. A plausible mechanism of action involving the vestibulocochlear nerve has been suggested. Awareness of this possible link may help healthcare professionals and those vaccinated to monitor symptoms and seek care, as appropriate. As there is still only limited data in the literature providng evidence for this link, further monitoring is required.

Introduction

The emergence of the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the World Health Organization's declaration of the associated coronavirus disease 2019 (COVID-19) as a global pandemic, have led to a worldwide prioritization of research and development of protective vaccines. To date, several potential vaccines are under development and a few have received market authorization or emergency use authorization, including ChAdOx1-S - (AZD1222) (Covishield) developed by AstraZeneca/University of Oxford, mRNA-1273 developed by Moderna and the National Institute of Allergy and Infectious Diseases, and BNT162 developed by BioNTech, Pfizer and Fosun Pharma. At the time of this report, the current vaccines used have different

[i] Renewed search was conducted on 18 November 2021 (see Adendum on 24 November 2021)

mechanisms to provide protection against COVID-19.[1–3]

Hearing loss generally refers to the partially or completely diminished ability to hear in one or both ears. Hearing loss includes deafness, i.e. the inability to comprehend aural/verbal language, as well as sensorineural hearing loss which is defined by a hearing acuity below 30 dB and generally involves damage to the inner ear, cochlear nerve or vestibulocochlear nerve, or brain.[4,5] Sensorineural hearing loss can occur suddenly within three days or less, and it may be associated with tinnitus and vertigo.[4] Tinnitus can also occur as an isolated symptom and is defined as perception of an auditory sensation despite the absence of a auditory trigger.[6] Incidence of sensorineural hearing loss in the US is estimated at 27 per 100,000 persons per annum, with the incidence increasing with age.[7]

Depending on the aetiology, the age of onset for hearing loss can vary.[8] Hearing loss can be congenital, e.g. Alport-syndrome, or acquired through infections and inflammations due to viruses, as well as systemic disorders, such as hypertension.[9–12] Specific medications, e.g., aminoglycoside antibiotics, are known to be ototoxic and can cause direct damage to the vestibulocochlear apparatus. [13]

Reports in VigiBase

In a signal detection activity on 22 February 2021 screening for COVID-19 vaccines in the WHO global database of ICSRs, VigiBase, disproportional reporting was detected for 'COVID-19 vaccine' associated with MedDRA Preferred Terms (PTs) 'Sudden hearing loss' (24 observed and 8 expected; lower limit of the 95% credibility interval (IC_{025}=0.9) and 'Tinnitus' (367 observed and 259 expected; IC_{025}=0.4). In addition to the PT 'Sudden hearing loss' the search was extended to the High Level Term (HLT) 'Hearing losses' which included an additional 148 relevant cases, among which the PT 'Deafness unilateral' (31 observed and 15 expected; IC_{025}=0.4), and PT 'Deafness neurosensory' (19 observed and 9 expected; IC_{025}=0.4) also showed disproportional reporting. Other PTs within the HLT Hearing losses considered, but not disproportionate, were: Hypoacusis, Deafness, Deafness transitory and Neurosensory hypoacusis.

Hearing loss

Among the 172 ICSRs reporting hearing loss, 8 were duplicate cases, resulting in a total of 164 unique ICSRs. Of these 164 ICSRs, 104 (63%) were for females and 59 (36%) for males, in one case sex was not provided. The age in the reported cases ranged from 19 to 93 years with a median of 49. Reports were received from 10 countries including the USA (66), UK (36), and Italy (15). More than a third of the ICSRs (62, 38%) were from healthcare professionals; 'reporter category unknown' was stated in 66 reports (40%), and 'consumer/non health professionals' in 37 (23%). Some consumer reports were from physicians or other healthcare professionals who had been vaccinated. The most reported COVID-19 vaccines in these cases were Pfizer/BioNTech (142 cases), followed by Moderna (15 cases) and AstraZeneca (7 cases).

While most of the cases were recorded as non-serious (93 cases, 57%), 71 cases (43%) were recorded as serious. Seriousness criteria were most often 'Other medically important condition' (37 case reports), and 'Disabling/incapacitating' (29), followed by 'Caused/prolonged hospitalization' (5), and 'Life threatening' (2).

Of the 164 ICSRs the most commonly co-reported PTs were tinnitus (56), headache (26), dizziness (19), nausea (19), fatigue (14), hypoaesthesia (12), pyrexia (12), acoustic stimulation tests abnormal (11), vertigo (11), and ear discomfort (11).

Only a few reports included information on concomitant treatments and the most commonly reported was the influenza vaccine (four reports), which had been given at least 30 days prior to the COVID-19 vaccine, according to the narratives. Other medications mentioned included omeprazole, acetylsalicylic acid, propranolol, estradiol, calcium carbonate, dexamethasone, paracetamol, rivaroxaban, iron, and folic acid. All appeared in less than four reports and were only reported as concomitant. In some reporting interfaces there are limited options for reporters to note concomitant medication, so this may be underreported.

Time-to-onset (TTO) varied between the same day, i.e., several minutes, to 19 days, with a median of one day. Of the 164 ICSRs, 95 provided narratives for in-depth analysis. Table 1 presents the characteristics of the reports for sudden hearing loss (23), and Table 2 the selected reports of hearing loss

(HLT) with informative narratives (25) in association with a COVID-19 vaccine.

Based on Tables 1 and 2, the TTO is similar for all 164 reports. In 31 cases of the 48 reports displayed in Table 1 and 2, there were no apparent risk factors . In seven cases the reports specified hearing loss related to the second dose, and of these, two reported onset of hearing loss within half an hour to several hours, three within one to two days, and another two six or seven days after the second dose of COVID-19 vaccine. In three cases the reports described hearing loss as occurring with the first COVID-19 vaccine dose and re-occurring and worsening after administration of the second dose. One case of tinnitus following the first dose decreased over a couple of days but hearing loss recurred after the second dose, and the patient was started on steroid treatment; no risk factors were recorded. Another case described bilateral tinnitus more than a week after the first dose and worsening 1.5 weeks after the second dose. Receipt of unspecified medications were recorded, and the patient consulted an ear, nose and throat (ENT) physician. Another described hearing loss occurring which decreased within two days after the first dose, but re-occurring with the second dose, which required steroid treatment.

In 29 cases, patients contacted a physician or ENT specialist within a few days after receiving the vaccination due to hearing loss. Some of the reports were provided by consumers who were themselves physicians or other healthcare professionals. Seven patients confirmed an abnormal audiogram conducted by their physician, and 20 were treated with systemic steroids.

In the narratives of these cases where information on medical history and potential risk factors was present, the following are of note: prior history of hearing loss (n=6), hypothyroidism (n=3) and previous autoimmune thyroiditis (n=1), high blood pressure and cardio-vascular diseases (n=4), allergies, including nut allergy (n=2), and one case each of diabetes mellitus, antiphospholipid syndrome, prior COVID-19, hearing loss related to another viral infection, and unspecified auto-immune reaction or disease.

Of the 164 cases of hearing loss, four also described the feeling of numbness of the face on the affected side. In two narratives, the patients had consulted an ENT physician and received a potential diagnosis of labyrinthitis and vestibular neuritis. In five cases with information on the recovery of hearing following steroid treatment, two reported recovery after three days of steroids and another experienced hearing loss subsiding spontaneously after the first COVID-19 vaccine dose but requiring steroid treatment after the second COVID-19 vaccine dose, with partial recovery (report was received 18 days post-vaccination). A fourth case described mild improvements with steroid treatment (report received five days post-vaccination) and another had mild improvements five days after steroid treatment (report received 17 days post-vaccination).

Of the 164 cases, at the time of the report 51 (31%) were recovering or recovered from their symptoms and 50 (30%) had not recovered. In the remaining 63 (38%) cases no outcome information was recorded.

Tinnitus

There were 367 ICSRs reporting tinnitus with COVID-19 vaccines, of which 56 were also grouped into hearing losses (HLT). Of these 367, 268 (73%) were in females and 92 in males (25%), sex was missing in 7. Their ages ranged from 19 to 91 years with a median of 48. They came from 27 countries with the UK (115), the US (113), and Italy (42) having the most reports. More than a third of the ICSRs (160, 44%) were from healthcare professionals. Reporter category was unknown in 113 reports (31%) and consumer/non healthcare professionals in 97 (26%). The vaccines received were Pfizer/BioNTech (293, 80%), Moderna (39, 11%) AstraZeneca (31, 8.4%), and Sinovac (1, 0.3%). The TTO ranged from several minutes to 30 days after vaccination, with a median one of 1 day. Of the 367 reports, 90 were recorded as not recovered (25%), 164 as recovered (45%) and 112 were unknown (31%).

Most cases were recorded as non-serious (270, 74%), but 97 cases (26%) were recorded as serious. Seriousness criteria included 'other medically important condition' (59, 16%), 'disabling/incapacitating' (33, 9.0%), 'caused/prolonged hospitalization' (8, 2.2%) and 'life threatening' (2, 0.5%). The most co-reported PTs with tinnitus were headache (131, 36%), dizziness (65, 18%), fatigue (65, 18%), nausea (65, 18%), pyrexia (60, 16%), myalgia (54, 15%), chills (47, 13%), arthralgia (37, 10%), asthenia (33, 9.0%) and pain in extremity (30, 8.2%). Eight case narratives reported progression

from tinnitus to hearing loss, i.e., inability to hear in the affected ear.

Labelling and literature

The product labelling for COVID-19 vaccines does not refer to hearing loss. [1–3] However, for both mRNA vaccines, acute peripheral facial paralysis is listed as a rare adverse reaction. Apart from headaches, no other form of nerve or cranial nerve involvement is listed under adverse reactions.

No additional information exists in the scientific literature of an association between COVID-19 vaccines and hearing loss.

Discussion and conclusion

This analysis of reports in VigiBase includes 164 unique cases of hearing loss with COVID-19 vaccines.

The TTO ranged from 0 to 19 days. However, 97 (59%) cases indicated a TTO ranging from 0 to 1 day. The narratives contain information about relatively quick reactions, occurring from minutes to several hours after the injections, often described with tinnitus-like or muffled-hearing sensations, and in some instance headaches, vertigo, and nausea. Some patients described the muffled-hearing or tinnitus progressing into partial or complete hearing loss. Some well documented cases recorded an audiogram confirming the sudden hearing loss diagnosis, and in many cases, the need for treatment with high dose steroids.

Half of the cases noted that the patient was recovering or had recovered from their hearing loss, while no (or limited) additional information on follow-up was recorded for the other cases. The evidence for long-term hearing loss is therefore incomplete.

The analysis also shows that ICSRs with hearing loss came from ten countries and that most cases were young healthy adults with no comorbidities. The median age was 47 years, which appears young and reflects several countries' prioritization of healthcare worker vaccination. Some cases describe patients with a medical history of prior hearing loss, high blood pressure, environmental or seasonal allergies, as well as thyroid dysfunction. In seven cases the reaction of hearing loss was reported with the second dose of the COVID-19 vaccine, and in two cases a positive re-challenge was described.

In addition, several patients reported other co-occurring reactions such as headaches, nausea, and dizziness. The additional description of dizziness and nausea may suggest the involvement not only of the cochlear nerve, but also the vestibular nerve. Furthermore, among the ICSRs reporting hearing loss, two also reported facial paralysis, and four narratives a feeling of numbness in the face, both of which would point to the potential involvement of other cranial nerves apart from the vestibulocochlear, i.e., the facial nerve and trigeminal nerve. The product information for the COVID-19 vaccines does include the rare occurrence of acute facial nerve paralysis. No other reactions specific to other cranial nerves, including hearing loss, are listed. In a study on motor palsies of cranial nerves after vaccination the need for further studies was recommended.[14] The TTO for cranial nerve palsies was reported to be a median of 9-10 days, and with patients of all age groups.

To date, no studies assessing novel COVID-19 vaccines and hearing loss or cranial nerve involvement have been reported. The literature provides anecdotal references to an association between other vaccines and hearing loss.[15–18] In addition, there has been some publications about the potential role of vaccines in adverse reactions involving other cranial nerves.[14,19] However, a case-centred analysis of sudden-onset sensorineural hearing loss after immunization did not report any significant association for 28 different vaccines.[20] The study used a large medical records database and analyzed the first episodes of sensorineural hearing loss in patients who had been vaccinated in the preceding nine months between 2007 and 2013. The study identified 1,929 cases of sensorineural hearing loss within nine months of receiving a vaccine, and 57 that occurred within a week.[14] In addition, in 2020 the Brighton Collaboration published a case definition of sensorineural hearing loss to aid investigation of adverse events following immunization.[12]

A potential mechanism for COVID-19 vaccine-associated hearing loss could be an autoimmune process involving molecular mimicry related to the vaccine's antigen, or bystander activation of autoreactive T-cells that may involve the vestibulocochlear nerve (vestibular nerve is involved in balance and equilibrium functions, and cochlear nerve in hearing function).[21–24] Involvement of this nerve can contribute to symptoms related to labyrinthitis, which involves both vestibular and cochlear branches of the nerve or

vestibular neuritis, which involves vertigo, dizziness and nausea.[25] Two cases in the VigiBase analysis mentioned the potential diagnosis of labyrinthitis and vestibular neuritis made by ENT specialists. Furthermore, analysis of VigiBase in patients vaccinated with COVID-19 vaccine showed a disproportionality for vestibular neuronitis (13 observed and 2 expected) and labyrinthitis (19 observed and 6 expected). Studies on vaccinations and neurological disorders, including cranial nerve involvement reported the potential time windows for symptom onset as being several hours to several weeks depending on the neurological disorder.[14,20,21,26] Currently, clinical evidence and studies on potential mechanisms and the relation between vaccines and neurological disorders, cranial nerve palsies and hearing loss, remain limited.

Under-reporting is a well-known limitation of spontaneous adverse drug reaction reporting. However, there is high interest in COVID-19 and COVID-19 vaccines, which may contribute to increased reporting and therefore, potentially an overestimation of the risk. Additionally, the observed versus expected numbers and IC_{025} values need to be interpreted with caution, since reporting by healthcare providers and the sites is a requirement under the terms of the Emergency Use Authorizations for COVID-19 vaccines in some places (e.g., the USA where most of the cases were reported). For approved medicinal products this is not the case. Therefore, when an expected number is estimated using other medicinal products prior to the pandemic and then compared with the observed cases for COVID-19 vaccines, the result may overestimate the risk. It may be useful to approach the individual countries for more in-depth information and could be considered in future signal investigations.

In summary, cases of (sudden) hearing loss following COVID-19 vaccination have been reported to VigiBase from ten countries. Most of the patients were females (62%) and the age range was 19 to 93 years with a median of 49. However, it should be noted that 75% of the COVID-19 virus vaccine adverse reactions included in VigiBase concern female vaccinees, and the median age is just over 40 years. Most of the cases were young healthy adults with no comorbidities. A close temporal relationship has been observed, and based on well-documented cases, most of the patients did not have alternative causes identified, although some patients may have had contributing morbidities (e.g., high blood pressure, allergies, prior hearing loss, auto-immune related disorders). The most common co-reported symptoms were tinnitus, followed by headache, dizziness and nausea, and many patients experienced a quick recovery, although some patients needed steroid treatment. A plausible mechanism of action has been suggested and awareness of this possible link may help healthcare professions and those vaccinated to monitor symptoms and seek care as appropriate. As the literature and ICSR data are still limited for this link, further monitoring is required.

Addendum on 24 November 2021

Tinnitus is only listed as an adverse reaction for the Janssen COVID-19 vaccine.

An updated search of VigiBase has been performed for the PTs included in this signal assessment (Table-A) and for the terms with a positive (>0) IC_{025} values for each COVID-19 vaccine (Table-B).

In brief, the terms selected for hearing disorders included sudden hearing loss, tinnitus, deafness unilateral, neurosensory hypoacusis, deafness, deafness transitory, and hypoacusis. On 18 November 2021 there were 37 529 deduplicated cases, for which at least one of these terms was reported, from 86 countries: 21 countries reported more than 100 cases; another 22 countries reported 10-99 cases; 15 countries reported 5-9 cases and 28 countries reported 1-4 cases.

It seems that hearing disorders have been reported for most of the COVID-19 vaccines, but with different IC_{025} values. More in-depth assessment of narratives has not been performed for the recently reported cases.. The limitations and precautions for the data and its interpretation mentioned above need to be taken into consideration.

Table-A. The observed and expected numbers of selected hearing disorders with positive (>0) IC_{025} values in VigiLyze on 22 February 2021 and in a repeated search on 18 November 2021.

	Search on 22 February 2021			**Search on 18 November 2021**		
	Observed	Expected	IC_{025}	**Observed**	**Expected**	**IC_{025}**
Sudden hearing loss	24	8	0.9	**1290**	**284**	**2.1**
Tinnitus'	367	259	0.4	**31 644**	**8549**	**1.9**
Deafness unilateral	31	15	0.4	**1676**	**495**	**1.7**
Neurosensory hypoacusis			ND*	**55**	**20**	**1.1**
Deafness			ND*	**3167**	**2378**	**0.4**
Deafness transitory			ND*	**97**	**70**	**0.2**
Hypoacusis			ND*	**3278**	**3608**	**ND***

*Not disproportionate

Table-B. The observed and expected numbers of selected hearing disorders with positive (>0) IC_{025} values for each COVID-19 vaccine in VigiLyze on 18 November 2021.

	Observed	**Expected**	**IC_{025}**
Sudden hearing loss	**1290**	**284**	**2.1**
Tozinameran	**837**	**135**	**2.5**
Elasomeran	**218**	**53**	**1.8**
COVID-19 vaccine NRVV Ad (ChAdOx1 nCoV-19)	**199**	**74**	**1.2**
COVID-19 vaccine NRVV Ad26 (JNJ 78436735)	**28**	**12**	**0.6**
Tinnitus	**31 644**	**8549**	**1.9**
COVID-19 vaccine inact (Vero) HB02	**1507**	**142**	**3.3**
COVID-19 vaccine NRVV Ad26 (JNJ 78436735)	**1692**	**363**	**2.1**
Tozinameran	**15276**	**4049**	**1.9**
Elasomeran	**5946**	**1583**	**1.9**
COVID-19 vaccine NRVV Ad (ChAdOx1 nCoV-19)	**7131**	**2215**	**1.7**
Deafness unilateral	**1676**	**495**	**1.7**
Elasomeran	**458**	**92**	**2.2**
Tozinameran	**999**	**234**	**2.0**
COVID-19 vaccine NRVV Ad26 (JNJ 78436735)	**63**	**21**	**1.2**
Neurosensory hypoacusis	**55**	**20**	**1.1**
Tozinameran	**45**	**9**	**1.8**
Deafness	**3167**	**2378**	**0.4**
Tozinameran	**1854**	**1126**	**0.7**
COVID-19 vaccine NRVV Ad26 (JNJ 78436735)	**153**	**101**	**0.4**
Elasomeran	**571**	**440**	**0.3**
Deafness transitory	**97**	**70**	**0.2**
Tozinameran	**57**	**33**	**0.4**
Hypoacusis	**3278**	**3608**	**ND***
Tozinameran	**1965**	**1709**	**0.1**
COVID-19 vaccine NRVV Ad26 (JNJ 78436735)	**186**	**153**	**0.1**

*Not disproportionate

References

1. EMA Committee for Medicinal Products for Human Use (CHMP). Summary of product characteristics for COVID-19 vaccine Moderna [website]. 2021 [cited 2021 Feb 7]. Available from: https://www.ema.europa.eu/en/documents/product-information/covid-19-vaccine-moderna-epar-product-information_en.pdf

2. EMA Committee for Medicinal Products for Human Use (CHMP). Summary of product characteristics for Comirnaty. [website]. 2021 [cited 2021 Feb 7]. Available from: https://www.ema.europa.eu/en/documents/product-information/comirnaty-epar-product-information_en.pdf.

3. EMA Committee for Medicinal Products for Human Use (CHMP). Summary of product characteristics for COVID-19 vaccine AstraZeneca. [website]. 2021 [cited 2021 Feb 7]. Available from: https://www.ema.europa.eu/en/documents/product-information/covid-19-vaccine-astrazeneca-product-information-approved-chmp-29-january-2021-pending-endorsement_en.pdf

4. Schreiber BE, Agrup C, Haskard DO, Luxon LM. Sudden sensorineural hearing loss. Lancet. 2010 Apr 3;375(9721):1203–11.

5. Roeser RJ, Valente M, Hosford-Dunn H, editors. Audiology. Diagnosis. 2nd ed. New York: Thieme; 2007. 602 p.

6. Nondahl DM, Cruickshanks KJ, Huang G-H, Klein BEK, Klein R, Nieto FJ, et al. Tinnitus and its risk factors in the Beaver Dam offspring study. Int J Audiol. 2011 May;50(5):313–20.

7. Alexander TH, Harris JP. Incidence of sudden sensorineural hearing loss. Otol Neurotol. 2013 Dec;34(9):1586–9.

8. Shi X. Physiopathology of the cochlear microcirculation. Hear Res. 2011 Dec;282(1–2):10–24.

9. Ibekwe TS, Okokhere PO, Asogun D, Blackie FF, Nwegbu MM, Wahab KW, et al. Early-onset sensorineural hearing loss in Lassa fever. Eur Arch Otorhino-Laryngol . 2011;268(2):197–201.

10. van Beeck Calkoen EA, Engel MSD, van de Kamp JM, Yntema HG, Goverts ST, Mulder MF, et al. The etiological evaluation of sensorineural hearing loss in children. Eur J Pediatr. 2019 Aug;178(8):1195–205.

11. Korver AMH, Smith RJH, Van Camp G, Schleiss MR, Bitner-Glindzicz MAK, Lustig LR, et al. Congenital hearing loss. Nat Rev Dis Primer. 201712;3:16094.

12. Carol Liu Y-C, Ibekwe T, Kelso JM, Klein NP, Shehu N, Steuerwald W, et al. Sensorineural hearing loss (SNHL) as an adverse event following immunization (AEFI): Case definition & guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine. 2020;38(30):4717–31.

13. Guthrie OW. Aminoglycoside induced ototoxicity. Toxicology. 2008;249(2–3):91–6.

14. Woo EJ, Winiecki SK, Ou AC. Motor palsies of cranial nerves (excluding VII) after vaccination. Hum Vaccin Immunother. 2014;10(2):301–5.

15. Kolarov C, Löbermann M, Fritzsche C, Hemmer C, Mlynski R, Reisinger EC. Bilateral deafness two days following influenza vaccination: a case report. Hum Vaccin Immunother. 2019;15(1):107–8.

16. Huang H-H, Huang C-C, Hsueh P-Y, Lee T-J. Bilateral sudden deafness following H1N1 vaccination. Otolaryngol Head Neck Surg. 2010;143(6):849–50.

17. De Marco F, De Cesare DP, Di Folco F, Massoni F, Tomei G, Di Luca NM, et al. Post vaccinal temporary sensorineural hearing loss. Int J Environ Res Public Health. 2018;15(8):1780.

18. Okhovat S, Fox R, Magill J, Narula A. Sudden onset unilateral sensorineural hearing loss after rabies vaccination. BMJ Case Rep. 2015 bcr2015211977

19. Mutsch M, Zhou W, Rhodes P, Bopp M, Chen RT, Linder T, et al. Use of the inactivated intranasal influenza vaccine and the risk of Bell's palsy in Switzerland. N Engl J Med. 2004;350(9):896–903.

20. Baxter R, Lewis N, Bohrer P, Harrington T, Aukes L, Klein NP. Sudden-onset sensorineural hearing loss after immunization: a case-centered analysis. Otolaryngol Head Neck Surg. 2016;155(1):81–6.

21. Principi N, Esposito S. Do vaccines have a role as a cause of autoimmune neurological syndromes? Front Public Health. 2020;8:361.

22. Ozonoff A, Nanishi E, Levy O. Bell's palsy and SARS-CoV-2 vaccines. Lancet Infect Dis. 2021;21(4):450-2

23. Liang Y, Meng F-Y, Pan H-F, Ye D-Q. A literature review on the patients with autoimmune diseases following vaccination against infections. Hum Vaccin Immunother. 2015;11(9):2274–80.

24. Institute of Medicine 2012. Adverse effects of vaccines: evidence and causality. Washington, DC: The National Academies Press. https://doi.org/10.17226/13164.

25. Baloh RW. Clinical practice. Vestibular neuritis. N Engl J Med. 2003;348(11):1027–32.

26. Paul R, Stassen LFA. Transient facial nerve paralysis (Bell's palsy) following administration of hepatitis B recombinant vaccine: a case report. Br Dent J. 2014;216(2):69–71.

Table 1. Individual characteristics of reports in VigiBase of sudden hearing loss in association with COVID-19 vaccines (n=23).

Case	Age / sex	Type of vaccine	Dose number	Relevant reactions (MedDRA preferred terms)	Time to onset	Outcome	Type of reporter	Additional information
1.	46/M	Pfizer/BioNTech	-	Tinnitus Sudden hearing loss	7 days	Not recovered	Physician	-
2.	52/F	Pfizer/BioNTech	-	Headache Myalgia Tinnitus Chest pain Sudden hearing loss	0 days	Recovered	Physician	-
3.	-/F	Moderna	-	Deafness neurosensory Deafness unilateral Sudden hearing loss	3 days	-	-	Lost hearing in left ear three days after the vaccination, diagnosed by an ENT with "sudden sensory nerve severe hearing loss".
4.	61/F	Pfizer/BioNTech	-	Acoustic stimulation tests abnormal Deafness Sudden hearing loss	1 day	-	-	Sudden total hearing loss, left ear; numbness in face and outer ear.
5.	54/M	Pfizer/BioNTech	-	Tinnitus Sudden hearing loss	1 day	Not recovered	Pharmacist	One day after the vaccine tinnitus in ear, 14 days later still constant tinnitus in ear, sudden hearing loss left diagnosed by a physician.
6.	70/M	Pfizer/BioNTech		Deafness unilateral Nausea Sudden hearing loss Tinnitus Vertigo Vision blurred	18 hours	-	Consumer	woke up with vertigo and imbalance, clogged left ear and tinnitus, started hyperventilating, went to the hospital with CT and MRI not showing any abnormalities, later referred to ENT, who started high dose steroids after audiogram showed abnormal findings, no improvements five days after treatment initiation.
7.	77/F	Pfizer/BioNTech	-	Acoustic stimulation tests abnormal Deafness unilateral Injection site pain Sudden hearing loss Tinnitus	1 day	-	Consumer	No medical history, arm tender after injection, one day later tinnitus right ear, two days after the vaccine consultation with an ENT for earwax removal, few minutes later reoccurrence of tinnitus and humming, three days after the vaccination complete hearing loss right ear and started on prednisolone 40 mg from ENT, four days after the treatment initiation still no improvement.
8.	61/F	Pfizer/BioNTech	-	Injection site inflammation Injection site pain Sudden hearing loss	1 day	Recovered	Consumer	Movicolon, pantoprazole
9.	46/M	Pfizer/BioNTech	-	Sudden hearing loss	5 days	Not recovered	Consumer	-
10.	52/F	Pfizer/BioNTech	-	Sudden hearing loss	6 days	Recovering	Consumer	-

				Hyperacusis				
11.	57/M	Pfizer/BioNTech	-	Sudden hearing loss	Same day	Not recovered	Physician	Previously known with acoustic neuroma right, cyberknife treated 2019, Last MRI November 2020 without new abnormalities.
12.	25/M	Pfizer/BioNTech	-	Sudden hearing loss	30 min	Not recovered	Physician	30 min post-vaccination sudden hearing loss, recovered three days after high dose steroid treatment.
13.	52/M	Pfizer/BioNTech	-	Sudden hearing loss	5 days	Not recovered	Consumer	-
14.	68/F	Moderna	-	Acoustic stimulation tests Deafness neurosensory Hypoacusis Sudden hearing loss Tinnitus	Same day	-	-	Sudden sensorineural hearing loss in left ear, day later sudden pop in left ear, two days after the vaccine could barely hear, hearing test proved SSHL and patient was started on steroid treatment plus local steroid treatment in ear, doctors feel it is a side effect due to compromised immune system, patient had a similar reaction 15 years ago from a virus.
15.	19/M	Moderna	-	Deafness Deafness unilateral Hypoacusis Sudden hearing loss Tinnitus	3 days	-	-	Three days after vaccination tinnitus and muffled hearing that went away and next day complete hearing loss left ear, still has tinnitus and muffled hearing at time of report.
16.	70/M	Pfizer/BioNTech	-	Sudden hearing loss Rash	Same day	-	Consumer	Rash over face and even over the ears, uses rivaroxaban.
17.	89/M	AstraZeneca	-	Sudden hearing loss	Same day	Not recovered	Physician	Not tested positive for COVID-19.
18.	39/F	Pfizer/BioNTech	-	Sudden hearing loss	2 days	Recovered	Consumer	-
19.	52/F	Pfizer/BioNTech	-	Sudden hearing loss	1 day	Not recovered	Consumer	Sudden hearing loss, one day after vaccination.
20.	37/F	Moderna	-	Acoustic stimulation tests abnormal Deafness unilateral Sudden hearing loss Tinnitus	10 days	-	-	Sudden hearing loss right, accompanied by tinnitus.
21.	31/M	Pfizer/BioNTech	-	Dizziness Sudden hearing loss Hypoaesthesia	12 days	Recovering	Consumer	13 days after vaccination developed sudden hearing loss and dizziness and hypoesthesia, lasting four days.
22.	-/M	Pfizer/BioNTech	-	Sudden hearing loss	6 days	-	Consumer	Six days after vaccine started on high dose prednisone for one week, high dose 250 mg for three days then daily reduction by 50 mg.
23.	40/F	Pfizer/BioNTech	-	Sudden hearing loss	1 day	Not recovered	Physician	Reporter is patient and healthcare professional, second dose with febrile reaction, and systemically ill, 20 hours later woke up due to tinnitus left ear, got prednisone from ENT after confirmed sensorineural hearing loss left, ENT believes inflammatory response to vaccination is possible, concomitant medications include estrogel, propranolol, utrogestran.

Table 2. Individual characteristics of selected reports in VigiBase of hearing loss (HLT) in association with COVID-19 vaccines (n=25).

Case	Age / sex	Type of vaccine	Dose number	Relevant reactions (MedDRA preferred terms)	Time to onset	Outcome	Type of reporter	Additional information
1.	68/F	Pfizer/BioNTech	-	Balance disorder Deafness unilateral Hypoaesthesia	8 hours	Recovering	Consumer	Past medical history with COVID in November and high blood pressure, 8 hours after injection feeling of ear "closing up", few days later hearing loss in right ear same side as the injected arm, had problems with hearing and equilibrium, contacted physician and was started on prednisone with partial improvement five days later.
2.	71/M	Moderna	-	Deafness unilateral Hypoacusis	3 days	-	-	Immediate loss of hearing right ear which recovered after six hours, next day partial loss of hearing left ear which did not return to normal.
3.	63/M	Pfizer/BioNTech	-	Deafness unilateral Malaise	2 days	-	Consumer	Patient received the first dose and experienced hearing loss left ear, had only 60% of hearing, unspecified treatment was initiated, and hearing returned to 90%, physician informed that hearing loss could be due to stress or a virus but was not sure if it was due to the vaccine.
4.	40/M	Moderna	2	Audiogram Deafness neurosensory Hypoacusis Tinnitus	1 day	-	-	Acute left sensorineural hearing loss with tinnitus, significant hearing impairment noted on audiometric evaluation, symptoms began a day after receiving the second dose of the vaccine.
5.	69/M	Pfizer/BioNTech	-	Deafness Deafness neurosensory Ear discomfort Hyperacusis Tinnitus	4 days	Recovered	-	Four days after the vaccine sudden onset of bilateral fullness in ears, tinnitus, hearing loss, hyperacusis without vertigo. Weber's test did not lateralize. Rinne's test showed air conduction greater than bone conduction consistent with neurosensory loss, initiated treatment with dexamethasone 8 mg a day for three days and symptoms resolved.
6.	40/F	Pfizer/BioNTech	-	Audiogram Hypoacusis	11 days	-	-	Approximately 11 days after receiving the first dose woke up with decreased hearing, went to audiologist and otolaryngologist, both concerned symptoms are related to having antibodies for COVID-19 or having had the vaccine.
7.	37/F	Pfizer/BioNTech	-	Acoustic stimulation tests abnormal Deafness neurosensory	7 days	-	-	Sudden onset right sensorineural hearing loss.
8.	28/F	Pfizer/BioNTech	-	Nervous system disorder Deafness unilateral Vertigo Endolymphatic hydrops Nausea	2 days	Recovering	-	One day post-vaccination sudden vertigo and nausea. Two days post vaccination sudden hearing loss right ear and feeling of fullness, no pain, hearing loss confirmed with audiogram and started on steroids for several days, differential diagnosis is endolymphatic hydrops.
9.	63/M	Pfizer/BioNTech	-	Deafness neurosensory Thyroid function test normal	2 days	Recovered	-	Left sudden sensorineural hearing loss and ear numbness 48 hours after injection, five days after vaccination started on prednisolone and trans-tympanic dexamethasone shots due to hearing loss, partial recovery after 3 weeks.

10.	32/M	Pfizer/BioNTech	2	Hypoacusis SARS-CoV-2 test negative Tinnitus VIIIth nerve injury	-	-	-	Took unspecified medications and stopped several of them prior to second vaccination, no prior medical history, worked as registered nurse, first vaccination dose in mid-December and second dose in January, bilateral tinnitus end of December and beginning of January, tinnitus got worse after the second dose, consultation with ENT who assumed it was the nerve, but could not explain bilateral hearing problem, COVID-19 test was negative.
11.	39/F	Pfizer/BioNTech	-	Acoustic stimulation tests abnormal Audiogram abnormal Deafness unilateral Fear Hypoacusis SARS-CoV-2 test negative	19 days	-	-	19 days after the first dose hearing loss and muffled sounds left, anaemia in past medical history and no medications, no prior hearing problems, contacted ENT who diagnosed 20% decreased hearing in affected ear and was started on steroid treatment without recovery at time of report, took COVID-19 test which was negative.
12.	89/F	Pfizer/BioNTech	-	Dizziness Deafness	4 days	Not recovered	Physician	Acute sudden hearing loss left with dizziness, audiology confirmed acute sudden hearing loss left with normal ear canals, started on prednisone treatment with improvements in dizziness symptoms, day later fall accident with worsening dizziness, ENT suspected viral labyrinthitis, likely to be viral infection but occurred four days after vaccination, did not test positive for COVID-19, CT head was nil, concomitant medications: influenza virus vaccine, furosemide, latanoprost, omeprazole, simvastatin, THEICAL-D3.
13.	34/F	Pfizer/BioNTech	2	Audiogram Deafness Hypoacusis	Few hours	-	-, -	Few hours after vaccination tinnitus right ear, recovered after a couple of days, after 2nd dose muffled hearing and did not subside and severe right sided low frequency hearing loss was noted, patient was started on high dose steroids with partial recovery.
14.	52/F	Pfizer/BioNTech	-	Acoustic stimulation tests Deafness Headache Injection site pain Tinnitus	1 day	-	-	Arm pain two days on injection site, day after injection right ear felt uncomfortable, felt like hearing loss and constant buzzing and fullness feeling, consulted ENT who started patient on prednisone, no information on recovery.
15.	79/M	Pfizer/BioNTech	-	Deafness neurosensory Deafness unilateral Fatigue Headache Myalgia Tinnitus	9 days	-	-	After nine days awoke with deafness and was started on high dose steroids 60 mg prednisone, ENT consulted severe neurosensory hearing loss right ear.
16.	34/F	Pfizer/BioNTech	2	Acoustic stimulation tests abnormal Audiogram abnormal Deafness unilateral	1 day	-	-	Fullness right ear, felt like fluid in ear, hearing loss right ear, soreness left arm, hearing loss two days after vaccination and subsided, then received second dose followed by myalgia, chills back pain, and constant ringing right ear, hearing loss had worsened, prescribed

				Myalgia Tinnitus				prednisone and local injections dexamethasone by ENT due to abnormal audiogram right ear, only 52% acuity, tested negative for COVID-19.
17.	25/F	Moderna	-	Deafness neurosensory	9 days	-	-	Sudden hearing loss right ear, currently treated with steroids, audiology and ENT assessment performed.
18.	57/F	Pfizer/BioNTech	2	Audiogram abnormal Auditory disorder Balance disorder Deafness Deafness bilateral Fatigue Myalgia Pyrexia Tinnitus Vertigo	1 day	-	Physician	Physician self-reports, after second dose of the vaccine severe myalgias, high fever and fatigue, two days after vaccine got vertigo, did not hear well in left ear, had hearing aid which was functioning, three days after vaccine severe vertigo and hearing loss, Epley's manoeuvre with no effect, could not work and was admitted to emergency department, audiogram showed profound hearing loss both ears, got prednisone, MRI negative, mild improvement after steroids.
19.	37/F	Pfizer/BioNTech	-	Deafness neurosensory Headache	1 day	-	-	Headache 24-48 hours after vaccine, 1 week after vaccine complete sensorineural hearing loss left ear, penicillin allergy, no other medications, started on prednisone via medical doctor, not recovered so far.
20.	36/F	Pfizer/BioNTech	-	Deafness	4 hours	Not recovered	-	Four hours after vaccination acute hearing loss, went to ENT and was started on high dose prednisolone 250 mg for three days.
21.	58/M	Pfizer/BioNTech	-	Audiogram abnormal Hypoacusis Inner ear disorder Tinnitus	1 day	-	-	One day later woke up with ringing both ears, called pcp, consulted ENT diagnosed abnormality left inner ear, started on prednisolone high dose, two weeks in the tinnitus got worse.
22.	58/F	Pfizer/BioNTech	-	Deafness unilateral Hypoaesthesia	Same day	-	-	Lost hearing right ear and right-side face was numb hours after vaccination.
23.	69/M	Pfizer/BioNTech	-	Acoustic neuritis Deafness neurosensory Dizziness Hyperacusis Tinnitus	5 days	-	-	Sudden onset acoustic neuritis without labyrinthitis, hyperacusis, loss of hearing and tinnitus, atrial fibrillation in history. No medications. Nerve related hearing loss recovered.
24.	42/F	Pfizer/BioNTech	-	Deafness unilateral	6 days	-	-	Left sided hearing loss, physician was the patient, Antiphospholipid syndrome in history.
25.	45/M	Pfizer/BioNTech	-	Acoustic stimulation tests abnormal Deafness neurosensory Tinnitus	1 day	-	-	Right ear tinnitus and sensorineural hearing loss, left arm injection, diabetes type 2, latex allergy and asthma, woke up with tinnitus, MD did test and found right sided hearing loss, prescribed prednisone for 10 days 60 mg, not recovered, concomitant medications, metformin and glipizide.

Methotrexate and muscle spasm

Rosa María Papale, Argentina and Mónica Tarapués, Ecuador

Summary

Methotrexate is a structural analogue of folic acid. As a folic acid antagonist, it blocks the synthesis of purines by inhibiting numerous regulatory enzymes. It produces an intense anti-inflammatory action and inhibits cell division. A screening of VigiBase, the WHO global database of individual case safety reports (ICSRs), identified the association of the MedDRA Preferred Term (PT) 'muscle spasm' with methotrexate. A qualitative analysis of 47 cases was undertaken with a completeness score of over 0.70. The similarity of characteristics with respect to time to onset, the biological plausibility, the improvement after drug withdrawal, all provide evidence of this association. The muscle spasms could be associated with methotrexate, especially in patients on long-term low doses. Prescribers and patients need to be aware that muscle spasms could be present with the use of methotrexate. This adverse reaction could impair the patients' quality of life, especially long-term users with chronic diseases.

Introduction

Methotrexate was granted US FDA approval in December 1953. Since then, it has been used via oral, intramuscular, intravenous, subcutaneous, intrapleural, and intrathecal routes of administration. Methotrexate acts by inhibiting enzymes responsible for nucleotide synthesis. It is used for the treatment of several neoplasmic conditions, such as acute leukaemia, lymphomas, osteosarcoma, breast cancer, and in autoimmune diseases, such as rheumatoid arthritis and psoriasis. In addition, it is used to treat gestational choriocarcinoma, chorioadenoma, hydatiform mole, and advanced mycosis fungoides.[1,2]

Muscle spasm covers several overlapping concepts of true spasm and cramps. Spasms are involuntary muscle contractions. When these are prolonged and painful, they are often referred to as cramps. Muscle cramps are sustained, painful contractions of muscle which occur in individuals with or without medical conditions. Muscle cramps are common in the general population and can be disabling. This description distinguishes muscle cramps from other painful muscle disorders that either do not include shortening of the muscle, e.g., myositis and myalgia, or that include involuntary shortening of muscle but do not cause pain, e.g., myotonia and tetany.[3] Myalgia and arthralgia are listed in the Summary of Product Characteristics (SPC) of methotrexate as rare adverse drug reactions (ADRs).[4,5] Other drugs such as diuretics may cause muscle spasm through dehydration or an electrolyte imbalance, especially hypokalaemia, hypocalcaemia, or hypomagnesemia. Muscle spasm can accompany myopathy, which has been associated with numerous drug classes, including antimalarials and statins. Other medications can cause muscle spasms, including beta-agonists, acetylcholinesterase inhibitors (often used for the treatment of myasthenia gravis), cimetidine, steroids, morphine, penicillamine, cardiotropic medications, antiretrovirals, and psychotropic medications.[6,7]

Reports in VigiBase

As of May 2020, there were 397 reports for the MedDRA Preferred Term 'muscle spasms' associated with methotrexate. Due to the large number of cases, a completeness score over 0.7 was set for this analysis so as to identify the causality patterns that strengthen the signal. In the present case series, 47 cases were evaluated.

The reports came from 18 countries, most of them in Europe but also from the Americas, Africa, and Asia. There were 30 females and 17 males. The age was recorded for 45 patients, ranged from 13 to 87 years (median 57); 31 were adults. Thirty-six cases (76%) were reported by health professionals (20 by physicians and 16 by pharmacists). Sixteen cases were considered serious, mainly under the criterion of other medically important condition (10 cases). The last report was received in March 2020. Thirty-three of the cases had a narrative; their characteristics are summarized in Table 1.

The most frequent therapeutic indication was rheumatoid arthritis (17 cases), followed by psoriasis or psoriatic arthritis.[8] There were also cases with neoplastic indications (6) and with polymyositis, meningitis, and Crohn's Disease (one of each). In 13 reports the therapeutic indications were not given. Methotrexate was administered orally in 26 (55%) patients, parenterally in 8 patients (6 intravenous and 2 intrathecal), and subcutaneously in four patients. The time to onset was highly variable in the whole group, ranging from one day to six years. However, 26 patients received a weekly dose: 17 orally, 4 subcutaneously, and 5 were unknown. In this subgroup of 26 patients, the time to onset, reported for 14, ranged from 1 day to 18 months, with a median of 29 days. A daily dose was reported for five patients who developed muscle spasms on the day of administration.

Methotrexate was the only suspected drug in 28 patients, and in 18 others, it was the only drug reported. Adalimumab was reported as a co-suspected drug in five patients, but methotrexate

was the last medication taken for two patients, and the other three patients were on chronic methotrexate treatment when adalimumab was administered. Etanercept was a co-suspected drug in two patients. Dates were available for only one patient who was a chronic user of methotrexate and etanercept was recently administered. Proton pump inhibitors (PPIs), were reported in five patients as co-suspected (lansoprazole (1), pantoprazole (2), and esomeprazole (2)). In additions PPIs were reported as concomitant medication, in eight patients but only four had dates that suggest that the PPI administration came before the ADR and was concurrent with the use of methotrexate. Esomeprazole was used after the occurrence of the ADR in one patient. Non-steroidal anti-inflammatory drugs (NSAIDs) were concomitant drugs for three patients (diclofenac (2), naproxen (1)) . Three cases reported concomitant statins, (atorvastatin and simvastatin).

Another ADR, decreased levels of calcium and magnesium was reported for one patient. Diarrhoea or vomiting were reported at the same time as muscle spasms in seven patients. The LLT term used for 31 patients was muscle cramps, and for some patients the location of the cramps was reported as a limb, legs, hand, or foot. The reported LLT was muscle spasms for 16 patients some of which were described as a cervical or back muscle spasm. The intensity of this ADR for a 63 year-old male patient, reported by a pharmacist, was described as *"very intense, disabling and painful on the arms or the legs, with frequency variable, 1 to 3 times a day".* . Methotrexate and pantoprazole were reported as suspected drugs. This patient also had concomitant diltiazem, digoxin, and paracetamol. Methotrexate was first used subcutaneously for rheumatoid arthritis. After about six months, the patient presented with muscle cramps, and five months later methotrexate was changed to an oral route. The patient was reported as not recovered.

Another 65 year-old patient, reported by a pharmacist, had muscle cramps that occurred at night following the administration of methotrexate (15 mg a week) for rheumatoid arthritis, with a latency of 14 days after increasing the dose. The dose was subsequently reduced to 7.5 mg a week and the patient felt better with fewer complaints. Only methotrexate was reported as suspected. The concomitant medications were carbasalate, diclofenac, misoprostol, amlodipine, isosorbide dinitrate, folic acid, metoprolol, alendronic acid, and simvastatin. The patient had never had a muscle disorder in association with simvastatin. The national centre mentioned that the official product information of methotrexate only describes myalgia.

Positive dechallenge was reported for 21 patients. Methotrexate was stopped in 18 patients, of whom 16 were reported as recovered, 1 was recovering, and 1 was recovered with sequelae. In the remaining three patients the dose was reduced, and the reported outcome was recovered. Individual causality assessment was undertaken for 16 patients, (10 using the Naranjo algorithm and 6 using the UMC/WHO global introspection method). The reported result was 'possible', for 15 patients and not assessable by the UMC/WHO method for the remaining patient.

Rechallenge was undertaken in 8 of the 47patients, and in three there was a positive rechallenge; however, there were no narratives for these patients. The outcome was reported as unknown for the other rechallenged patients, although they reported some interesting details. For example, a 57 year-old man, whose physician described muscle cramps and increased blood creatine phosphokinase with the use of methotrexate and lansoprazole. In the narrative, the physician wrote: "*This patient is being followed for non-erosive rheumatoid arthritis. Treatment with methotrexate 10 mg/week was introduced in February. The patient reports from the start of his treatment disabling muscle cramps preventing any sporting activity. He has also been treated with lansoprazole since February. This patient was also on hydrochlorothiazide- irbesartan, stopped in November of the same year, but without improvement in muscle symptoms".* It is worth noting that the rechallenge had an unknown outcome. However, with the dates given in the original report, it is possible to deduce that the rechallenge was without the lansoprazole, because at the beginning in February the patient was exposed to both drugs, but for the rechallenge, only methotrexate was reintroduced.

A 33 year-old woman, reported by a physician, with pain, muscle spasm, and tetany was rechallenge. The suspected drugs were methotrexate and adalimumab (both subcutaneous, weekly) and opipramol (daily, oral). The medical history included former smoker, adiposity, allergic bronchial asthma, depression, onychomycosis, bilateral gonalgia, and psoriatic arthritis. The starting date for methotrexate was January and for adalimumab, March of the same year. The muscle cramps began on 30 April and the tetany on 4 May. Complete tetany of the right leg, which was not resolved by administration of tetrazepam was reported for this patient. The patient was reported as rechallenged with an unknown outcome.

Literature and labelling

The main risks with the use of methotrexate are related to haematological toxicity, and reduced immunity in the presence of infections. However, neither the SPC in the US nor in Europe describe muscle spasm or cramps as ADRs. Myalgia,

arthralgia, osteonecrosis, and osteoporosis are listed as musculoskeletal ADRs.

There are several special warnings and precautions for use of methotrexate regarding potential interactions with other drugs. There is a warning for the concomitant use with NSAIDs, because it has been found to decrease the tubular secretion of methotrexate and possibly to increase its toxicity. Likewise, there is a precaution in the concomitant use of omeprazole and pantoprazole because of their potential impact on methotrexate elimination .[5] However, there are no warnings regarding concomitant use of statins or adalimumab, or other drugs that can cause musculoskeletal disorders.

There are no case reports about muscle cramps in the literature, although there are two case reports about musculoskeletal ADRs. One describes two cases of acute diffuse muscular pain following initiation of weekly low dose oral methotrexate in rheumatoid arthritis (women 70 and 49 years old).[8] The other report concerns a 59-year-old man with a folliculotropic cutaneous T-cell lymphoma taking low dose pulse methotrexate (15 mg intramuscularly, once a week), at the same time as being treated with pantoprazole (20 mg/day, orally). After the first injection of methotrexate the patient presented with generalized myalgia and bone pain. The symptoms recurred over the following four methotrexate cycles. Pantoprazole was replaced by ranitidine and the muscle symptoms disappeared. The report mentioned a positive rechallenge, during which a laboratory test showed an elevation in the serum concentration of the 7-hydroxymethotrexate, which the authors interpreted as an interaction in renal elimination, rather than a metabolic interaction.[9]

Discussion

Muscle spasms or cramps may sometimes overlap with myalgia, and myalgia has already been identified as an ADR. Nevertheless, this analysis presents a group of patients who suffered from spasm or cramp, with most cases reported by physicians. For that reason, it is plausible to think the muscle spasm or cramp is a worrisome clinical event that may prevent some patients from performing daily activities.

Methotrexate inhibits aminoimidazole caboxamide ribonucleotide transformylase (AICART). This inhibition leads to the accumulation of AICART ribonucleotide, which inhibits adenosine deaminase, leading to an accumulation of adenosine triphosphate and adenosine in the extracellular space, stimulating adenosine receptors. This action is well-known as the basis for its anti-inflammatory properties, however, this also acts on the skeletal muscle by the adenosine monophosphate-activated protein kinase (AMPK). Hence, the potential action of the methotrexate on the skeletal muscle is a concern. Recent research suggests that methotrexate could reduce the threshold for AMPK activation by AICART. AMPK has recently emerged as a novel target for the treatment of pain, with the exciting potential for disease modification. AMPK activators inhibit signalling pathways that are known to promote changes in the function and phenotype of peripheral nociceptive neurons and promote chronic pain.[2,10–12]

The literature suggests that muscle spasms could be associated with peripheric neuropathy and hypothyroidism, which were not identified in this case series due to the intrinsic limitations of spontaneous reporting. Other causes could be electrolyte imbalances, and calcium and magnesium imbalances were reported for one patient. It is well known that hypokalaemia can be associated with muscle cramps or other muscle disorders, however, hypokalaemia was not reported for any of the patients.

The concomitant drugs found in the case reports raise concerns about an incomplete profile of methotrexate interactions. Some drugs, such as adalimumab, or statins, could be strongly associated with the muscle ADRs, however, it is not possible to rule out the suspected role of methotrexate as its administration fits the same timeframe. Also, results with animal models and some pharmacokinetics studies suggest that other drugs such as NSAIDs and PPIs can decrease renal elimination and tubular secretion. Some studies that have analysed this interaction with low and high doses of methotrexate concluded that the elevation in methotrexate concentration as a consequence of the interaction has a low clinical impact, however, it is important to carefully assess the risk-benefit balance before deciding to prescribe it, and to follow-up the patients, especially those who are long-term users of methotrexate.[5,13,14]

Conclusion

Muscle spasms or muscle cramps are not currently mentioned in the SPC for methotrexate, and this ADR could have an impact on the quality of life of patients undergoing treatment with methotrexate. Patients, as well as physicians, should be aware of these ADRs to avoid a reaction that could affect the quality of life of patients. For this reason, it is reasonable to consider an in-depth clinical analysis when the patient mentions these complaints, especially patients on low doses.

Table 1. Summary characteristics of 47 cases in VigiBase of muscle cramps in association with methotrexate with a completeness score over 0.70.

Characteristic	47 cases with completeness score over 0.70
Age (mean / range)	53 years / 13-87
Patient sex distribution	30 females / 17 males, ratio 2:1
Top ten countries	Netherlands (15), France (6), Canada (5), Australia (2), Republic of Korea (2), Sweden (2), Croatia (2) Germany (2), Italy (2), Costa Rica (1)
Reporters	Physician (26), Pharmacist (10), Consumer (7), Other Healthcare Professional (4)
Single suspected drug	28 reports (59%)
Single reported drug	18 reports
Time-to-onset	1 day to 6 years
The action taken with the drug /outcome	25 cases with drug withdrawn / 16 recovered, 1 recovered with sequelae, 1 recovering, and 1 outcome unknown. 4 cases with dose reduced / 3 recovered and 1 not recovered. 12 cases with the drug not changed / 3 recovered, 1 recovered with sequelae, 7 not recovered and 1 outcome unknown. 6 drug action unknown / 3 recovered and 3 outcomes unknown

References

1. Cipriani P, Ruscitti P, Carubbi F, Liakouli V, Giacomelli R. Methotrexate in rheumatoid arthritis: optimizing therapy among different formulations. Current and emerging paradigms. Clin Ther. 2014;36(3):427–35.

2. Inoue K, Yuasa H. Molecular basis for pharmacokinetics and pharmacodynamics of methotrexate in rheumatoid arthritis therapy. Drug Metab Pharmacokinet. 2014;29(1):12–9.

3. Jansen PHP, Gabreëls FJM, van Engelen BGM. Diagnosis and differential diagnosis of muscle cramps: A clinical approach. J Clin Neuromuscul Dis. 2002;4(2):89–94.

4. Methotrexate 2.5 mg Tablets - Summary of Product Characteristics (SmPC). In: Electronic Medicines Compendium (emc) [website]. 2020 (https://www.medicines.org.uk/emc/product/511/smpc, accessed 30 November 2021).

5. DailyMed - METHOTREXATE- methotrexate sodium tablet [website]. In: US National Library of Medicine, Dailymed2021 (https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=8f1260de-b60c-4f0e-8af6-0e957b0a281b, accessed 30 November 2021).

6. Stamford B. Muscle cramps. Phys Sportsmed. 1993;21(7):115–6.

7. Miller TM, Layzer RB. Muscle cramps. Muscle Nerve. 2005:;32:431–42.

8. Eames P, Jones AC. Acute diffuse muscular pain following initiation of methotrexate therapy. Ann Rheum Dis. 1994;53(7): 478–9.

9. Tröger U, Stötzel B, Martens-Lobenhoffer J, Gollnick H, Meyer FP. Drug points: severe myalgia from an interaction between treatments with pantoprazole and methotrexate. BMJ. 2002;324(7352):1497.

10. Dolinar K, Jan V, Pavlin M, Chibalin AV, Pirkmajer S. Nucleosides block AICAR-stimulated activation of AMPK in skeletal muscle and cancer cells. Am J Physiol Cell Physiol. 2018;315(6):C803–17.

11. Asiedu MN, Dussor G, Price TJ. Targeting AMPK for the alleviation of pathological pain. 2016;107:257–85.

12. Pirkmajer S, Kulkarni SS, Tom RZ, Ross FA, Hawley SA, Hardie DG, et al. Methotrexate promotes glucose uptake and lipid oxidation in skeletal muscle via AMPK activation. Diabetes. 2015;64(2):360–9.

13. Reeves DJ, Moore ES, Bascom D, Rensing B. Retrospective evaluation of methotrexate elimination when co-administered with proton pump inhibitors. Br J Clin Pharmacol. 2014;78(3):565–71.

14. Hall JJ, Bolina M, Chatterley T, Jamali F. Interaction between low-dose methotrexate and nonsteroidal anti-inflammatory drugs, penicillins, and proton pump inhibitors: a narrative review of the literature. Ann Pharmacother. 2017;51(2):163–78.

Tocilizumab and gastric perforation

Dr Qun-Ying Yue and Dr Elenor Kaminsky, Uppsala Monitoring Centre

Summary

Tocilizumab (TCZ), a humanized monoclonal antibody acting as an interleukin6 (IL-6) receptor antagonist, belongs to an important group of biological agents that has revolutionized the anti-inflammatory therapy of rheumatoid arthritis (RA). However, drugs that block IL-6 are reported to be associated with increased risk of gastrointestinal (GI) perforation, mainly intestinal. Gastric perforation associated with TCZ was identified as a potential signal in a screening of VigiBase, the WHO global database of individual case safety reports. As of March 2020, there were 20 unique patients (compared with 3 expected), from 9 countries, reporting gastric perforation with TCZ as a suspected medicine, in VigiBase. These cases occurred with a time to onset ranging from 0.5 to 36 months (median 5 months); 17/20 (85%) were considered as serious, 1 with a fatal outcome. The indication (known in 18 patients) for TCZ treatment was RA in 16 and temporalis arthritis, or giant cell arthritis (GCA), in two patients. The outcome was unknown for 7 patients, 11 patients recovered or were recovering, including four where a surgical procedure was reported, and two did not recover, including the fatal case. Known risk factors for gastric perforation existed in 10 patients, including co-mobilities or a history of GI disorders, smoking; and concomitant treatment with methotrexate (MTX), rituximab, steroids, NSAIDs, or a combination of these. There seemed to be more patients with a high body weight than with a low body weight, when information was available. Considering the seriousness of this reaction, it would be prudent to recommend close monitoring of patients when treated with TCZ, in particular those with risk factors for GI perforation as well as those with a high body weight, as its dose is determined by the patient's total body weight.

Introduction

Tocilizumab (TCZ) is a humanized monoclonal antibody that acts as an interleukin6 (IL-6) receptor antagonist. Thus, it is an immunosuppressive and interleukin repressive medicine, indicated for adult treatment of severe active and progressive rheumatoid arthritis (RA), especially in combination with methotrexate (MTX),[1] and giant cell arteritis (GCA).[2, 3] TCZ is often given to patients responding inadequately or being intolerant to previous therapy with disease-modifying anti-rheumatic drugs or tumour necrosis factor (TNF) antagonists.[4] Further, it can be given as monotherapy in case of intolerance to, or inappropriate continued treatment with glucocorticoids or MTX. TCZ reduces progression rate of joint damage and improves physical function when given in combination with MTX. It is also indicated for treatment of juvenile idiopathic polyarthritis in patients from two years of age who have not responded to previous MTX treatment. More recently, TCZ has been discussed and tested as an alternative treatment for COVID-19 patients with a risk of cytokine storms, since it has been suggested that IL-6 is one of the most important cytokines in the storms.[5]

Gastrointestinal (GI) perforation is a hole in the wall of GI tract which could include the oesophagus, stomach, small intestine and large intestine. Underlying causes of GI perforation may be gastric ulcers, duodenal ulcers, appendicitis, GI cancer, diverticulitis, inflammatory bowel disease, and use of medicines such as NSAIDs. Surgical intervention is usually required for haemostasis, and closure of perforation and conservative treatment is indicated only in selected patients who are clinically stable.[6]

Gastrointestinal perforation is mentioned in both the EMA and FDA labelling. However, the labelling is focused on **intestinal** perforation, and as a complication of diverticulitis. This was why **gastric** perforation was identified as a potential signal in a screening of VigiBase.

The objective of this study was to analyze the pattern and clinical features of gastric perforation associated with TCZ in the VigiBase cases, and to assess the causality alongside literature findings.

Reports in VigiBase

A clinical review of reports with gastric perforation (PT) associated with TCZ retrieved from VigiBase up to March 2020 was performed.

VigiBase contained 20 unique patients reporting gastric or stomach perforation with TCZ as a suspected or interacting medicine, compared with 3 expected. Table 1 shows the patients' demographics and their characteristics. The reports came from nine countries (Japan (5), USA (5), Colombia (3), Austria (2), and 1 each from UK, Ireland, Greece, Portugal and Hungary). The indications of TCZ, available for 18 patients, were RA (n=16) and GCA (n=2). There were 13 females, 6 males and one gender information missing, which reflects the population treated under the indications. Their ages ranged from 37 to 83 years (median: 61 years). When reporter category information was available, most reports came from physicians (n=16). Of the 20 cases, 17 (85%) were serious, including 4 life-threatening and one with a fatal outcome. In 11

cases (55%) there were narratives, although some of these were considered not informative.

In addition to gastric perforation, seven patients had co-reported reactions such as acute coronary syndrome, pulmonary embolism, cerebrovascular accident, neutropenia, transaminases increased, respiratory or urinary tract infections, while some patients had multiple co-reported reactions. TCZ was the only suspected drug in 15 patients (75%),. In the remaining five cases the co-reported suspected drugs included MTX, prednisolone, hormones (unspecified) and celecoxib, and two of these patients, on NSAIDs or steroid, no gastroprotection (such as antacids) was mentioned. Where information was provided, 12 patients were taking concomitant medications.

TCZ dosing information was available for eight patients: the mean dose, corresponding to four-weekly intervals, was 7.9 (SD 1.1; median 8.0) mg/kg, ranging from 6.0 to 10.0 mg/kg, based on the highest dose if different doses had been given. When information was available (n=9), the mean body weight was 80 kg (SD 24; median 89), ranging from 49 to 114 kg (49, 52, 53, 75, 88, 90, 98, 100 and 114 kg, respectively).

The time to onset (TTO) was reported for 13 patients, and ranged from 0.5 to 36 months (mean: 10; SD: 11; median: 5). The reaction led to withdrawal of TCZ in seven patients, when information was available. The outcome was reported as recovery for 11 patients, no recovery for 1, fatal for 1, and unknown for 7. Positive dechallenge was reported for four patients and rechallenge for one patient , who had no gastric symptoms reported two weeks after the restart of TCZ, at the time of reporting. Surgery was specifically mentioned in the management of the reaction for four patients.

Where information on the medical history and concomitant medications was available, known risk factors for gastric perforation were reported for 10 patients, including GI disorders, smoking; concomitant treatment with MTX, rituximab, steroids, NSAIDs, or a combination of these.

Table 1. Patients' demographics and characteristics of gastric perforations associated with tocilizumab in VigiBase.

Case	Age/sex /body weight	Indication / Dose (mg /4 w)	Other suspected (S) or concomitant drugs	Time to onset (months)	Outcome Recovery: Yes/No/ unknown	Co-reported adverse events	Relevant medical history and concomitant medicines
1	-/-/-	Unknown / -	-	Unknown	Unknown	-	-
2	55/F/ 88 kg	RA / -	Calcium carbonate, levothyroxine, losartan, omeprazole, vitamin D nos	Unknown	Unknown	Acute coronary syndrome, UGI haemorrhage	PPI; BW 88 kg
3	53/F/-	RA / 560	-	5	Yes (sequelae)	-	-
4	70/F/-	RA / 400	-	3	Yes (sequelae)	-	-
5	50/F/-	RA / 504	-	36	Yes	-	-
6	37/F/ 98 kg	RA / 780	Etoricoxib leflunomide hydroxychloroquine tramadol	2	Yes, after surgery	-	NSAID, diverticulitis, BW 98 kg
7	-/F/-	RA / -	-	Unknown	Unknown	-	-
8	67/-/-	RA / -	Rituximab (S), beclometasone, budesonide, fluticasone, folic acid, formoterol, furosemide, gabapentin, ipratropium, metformin, MTX, montelukast, pantoprazole, prednisone, ranitidine, salbutamol, salmeterol, simvastatin, sitagliptin, warfarin	Unknown	Unknown	Oesophagitis, pulmonary embolism, tongue ulceration	Steroid high dose, MTX, PPI, rituximab, higher than max dose
9	65/F/-	RA / 400		13	Yes	-	-

10	49/F/ 52 kg	RA / -	DMARDs, NSAIDs	17	Unknown	GI haemorrhage, neutropenia	NSAID
11	55/M/ 90 kg	RA / 680/35-40	Folic acid (S), hydroxy-chloroquine (S), MTX. Corticosteroids, PPI	27	Yes, after surgery	Transaminases increased, URTI	Smoking, MTX, steroids; PPI; high dose; BW 90 kg
12	58/M/ 49 kg	RA / 400	MTX (S), Prednisol (S), alfacalcidol allpurinol, aspartate calcium, diclofenac, dimeticone, etizolam, iron, lansoprazol, mizoribine, risedronic acid, tacrolimus, zopiclone	3	Yes	-	MTX, steroids, max dose
13	46/M/ 100 kg	RA / 800	Diclofenac, leflunomide omeprazole, prednisolone	3	Yes, after surgery	Abscess, (probably tamponated)	NSAID, steroids, PPI, BW 100 kg
14	-/F/-	Unknown / -	-	Unknown	Unknown		-
15	73/M/ 75 kg	RA / 600	Meloxicam, MTX, PPI.	11	Yes, after surgery	-	NSAID, PPI, MTX. ***No*** *history of GI disorders (ulcers, diverticulosis etc).*
16	62/F/ 113 kg	RA / -	Folic acid, metoprolol, oxybutynin, pravastatin, rivaroxaban, omeprazole	Unknown	Unknown	UTI, influenza	(Rivaroxaban), PPI, BW 113.5 kg. Mg/kg unknown.
17	79/M/-	GCATemp .art/-	-	Unknown	No	-	-
18	83/M/-	RA/162/1o r2v =	Hormones (S), iguratimod, Sulfasalazine	8	Yes	-	-
19	76/F/-	Temp.art / 162/1v (=648?) s.c./i.m.	Prednisone	3	Death	Cerebrovascular accident	Steroids; fatal
20	50/F/ 53 kg	RA /162/2v (= 324 mg?)	Celecoxib (S), prednisolone (S), folic acid, MTX, paracetamol, tramadol	0.5	Yes	-	NSAID, steroids, MTX

BW: Body weight; DMARDs: Disease-modifying antirheumatic drugs; F:Female; GCA: Giant cell arteritis; GI: Gastrointestinal; M: Male; MTX: Methotrexate; NSAIDs: Nonsteroidal anti-inflammatory drugs; PPI: Proton pump inhibitor; RA: Rheumatoid arthritis; TCZ: Tocilizumab; URTI: Upper respiratory tract infection;

Literature and labelling

Tocilizumab (RoActemra) EU summary of product characteristics (SPC)[4]

Posology and method of administration

Treatment should be initiated by healthcare professionals experienced in the diagnosis and treatment of RA, systemic juvenile idiopathic arthritis (sJIA), juvenile idiopathic polyarthritis (pJIA) or cytokine release syndrome (CRS). TCZ should be administered as an intravenous infusion over one hour.

For RA patients, the recommended posology is 8 mg/kg body weight, given once every four weeks.

For individuals whose body weight is more than 100 kg, doses exceeding 800 mg per infusion are not recommended. Dose adjustments are needed if laboratory abnormalities (liver enzyme abnormalities, low absolute neutrophil count, and low platelet count) are found. No dose adjustment is required in elderly patients >65 years of age, or in patients with mild renal impairment.

Special warnings and precautions for use

Complications of diverticulitis: perforations as complications of diverticulitis have been reported uncommonly with TCZ in RA patients. TCZ should be used with caution in patients with a previous history of intestinal ulceration or diverticulitis. Patients presenting with symptoms potentially indicative of complicated diverticulitis, such as abdominal pain, haemorrhage or unexplained change in bowel habits with fever should be evaluated promptly for early identification of diverticulitis, which can be associated with gastrointestinal perforation.

Adverse drug reactions relevant to the signal are presented in Table 2**.**

Table 2. Adverse drug reactions (relevant to the signal, selected by the authors).

MedDRA System Organ Class	Frequency categories with preferred terms
Infections and infestations	**Uncommon:** diverticulitis
Gastrointestinal disorders	**Common:** abdominal pain, mouth ulceration, gastritis **Uncommon:** stomatitis, gastric ulcer

Gastrointestinal perforation: during the 6-month controlled clinical trials, the overall rate of gastrointestinal perforation was 0.26 events per 100 patient years with TCZ therapy. The overall rate of gastrointestinal perforation was 0.28 events per 100 patient years in the long-term exposure population. Reports of gastrointestinal perforation in patients taking TCZ were primarily reported as complications of diverticulitis including generalized purulent peritonitis, lower gastrointestinal perforation, fistulae and abscess.

Discussion

TCZ, a monoclonal antibody targeting the IL-6 receptor, has been reported to increase the risk of GI perforation.[7] The risk for lower GI perforation associated with TCZ was estimated to be more than twice that for anti-tumour necrosis factor agents.[8] In a registry of lower intestinal perforation (LIP), the crude incidence rate of LIP was found to be significantly higher in patients taking TCZ (2.7/1000 person-years), compared with all other treatments (0.2−0.6/1000 person-years).[9] In the literature, more data are available for the risk of for lower GI tract perforation. More recently, based on updated data it was reported that, although data are limited, drugs that block IL-6 are associated with a greater increased risk of GI perforation, than other RA therapies.[7] In our current study, 20 patients with gastric perforation in VigiBase were reviewed with a focus on the clinical features. TTO ranged from 0.5 to 36 months (mean 10; median 5). About 2/3 of the patients were females, reflecting the treatment indication of RA where a female to male prevalence ratio of 2-3:1 has been reported.[10]

When TCZ (RoActemra) was approved in the EU (2009), the Member States were required to implement an educational pack to inform physicians and patients about the risks of serious infections and complications of diverticulitis.[11] In the summary of the Risk Management Plan (RMP) it was stated that the rate of serious infections appeared to increase with body weight.[12] The dose of TCZ is dependant on body weight: 8 mg/kg body weight, given once every four weeks. For individuals whose body weight is more than 100 kg, doses exceeding 800 mg per infusion are not recommended.[13]

In the current study, the mean body weight was about 80 kg. However, no patient weighed 80 kg. Only one patient weighed 75 kg, which was close to the mean body weight, while five patients were heavier (88.2, 90, 98, 100 and 113.5 kg) and three were lighter (49, 52.2 and 53 kg). It would seem that heavier patients are over-represented in this study. It has been reported that chronic dosing using total body weight can lead to drug toxicity in obese adults.[14] Although the body composition (lean versus adipose weight) and the body mass index were not reported, it seems prudent to recommend close monitoring of patients, in particular, those with a high body weight when the drug is dosed according to total body weight.

The findings in the present case series are in line with the literature reporting the commonly used concomitant medicines in RA, e.g. MTX, NSAIDs, and corticosteroids, all known to present risks for GI disorders, in particular gastric perforation.[7] As shown in Table 1, in five patients MTX was used, in five cases NSAIDs, and in six cases steroids, including one with higher dose of steroids. In addition, one patient concomitantly used rivaroxaban which is known to increase the risk of GI bleeding. Therefore, these drugs may also have contributed to the adverse events. In addition, six patients had also concomitantly used PPI, although it is unknown if it was used to prevent or treat GI problems.

Diverticulosis, was specifically mentioned for only two patients, one where it was reported present, and another where it was absent. Diverticular inflammation was reported for 0.8% of patients, who underwent colonoscopy but who lacked symptoms or clinical evidence of diverticulitis.[15] Up to 40% of the Western population may have diverticulosis.[16] It is unclear if patients with known severe diverticulosis should be excluded from TCZ treatment, or if they should have a colonoscopy before starting TCZ to assess whether they have diverticulosis. [17] It has also been suggested that IL-6 blockers should be avoided in patients with a history of diverticulitis, as they are known to increase the risk of subsequent intestinal perforation.[7] The impact of diverticulitis on gastric perforation is unclear.

One patient was a smoker, which could induce pathogenic and carcinogenic processes in the GI

tract.[18] This is because active compounds in cigarette smoke can damage GI tract structure through cellular apoptosis induction, and hamper the mucosal cell renewal. Cigarette smoke also interferes with the protective mechanisms of the GI tract through modulating the mucosal immune system, and reducing the mucosa blood flow. In addition, it inhibits the synthesis and release of EGF and polyamines, which reduces mucus secretion, which may compromise the integrity of the mucosal defence.

Eleven patients, when information was provided, had at least one factor that may have contributed to the occurrence of gastric damage, such as concomitant drugs (e.g., MTX, NSAIDs, steroids, rivaroxaban), or conditions (e.g., smoking, high body weight and associated high dose of TCZ). Eight of these patients had more than one of the factors, suggesting compounded risk for the reaction to occur.

Only four reports specifically mentioned surgery for the ADR. The current treatment of perforated peptic ulcer is surgical repair, although conservative treatment can be adopted in selected patients.[6] It is unclear in our case series whether the perforations without surgery mentioned in the reports were 'microperforation' (see definition of GI perforation[7]) for which surgery is not indicated, or if surgery was performed but not noted in the reports.

Conclusion

Gastrointestinal perforation is an important identified risk of TCZ treatment which may be life-threatening. However, the current labelling is focused on intestinal perforation, and as a complication of diverticulitis. In VigiBase, cases of gastric perforation have been reported, particularly in patients with high body weight and taking concomitant medications known to cause gastric perforation. Healthcare professionals should be aware of this potential risk and closely monitor patients, in particular those with risk factors for GI perforation, as well as those with high body weight, during treatment with TCZ, which is dosed according to total body weight.

We acknowledge with thanks the pharmacovigilance centres that provided additional case information upon request.

References

1. Dhillon, S. Intravenous tocilizumab: a review of its use in adults with rheumatoid arthritis. BioDrugs. 2014;28:75–106.

2. Toussirot É, Martin A, Soubrier M, Redeker S, Régent A. Rapid and sustained response to tocilizumab in patients with polymyalgia rheumatica resistant or intolerant to glucocorticoids: a multicenter open-label study. J Rheumatol. 2016;43(1):249-51.

3. Stone JH, Tuckwell K, Dimonaco S, Klearman M, Aringer M, Blockmans D, et al. Trial of Tocilizumab in Giant-Cell Arteritis. N Eng JMed. 2017;377(4)317-28.

4. Summary of Product Characteristics for Tocilizumab. In: Electronic Medicines Compendium [website]. (https://www.medicines.org.uk/emc/product/6673/smpc, accessed 5 April 2019

5. Luo P, Liu Y, Qiu L, Liu X, Liu D, Li J. Tocilizumab treatment in COVID-19: A single center experience. J Med Virol. 2020;1–5.

6. Hanumanthappa MB, Gopinathan S, Guruprasad Rai D, Dsouza N. A non-operative treatment of perforated peptic ulcer: a prospective study with 50 sases. JClinDiagn Res. 2012;6(4):696-9.

7. Jagpal A, Curtis J. Gastrointestinal perforations with biologics in patients with rheumatoid arthritis: implications for clinicians. Drug Saf. 2018;41(6):545–53

8. Xie F, Yun H, Bernatsky S, Curtis JR. Risk of gastrointestinal perforation among rheumatoid arthritis patients receiving tofacitinib, tocilizumab, or other biologic treatments. Arthritis Rheumatol., 2016;68(11);2612–7.

9. Strangfeld A, Richer A, Siegmund B, Herzer P, Rockwitz K, Demary W, et al. Risk for lower intestinal perforations in patients with rheumatoid arthritis treated with tocilizumab in comparison to treatment with other biologic or conventional synthetic DMARDs. Ann Rheum Dis. 2017;76(3):504-10.

10. Tedeschi SK, Bermas B, Costenbader KH. Sexual disparities in the incidence and course of SLE and RA. Clin Immunol. 2013;149(2):211-8.

11. European Medicines Agency. 2011. Conditions or restrictions with regard to the safe and effective use of medicinal product to be implemented by the member states – Annex IV. Available from: https://www.ema.europa.eu/en/documents/con

ditions-member-states/roactemra-epar-conditions-imposed-member-states-safe-effective-use-annex-iv_en.pdf, accessed 1 December 2021

12. European Medicines Agency. 2020. Summary of risk management plan for RoActemra (tocilizumab). (https://www.ema.europa.eu/en/documents/rmp-summary/roactemra-epar-risk-management-plan-summary_en.pdf, accessed 1 December 2021).

13. European Medicines Agency. 2021. EPAR, (EMA/686079/2018, EMEA/H/C/000955; https://www.ema.europa.eu/en/medicines/human/EPAR/roactemra, accessed 1 December 2021).

14. Barras M, Legg A. Drug dosing in obese adults. Aust Prescr. 2017;40(5):189–93.

15. Ghorai S, Ulbright TM, Rex DK. Endoscopic findings of diverticular inflammation in colonoscopy patients without clinical acute diverticulitis: prevalence and endoscopic spectrum. Am J Gastroenterol. 2003;98(4):802-6.

16. Storz C, Rothenbacher T, Rospleszcz S, Linseisen J, Messmann H, DeCecco CN, et al. Characteristics and associated risk factors of diverticular disease assessed by magnetic resonance imaging in subjects from a Western general population. Eur Radiol. 2019;29(3):1094–103

17. Giang J, Settergren N, Lute M, Fernandez, H. Tocilizumab associated hemorrhagic shock from gastrointestinal bleeding: Abstract 2606. Am J Gastroenterol. 2016;111(suppl):S1311-3

18. Li LF, Chan RLY, Lu L, Shen J, Zhang L, Wu WKK, et al. Cigarette smoking and gastrointestinal diseases: the causal relationship and underlying molecular mechanisms (review) Int J Mol Med. 2014;34(2):372-80.

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.

Uppsala Monitoring Centre (UMC)
Box 1051, SE-751 40 Uppsala, Sweden
Tel: +46-18-65 60 60, E-mail: info@who-umc.org
www.who-umc.org

Advisory Committee on Safety of Medicinal Products (ACSoMP)
Eighteenth meeting

World Health Organization, Geneva (virtual Meeting)

26-27th October 2021

The WHO Advisory Committee on Safety of Medicinal Products (ACSoMP) was established in 2003, to provide advice to WHO, including its Collaborating Centre for International Drug Monitoring (the UMC), and through it, to the Member States, on safety issues relating to medicinal products. Topics discussed in the 18th meeting of ACSoMP consisted of updates on previously discussed safety issues such as the safety of sodium valproate in pregnancy, and request for advice on new topics such as integrating pharmacovigilance into the global leprosy programme. A full list of topics discussed is below:

1. Update on therapeutic investigational drugs for treatment of COVID-19 and latest vaccine safety issues.
2. Update on results of studies investigating neural tube defects and the use of dolutegravir.
3. Update on the use of sodium valproate during pregnancy.
4. Monitoring the safety of drugs used in leprosy.
5. Safety signal of hallucinations with the use of delamanid in children for tuberculosis.
6. Ocular adverse events with the use of miltefosine for visceral leishmaniasis and post-kala-azar dermal leishmaniasis.
7. Update on the safety of fexinidazole used for African trypanosomiasis in the Democratic Republic of Congo.

An overview of recommendations from the meeting will be published in a following issue of the Pharmaceuticals Newsletter.

9789240042452