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

Contents

Regulatory matters
Safety of medicines
Signal
# Table of Contents

## Regulatory Matters
- Atezolizumab ........................................................................................................ 4
- Cetuximab (genetic recombination) ........................................................................ 4
- COVID-19 vaccine NRVV Ad (ChAdOx1 nCoV-19) ................................................ 4
- COVID-19 vaccine NRVV Ad26 (JNJ 78436735) ................................................... 4
- Durvalumab (genetic recombination) ..................................................................... 5
- Iopamidol .............................................................................................................. 5
- Levothyroxine (tablet) ............................................................................................ 5
- Nivolumab ............................................................................................................. 5
- Obeticholic acid ..................................................................................................... 6
- Polyethylene glycol (PEG) laxatives and starch-based thickeners ......................... 6
- Pomalidomide, thalidomide ................................................................................... 6
- Ritodrine and Magnesium sulfate (co-administration) ........................................... 7
- Shosaikotokakikyosekko ....................................................................................... 7
- Tozinameran ......................................................................................................... 7
- Vascular endothelial growth factor (VEGF) inhibitors (systemic use) ................. 7

## Safety of medicines
- Amitriptyline .......................................................................................................... 9
- Bendamustine ....................................................................................................... 9
- Clonidine ............................................................................................................... 9
- Clopidogrel ........................................................................................................... 9
- Donepezil .............................................................................................................. 10
- Fluoroquinolones ................................................................................................ 10
- Indapamide ........................................................................................................ 10
- Lamotrigine ......................................................................................................... 11
- Nivolumab ........................................................................................................... 11
- Theophylline ...................................................................................................... 11
- Tozinameran, COVID-19 vaccine mRNA (mRNA 1273) ........................................... 11

## Signal
- Levetiracetam and Hypokalaemia........................................................................... 12
- Remdesivir and pancreatic toxicity .................................................................... 16
- Tocilizumab and Pancreatitis .............................................................................. 22
**Atezolizumab**

**Risk of severe cutaneous adverse reactions (SCAR)**

**Malaysia.** The National Pharmaceutical Regulatory Agency (NPRA) has announced that the product information for atezolizumab (Tecentriq®) has been updated to include the risk of severe cutaneous adverse reactions (SCAR).

Atezolizumab is indicated to treat non-small cell lung cancer, small cell lung cancer and triple-negative breast cancer. SCARs include acute generalized exanthematous pustulosis (AGEP), Stevens-Johnson syndrome (JSJ), toxic epidermal necrolysis (TEN) and drug rash with eosinophilia and systemic symptoms (DRESS).

Based on analysis from the company’s global safety data 99 cases of SCARs have been identified, of which 36 cases were confirmed by histopathology or specialist diagnosis.

**Reference:** Safety Alerts, NPRA, 22 April 2021 (www.npra.gov.my/)

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**Cetuximab (genetic recombination)**

**Risk of hypomagnesaemia**

**Japan.** The Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA) have announced that the package insert for cetuximab (genetic recombination) (Erbitux®) must not be given to anyone who has had thrombosis with thrombocytopenia syndrome (TTS).

COVID-19 vaccine NRVV Ad26 (JNJ 78436735)

**Risk of thrombosis with thrombocytopenia syndrome (TTS)**

**Europe.** The Committee for Medicinal Products for Human Use (CHMP) has recommended that COVID-19 vaccine NRVV Ad (ChAdOx1 nCoV-19) (Vaxzevria®) must not be given to anyone who has had thrombosis with thrombocytopenia syndrome (TTS).

COVID-19 vaccine NRVV Ad26 (JNJ 78436735) is a vaccine for preventing COVID-19 in people aged 18 years and older.

As TTS requires specialist treatment, health-care professionals should consult applicable guidance and/or specialists to diagnose and treat the condition.

Also, health-care professionals should check for signs of thrombosis in any person who has thrombocytopenia within three weeks of vaccination and should advise people to seek urgent medical attention if they have any symptoms suggesting thrombosis or thrombocytopenia.

**Reference:** EMA, 7 May 2021 (www.ema.europa.eu)

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Regulatory Matters

Durvalumab (genetic recombination)

Risk of immune thrombocytopenic purpura

**Japan.** The MHLW and the PMDA have announced that the package insert for durvalumab (Imfinzi®) should be revised to include the risk of immune thrombocytopenic purpura as an adverse drug reaction.

Durvalumab is indicated for the treatment of locally-advanced, unresectable non-small cell lung cancer and extensive stage small cell lung cancer.

A total of 15 cases of immune thrombocytopenic purpura have been reported in patients treated with durvalumab in Japan in the past three years, including three cases for which a causal relationship between the drug and event was assessed to be reasonably possible. No patient mortalities have been reported.

The MHLW and PMDA concluded that the revision of the package insert was necessary.

**Reference:**
Revision of Precautions, MHLW/PMDA, 30 March 2021 (www.pmda.go.jp/english/)

Iopamidol

Risk of acute generalized exanthematous pustulosis

**Japan.** The MHLW and the PMDA have announced that the package insert for iopamidol (Iopamiron®) should be revised to include the risk of acute generalized exanthematous pustulosis (AGEP) as an adverse drug reaction.

Iopamidol is used for diagnostics such as angiocardiography, aortography and extremity angiography.

A total of four cases of AGEP have been reported in patients treated with iopamidol in Japan in the past three years, including three cases for which a causal relationship between the drug and event was assessed to be reasonably possible. No patient mortalities have been reported.

The MHLW and the PMDA concluded that the revision of the package insert was necessary.

**Reference:**
Revision of Precautions, MHLW/PMDA, 30 March 2021 (www.pmda.go.jp/english/)

Levothyroxine (tablet)

Risk of related to aggravating thyroid symptoms when switching between different products

**United Kingdom.** The Medicines and Healthcare Products Regulatory Agency (MHRA) has announced that the product information for levothyroxine should be updated to include the risk of aggravating thyroid symptoms when switching between different levothyroxine products (tablets).

Levothyroxine is indicated for the control of hypothyroidism. In the UK, prescribing of levothyroxine is usually generic, so patients may switch between different levothyroxine products according to what is available at their local pharmacies.

From 2015 to 2019, the MHRA received 335 reports of the thyroid condition being aggravated or ineffectiveness of the levothyroxine product following substitution with another. Associated symptoms were mostly consistent with hypothyroidism or hyperthyroidism and included fatigue, headache, malaise, anxiety, palpitation, nausea, myalgia and dizziness. The underlying causes for the symptoms experienced after switching between products are generally unclear.

Generic prescribing of levothyroxine remains appropriate for the majority of patients and the licensing of these generic products is supported by bioequivalence testing.

If a patient reports persistent symptoms of their condition being aggravated when switching between different levothyroxine products, healthcare professionals should consider consistently prescribing a specific product known to be well tolerated by the patient. Also, if symptoms or poor control of thyroid function persist, prescribing an oral solution formulation of levothyroxine should be considered.

**Reference:**
Drug Safety Update, MHRA, 19 May 2021 (www.gov.uk/mhra)

(See also WHO Pharmaceuticals Newsletter No.1, 2020: Potential adverse reactions when switching brands in Ireland)

Nivolumab

Potential risk of certain blood disorders and cytokine release and tumor lysis syndromes

**Canada.** Health Canada has announced that the product...
safety information (Canadian Product Monograph, CPM) for nivolumab (Opdivo®) has been updated to include a warning of the risk of autoimmune hemolytic anemia and it is working with the manufacturers to include the risks of aplastic anemia, cytokine release syndrome and tumor lysis syndrome in CPM. Nivolumab is used alone or in combination to treat certain type cancers of the skin, head and neck, blood cells, lungs and kidneys.

Health Canada reviewed information received from the manufacturer by searching the Canada vigilance database, international databases and published literature. It concluded that there may be a link between nivolumab and the risks of autoimmune hemolytic anemia, aplastic anemia, cytokine release syndrome and tumor lysis syndrome.


(See also WHO Pharmaceuticals Newsletter No.4, 2019: Potential risk of hemophagocytic lymphohistiocytosis (HLH) in Canada; No.2, 2019: Risk of serious blood disorder in Japan)

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**Obeticholic acid**

**Risk of serious liver injury**

**USA.** The US Food and Drug Administration (FDA) has announced that it has revised the boxed warning for obeticholic acid (Ocaliva®) to include the risk of serious liver injury in patients with primary biliary cholangitis (PBC) and advanced cirrhosis of the liver.

Obeticholic acid is indicated to treat PBC.

The FDA identified 25 cases of serious liver injury that led to liver decompensation or liver failure associated with the use of obeticholic acid in PBC patients with cirrhosis. The FDA believes the benefits of obeticholic acid outweigh the risks for PBC patients who do not have advanced cirrhosis.

Health-care professionals should determine whether a patient with PBC has advanced cirrhosis before starting obeticholic acid.

Also, health-care professionals should routinely monitor patients during the treatment for progression of PBC with laboratory and clinical assessments to determine whether to discontinue obeticholic acid.


(See also WHO Pharmaceuticals Newsletter No.4, 2018: Risk of serious liver injury in Ireland; No.3, 2018: Risk of serious liver injury in UK; No.5, 2017: Risk of serious liver injury in USA)

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**Polyethylene glycol (PEG) laxatives and starch-based thickeners**

**Potential interaction: risk of aspiration**

**United Kingdom.** The MHRA has announced that it has requested that the manufacturers of Polyethylene glycol (PEG) laxatives to update the summary of product characteristics (SmPC) and the patient information leaflet (PIL) to include information about a potential interaction with starch based thickeners that can increase the risk of aspiration in patients with dysphagia.

PEG laxative products are used to treat constipation through an osmotic effect. Thickeners are used to thicken liquids taken by patients with dysphagia, including elderly and those who have trouble swallowing. There are two main types of thickening agents: starch- and gum-based.

Adding a PEG-based laxative to a liquid that has been thickened with a starch-based thickener may counteract the thickening action.

Constipation and dysphagia coexist more commonly in the elderly and in those with swallowing difficulties.

Although the MHRA is not aware of any cases of this potential interaction in the UK, an institute in Canada has issued a safety bulletin discussing a potential harmful interaction between PEG laxative and starch-based thickeners.

Reference: Drug Safety Update, MHRA, 27 April 2021 (www.gov.uk/mhra)

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**Pomalidomide, thalidomide**

**Potential risk of progressive multifocal leukoencephalopathy (PML)**

**Canada.** Health Canada has announced that the product safety information for pomalidomide (Pomalyst®) has been updated to include a warning of the risk of progressive multifocal leukoencephalopathy (PML). Health Canada will also include this warning in the safety information for thalidomide (Thalomid®).

Pomalidomide and thalidomide are indicated to treat multiple myeloma.

Health Canada reviewed the available information by performing a search in the Canada vigilance database, international database, published literature and using information provided by the manufacturer.

Health Canada’s review concluded that there is a possible link between pomalidomide or thalidomide and the risks of PML.
Ritodrine and Magnesium sulfate (co-administration)

Increased risk of hyperkalaemia

**Japan.** The MHLW and the PMDA have announced that the package inserts for ritodrine (Utemerin®) and magnesium sulfate (Magsent® and Magnesol®) should be revised to include the risk of hyperkalaemia in preterm infants born to mothers who were co-administered ritodrine and magnesium sulfate.

Ritodrine is indicated for threatened abortion/premature labor. Magnesium sulfate is indicated for inhibition of uterine contractions and for prophylaxis and treatment of eclampsia.

A total of eight cases of neonatal hyperkalaemia have been reported in the newborns of patients treated with ritodrine and magnesium sulfate in Japan in the past three years, including four cases for which a causal relationship between the drug and event was assessed to be reasonably possible. There has been one death reported, but a causal relationship could not be established.

The MHLW and the PMDA concluded that the revision of the package insert was necessary.

**Reference:**
Revision of Precautions, MHLW/PMDA, 13 May 2021 (www.pmda.go.jp/english/)

Tozinameran

**Risk of facial swelling**

**Europe.** The PRAC has recommended that the SmPC and the PIL for tozinameran (Comirnaty®) should be revised to include facial swelling in people with a history of injections with dermal fillers as an adverse reaction.

Tozinameran is indicated for active immunization to prevent COVID-19 caused by SARS-CoV-2 virus, in individuals 12 years of age and older.

The PRAC reviewed the available evidence including cases of facial swelling reported to the European database for suspected adverse effects (EudraVigilance) and scientific literature. A causal association between the vaccine and the reported cases of facial swelling in people with a history of injections with dermal fillers was considered to be reasonably possible.

**Reference:**
EMA, 7 May 2021 (www.ema.europa.eu)

Vascular endothelial growth factor (VEGF) inhibitors (systemic use)

**Risk of artery dissections and aneurysms**

**Malaysia.** The NPRA has issued a directive for all registration holders of vascular endothelial growth factor (VEGF) inhibitors for systemic use, requesting that the local package inserts should be updated to include the risk of artery dissections and aneurysms.

VEGF inhibitors are indicated to treat various types of cancers including renal cell carcinoma, thyroid and soft tissue cancers. There are 21 registered products containing VEGF inhibitors for systemic use in Malaysia.

The NPRA has received two reports of aneurysms associated with bevacizumab use in Malaysia.

The mechanism of VEGF inhibitors causing artery dissections and aneurysms is unclear but thought to be due to the weakening of vascular wall integrity. Risk factors include hypertension or aggravation of pre-existing hypertension, a previous history of aneurysm, smoking,
Regulatory Matters

diabetes mellitus, coronary, cerebrovascular or peripheral arterial disease.

Health-care professionals should carefully consider the risk of artery dissections and aneurysms in patients with risk factors before prescribing VEGF inhibitors for systemic use.

Reference:
Safety Alerts, NPRA, 20 April 2021 (www.npra.gov.my/)

(See also WHO Pharmaceuticals Newsletter No.5, 2020: Risk of aneurysms and artery dissections in New Zealand; No.6, 2020: Risk of aneurysm and artery dissection in Ireland; No.1, 2019: Risk of artery dissections and artery aneurysms in Canada)
Amitriptyline

Potential risk of drug reaction with eosinophilia and systemic symptoms

Saudi Arabia. The Saudi Food and Drug Authority (SFDA) has released a potential safety signal about drug reaction with eosinophilia and systemic symptoms (DRESS) associated with the use of Amitriptyline. Amitriptyline is a tricyclic antidepressant with sedative properties.

In 2021, the SFDA reviewed all the evidence available on the association between amitriptyline and DRESS after receiving an individual case safety report (ICSR).

The SFDA’s investigation concluded that the current available evidence from assessment of the ICSRs might support a relationship between amitriptyline and DRESS. This potential signal needs further investigation to confirm the risk, and health-care professionals should be aware of this potential adverse reaction.

Reference:
Safety Alerts, SFDA, 2021 (www.sfda.gov.sa)

Bendamustine

Increased risk of non-melanoma skin cancer and progressive multifocal encephalopathy (PML)

United Kingdom. The MHRA has announced that an increased risk for non-melanoma skin cancers and progressive multifocal encephalopathy (PML) has been observed in patients treated with bendamustine (Levact®).

Bendamustine is indicated for cardiovascular effects such as high blood pressure, migraine and menopausal flushing. Bendamustine is also prescribed off-label under careful medical supervision for behavioral disorders in children with attention deficit hyperactivity disorder (ADHD), tic disorders and sleep disturbances.

There have been 43 cases of adverse drug reactions reported to the TGA that relate to overdose, incorrect dose or off-label use of bendamustine in children. Many of the events required medical intervention or hospitalization. The number of reports of poisoning has increased in recent years and similar trends have been observed overseas.

Reference:
Medicines Safety Update, TGA, 29 April 2021 (www.tga.gov.au/)

Clonidine

Risk of overdosing in children

Australia. The Therapeutic Goods Administration (TGA) has reminded health-care professionals that serious adverse events can occur in children who are accidentally overdosed with clonidine (Catapres® and generic brands), and even relatively minor overdoses can result in toxicity in young children.

Clonidine is indicated for cardiovascular effects such as high blood pressure, migraine and menopausal flushing. Clonidine is also prescribed off-label under careful medical supervision for behavioral disorders in children with attention deficit hyperactivity disorder (ADHD), tic disorders and sleep disturbances.

There have been 43 cases of adverse drug reactions reported to the TGA that relate to overdose, incorrect dose or off-label use of clonidine in children. Many of the events required medical intervention or hospitalization. The number of reports of poisoning has increased in recent years and similar trends have been observed overseas.

Reference:
Medicines Safety Update, TGA, 29 April 2021 (www.tga.gov.au/)

Clopidogrel

Potential risk of hypertension

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

Clopidogrel is indicated for use in adult patients suffering from myocardial infarction, ischaemic stroke or established peripheral arterial disease. In 2020, the SFDA reviewed all the evidence available on the association between clopidogrel and hypertension following an ICSR sent to the Saudi National Pharmacovigilance Centre.

Causality assessment of this case was associated with a positive dechallenge and was considered to be probable. In the WHO global database of ICSRs (VigiBase), 357 ICSRs were found for this drug/adverse drug reaction combination as of September 2020.

The SFDA’s investigation
concluded that the current available evidence from assessment of the ICSRs might support a relationship between clopidogrel and hypertension. This signal needs further investigation to confirm the risk and health-care professionals should be aware of this potential adverse reaction.

**Reference:**
Safety Alerts, SFDA, 2021 (www.sfda.gov.sa)

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### Donepezil

#### Potential risk of QT prolongation

**Saudi Arabia.** The SFDA has released a potential safety signal concerning QT prolongation associated with the use of donepezil.

Donepezil is indicated for symptomatic treatment of mild to moderately severe Alzheimer’s dementia.

The SFDA has comprehensively reviewed all relevant data and evidence to evaluate this risk, which includes case-report analysis, data mining of the WHO global database of ICSRs, and relevant evidence from the literature. A total of 132 ICSRs were found globally in the WHO database of ICSRs in December 2020. Casualty assessments were made on a selection of good quality reports.

More than half of the selected ICSRs were assessed to have a supportive association (seven probable and 14 possible). Statistical data mining of reports in VigiBase showed that the number of observed cases were more than expected.

Multiple articles in the literature supported this association, and included evidence of a class effect and a published case-report for donepezil.

Health-care professionals should be aware of this potential risk and monitor any signs or symptoms in treated patients.

**Reference:**
Safety Alerts, SFDA, 2021 (www.sfda.gov.sa)

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### Fluoroquinolones

#### Risk of heart valve regurgitation

**Singapore.** The Health Sciences Authority (HSA) has announced that the use of systemic fluoroquinolones are associated with a small increased risk of heart valve regurgitation.

Fluoroquinolones are indicated to treat infections such as acute sinusitis and acute bronchitis. There are seven systemic fluoroquinolones used in Singapore: ciprofloxacin, ofloxacin, norfloxacin, lomefloxacin, levofloxacin, moxifloxacin and pefloxacin. Fluoroquinolones are known to increase the risk of collagen-related disorders such as tendonitis, tendon rupture, and aortic aneurysm and dissection.

In September 2020, the EMA concluded that fluoroquinolone use may increase the risk of heart valve regurgitation, and as a result the EMA recommended that the existing warning on aortic aneurysm and dissection in the package inserts of systemic and inhaled fluoroquinolone-containing products should be expanded to include heart valve regurgitation.

The HSA has not received any local reports of heart valve-related disorders associated with fluoroquinolone.

Health-care professionals are advised to take into consideration the risk when prescribing systemic fluoroquinolones and the availability of other therapeutic options for patients with pre-existing risk factors such as heart valve diseases, connective tissue disorders, hypertension or rheumatoid arthritis.

**Reference:**
Product Safety Alerts, HSA, 12 May 2021 (www.hsa.gov.sg)

(See also WHO Pharmaceuticals Newsletter No.1, 2021: Risk of heart valve regurgitation in UK; No.2, 2020: Risk of aortic aneurysm and dissection in Australia; No.6, 2019: Risk of tendon disorders, peripheral neuropathy and psychiatric symptoms in Japan)

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### Indapamide

#### Potential risk of Rhabdomyolysis

**Saudi Arabia.** The SFDA has released a potential safety signal of rhabdomyolysis associated with the use of indapamide.

Indapamide is a thiazide-like diuretic medication generally used in the treatment of hypertension.

SFDA has reviewed the local and WHO global databases to find and assess related case reports of indapamide associated rhabdomyolysis. The search resulted in 33 case-reports. Casualty assessments were made on a selection of good quality reports.

Seven cases of rhabdomyolysis with indapamide reported a positive dechallenge, four were assessed to be probable, five possible and one unassessable.

Additionally, The disproportionality of the observed and the expected reporting rate for this drug/adverse drug reaction pair was supportive for an association.

In conclusion, the weighted cumulative evidence identified from causality assessment of the reported cases and data mining are sufficient to support a potential association between indapamide and the risk of rhabdomyolysis. Health-care professionals should be aware of this potential risk and monitor any signs or symptoms.
Safety of Medicines

Lamotrigine

Potential risk of arrhythmia

USA. The US FDA has announced that study findings showed a potential risk of arrhythmias in patients with heart disease who are taking lamotrigine (Lamictal®). Lamotrigine is indicated to treat seizures and bipolar disorder. Laboratory tests performed at therapeutically relevant concentrations have shown that lamotrigine can increase the risk of serious arrhythmias, which can be life-threatening in patients with important structural or functional heart disorders.

The risk of arrhythmias may increase further if used in combination with other medicines that block sodium channels in the heart.

Health-care professionals should assess whether the potential benefits of lamotrigine outweigh the potential risk of arrhythmias for each patient.


Theophylline

Potential risk of encephalopathy

Saudi Arabia. The SFDA has released a potential safety signal concerning encephalopathy associated with the use of theophylline. Theophylline is indicated for the treatment of the symptoms and reversible airflow obstruction associated with chronic asthma and other chronic lung diseases.

In 2021, the SFDA reviewed all the evidence available on the association between theophylline and encephalopathy following an ICSR sent to the Saudi National Pharmacovigilance Centre.

The SFDA’s investigation concluded that further investigation to confirm the risk and health-care professionals should be aware of this potential adverse reaction.


Nivolumab

Potential risk of hypoparathyroidism

Saudi Arabia. The SFDA has released a potential safety signal of hypoparathyroidism associated with the use of nivolumab. Nivolumab is indicated for the treatment of unresectable malignant melanoma.

In 2021, the SFDA reviewed all the evidence available on the association between nivolumab and hypoparathyroidism following an ICSR sent to the Saudi National Pharmacovigilance Centre.

The SFDA’s investigation concluded that this needs further investigation to confirm the risk and health-care professionals should be aware of this potential adverse reaction.


Tozinameran, COVID-19 vaccine mRNA

(mRNA 1273)

Risk of myocarditis

Europe. The PRAC has requested more detailed information on myocarditis and pericarditis from the marketing authorization holder of tozinameran. This should be included in the next pandemic summary safety report before considering if any other regulatory action is needed.

Additionally, the PRAC has requested the marketing authorization holder for COVID-19 vaccine mRNA (mRNA 1273) (COVID-19 vaccine Moderna®) to also monitor for cases of myocarditis and pericarditis and to provide a detailed analysis.


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 upon 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 26 million reports of suspected adverse drug reactions, submitted by National Pharmacovigilance Centres participating in the WHO Programme for International Drug Monitoring. VigiBase is, on behalf of the WHO, maintained by the Uppsala Monitoring Centre (UMC) 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 ICSR, their limitations and proper use, is provided in the UMC Caveat document available at the end of Signal (page 28). 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.

Levetiracetam and Hypokalaemia

Mónica Tarapués, Ecuador

Summary

Levetiracetam is considered a remarkable antiepileptic drug due to its mechanism of action, which is unrelated to the Na+ channels or to GABAergic transmission. Few interactions are described for this drug due to its minimal hepatic metabolism; however, sixty-six percent of its elimination depends on the renal function. Drug-induced hypokalaemia is a hazardous reaction that could lead, in the worst cases, to death. A screening of VigiBase, the WHO global database of individual case safety reports, identified disproportionate reporting of the MedDRA Preferred Term (PT) “Hypokalaemia” with levetiracetam. A selection of the cases with a completeness score above 0.60 was made to analyse drug–reaction association patterns. A consistent time to onset and a biological plausibility support this signal. Through this analysis, it seems reasonable to consider the association between hypokalaemia and levetiracetam use. Currently, only the product information from Canada warns of hypokalaemia as an adverse reaction to levetiracetam, but all clinicians should be aware of this adverse event.

Introduction

In December 1999, levetiracetam was approved in the United States (US) as an antiepileptic drug for the treatment of adults with partial seizures, and approval by the European Union (EU) followed in September 2000. Around 2005, oral tablets and solutions were approved for children, and in 2006, it began to be used for the treatment of status epilepticus. At the time of writing, levetiracetam is indicated for the treatment of epilepsy in adults, adolescents, children, and infants. It is a pyrrolidone derivative (S-enantiomer of α-ethyl-2-oxo-1-pyrrolidine acetamide), chemically unrelated to existing antiepileptic active substances. Regarding its mechanism of action, it is well known that the interaction is between levetiracetam and the synaptic vesicle protein 2A. In this way, it does not exhibit the classical action of other antiepileptic drugs because there is no effect on voltage-dependent Na+ channels or GABAergic transmission. (1)

Hypokalaemia is a common and sometimes serious electrolyte imbalance. Its presence can aggravate the baseline clinical conditions of patients. The hypokalaemia categories are well known: mild with plasma levels of >3.0–3.5 mmol/L generally asymptomatic; moderate 2.5–3.0 mmol/L its symptoms are cramping, malaise, myalgia, weakness; and severe < 2.5 mmol/L associated with electrocardiogram changes (including ST-segment depression, U-wave elevation, T-wave inversion), arrhythmias and paralysis. Drug-induced hypokalaemia could be associated with a decrease in potassium intake, or with increased potassium shifting (transcellular shifts). This electrolyte disbalance is commonly associated with diuretics,
β2-receptor agonists drugs, corticosteroids, some antimicrobials, or high doses of insulin (2).

Reports in VigiBase

During 2017, the MedDRA Preferred Term "hypokalaemia" was highlighted for the drug levetiracetam in VigiBase, the WHO global database of individual case safety reports. This combination was kept under review in order to gather more cases. As of 15 September 2019, in an updated and extended search in the database, there were 74 reports of this drug–adverse drug reaction (ADR). Seventeen cases were suspected as duplicates; therefore, 57 were considered. Due to the high number of cases, an analysis of the reports with a completeness score over 0.6 was undertaken. In the present case series, 23 cases were evaluated.

The reports came from eight countries. Eleven patients were female, the other eleven were male, and gender was not specified in one report. The age was recorded in twenty-one patients. Ten out of twenty-one were adults, nine were elderly, one was aged 5, and one a new-born. More than half of the cases were submitted by physicians (sixteen reports). In fourteen cases the ADR was considered as serious, mainly because of prolonged hospitalization (eight cases), or concomitant medically important conditions (five cases). One case was reported as serious because the patient died. The summary of case characteristics is set out in Table 1.

Levetiracetam was the unique suspected drug in 14 reports, the therapeutic indication being epilepsy (focal seizures, convulsions, partial seizures with secondary generalization). The time to onset was mentioned in eighteen reports, in seventeen cases a range from the same day up to two months was given. In one case the patient experienced the ADR after two years of treatment. Half of the patients had a time to onset around ten days after starting levetiracetam. The route of administration was mentioned in twenty reports, the more frequent being oral route (ten reports), followed by intravenous (nine) and transplacental (one). In the case of the transplacental route, it seems according to the narrative text that exposure of the new-born was during the pregnancy span. Regarding the concomitant medicines, hydrocortisone was reported as a co-suspected drug in two cases, however, in one report, the starting date was given in the same timeframe as levetiracetam.

Lacosamide was also mentioned as co-suspected in two other cases, within the same timeframe as levetiracetam. In four reports the use of proton pump inhibitors such as esomeprazole (one as co-suspected and another one as concomitant) and pantoprazole (two cases as concomitant) was mentioned.

Hypokalaemia was described as the single ADR in eleven cases. Hypomagnesemia was reported in four cases as a co-reported reaction, and in two of these cases, the starting dates mentioned were the same as hypokalaemia. Likewise, three reports mentioned diarrhoea, two during the same time period as hypokalaemia. The plasmatic level of potassium concentrations was registered in fourteen cases, with a range of 2.2 – 3.3 mmol/L, in all cases the levels being reported after the levetiracetam was started.

Levetiracetam was withdrawn from three patients and the dose reduced in another one, all these being reported as recovered. In ten patients the dose was not changed, and of these, four were described as recovered, another four as recovering, one as not recovered, and for the last one the outcome was unknown. Sixteen cases had a narrative; in seven of these a supplement of potassium was mentioned. One patient died; this was an elderly person (aged 83), with co-reported ADRs pneumonia, atrial fibrillation, tachycardia, hypoproteninaemia, hypoalbuminemia, and blood lactate dehydrogenase increased, but there was no narrative. It is difficult to attribute the fatal outcome to the hypokalaemia.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>23 cases with high completeness score (above 0.6)</th>
<th>34 cases with low completeness score (less than 0.59)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median / range)</td>
<td>57 years / 0* - 90 years</td>
<td>45 years / 5 – 87 years</td>
</tr>
<tr>
<td>Patient sex distribution</td>
<td>11 female / 11 male / 1 unknown</td>
<td>21 female / 13 male</td>
</tr>
<tr>
<td>Geographical spread</td>
<td>India (n=7), Germany (n= 4), Italy (n=3), Japan (n=3), Greece (n=2), France (n=2), US and Ireland (n=1 each)</td>
<td>US (n=17), Germany (n=6), United Kingdom n=2 and Italy, Korea, Japan, Turkey, Denmark, France, Hungary, Belgium , Ireland (n= 1 each)</td>
</tr>
<tr>
<td>Reporter types</td>
<td>16 physicians; 4 pharmacists; 3 other health professionals</td>
<td>17 physicians; 3 pharmacists; 9 other health professionals; 2 consumers; 3 unknown</td>
</tr>
<tr>
<td>Single suspect drug</td>
<td>14 reports</td>
<td>9 reports</td>
</tr>
<tr>
<td>Single reported drug</td>
<td>7 reports</td>
<td>4 reports</td>
</tr>
</tbody>
</table>
**Signal**

<table>
<thead>
<tr>
<th>Category of hypokalaemia</th>
<th>3 reported as mild, 7 reported as moderate, 4 reported as severe, 9 reports unknown</th>
<th>5 reported as mild, 1 reported as severe, 28 reports unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time-to-onset</td>
<td>Mentioned in 18 reports with a median of 10 days</td>
<td>Mentioned in 2 reports 30 and 60 days</td>
</tr>
<tr>
<td></td>
<td>12 reports after 1 to 10 days, 3 reports after 11 to 20 days, 2 report after 60 days, 1 report after 2 years</td>
<td></td>
</tr>
<tr>
<td>Withdrawn/recovered</td>
<td>1 report with dose reduced, 3 reports with drug withdrawn and all with reaction abated</td>
<td>1 report with drug withdrawn and the reaction abated</td>
</tr>
<tr>
<td></td>
<td>8 reports with dose not changed and reaction abated or in recovering</td>
<td></td>
</tr>
</tbody>
</table>

**Literature and Labelling**

The literature suggests that levetiracetam is widely used due to high tolerability comparing favourably with other antiepileptic drugs used in epilepsy, and because it can be used when other drugs are contraindicated or patients have a refractory condition to other antiepileptics. (1)

Sixty-six percent (66%) of levetiracetam is excreted unchanged by glomerular filtration in the kidney, with subsequent tubular reabsorption, as well as its primary metabolite (ubc L057). The plasma half-life of levetiracetam across studies is 6 to 8 hours, however the labelling mentions it could be greater in subjects with renal impairment and in the elderly, primarily due to impaired renal clearance. In patients with severe hepatic impairment, the creatinine clearance may underestimate the renal insufficiency. Therefore a 50% reduction of the daily maintenance dose is recommended when the creatinine clearance is <60 mL/min/1.73m². (3,4)

The Summary of Product Characteristics (SPC) of levetiracetam in the US and Europe does not list hypokalaemia as an ADR. However, the SPC in Canada mentions hypokalaemia as an ADR observed in the post-marketing surveillance. (5–8)

In the literature, a case report published in 2014 from Turkey described a 23-year-old man where hypokalaemia was found during routine blood tests six weeks after taking 500 mg levetiracetam twice daily. After the nephrology consultation, his hypokalaemia (3.1 mmol/L; normal: 3.5–5.5 mmol/L) and hypomagnesaemia (0.56 mmol/L; normal: 0.75–1.30 mmol/L) were considered to be associated with levetiracetam; it was withdrawn and the electrolytes returned to normal after two weeks. (9) In 2015 a publication from Greece described hypokalaemia and hypomagnesaemia associated with levetiracetam in two patients. A 90 year-old female patient had received levetiracetam 500 mg twice daily intravenously; two days later a low plasma level of potassium and magnesium were identified (2.4 mmol/L and 0.58 mmol/L, respectively). The other patient was a 79 year-old female who had been administrated levetiracetam at 1 gr twice daily intravenously, and three days later the level of potassium was 2.4 mmol/L and magnesium 1.35 mg/dL. Despite the potassium supplement at the hospital, the patients did not fully recover, and consequently levetiracetam was withdrawn. (10) In 2018, another case from Turkey described a 34 year-old woman who was admitted to hospital after attempting to commit suicide. In the laboratory test hypokalaemia (3.1 mEq/lt) and hypomagnesemia (1.2 mg/dl) were observed; the patient was taking 2500 mg/day levetiracetam for epilepsy although the duration of treatment was not described. (11) These publications suggest that the hypokalaemia observed could be due to a transcellular shift mechanism, an unknown side effect of the levetiracetam, given that they ruled-out other potential causes such as metabolic alkalosis or gastrointestinal losses. (9–11)

**Discussion and Conclusion**

In this case series, it is difficult to rule out other potential causes as there is a lack of information regarding the baseline condition of the patients. However, the association should be considered, given the high suspicion of the reporters and the fourteen reports where levetiracetam was the only drug mentioned. On the other hand, diarrhoea – another potential cause – was only mentioned in two cases. It is worth noting that the time to onset in most cases (twelve patients out of twenty-three) was within ten days after starting levetiracetam.

Regarding other drugs that can be associated with hypokalaemia, corticosteroids, and methylxanthines are strongly associated with drug-induced hypokalaemia and other electrolyte imbalances. (2) In one patient, hydrocortisone and theophylline were reported as co-suspected drugs. However, levetiracetam was used in the same temporal sequence of these drugs, and for that reason it is not possible to rule out their potential association with hypokalaemia.

Magnesium deficiency exacerbates potassium wasting by increasing distal potassium secretion. However, hypomagnesemia alone does not necessarily cause hypokalaemia. (12) In this case series, four patients had hypomagnesemia, but in two cases the starting dates were unknown and in
the other two cases, they had the same starting date as hypokalaemia, making the analysis of the potential causal relationship between hypomagnesaemia and hypokalaemia difficult. Then again, there are several reports regarding the association of proton pump inhibitors and hypomagnesemia.(13,14) Esomeprazole was mentioned as a co-suspected drug for hypokalaemia and hypomagnesemia in one patient. This potential interaction needs further analysis in large studies.

In a prospective study of 32 children in Greece (18 females, 14 males, mean age 5.94 ± 4.1 years, range 1-15 years) being treated with levetiracetam for the onset of epilepsy, no statistical differences were observed in the alteration of serum sodium, potassium, and magnesium from two to six months with the use of levetiracetam. (15) However, the authors point to the small number of patients studied as a major limitation of their study, and suggest that the young age of patients may have played a protective role in the prevention of electrolyte imbalance. Following clinical trials made in this age group, levetiracetam has been authorized for use in children, and is therefore considered a safe therapeutic option for this group of patients. (16) However, our sample has two patients under 18 years old, even one case of a new-born patient with hypokalaemia.

In the twenty-three patients, only four had their dose of levetiracetam reduced or withdrawn, and these patients were reported as recovered. However, some patients started with the potassium supplement, such as in three cases reported as recovered, despite no change in the dose of levetiracetam, nor withdrawal. In the same way, in two other patients in whom the action with levetiracetam was reported as unknown, the outcome was reported as recovered. It is important to consider the treatment received for this ADR, and whether patients would have an asymptomatic hypokalaemia; the dechallenge as an outpatient could be difficult to identify and report, because the levels of potassium could return to normal two to four weeks after withdrawal, and the reporter might not have had this information at the time that they sent the report.

The biological plausibility comes through a transcellular shift imbalance of potassium, as discussed in the case reports. (9–11) This hypothesis goes in tandem with the alterations of the potassium homeostasis described as a cause of drug-induced hypokalaemia. (17,18) A previous signal regarding acute renal failure associated with levetiracetam was published in 2016 by Uppsala Monitoring Centre; this ADR is already mentioned in the available evidence based on the pharmacokinetics of the drug, suggest a potential causal relationship between levetiracetam and hypokalaemia. Current product information for levetiracetam does not sufficiently inform physicians about electrolyte imbalance, and the product labelling may need to be revised worldwide since the Canadian SPC already includes hypokalaemia as an ADR identified in post-marketing (6).

References
8. Keppra 500 mg film-coated tablets - Summary of Product Characteristics (SmPC) - (emc) [Internet]. [cited 2020 May 9]. Available from: https://www.medicines.org.uk/emc/product/2293/smpc
11. Key A, Sch T, Case JM, Demir M, Canpolat O, Yigit IP, et al. Levetiracetam-Induced
Remdesivir and pancreatic toxicity

Elena Rocca, Uppsala Monitoring Centre

Summary

Remdesivir is a novel antiviral which, during the 2020 COVID-19 pandemic, gained emergency approval in several countries for use in hospitalized COVID-19 patients. The knowledge of remdesivir’s safety profile is therefore still limited. On a molecular level remdesivir is an adenosine analogue that competes with endogenous adenosine triphosphate (ATP) resulting in abnormal replication of viral RNA with loss of further replication. A recent analysis by the UMC, focusing on ICSRs from COVID-19 treatments, found that as of December 2020 there were 13 relevant reports with remdesivir and the MedDRA High Level Term (HLT) ‘Acute and Chronic Pancreatitis’, or with related investigations, in VigiBase, the WHO global database of ICSRs. The reports were from five countries in the European and American (Region of the Americas) WHO regions. Remdesivir was the single suspected drug in nine cases of which five mentioned positive dechallenge. In eight of the cases, pancreatic symptoms were the only ones reported. The time to onset ranged from one to nine days (median four). One patient died of COVID-19 infection nine days after positive dechallenge and after recovery from pancreatic symptoms. In two cases, the patients presented with pancreatic symptoms after recovery from COVID-19. Although the cases of positive dechallenge are confounded by concomitant drugs, some of which have been rarely associated with pancreatitis, the series offers evidence for a drug-induced, COVID-19-independent onset of pancreatic symptoms. The summary of product characteristics does not contain any information about remdesivir-induced pancreatic effects. Other approved antivirals of the nucleoside analogue class are thought to cause pancreatitis, and their mechanism of toxicity is defined in the literature. The temporality and the positive dechallenge in several of the cases, together with biological plausibility, and analogy with other antiviral drugs, and the uncertainties in relation to COVID-19, support our claim that the hypothesis of a causal relationship between remdesivir treatment and pancreatic toxicity needs to be further monitored.

Introduction

Remdesivir is an antiviral drug indicated for the treatment of coronavirus disease 2019 (COVID-19) in hospitalized patients and/or in hospitalized COVID-19 patients in need of supplemental oxygen. The drug is approved for intravenous administration under the supervision of a health professional. Remdesivir is an adenosine analogue prodrug which is metabolized within host cells to form the pharmacologically active nucleoside analogue triphosphate metabolite. The phosphorimidate prodrug allows a faster cell uptake of remdesivir, compared to the non-phosphorimidated active metabolite (designated as
GS-441524). Remdesivir competes with the natural adenosine substrate for incorporation into RNA chains being formed by the SARS-CoV-2 RNA-dependent RNA polymerase, resulting in abnormal replication of the viral RNA. Preliminary pharmacokinetic data indicates that remdesivir is extensively metabolized by cytochrome P450 enzymes CYP2C8, CYP2D6 and CYP3A4. Remdesivir and metabolites are predominantly excreted in urine and the terminal half-life is approximately 24 hours. According to this, complete excretion of the metabolite GS-441524 takes about five days from the last administration of remdesivir.

The most common aetiologic factors for pancreatitis are gallstones and alcohol consumption, with severe hypertriglyceridaemia, infective agents, and drug adverse reactions also among described causes for pancreatic inflammation. A possible causal association between COVID-19 and acute pancreatitis has been reported with obesity and diabetes being predisposing conditions. Genetic factors, drug-induced pancreatitis is thought to account for about 5% of acute pancreatitis cases and there is a substantial list of drugs that have been associated with the condition, primarily based on case reports containing rechallenge information. However, possible mechanisms and times to onset are variable which makes drug-induced pancreatitis a difficult adverse effect to evaluate. Dysfunction of the sphincter of Oddi, which regulates the flow of pancreatic secretions into the intestine, is suggested as one possible mechanism underlying acute pancreatitis, and this may be drug-induced in patients with a history of cholecystectomy.

Reports in VigiBase
A recent analysis of VigiBase by the UMC focused on ICSRs related to drugs used in COVID-19 patients. Remdesivir related ICSRs were therefore within the focus of this analysis. As of 8th December 2020, there were 12 unique individual case safety reports (ICSRs) for remdesivir with the MedDRA High Level Term (HLT) 'Acute and Chronic Pancreatitis' in VigiBase: six contained the PT 'Pancreatitis', four 'Pancreatitis acute', and two 'Oedematous pancreatitis'. A search with HLT 'Digestive enzymes' (SOC investigations) gave nine additional ICSRs (three with PT 'Pancreatic enzymes increased', two with 'Lipase increased', one with 'Lipase urine', two with 'Amylase increased', and one with 'Hyperamylasemia'). Of these, three ICSRs are included in this case series as informative (one with PT 'Hyperamylasemia', one with PT 'Amylase Increased', and one with the PTs 'Lipase increased' and 'Amylase increased'), while the others were excluded because of numerous co-reported symptoms, which make the association with pancreatitis more uncertain. In two of the reports temporality was incompatible with causation, leaving 13 relevant reports from five countries in the European and American WHO regions. The details of these reports are shown in Table 1. The patient's age ranged from 38 to 79 years (median 55), with nine males and four females. Nine cases were reported as serious and ten as recovered or recovering. Remdesivir was the single suspected drug reported in nine cases and there were five with positive dechallenge. In eight of the cases, pancreatic symptoms were the only ones reported. The time to onset ranged from 1 to 9 days (median 4). In two cases the time to onset was five days after the last dose.

Diagnostic criteria, where reported, were based on abdominal pain in association with increased levels of biomarkers such as serum amylase and lipase. Imaging was used in three cases (2, 5, 7 in Table 1). Five cases (3, 6, 11, 12, 13), described increased biomarkers without clinical symptoms, giving a weaker basis for a diagnosis of pancreatitis.

Table 1. Characteristics of the ICSRs of remdesivir and pancreatic PTs in VigiBase. Known risk factors for pancreatitis are highlighted in bold.

<table>
<thead>
<tr>
<th>Case</th>
<th>Age/Sex</th>
<th>Co-reported suspected (S) or concomitant drugs</th>
<th>Reported MedDRA Preferred Terms</th>
<th>Time to onset (days)</th>
<th>Action taken/ outcome</th>
<th>Other information</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>52/M</td>
<td>Dexamethasone Ascorbic acid Ergocalciferol Rivaroxaban Ondansetron Paracetamol</td>
<td>Pancreatitis acute Therapy interrupted</td>
<td>2</td>
<td>Dechallenge/recovering</td>
<td>Treatment duration: 2 days. No previous history suggesting predisposition to pancreatitis. Symptoms and biomarkers level (lipase) compatible with pancreatitis. Dexamethasone administered and interrupted at nearly overlapping dates.</td>
</tr>
<tr>
<td>2</td>
<td>53/M</td>
<td>Dexamethasone Paracetamol</td>
<td>Pancreatitis acute</td>
<td>8 (5 after last dose)</td>
<td>Not applicable/recovering</td>
<td>Treatment duration: 3 days. No previous history suggesting predisposition to pancreatitis. Biomarkers (lipase, amylase) and symptoms compatible with acute pancreatitis. Choledocholithiasis or cholecystitis were ruled out sonographically.</td>
</tr>
<tr>
<td>Case</td>
<td>Age/Sex</td>
<td>Co-reported suspected (S) or concomitant drugs</td>
<td>Reported MedDRA Preferred Terms</td>
<td>Time to onset (days)</td>
<td>Action taken/outcome</td>
<td>Other information</td>
</tr>
<tr>
<td>------</td>
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<td>------------------------------------------------</td>
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<td>---------------------</td>
<td>----------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>3</td>
<td>64/F</td>
<td><strong>Dexamethasone (S)</strong>&lt;br&gt;<strong>Tocilizumab</strong>&lt;br&gt;Azithromycin&lt;br&gt;Bemiparin&lt;br&gt;Ceftriaxone&lt;br&gt;Enoxaparin&lt;br&gt;Oxygen&lt;br&gt;Acetylsalicylic acid&lt;br&gt;Chlorthalidone&lt;br&gt;Finasteride&lt;br&gt;Levosulpiride</td>
<td>Pancreatitis acute</td>
<td>3</td>
<td>Dechallenge/recovering</td>
<td>Symptoms of acute pancreatitis appear after the patient has recovered from COVID-19. Patient is re-hospitalized for acute pancreatitis. Dexamethasone administered at nearly overlapping dates.</td>
</tr>
<tr>
<td>4</td>
<td>52/F</td>
<td>None reported</td>
<td>Pancreatitis acute&lt;br&gt;Cholelithiasis</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>5</td>
<td>38/M</td>
<td><strong>Tocilizumab (S)</strong>&lt;br&gt;Lopinavir;ritonavir&lt;br&gt;Hydroxychloroquine</td>
<td>Pancreatitis&lt;br&gt;Pyrexia&lt;br&gt;Dyspnoea</td>
<td>2</td>
<td>None/recovering</td>
<td>Treatment duration: 10 days. Concomitant condition: <strong>class 1 obesity</strong>. 'Five months later, a CT scan showed improvement of the pancreatic injury'. Tocilizumab: treatment duration 1 day, TTO 2 days.</td>
</tr>
<tr>
<td>6</td>
<td>69/F</td>
<td>None reported</td>
<td>Pancreatitis&lt;br&gt;Covid-19 Pneumonia</td>
<td>5</td>
<td>None/not reported</td>
<td>Treatment duration: 5 days. <strong>90.4 kg</strong>. 'On day 5, patient's lipase was elevated to 1056, consistent with pancreatitis'.</td>
</tr>
<tr>
<td>7</td>
<td>42/F</td>
<td><strong>Escitalopram</strong>&lt;br&gt;Enoxaparin&lt;br&gt;<strong>Dexamethasone</strong>&lt;br&gt;Famotidine&lt;br&gt;Insulin&lt;br&gt;Metoprolol&lt;br&gt;Pantoprazole&lt;br&gt;Gabapentin&lt;br&gt;Oxygen</td>
<td>Pancreatitis</td>
<td>9 (5 after last dose)</td>
<td>Not applicable/recovering</td>
<td>Treatment duration: 4 days. Previous history: <strong>diabetes, obesity</strong>, depression. Reported symptoms and biomarkers (lipase elevated to 262 U/L) compatible with mild pancreatitis. Ultrasound imaging excluded gallstones Symptoms appeared after recovery from COVID-19 symptoms, although CT scan of the lungs shows signs of multifocal pneumonia.</td>
</tr>
<tr>
<td>8</td>
<td>79/M</td>
<td><strong>Tocilizumab (S)</strong></td>
<td>Pancreatitis</td>
<td>4</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>9</td>
<td>70/M</td>
<td><strong>Furosemide (S)</strong>&lt;br&gt;Paracetamol&lt;br&gt;Amiodarone&lt;br&gt;Warfarin&lt;br&gt;Acetylsalicylic acid&lt;br&gt;Tazobactam&lt;br&gt;Ramipril&lt;br&gt;Piperacillin&lt;br&gt;Prednisolone&lt;br&gt;Ciprofloxacin&lt;br&gt;Bisoprolol&lt;br&gt;Spiramycin</td>
<td>Pancreatitis</td>
<td>7</td>
<td>Dechallenge/recovered</td>
<td>Treatment duration: 6 days. Died of COVID-19 infection nine days after pancreatic symptoms resolved. Furosemide: treatment duration 2 days, TTO 3 days, withdrawn. Diagnostic criteria not provided.</td>
</tr>
</tbody>
</table>
### Signal

<table>
<thead>
<tr>
<th>Case</th>
<th>Age/Sex</th>
<th>Co-reported suspected (S) or concomitant drugs</th>
<th>Reported MedDRA Preferred Terms</th>
<th>Time to onset (days)</th>
<th>Action taken/Outcome</th>
<th>Other information</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>42/M</td>
<td>Heparin Cefotaxime</td>
<td>Oedematous pancreatitis Hepatitis</td>
<td>6</td>
<td>Not applicable/recovering</td>
<td>Treatment duration: unclear. Concomitant condition: abdominal pain (since 14 days before pancreatitis). Hepatitis: TTO 4 days. No diagnostic criteria are provided for oedematous pancreatitis.</td>
</tr>
<tr>
<td>11</td>
<td>59/M</td>
<td>Simvastatin</td>
<td>Amylase increased</td>
<td>1</td>
<td>Not withdrawn/not recovered (but amylase levels are decreasing after therapy conclusion)</td>
<td>Reported symptom: increased amylase to 243U/L one day after treatment initiation and 469U/L six days after initiation. Amylase increase has a registered peak (841U/L) nine days after initiation and start decreasing again (512U/L) 13 days after initiation (3 days after therapy completion). No medical history pointing to predisposition to pancreatitis.</td>
</tr>
<tr>
<td>12</td>
<td>55/M</td>
<td>Methylprednisolone Furosemide</td>
<td>Hyperamylasaemia</td>
<td>1</td>
<td>Dechallenge/recovering</td>
<td>Treatment duration: 4 days. From the start of treatment with remdesivir, serum amylase progressively increased to 4500 U/L (upper limit normal 136 U/L) and began to decrease after the last dose was omitted.</td>
</tr>
<tr>
<td>13</td>
<td>74/M</td>
<td>Venlafaxine Hydroxy carbamidie</td>
<td>Amylase increased Lipase increased</td>
<td>4</td>
<td>Dechallenge/recovering</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

TTO = Time to onset

### Literature and labelling

Publicly available information on remdesivir’s safety profile, though still limited, includes hypersensitivity, infusion-related and anaphylactic reactions (rare), transaminase elevation (very common), nausea (common), headache (common), rash (common), and renal impairment (precaution). Interactions including risk of decreased antiviral activity when co-administered with chloroquine and hydroxychloroquine have also been signalled. The summary of product characteristics does not contain any information about remdesivir-induced pancreatic effects.

Antivirals of the nucleoside analogue class, such as those used to treat HIV, have been causally associated with pancreatitis, with inhibition of mitochondrial DNA synthesis as the underlying mechanism. Given that remdesivir is also a nucleoside analogue, based on the criteria of plausibility and analogy, it seems sensible to monitor pancreatic reactions reported in connection with remdesivir. Despite scarce data, the theoretical possibility of a similar mechanism for remdesivir, together with the need for monitoring, has been pointed out.

### Discussion and conclusion

When evaluating the plausibility of a causal relation between the use of remdesivir and development of pancreatitis, a confounding factor is that pancreatitis might be a clinical manifestation of COVID-19 itself. Although still uncertain, such a clinical feature of COVID-19 is indicated by the pancreatic expression of SARS-CoV-2 molecular target ACE-2, by case reports, and by the fact that the infection was associated with increased biomarkers of pancreatic injury (which, however, taken alone should not necessarily be interpreted as pancreatic dysfunction). Reports that can help discern confounding with underlying COVID-19 disease are therefore of particular interest.

This series contains three cases that are interesting in that they point to a COVID-19 independent onset of the pancreatic symptoms (cases 2, 7 and 9 in Table 1). Cases 2 and 7 describe symptoms of pancreatic injury appearing after recovery from the COVID-19 infection, both on day 5 after the last dose of remdesivir. Bearing in mind the available pharmacokinetic data these timeframes may be considered clinically reasonable, if we accept the possibility that the process of injury commenced before the symptoms appeared. In both cases remdesivir is the only suspected drug, although dexamethasone, which has on rare occasions been associated with pancreatitis, is reported as concomitant in both. The cases thus provide some indication of a COVID-19 independent pancreatic injury. Since in both cases alternative causes were excluded by imaging, and since the patient in case
remdesivir, and dexamethasone suspect. Evidence in the same direction is provided by case 9, reporting a positive dechallenge with improvement of pancreatitis while the patient was still severely unwell from COVID-19. Here, furosemide, for which pancreatitis is a known rare reaction, is reported as co-suspected with a short treatment duration (two days) and a time to onset of three days. Death from COVID-19 occurred nine days after recovery from pancreatitis, although detailed diagnostic criteria for pancreatitis (and recovery) are not provided in the report.

In two of the cases remdesivir is the only reported drug, however these are not very informative. In one of them (case 6) elevated lipase is reported on the fifth and last day of remdesivir treatment.

Most cases in the series are confounded by concomitant or co-suspected drugs that might contribute to, or cause, the pancreatic symptoms. Dexamethasone, associated on rare occasions to pancreatitis, is reported as concomitant or co-suspected, and administered at almost overlapping days with remdesivir in four cases. One case of increased serum amylase (case 12, Table 1) also mentioned the concomitant use of furosemide, for which pancreatitis is a known reaction, however the rise in serum amylase was noted after the beginning of remdesivir therapy, increased as therapy continued, and normalised after discontinuation. Tocilizumab, also linked to pancreatitis in three case studies and one FDA case report, is co-suspected and concomitant in two of the cases here analysed. Tocilizumab has also been signalled as being causally related to pancreatitis following the COVID-19 focused analysis at UMC. For tocilizumab, the causality assessment is aided by the fact that the drug has a longer history of use and almost 200 ICSRs could be identified regardless of the indication. With a novel medication such a remdesivir, exclusively indicated for COVID-19, evidence is still sparse.

One case (case 3, Table 1) describes a COVID-19 patient with a history of cholecystectomy who presented with increased serum amylase after three days of therapy with remdesivir and dexamethasone. In rare cases, recent cholecystectomy predisposes to acute pancreatitis, but the details do not provide the date of surgery, making it difficult to evaluate the predisposition of this patient. Remdesivir and dexamethasone may have increased the risk for developing pancreatitis in a patient with prior cholecystectomy.

In summary, at the time of writing, remdesivir has recently received emergency approval, with scarce pre-approval experimental use for this indication. The first reports of clinical experiences with remdesivir for COVID-19 treatment have started to appear in the literature but are still sparse; to our knowledge, none present safety concerns regarding pancreatic reactions. Limited remdesivir characterisation, incomplete knowledge about COVID-19 pathophysiology, and the substantial number of concomitant medications used to treat COVID-19, make causality assessment and clinical analyses of ICSRs particularly challenging.

In this situation, we argue that the criteria of analogy with similar drugs and biological plausibility could be used for support. Remdesivir shares the mechanism of action with other approved nucleoside analogues, including those used to treat HIV, which are thought to cause pancreatitis, most commonly through mitochondrial toxicity. Although there is no evidence for the pancreatic toxicity of remdesivir, it has been pointed out that there is a theoretical possibility for a common mechanism of action between remdesivir and similar antiviral drugs.

The case series here presented offers some evidence of COVID-19 independent, drug-induced pancreatic symptoms in COVID-19 patients. The temporality and the positive dechallenge in several of the cases supports the hypothesis that remdesivir, together with other COVID-19 treatments, may have caused or contributed to the onset of symptoms compatible with pancreas injury.

Taking into account the particular uncertainties in relation to the disease treated, and the possible role of concomitant treatments, although not a strong signal, there is reason to further monitor the hypothesis of a causal relationship between remdesivir treatment and pancreatic toxicity.

References


**Response from Gilead**

For the response to the WHO-UMC regarding pancreatic toxicity and RDV:

First, we would like to thank you for the opportunity to review the draft signal report prepared by the Uppsala Monitoring Center (UMC) in which a potential association between remdesivir and pancreatic toxicity is discussed. Gilead has been and is continuously monitoring events reported as pancreatic toxicity as part of its standard signal detection process. In fact, a signal of acute pancreatitis was identified by Gilead in March 2021 based on a literature case report where acute pancreatitis was deemed possibly associated with remdesivir by the author (Khadka 2021). A total of 29 potential pancreatitis cases were identified for review in the context of over 1 million patients treated with remdesivir. Review of the cases reported to Gilead did not provide sufficient evidence of a causal association with acute pancreatitis and remdesivir (i.e., the signal was not validated). Of the cases reviewed, 14% were inconsistent with a diagnosis of acute pancreatitis or were complications of concurrent bacterial infection or malignancy, in 17% the pancreatitis symptoms predated the exposure to remdesivir, 24% contained insufficient information, and 45% included drugs known to induce pancreatitis, with some cases also involving contribution of risk factors for pancreatitis and/or severe complications of COVID-19 infection and its treatment (including the Khadka report). In summary, consistent with the findings of UMC, uncertainties in relation to the role of COVID-19 disease, severity of the patient’s illness and the possible role of concomitant treatments provided alternative etiologies for the events of pancreatitis.

Gilead will continue to monitor events of pancreatitis through routine pharmacovigilance. Safety information received from all sources is carefully evaluated on an ongoing basis for any new safety signals and the prescribing information is updated promptly as new adverse drug reactions are identified.
Summary

Tocilizumab (TCZ) is a humanised monoclonal antibody against interleukin-6 (IL-6) and is indicated in the treatment of rheumatoid arthritis (RA) as well as some other forms of arthritis. TCZ has also been approved for chimeric antigen receptor T-cell therapy induced cytokine release syndrome and has been used recently in the treatment of patients with severe COVID-19 infection. A recent analysis by the UMC of the WHO global database of ICSRs, VigiBase, focused on drugs used in COVID-19 patients. As of 29 November 2020, the UMC analysis identified five individual case safety reports (ICSRs) in VigiBase which reported pancreatitis or pancreatitis acute with the use of TCZ for COVID-19. There are 202 reports (189 de-duplicated) for the combination, regardless of indication, and in respect of the 189 de-duplicated cases the IC is 0.6 and the IC025 is 0.4, which indicates a disproportionate association. An analysis of the 189 cases was considered impractical so it was restricted to those 41 cases with more complete information. These reports were from Belgium, Croatia, Denmark, France, Germany, Greece, Japan, Spain, and the United Kingdom.

TCZ appears to be a likely cause as it was the only suspected drug in 31 of the 41 reports. With 25 cases which occurred from one week to ten months, the time to onset is consistent with other well recognised drug causes of pancreatitis. Patients were reported as recovered or recovering in 32 of the 41 cases, not recovered in eight cases, and there was a fatal outcome in the remaining case. In the 32 cases where recovery was reported, TCZ was withdrawn in 25 cases. Recovery after withdrawal is consistent with an effect of the drug. There are also reports of the association in the literature.

Introduction

Tocilizumab (TCZ) is a humanised monoclonal antibody against interleukin-6 (IL-6) and is indicated in the treatment of rheumatoid arthritis (RA) as well as some other forms of arthritis. TCZ has also been approved for chimeric antigen receptor T-cell therapy induced cytokine release syndrome and has been used recently in the treatment of patients with severe COVID-19 infection. The most reported adverse reactions include upper respiratory tract infections, nasopharyngitis, headache, hypertension, and increased liver function tests. More serious adverse reactions include serious infections, complications of diverticulitis, and hypersensitivity reactions. Acute pancreatitis is an inflammatory disease of the pancreas, characterized by abdominal pain, frequently severe and of sudden onset, and is almost always accompanied by increased pancreatic enzymes in the blood and urine. Although in about 80% of cases the disease is mild to moderate, severe pancreatitis has a mortality rate of 20%. Drug-induced pancreatitis is usually an acute condition.2,3

Gallstones are the leading cause of acute pancreatitis (21-33%) with alcohol as the next most common cause (16-27%). Other common causes include hypertriglyceridaemia, hypercalcaemia, familial (hereditary) pancreatitis, and viral infections.4 Approximately 0.1-5% of cases of acute pancreatitis are drug-related.2,4 More than 500 medications have been implicated as a cause of acute pancreatitis and many of them have been shown to have a definite association.4 Responsible drugs include azathioprine, 6-mercaptopurine, oestrogens, tetracycline, valproic acid, sulindac, ACE inhibitors, HMG-CoA reductase inhibitors (statins), isoniazid and anti-HIV medications.1,4

Reports in VigiBase

A recent analysis by the UMC focused on drugs used in COVID-19 patients. It has been suggested that severe COVID-19 infection is associated with a cytokine storm and pulmonary inflammation secondary to a dysregulated host immune response. As TCZ is indicated for clinical management of cytokine release syndrome, it may be useful to ameliorate the intense inflammatory manifestations associated with severe COVID-19 infection. There were many publications in 2020 which described studies on the use of TCZ in COVID-19 patients, and although the results have been mixed, a recent publication has demonstrated that TCZ reduced the likelihood of progression to the composite outcome of mechanical ventilation or death, but it did not improve survival.5 As of 29 November 2020, the UMC analysis identified five individual case safety reports (ICSRs) which reported pancreatitis or pancreatitis acute with TCZ for the indications 'COVID-19' or 'Corona virus infection' in the WHO global database of ICSRs, VigiBase. There are 202 reports (189 de-duplicated) for the combination regardless of indication. With respect to the 189 de-duplicated cases regardless of indication, the Information Component (IC) is 0.6 (189 observed, 125 expected) and the IC025 is 0.4 which indicates a disproportionate association. In 148 of these cases, TCZ is the only suspected drug. An analysis of the 189 cases was considered impractical so it was restricted to those cases with more complete information and only those cases with age and gender, start date and action taken with TCZ, date of onset and recovery.
There were 41 such cases submitted by France (18 cases), Spain and the United Kingdom (both 5), Japan (4), Germany (3), Croatia and Greece (both 2), and Belgium and Denmark (both 1). There was one additional case from Switzerland involving a 30-year-old male which met the criteria, but use of TCZ occurred after onset of the reaction and it was not considered. A majority of the patients were female (26), which is not surprising as the most common indication was RA, a disease which has a predominance of female patients. Ages ranged from 5 to 83 years, with a median age of 54.5 years which is relatively young.

TCZ was the only suspected drug in 31 of the 41 cases. In the remaining ten, there were multiple suspected drugs, but the only other drugs suspected more than once were the closely related corticosteroids, prednisone, prednisolone, and methylprednisolone (in 4 cases), and hydroxychloroquine (in 2 cases). Other commonly occurring concomitant drugs included corticosteroids (13 cases), drugs for the treatment of hypertension (11 cases), proton pump inhibitors and other drugs for the treatment of the gastrointestinal tract (9), methotrexate (8), drugs for the treatment of pain (7), statins (6), and drugs for the treatment of diabetes (4) and osteoporosis (4). Corticosteroids and methotrexate are commonly used in association with TCZ and the other concomitant drugs were generally reflective of other underlying conditions which accompany the condition for which TCZ was prescribed, particularly RA. In fact, RA was the indication in 28 of the 41 reports. There were a variety of indications in the other 13 reports with Horton’s disease, Takayasu’s disease, polymyalgia rheumatica, and COVID-19 all being implicated in two reports. Dosages varied greatly depending on the indication and the condition of the patient. The most common dosage (10 patients) was 162-167 mg per week; 400-720 mg per month was reported in seven patients, and 560-800 mg over an unknown period was reported in seven patients.

Time to onset varied significantly from one day to eight years, with a median of five months. Nine cases occurred within a month and nine cases occurred from two to eight years, while almost half the cases (18) had an onset from one to eight months.

Patients were reported as recovered or recovering in 32 of the 41 cases, not recovered in eight cases, and there was a fatal outcome in the remaining case. Two of those patients who recovered were reported as recovered with sequelae but there was no information on the nature of these sequelae. In the 32 cases where recovery was reported, TCZ was withdrawn in 25 cases, continued in three cases, and reported as “not applicable” in the remaining four cases. In the 25 cases in which TCZ was withdrawn, it was the only drug reported in five cases, and the only drug reported withdrawn in 16 cases. In the remaining four cases, there were other drugs which were withdrawn but in three of these cases, they are not known to be associated with pancreatitis. In one case (Case 1), a medicine containing both an ACE inhibitor and a statin (which are possible causes of pancreatitis) was also withdrawn. Patients were reported as not recovered in eight cases. In these cases, TCZ was withdrawn in four cases, continued in three cases and the action with the drug was reported as “not applicable” in the remaining case. The other case had a fatal outcome.

Pancreatitis or acute pancreatitis was the only reaction reported in 28 of the 41 reports. In another four cases, there were additional reactions that related to pancreatitis such as abdominal pain (4 cases), amylase increased (2), and diarrhoea (2). In the remaining nine cases, there was a variety of other reactions but no obvious pattern to these reactions apart from some known to be associated with TCZ use, such as hypertriglyceridaemia (3 cases) and abnormal liver functions tests (3).

Labelling and literature

The product literature does not refer to pancreatitis. It does, however, indicate that hypertriglyceridaemia is an uncommon reaction. As noted above, hypertriglyceridaemia is a possible cause of pancreatitis and three of the cases in this series refer to hypertriglyceridaemia as an additional adverse reaction.

There have, however, been several cases of pancreatitis in association with TCZ reported in the literature. Flaig and co-workers described a 40-year-old male who developed pancreatitis about two weeks after the second dose of TCZ for treatment of RA. The authors ruled out other causes of pancreatitis, TCZ was withdrawn and the patient recovered. The authors also noted that there had been three previous reports of this association. Parekh and colleagues described a patient receiving TCZ for RA who developed acute necrotising pancreatitis, and in a paper on the REACTION study, Takeuchi and colleagues reported acute pancreatitis as an adverse event in one patient.

In the other case, a 60-year-old man with RA developed severe hepatitis after the use of TCZ for three months. At the same time, he was noted to have developed mild pancreatitis, characterised by elevated lipase levels. Flaig and colleagues also reviewed the FAERS database in the United States and noted 74 pancreatic adverse events in association with TCZ including 52 cases of acute pancreatitis. More recently, in response to the increased use of TCZ in COVID-19, the FAERS database was investigated for the occurrence of statistically significant reporting odds ratios (RORs) for hepatic reactions in association with TCZ. Statistically significant RORs were found for the 61 cases of acute pancreatitis (ROR: 1.99, 95% CI 1.55-2.56) and for the 151 cases of pancreatitis (ROR: 1.65, 95% CI 1.41-1.94). In another recent
Discussion and Conclusion

A UMC analysis has identified 189 de-duplicated cases of pancreatitis or pancreatitis acute with TCZ regardless of indication, with an IC of 0.6 and an IC025 of 0.4 which indicates a disproportionate association. An analysis of the 189 cases was considered impractical so it was restricted to those cases with more complete information.

TCZ appears to be a likely cause as it was the only suspected drug in 31 of the 41 reports. In the remaining ten reports, there were multiple suspected drugs, but the only other drugs suspected more than once were the closely related corticosteroids, prednisone, prednisolone, and methylprednisolone (in four cases) and hydroxychloroquine (in two cases).

Time to onset varied significantly, from one day to eight years, with a median of five months. Nine cases occurred within a month and another nine occurred from two to eight years, while almost half the cases (18) had an onset of one to eight months. With 25 cases which occurred from one week to ten months, the time to onset is consistent with other well recognised drug causes of pancreatitis. A case control study with ACE inhibitors has shown that the highest risk was during the first six months of therapy while the time to onset with enalapril has been reported to be from five weeks to one year.4 Two cases of rechallenge with angiotensin receptor antagonists occurred, initially from days to three months, while pancreatitis rarely occurs within the first three months of treatment with statins.4 Two cases of rechallenge with tetracycline occurred initially within four days to three months, while time to onset with isoniazid occurred between 11 and 21 days.4 Onset with azathioprine and mercaptopurine occurred within the first few weeks.4 It was interesting that the two cases in which TCZ was used for treatment of COVID-19, the time to onset was short at one and eight days, respectively. The time to onset in those other cases (with a lower level of information) in which TCZ was used to treat COVID-19, although unknown, must have also been relatively short due to the short time period from the date TCZ was first used for that indication to the date the most recent cases have been submitted. On the other hand, those cases with a longer time to onset would not have yet occurred so it is not possible to draw any conclusions on this point. There have also been case reports of acute pancreatitis in association with COVID-19, although strong evidence of causality is lacking. If both COVID-19 and TCZ were possible causes, the time to onset may be shortened.12,13,14

Patients were reported as recovered or recovering in 32 of the 41 cases, not recovered in eight cases and there was a fatal outcome in the remaining case. In the 32 cases where recovery was reported, TCZ was withdrawn in 25 cases, continued in three cases, and reported as “not applicable” in the remaining four cases. Recovery after withdrawal is consistent with an effect of the drug. When drugs such as TCZ are used periodically, the nature of drug withdrawal may not be straightforward and the reporting of “not applicable” for the action taken with the drug may reflect such difficulties in interpretation. In two of these four cases, the reaction appeared a few days after the completion of a course of TCZ, so the result is the same as if the drug was deliberately withdrawn. In another case, the reaction appeared and resolved in the period between two doses one month apart. The remaining case was difficult to interpret.

In the eight cases where patients were reported as not recovered, TCZ was withdrawn in four cases, continued in three cases and the action with the drug was given as “not applicable” in the remaining case. In one of the four cases in which TCZ was withdrawn, this was only done after a final dose was given a day after onset of pancreatitis so interpretation in this case is difficult. In another case, TCZ was continued on a weekly basis for another three months after the onset of pancreatitis and then for a further three months after a four-month period of no treatment. The remaining two cases describe a lack of recovery despite drug withdrawal. The remaining case where the action with the drug was “not applicable”, was difficult to interpret.

The lack of recovery in the three cases in which the drug was continued is consistent with an effect of the drug. In one of the cases, however, the patient died five days after onset of pancreatitis. The cause of death appeared to be complications of COVID-19 disease. The remaining case also had a fatal outcome. The patient developed acute, necrotising pancreatitis three months after commencing TCZ and four weeks after it was withdrawn. The patient died three weeks later. The cause of death was not stated but necrotising pancreatitis has a relatively high rate of mortality and may have been the cause of death.

The product literature does not refer to pancreatitis but there have been several cases of pancreatitis in association with TCZ reported in the literature. The case report by Flaig and coworkers is well documented, with other causes of pancreatitis ruled out, recovery after TCZ withdrawal, and strongly suggests that TCZ is the cause of the pancreatitis.6 Although not as well documented, the other four publications which describe pancreatitis or increased serum amylase levels in association with TCZ strengthen the proposition that TCZ is a possible cause of pancreatitis. This possibility is further strengthened by the disproportionate ROR of the association in the FDA database.10

In summary, there is a signal for the association of pancreatitis and acute pancreatitis in association with TCZ. There are a significant number of reports in VigiBase and those which are well documented...
have TCZ as the only suspected drug in 76% of the cases. Time to onset supports an association as does recovery after withdrawal. There are reports in the literature and both VigiBase and FAERS show a disproportionation in favour of the association.

References

Table 1. Characteristics of selected reports in VigiBase of pancreatitis in association tocilizumab

<table>
<thead>
<tr>
<th>Case</th>
<th>Age/Gender</th>
<th>Other suspected (S) or concomitant (C) drugs</th>
<th>Reactions (MedDRA preferred terms)</th>
<th>Outcome</th>
<th>Action taken with drug</th>
<th>Time to onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>50/M</td>
<td>Atorvastatin/acid/Isaicylic acid/ramipril (S), metotrexate (C)</td>
<td>Pancreatitis</td>
<td>Recovered</td>
<td>Withdrawn</td>
<td>7 m</td>
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<tr>
<td>2</td>
<td>57/F</td>
<td>None</td>
<td>Pancreatitis acute</td>
<td>Recovered</td>
<td>Continued</td>
<td>8 y</td>
</tr>
<tr>
<td>3</td>
<td>57/F</td>
<td>Rosuvastatin, sitagliptin (both S), metformin, glimepiride (both C)</td>
<td>Pancreatitis acute, asthenia, abdominal pain upper</td>
<td>Recovered</td>
<td>Not applicable</td>
<td>8 y</td>
</tr>
<tr>
<td>4</td>
<td>39/M</td>
<td>Prednisone, atorvastatin, hydrochlorothiazide (all S), clopidogrel, bisoprolol, acetylsaicylic acid, amlodipine/perindopril, lansoprazole, spironolactone (all C)</td>
<td>Pancreatitis acute</td>
<td>Recovering</td>
<td>Withdrawn</td>
<td>5 m</td>
</tr>
<tr>
<td>5</td>
<td>69/F</td>
<td>None</td>
<td>Pancreatitis acute</td>
<td>Recovered</td>
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<td>2 d</td>
</tr>
<tr>
<td>6</td>
<td>58/M*</td>
<td>Hydroxychloroquine, ceftriaxone, azithromycin, methylprednisolone, lopinavir/ritonavir (all S)</td>
<td>Pancreatitis acute, hypertriglyceridaemia</td>
<td>Recovered</td>
<td>Withdrawn</td>
<td>7 d</td>
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<tr>
<td>7</td>
<td>21/F*</td>
<td>Hydroxychloroquine, linezolid, amphotericin b (all S)</td>
<td>Pancreatitis acute, acute kidney injury, hepatitis, hypocoagulable state</td>
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<td>Continued</td>
<td>1 d</td>
</tr>
<tr>
<td>Case</td>
<td>Age/Gender</td>
<td>Other suspected (S) or concomitant (C) drugs</td>
<td>Reactions (MedDRA preferred terms)</td>
<td>Outcome</td>
<td>Action taken with drug</td>
<td>Time to onset</td>
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<tr>
<td>8</td>
<td>59/F</td>
<td>Methotrexate (C)</td>
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<td>Recovered</td>
<td>Withdrawn</td>
<td>9 m</td>
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<tr>
<td>9</td>
<td>53/F</td>
<td>None</td>
<td>Pancreatitis acute</td>
<td>Recovering</td>
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<td>2 m</td>
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<tr>
<td>10</td>
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<td>Colecalciferol, tramadol, bisoprolol,</td>
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<td>2 y</td>
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<td></td>
<td></td>
<td>trimethubine, atorvastatin, ramipril,</td>
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<td>paracetamol, acetylsalicylic acid (all C)</td>
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<tr>
<td>11</td>
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<td>Calcium/colecaltiferol, potassium,</td>
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<td>Withdrawn</td>
<td>5 m</td>
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<td>teriparadine, paracetamol, morphine,</td>
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<td>metoprolol, promethazine, vancomycin,</td>
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<td>6 w</td>
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<td>Alprazolam, atorvastatin, bisoprolol,</td>
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<tr>
<td>21</td>
<td>5/M</td>
<td>Inotuzumab, tisagenlecleucel-T (both S)</td>
<td>Pancreatitis, acute lymphocytic</td>
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<td>Not applicable</td>
<td>8 m</td>
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<td>Indapamide, lansoprazole, sulphasalazine</td>
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<td>5 m</td>
</tr>
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<td>(all C)</td>
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<tr>
<td>23</td>
<td>47/M</td>
<td>Prednisone (C)</td>
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<td>Recovered</td>
<td>Withdrawn</td>
<td>4 y</td>
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<td>24</td>
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<td>Levohydroxine (C)</td>
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<td>Recovered</td>
<td>Withdrawn</td>
<td>6 m</td>
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<td></td>
<td>diarrhoea, pustule</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>56/M</td>
<td>Prednisolone (S), acetylsalicylic acid,</td>
<td>Pancreatitis acute</td>
<td>Recovered</td>
<td>Withdrawn</td>
<td>16 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>altizide/spironolactone, anagrelide,</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>levohydroxine, potassium, sotalol (all C)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>26</td>
<td>41/M</td>
<td>Methotrexate (C)</td>
<td>Pancreatitis, hypertriglyceridaemia</td>
<td>Recovering</td>
<td>Withdrawn</td>
<td>3 w</td>
</tr>
<tr>
<td>27</td>
<td>28/F</td>
<td>Clopidogrel, lansoprazole, prednisone,</td>
<td>Pancreatitis</td>
<td>Recovered</td>
<td>Not applicable</td>
<td>4 m</td>
</tr>
<tr>
<td></td>
<td></td>
<td>rosuvastatin (all C)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>28</td>
<td>46/M</td>
<td>Brinzolamide, bisoprolol, latanoprost,</td>
<td>Pancreatitis acute</td>
<td>Not recovered</td>
<td>Continued</td>
<td>4 y</td>
</tr>
<tr>
<td></td>
<td></td>
<td>prednisone (all C)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>29</td>
<td>53/M</td>
<td>Leflunomide (S)</td>
<td>Pancreatitis acute</td>
<td>Recovered</td>
<td>Withdrawn</td>
<td>2 y</td>
</tr>
<tr>
<td>Case</td>
<td>Age/ Gender</td>
<td>Other suspected (S) or concomitant (C) drugs</td>
<td>Reactions (MedDRA preferred terms)</td>
<td>Outcome</td>
<td>Action taken with drug</td>
<td>Time to onset</td>
</tr>
<tr>
<td>------</td>
<td>-------------</td>
<td>---------------------------------------------</td>
<td>-----------------------------------</td>
<td>---------</td>
<td>------------------------</td>
<td>--------------</td>
</tr>
<tr>
<td>30</td>
<td>35/F</td>
<td>Folic acid, loxoprofen, methotrexate (all C)</td>
<td>Pancreatitis acute</td>
<td>Recovering</td>
<td>Withdrawn</td>
<td>17 m</td>
</tr>
<tr>
<td>31</td>
<td>49/F</td>
<td>None</td>
<td>Pancreatitis acute</td>
<td>Recovered</td>
<td>Withdrawn</td>
<td>13 m</td>
</tr>
<tr>
<td>32</td>
<td>67/F</td>
<td>None</td>
<td>Pancreatitis</td>
<td>Recovered</td>
<td>Withdrawn</td>
<td>5 w</td>
</tr>
<tr>
<td>33</td>
<td>35/F</td>
<td>Prednisolone (C)</td>
<td>Pancreatitis acute</td>
<td>Recovered</td>
<td>Continued</td>
<td>6 y</td>
</tr>
<tr>
<td>34</td>
<td>81/F</td>
<td>Amlodipine/atorvastatin, bucillamine, eldecalcitrol, lansoprazole, minodronic acid, pilocarpine, prednisolone, sulfasalazine, tacrolimus (all C)</td>
<td>Pancreatitis acute</td>
<td>Recovering</td>
<td>Withdrawn</td>
<td>3 y</td>
</tr>
<tr>
<td>35</td>
<td>35/M</td>
<td>Azathioprine (C)</td>
<td>Pancreatitis acute, acute abdomen, amylase increased</td>
<td>Recovered</td>
<td>Withdrawn</td>
<td>3 m</td>
</tr>
<tr>
<td>36</td>
<td>71/F</td>
<td>Omeprazole, prednisolone, risedronic acid (all C)</td>
<td>Pancreatitis acute</td>
<td>Recovering</td>
<td>Withdrawn</td>
<td>11 m</td>
</tr>
<tr>
<td>37</td>
<td>28/M</td>
<td>Azathioprine, prednisolone (both C)</td>
<td>Pancreatitis, abdominal distension, abdominal pain, abdominal sepsis, abdominal tenderness, back pain, blood pressure decreased, body temperature increased, condition aggravated, heart rate increased, immunosuppression, oxygen saturation decreased, respiratory rate increased, splenic infarction, Takayasu’s arteritis</td>
<td>Recovered with sequelae</td>
<td>Withdrawn</td>
<td>11 d</td>
</tr>
<tr>
<td>38</td>
<td>57/F</td>
<td>Deflazacort, oxandrolone (both C)</td>
<td>Pancreatitis</td>
<td>Recovered</td>
<td>Withdrawn</td>
<td>1 m</td>
</tr>
<tr>
<td>39</td>
<td>40/M</td>
<td>Metamizole, prednisolone, ramipril, calcium/colecalciferol, omeprazole (all C)</td>
<td>Pancreatitis acute</td>
<td>Recovering</td>
<td>Withdrawn</td>
<td>6 w</td>
</tr>
<tr>
<td>40</td>
<td>73/F</td>
<td>Blinded methotrexate (S), alfacalcidol, amlodipine, clopidogrel, folic acid, hydroxychloroquine, ibandronic acid, metformin, sitagliptin, simvastatin, valsartan (all C)</td>
<td>Pancreatitis acute</td>
<td>Recovered</td>
<td>Withdrawn</td>
<td>14 m</td>
</tr>
<tr>
<td>41</td>
<td>62/F</td>
<td>Amlodipine, citalopram, iron, lisinopril, naproxen, omeprazole, simvastatin, tramadol (all C)</td>
<td>Pancreatitis acute, pancreatitis necrotising</td>
<td>Died</td>
<td>Withdrawn</td>
<td>3 m</td>
</tr>
</tbody>
</table>

*COVID-19 cases*
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.

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

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2. 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
3. affirming that the information does not represent the opinion of the UMC or the World Health Organization.

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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