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WHO Vision for Medicines Safety
No country left behind: worldwide pharmacovigilance for safer medicines, safer patients

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

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

Safety and Vigilance: Medicines,

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This Newsletter is also available at:
http://www.who.int/medicines

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.

This newsletter also includes a short report from the 41st Annual Meeting of Representatives of National Pharmacovigilance Centres participating in the WHO Programme for International Drug Monitoring and from an Advanced Workshop for Strengthening Pharmacovigilance (PV) Systems.

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Fingolimod

Risk of worsening of multiple sclerosis after stopping

USA. The US Food and Drug Administration (FDA) has updated the prescribing information for fingolimod (Gilenya®) to include a warning about the risk of worsening of multiple sclerosis (MS) when the medicine is stopped.

Fingolimod is indicated for the treatment of relapsing MS.

Health-care professionals should inform patients before starting treatment about the potential risk of a severe increase in disability after stopping fingolimod.

Also, patients should be carefully observed for evidence of an exacerbation of their MS and treated appropriately when fingolimod is stopped.

Reference:
Safety Alerts for Human Medical Products, US FDA, 20 November 2018
(www.fda.gov)

Fluoroquinolone and quinolone antibiotics

Risk of long-lasting and disabling effects

Europe. The European Medicines Agency (EMA) has announced that the prescribing information for individual fluoroquinolone antibiotics will be updated to include new restrictions on the use due to risk of long-lasting and disabling adverse effects such as inflamed tendon, muscle pain, feeing pins, tiredness, depression, confusion, and sleep disorders.

Fluoroquinolones and quinolones are a class of broad-spectrum antibiotics that are active against bacteria of both Gram-negative and Gram-positive classes.

The restrictions were made following recommendations made by the Pharmacovigilance Risk Assessment Committee (PRAC). PRAC evaluated the adverse effects of fluoroquinolone and quinolone antibiotics. The review incorporated the views of patients, health-care professionals and academics presented at EMA's public hearing.

PRAC recommended that some medicines, including all those that contain a quinolone antibiotic (cinoxacin, flumequine, nalidixic acid and pipemidic acid), should be removed from the market as they are authorised for infections that should no longer be treated with quinolones. PRAC recommendations outlined situations in which the remaining fluoroquinolone antibiotics should not be used (e.g. to treat infections that might get better without treatment); and emphasized that fluoroquinolones should be used with caution in patients at risk (e.g. the elderly, patients with kidney problems and patients who have had an organ transplantation).

EMA's human medicines committee (CHMP) has endorsed the recommendations of PRAC.

Reference:
EMA, 5 October and 16 November 2018
(www.ema.europa.eu)

(See WHO Pharmaceuticals Newsletter No.4, 2018: Strengthened warnings on the risk of hypoglycaemia and mental health adverse effects in USA; No.2, 2017: Potential risk of persistent and disabling side effects in Canada; No.5, 2016: Disabling and potentially permanent adverse effects of the tendons, muscles, joints, nerves, and central nervous system in USA; No.3, 2016: Restricting use in USA; No.5, 2012: Tendon rupture and tendinitis associated with the use of quinolone antibiotics in New Zealand)

HMG-CoA reductase inhibitors and fibrates: co-administration

Risk of rhabdomyolysis: contraindication removed.

Japan. The Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA) have announced that the package inserts for hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins: atorvastatin (Lipitor®), simvastatin (Lipovas®), pitavastatin (Livalo®), pravastatin (Mevalotin®), fluvastatin (Lochol®), rosuvastatin (Crestor®), amlodipine basilate/atorvastatin (Caduet®) and ezetimibe/atorvastatin (Atozet®)) and fibrates (clinofibrate (Lipoclin®), clofibrate (Clofibrate®), fenofibrate (Tricor® and Lipidil®), bezafibrate (Bezatol®) and pemafibrate (Parmodia®)) should be revised to remove the contraindications regarding co-administration of HMG-CoA reductase inhibitors with fibrates.

HMG-CoA reductase inhibitors are indicated for hypercholesterolemia/familial hypercholesterolemia or hyperlipidaemia/familial hyperlipidaemia, whereas fibrates are indicated for hyperlipidaemia.

Available post marketing information concerning the co-administration of HMG-CoA reductase inhibitors and fibrates were investigated. There were limited data in patients with abnormal renal function and cases that reported the co-administration of these medicines were rare. There is a risk of rhabdomyolysis accompanied by rapid deterioration of renal function when HMG-CoA reductase inhibitors are co-administered with fibrates. If prescribing this combination is unavoidable, clinical laboratory

tests examining renal function should be performed periodically.

The PMDA concluded that the contraindication of combining HMG-CoA reductase inhibitors and fibrates should be removed from the package insert, however a precaution regarding rhabdomyolysis in patients with abnormal renal function values associated with this combination will remain.

Reference:
Revision of Precautions, MHLW/PMDA, 16 October 2018 *(www.pmda.go.jp/english/)*

(See WHO Pharmaceuticals Newsletter No.6, 2016: Risk of immune-mediated necrotizing myopathy in Japan; No.4, 2015: Risk of rhabdomyolysis by drug-drug interaction in Ireland)

Hydrochlorothiazide

Risk of non-melanoma skin cancer

United Kingdom. The Medicines and Healthcare Products Regulatory Agency (MHRA) has announced that the Summary of Product Characteristics and Patient Information Leaflets for hydrochlorothiazide containing products have been updated to include the risk of non-melanoma skin cancer as an adverse effect.

Hydrochlorothiazide is indicated for hypertension and oedema associated with cardiac or hepatic diseases.

Pharmacoepidemiological studies have shown a dose-dependent risk of non-melanoma skin cancer with exposure to increasing cumulative doses of hydrochlorothiazide.

Health-care professionals are advised to inform patients taking hydrochlorothiazide of the risk of non-melanoma skin cancer, particularly when used long-term, and advise them to report and check regularly for new or changed skin lesions or moles.

Patients are also advised to limit exposure to sunlight and UV rays, and use adequate protection to minimise the risk of skin cancer.

Reference:
Drug Safety Update, MHRA, 14 November 2018 *(www.gov.uk/drug-safety-update)*

Insulin-containing products: cartridges and pre-filled pens

Risk of medication errors from extraction of insulin

Ireland. The Health Products Regulatory Authority (HPRA) has updated the product information for insulin cartridges for reusable pens and prefilled (disposable) pens to include a warning on the risk of potential medication errors when extracting insulin, which could lead to serious hyper and/or hypoglycaemic episodes.

Insulin pens and cartridges for reusable pens are for single patient use only. Blood and biological matter can regurgitate into the insulin cartridge during injection. Re-using a cartridge or pen for another patient exposes the second patient to a risk of transmission of any blood borne pathogens.

The HPRA provided advice on actions to take if a device is not working and emphasized that extraction of insulin-containing product from cartridges and pre-filled pens via a syringe is not recommended.

Reference:
Drug Safety Newsletter, HPRA, November 2018 *(www.hpra.ie)*

Ketoconazole

Risk of severe liver injury and adrenal gland problems

Ghana. The Food and Drugs Authority in Ghana has suspended the registration, importation and manufacturing of oral ketoconazole products due to the risk of severe liver injury, adrenal gland problems and harmful drug interactions.

Ketoconazole is a synthetic antifungal agent available as a preparation for oral administration and as a cream or shampoo for topical application.

Risk minimization measures recommended by the Technical Advisory Committee on Safety of Medicines (TAC-SM) in 2013 were not effective in preventing the risk of liver related adverse drug reactions associated with the use of oral ketoconazole. The use of less harmful alternatives to oral ketoconazole (itraconazole, terbinafine and fluconazole) should be used in place of oral ketoconazole.

Reference:
Food and Drugs Authority, Ghana, 2 November 2018 *(https://fdaghana.gov.gh)*

(See WHO Pharmaceuticals Newsletter No.5, 2013: Potentially fatal liver injury, risk of drug interactions and adrenal gland problems in USA; Suspension of marketing authorisations for oral ketoconazole recommended in Europe; No.4, 2013: Risk of potentially fatal liver toxicity in Canada)

Lamotrigine

Risk of haemophagocytic syndrome

Japan. MHLW and PMDA have announced that the package insert for lamotrigine (Lamictal®) should be revised to include haemophagocytic syndrome as an adverse reaction.

Lamotrigine is indicated for several types of seizures in epileptic patients.

Cases of haemophagocytic syndrome have been reported in patients treated with lamotrigine in Japan and overseas. MHLW/PMDA concluded that revision of the package insert was necessary based on the results of their

investigation using currently available information.

Reference:
Revision of Precautions, MHLW/PMDA, 23 October 2018 *(www.pmda.go.jp/english/)*

(See WHO Pharmaceuticals Newsletter No.3, 2018: Serious immune system reaction in USA)

Lenvatinib

Risk of pneumothorax

Japan. MHLW and PMDA have announced that the package insert for lenvatinib (Lenvima®) should be revised to include pneumothorax as an adverse reaction.

Lenvatinib is indicated for unresectable thyroid cancer and unresectable hepatocellular carcinoma.

There was a total of 11 cases reporting pneumothorax in Japan during the last three fiscal years. In ten of the 11 cases, a causal relationship with lenvatinib could not be excluded. One of the 11 cases reported a fatality. MHLW/PMDA concluded that revision of the package insert was necessary based on the results of their investigation using currently available information.

Reference:
Revision of Precautions, MHLW/PMDA, 23 October 2018 *(www.pmda.go.jp/english/)*

Ponatinib

Risk of posterior reversible encephalopathy syndrome (PRES)

United Kingdom. The MHRA has updated the Summary of Product Characteristics and Patient Information Leaflet for ponatinib to include the risk of posterior reversible encephalopathy syndrome (PRES) as an adverse reaction.

PRES is a neurological disorder that can present with signs and symptoms such as seizure, headache, decreased alertness, vision loss and neurological disturbances.

Ponatinib is indicated for adult patients with chronic myeloid leukaemia or Philadelphia chromosome positive acute lymphoblastic leukaemia.

Five cases of posterior reversible encephalopathy syndrome (PRES) have been identified in patients receiving ponatinib (Iclusig®) in a routine EU review.

Health-care professionals are advised to interrupt treatment if PRES is confirmed and resume treatment only once the event is resolved and if the benefit of continuing treatment outweighs the risk of PRES.

Reference:
Drug Safety Update, MHRA, 11 October 2018 *(www.gov.uk/drug-safety-update)*

Ritonavir

Interaction with levothyroxine leading to reduced thyroxine levels

United Kingdom. The MHRA has updated Summaries of Product Characteristics and Patient Information Leaflets for ritonavir-containing medicines and levothyroxine to include a potential drug interaction which could lead to reduction in thyroxine levels.

An EU review identified reduced thyroxine levels in patients taking ritonavir-containing products and levothyroxine concomitantly.

Ritonavir is indicated in combination with other antiretroviral agents for the treatment of HIV infected patients, and for the treatment of chronic hepatitis C.

Health-care professionals are advised to monitor thyroid-stimulating hormone (TSH) in patients treated with levothyroxine for at least the first month after the start and end of ritonavir treatment.

Reference:
Drug Safety Update, MHRA, 11 October 2018 *(www.gov.uk/drug-safety-update)*

(See WHO Pharmaceuticals Newsletter No.1, 2017: Risk of adrenal suppression due to a pharmacokinetic interaction in UK; No.3, 2012: Drug Interactions with ritonavir-boosted Human Immunodeficiency Virus (HIV) protease inhibitor drugs in USA)

Secukinumab

Risk of inflammatory bowel disease

Japan. MHLW and PMDA have announced that the package insert for secukinumab (Cosentyx®) should be revised to include risk of inflammatory bowel disease as an adverse reaction.

Secukinumab is indicated for psoriasis vulgaris, psoriatic arthritis and pustular psoriasis in patients who were not sufficiently responsive to conventional therapies.

Cases of inflammatory bowel disease have been reported in patients treated with secukinumb in Japan. MHLW/PMDA concluded that revision of the package insert was necessary based on the results of their investigation of currently available information.

Reference:
Revision of Precautions, MHLW/PMDA, 23 October 2018 *(www.pmda.go.jp/english/)*

Zoster and Influenza vaccines

Possible risk of lichen planus or lichenoid drug eruption

New Zealand. Medsafe has placed zoster and influenza vaccines on the medicines monitoring scheme to obtain further information on the risk of lichen planus or lichenoid drug eruption.

Zoster vaccine (Zostavax®) is a live attenuated virus vaccine used to prevent herpes zoster (shingles). Annual influenza vaccination (Afluria Quad®, Fluarix Tetra®, FluQuadri® and Influvac Tetra®) is an important measure for preventing influenza infection and mortality. Patients can receive both vaccines at the same time using separate syringes and injection sites.

The potential safety signal was triggered by a report received by the Centre for Adverse Reaction Monitoring (CARM). The report describes a 67-year-old female patient who experienced a lichen planus rash after receiving both zoster and influenza vaccines.

The overall benefit-harm balance of zoster and influenza vaccines remains positive.

Reference:

Early Warning System – Monitoring Communication Medsafe, 26 October 2018 *(www.medsafe.govt.nz/)*

Daclizumab beta

Risk of immune-mediated encephalitis

United Kingdom. The MHRA has announced that monitoring for encephalitis should continue for 12 months following discontinuation of daclizumab (Zinbryta®).

Daclizumab is indicated to treat relapsing forms of multiple sclerosis.

In March 2018, the marketing authorisation for daclizumab beta was suspended and the medicine recalled from the EU market following reports of serious and potentially fatal immune reactions affecting the brain, liver and other organs.

As of 10 July 2018, seven cases of encephalitis have been reported after discontinuation of daclizumab; two of them were confirmed as anti-N-methyl-D-aspartate (NMDA) receptor encephalitis. The reported cases of anti-NMDA receptor encephalitis occurred around three to four months after discontinuation of daclizumab beta.

Clinicians are advised to watch any symptoms suggestive of autoimmune encephalitis and to inform all patients previously treated with daclizumab and their caregivers of possible presenting symptoms and provide advice on what to do if they occur.

It is important to be aware that many patients may not have typical autoimmune encephalitis antibodies, thus a clinical diagnosis may be necessary and not consistently supported by investigations.

Reference:
Drug Safety Update, MHRA, 25 September 2018 *(www.gov.uk/drug-safety-update)*

(See WHO Pharmaceuticals Newsletter No.4, 2018: Potential risk of immune reactions in Europe; No.2, 2018: Immediate suspension: risk of serious inflammatory brain disorders in Europe)

Dolutegravir

Risk of neural tube defects

Europe. The EMA has announced that PRAC confirmed its precautionary advice issued earlier this year on the use of dolutegravir in pregnant women and women who can become pregnant.

Women who can become pregnant should use effective contraception while taking dolutegravir. Additionally, women should undergo a pregnancy test before starting treatment and the medicine should not be used during the first trimester of pregnancy unless there is no alternative.

Dolutegravir is an antiretroviral medicine used in combination with other antiretroviral medicines to treat human immunodeficiency virus (HIV).

The evaluation assessed preliminary results from a study that found cases of neural tube defects in babies born to mothers who used dolutegravir during pregnancy.

Reference:
EMA, 5 October 2018 *(www.ema.europa.eu)*

Also, WHO issued a follow on statement to the one that was issued on 18 May 2018 on dolutegravir.

Reference:
Full List of WHO Medical Product Alerts, WHO, October 2018 *(http://www.who.int/medicines/publications/drugalerts/DTG_followon_may2018.pdf?ua=1)*

(See WHO Pharmaceuticals Newsletter No. 5, 2018: Possible risk of neural tube defects in New Zealand and in Europe; No.4, 2018: Potential risk of neural tube birth defects in USA and in Europe)

Fentanyl (transdermal patches)

Life-threatening and fatal opioid toxicity from accidental exposure

United Kingdom. The MHRA has reminded health-care professionals to give clear information to patients and caregivers about how to minimise the risk of accidental exposure to fentanyl patches, particularly in children, and the importance of appropriate storage and disposal of patches.

Fentanyl is a potent opioid analgesic and its overdose could cause: respiratory depression; tiredness; extreme sleepiness or sedation; inability to think, walk, or talk normally; and feeling faint, dizzy or confused.

Despite issuing advice to health-care professionals in 2014, the MHRA continue to receive reports of unintentional opioid toxicity and overdose of fentanyl due to accidental exposure to patches. Since July 2014, five reports of fatal incidents specifying accidental exposure, accidental overdose, or product adhesion issues were received.

Accidental exposure to transdermal fentanyl can occur if a patch is swallowed or transferred to another individual. Fentanyl patches should be stored out of sight and reach of children.

Reference:
Drug Safety Update, MHRA, 11 October 2018 *(www.gov.uk/drug-safety-update)*

(See WHO Pharmaceuticals Newsletter No.4, 2014: Reminder of potential life-threatening harm from accidental exposure, particularly in children; No.6, 2013: Packaging changes to minimize risk of accidental exposure in USA)

Fluoroquinolones

Potential risk of aortic aneurysm and dissection

United Kingdom. The MHRA has announced that fluoroquinolones should only be used after careful assessment of benefits and risks, and after consideration of other therapeutic options in patients at risk for aortic aneurysm and dissection.

Fluoroquinolones are antibiotics authorized for serious, life-threatening bacterial infections and four of them (ciprofloxacin, levofloxacin, moxifloxacin and ofloxacin) are available in UK.

Data from epidemiologic and non-clinical studies indicate an increased risk of aortic aneurysm and dissection after intake of fluoroquinolones.

Health-care professionals are advised to inform patients, particularly those at risk (e.g. elderly), about rare events of aortic aneurysm and dissection. It is important that patients seek immediate medical attention in case of sudden-onset severe abdominal, chest or back pain.

Reference:
Drug Safety Update, MHRA, 14 November 2018 *(www.gov.uk/drug-safety-update)*

Nusinersen

Potential risk of communicating hydrocephalus

United Kingdom. The MHRA has announced that five international cases of communicating hydrocephalus have been reported during routine clinical use of nusinersen (Spinraza®). Of the five cases, four were children and one was an adult.

Nusinersen is an antisense oligonucleotide indicated for the treatment of 5q spinal muscular atrophy.

There is no known association between spinal muscular atrophy and communicating hydrocephalus, and investigations did not reveal an underlying cause such as intracranial haemorrhage or infection.

The MHRA encourages health-care professionals to advise patients to seek urgent medical attention if any possible symptoms or signs develop including: persistent vomiting or headache, decreased consciousness, or a rapid increase of head size in children.

Reference:
Drug Safety Update, MHRA, 25 September 2018 *(www.gov.uk/drug-safety-update)*

Rivaroxaban

Increase in all-cause mortality

United Kingdom. The MHRA has announced that rivaroxaban (Xarelto®) treatment in patients who undergo transcatheter aortic valve replacement (TAVR) should be stopped and the patient should be switched to standard care.

Rivaroxaban is indicated for the prevention of venous thromboembolism and treatment of deep vein thrombosis.

Preliminary analysis of a phase three trial shows that risks of all-cause death and bleeding post-TAVR were approximately doubled in patients assigned to a rivaroxaban-based anticoagulation strategy compared with those assigned to receive an antiplatelet-based strategy (clopidogrel and aspirin).

Reference:
Drug Safety Update, MHRA, 11 October 2018 *(www.gov.uk/drug-safety-update)*

Ruxolitinib

Limited evidence of interaction with P-glycoprotein substrates

Canada. Health Canada has announced that its review of available information did not establish a link between the use of ruxolitinib (Jakavi®) and the risk of interactions with P-glycoprotein substrates.

Ruxolitinib is indicated for enlarged spleen and symptoms caused by myelofibrosis, a rare form of blood cancer.

Health Canada received one Canadian report of increased blood cholesterol due to a potential interaction between ruxolitinib and rosuvastatin, which is a drug that is transported by P-glycoprotein. The review also looked at two articles that did not suggest an interaction between ruxolitinib and other drugs that are known to be transported by P-glycoprotein (e.g. digoxin, dabigatran and cyclosporine).

Available evidence at the time of review suggested that an interaction between ruxolitinib and rosuvastatin was unlikely because ruxolitinib did not appear to inhibit P-glycoprotein at doses typically used in patient treatment.

Reference:
Summary Safety Review, Health Canada, 9 October 2018 *(www.hc-sc.gc.ca)*

Sildenafil

Risk of persistent pulmonary hypertension of the newborn (PPHN)

United Kingdom. The MHRA has announced that a clinical trial, which was investigating the use of sildenafil (Revatio® and Viagra®) in pregnancy for intrauterine growth restriction, has been prematurely discontinued due to a higher incidence of persistent pulmonary hypertension of the newborn (PPHN) and neonatal

mortality in the sildenafil arm of the study.

Sildenafil (Revatio®) is indicated for the treatment of adults and children with pulmonary arterial hypertension (PAH), but not recommended in pregnancy. Sildenafil (Viagra®) is also used in the treatment of men with erectile dysfunction, and is not authorised for use in women.

The benefit-risk balance of sildenafil in the authorized indication of pulmonary artery hypertension remains unchanged for pregnant women. However, this will be kept under review as further data emerge.

Reference:

Drug Safety Update, MHRA, 14 November 2018 *(www.gov.uk/drug-safety-update)*

(See WHO Pharmaceuticals Newsletter No.3, 2014: Clarification on warning about paediatric use for pulmonary arterial hypertension in USA; No.5, 2012: Recommendation against use in children for pulmonary arterial hypertension (PAH) in USA)

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 18 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. Signals are first communicated to National Pharmacovigilance Centres through SIGNAL (a restricted document from UMC), before being published in this Newsletter. Signal texts from UMC might be edited to some extent by WHO and may differ from the original version.
More information regarding the ICSRs, their limitations and proper use, is provided in the UMC Caveat document available at the end of Signal (page 31). 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, 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.

Aflibercept and deep vein thrombosis/pulmonary embolism

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Summary

A novel approach to signal detection screening was recently investigated at UMC. Designed to be sensitive to disproportionality between sub-populations, the screening highlighted a significant increased reporting of deep vein thrombosis with the use of aflibercept in males compared to females.

Aflibercept is an antagonist of VEGF (vascular endothelial growth factor) receptors and through this mechanism inhibits angiogenesis or the growth of new blood vessels. Aflibercept is used in the treatment of a number of ocular conditions with an ocular preparation called Eylea and in the treatment of metastatic colorectal cancer with an intravenous preparation called Zaltrap.

Clinical assessment of the combination of aflibercept and deep vein thrombosis included review of deep vein thrombosis and pulmonary embolism in both indications of use for aflibercept as well as a closer investigation of potential gender related factors which could support a hypothesis of an increased risk for these events in men.

Introduction

Aflibercept is a recombinant protein consisting of specific domains of two human VEGF (vascular endothelial growth factor) receptors, VEGF-R1 and VEGF-R2, fused to an immunoglobulin G1 Fc. It acts as an antagonist that binds and inactivates circulating VEGF and placental growth factor 1; through this mechanism, it inhibits angiogenesis or the growth of new blood vessels. Under the trade name Eylea, aflibercept is licensed for use in a number of ocular conditions, including neovascular (wet) age-related macular degeneration (AMD), macular oedema secondary to retinal vein occlusion (branch RVO or central RVO), diabetic macular oedema (DME), and myopic choroidal neovascularisation.[1] Under the trade name Zaltrap, it is licensed for use against metastatic colorectal cancer (MCRC) that is resistant to or has progressed after an oxaliplatin-containing regimen in combination with irinotecan/5-fluorouracil/folinic acid (FOLFIRI) chemotherapy.[2]

Deep venous thrombosis (DVT) is the formation of a blood clot, or thrombus, in one of the deep veins of the body, most commonly in veins of the lower extremities. The mechanism of thrombus formation typically involves a combination of decreased blood flow, injury to the blood vessel wall (endothelium), and an increased tendency to clot. The annual incidence of DVT in the USA has been estimated to be 80 cases per 100,000. Of the more than 200,000 people that develop venous thrombosis in that country each year, 50,000 cases are complicated by pulmonary embolism.[3] Deep venous thrombosis usually affects individuals older than 40 years, with increasing incidence with age.

Arterial and venous thromboembolic events are both included in the product label for aflibercept for its use in the cancer indication. In the label for its use in ocular indications, only a theoretical risk of arterial thromboembolic events is mentioned.[1,2]

The mechanism for thromboembolic events by VEGF inhibitors is probably multifactorial, given the number of effects VEGF has on vascular walls and the coagulation system.[4] Inhibition of circulating VEGF may diminish the ability of the endothelial cells in the vascular wall to regenerate, thereby allowing any defects that expose pro-coagulant phospholipids on the luminal plasma membrane or underlying matrix to lead to thrombosis or haemorrhage.[5] Furthermore, inhibition of the VEGF decreases production of NO and prostacyclin (PGI_2, prostaglandin I_2) which can predispose to thromboembolic events.[6] Finally, an overproduction of erythropoietin caused by vascular endothelial growth factor inhibition may also increase risk of thrombosis by increasing haematocrit and blood viscosity.[7-8]

This signal assessment aims to present evidence that support two hypotheses regarding the association between aflibercept and deep venous thrombosis / pulmonary embolism: 1) male gender may be a potential risk group for deep venous thrombosis / pulmonary embolism with the use of aflibercept, 2) intravitreal use can have systemic effects.

Reports in VigiBase

The analysis was performed on all reports included in VigiBase, the WHO global database of individual case safety reports (ICSRs), on 31 December 2017.

In a signal detection exercise designed to identify drug-ADR pairs with statistically significant increases in disproportionality only within subgroups, the combination of aflibercept – deep vein thrombosis was found to be disproportionately reported in males compared to females. Upon further investigation, this gender difference was also seen for the combination of aflibercept-pulmonary embolism.

There was a total of 8,711 individual case safety reports for the substance aflibercept in VigiBase. Thirty-one aflibercept ICSRs reported the PT deep vein thrombosis. Nineteen were male, nine were female and three reports had no gender reported. Twenty-three reports were serious, three were non-serious and five reports had no seriousness reported. Countries from which the reports originated were the USA (6), Germany (5), Sweden (2), Spain (4), Hungary (2), Italy (2), Greece (1), Cyprus (1), Australia (5) and Japan (3). The ages ranged from 44 to 89 years. The drug-ADR combination of aflibercept - deep vein thrombosis had an overall measure of disproportionality, IC_{025} - 0.38. However, for females the IC_{005} is -2.15 while for males it is 0.21.

Sixty aflibercept ICSRs reported the PT pulmonary embolism. Thirty-three were male, 21 were female and six reports had no gender reported. Fifty-seven reports were serious, and three reports had no seriousness reported. Countries from which the reports originated were the USA (9), Germany (15), the UK (6), Sweden (5), Spain (4), Italy (6), Czech Republic (2), Belgium (2), Switzerland (2), Finland (1), France (1), Hungary (1), Greece (1), Slovakia (1), Australia (3) and Japan (1). The age ranged from 25 to 92 years. The same pattern was observed for the drug-ADR combination of aflibercept - pulmonary embolism. The overall IC_{025} was 0.38, IC_{005} -0.55 for females and 1.02 for males.

Posology and Pharmacokinetics of Aflibercept

In the ocular indications, aflibercept is administered intravitreally as a 2 mg dose, to be repeated every month for three consecutive months, followed by every other month. In the cancer indications, it is administered intravenously 4 mg per kg of body weight prior to each FOLFIRI treatment cycle (every 2 weeks).[1,2]

Free aflibercept is primarily cleared by binding to endogenous VEGF to form a stable, inactive complex. Free aflibercept exhibits a faster (non-linear) clearance at doses below 2 mg/kg, likely due to the high affinity binding of aflibercept to endogenous VEGF. At higher doses, linear clearance is observed, probably due to non-saturable biological mechanisms of elimination such as protein catabolism; at such doses, free aflibercept clearance was measured to be approximately 1.0 L/day with a terminal half-life of six days.[2]

Male gender as a potential risk group

The increased disproportionality of the ADRs of deep vein thrombosis and pulmonary embolism in males compared to females suggests that male gender may be a potential risk group for thromboembolic disease caused by aflibercept. There are conflicting results from epidemiological studies regarding gender-specific baseline risk for DVT [3,9-10]. In the most recent publication on this topic, an increased risk in men was estimated, and the authors note that "…the pathophysiology behind these observations has yet to be unravelled" and "… this risk difference may have implications for future sex- specific treatment and prevention strategies for venous thrombosis." [9]

There was a total of 46 reports of DVT and/or PE for aflibercept in males compared to 28 reports in

females. 67% (31) of the male reports were between the ages of 45 to 74. Sixty four percent (18) of the female reports were 65 years and older. Reports were distributed between the Americas, Europe and Oceania for both genders; Asia had reports only for males (four reports). When product trade name was available, males had a greater proportion of reports for Zaltrap (cancer indication) at 38% compared to Eylea (ocular indications) at 26%; females had a greater proportion of reports for Eylea at 41% compared to Zaltrap at 28%. The most commonly reported concomitant medications were the same for both genders: 5-fluorouracil, folinic acid, and irinotecan; all other concomitant drugs were reported in 15% or less of the reports.

Alternative explanations for the disproportional increase in males have been considered. First, this increase could be a "statistical artefact", given the large proportion of reports of DVT in VigiBase with oral contraceptive agents in females. Calculations were therefore made restricting the database to reports from patients aged 45 and above; the increased disproportionality of these events with aflibercept in males remained. Second, this increase could be a reflection of the overall increased baseline risk for DVT in males. However, this baseline increased risk is not reflected in VigiBase data, as there are increased numbers of reports for DVT in females in all age groups, although the difference is smallest in the age group 65 to 74 years (51.2% in females, 47.6% males). Third, a review of the case series did not reveal evidence of an obvious cause for the gender disparity. Two of the most important risk factors for DVT/PE are cancer and advanced age, the former of which was recorded in a greater proportion of males, the latter in a greater proportion of females.

The EU labelling for aflibercept notes that gender was found to be a significant covariate for explaining the inter-individual variability of free aflibercept clearance and volume. Males exhibited a 15.5% higher clearance and a 20.6% higher volume of distribution compared to females. However, these differences were considered not to effect exposure due to weight-based dosing, and therefore, no dose modifications based on gender were recommended. Furthermore, within a review of clinical trial data supplied to the US FDA, an exploratory subgroup analysis in a Phase 3 study (VIEW2) was identified which did not reveal any clinically relevant influence of gender on the plasma concentrations of free aflibercept or aflibercept:VEGF complex.[11]

However, in a literature review, a number of publications were found which describe a gender influence on circulating levels of VEGF. Experimental studies suggest that estrogen may regulate VEGF gene expression and thereby may influence circulating VEGF levels.[12-15] Furthermore, there is evidence that females have higher serum VEGF levels than males at all stages of life, including post menopause.[16] The overall hypothesis therefore is that females may be at less risk for thromboembolic events with aflibercept therapy as there remains a greater fraction of un-antagonised VEGF during aflibercept therapy.

Systemic effects of intravitreal aflibercept

Within the total of 91 reports for aflibercept and DVT and/or PE, 23 noted the intravitreal formulation for use in ocular indications. Disproportionality analysis at the indication level did not reveal a statistical signal for DVT with aflibercept. However, clinical review of the case series, as well as a review of the literature, support the potential for a causal association.

Ten reports concerned males, 13 females. The ages ranged from 53 to 92; no age was provided in three reports. Time to onset was provided in 16 reports and ranged from days up to 13 months.

Arguments against a causal association with aflibercept could be the increased baseline risk in the specific population receiving this drug for this indication: elderly persons with a potentially largely sedentary lifestyle secondary to visual difficulties. However, the cases included in the case series demonstrate geographical spread and consistency in aflibercept being the single suspected agent even months after initial administration.

The product labelling of aflibercept presents data on the pharmacokinetics of intravitreal administration. With a dose of 2 mg per eye, the mean plasma Cmax was 0.02 mcg/mL which was reached within 1 to 3 days, while the aflibercept:VEGF complex concentrations reach a Cmax of 0.186 mcg/mL within 14 to 28 days of a 2 mg dose. Aflibercept did not accumulate in the plasma with repeated intravitreal dosing every 4 weeks.[1] For comparison, the dosing used in the cancer indication (4 mg/kg every 2 weeks) results in an excess of circulating free aflibercept compared to VEGF-bound aflibercept, and that steady states levels of free aflibercept concentration are reached by the second cycle.[2] Based on these results, the risk for systemic adverse events, such as arterial and venous thromboembolism, has been estimated to be low.[1]

Multiple publications since the time of licensure, however, suggest that systemic exposure of aflibercept after intravitreal use of aflibercept is

not theoretical. Studies have examined VEGF serum levels following intravitreal anti-VEGF injection and have reported longer duration and more VEGF suppression in the serum after aflibercept compared to another anti-VEGF agent, ranibizumab.[17-19] A more recent publication using radiolabelled anti-VEGF agents in non-human primates to investigate intravitreal pharmacokinetic properties and systemic biodistribution revealed aflibercept to have an intravitreal half-life of 2.44 days and to be detectable throughout the body until day 21.[20]

A signal of higher systemic exposure after intravitreal injection of aflibercept compared to ranibizumab was identified by the EMA in October 2014. The Pharmacovigilance Risk Assessment Committee (PRAC) noted that, during the clinical development for the intravitreal preparation of aflibercept, concerns were raised on its potential role in the development of systemic arterial thromboembolic events, especially cerebrovascular events and transient ischemic attack (TIA). At the time of licensure, MAH had committed in their Risk Management Plan to conduct a post-authorisation study addressing this risk.[21] Although the PRAC initially agreed that the signal should be further investigated, minutes from a PRAC meeting in November 2015 note that, after analysis of data by the MAH, there remained no clinically relevant safety signal and the originally planned PASS study, (Long-term Investigation and Risk Benefit analysis of the Real-life utilisation of Aflibercept in macular disease, or LIBRA), was no longer required.[22]

In contrast to the EMA decision, Avery argues in his paper "What is the evidence for systemic effects of intravitreal anti-AGEF agents, and should we be concerned?" that because numerous studies show reduced systemic VEGF levels after intravitreal injections and individual trials were underpowered to detect statistically significant differences, analyses of large populations will be critical to identify if there is a systemic risk to these intravitreal agents. Also, he emphasized the importance of identification of vulnerable subgroups: "There may be subsets of patients…who may be at increased risk after intravitreal anti-VEGF injection, but further studies are required to evaluate this potential risk."[23]

As further support to this hypothesis, the authors of Prescrire recently issued a review of published meta-analyses and concluded that there is probably a two-fold increased risk of arterial or venous thrombosis with use of intravitreal anti-VEGF administration.[24]

Conclusion

Within this signal assessment we have used statistical signal detection methodology to prioritise sub-populations at potential risk for further review. Clinical assessment of the cases, pharmacokinetic data, as well as published literature support hypotheses that patients receiving aflibercept in the intravitreal indication, as well as patients who are men are at increased risk of deep vein thrombosis and pulmonary embolism. We hope that further development of such methodologies and identification of signals such as these usher in a new era of "precision pharmacovigilance" with a goal to achieve more finely tuned benefit/risk assessments at the level of the individual patient.

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Table 1. Case reports of deep vein thrombosis and/or pulmonary embolism in association with intravitreal use of aflibercept in VigiBase.

Case	Age/Sex	Medications	Reactions	Time to onset	Notes	Outcome
Intravitreal use						
1	71 y/M	Aflibercept (S) Amlodipine (C) Candesartan (C) Fenofibrate (C) Unknown medication for hyperuricemia	Deep vein thrombosis leg Pulmonary thrombosis	5 months from first dose	Received a total of 4 doses	Recovered
2	74 y/M	Aflibercept (S) Finasteride (C) Atorvastatin(C)	Deep vein thrombosis leg	7 months	Received a total of 4 doses. Treated with Fragmin and then Xarelto	Unknown
3	72 y/M	Aflibercept (S)	Pulmonary embolism Deep vein thrombosis	6 months (4 total doses given)		Recovered
4	74 y/M	Aflibercept (S)	Deep vein thrombosis		Spontaneous report	Not recovered

Case	Age/Sex	Medications	Reactions	Time to onset	Notes	Outcome
Intravitreal use						
5	70 y/M	Aflibercept (S)	Deep vein thrombosis	13 months		Not recovered
6	78 y/M	Aflibercept (S) Allopurinol (C) Eicosapentaenoic acid (C) Pravastatin (C) Candesartan (C) Rabeprazole (C)	Pulmonary embolism Deep vein thrombosis leg	8 months after the first dose, 1 month after the last dose.	Spontaneous report. Received a total of 5 doses	Recovering
7	53 y/M	Aflibercept (S) Perindopril (C Doxazosin (C) Furosemide (C) Empagliflozin (C) Potassium (C) Allopurinol (C) Nebivolol (C) Simvastatin (C)	Pulmonary embolism	13 months after first dose. 2 months after last dose.	Spontaneous report. Received a total of 4 doses. Placed on long term anticoagulant therapy.	Recovered
8	-/M	Aflibercept (S)	Pulmonary embolism		Spontaneous report.	Unknown
9	78 y/M	Aflibercept (S)	Pulmonary embolism	5 months since initiation of Aflibercept.	Spontaneous report. Had been treated with anti-VEGF agents since 2013. Previously with Avastin. Discontinued treatment	Unknown
10	90 y/M	Aflibercept (S)	Pulmonary embolism	11 months	Spontaneous report. Treated with warfarin.	Unknown
11	78 y/F	Aflibercept (S) Levothyroxine (C) Zolpidem (C) Metoprolol (C) Tiotropium (C) Atorvastatin (C)	Pulmonary embolism Difficulty breathing Air hunger	Within days of first dose of aflibercept. Had received 8 doses of ranibizumab prior.	Spontaneous report.	Recovered
12	75 y/F	Aflibercept (S) Ranibizumab (S) Acetylsalicylic acid (C) Candesartan / Hydrochlorothiazine (C) Levothyroxine (C)	Pulmonary embolism	2 months after first dose aflibercept. Had received ranibizumab for 3 years prior.	Spontaneous report.	Recovering
13	92 y/F	Aflibercept (S)	Embolism pulmonary	20 days	Spontaneous report.	Unknown
14	75 y/F	Aflibercept (S)	Acute massive pulmonary embolism Chest pain Dyspnoea exertional Hypertension Hyperventilation Lividity (R leg) Nails cyanosed Pain NOS Tachycardia Uncontrolled hypertension	1 month after last dose. Received at least 3 doses.	Spontaneous report. Sonography of carotid, subclavian and coronary vessels with only evidence of mild stenosis.	Died
15	-/F	Aflibercept (S)	Deep vein thrombosis Diabetes mellitus inadequate control Headache		Spontaneous report.	Unknown
16	-/F	Aflibercept (S)	Pulmonary embolism		Spontaneous report.	Unknown
17	87 y/F	Aflibercept (S)	Pulmonary embolism	12 months	Spontaneous	Recovered

Case	Age/Sex	Medications	Reactions	Time to onset	Notes	Outcome
Intravitreal use						
		Lactulose (C) Calcium carbonate / Colecalciferol (C) Folic acid (C) Isosorbide mononitrate (C) Bisoprolol (C) Levothyroxine (C) Citalopram (C) Formoterol (C) Budesonide (C) Buprenorphine (C) Glyceryl trinitrate (C) Heparinoid (C) Paracetamol (C) Zolpidem (C) Terbutaline (C) Hypromellose (C)			report.	with sequelae.
18	82 y/F	Aflibercept (S)	Pulmonary embolism		Spontaneous report.	Recovered
19	86 y/F	Aflibercept (S) Pravachol (C) Thyroid medication (C)	Pulmonary embolism Photosensitivity reaction Eye pain Corneal erosion		Spontaneous report.	
20	89 y/F	Aflibercept (S)	Deep vein thrombosis		Spontaneous report.	Not converted
21	73 y/F	Aflibercept (S)	Deep vein thrombosis Thrombophlebitis superficial		Spontaneous report.	
22	83 y/F	Aflibercept (S) Candsartan (C) Simvastatin (C) Acetylsalicylic acid (C) Alendronic acid; colecalciferol (C) Doxepin (C) Cyanocobalamin; Folic acid; pyridoxine (C) Estradiol (C) Glyceryl trinitrate (C) Paracetamol (C)	Pulmonary embolism	27 days	Spontaneous report.	Not recovered
23	72 y/F	Aflibercept (S) Ranibizumab (S)	Popliteal vein thrombosis	23 days after dose of aflibercept. Had received ranibuzimab in past, last dose 14 months prior	Spontaneous report.	Unknown

Response from Bayer on the intravitreal formulation of aflibercept (Eylea®)

Sanofi was invited to comment on the intravenous formulation of aflibercept with systemic effect but declined the invitation. Thus, the following text, submitted by Bayer, only addresses the intravitreal formulation

To date, venous thromboembolic events (VTEs) including deep vein thrombosis (DVT) and pulmonary embolism (PE) have not been established as an identified risk with local intravitreal (IVT) use of 2mg aflibercept (Eylea®) in ophthalmologic indications.[1] VTEs have been associated and are considered an identified risk with systemically administered anti-VEGFs with significantly higher systemic exposure for cancer treatment, including intravenously administered ziv-aflibercept (Zaltrap®, dosed with 4mg/kg BW). The systemic exposure of pharmacologically active aflibercept is 3000-fold lower after the intravitreal ophthalmic injection of 2mg aflibercept than after the systemic oncological intravenous administration of 4 mg/kg ziv-aflibercept.

The Uppsala Monitoring Center (UMC) describes about an increased disproportionality for events of deep vein thrombosis and pulmonary embolism in

males compared to females with the use of aflibercept across indications and routes of administration, hypothesizing that male gender may be a potential risk factor for venous thromboembolic events associated with aflibercept. Disproportionality analysis performed by UMC, for the ophthalmologic indications did, however, not reveal a statistically significant finding. Thus there is no support for a signal with use of intravitreal aflibercept. In 23 UMC reports on ophthalmologic aflibercept on DVT and PE, no male predominance was observed (10 male, 13 female). This is inconsistent with their hypothesis of males being a risk group. Furthermore, a cumulative review of worldwide post-marketing IVT aflibercept case reports in the Global Pharmacovigilance Safety Database of the Marketing Authorization Holders (MAHs) of Eylea® (Bayer AG and Regeneron Pharmaceuticals, Inc.) has shown that no predominance of males is observed in post-marketing cases with VTEs.[2]

UMC cited a paper published by Avery et al[3] in support of potential remaining uncertainties with respect to a systemic signal due to plasma VEGF suppression. The EMA's Pharmacovigilance Risk Assessment Committee (PRAC) has previously refuted that a clinically relevant safety signal was present based on a comprehensive scientific evaluation of published studies, including the Avery et al paper. Aflibercept is systemically available in two distinct forms: The "free" form of aflibercept is the active drug moiety. Free aflibercept binds endogenous VEGF to form a stable, inert VEGF:aflibercept complex (referred to as bound aflibercept), that is incapable of further VEGF binding and is thus biologically inactive. After IVT administration, aflibercept is slowly absorbed from the eye into the systemic circulation, where it is predominately observed in its bound form, i.e. as the inactive, stable complex with VEGF. The sum of both, free and bound, aflibercept is referred to as total aflibercept. Aflibercept concentrations reported by Avery et al.[3] reflect total aflibercept concentrations and therefore largely represent the biologically inactive, bound form of aflibercept. Furthermore, a role for VEGF plasma/serum level modulation as a marker with implications for systemic safety remains highly questionable since the physiological role of the localized acting VEGF in the plasma/serum is unclear and no confirmed link to any untoward affects has been shown. The small amounts of systemic VEGF complexed after IVT administration of 2 mg aflibercept are insufficient to cause a systemic bio-effect as measured by blood pressure changes, which is believed to be a sensitive, robust, and leading indicator of systemic VEGF inhibition. Moreover, assays used to quantify VEGF levels and anti-VEGF levels in plasma/serum reported by these authors were not validated. In contrast it was experimentally shown that the presence of an anti-VEGF compound in the plasma sample interferes with the VEGF quantitation in the assay used resulting in unreliable results.[4] This lack of validation is corroborated by the fact that none of the reported adverse events discussed within these publications can be attributed directly to the neutralization of VEGF in plasma or serum. This is fully consistent with the observations in the pivotal Phase III program of aflibercept across all ophthalmologic indications. Thus, none of these publications provide evidence for any clinical systemic safety signal. I.e. no correlation of the reported findings with systemic adverse events was provided and thus the reported disproportionality across indications and routes of administration are considered of no concern for intravitreal use of aflibercept.

In conclusion, VTEs are not an identified risk for aflibercept used intravitreally for ophthalmologic indications. No disproportionality or male predominance was detected by UMC in cases with aflibercept in ophthalmologic indications. Cumulative review of VTEs in the MAHs Global Safety Database does not suggest a causal association of VTEs and intravitreal aflibercept and no predominance of males is observed in post-marketing cases with VTEs. The safety observation of suggested higher risk of DVTs and PE in males can be refuted for aflibercept intravitreal (IVT) use in its ophthalmologic indications.

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Brivudine and 5-fluorouracil – Persistence of a fatal drug-drug interaction

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Introduction

Herpes zoster (shingles) is a viral disease often presenting as painful rashes primarily affecting the elderly population. It is caused by the reactivation of latent Varicella Zoster Virus (VZV) usually decades after a primary varicella infection. Shingles is the result of reactivated VZV spreading into the corresponding dermatome and neural tissue, forming a unilateral maculopapular rash, with or without vesicles or lesions. The acute neuritis produced by herpes zoster is painful and associated with symptoms such as unusual aching, burning or stabbing pain, itching or tingling. Painful symptoms can be experienced anywhere during the spread of VZV, from before the appearance of a rash to well after vesicular eruption and healing. Post-herpetic neuralgia (PHN) is a syndrome of chronic pain persisting after the resolution of a shingles rash. This chronic pain is debilitating; it can affect quality of life and lead to psychological distress. Elderly patients with advanced cancer and on immunotherapy are at significantly higher risk of shingles. Herpes zoster is generally a self-limited disease. However, systemic antiviral therapy is indicated in patients aged 50 and above, for/with immunodeficiency, malignant primary disease, and in patients with involvement of cranial nerves; prevention and/or reduction of PHN is the focus of therapeutic intervention.[1,2]

Brivudine is a nucleoside analogue used in the treatment of herpes zoster, for which it is approved in a number of EU countries. Brivudine owes its effect to preferential phosphorylation by VZV encoded tyrosine kinase (TK) to its 5'-diphosphate form. After further conversion to triphosphate form, it acts as an inhibitor or alternate substrate for the viral DNA polymerase. It has a terminal half-life of 16 hours, and is degraded to its base form, bromovinyl uracil (BVU), by thymidine phosphorylase.[3] Brivudine is also characterized by a well described fatal drug interaction with a commonly prescribed antitumour drug, 5-fluorouracil (5-FU). This drug interaction and possible mechanisms of action have been described well for many years in medical literature.[4-9]

In a recent screening of VigiBase, the WHO global database of ICSRs focusing on medication errors, brivudine was highlighted with the MedDRA preferred term "drug-drug interaction medication error". An alarming number of cases had fatal outcomes and the most recent case was from 2017. The purpose of this communication is to highlight the continued appearance of fatal cases due to medication error with use of brivudine and 5-FU.

Reports in VigiBase

The medication error focused screening of VigiBase highlighted a series of 30 reports from Germany (15), Spain (11), Italy (2), Austria (1), and Switzerland (1) reporting brivudine with MedDRA terms within the SMQ Medication Errors. Of particular interest were 22 reports in which a drug-drug interaction was described between brivudine and 5-FU (8 reports) or its prodrug, capecitabine (14 reports); 15 of which resulted in death. Cases of this interaction were first received into VigiBase in 2008 (4 reports, 3 of which were fatal); the most recent was in 2017 (4 reports, 3 fatal).

A number of example cases illustrate how the medication error by using brivudine and 5-FU together can occur:

Case 1: An elderly patient was given a 6-day treatment of brivudine for shingles. Three days later, brivudine treatment was ended, and the patient was administered a 5-FU bolus to manage his colon cancer. Five days later the patient was hospitalised for severe mucositis and developed severe bone marrow aplasia. He died soon after on an unspecified date.

Case 2: A patient on long-term capecitabine (Xeloda) treatment for breast cancer who developed herpes zoster while on vacation abroad. The local treating physician prescribed brivudine and the patient took both medications together. After returning to her home country she presented to the hospital feeling generally unwell. She was hospitalized and eventually developed massive mucositis with ulcers in the mouth and throat region. The report does not state the outcome.

Case 3: A patient was prescribed three cycles of 5-FU treatment following surgery for colon cancer. After the second cycle the patient developed shingles and the treating dermatologist prescribed brivudine (Nervinex). Three days after completing the 7-day course of brivudine, the final cycle of 5-FU was administered; two days later the patient presented feeling very tired and generally unwell. The patient was hospitalised, blood tests showed severe pancytopenia, and 10 days later the patient died.

Case 4: A patient was prescribed brivudine (Zostex) only during pauses in her treatment of capecitabine (Xeloda), which she kept at home and would use often because of frequent herpes simplex infections from massive herpes labialis. The patient started treatment with capecitabine in March and the treatment cycle ended on 22 March. During a treatment pause of seven days, the patient started treatment with brivudine, on

27 March. On 28 March, brivudine was discontinued, and the patient started the next treatment cycle with capecitabine two days later. On 1 April, the patient started treatment with brivudine. On 2 April, she stopped the treatment with brivudine, after an intake of two tablets. On 5 April, capecitabine was withdrawn, the patient was hospitalised and eventually died due to bone marrow depression.

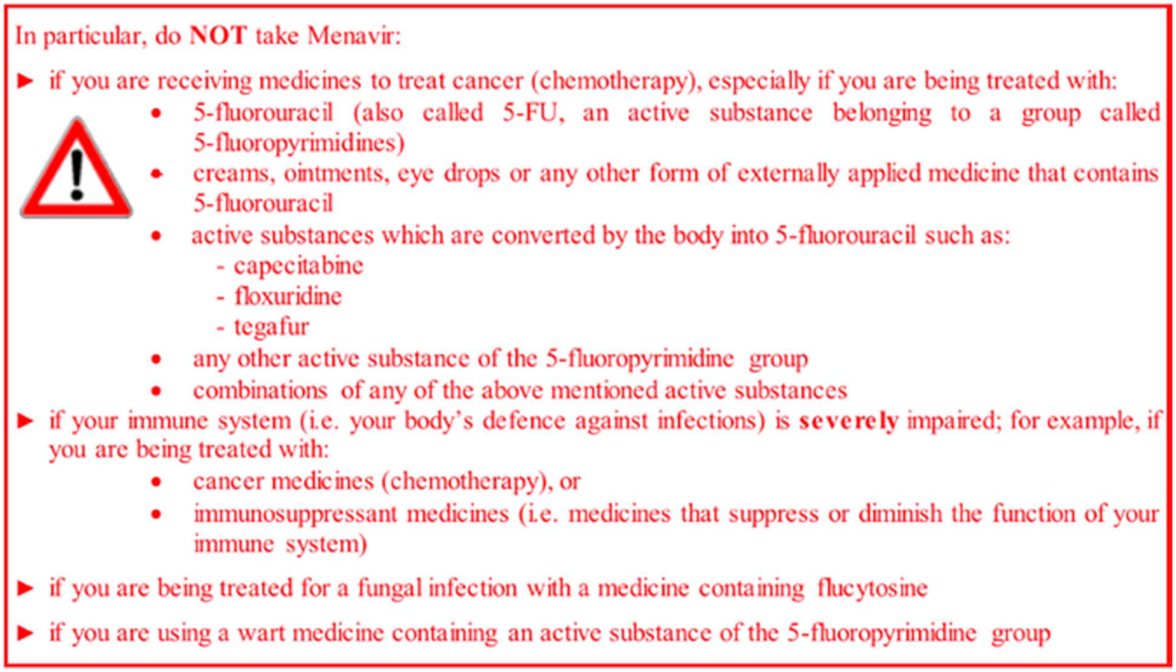
Labelling

Brivudine has not been licensed by the US FDA or the EMA; rather, it has been approved in a number of individual countries worldwide. Prescribing information intended for health care providers for brivudine was found upon review of websites in a number of countries in which it is approved (Switzerland, Germany, France, and Spain).[10-13] Product information intended for patient packages is found on the Heads of Medicine Agencies' (HMA) website for a number of German products (Zostex, Menavir, and Premovir).[14-16]

Within the patient leaflet for Menavir from the HMA is the following warning (Figure 1) (which is the same for all brivudine products on this website). In another part of the leaflet is the additional information (Figure 2.).

Information about the interaction intended for health care providers can be found in the labelling for 5-FU and its prodrug products, Xeloda and Teysuno, which have been authorised within the European Union at the EMA. The summary of product characteristics (SmPC) of both products clearly describe the drug-drug interaction and in Section 4.5 advise on the need to wait four weeks before starting the anti-tumour drugs. It also specifically lists treatment with sorivudine and its analogues, such as brivudine, as contraindicated in Section 4.3.[17-19]

Figure 1. Menavir package leaflet, boxed warning[15]


In particular, do **NOT** take Menavir:

- if you are receiving medicines to treat cancer (chemotherapy), especially if you are being treated with:
  - 5-fluorouracil (also called 5-FU, an active substance belonging to a group called 5-fluoropyrimidines)
  - creams, ointments, eye drops or any other form of externally applied medicine that contains 5-fluorouracil
  - active substances which are converted by the body into 5-fluorouracil such as:
    - capecitabine
    - floxuridine
    - tegafur
  - any other active substance of the 5-fluoropyrimidine group
  - combinations of any of the above mentioned active substances
- if your immune system (i.e. your body's defence against infections) is **severely** impaired; for example, if you are being treated with:
  - cancer medicines (chemotherapy), or
  - immunosuppressant medicines (i.e. medicines that suppress or diminish the function of your immune system)
- if you are being treated for a fungal infection with a medicine containing flucytosine
- if you are using a wart medicine containing an active substance of the 5-fluoropyrimidine group

Figure 2. Menavir package leaflet, section Other medicines and Premovir[15]

Menavir (brivudin 125 mg tablet) **MRP nos. DE/H/0343/001**
Package leaflet (EU)

PLEASE NOTE:

Special warning for patients receiving therapy with products containing 5-fluorouracil or other 5-fluoropyrimidines (see also the red box above):

Menavir must **not** be used together with any cancer chemotherapy medicine which contains one of the following active substances, as the harmful effects of these medicines could be strongly increased and may be fatal:

- 5-fluorouracil, including forms to be used locally
- capecitabine
- floxuridine
- tegafur
- other 5-fluoropyrimidines
- combinations of any of the above mentioned substances with other active substances.

Do not take Menavir together with medicines containing the active substance flucytosine used to treat fungal infections.

Do not take Menavir and contact your doctor immediately if you:

- are receiving therapy with any of the above medicines
- will be receiving therapy with any of the above medicines within 4 weeks of the end of treatment with Menavir.

Discussion

The concomitant use of thymidine nucleoside analogues and 5-FU products is known to cause fatal 5-FU toxicity. In the early 1990s, sorivudine, another nucleoside thymidine analogue, was reported to have caused 18 deaths in Japan when used in conjunction with 5-FU; consequently, sorivudine was removed from the market.[6] The mechanism of action for this fatal drug interaction is the same for brivudine; bromovinyl uracil, the major metabolite of both drugs, irreversibly binds to and inhibits dihydropyrimidine dehydrogenase (DPD). DPD is an enzyme in the hepatic system responsible for the inactivation of 5-FU.[4] In animal studies, this inhibition of DPD by co-administration of sorivudine, has led to a 5.5-fold increase in plasma 5-FU area under the curve (AUC) on the first day and up to eight times increase by day 6, when compared to the administration of 5-FU alone.[6] An important additional fact is that DPD is responsible for about 85% of 5-FU metabolism. Its activity is immediately and almost completely suppressed, with the introduction of BVU, and toxicity-averting DPD activity did not return until at least 14 days after the cessation of SRV. A four-week period between the use of 5-FU and brivudine or other BVU producing substances should be enough to avoid 5-FU toxicity.[7]

In spite of the fact that this drug-drug interaction is well understood and there are warnings on both products, fatalities secondary to the interaction continue to occur. Concerns regarding continuing fatalities have been raised in both Germany and Spain. In Germany, an independent medical journal, Arznei-Telegramm, published a similar analysis of cases involving the brivudine-5FU interaction and recommended that withdrawal of brivudine is the only reliable way to prevent more fatal cases.[20] In a recent issue of the WHO Pharmaceuticals Newsletter, the concerns of the Agencia Española de Medicamentos y Productos Sanitarios (AEMPS) in Spain about the continued fatal cases, were reported, alongside reiterated warnings to healthcare professionals.[21]

Review of our case series revealed some features which could be considered as potential reasons for the persistence of fatalities. In cases 1, 3 and 4, the interacting drugs were not administered concomitantly; however, the time intervals between receipt of each drug were limited to only a few days. The patients in these cases appear to have adhered to the red warning section of the patient leaflet: they did not take brivudine while receiving 5-FU. However, the patients did not follow the non-highlighted, somewhat hidden warning "Do not take Menavir and contact your doctor immediately if you will be receiving therapy with any of the above medicines within four weeks of the end of treatment with Menavir". Reasons for failure to heed such a warning may be that, 1) patients limit their focus to the boxed, red section of the package leaflet which does not contain this information, and 2) patients may simply not be aware if they will be receiving chemotherapy within four weeks of stopping brivudine. In cases 2 and 3 scenarios were described in which multiple treating

physicians were involved; it appears that the health care providers recommending brivudine were not the oncologists overseeing the chemotherapy care of the patients. Prescribing information for brivudine was found inconsistently upon review of websites in a number of countries in which it is approved (Switzerland, Germany, France and Spain).[10-16] In contrast, information for health care professionals regarding the interaction was easily found within the labelling for the oncology products on the eMC website.[17-19]

Of particular importance is that, within the last few years, there has been approval of an antidote for fluorouracil and capecitabine toxicity.[22] Uridine triacetate was approved by the US FDA in December 2015 as an emergency treatment for unintended overdose of 5-FU or capecitabine. Uridine triacetate is an acetylated form of uridine; following oral administration, it is deacetylated, and uridine competitively inhibits cell damage and death by fluorouracil. In a study of 135 patients at elevated risk for 5-FU toxicity, 96% were alive and fully recovered at 30 days.[23] In the United States, under a named patient programme, VISTOGARD is provided to patients at risk of excess 5-FU toxicity due to overdose and to patients exhibiting severe toxicities to 5-FU within 96 hours of 5-FU administration.[24]

Conclusions

Given the spectrum of cases from a number of European countries, as well as communications from the German and Spanish authorities, a regulatory review of the adequacy of current risk minimisation measures could be considered, including the wording of current product information; a discussion could take place on the benefit/harm profile of this product given the availability of other antiviral products to treat herpes zoster; and information regarding the availability of a potentially life-saving antidote for this drug-drug interaction should be better disseminated.

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Ceftriaxone and Hepatitis in Patients 75 Years and Older

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Summary

Ceftriaxone is a cephalosporin antibiotic which inhibits bacterial cell wall synthesis following attachment to penicillin binding proteins (PBPs). It is used in the treatment of a large variety of infections. The most frequently reported adverse reactions for ceftriaxone are eosinophilia, leucopenia, thrombocytopenia, diarrhoea, rash, and hepatic enzymes increased.

In VigiBase, the WHO global database of individual case safety reports (ICSRs), there are currently (7 October 2017) 67 ICSRs of hepatitis in association with ceftriaxone in patients 75 years and older. The cases were submitted from Australia, France, Germany, Italy, Republic of Korea, Singapore, Spain and the United States. Ceftriaxone was the only drug suspected in 27 of these cases. Time to onset was reported in 59 of the 67 ICSRs, ranging from 11 days before administration to 3 years after, but apart from these two outliers and one other case in which onset was before administration, the range was from the same day that administration began to about four months with a median of six days. However, in an unusual example of consistency in spontaneous reports, the onset in 53 cases ranged from the same day to 17 days.

The outcome was stated in 59 reports. The patients were reported as recovered or recovering in 52 cases and not recovered in the remaining seven reports. In the reports where the outcome was reported as recovered or recovering, the drug was withdrawn in 50 cases. The consistent time to onset and the cases reported as recovered or recovering after ceftriaxone withdrawal are highly suggestive of a drug-induced effect. In addition, the product information mentions raised liver enzymes and there are five reports of the association in the literature.

In conclusion, although hepatitis may have other possible causes in some patients in this series, the use of ceftriaxone appears the most likely reason.

Introduction

Ceftriaxone is a cephalosporin antibiotic which inhibits bacterial cell wall synthesis following attachment to PBPs. This results in the interruption of cell wall (peptidoglycan) biosynthesis, which leads to bacterial cell lysis and death. It is used in the treatment of a large variety of infections. The most frequently reported adverse reactions for ceftriaxone are eosinophilia,

leucopenia, thrombocytopenia, diarrhoea, rash, and hepatic enzymes increased.[1]

Hepatitis refers to an inflammatory condition of the liver. It's commonly caused by a viral infection, but there are other possible causes of hepatitis including as a secondary result of medications, drugs, toxins, and alcohol. A large number of drugs have been implicated as a cause of hepatitis. These include paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), amiodarone, anabolic steroids, oral contraceptives, chlorpromazine, erythromycin, halothane, methyldopa, isoniazid, methotrexate, statins, sulfa drugs, tetracyclines, amoxicillin-clavulanate and some anti-seizure medicines.[2]

Hepatitis is a preferred term in both WHO-ART and MedDRA, although in MedDRA there are many other related terms. As VigiLyze no longer supports WHO-ART, only MedDRA terms will be discussed in this assessment. The Council for International Organizations for Medical Sciences (CIOMS) recommends that in the absence of a histologically established diagnosis, the term liver injury is to be preferred to hepatocellular damage; the latter should be used only when there is pertinent histological evidence.[3] Specific terms such hepatitis should be used only when the condition has been confirmed by histological or other means. It is, however, common practice for clinicians to use the term hepatitis. Liver injury (or hepatitis) can be further characterised as hepatocellular or cholestatic if the pertinent values of specific liver enzymes are available. Hepatocellular is defined when the ratio of the serum activity of alanine aminotransferase (ALT) expressed as a multiple of the upper limit of normal (ULN) divided by the serum activity of alkaline phosphatase (AP) expressed as a multiple of the ULN is greater than or equal to five. Cholestatic is defined when that ratio is less than two. The term mixed is used for values between two and five.[3]

Reports in VigiBase

A recent analysis by the UMC focussed on risk group identification looking at various covariates such as age, body mass index (BMI), gender and country. This found an association between ceftriaxone and hepatitis in patients aged 75 years and older. As of 7 October 2017, there are 67 ICSRs of hepatitis in association with ceftriaxone in patients 75 years and older in the VigiBase, the WHO global database of ICSRs. In the database as a whole, the association has an IC value of -0.16 with an IC_{025} value of -0.35. In the 75 years and older age group, however, the IC value is 0.86 with an IC_{025} value of 0.25. The cases were submitted from France (51 cases), Spain (5), Australia (4), the United States (3), Germany, Italy, Singapore and South Korea (all one each). The patients ranged in age from 75 to 94 years with a median of 84 years. The gender distribution was 21 males, 45 females and one not specified.

Ceftriaxone was the only drug suspected in 27 of the 67 cases. In the remaining 40 cases, one other drug was suspected in 16 cases and from three to five other drugs suspected in 24 cases. Multiple suspected drugs include metronidazole, paracetamol, amoxicillin/clavulanic acid, ciprofloxacin, ofloxacin, levofloxacin, spiramycin, clozapine, esomeprazole, fluindione, furosemide, gentamicin, heparin, and indapamide. Concomitant drugs were reported in 37 cases, and together with 15 other cases in which there were multiple suspected drugs, there were only 15 reports in which ceftriaxone was the only drug reported to be used. The number of other drugs involved makes a detailed analysis difficult, but it does indicate a patient population with a significant level of morbidity.

The indication for ceftriaxone was stated in 32 of the 67 reports and included urinary tract infection, bronchitis, other respiratory tract infections, other specified infections and unspecified infections. Dosage was indicated in 44 of the 67 reports and was most commonly one or two grams daily. The method of administration was reported in 57 of the 67 reports. This was by the intravenous route in 44 cases, the intramuscular route in 8 cases, and parenterally in one other case. The other four cases describe subcutaneous (two cases) and oral administration (two cases).

Time to onset was reported in 59 of the 67 ICSRs. It ranged from 11 days before administration to 3 years after, but apart from these two outliers and one other case in which onset was before administration, the range was from the same day that administration began to about four months with a median of six days. However, in an unusual example of consistency in spontaneous reports, the onset in 53 cases ranged from the same day to 17 days.

The outcome was stated in 59 reports. The patients were reported as recovered or recovering in 52 cases and not recovered in the remaining seven. In those where the outcome was reported as recovered or recovering, the drug was withdrawn in 50 cases, including eight cases in which the drug was stopped before onset and one case in which the drug was withdrawn long after recovery. In the two remaining cases, the drug was continued in one case and the action taken with the drug was unknown in the other case. In the cases where the patients had not recovered, the drug was withdrawn in six cases, including three cases in which the drug was withdrawn before onset, and the action taken with the drug was unknown in the remaining case.

Other reactions were described in 18 of the reports. These included other hepatic reactions in nine cases including jaundice or cholestasis in five reports and increased levels of hepatic enzymes in five. Other reactions included skin reactions in

four cases, gastrointestinal reactions in three cases, haematological reactions in three cases, renal reactions in two cases and sepsis in two cases.

Literature and Labelling

The product literature does not refer to hepatitis. Currently, the only hepatic reaction mentioned in the adverse drug reaction section of the product labels is hepatic enzymes increased which is reported as one of the most frequently reported adverse reactions.[1]

There are a number of reports in the literature of hepatitis in association with ceftriaxone. Nadelman and co-workers reported the development of granulocytopenia, fever, hepatitis, and Clostridium difficile-associated diarrhea after three weeks treatment with intravenous ceftriaxone.[4] Longo et al described an 80-year-old male who developed hepatitis shortly after starting oral ceftriaxone. Although transaminases returned to baseline after ceftriaxone withdrawal, there was development of haemolytic anaemia and erythoblastocytopenia.[5] Bell and co-workers described an adolescent who experienced acute haemolytic anaemia and severe hepatitis after four days of ceftriaxone therapy. All hepatic enzymes increased dramatically to levels over 20,000 IU/L and the outcome was fatal.[6] Peker et al described a 12-year-old who developed hepatitis after three days of ceftriaxone for tonsillitis. After ceftriaxone withdrawal and the use of steroids, the patient recovered after about ten weeks.[7] Kaur and Singh reported the development of cholestatic hepatitis in a 24-year-old female patient a few days after the use of intravenous ceftriaxone. The patient recovered after three weeks.[8]

Discussion and Conclusion

Case reports in VigiBase suggest that there is a signal for the association of ceftriaxone and hepatitis in patients 75 years and older.

Ceftriaxone was the only drug suspected in 27 of the 67 cases. In the remaining 40 cases, one other drug was suspected in 16 cases and from three to five other drugs suspected in the remaining 24 cases. A detailed analysis of the respective causalities of all suspected drugs in each of the cases is beyond the scope of this assessment. However, of the suspected drugs which occur most in multiple cases, hepatotoxicity is mentioned as an adverse reaction in the product information for metronidazole, amoxicillin/clavulanic acid, ciprofloxacin, ofloxacin and levofloxacin, while hepatotoxicity is not mentioned as an adverse reaction in the product information for paracetamol (except in overdose).[9-13]

It is possible that in some of these cases, one or more of the other suspected drugs may be a more likely cause of the adverse reaction but in most cases, it is difficult to assign causality with any degree of certainty.

Time to onset was reported in 59 of the 67 ICSRs. It ranged from 11 days before administration to three years, but apart from these two outliers and one other case in which onset was before administration, the range was from the same day that administration began to about four months with a median of six days. The report in which onset was three years after administration began (Case 1) and the two reports which described onset before administration (Cases 27 and 64) can be eliminated as indicating ceftriaxone as a possible cause but of the remaining 56 reports which reported onset dates, the onset in 52 cases ranged from the same day to 17 days, in an unusual example of consistency in spontaneous reports, which is suggestive of ceftriaxone as a cause. The time to onset is shorter than that reported with penicillin-induced hepatotoxicity but consistent with that reported with other reports with ceftriaxone.[3-7,14,15]

The outcome was stated in 59 reports. The patients were reported as recovered or recovering in 52 cases and not recovered in the remaining seven reports. Three of the 52 cases documenting recovery had an implausible time to onset as discussed above, so of the remaining 49 cases where the outcome was reported as recovered or recovering, the drug was withdrawn in 47 cases, which included eight cases in which the drug was stopped before onset. In the two remaining cases, the drug was continued in one and the action taken with the drug was unknown in the other. It should be noted that in reports of other antibiotic-induced hepatotoxicity involving both flucloxacillin and amoxicillin/clavulanic acid, it is common that the hepatic reaction develops after the drug has been stopped.[14,15] In the cases where the patients had not recovered, the drug was withdrawn in six cases, including three in which the drug was withdrawn before onset and the action taken with the drug was unknown in the remaining case. This high degree of recovery after withdrawal is strong evidence for a causal role of ceftriaxone. While for those reports with other suspected drugs, those other drugs were also often withdrawn, also, for the 27 cases in which there were no other suspected drugs, the outcome was stated in 22 of the reports. The patients recovered after drug withdrawal in 19 cases and had not recovered in the remaining three cases. The drug was withdrawn in two of those cases and the action taken with the drug was unknown in the other case. This information confirms the evidence for a causal role for ceftriaxone.

Hepatotoxicity is uncommon but well known to occur with antibacterials, particularly penicillins.[16] The same publication notes that clinical hepatotoxicity seems extremely rare with cephalosporins although a transient elevation of transaminases is quite common varying from 0.7% of patients on cefixime to 11% of patients taking

cefaclor. As stated above, the product information for ceftriaxone notes that hepatic enzymes increased is reported as one of the most frequently reported adverse reactions.[1] There are, however, a number of reports in the literature of hepatitis in association with ceftriaxone. Although only one of the patients was elderly, time to onset ranged from three days to three weeks after commencing ceftriaxone with most cases describing onset within a few days,[3-7] consistent with the cases described in this assessment. In addition, when other hepatic terms from the High-Level Terms (HLTs) of "Cholestasis and jaundice", "Hepatic failure and associated disorders" and "Hepatocellular damage and hepatitis NEC" are included, there are 218 additional reports of hepatotoxicity in association with ceftriaxone in patients aged 75 years or greater. Commonly reported terms include an additional 70 reports of cholestasis, 33 separate reports of hepatocellular injury, 26 separate reports of jaundice, 21 separate reports of hepatitis cholestatic and 20 separate reports of the HLT, "Hepatic failure and associated disorders". As noted in the Introduction, hepatitis can be designated as hepatocellular or cholestatic. Of those reports where this designation could be made on the basis of enzyme values, there were about 15 reports of hepatocellular hepatitis and about the same number of reports of cholestatic hepatitis with a handful of reports of mixed hepatitis. On the basis of other liver reactions reported, however, such as cholestasis and jaundice, cholestatic hepatitis may be more common in association with ceftriaxone.

It is interesting to speculate on the possibility of a mechanism to explain why patients 75 years and older may be susceptible to this association. Renal clearance of ceftriaxone is 5 - 12 ml/min with 50 - 60% of ceftriaxone excreted unchanged in the urine, primarily by glomerular filtration, while 40 - 50% is excreted unchanged in the bile. The elimination half-life of total ceftriaxone in adults is about 8 hours. The product information notes that in patients with impaired renal function, there is no need to reduce the dosage of ceftriaxone provided hepatic function is not impaired. Only in cases of preterminal renal failure (creatinine clearance < 10 ml/min) should the ceftriaxone dosage not exceed 2 g daily. However, the product information also states that in older people aged over 75 years the average elimination half-life is usually two to three times that of young adults.[1] Adverse drug reactions are well known as a major problem in the elderly population and reduced renal function is an important reason.[17] It is possible that the prolonged clearance in elderly patients may result in such patients being exposed to ceftriaxone for a longer period of time and a resulting increased risk of hepatotoxicity. It is noteworthy that increasing age is a risk factor for the development of hepatotoxicity in association with two penicillin antibiotics.[18,19]

It is significant that the association is not disproportionate in the database as a whole, but in the 75 years and older age group, the IC value is 0.86 with an IC_{025} value of 0.25. In VigiBase as a whole, there are 16,438,393 reports as at 11 February 2018. Of those, 1,543,092 involve patients aged 75 years and older (9.39%). For ceftriaxone, of the 96,426 reports submitted, 12,285 involve patients aged 75 years and older (12.74%). For hepatitis, there are 45,806 reports with 4,835 involving patients aged 75 years and older (10.55%). For the association of ceftriaxone and hepatitis, there are 240 reports with 70 reports (three additional reports since the date of this assessment) involving patients aged 75 years and older (28.93%). This crude statistical assessment indicates that hepatitis in association with ceftriaxone occurs two to three times more commonly than would be otherwise expected.

In conclusion, there is a signal for the association of ceftriaxone with hepatitis in patients aged 75 years and older. There are a relatively large number of reports of hepatitis, a consistent time to onset and a consistent response to drug withdrawal. Raised liver enzymes is mentioned in the product information and there are five reports of hepatitis in association with ceftriaxone.

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Table 1. Case overview of ICSRs in VigiBase of hepatitis in association with ceftriaxone in patients aged 75 years and older

Case	Age/ Gender	Other suspected (S) or concomitant (C) drugs	Reactions (MedDRA preferred terms)	Outcome
1	78/F	Clarithromycin (S) Chlortalidone, methylprednisolone, paracetamol, salbutamol, ipratropium (C)	Hepatitis	Recovered
2	84/F	Enoxaparin (S)	Hepatitis	Recovered
3	76/F	None	Hepatitis	Recovered
4	76/F	Clozapine (S) Colecalciferol, lamotrigine, lactulose, paracetamol, pantoprazole, valproic acid (C)	Hepatitis	Recovering
5	92/F	Ezetimibe, gliclazide, sitagliptin (S) Valsartan (C)	Hepatitis	Recovered
6	82/F	Ciprofloxacin, metronidazole, paracetamol (S) Apixaban, bisoprolol, furosemide, levothyroxine, oxazepam (C)	Hepatitis, cholestasis	Recovering
7	88/M	Cefotaxime, esomeprazole, sulfamethoxazole/trimethoprim (S)	Hepatitis	Recovering
8	89/M	Carbimazole, metronidazole (S)	Hepatitis, jaundice, metabolism disorder	Recovering
9	90/F	Bisoprolol, heparin, metronidazole, paroxetine (S) Fluindione, potassium (C)	Hepatitis	Recovered
10	82/F	None	Hepatitis	Recovered
11	76/F	Metronidazole, pristinamycin (S)	Hepatitis	Recovered

Case	Age/ Gender	Other suspected (S) or concomitant (C) drugs	Reactions (MedDRA preferred terms)	Outcome
		Alprazolam, felodipine/metoprolol, hydroxyzine, indapamide, irbesartan, metoclopramide, paracetamol/ tramadol, paroxetine (C)		
12	77/M	Paracetamol (S) Gemfibrozil (C)	Hepatitis	Recovered
13	75/F	None	Hepatitis, nausea, rash, vomiting	Recovered
14	94/M	Clozapine (S) Acetylsalicylic acid, alprazolam, benserazide/levodopa, econazole, gliclazide, hydroxyzine, irbesartan, rotigotine (C)	Hepatitis	Recovering
15	84/F	Acetylsalicylic acid, atorvastatin, fluindione, ofloxacin, oxazepam, paroxetine, piribedil, prednisolone, verapamil (C)	Hepatitis	Recovered
16	75/F	Ciprofloxacin, dalteparin, methotrexate, prednisolone, rituximab, spiramycin, vincristine (S) Clobazam, dalteparin, sulfamethoxazole/trimethoprim, valaciclovir (C)	Hepatitis	Recovering
17	88/F	Fluindione, folic acid, furosemide, iron, potassium (C)	Hepatitis	Recovering
18	90/F	Allopurinol, bisoprolol, colecalciferol, econazole, fluindione, plantago ovata (C)	Hepatitis	Recovering
19	77/F	Amoxicillin/clavulanic acid, fluindione, methylprednisolone, nicardipine, ramipril, vildagliptin (S)	Hepatitis, jaundice	Recovering
20	86/F	Acepromazine/aceprometazine/clorazepic acid, furosemide, lormetazepam, paracetamol (S) Enoxaparin (C)	Hepatitis	Recovered
21	87/M	Bumetanide (S) Acetylsalicylic acid, budesonide /formoterol, Macrogol 4000, salbutamol, tiotropium (C)	Hepatitis	Recovering
22	82/M	Amoxicillin, levofloxacin (S) Acetylsalicylic acid, cloxacillin, diltiazem, enoxaparin, rosuvastatin (C)	Hepatitis	Recovered
23	86/F	Amoxicillin/clavulanic acid (S) Atorvastatin, clopidogrel (C)	Hepatitis	Not recovered
24	86/F	Atorvastatin, gentamicin, spiramycin (S) Dronedarone, fluindione, gliclazide, lercanidipine, perindopril, simvastatin, sotalol (C)	Hepatitis, renal failure	Recovering
25	78/F	Ciprofloxacin (S)	Hepatitis	Recovered
26	80/F	Alprazolam, enoxaparin, manidipine, milnacipran, pantoprazole, tramadol, valsartan (C)	Hepatitis	Recovering
27	76/F	Esomeprazole, heparin, paracetamol (S) Amikacin, enoxaparin, pipobroman, pravastatin, pregabalin, propranolol, tramadol (C)	Hepatitis	Recovered
28	90/M	Digoxin, furosemide, paroxetine, ramipril (C)	Hepatitis	Recovered
29	87/F	None	Hepatitis	Recovered
30	79/F	None	Hepatitis	Recovered
31	83/F	Amiodarone, furosemide (S) Bisoprolol, bromazepam, fluindione (C)	Hepatitis, rash	Recovering
32	88/F	None	Hepatitis	Recovered
33	80/M	Ofloxacin (S)	Hepatitis	Recovered
34	76/F	Bromazepam, clopidogrel, enalapril, fluticasone, furosemide, hydrocortisone, omeprazole, tiotropium, tramadol, zolpidem (C)	Hepatitis	Recovered
35	86/M	Amoxicillin/clavulanic acid, fluindione, voriconazole (S)	Hepatitis	Recovered
36	76/F	Ethambutol, isoniazid, levofloxacin, pyrazinamide, rifampicin (S)	Hepatitis, hyperbilirubinaemia	Recovering
37	84/M	Acenocoumarol (C)	Hepatitis	Recovered
38	83/M	None	Hepatitis, acute respiratory distress syndrome, liver function tests abnormal, sepsis, shock	Not recovered but died from other causes
39	82/F	Metoprolol, metronidazole, paracetamol, propofol, tramadol (S)	Hepatitis	Not recovered

Case	Age/ Gender	Other suspected (S) or concomitant (C) drugs	Reactions (MedDRA preferred terms)	Outcome
40	80/-	Clindamycin (S)	Hepatitis	Recovered?
41	85/F	None	Hepatitis	Unknown
42	92/F	Acetylcysteine, furosemide, polygeline (C)	Hepatitis	Unknown
43	78/F	Colchicine/papaver somniferum /tiemonium, levofloxacin, norfloxacin, ofloxacin (S)	Hepatitis, neutropenia	Recovered
44	78/F	Ciprofloxacin, amoxicillin/clavulanic acid (S)	Hepatitis	Recovered
45	83/F	Indapamide (S) Acetylsalicylic acid, buflomedil, candesartan, pantoprazole (C)	Hepatitis	Unknown
46	84/F	Moxifloxacin (S)	Hepatitis, agranulocytosis, jaundice, rash	Recovering
47	89/F	None	Hepatitis, ALT increased, AST increased, GGT increased, jaundice	Recovered
48	80/M	Simvastatin (C)	Hepatitis	Recovered
49	84/M	Spiramycin (S) Amiodarone, buflomedil, nifedipine, sertraline (C)	Hepatitis	Recovering
50	86/F	None	Hepatitis	Recovered
51	85/F	Furosemide, gliclazide, methyldopa, omeprazole, ramipril (C)	Hepatitis, nausea, vomiting	Not recovered
52	91/F	Nefopam, ofloxacin (S) Furosemide, omeprazole, tamoxifen (C)	Hepatitis	Recovered
53	87/M	None	Hepatitis, abdominal pain, cholecystitis, pyrexia	Not recovered
54	81/M	Flucloxacillin, gentamicin, indapamide, metronidazole, penicillin nos (C)	Hepatitis	Not recovered
55	87/M	Ambroxol (S) Amineptine, buflomedil, methyldopa, nitrendipine (C)	Hepatitis	Unknown
56	81/F	None	Hepatitis, pancreatitis	Unknown
57	90/M	Carbocisteine, formoterol, phloroglucinol/trimethylphloro-glucinol (S) Amoxicillin/clavulanic acid, metopimazine (C)	Hepatitis	Recovered
58	86/M	None	Hepatitis, acute kidney injury, anuria	Unknown
59	87/M	Metoclopramide (S) Acetylsalicylic acid, cyproterone, leuprorelin, nicergoline (C)	Hepatitis	Not recovered
60	85/F	Dipyridamole, lorazepam, mianserin (S) Amiodarone, digoxin (C)	Hepatitis	Recovered
61	84/F	Ofloxacin (S) Allopurinol, danazol, omeprazole, paracetamol (C)	Hepatitis	Recovered
62	91/F	None	Hepatitis, hepatic function abnormal	Recovered?
63	82/F	Amoxicillin/clavulanic acid, enoxaparin, methylprednisolone, nifuroxazide, sucralfate (C)	Hepatitis	Recovered
64	78/F	Cefuroxime, netilmicin, piroxicam, roxithromycin (S) Labetalol (C)	Hepatitis	Recovered
65	83/F	Clorazepic acid, diltiazem, drug name/s under assessment for WHO-DD (C)	Hepatitis	Recovered
66	83/M	None	Hepatitis, circulatory collapse, hepatic function abnormal, sepsis	Unknown
67	82/M	Amoxicillin/clavulanic acid, paracetamol (S)	Hepatitis, bone marrow failure, erythema multiforme	Unknown

CAVEAT DOCUMENT

Accompanying statement to data released from VigiBase, the WHO international database of suspected adverse drug reactions

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

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

Reports submitted to National Centres come from both regulated and voluntary sources. Some National Centres accept reports only from medical practitioners; other National Centres accept reports from a broader range of reporters, including patients. Some National Centres include reports from pharmaceutical companies in the information submitted to UMC; other National Centres do not.

The volume of reports for a particular medicinal product may be influenced by the extent of use of the product, publicity, the nature of the reactions and other factors. No information is provided on the number of patients exposed to the product.

Some National Centres that contribute information to VigiBase make an assessment of the likelihood that a medicinal product caused the suspected reaction, while others do not. Time from receipt of a report by a National Centre until submission to UMC varies from country to country. Information obtained from UMC may therefore differ from those obtained directly from National Centres.

If in doubt or in need of help for interpretation of country specific data, UMC recommends to contact the concerned NC before using the data.

For the above reasons interpretations of adverse reaction data, and particularly those based on comparisons between medicinal products, may be misleading. The supplied data come from a variety of sources. The likelihood of a causal relationship is not the same in all reports. Any use of this information must take these factors into account.

Confidential data

According to WHO policy and UMC Guidelines, ADR reports sent from the WHO PIDM member countries to VigiBase are anonymized, but they are still to be considered sensitive due to the nature of the data.

When receiving and using adverse reaction data ("Data"), the user agrees and acknowledges that it will be the controller of any such Data. Accordingly, the user shall adhere to all applicable legislation such as, but not limited to, EU and national legislation regarding protection of personal data (e.g. the Data Protection Directive 95/46/EC and Regulation (EC) No 45/2001, as applicable). Transfer of sensitive data to a third party is generally prohibited subject to limited exceptions explicitly stated in applicable legislation.

As the controller of the Data, the user shall be liable for any and all processing of the Data and shall indemnify and hold the UMC harmless against any claim from a data subject or any other person or entity due to a breach of any legislation or other regulation regarding the processing of the Data.

Non-permitted use of VigiBase Data includes, but is not limited to:

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

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

(i) regarding the source of the information
(ii) that the information comes from a variety of sources, and the likelihood that the suspected adverse reaction is drug-related is not the same in all cases,
(iii) that the information does not represent the opinion of the World Health Organization.

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

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

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41st Annual Meeting of Representatives of National Pharmacovigilance Centres participating in the WHO Programme for International Drug Monitoring, Geneva 6-8 November 2018

Major Milestones in Global Health and Pharmacovigilance

The WHO annual meeting of National Pharmacovigilance Centres (NPCs) is a platform for countries from around the world to meet and discuss pharmacovigilance issues. 2018 was an exceptional year as it marked 50 years of the WHO Programme for International Drug Monitoring (PDIM), 70 years since the establishment of WHO and 40 years of the WHO Collaborating Centre for International Drug Monitoring (the Uppsala Monitoring Centre, UMC). To celebrate these milestones, an open session was held on 5 November 2018 at WHO headquarters. Swissmedic (the Swiss Agency for Therapeutic Products) hosted the closed meeting (only for delegates from the NPCs) which took place from 6 to 8 December 2018 at the Crown Plaza Hotel in Geneva.

Celebrating 50 years of the WHO Programme for International Drug Monitoring: open session

Nearly 200 people from 82 Member States and non-state actors such as the International Society of Pharmacovigilance (ISOP), Council for International Organizations of Medical Sciences (CIOMS), former WHO staff members, and patient representative groups attended the open session which took place in the Executive Board room at WHO Headquarters in Geneva on 5 December 2018. The session started with a song and a screening of an international musical video "Vaishnav Jan To Tene Kahiye" by artists from several countries. The video was produced by the Government of India, to celebrate the 150th birth anniversary of Mahatma Gandhi.

The history, development, growth and achievements of the programme were conveyed in a second video. This led to an animated keynote discussion between Marie Lindquist, Director, UMC, and two students about the future of PV. The key message was "catch them young and teach them well". The importance of PV to patients' lives was highlighted in a stimulating dialogue between David Haerry (Switzerland), Björn Håkansson (Sweden), Mariângela Simao (WHO) and moderated by Katja Gentinetta, a prominent Swiss political philosopher during a panel discussion. The panellists shared their perspectives on medicines safety, drawing on their experiences with individuals born with malformations due to thalidomide in utero exposure, and management of diseases such as HIV which require lifelong treatment with medicines. Other activities during the 50-year celebrations included: the launch of the new, interactive, technologically advanced version of the WHO PV toolkit. In the presentations of success stories from Chile, Iraq and Montenegro, the speakers shared how pharmacovigilance (PV) has grown in their countries, highlighted the impact of PV in decision making and regulatory functions, and as a key enabler for the access of new medicines in their countries. The presence of multiple stakeholders set an ideal environment to discuss the Coalition of Interested Partners (CIP) initiative. WHO's Mike Ward spoke on how CIP could convene all stakeholders involved in building PV capacities to form an environment where the duplication of work can be avoided, bringing PV into sustainable regulatory systems.

Closed session

The closed meeting sessions consisted of plenaries, working groups, signals of current interest and tutorials. The choice of topics covered in the 41st annual meeting stemmed from the requests of Member States made in the 40th annual meeting.

Plenary sessions

The plenary sessions started with a report on progress and achievements that WHO and WHO Collaborating Centres have made on the recommendations of the previous Annual Meeting in Kampala, Uganda, 2017. Following this, previous hosts from Uganda NPC provided an update on PV developments in the country following the 40th annual meeting of NPCs. During the first two days of the meeting (6th and 7th of December) a variety of topics were presented during the plenary sessions. These included: the importance of applying a competency-based technique to the PV curriculum to certify PV experts; an overview of the WHO global bench marking tool for regulatory functions; PV collaborations with HIV and TB disease programmes at international and national levels; and prevention of medication errors. The WHO Collaborating Centre for International Drug monitoring, Uppsala monitoring Centre updated participants on latest research developments and the proposed revisions on the WHO policy of data access.

Signals of Current interest

This session consisted of short presentations based on abstracts that were submitted prior to the meeting. Participants from Argentina, Australia, Brazil, China, Estonia, Iran, Iraq, Japan, Libya, Mauritius, Morocco, Sierra Leone, Togo, Uganda, and Vietnam took the opportunity to present PV issues. A variety of subjects were discussed which ranged from the organization of National PV Systems, teratogenicity of medicines, signal detection methods, adverse effects of antiepileptic medicines and antibiotics, and vaccine safety.

Tutorials

Eight different tutorials ran parallel to each other on each day and included topics such as VigiFlow, active surveillance, benefit-harm, and developing a PV bulletin.

Working Groups

Eight working groups were offered over a period of two days. Prior to the workshop, delegates were provided with a list of objectives and outcomes and had the opportunity to attend two workshops of preference. During each workshop, moderated discussions were held, and attendees formulated and agreed on a list of recommendations that were specifically targeted at WHO, WHO CCs and/or the NPCs. A rapporteur from amongst the workshop participants presented the recommendations to the whole delegation during the plenary session on the last day of the meeting. Working groups consisted of: 1) Regional Platforms: fact & fiction, 2) Educational Tools: what and when, 3) Improving Communication, 4) Strategies for improving quality of information in Individual Case Safety Reports (ICSR), 5) Rational use of drugs, 6) Monitoring the safety of medicines in special populations, 7) Reporting and preventing medication errors, and 8) Reporting quality problems. The recommendations from the working groups will be available in the next issue of the WHO Pharmaceuticals Newsletter.

42nd Annual Meeting of Representatives of the National Pharmacovigilance Centres participating in the WHO Programme for International Drug Monitoring

Representatives from the NPC in Colombia invited participants to attend the 42nd Annual Meeting of Representatives of the NPCs in Bogota, 28 October – 1 November 2019.

Advanced Workshop for Strengthening Pharmacovigilance (PV) Systems and PV Preparedness Geneva, Switzerland, 3-7 December

Pharmacovigilance (PV) can facilitate access to new and innovative treatments by contributing to a better understanding of appropriate use and to address patient safety issues promptly. WHO is working with Member States and partners to ensure that new treatments introduced in countries are more effective, safer and are better tolerated by patients. In the last few years WHO has used a "smart" strategy, to support a selection of low and middle-income countries to implement PV by focusing on a few products which have been prioritized by national disease programmes.

The smart strategy involves an initial assessment of PV preparedness (for priority products) by using the WHO PV preparedness assessment tool to identify gaps in PV. A plan to enhance PV capacity and preparedness is then tailored to identified gaps in national settings. When Botswana, Kyrgyzstan, Kenya, Republic of Moldova and Ukraine were assessed for their PV preparedness, some common gaps were identified in: the ability to analyse safety data and detect signal; skills to perform benefit-harm assessments; capacity to implement risk minimisation measures; routine use of PV data for regulatory recommendations. A workshop to address these gaps was organized by WHO, 3 to 7 December 2018 in Geneva, Switzerland. Representatives from the National Pharmacovigilance Centres and a National Disease Programme (TB or HIV) from the six countries participated. The workshop was designed to be hands-on, and the participants brought individual case safety reports from their countries to the workshop. During the course, participants completed causality assessments, and case by case signal detection on these reports. Once potential signals were identified, they were validated and assessed. At the end of the workshop participants formed a 'mock' safety committee, to provide recommendations on the signals that were identified.

The integration of National PV Centres with National Disease Programmes created an atmosphere of mutual collaboration and demonstrated the importance of sharing expertise, information, and knowledge to make sense of safety data and put in place safety measures that will promote access to new innovative treatments, with minimum harm to patients.