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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:

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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.

In addition, this edition of the Newsletter includes recommendations from the 42nd Global Advisory Committee on Vaccine Safety (GACVS) meeting.

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Apalutamide

Risk of toxic epidermal necrolysis (TEN)

Japan. The Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA) have announced that the package inserts for apalutamide (Erleada®) should be revised to include toxic epidermal necrolysis (TEN) as an adverse drug reaction.

Apalutamide is indicated to treat castration-resistant prostate cancer without remote metastasis.

A total of two cases involving TEN in patients with apalutamide have been reported in Japan during the previous three years, for which a causal relationship between the drug and event was deemed a reasonable possibility. One of the two cases led to patient mortality, for which a causal relationship between the drug and the subsequent death was deemed reasonably possible.

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

Reference:
Revision of Precautions, MHLW/PMDA, 19 May 2020 *(www.pmda.go.jp/english/)*

Bevacizumab

Risk of artery dissection

Japan. The MHLW and the PMDA have announced that the package inserts for bevacizumab (Avastin®) should be revised to include artery dissection as an adverse drug reaction.

Bevacizumab is indicated to treat several conditions such as incurable, unresectable advanced/recurrent colorectal cancer and malignant glioma.

A total of seven cases involving artery dissection in patients with bevacizumab have been reported in Japan during the previous three years, including one case for which a causal relationship between the drug and event was deemed reasonably possible. Two mortalities have been reported among the seven cases. A causal relationship could not be established for either cases.

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

Reference:
Revision of Precautions, MHLW/PMDA, 16 June 2020 *(www.pmda.go.jp/english/)*

Carbimazole

1. Risk of congenital malformations

Ireland. The Health Products Regulatory Authority (HPRA) has announced that the product information (Summary of Product Characteristics (SmPC) and Package Leaflet (PL)) for carbimazole has been updated to reflect the risk of congenital malformations.

Carbimazole is a pro-drug that undergoes rapid metabolism into the active metabolite, thiamazole.

The Pharmacovigilance Risk Assessment Committee (PRAC) completed a review of the known risk of congenital malformations associated with carbimazole exposure during pregnancy. Data from epidemiological studies and case reports strengthens the evidence that carbimazole/thiamazole exposure during pregnancy is associated with an increased risk of congenital malformations, especially when administered in the first trimester of pregnancy and at high doses.

Women of childbearing potential should use effective contraception during treatment with carbimazole. Carbimazole must only be used during pregnancy after a strict individual benefit/risk assessment and only at the lowest effective dose without additional administration of thyroid hormones.

Reference:
Drug Safety Newsletter, HPRA, May 2020 *(www.hpra.ie)*

(See also WHO Pharmaceuticals Newsletter No.2, 2019: Increased risk of congenital malformations in UK)

2. Risk of acute pancreatitis

Ireland. The HPRA has announced that the product information (SmPC and PL) for carbimazole has been updated to reflect the risk of acute pancreatitis.

Post-marketing reports of acute pancreatitis in association with the use of carbimazole/thiamazole have been received in EU. Although the mechanism is not fully understood, decreased time to onset after re-exposure could suggest an immunological mechanism.

Immediate discontinuation is required in patients who develop pancreatitis following exposure to carbimazole and the patients should be switched to alternative treatment.

Reference:
Drug Safety Newsletter, HPRA, May 2020 *(www.hpra.ie)*

(See also WHO Pharmaceuticals Newsletter No.2, 2019: Risk of acute pancreatitis in UK)

Cyproterone

Restrictions in use due to risk of meningioma

1. Ireland. The HPRA has announced that the SmPC and PL for cyproterone containing medicines will be updated to include the risk of meningioma associated with treatment.

Cyproterone is an antiandrogen medicine acting in the same way as progesterone. It is

indicated to treat various androgen-dependent conditions such as hirsutism, alopecia, acne, prostate cancer and reduction of sex drive in sexual deviations in men.

A PRAC review concluded that the risk of meningioma increases with increasing cumulative doses of cyproterone. It also noted that most cases occur after prolonged exposure to high doses of cyproterone.

The PRAC recommended that in all indications except prostate carcinoma, treatment with higher doses should be restricted to situations where alternative treatments are unavailable and that low doses should also be contraindicated in patients with a history of meningioma.

Patients should be monitored for meningioma in accordance with clinical practice. If a patient taking cyproterone is diagnosed with meningioma, treatment must be discontinued permanently.

Reference:
Drug Safety Newsletter, HPRA, May 2020 *(www.hpra.ie)*

2. United Kingdom. The Medicines and Healthcare Products Regulatory Agency (MHRA) has announced that a European review concluded that treatment with high dose cyproterone should be restricted to situations where alternative treatments or interventions are unavailable, for all indications except prostate carcinoma.

Up to 12 May 2020, there have been 10 reports in the UK describing meningioma, which were suspected to be associated with high dose cyproterone. There were no reports of meningioma with low dose cyproterone.

Reference:
Drug Safety Update, MHRA, 29 June 2020 *(www.gov.uk/mhra)*

(See also WHO Pharmaceuticals Newsletter No.3, 2020: Restrictions in use due to risk of meningioma in EU; No.2, 2020: Risk of meningioma in EU; No.4, 2019; Risk of meningioma in EU)

Fluoxetine, levothyroxine

Potential interaction affecting TSH level

New Zealand. Medsafe is highlighting a safety concern and encouraging reporting of cases of potential interaction between fluoxetine (Arrow®, Fluox® etc.) and levothyroxine (Eltroxin®, Synthroid® etc.) leading to reduced serum levels of levothyroxine and increased thyroid-stimulating hormone (TSH) levels.

Fluoxetine is a selective serotonin reuptake inhibitor (SSRI) indicated for depression, bulimia, obsessive-compulsive disorder and premenstrual dysphoric disorder. Levothyroxine is a synthetic form of the natural hormone thyroxine (T4) indicated for the treatment of hypothyroidism.

This investigation was triggered by a report received by the Centre for Adverse Reactions Monitoring (CARM). There are also some published case reports describing reduced thyroid function during treatment with other SSRIs such as escitalopram, paroxetine and sertraline.

The mechanism for this potential interaction and whether this is a class effect of SSRIs are not clear.

The monitoring will continue until November 2020.

Reference:
Safety Communication, Medsafe, 21 May 2020 *(www.medsafe.govt.nz/)*

(See also WHO Pharmaceuticals Newsletter No.6, 2018: Interaction with levothyroxine leading to reduced thyroxine levels in UK; No.1, 2017: Risk of adrenal suppression due to a pharmacokinetic interaction in UK)

Fulvestrant

Risk of injection site necrosis and ulcer

Japan. The MHLW and the PMDA have announced that the package inserts for fulvestrant (Faslodex®) should be revised to include injection site necrosis and ulcer as adverse drug reactions.

Fulvestrant is indicated to treat breast cancer.

A total of six cases involving injection site necrosis and ulcer in patients with fulvestrant have been reported in Japan during the previous three years, including five cases for which a causal relationship between the drug and event was deemed reasonably possible. No patient mortalities have been reported to date.

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

Reference:
Revision of Precautions, MHLW/PMDA, 19 May 2020 *(www.pmda.go.jp/english/)*

Ketamine

Potential risk of liver and bile duct damage

Canada. Health Canada has announced that it will work with manufacturers to update the product safety information of ketamine-containing products (Ketalar® and generic) to inform about the potential risk of liver and bile duct damage.

Ketamine is used to make patients unconscious (anesthesia) during surgery or medical procedures.

Health Canada conducted a review on the risk of liver and bile duct damage with the use of ketamine, following a risk communication published by the French regulatory agency.

The assessment reviewed 19

international epidemiologic studies, which could not confirm or refute a link between the liver and/or bile duct damages and the use of ketamine. An additional 22 individual patient case reports (one was Canadian) were reviewed, among which one was found to be probably linked to the used of ketamine, and 17 possibly linked. Hence, Health Canada concluded that there is a potential link between the use of ketamine and damage to the liver and bile duct.

Reference:
Summary Safety Review, Health Canada, 10 June 2020 (www.hc-sc.gc.ca)

(See also WHO Pharmaceuticals Newsletter No.5, 2017: Risk of severe liver injury with repeated and/or prolonged high-dose use in France)

Levetiracetam

Risk of abnormal and aggressive behaviours

Ireland. The HPRA communicated a PRAC recommendation that the product information for levetiracetam (Keppra®, Matever® etc.) should be updated to include a warning on the risk of abnormal and aggressive behaviours. The recommendation resulted from a periodic review of safety data in association with levetiracetam.

Levetiracetam is indicated in the treatment of specified forms of epilepsy.

Patients treated with levetiracetam should be monitored for developing psychiatric signs suggesting important mood or personality changes. If such behaviours are noticed, treatment adaptation or gradual discontinuation should be considered.

Reference:
Drug Safety Newsletter, HPRA, May 2020 (www.hpra.ie)

Memantine

Risk of bradyarrhythmia

Japan. The MHLW and the PMDA have announced that the package inserts for memantine (Memary®) should be revised to include bradyarrhythmia such as complete atrioventricular block and severe sinus bradycardia as an adverse drug reaction.

Memantine is indicated to control the progression of moderate to severe dementia of the Alzheimer's type.

A total of four cases involving bradyarrhythmia in patients with memantine have been reported in Japan during the previous three years, for two of which a causal relationship between the drug and event was deemed reasonably possible. No patient mortalities have been reported to date.

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

Reference:
Revision of Precautions, MHLW/PMDA, 16 June 2020 (www.pmda.go.jp/english/)

Nutrition preparations (parenteral)

Contraindication loosened

Japan. The MHLW and the PMDA have announced that the package inserts for parenteral nutrition preparations was revised, regarding the use in patients on dialysis or hemofiltration, from contraindications into careful administration. The implicated products include amino-acid preparations, peripheral parenteral nutrition preparations and total parenteral nutrition preparations (Amizet®, Amiparen®, Pareplus®, Hicaliq®, Rehabix® etc.).

Parenteral nutrition preparations are widely used to supplement nutrition such as water, electrolyte, amino acid under malnutrition of before/after surgery.

The revision is based on a 2020 investigation by MHLW and PMDA, on the safety of the parenteral nutrition preparations in patients with serious renal disorder on dialysis of hemofiltration.

After reviewing published scientific journals, overseas guidelines and package inserts, the PMDA considered acceptable to exclude patients on dialysis or hemofiltration from the contraindication section, but emphasized precautions for administration in those patients. This is due to the abundance of acidic amino acid in amino acid preparations for hepatic failure, which may cause acidosis in patients with renal failure on dialysis.

Reference:
Revision of Precautions, MHLW/PMDA, 25 June 2020 (www.pmda.go.jp/english/)

Ondansetron

Potential risk of oral cleft defects

New Zealand. Medsafe has announced that the data sheets of ondansetron-containing medicines are being updated with information on the increased risk of oral cleft defects associated with first trimester use.

Ondansetron is a selective serotonin receptor antagonist and is used to manage and prevent nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy. Ondansetron is also used off-label during early pregnancy. In New Zealand, first trimester use of ondansetron is increasing.

Two recent epidemiological studies investigated the risk of

orofacial cleft defects and other congenital malformations in infants who were exposed to ondansetron in utero, using data in the United States. The result of one study showed statistically significant increase in oral cleft with the use of ondansetron, whereas the result from the other study was not statistically significant.

The Medicines Adverse Reactions Committee (MARC) noted that although the effect sizes in the studies were small and there is some uncertainty in the data, the current evidence suggests a small increase in the risk of oral cleft defects associated with the use of ondansetron in the first trimester.

Reference:
Prescriber Update, Medsafe, June 2020 (www.medsafe.govt.nz/)

(See also WHO Pharmaceuticals Newsletter No.2, 2020: Risk of oral clefts in UK; No.6, 2016: Assessing potential harm to the foetus: insufficient information in Canada)

Ruxolitinib, Tofacitinib

Risk of blood clots in the deep veins

Canada. Health Canada has announced that it had worked with the manufacturer for tofacitinib (Xeljanz®) to update the product safety information to include the serious risk of blood clots in the veins and will also work with the manufacturer for ruxolitinib (Jakavi®) to update the product safety information to include the risk of thromboembolic events.

Tofacitinib is used for the treatment of inflammatory diseases such as rheumatoid arthritis, psoriatic arthritis and ulcerative colitis. Ruxolitinib is used for the treatment of certain rare blood cancers, such as primary myelofibrosis and polycythemia vera.

Health Canada conducted a safety review and found that an ongoing safety study for tofacitinib showed an increased risk of blood clots in the lungs and death. A review of an additional 51 cases (eight Canadian and 43 international) of thromboembolic events in people taking tofacitinib showed that 38 were possibly linked to tofacitinib.

A further assessment of eight Canadian cases of thromboembolic events in patients taking ruxolitinib found that three cases showed a possible link to ruxolitinib.

Health Canada concluded that there is a link between the risk of thromboembolic events and the use of tofacitinib or ruxolitinib.

Reference:
Summary Safety Review, Health Canada, 18 June 2020 (www.hc-sc.gc.ca)

(See also WHO Pharmaceuticals Newsletter No.3, 2020: Risk of venous thromboembolism and serious and fatal infections in UK; No.6, 2019: Risk of blood clots in EU; No.5, 2019: Increased risk of blood clots and death with higher dose in US and Japan)

Testosterone

Caution in patients with thrombophilia or risk factors for venous thromboembolism

Ireland. The HPRA warned that testosterone-containing medicinal products should be used with caution in patients with thrombophilia or risk factors for venous thromboembolism, following a PRAC recommendation to update the product information (SmPC and PL) for these products.

Testosterone-containing medicinal products are used as testosterone replacement therapy for male hypogonadism in Ireland.

Cases of venous thromboembolism have been reported in patients with thrombophilia, some of whom were on anticoagulant treatment. Continuing testosterone treatment in such patients requires careful evaluation after a first thrombotic event.

Reference:
Drug Safety Newsletter, HPRA, May 2020 (www.hpra.ie)

(See also WHO Pharmaceuticals Newsletter No.3, 2017: Risk of arterial thromboembolism/venous thromboembolism in Australia; No.4, 2014: Risk of venous blood clots in the USA)

Ticagrelor

Potential risk of bradyarrhythmia

Canada. Health Canada has announced that it will work with manufacturers to update the product safety information of ticagrelor (Brilinta®) to inform about the potential risk of worsening of a slow and irregular heartbeat (bradyarrhythmia) and partial or complete block in the transmission of heart impulses (second-and third-degree atrioventricular block).

Ticagrelor is used to decrease the risk of having a stroke, another heart attack or dying from heart or blood vessel disease.

Triggered by published international reports of partial or complete block in the transmission of heart impulses in patients with ticagrelor, Health Canada reviewed two potential risks, bradyarrhythmia and second- and third-degree atrioventricular block.

Of the 18 international cases of patients with bradyarrhythmia taking ticagrelor assessed, 15 were found to be possibly linked to the use of ticagrelor.

Among the 44 cases (42 international and two

Canadian) assessed regarding the risk of second or third-degree atrioventricular block related to the use of ticagrelor, two reports were found to be probably linked to the use of ticagrelor, 40 including two Canadian cases were possibly linked. Of the 9 mortalities among the 44 reports, three were found to be possibly linked with the use of ticagrelor.

Health Canada concluded that there may be a link between the use of ticagrelor and the risk of bradyarrhythmia including second- and third-degree atrioventricular block.

Reference:
Summary Safety Review, Health Canada, 6 July 2020 (www.hc-sc.gc.ca)

Tramadol

Contraindication in children

New Zealand. Medsafe has informed health-care professionals of updated advice on the use of tramadol in children.

Tramadol is centrally-acting synthetic analgesic, used to relieve moderate to severe pain when paracetamol or non-steroidal anti-inflammatory drug (NSAID) is not adequate. Tramadol is metabolized by CYP2D6 to yield principal active metabolite. Patients with a deficiency of CYP2D6 may have reduced benefit from tramadol, whereas patients who are ultra-rapid metabolizers may be more sensitive to adverse drug reactions (ADRs).

Following review of their safety data, the companies have now contraindicated the use of tramadol in children aged under 12 years, as well as in children under 18 years for post-operative pain management.

The CARM has received 83 ADRs relating to tramadol from 2015 to 2019, where the most frequent ADRs were rash, vomiting, and nausea. Serotonin syndrome and convulsions were also reported in five cases each.

Reference:
Prescriber Update, Medsafe, June 2020 (www.medsafe.govt.nz/)

(See also WHO Pharmaceuticals Newsletter No.6, 2015; Risk of slowed or difficult breathing in children in USA; No.5, 2015: Tramadol oral drops not for children under the age of 12 years in Australia)

Aminophylline

Risk of urinary retention

Malaysia. The National Pharmaceutical Regulatory Agency (NPRA) has reported the case of urinary retention in a 75-year-old male patient after treatment with intravenous aminophylline for acute exacerbation of chronic obstructive pulmonary disease (COPD).

Aminophylline is a combination of theophylline and ethylenediamine. Theophylline exerts bronchodilatory effect and is used for the treatment of COPD. Two products containing aminophylline are registered in Malaysia.

The NPRA has received 46 case reports with 76 adverse events associated with aminophylline use, two of which were linked to urinary retention. On the other hand theophylline has one report each for urinary retention and difficulty in urination. As of February 2020, WHO's Vigibase contains 25 and 30 reports of urinary retention suspected to be cause by aminophylline and theophylline respectively.

The dosage for aminophylline should be reduced in the elderly population. Patients on aminophylline therapy should be monitored for symptoms of urinary retention or difficulty urinating.

Reference:
MADRAC Bulletin, NPRA, 01/2020 *(www.npra.gov.my/)*

Antipsychotic medicines

Risk of cardiovascular events

New Zealand. Medsafe has reminded prescribers of the risks of cardiovascular adverse effects from antipsychotic medicines. The CARM was alerted to a case where a patient suffered a non-fatal cardiac arrest shortly after administration of an antipsychotic.

Antipsychotic medicines are generally indicated to treat psychosis such as hallucinations, paranoia and delusions. They may cause QT-prolongation, tachycardia, arrhythmias and changes in blood pressure. Clozapine is also associated with myocarditis and cardiomyopathy.

In addition to direct effects on the cardiovascular system, antipsychotic medicines are associated with metabolic changes such as dyslipidaemia, hyperglycaemia and central obesity.

Monitoring cardiovascular risk factors in patients taking antipsychotic medicines is necessary to minimize the risk of serious outcomes.

Reference:
Prescriber Update, Medsafe, June 2020 *(www.medsafe.govt.nz/)*

Direct-acting oral anticoagulants (DOACs)

Risk of bleeding

United Kingdom. The MHRA has advised health-care professionals to use caution when prescribing direct-acting oral anticoagulants (DOACs) to patients at increased risk of bleeding, such as older people or people with renal impairment.

DOACs are used for anticoagulation such as prevention of atherothrombotic events and of stroke and systemic embolism. Available DOACs include the direct factor Xa inhibitors apixaban (Eliquis®), edoxaban (Lixiana®), rivaroxaban (Xarelto®) and the direct thrombin inhibitor dabigatran (Pradaxa®).

Use of DOACs increases the risk of bleeding and can cause serious bleeds. In the UK, the MHRA continues to receive reports of bleeds, often life-threatening or fatal, in association with DOACs in patients. Thus DOACs should be used with caution in patients at increased risk of bleeding such as older people and patients with low body weight or renal impairment.

Exposure to DOACs is increased in patients with renal impairment and it is therefore important that patients receive an appropriate dose depending on renal function. DOACs can be used in patients with moderate renal impairment but a reduced dose may be required. In patients with severe renal impairment use of dabigatran is contraindicated.

Reference:
Drug Safety Update, MHRA, 29 June 2020 *(www.gov.uk/mhra)*

(See also WHO Pharmaceuticals Newsletter No.5, 2019: Risk of recurrent thrombotic events in Australia and New Zealand; No.4, 2019: Increased risk of recurrent thrombotic events in UK; No.3, 2016: Risk of thrombocytopenia in Japan)

Flucloxacillin

Risk of renal toxicity

New Zealand. Medsafe has announced that flucloxacillin can injure the kidneys as well as the liver. Both interstitial nephritis and hepatitis are listed in the flucloxacillin data sheets.

Flucloxacillin is beta-lactam antibiotic and generally indicated to treat infections caused by susceptible Gram-positive bacteria.

The CARM has received 39 reports of liver-related reactions and 13 reports of kidney-related reactions, suggesting that interstitial nephritis may be an under-recognized reaction to

flucloxacillin. Of the 13 reports of renal reactions, the majority occurred in patients aged over 70 years.

Early recognition of flucloxacillin-induced interstitial nephritis and prompt treatment reduces the risk of long-term renal impairment.

Reference:
Prescriber Update, Medsafe, June 2020 (*www.medsafe.govt.nz/*)

Ingenol mebutate

Potential risk of skin cancer

Canada. Health Canada communicated a potential link between ingenol mebutate (Picato®) and the risk of skin cancer.

Ingenol mebutate is applied topically on the skin, in adults, to treat actinic keratosis.

Based on new safety information from international clinical trials, A Health Canada review found an increased risk of skin cancer in patients treated with ingenol mebutate.

Of the 29 case reports (one Canadian) of skin cancer reviewed, 26 cases were found to be possibly linked to ingenol mebutate. A further assessment of 12 scientific literature found 6 studies with evidence of the possible link. Thus Health Canada concluded that there may be a link between ingenol mebutate and the risk of cancer.

Health Canada will ask for additional information from the manufacturer to determine if the benefits of the use of ingenol mebutate continue to outweigh its risks as a treatment option for actinic keratosis.

Reference:
Summary Safety Review, Health Canada, 2 July 2020 (www.hc-sc.gc.ca)

(See also WHO Pharmaceuticals Newsletter No.3, 2020: Risks of skin cancer outweigh benefits in EU; No.2, 2020: Risk of skin malignancy in UK; No.1, 2020: Use with caution in patients with a history of skin cancer in Ireland; Suspension during safety review in EU)

Levothyroxine

Risk of myocardial infarction

Malaysia. The NPRA has reported a case of non-ST segment elevation myocardial infarction (NSTEMI) in an 80-year-old female patient after treatment with levothyroxine for subclinical hypothyroidism. After levothyroxine was withdrawn, the reaction subsided and patient gradually recovered.

Levothyroxine is indicated as a substitution therapy in hypothyroidism. Six products containing levothyroxine are registered in Malaysia. The risk of developing myocardial infarction following levothyroxine use is documented in the product information.

The NPRA has received 223 local ADR reports with 571 adverse events suspected to be related to levothyroxine. There is one report associated with NSTEMI, as above-mentioned. The WHO's Vigibase revealed five reports of NSTEMI and 27 reports of acute myocardial infarction suspected to be associated with levothyroxine.

Health-care professionals should exercise extra caution when initiating levothyroxine in elderly patients and in patients with underlying cardiovascular disease. In those, the lowest possible dose should be initiated followed by gradual increase.

Reference:
MADRAC Bulletin, NPRA, 01/2020 (*www.npra.gov.my/*)

Water (for injection)

Risk of haemolysis

Australia. The Therapeutic Goods Administration (TGA) has reminded health-care professionals that water for injection can cause haemolysis resulting in patient harm including death, if large quantities are inadvertently administered intravenously without being rendered isotonic.

Water for injection is indicated for dissolving or diluting injectable therapeutic substances for parenteral administration. Water for injection is hypotonic. It is contraindicated for intravenous administration if it is not adjusted to isotonicity by the addition of suitable solutes.

The TGA is aware of international reports of mix-ups between 1 L bags of water for injection and other 1 L bags including sodium chloride 0.9% and glucose 5%.

All registered injection products in Australia with a volume of 100 mL or more are required to include a statement on the label to indicate if the injection is hypotonic, hypertonic or isotonic.

Health-care professionals should check the label to ensure there is no confusion between water for injection and other intra venous bags.

Reference:
Medicines Safety Update, TGA, 24 June 2020 (www.tga.gov.au/)

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

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

Aciclovir or valaciclovir - Acute generalised exanthematous pustulosis

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Summary

The combination of aciclovir and acute generalised exanthematous pustulosis (AGEP) was found in a routine signal detection screening of VigiBase, the WHO global database of individual case safety reports, performed in December 2018, and valaciclovir was later added to the assessment. Based on the overall reporting of adverse reactions for aciclovir or valaciclovir and the adverse reaction AGEP in VigiBase, the expected value for the number of reports for the combinations was five and three respectively, while the observed numbers were 10 and 14. The combinations were highlighted as disproportionately reported by IC analysis. Age range, time-to-onset (TTO) and drug withdrawal were similarly described in the case series and corresponded with the clinical picture of AGEP in most reports. However, the valaciclovir case series had few narratives, and a number of co-suspected drugs known to cause skin eruptions, making the assessment difficult. In many of the reports in both case series, co-reported drugs included labelled causes of AGEP or other severe cutaneous adverse reactions (SCARs) such as Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN). Though inconsistently, SJS and TEN are labelled for some aciclovir products. It is possible that initial presentations of these SCARs could be confused with AGEP.

In these two case series, despite the limitations, there are several reports indicating that aciclovir/valaciclovir can be strongly suspected to have been the cause of the drug induced skin reaction, and in two published case reports, this was confirmed by patch tests. In addition, since AGEP can be confused with a herpes eruption, it seems important to warn that aciclovir and valaciclovir can potentially cause AGEP.

Introduction

Aciclovir is an antiviral drug used to treat herpes simplex and zoster infections. The antiviral effect is due to inhibition of the herpes virus DNA polymerase enzyme, thereby inhibiting viral DNA synthesis and replication. When taken orally, aciclovir is slowly and poorly absorbed. Aciclovir is widely distributed in tissues and body fluids, including brain, kidney, lung, liver, muscle, spleen, uterus, vaginal mucosa, vaginal secretions, cerebrospinal fluid, and herpetic vesicular fluid. Valaciclovir is the L-valine ester of aciclovir and is almost completely converted to aciclovir and valine in the body.[1,2]

Acute generalised exanthematous pustulosis (AGEP) is a severe skin reaction, characterized by an acute onset (less than 10 days and typically within 48 hours)[3,4] of mainly small non-follicular pustules on an erythematous base. Systemic involvement sometimes occurs, but only in about one fifth of cases. The reaction is usually drug-related, with more than 90% of AGEP cases provoked by medications. Most often these are beta-lactam antibiotics (penicillins, cephalosporins, quinolones). Other medicines that have been implicated include pristinamycin, tetracyclines, sulphonamides, oral antifungals, diltiazem, hydroxychloroquine,

carbamazepine, and paracetamol.[4,5] However, AGEP is not listed in the product labelling for all of these medicines. Treatment consists of the removal of the drug causing the reaction and use of potent topical or systemic steroids, plus symptom management and infection prevention. Spontaneous resolution usually occurs within two weeks after discontinuation of the causative drug.[4,5,6]

AGEP is classified among the severe cutaneous adverse reactions (SCARs), which are very rare but potentially life-threatening reactions of delayed hypersensitivity. SCARs include AGEP, drug reactions with eosinophilia and systemic symptoms (DRESS), and the most severe form of SCARs: the Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) spectrum.

The mechanism and classification of SCARs are described by Bellón as "delayed T-cell-mediated type IV hypersensitivity reactions in the Gell and Coombs classification in which drug-specific T cells can be identified in the peripheral blood or skin infiltrates. The variation in clinical conditions has resulted in type IV reactions being further sub-classified according to different cytokine production patterns by T cell subsets and to the contribution of certain subpopulations of leukocytes to the inflammation and tissue damage. Traditionally, DRESS is considered a type IVb Th2-driven reaction, SJS/TEN a type IVc cytotoxic reaction, and AGEP a type IVd reaction". [7]

Reports in VigiBase

The combination of aciclovir and AGEP was found in a routine signal detection screening of VigiBase, the WHO global database of individual case safety reports, performed in December 2018. As of 6 October 2019, there were 16 cases reporting the combination. The expected value for the number of reports on the combination was five, and the association was highlighted as disproportionally reported, by IC analysis (IC_{025} = 0.8). After excluding suspected duplicates, 10 cases remained in the series. Age ranged between 20 and 96 years, with a median of 65 years, and there was an equal distribution of men and women. Valaciclovir was added to the assessment at a later stage. As of 1 December 2019, there were 14 cases of valaciclovir and AGEP found in VigiBase (de-duplicated data). Age ranged between 33 years and 86 years (two unknown), with a median of 66 years and, as with aciclovir, half of the reports concerned women, and half men. The expected number of cases was three and the IC_{025} value for valaciclovir and AGEP was 1.2.

All but two aciclovir reports, where the reporter was unknown, were submitted by a healthcare professional. For eight patients, the drug was stopped, and the reaction was reported to have abated in six cases. An outcome 'recovering' or 'recovered' was reported for eight of the aciclovir cases. Six of these eight patients had stopped the drug; it was not stated what action was taken in the other two reports.

In 10 of the 14 valaciclovir reports, the patient had recovered or was recovering after stopping the drug, and for one patient the outcome after stopping valaciclovir was stated as unknown. In three reports however, the patients had not improved or recovered despite a documented withdrawal of valaciclovir in one of these. For aciclovir, the time-to-onset (TTO) ranged between one and 21 days, and for valaciclovir, between one day and six months.

Countries represented in the combined case series were Australia, China, Czech Republic, France, India, Italy, Japan, Malaysia, Portugal, Switzerland, Thailand and the United States of America (US). The characteristics of the case series are set out in Table 1 for the aciclovir cases, and in Table 2 for valaciclovir.

Table 1. Characteristics of case reports in VigiBase of AGEP in association with aciclovir

Case	Age/ Sex	Suspected (S) or concomitant (C) drugs	Reactions (MedDRA PT)	Biopsy or patch test result	TTO	Action taken with drug	Outcome	Comment
1	75/M	Aciclovir*, Solifenacin* (S) *Concomitant lisinopril, nitrendipine, solifenacin; tamsulosin mentioned in the published case report*	AGEP, Erythema, Swelling	Skin biopsy proved drug induced reaction	-	Drug withdrawn/ *unknown outcome*	Unknown	Published case report describes aciclovir as treatment for the reaction and points to solifenacin as prime suspect
2	68/F	Aciclovir* (S) Alprazolam, Budesonide;Formoterol, Lercanidipine, Metformin, Simvastatin, Venlafaxine* (C)	AGEP	-	1 days	-	Recovering	TTO seems to have been 2 days. No dates reported for concomitant drugs
3	70/M	Aciclovir*, Benzylpenicillin, Gabapentin*, Olanzapine (S)	AGEP	-	3 days	-	Recovering	Both benzylpenicillin and gabapentin were started after aciclovir (TTO 1 and 0 days).
4	26/F	Aciclovir* (S), Dexamethasone (C)	AGEP	-	11 days	Drug withdrawn/ Reaction abated	Recovering	TTO probably shorter since narrative states that eruptions appeared before admission to ICU and reaction start date

Case	Age/ Sex	Suspected (S) or concomitant (C) drugs	Reactions (MedDRA PT)	Biopsy or patch test result	TTO	Action taken with drug	Outcome	Comment
		Concomitant ranitidine and calcium mentioned in narrative						reported to be day after admission.
5	73/F	Aciclovir*, Cefotaxime*, Dexamethasone (S) Duloxetine*, Ofloxacin**, Omeprazole*, Perindopril*, Pregabalin*, Valproic acid* (C)	AGEP	-	4 days	Drug withdrawn/ Reaction abated	Recovered	Cefotaxime and dexamethasone were started 11 days before (TTO=15 days) but discontinued together with aciclovir according to narrative
6	61/F	Aciclovir*, Cilastatin;Imipenem*, Ciprofloxacin*, Vancomycin** (S) Cytarabine, Daunorubicin, Gemtuzumab (C)	AGEP	Biopsy indicated AGEP	4 days	Drug withdrawn/ Reaction abated Rechallenge /No recurrence	Recovered	According to narrative, the patients journal vaguely states macular eruptions 3-4 months prior to reported event. TTO=22 days for co-suspected drugs.
7	20/F	Acetylcysteine;Benzalkonium; Tuaminoheptane***, Aciclovir*, Amoxicillin**, Biclotymol (S)	AGEP, Rash	-	3 days	Drug withdrawn/ *unknown outcome*	-	Antibiotic was discontinued but aciclovir was continued, together with a topical corticosteroid. The day after, the reaction was aggravated
8	50/M	Aciclovir* (S) Drug name/s under assessment for who-dd (herbal remedy) (C)	AGEP	-	-	Drug withdrawn/ Reaction abated	Recovered	Treatment duration = 2 days. However, not much information in report
9	53/M	Aciclovir* (S) Methylprednisolone (C)	AGEP	Biopsy confirmed AGEP. Positive patch test for aciclovir	21 days	Drug withdrawn/ Reaction abated Rechallenge /Reaction recurred	Recovered	Published case report.
10	96/M	Aciclovir* (S) Piperacillin;Tazobactam** (S)	AGEP	-	3 days	Drug withdrawn/ Reaction abated	Recovered	Antibiotics started and stopped on the same day as the reaction occurred. Aciclovir continued for an additional 6 days.

** SJS, TEN, or Erythema multiforme (EM) labelled in an SmPC from the Electronic Medicines Compendium https://www.medicines.org.uk/emc*
*** AGEP + SJS, TEN or EM labelled in an SmPC from the Electronic Medicines Compendium https://www.medicines.org.uk/emc*
**** SJS, TEN or EM reported but only with other drugs*

Case 2 in Table 1 has venlafaxine as a co-reported drug, however, the narrative describes the start of aciclovir treatment for submammary erythema and the eruption of AGEP after two days. Case 4 was from a dermatologist who described how the patient took aciclovir and shortly after developed eruptions all over the body. The patient was admitted to the intensive care unit (ICU). The reporter assesses the causality as probable. The narrative of case 7 indicates that an antibiotic taken concomitantly was discontinued but oral aciclovir was continued, after which the reaction was aggravated.

Table 2. Characteristics of case reports in VigiBase of AGEP in association with valaciclovir

Case	Age/ Sex	Suspected (S) or concomitant (C) drugs	Reactions (MedDRA PT)	Biopsy or patch test result	TTO	Action taken with drug	Outcome	Comment
1	33/F	Amoxicillin;Clavulanic acid**, Ampicillin;Sulbactam, Cotrimoxazole*, Valaciclovir, Vancomycin** (S)	AGEP	Skin biopsy confirmation. Positive patch test for amoxicillin; clavulanic acid	-	Drug withdrawn/ Reaction abated	Recovered	Published case report. Valacoclovir used as treatment for eruptions

Case	Age/ Sex	Suspected (S) or concomitant (C) drugs	Reactions (MedDRA PT)	Biopsy or patch test result	TTO	Action taken with drug	Outcome	Comment
2	52/ M	Paracetamol, Valaciclovir (S) Ceftriaxone**, Minocycline* (C)	AGEP	-	5 days	Drug withdrawn/ Reaction abated Rechallenge /*unknown outcome*	Recovered	Negative rechallenge reported for Paracetamol. No dates reported for ceftriaxone or minocycline. Ceftriaxone was also withdrawn
3	-/M	Doxorubicin, Folinic acid, Gemcitabine*, Metoclopramide, Ondansetron, Sulfamethoxazole; Trimethoprim*, Valaciclovir, Vinorelbine (S)	AGEP	-	2 days	Drug withdrawn/ Reaction abated	Recovered	All drugs (except metoclopramide) started on the same day and were withdrawn. Dose reportedly not changed for metoclopramide
4	-/F	Ceftriaxone**, Valaciclovir (S)	AGEP	-	2 days	Drug withdrawn/ Reaction abated	Recovered	TTO for ceftriaxone: 5 days
5	43/F	Valaciclovir (S)	AGEP	-	-	Drug withdrawn/ *unknown outcome*	Unknown	Reporter: Other Health Professional, Consumer/Non-Health Professional
6	86/ M	Valaciclovir (S)	AGEP, Syncope	-	1 days	-	Not recovered	Treatment continued 5 days after onset of AGEP. Syncope outcome also reported as not recovered
7	76/F	Naproxen*, Valaciclovir (S) Amlodipine;Ator-vastatin*, Mecobalamin, Phenol;Zinc, Teprenone (C)	AGEP, Acute kidney injury	-	2 days	Drug withdrawn/ Reaction abated	Recovered	TTO = 2 days for naproxen, mecobalamin, teprenone and phenol;zinc. Amlodipine;atorvastatin treatment ongoing since several years
8	75/ M	Dexamethasone, Lenalidomide*, Phenoxymethyl-penicillin, Sulfamethoxazole; Trimethoprim*, Valaciclovir (S)	AGEP	Patch test positive for amoxicillin	5 days	Drug withdrawn/ Reaction abated	Recovered	All drugs started and stopped on the same day. Phenoxymethylpenicillin was the only drug the patient had not taken before
9	68/F	Cefpodoxime, Piperacillin;Tazob actam**, Valaciclovir (S) Glimepiride, Metformin, Pioglitazone, Torasemide* (C)	AGEP, Biopsy skin abnormal, C-reactive protein increased, Leukocytosis, Lymphopenia, Neutrophilia, Pyrexia, Skin exfoliation	AGEP was biopsy confirmed on two occasions	2 days	Drug withdrawn/ No effect observed	Not recovered	According to the narrative, cefpodoxime was primary suspect drug, but valaciclovir or an infectious cause were not excluded as alternative explanations. Piperacillin;tazobactam was administered about 20 days after first onset of AGEP, and this resulted in new eruptions, erythroderma and circulatory collapse requiring intensive care.
10	62/ M	Amoxicillin**, Carbamazepine**, Valaciclovir (S)	AGEP	-	14 days	Drug withdrawn/ Reaction abated Rechallenge /*unknown outcome*	Recovered	Reported drug start date for amoxicillin is after reported reaction start. However, it is included in the "dose regimen" described in the narrative and the nature of the date could suggest an error in reporting
11	81/ M	Influenza vaccine (Vaxigrip), Sulfamethoxazole;	AGEP	The biopsy was in favour of a post-viral or medically	6 months	Dose not changed/No effect observed	Not recovered	TTO vaccine: 9 days Eruptions are reported to have started "at the same time as a pharyngitis".

Case	Age/ Sex	Suspected (S) or concomitant (C) drugs	Reactions (MedDRA PT)	Biopsy or patch test result	TTO	Action taken with drug	Outcome	Comment
		Trimethoprim*, Valaciclovir (S)		induced reaction.		Rechallenge /*unknown outcome*		
12	81/F	Valaciclovir (S), *Ebastine, Monotildiem, Co Aprovel, Elisor, Inexium are mentioned as ongoing treatment in narrative*	AGEP	Two biopsies, taken on thigh and arm, indicated a drug induced SCAR-type reaction	3 days	Drug withdrawn/ Reaction abated	Recovering	Narrative mentions codeine;paracetamol taken during three days about 8 days before eruption of temporal lesions which in turn was treated with valaciclovir since herpes zoster was suspected. Patient had taken topical aciclovir before without any problem.
13	50/ M	Valaciclovir (S)	AGEP	Biopsy indicate drug induced reaction	2 days	Drug withdrawn/ Reaction abated	Recovered	Patient experienced pustular eruptions twice before current event. Allergologic work up then positive for amoxicillin and Introna® (Interferon alfa-2b). No work up performed for valaciclovir after most recent event.
14	64/F	Amlodipine*, Bortezomib*, Dexamethasone, Enoxaparin, Thalidomide*, Valaciclovir (S)	AGEP, Rash pustular, Urticaria	Biopsy showed leukocytoclastic vasculitis with secondary epidermal lesions	12 days	Drug withdrawn/ Reaction abated	Recovered	TTO urticaria/AGEP suspicion: Thalidomide: 7/11 days Amlodipine: 19/24 days Valaciclovir: 8/12 days Bortezomib: 7/11 days Dexamethasone: -1/3 days Enoxaparin: -4/0 days Reporter mentions low extrinsic imputability for valaciclovir

** SJS, TEN, or EM labelled in an SmPC from the Electronic Medicines Compendium https://www.medicines.org.uk/emc*
*** AGEP + SJS, TEN or EM labelled in an SmPC from the Electronic Medicines Compendium https://www.medicines.org.uk/emc*

Narratives of valaciclovir cases 12 and 13 describe clinical scenarios where the patient took valaciclovir and developed pustular eruptions shortly after. The patient in case 12 was treated for herpes zoster with "bétadine" and valaciclovir. After three days, about five days after stopping codeine+paracetamol, taken for post-surgical pain, pruritic lesions appeared. The patient in case 13 had experienced pustular eruptions twice before. The first time, valaciclovir was one of four drugs taken, but no allergy tests were made. The second time, amoxicillin and interferon were deemed causative after positive allergy tests. The third time, valaciclovir was introduced and the eruptions appeared within two days.

Literature and labelling

AGEP is not labelled for either aciclovir or valaciclovir. Erythema multiforme (EM) and SJS/TEN are labelled with the frequency "Not known" for aciclovir 200 mg tablets from Wockhardt UK Ltd, and "Rare" for aciclovir 800 mg tablets from Accord.[1,8] However, in labels for other formulations, no mention is made of severe skin reactions.[9,10] The valaciclovir labels in the UK do not mention SCARs.[2]

In aciclovir labels from the US, EM, SJS and TEN are mentioned frequently.[11,12] However, the reaction is typically not mentioned in topical formulations. In labels for valaciclovir, only EM is mentioned.[13] EM is not a SCAR but it is important to note as it is often caused by herpes simplex virus, and may not be clearly distinguishable from AGEP in its early stage.[5]

Two of the cases in the series for aciclovir have been published in the literature. The first concerns case 1 in Table 1 where solifenacin is suspected to be the causative drug.[14] The second corresponds with case 9, and describes in detail the diagnosis where a biopsy revealed typical characteristics of AGEP. Aciclovir was suspected and replaced, and the reaction abated. Two months later, the exclusion of other potential causative agents than aciclovir was made, using patch tests.[15]

An additional published case report from Finland, not corresponding to any in the case series, describes a 44-year-old woman developing pustules after treatment with aciclovir against labial herpes. The diagnosis of AGEP secondary to aciclovir therapy was confirmed by positive patch testing.[16]

Case 1 in Table 2 is described in the literature, mentioning acute localised exanthematous pustulosis (ALEP) as the reaction, though the term reported to VigiBase was AGEP. The case report presents an antibiotic as the cause of the reaction and valaciclovir as a treatment of an assumed diagnosis of shingles.[17]

Discussion

Aciclovir case reports that strongly implicate aciclovir as the cause of AGEP, include two published cases where the causative drug was confirmed by patch test, and two unconfounded reports with good narratives (cases 2 and 4). Case 7, describing an aggravated skin reaction after discontinuation of confounding drugs also indicates aciclovir as the causative drug.

Most aciclovir reports (n=7) have a time to onset of between one and four days, consistent with the expected onset time for the reaction, and two reports have 11 and 21 days between drug intake and reaction onset. However, the report where it took 21 days to develop the reaction is the published case with patch test confirmation (case 9). It seems that there are circumstances where the reaction is delayed, and in this particular case, the concomitant administration of a corticosteroid is mentioned as one suspected cause of the delay, together with the absence of prior exposure to aciclovir and the "low sensitizing potential of the drug". Interestingly, in the aciclovir case where time to onset was reported as 11 days, an oral corticosteroid is reported to have been taken concomitantly. For valaciclovir, TTO ranged between one day and six months. However, the latter case is unusual, and if excluding it as an outlier, the longest TTO in the case series was 14 days.

Case reports that strongly implicate valaciclovir as the cause of AGEP include cases 12 and 13 where the narratives describe clinical scenarios where the patient took valaciclovir and developed pustular eruptions shortly after. The patient in case 12 was treated with codeine+paracetamol before the eruption of a temporal lesion, and paracetamol has been implicated as a cause of AGEP. However, the treatment only continued for three days, which means that it was stopped well before the temporal lesion emerged some days later. The lesion was suspected to be herpes zoster and treated with "bétadine" and valaciclovir, and after three more days, pruritic lesions appeared. The patient in case 13 had experienced pustular eruptions twice before. The third time, valaciclovir was introduced and the eruptions appeared within two days.

Most valaciclovir cases are co-reported with one or more antibiotics labelled to cause AGEP or a different SCAR, and in some of the reports, it seems more likely that a different drug was the cause of the reaction. In three cases (1, 8 and 9), an antibiotic is confirmed or strongly suspected as the cause, and in one case (11), it is more likely that the causative drug was the vaccine which was administered nine days before onset, alternatively an ongoing infection, while valaciclovir had been taken for six months. In case 14, the eruptions appeared some time into the treatment for leukaemia the patient was undergoing. All drugs were withdrawn, however bortezomib was re-introduced without the eruptions reappearing. Therefore, thalidomide, valaciclovir and amlodipine were still all suspects, although the reporter mentions a "low extrinsic imputability" of valaciclovir.

The fact that there are few reports where one or more co-reported drugs do not have a SCAR in the label, usually SJS/TEN but sometimes AGEP, as found in trials or as post-marketing experience, is the most important possible confounder for both case series. Overlap between SJS/TEN and AGEP does occur but this is rare,[18] so it is not clear if this would increase the possibility of aciclovir or valaciclovir causing AGEP, despite related mechanisms.

However, diagnostic confusion between SCARs can occur in the early stages[18] and also between severe AGEP, especially with mucous membrane involvement and SJS/TEN.[4] The latter might not have greatly impacted the case series as it is more likely that AGEP would be diagnosed as SJS/TEN than the reverse because of the characteristic pustules. However, a limitation of the case series is the absence of histopathology which clearly distinguishes between the SCARs.

Finally, it is important to note that AGEP might be confused with a herpes eruption, and two reports mention that aciclovir/valaciclovir was used as treatment for the eruptions (case 1 in Tables 1 and 2). In addition, a literature report not in the series described a case where AGEP was confused with a herpes eruption.[19]

Conclusion

In these case series, there are several cases where aciclovir and, though to a lesser extent, valaciclovir, can be strongly suspected to have been the cause of AGEP, and in two literature reports, this was confirmed by patch tests. Since the condition can be confused with a herpes eruption, it seems important to warn that also aciclovir could potentially cause the skin reaction.

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Alectinib – Rhabdomyolysis

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Summary

Alectinib is a highly selective and potent ALK (anaplastic lymphoma kinase) and RET ("rearranged during transfection") tyrosine kinase inhibitor. Alectinib (Alecensa® in the EU, US; Alecensaro® in Canada) is indicated as first-line monotherapy for adults with ALK-positive advanced non-small-cell lung cancer (NSCLC). As monotherapy it is also indicated for the treatment of adults with ALK-positive advanced NSCLC who have been previously treated with crizotinib. The EU Summary of Product Characteristics (SmPC) lists myalgia or musculoskeletal pain and raised creatine phosphokinase (CPK) as reported in patients in pivotal trials with alectinib, including grade 3 events. The median time to increased grade 3 CPK was 14 days across clinical trials. Myalgia and increased blood CPK are labelled for alectinib in the EU and the US product labels. However, it is not labelled for rhabdomyolysis.

As of 19 May 2019, there were eight reports in VigiBase, the WHO global database of individual case safety reports, for alectinib and the adverse drug reaction (ADR), rhabdomyolysis. The reports support a relationship between alectinib and rhabdomyolysis, with six cases giving alectinib as the only suspected drug, and six cases reporting a positive dechallenge, of which two also had a positive rechallenge. In addition, the time-to-onset is consistent in the cases where this information is available (12-14 days).

Current product information for alectinib does not contain sufficient precautions and warnings to inform healthcare professionals and patients about the potential of rhabdomyolysis as an adverse effect.

Introduction

Tyrosine kinases such as anaplastic lymphoma kinase (ALK) are becoming major areas of interest for the development of new chemotherapy agents. ALK plays an important role in the development of the brain; it also drives the progression of several cancers, including anaplastic large-cell lymphoma, neuroblastoma, and non-small-cell lung cancer (NSCLC). Alectinib is a highly selective and potent ALK and RET ("rearranged during transfection") tyrosine kinase inhibitor. In preclinical studies, inhibition of ALK tyrosine kinase activity led to blockage of downstream signalling pathways including STAT 3 ("signal transducer and activator of transcription 3") and PI3K/AKT ("phosphoinositide 3-kinase"/"protein kinase B", also called AKT) and induction of tumour cell death (apoptosis).[1,2] Alectinib demonstrated *in vitro* and *in vivo* activity against mutant forms of the ALK enzyme, including mutations responsible for resistance to crizotinib. The major metabolite of alectinib (M4), metabolised by CYP3A4, has shown similar *in vitro* potency and activity.[1,2]

Activating mutations or translocations in the gene encoding ALK have been identified in different tumours, including NSCLC, where it is present in about 2 to 5% of cases and in 3 to 7% of adenocarcinomas.[3-5] ALK is a receptor tyrosine kinase that shows striking homology with members of the insulin receptor family, whose physiological function is still unclear.[6] The translocation of ALK determines the expression of the resulting fusion protein and the consequent aberrant signalling of ALK in the NSCLC. The identification of ALK as a potential therapeutic target in the treatment of NSCLC has led to the development of drugs aimed at inhibiting its activity. The first two with this mechanism of action to be authorized were crizotinib (Xalkori®), and subsequently ceritinib (Zykadia®), both for patients not previously treated and for those who have already received treatment for the disease.[7-10] Other tyrosine kinase inhibitors (with stem –*tinib*) that are used in NSCLC include alectinib, brigatinib and lorlatinib.

Alectinib was granted an accelerated approval by the US Food and Drug Administration (FDA) in December 2015 to treat patients with ALK-positive advanced NSCLC whose disease worsened after, or who could not tolerate, treatment with crizotinib; this was converted into full approval in November 2017. It had conditional approval from the European Medicines Agency (EMA) in February 2017 for the same indication, which was extended in October 2017 with the indication to first-line treatment of adult patients with ALK-positive advanced NSCLC.[11]

Currently alectinib as monotherapy is indicated for the first-line treatment of adult patients with ALK-positive advanced NSCLC; and as monotherapy for the treatment of adult patients with ALK-positive advanced NSCLC previously treated with crizotinib.[1] Alectinib is available as capsules (150 mg). The recommended dose is four capsules taken twice a day with food (a total of 1,200 mg daily). For patients with severe hepatic impairment the recommended dose is three capsules twice a day with food (900 mg). The doctor may reduce the dose or stop treatment temporarily if side effects occur. In certain cases, treatment should be permanently stopped.[1] Most adverse effects due to ALK inhibitors can be managed efficiently via dose modifications or interruptions.[12-14]

Medicines-related myotoxicities such as rhabdomyolysis or myoglobinuria are the most serious medical emergencies. Rhabdomyolysis is an acute and fulminant necrotizing myopathy that can cause severe myalgia, muscle swelling and weakness, and increased serum CPK as high as 2,000 times upper limit of normal (ULN). It is associated with myoglobinuria (urine that appears dark brown or pink due to the presence of pigmented myoglobin), which can cause acute renal failure and death. If the offending agent is removed and patients are aggressively treated, the muscle typically heals well.[15]

Reports in VigiBase

The combination alectinib–rhabdomyolysis was first identified in 2016 in a screening of VigiBase, the WHO global database of individual case safety reports (ICSRs), focussing on new drugs and serious adverse drug reactions (ADRs). Alectinib is labelled for myalgia and increased blood CPK in both the EU and the US product labels. However, it is not labelled for rhabdomyolysis.[1,2]

As of May 2019, out of over 20 million ICSRs in VigiBase, there were 1,993 ICSRs with alectinib as a suspected medicine. A total of eight ICSRs (0.4% of the alectinib reports), with the combination alectinib and rhabdomyolysis were retrieved from VigiBase on 19 May 2019 and reviewed case by case. The number expected was three; the $IC_{0.25}$ was -0.1; the most recent report was 19 May 2019; the number of reports where it was the single suspected drug was six; the number of positive dechallenges was six; the number of positive

rechallenges two. There were eight ICSRs classified as 'serious'.

The reports were submitted from six countries: Germany (two reports), Portugal (two), Austria, Canada, USA, and Australia (one each). Details of case reports are set out in Table 1.

Table 1: Characteristics of case reports in VigiBase of rhabdomyolysis in association with alectinib

Case	Age/ Sex	Suspected (S) or concomitant (C) drugs	Daily dose	Reactions	Time-to-onset (TTO)	Dechallenge/ Rechallenge	Outcome
1*	57/m	Alectinib (S), pantoprazole (C), levetiracetam (C)	1,200 mg	Rhabdomyolysis	14 days	Positive/Not applicable, negative due to reduced dosage (450 mg twice daily)	First doses were withdrawn after TTO, recovered in 5 days, two days later new dose reduced to 900mg/day
2	53/m	Alectinib (S), tinzaparin sodium(C)	unknown	Rhabdomyolysis, CPK increased	14 days	Positive/Positive at lower dose	
3	64/f	Alectinib (S), enoxaparin (C), dexamethasone (C), nadroparin (C), mirtazapine (C), pantoprazole (C), zopiclone (C), naloxone (C), oxycodone (C), torasemide (C), calcium carbonate + colecalciferol (C)	1,200 mg	Decreased appetite, blood CPK increased, pyrexia; gastritis; nausea; arthralgia; pelvic pain; large intestine perforation: peritonitis; pyelonephritis; rhabdomyolysis; sepsis; transaminases increased; pelvic hematoma; general physical health deterioration; retroperitoneal hematoma; retroperitoneal hemorrhage; diverticulitis	12 days	Unknown / Unknown with reduced dosage (450 mg twice daily, and 300 mg twice daily)	Recovered with some sequelae
4	49/m	Alectinib (S), dexamethasone (C)	1,200 mg	Rhabdomyolysis, edema lower limb, myalgia, blood CPK increased, asthenia, grip strength decreased	13 days	Positive/Positive	Recovering
5	?/m	Alectinib (S), dexamethasone (C), furosemide (C)	1,200 mg	Rhabdomyolysis, hepatic function abnormal, edema lower limb	No data	Positive/Negative	Recovered; but hepatic function abnormal - Not recovered
6	64/f	Alectinib (S), rosuvastatin calcium (S)	---	Rhabdomyolysis (CPK >10,000)	No data	Positive/No data	Recovering/re-solving
7	-/m	Alectinib (S), tamsulosin (C), finasteride (C), bisoprolol (C), pantoprazole (C), linagliptin (C), rosuvastatin calcium (C), folic acid (C), crizotinib (C), apixaban (C), simvastatin (C),	1,200 mg	Rhabdomyolysis	No data	Unknown/No data	Unknown
8	58/m	Alectinib (S), pirfenidone (S)	1,200 mg	Rhabdomyolysis, blood CPK increased, myalgia, swelling, peripheral swelling, wrong patient received product	No data	Positive/No data	Recovered

**Index case*

Illustrative case reports

Three of the eight ICSRs can illustrate important details: one index case, the first documented ICSR in the onset of this signal (alectinib and rhabdomyolysis) with positive dechallenge; one case with clear temporal sequence and rechallenge; and a third with pharmacological interactions for rhabdomyolysis syndrome:

Case 1: is the index case, from an oncologist, concerning a 57-year-old male patient. On 29 October laboratory tests showed blood CPK to be 420 U/L (normal range 39-190); one day later, the patient started oral alectinib, 600 mg twice daily for NSCLC, ALK positive; on 13 November, CPK was 1,615 U/L and the patient was diagnosed with rhabdomyolysis (severity not reported). The patient had muscle pain, but no increase in creatinine level was noted for the time of the event. No further investigations were performed to confirm the diagnosis, as the combination of clinical condition and the laboratory tests appeared to be sufficient. Therapy with alectinib was interrupted on the same day. No treatment was reported for the event. On

17 November CPK was 705 U/L, and according to the reporter, the rhabdomyolysis had resolved, as he described in the suspected ADR report. On 19 November, it was decided to restart therapy with oral alectinib at a reduced dose of 450 mg twice daily, with close monitoring. On 24 November CPK was 380 U/L.

Case 4: a 49-year-old adult male, who had increased CPK and rhabdomyolysis, associated with the use of alectinib, for ALK-positive lung cancer, started oral alectinib on 28 June, 600 mg twice daily for NSCLC. He was also taking dexamethasone for an unknown indication. The ADR occurred 13 days after the start of the administration of the suspected drug. The reporter noted that the medication was halted on 12 July due to symptoms of rhabdomyolysis, and that it was restarted with the same dose when CPK had decreased sufficiently. The reporter noted in his ADR report, "treatment resumed on 20 July maintaining an effective treatment". He did not mention if there was a dose reduction. With reintroduction, rhabdomyolysis reoccurred and the patient again experienced myalgia, asthenia and oedema of the lower limbs; but only a moderate to light increase of the CPK.

Case 7: an elderly male patient with type 2 diabetes, started therapy on 11 May with oral alectinib, 600 mg twice daily for NSCLC. Concomitant medication included tamsulosin, finasteride, bisoprolol, pantoprazole, linagliptin, rosuvastatin calcium, folic acid, vitamin D, crizotinib, apixaban, magnesium and simvastatin. On an unknown date, he had rhabdomyolysis and was admitted to hospital. Therapy with alectinib was interrupted; the outcome of the rhabdomyolysis was reported as unknown. Simultaneous treatment with two statins (rosuvastatin calcium and simvastatin), known potential causes of myopathy and rhabdomyolysis, was present in this ICSR, but the reporter did not consider statins as suspected for the ADR. By contrast, in Case 6 in Table 1 the reporter also included rosuvastatin calcium as a suspected drug, as well as alectinib. In conclusion, in this case, there could also have been a pharmacological interaction due to a synergistic effect.

A screening of VigiBase on 25 June 2019 using the MedDRA SMQ "*Rhabdomyolysis/Myopathy - Narrow*" with alectinib found 13 ICSRs, of which eight were those with rhabdomyolysis previously described (Table 1), and five other cases with MedDRA preferred terms (PTs) such as "myopathy" (four cases) and "myoglobin blood increased" (one), plus several co-reported preferred terms, such as "myalgia", "blood CPK increased", "asthenia", "oedema peripheral", "blood creatinine increased", and so on. A search with the SMQ "*Rhabdomyolysis/Myopathy - Broad*" with alectinib resulted in 258 ICSRs, with more PT related: myalgia, myositis, CPK increased, muscular weakness, etc.

Literature and labelling

As of 25 June 2019, no published cases of rhabdomyolysis associated with alectinib (or other ALK inhibitors such as ceritinib, crizotinib, brigatinib, lorlatinib) could be found in the literature. A recent alectinib review[12] found the same results. Also, two systematic reviews[13,14], the first with 15 trials (2,005 patients), the second with 14 studies (2,793 patients) found no rhabdomyolysis cases were associated with alectinib (or other ALK inhibitors).

Among the ALK inhibitors, alectinib is considered well tolerated. Compared to crizotinib, alectinib is associated with lower rates of vision disorder (10%) and gastrointestinal ADRs, but higher rates of serious hepatic or musculoskeletal ADRs.[12]

The EMA Committee for Medicinal Products for Human Use (CHMP) European Public Assessment Report[11] already indicates that the only signal of increased toxicity related to alectinib was myalgia/CPK increase. The most common side effects of alectinib in the EU SmPC[1] and US FDA product label[2] include: tiredness; constipation; swelling in hands, feet, ankles, face and eyelids; anaemia; muscle pain, tenderness and weakness (myalgia). Myalgia or musculoskeletal pain occurred in 26% of patients in pivotal clinical studies NP28761, NP28673 and BO28984=ALEX. Raised CPK occurred in 41% of 347 patients, with CPK laboratory data available in pivotal clinical studies NP28761, NP28673 and ALEX.

The EU SmPC[1] published by EMA in 2017 mentions safety data collected during drug development:

> *Severe myalgia and creatine phosphokinase (CPK) elevation*: cases of myalgia (28%) including myalgia events (22%) and musculoskeletal pain (7.4%) have been reported in patients treated with alectinib across pivotal clinical trials (NP28761, NP28673, BO28984=ALEX).

There is similar information on the US FDA and Canada product labels:[2,16]

> Elevations of CPK occurred in 41% of 347 patients with CPK laboratory data available across pivotal clinical trials (NP28761, NP28673, BO28984=ALEX) with alectinib. The incidence of grade 3 elevations of CPK was 4%. Median time to grade 3 CPK elevation was 14 days (interquartile range 13-28 days). Dose modifications for elevation of CPK occurred in 3.2% of patients.

There is a warning about severe myalgia and increases in CPK: patients should be advised to report any unexplained muscle pain, or muscle pain that does not go away, muscle tenderness or weakness, as mentioned in the EU SmPC, US FDA and Canada product labels.[1, 2, 16] CPK levels should be assessed every two weeks (14 days) for the first month of treatment, and as clinically indicated in patients reporting symptoms. Based on the degree

of the CPK increase, alectinib should be withheld, then resumed or have the dose reduced. In the EU, US, Canada product labelling, details are given on how to modify and reduce the dose according to CPK elevations, and other serious ADRs (ALT/AST or bilirubin elevations, bradycardia, renal impairment among other ADRs).[1,2,16]

In the EU, US and Canada product labelling, there is no information on pharmacological interactions with medicines that could increase blood CPK or induce rhabdomyolysis, such as statins.[1,2,16]

Discussion and conclusion

Besides hepatotoxicity, myalgia and CPK increase are the next category of ADRs to be watchful for. Among available ALK inhibitors, this is unique to alectinib, and brigatinib to a lesser extent (43% versus 30% respectively for CPK elevation of any grade).[12] As myalgia and CPK increase is not well recognized for patients, prior to treatment initiation, they need to be informed of potential symptoms such as muscle pain or weakness. As with hepatic ADRs, CPK increase also has an early onset, with mean time to grade 3 increase (>5 × ULN) occurring at approximately day 14, so CPK levels need to be monitored every two weeks for the first month and then as often as clinically indicated. If severe myalgia or an increase in CPK occurs, it is reasonable to withhold alectinib until it resolves to at least grade 1 in severity.

Currently rhabdomyolysis is not described in the labels for alectinib; only myalgia and increased CPK are.[1,2,16] However, the cases in VigiBase support an association between alectinib and rhabdomyolysis, with six cases reporting alectinib as the only suspected drug, and with six cases reporting a positive dechallenge, of which two also report a positive rechallenge. In addition, the time-to-onset is consistent in the cases where this was provided (12-14 days). Current product information for alectinib does not inform patients and health care providers about the potential interactions with statins and their synergistic effect on rhabdomyolysis.

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Response from Roche

First, we would like to thank you for the opportunity to review the signal report prepared by the Uppsala Monitoring Center (UMC) in which an association between alectinib and rhabdomyolysis is postulated.

Roche has been and is continuously monitoring events reported as rhabdomyolysis as part of its standard signal detection process. To date, this monitoring has not rendered evidence that the cases reported with the Preferred Term of 'rhabdomyolysis' are confirmed cases of drug-induced rhabdomyolysis which could be attributed to alectinib.

As noted in the signal report prepared by the UMC, rhabdomyolysis is a serious medical emergency which can be life-threatening. Upon the review of the cases reported during clinical trials and from the post-marketing experience with alectinib, Roche has observed cases of myalgia and of creatine phosphokinase (CPK) increase but none with a degree of severity and elements required to confirm the diagnosis of rhabdomyolysis. For the assessment of the cases reporting the verbatim "rhabdomyolysis" in this comment document, a case definition described by Holbrook et al (2011) was used. This considers the following 3 main criteria to establish a case of rhabdomyolysis:

- Muscle symptoms (such as unexplained myalgia or muscle weakness)
- Increase of CPK above 10000 U/L or above 10 times the upper limit of normal (ULN) [for the Health Canada definition; above 50 times ULN for the US MedWatch definition]
- and renal involvement such as:
    - serum creatinine elevation temporally linked to CPK elevation
    - and/or myoglobinemia
    - and/or myoglobinuria
    - and/or brown urine
    - or renal compromise.

The eight cases retrieved and described by the UMC have been reviewed by Roche and assessments for these cases are proposed in the paragraph below.

Case 1 [Roche ID 1492032]: In this case the patient reported muscle pain and a CPK increase up to 1615 U/L, corresponding 8.5 time the ULN (ULN=190). There were no renal signs or symptoms and there was no creatinine elevation at the time of the event. Concomitant medications include levetiracetam for which rhabdomyolysis, muscular weakness and CPK elevations are labeled events. Hence, there were elements lacking to confirm the diagnosis of rhabdomyolysis and an alternative explanation available.

Case 2 [Roche ID 1596813]: In this case the patient reported muscle pain, a CPK increase up to 16.42 µmol/L, that is 5.2 the ULN (ULN<3.17 µmol/L), and creatinine increased at 132 µmol/L (ULN=106 µmol/L) at the time when the highest CPK level was reported, and up to 152 µmol/L one month later, when CPK levels were back to normal. Serum myoglobin was also increased at 127 µg/L. The reported events do not match the definition of rhabdomyolysis as the maximum CPK increase reported remained below 10 time the ULN. In addition, there was an alternative explanation provided by the reporter since the patient did strenuous physical exercise followed by pain (he had cut a 50 meter long and 3 m high hedgerow by hand).

Case 3 [Roche ID 1603916]: In this case the patient reported many events among which CPK increase above 1500 UI/L, that is over 10 times the ULN (ULN=140), and elevated creatinine to a maximum of 1.9 mg/dL (ULN=0.9). Myalgia or muscular weakness are not described explicitly, but she reportedly had pain in the pelvis. These results could confirm the diagnosis of rhabdomyolysis. However the rhabdomyolysis occurred in a context of life threatening retroperitoneal bleeding and impaired medical condition including brain metastasis and cachexia. Concomitant medications included mirtazapine for which rhabdomyolysis is a labeled event. Therefore, a causal role of alectinib is not confirmed in the presence of strong alternative explanations from the patient concurrent conditions and concomitant medication.

Case 4 [Roche ID 2175246]: In this case the patient reported myalgia, muscle weakness ('grip strength decreased') and CPK increase without reported values. There was no renal signs or symptoms and no creatinine elevation. The reported elements are insufficient to

confirm a diagnosis of rhabdomyolysis.

Case 5 [Roche ID 2252786]: In this case the patient reported none of the elements pertaining to the rhabdomyolysis definition, therefore it is not possible to confirm the diagnosis due to insufficient information.

Case 6 [Case not identified in Roche Safety database]: As this case was not identified in Roche safety database, an evaluation is not possible due to insufficient information; however it is noted that a statin is reported as a co-suspect medication and rhabdomyolysis is a known adverse reaction with statins.

Case 7 [Roche ID 2171117]: In this case the patient reported extreme muscle weakness and pleural effusion leading to hospitalization. Rhabdomyolysis is reported but without CPK values, and no renal involvement is reported. In addition, and as noted by the UMC, a statin is reported as a concomitant medication.

Case 8 [Roche ID 2178566]: In this case the patient reported muscle pain and CPK increase at 3000 UI/L (no ULN reported). There was no renal involvement reported, so a diagnosis of rhabdomyolysis is not confirmed.

Roche found that one (Case 3) of the eight cases identified by the UMC matches the criteria for the diagnosis of rhabdomyolysis proposed by Holbrook et al. with CPK increase above 10 times the ULN and renal involvement. However, alternative explanations for the event were present in this case, therefore a causal relationship between the rhabdomyolysis and alectinib is deemed to be not confirmed. While the criteria for the diagnosis of rhabdomyolysis are not met in the remaining evaluable cases, the reported events of myalgia and CPK elevation are adequately reflected as adverse drug reaction in the alectinib product labels, including corresponding warning and precautionary information, monitoring of CPK levels as well as dose interruption/reduction guidelines in case of CPK elevations > 5 times the ULN.

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Tocilizumab and Cutaneous Vasculitis

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Summary

Tocilizumab is a biological agent that inhibits interleukin-6 that is indicated in rheumatoid arthritis, and recently, polymyalgia rheumatica and giant cell arteritis. Administration intravenously or subcutaneously leads to a rapid decline in C-reactive protein. The medicine is corticosteroid-sparing in polymyalgia and giant cell arteritis. Sixteen reports from VigiBase of cutaneous vasculitis, an inflammation of small blood vessels, the majority labelled as serious, occurred after a median of 60 days treatment but with a wide range for time to onset. Reports were entered in VigiBase from June 2012 until April 2019. Reactions were more prevalent in men and with higher dose rates of 8 mg/kg monthly intravenously. Fifteen of these cases were in patients with rheumatoid arthritis. A number of medicines taken in addition to tocilizumab were listed as 'suspected' contributors to the cutaneous vasculitis reaction, including other biological medicines, namely tumour necrosis factor inhibitors, abatacept, anakinra and leflunomide, all these in one case. Dechallenge was successful in six cases and rechallenge led to recurrence in the one subject re-exposed providing reasonable evidence for an association between tocilizumab and cutaneous vasculitis, although the standard of the 16 reports were generally poor. This potential adverse drug reaction, however, is not listed in the drug label approved by FDA.

Introduction

Tocilizumab is one of an important group of biological agents that have revolutionized the treatment of rheumatoid arthritis. It is a fully human monoclonal antibody that inhibits the inflammatory cytokine, interleukin-6 (IL-6). IL-6 synthesis is driven by interleukin-1(IL-1) and tumour necrosis factor-alpha, up-stream cytokines that are also targets for inhibitory therapies, including IL-1 receptor antagonist (anakinra) and a number of tumour necrosis factor inhibitor recombinant proteins, including etanercept, adalimumab, infliximab and golimumab. Tocilizumab also has an indication for juvenile idiopathic arthritis, and more recently, polymyalgia rheumatica (PMR)(1), and giant cell arteritis.(2)

Tocilizumab therapy is administered parenterally, either intravenously or subcutaneously (SC), and results in rapid reduction of C-reactive protein

(CRP) concentrations, the preferred biomarker for systemic inflammation. IL-6 promotes the production of CRP from the liver. Optimally, the drug is given with concomitant methotrexate in patients with rheumatoid arthritis (RA) or juvenile idiopathic arthritis (JIA), since the combination is more effective at slowing disease progression as manifest by joint bone erosions. In PMR, tocilizumab is corticosteroid-sparing, beneficial in reducing the dose and duration related adverse effects of corticosteroids, notably osteoporosis, type 2 diabetes mellitus, weight gain, muscle loss and sleep disturbance.

A number of cases of cutaneous vasculitis associated with tocilizumab have now been reported, including reports submitted to VigiBase.(3) Cutaneous vasculitis is inflammation of small blood vessels and is confined to the skin. Typically, it presents with palpable purpura and/or petechiae, essentially small haemorrhages that have formed small blood clots. However, it is also a recognised manifestation of rheumatoid arthritis.

Reports in VigiBase

Sixteen cases of apparent cutaneous vasculitis have been reported in association with tocilizumab from the middle of June 2012 up until April 2019. The cases were from nine countries (UK 4, USA 3, France 2, Japan 2 and one each from Germany, Belgium, Slovakia, Hungary and Canada). Fifteen cases had a diagnosis of RA and there was one person with JIA. There were 11 men and 5 women affected, an unexpected distribution given RA is more prevalent in women at around 75%.(4) Patients were aged 16 to 78 (median 63; n = 13). There were 13 of the 16 cases that were labelled serious. Four were associated with prolonged hospitalization with one of these described as a life-threatening condition. One case was described as disabling/incapacitating. Eight individual's reactions were labelled as 'other'. Only two subjects were participants in clinical trials. One patient was rechallenged with tocilizumab and the vasculitis recurred. This person had also been exposed to rituximab, but ultimately this was not considered as related to the vasculitis, an opinion in keeping with the result of the rechallenge.

The quality of the reports as assessed by 'completeness scores' were poor, range 0.2 to 0.9. Fourteen of the reports were submitted by physicians.

The drug was administered as an intravenous infusion monthly or, with a more recent formulation, via weekly or second weekly SC. Only two of the reports indicated administration via the SC, the dose being 162 mg and these cases were reported recently (2017 and 2018). The reported doses of tocilizumab were 8 mg/kg (2 cases), 4 mg/kg (1 case) and actual doses of 480 mg (female), 560 mg (male), 440 mg (female), 400 mg (male) and 580 mg (male), these latter five likely to be equivalent to 8mg/kg given that an individual patient would need to weigh 100 kg for a dose of at least 400 mg if the dose rate was 4 mg/kg. In six subjects, the dose was not reported. Therefore, for the 8 cases of 11 where the drug was delivered intravenously and the dose reported, seven of the eight were given 8 mg/kg. There is divergence in the 'label' regarding the recommended dose of RA. In some jurisdictions e.g. USA it is 4 mg/kg every 4 weeks (or 162 mg SC every 2 weeks)(5) and in others it is 8 mg/kg every 4 weeks (or 162 mg SC every week). The one case dosed with 4 mg/kg came from the USA.

Data on duration of therapy with tocilizumab until the onset of the vasculitis from the VigiBase reports is limited (6 of 16 case reports) and some reports only note 'start' and 'stop' months, not the day of the month, the reaction commenced. Median duration of therapy was 161 days however in the few cases (6) where 'time to onset' of reaction was recorded, the median was 60 days, but the range was from 2 to 540 days.

Regarding medications preceding and/or during and/or immediately following the period of exposure to tocilizumab, some were suspected as contributing to the vasculitis. There were three cases prescribed methotrexate, which was suspected as contributing in one of these. In one case rituximab, and in another, certolizumab, was suspected, along with tocilizumab, as contributing. One patient had been taking sulfasalazine and bucillamine but these were not suspected contributors to the vasculitis. One patient was described as having 'RA aggravated' and 'condition aggravated'. This patient was treated (in order of administration) with etanercept, then adalimumab, then abatacept, then tocilizumab, then anakinra, then leflunomide and finally, tofacitinib. It is uncertain if this patient's cutaneous vasculitis occurred in relation to tocilizumab, as all of the aforementioned drugs including leflunomide were recorded as suspected contributors. Glucocorticosteroids were noted as concomitant medications for three patients, one given 1000 mg methylprednisolone possibly for their cutaneous vasculitis, another person, doses of oral prednisone ranging from 15 to 45 mg/day for the six months following cessation of tocilizumab, suggesting treatment for the cutaneous vasculitis and one a therapeutic dose for RA of prednisone 5 mg/day. A patient who had JIA and suspected tocilizumab caused vasculitis was taking cortisone that was listed as 'suspected' as a cause of the vasculitis.

There were patchy reports of reactions, features or investigations accompanying the cutaneous vasculitis. Complement C4 was noted as decreased in two patients and one of these also had reduced C3, thus suggesting immune complex aetiology. The person with JIA exhibited splenomegaly, fever, Sweet's syndrome (acute febrile neutrophilic dermatosis) and Stevens-Johnson syndrome. In this person, cutaneous vasculitis occurred while taking methotrexate and about 6 months later, tocilizumab was commenced, and a rash was reported. Both

drugs were continued for about nine months. The diagnoses of Sweet's syndrome and Stevens-Johnson syndrome occurred together, about the time both methotrexate and tocilizumab were ceased. Therefore, there is significant doubt that the presumed vasculitis was caused by tocilizumab in this case.

Table 1. Cases of cutaneous vasculitis associated with tocilizumab in VigiBase

Case	Age/ Sex	Seriousness criteria*	Other suspected (S) or concomitant (C) drugs	Time to onset	Action drug	Outcome
1	70/M	-	Tocilizumab (S)	-	-	Not recovered
2	67/M	-	Tocilizumab, rituximab (S)	-	Drug withdrawn/Reaction abated Rechallenge/Reaction recurred	Recovered
3	-/F	-	Tocilizumab (S)	-	-	Unknown
4	48/M	Other	Tocilizumab (S) Folic acid, methotrexate, metoclopramide, naproxen, omeprazole, sildenafil, tramadol (C)	7 days	Drug withdrawn/Reaction abated	Recovering
5	55/M	Prolonged hospitalization	Tocilizumab (S)	18 months	Drug withdrawn/Reaction abated	Recovering
6	63/F	Other	Tocilizumab, etanercept, adalimumab, abatacept, anakinra, leflunomide (S) Tofacitinib (C)		Drug withdrawn	Unknown
7	55/M	Other	Tocilizumab (S)	-	-	Recovering
8	-/F	Life threatening, prolonged hospitalization	Tocilizumab (S) Methylpresdnisolone (C)	-	-	Unknown
9	78/M	Other	Tocilizumab, certolizumab pegol (S)	2 days	Drug withdrawn/Reaction abated 3.5 months after cessation of drug	Recovered
10	16/F	Prolonged hospitalization	Tocilizumab, methotrexate, cortisone (S)	10 months	Drug withdrawn	Unknown
11	65/M	Other	Tocilizumab (S) Sulfasalazine, bucillamine, isoniazid, prednisolone, omeprazole, celecoxib, nateglinide, alfacalcidol (C)	2 months	Drug withdrawn/Reaction abated	Recovering
12	74/M	Disabling, incapacitating	Tocilizumab (S) Methotrexate, folic acid, prednisolone, lansoprazole, metformin, acetylsalicylic acid, simvastatin, senna, furosemide, ramipril, doxazosin, bisoprolol, isosorbide monohydrate (C)	2 months	Drug withdrawn/Reaction abated	Recovered
13	54/M	Prolonged hospitalization	Tocilizumab (S) Dihydrocodeine, paracetamol, omeprazole, nitrazepam, folic acid, diazepam (C)		Drug withdrawn	Unknown
14	67/M	Other	Tocilizumab (S)	-	-	Recovering
15	52/F	Other	Tocilizumab (S)	-	-	Recovered
16	-/M	Other	Tocilizumab (S)	-	-	Recovered

**Seriousness is classified in accordance with the criteria defined in the ICH E2A guideline*

Literature and Labelling

Sakaue et al reported the first case of leukocytoclastic vasculitis in 2014.(3) There do not appear to be further publications in the literature. The case described by Sakaue and colleagues was a Japanese woman aged 62 years with RA for 25 years. Treatment with infliximab for five years was followed with etanercept but control was not achieved, and tocilizumab was commenced. The initial dose was 8 mg/kg for one month, then 4 mg/kg along with prednisone 3 mg/day, and good control of her RA was achieved for five years. An inflammatory disease flare along with palpable purpura on limbs and buttocks led to a skin biopsy that showed leukocytoclastic vasculitis without IgA deposition, and not fulfilling criteria for Henoch-Schönlein purpura. There were no other relevant laboratory findings apart from an elevated CRP. The prednisone dose was increased and abatacept commenced with good effect. There was no recurrence and no rechallenge with tocilizumab. Sakaue et al noted that the vasculitis in association with TNFI occurs on average around 30 weeks (210 days) compared to the median of 8 weeks (60 days) in the VigiBase cases. However, in Sakaue et al's case it was over five years and there were two VigiBase cases occurring after one year's tocilizumab therapy.

The FDA label notes that serious hypersensitivity reactions, including anaphylaxis, have occurred with tocilizumab but without further information. Cutaneous vasculitis is not listed as an adverse drug reaction.(5)

Discussion and Conclusion

Tocilizumab has been generally well tolerated. As with other biologic medicines there is a risk of serious infections including reactivation of tuberculosis (TB), hepatitis B and C, and opportunistic infections including disseminated fungal infections. Testing for latent TB and hepatitis infection prior to commencement is mandatory. The drug is associated with elevations of serum cholesterol in adults. The label indicates that elevations of hepatic enzymes can occur, and recently a warning regarding liver failure, transplantation and deaths has been published by Canadian and US regulatory agencies, and other agencies are considering their own responses.

Sakaue et al (2014) note that biologic agents used for inflammatory rheumatic conditions such as RA, psoriasis and psoriatic arthritis have been associated with autoimmune adverse events, especially the tumour necrosis factor inhibitor (TNFI) group of biologics. The most frequent conditions reported have been SLE but vasculitis and skin involvement in these conditions is common.

This series from VigiBase of 16 cases of associations between tocilizumab therapy, mainly for RA, and cutaneous vasculitis add to only one in the literature. There is an unusual proportion of males with RA in these cases. Regarding the strength of the association and possible causation, there is only one report with a rechallenge. In this case the vasculitis recurred, providing strong evidence of causality. Also, six of the cases responded positively to dechallenge, adding further strength to the case for an association. The stated treatment duration with tocilizumab had a median of 161 days, and median time to onset of reaction in six of the cases of 60 days, but both medians have a very wide range. This is quite long for drug-induced cutaneous vasculitis that is often in the order of 7-14 days until onset.(6) However, vasculitis induced by anti-TNF agents has been noted to occur after 30 weeks exposure.(7) It has been suggested that the immunogenic stimulus for autoimmune reactions such as vasculitis may be less for tocilizumab compared to TNF inhibitors.(3)

The doses of tocilizumab noted most commonly were high, at 8 mg/kg. Some guidelines groups and regulatory labels recommend 4 mg/kg monthly (162 mg SC second weekly), stating that the lower dose rate is better tolerated without substantial reduction in efficacy.

Unfortunately, there are no biopsy reports for any of the VigiBase cases. Although there are very few cases, there may be a predilection for males, the elderly and dosing at the higher end of the recommended range. Given the new indications of PMR and giant cell arteritis, prevalent and important conditions, in the light of these reports, vigilance is recommended.

In summary, the review of the 16 cases reported in VigiBase provides good evidence that tocilizumab, like TNF inhibitor biological agents, is associated with cutaneous vasculitis. The possible risk factors for the association are possibly male sex, duration of exposure of many months and higher dose rates namely 8 mg/kg monthly intravenously. The case for a causal relationship between the drug and vasculitis is quite strong with six of 16 responding to 'dechallenge' and one patient subject to a rechallenge manifesting the vasculitis again.

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CAVEAT DOCUMENT

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

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

Tentative and variable nature of the data

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

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

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

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

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

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

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

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

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

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

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

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

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

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Recommendations from the 42nd Global Advisory Committee on Vaccine Safety (GACVS) meeting

The Global Advisory Committee on Vaccine Safety (GACVS) was established in 1999 to provide independent, authoritative, scientific advice to WHO on vaccine safety issues of global or regional concern. In view of the COVID 19 pandemic, the 42nd GACVS meeting was an extraordinary meeting that took place virtually on 27 to 28 May 2020 aimed at providing guidance to countries in preparation for the potential introduction of COVID-19 vaccines.

The objectives of the meeting were

- to identify challenges that are specific to vaccine safety monitoring, particularly in low- and middle-income countries (LMICs);
- to determine systems and capacity that would be required, particularly in LMICs,
- to monitor, assess and manage known and unknown adverse events following immunization (AEFI) in the context of COVID-19 vaccines;
- to review and provide recommendations on the elements of a pharmacovigilance (PV) preparedness workplan for LMICs ahead of COVID-19 vaccine roll-out; and
- to review and provide recommendations on the proposed approach and roadmap for COVID-19 vaccine risk/benefit communication.

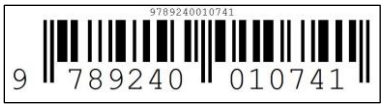
GACVS discussed the COVID-19 vaccines in the pipeline and current lead candidates under consideration, potential adverse events of special interest (AESI) after COVID-19 vaccines, regulatory perspectives and approaches to prepare countries for AEFIs and AESI in the context of COVID-19 vaccine introduction. Also discussed were the application of standardized templates for risk/benefit assessment of vaccines, COVID-19 vaccine risk/benefit communication and infodemic management during COVID-19 response. Following the GACVS deliberations, following recommendations were made.[1]

Key recommendations

- COVID-19 vaccine safety surveillance infrastructure and capacity should ideally be in place; existing infrastructures should be reactivated and actively engaged prior to vaccine introduction in all countries.
- A working group of experts should be established to provide guidance to countries and regions on prerequisites for vaccine introduction.
- Creation of a basic adverse events of special interest (AESI) list should be considered. Prioritization of AESI may be based on those identified in the COVID-19 clinical trials.
- Available and newly generated Brighton Collaboration case definitions for AESI and tools to assess certainty of cases should be shared widely for countries to use and to be aligned.
- A working group should be established to incorporate specific case definitions when Brighton Collaboration definitions do not exist for the prioritized AESI in the list; and that minimum institutional capacity is put in place in countries for their identification.
- Countries should consider using a Delphi method in instances where case definitions are not available from the Brighton Collaboration.
- WHO should work with national teams of Expanded Programme on Immunization in order to strengthen routine vaccine safety monitoring alongside COVID-19-related activities.
- National regulators should review risk management plans obtained from vaccine developers and share with immunization programmes and other stakeholders in countries and incorporate them into their vaccine safety preparedness strategies at the time of vaccine introduction.
- Developers should share available regional and international safety data including safety summaries with the reviewing regulatory authority.
- Any review of the safety of new vaccines should be based on the appropriate Brighton Collaboration standardized templates for risk/benefit assessment of vaccines.

[1] The full report is available in the Weekly Epidemiological Record (WER): https://apps.who.int/iris/bitstream/handle/10665/333136/WER9528-eng-fre.pdf?ua=1

- An ambitious, proactive plan for communicating vaccine safety is needed to assist Members States and relevant stakeholders before, during and after the COVID-19 vaccine's introduction. It was observed that while social media comments are highly visible and may influence political decision-making, they do not necessarily influence individual behaviour.
- The Communication approaches should clearly explain the difference between AESI and AEFI to relevant stakeholders.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