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The aim of the Newsletter is to disseminate information on the safety and efficacy of pharmaceutical products, based on communications received from our network of "drug information officers" 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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The WHO Pharmaceuticals Newsletter provides you with the latest information on the safety of medicines and legal actions taken by regulatory authorities across the world. It also provides signals based on information derived from Individual Case Safety Reports (ICSRs) available in the WHO Global ICSR database, VigiBase®.

This issue includes recommendations from the working groups of the thirty-seventh annual meeting of national pharmacovigilance centres that was held in Tianjin, China last year.

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Abiraterone acetate

Risk of hypokalaemia, thrombocytopenia and rhabdomyolysis

Japan. The Ministry of Health Labour and Welfare (MHLW) and the Pharmaceutical and Medical Devices Agency (PMDA) have announced revisions to the package insert for abiraterone acetate (Zytiga®).

Abiraterone acetate is indicated for castration-resistant prostate cancer.

The MHLW/PMDA stated that cases of hypokalaemia and thrombocytopenia have been reported in patients treated with abiraterone acetate in Japan. The MHLW/PMDA also stated that cases of rhabdomyolysis have been reported in patients treated with abiraterone acetate in other countries and the company core datasheet (CCDS) has been updated to include information on rhabdomyolysis.

Based on expert advice and available evidence, the MHLW/PMDA have recommended the following changes to the package insert:

- Patients with hypokalaemia or risks of hypokalaemia due to factors of complications or concomitant drugs should be added to the "Careful administration" section.
- An alert on hypokalaemia should be added in the "Important precautions".
- The following should be added to the "Clinically significant adverse reactions" section:
 - hypokalaemia
 - thrombocytopenia
 - rhabdomyolysis

Reference:

Revision of Precautions, 2 February 2015, MHLW/PMDA (www.pmda.go.jp/english/)

Aceclofenac

Updated cardiovascular advice in line with diclofenac and COX-2 inhibitors

UK. The Medicines and Healthcare products Regulatory Agency (MHRA) has announced that aceclofenac is now contraindicated in patients with certain established cardiovascular diseases.

Aceclofenac (Preservex®) is a non-steroidal anti-inflammatory drug (NSAID) licensed for the relief of pain and inflammation in osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis. Aceclofenac has little pharmacological activity by itself; its main mode of action is through its metabolites which include diclofenac and 4'-hydroxy diclofenac.

In June 2013 the MHRA told health-care professionals about the new contraindications and warnings for diclofenac. This was after a review by European regulators concluded that the risk of arterial thrombotic events (myocardial infarction; stroke) with diclofenac is greater than with other non-selective NSAIDs and similar to the COX-2 inhibitors.

There are limited data available regarding the arterial thrombotic effects of aceclofenac. The treatment advice for aceclofenac has been updated in line with diclofenac and COX-2 inhibitors. This was based on aceclofenac's structural similarity to diclofenac and its metabolism to diclofenac.

The MHRA reminds prescribers to base the decision to

- prescribe an NSAID on an assessment of each patient's individual risk factors including any history of cardiovascular and gastrointestinal illness.

- Use the lowest effective dose for the shortest duration necessary to control symptoms. Periodically re-evaluate the patient's need for symptomatic relief and response to treatment.

When using aceclofenac to relieve pain and inflammation in osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis, prescribers should:

- consider that aceclofenac is now contraindicated in patients with established:
 - ischaemic heart disease
 - peripheral arterial disease
 - cerebrovascular disease
 - congestive heart failure (New York Heart Association, NYHA, classification II-IV)
- switch patients with these conditions to an alternative treatment at their next routine appointment
- only start aceclofenac treatment after careful consideration of any significant risk factors for cardiovascular events, e.g.
 - hypertension
 - hyperlipidaemia
 - diabetes mellitus
 - smoking

Reference:

Drug Safety Update, MHRA, volume 8, issue 6: 5, January 2015 (www.gov.uk/mhra)

Ambroxol and bromhexine expectorants

Risk of allergy and skin reactions

EU. The European Medicines Agency (EMA) announced that the Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) has endorsed recommendations to update the product information for

ambroxol- and bromhexine-containing medicines with information about the small risk of severe allergic reactions and severe cutaneous adverse reactions (SCARs). The medicines are widely available in the EU for use as expectorants (to help clear mucus from the airways).

Ambroxol and bromhexine are mainly used by mouth as expectorants to help make the mucus thinner and therefore easier to be cleared away in patients with short- or long-term diseases of the lungs or airways.

Anaphylactic reactions and SCARs, including erythema multiforme, Stevens-Johnson syndrome/toxic epidermal necrolysis and acute generalised exanthematous pustulosis, have been reported in patients receiving ambroxol. As ambroxol is a metabolite of bromhexine, the risk of anaphylactic and severe cutaneous reactions is considered to apply also to bromhexine.

The risk of anaphylactic reactions and SCARs with ambroxol or bromhexine is low. Frequencies of these side effects are unknown.

Health-care professionals should advise patients that they should stop treatment immediately if symptoms of progressive skin rash occur.

Reference:

Press release, EMA, 27 February 2015 (www.ema.europa.eu)

Apixaban

Risk of interstitial lung disease

Japan. The MHLW and the PMDA announced the revision of the package insert for apixaban (Eliquis®).

Apixaban is indicated for reduction of the risk of ischaemic stroke and systemic embolism in patients with nonvalvular atrial fibrillation.

The MHLW/PMDA informed that cases of interstitial lung disease and haemorrhage including bloody sputum have been reported in patients treated with apixaban in Japan.

Based on expert advice and available evidence, the MHLW/PMDA have recommended the following texts be added to the "Clinically significant adverse reactions" subsection of "Adverse reactions".

Interstitial lung disease: Interstitial lung disease may occur. Patients should be carefully monitored. If any abnormalities such as cough, bloody sputum, shortness of breath, dyspnoea, pyrexia, and abnormal chest sound are observed, examinations including chest X-ray, chest CT scan, and serum marker test should be performed immediately. If interstitial lung disease is suspected, administration of this drug should be discontinued, and appropriate measures including administration of corticosteroid should be taken.

Reference:

Revision of Precautions, 17 February 2015, MHLW/PMDA (www.pmda.go.jp/english/)

Combined oral contraceptives and hormone replacement therapy

Risk of developing inflammatory bowel disease

Australia. The Therapeutic Goods Administration (TGA) has informed health-care

professionals that the TGA is working with sponsors of combined oral contraceptives and hormone replacement therapy to ensure information regarding inflammatory bowel disease is included in the Product Information documents.

The TGA has evaluated recently published research that links an increased risk of inflammatory bowel disease (IBD), including ulcerative colitis and Crohn's disease with the use of combined oral contraceptives (COCs). During assessment of this information, the TGA identified corresponding data that suggested hormone replacement therapy (HRT) was also a potential risk factor for development of IBD. The literature suggests that these risks may be increased in women who were smokers.

Progestogen-only contraceptive, HRT products and products containing tibolone as the active ingredient were not evaluated specifically, therefore the TGA could not determine the risk of IBD with these products.

One paper concluded that there was no difference in the IBD risk between oestrogen-only HRT products and oestrogen/progestogen combination HRT.

The TGA found that the literature had limitations. While the research did not confirm a causal relationship and the pathogenesis of IBD remained incompletely defined, the TGA concluded that health-care professionals should be made aware of this information.

While the Product Information (PI) documents for most COC products include a reference to the association between these drugs and IBD, this information is not consistent across all products.

Meanwhile, no PI documents for oestrogen/progestogen combination HRT products

contain information about a potential association with IBD.

The TGA is negotiating with the sponsors of COCs and oestrogen/progestogen combination HRT products to ensure adequate information is provided in their PI.

Reference:

Medicines Safety Update, TGA, Vol. 6, No. 1, February 2015 (www.tga.gov.au)

Dabigatran and dronedarone or amiodarone

Drug-drug interaction

Canada. Health Canada has reviewed the prescribing information for dabigatran (Pradaxa®), an anti-blood clotting drug, dronedarone (Multaq®) and amiodarone (Cordarone®), both used to control abnormal heart rates.

This revision is based on a review of information on the potential interaction between dabigatran and dronedarone or amiodarone that can raise the blood level of dabigatran and potentially increase the bleeding risk associated with it.

Dabigatran is used for the treatment and prevention of blood clots in the veins of legs and lungs, including patients with knee or hip replacement surgery. It is also approved for the prevention of stroke or blood vessel blockage due to blood clotting in patients with an abnormal heart rhythm called atrial fibrillation.

Amiodarone is approved for the treatment of certain abnormal heart rhythms called ventricular arrhythmias. Dronedarone is approved for the treatment of certain abnormal heart rhythms called atrial fibrillation.

Bleeding is a known risk of dabigatran. Bleeding of any type or severity may occur

with the use of dabigatran, from minor bruising to major or severe bleeding in any part of the body. It is possible that amiodarone or dronedarone can block one of the mechanisms by which dabigatran is transported out of the body (P-glycoprotein) and eliminated. This may raise the blood level of dabigatran leading to an increased risk of bleeding.

Health Canada reviewed information from Canadian adverse reaction reports, scientific literature, international safety data as well as what is known about the use of these products in Canada and internationally. The review evaluated the risk and suggested ways to minimize it.

At the time of the review, Health Canada had received 6 reports of bleeding in patients who were using dabigatran and dronedarone together, and 19 reports of bleeding in patients who were using dabigatran and amiodarone together.

Health Canada assessed that bleeding was possibly associated with the interaction between dabigatran and dronedarone in 4 cases, and between dabigatran and amiodarone in 7 cases.

At the time of this review, the WHO Vigibase® database contained 254 cases of events related to bleeding reported in patients using both dabigatran and amiodarone; and 199 cases of events related to bleeding in patients using both dabigatran and dronedarone. Most of these cases were from the United States (175 suspecting the dabigatran-amiodarone interaction and 185 suspecting the dabigatran-dronedarone interaction). While a drug-drug interaction may be suspected in these bleeding events, other causes cannot be ruled out as detailed case reports were not available.

At the time the safety review was completed, the available evidence supported that events related to bleeding may be associated with the drug-drug interaction between dabigatran and dronedarone or amiodarone.

Reference:

Safety Reviews, Health Canada, 12 February 2015 (www.hc-sc.gc.ca)

Domperidone

Serious abnormal heart rhythms and sudden death (cardiac arrest)

Canada. Health Canada has completed a safety review that evaluated the risk of serious abnormal heart rhythms and sudden death (cardiac arrest) with domperidone.

Domperidone is used to treat symptoms of slowed stomach emptying seen in people with some gastrointestinal (GI) disorders (e.g. gastritis or inflammation of the GI tract). Domperidone is also used to reduce symptoms such as nausea and vomiting caused by some drugs used to treat Parkinson's disease.

Changes in the electrical activity of the heart, such as QT prolongation, can lead to an abnormal heart rhythm. An abnormal heart rhythm refers to the heart beating too fast, too slow or irregularly. In some rare cases, fast, irregular heartbeats can cause death.

Domperidone is widely used in Canada. There were about 2,000,000 prescriptions for domperidone in Canada in 2013. At the time of this review, Health Canada had received 18 reports (no deaths) of serious adverse heart events with domperidone. Of these 18 reports, 12 reports were further evaluated to and domperidone was found to be

a possible cause for the development of cardiovascular events in most cases.

However, it is difficult to determine to what extent domperidone contributed to the events because other conditions known to cause electrical heart problems were also present in many cases.

Risks are increased (i) in patients taking domperidone at doses greater than 30 mg a day, (ii) in patients over 60 years of age, and (iii) in patients taking domperidone together with drugs that can lead to increased domperidone blood levels or with drugs that are known to affect the electrical activity of the heart. This safety information applies to patients taking domperidone for any conditions.

At this time, to further reduce the risk of serious heart effects with domperidone, Health Canada has requested the following additional measures:

- Manufacturers should update the prescribing information of domperidone products to: indicate the risk of serious abnormal heart rhythms and sudden death (cardiac arrest); recommend a maximum daily dose of 30 mg; and to recommend restricting use in patients with certain medical conditions or taking other drugs.
- Drug Safety and Effectiveness Network should continue to conduct a study on heart effects in association with the use of domperidone in patients who have Parkinson's disease. This study is ongoing, and once its results become available, Health Canada will assess whether any further actions are required.

Reference:

Safety Reviews, Health Canada, 27 January 2015 (www.hc-sc.gc.ca)

(See WHO Pharmaceuticals Newsletters No.1, 2014 and

No.3, 2014 for related information on domperidone)

Donepezil

Risk of rhabdomyolysis and neuroleptic malignant syndrome

Canada. Health Canada has issued an Information Update to inform health-care professionals and Canadians of the risks of rhabdomyolysis and/or NMS for donepezil after conducting a safety review. The review evaluated the available information on the potential risk of rhabdomyolysis (muscle breakdown) and/or Neuroleptic Malignant Syndrome (NMS), a life-threatening neurological disorder associated with donepezil.

Donepezil is used to treat the symptoms of Alzheimer's disease. Donepezil has been marketed in Canada under the brand names Aricept® since 1997 and Aricept® Rapidly Disintegrating Tablet since 2006. As of November 2014, 16 companies have also received authorizations to sell generic donepezil in Canada.

Rhabdomyolysis is a condition that results in the breakdown of muscle tissue. Typical clinical symptoms include muscle pain, fever, weakness, nausea, and dark urine. Rhabdomyolysis can lead to life-threatening abnormal heart rhythms and kidney failure. Rhabdomyolysis can be drug-induced, but can also happen due to chemicals causing muscular damage, physical overexertion or other causes.

NMS is a rare life-threatening condition with changes in the nervous, muscular and cardiovascular systems. Symptoms of NMS include fever, mental changes, agitation, delirium, and muscle rigidity that can potentially lead to rhabdomyolysis. NMS is

most often associated with the use of antipsychotics and dopamine enhancing drugs.

The prescribing information for donepezil has been updated to include the possible risks of rhabdomyolysis and NMS. It is important for health-care professionals and patients to be aware of the possibility of these rare serious reactions, and for steps to be taken for early detection of rhabdomyolysis and/or NMS.

Reference:

Safety Reviews, Health Canada, 21 January 2015 (www.hc-sc.gc.ca)

Lamotrigine

Risk of serious skin disorders

Japan. The MHLW and the PMDA made an urgent request for the package insert of lamotrigine (Lamictal®), to be revised to include additional cautions against serious skin disorders.

Cases of serious skin disorders associated with lamotrigine in post market reports included many cases that failed to comply with the recommended dosage and frequency of administration. In January 2012, the PMDA posted advice on the proper use of lamotrigine on its website.

A total of 16 cases of serious skin disorders leading to death have been reported (Dec 2008 -Jan 2015) in patients treated with lamotrigine in Japan (the estimated number of users is approximately 376 000 patients).

Previously, (September 2014 to December 2014), there were reports of 4 cases of serious skin disorders leading to death, in which causality between the serious skin disorders and the drug could not be ruled out in patients treated with lamotrigine in

Japan. In all 4 cases, treatment with lamotrigine did not comply with the recommended dosage and frequency of administration as stated in the package insert. In addition, lamotrigine was not discontinued until the symptoms became serious.

Based on expert advice and available evidence, the MHLW/PMDA concluded that this issue should be addressed in an urgent manner and warned that health-care professionals should comply with the dosage and administration as stated in the package insert of this drug.

MHLW/PMDA recommend that:

- During the initial phase of treatment, lamotrigine should not be used at doses higher than the recommended dosage and frequency of administration.
- When used concomitantly with sodium valproate, lamotrigine should be administered on alternate days for the first 2 weeks (only for adult patients).
- Lamotrigine should not be used at higher than recommended dosages or and frequencies of administration even during dose titration before maintenance dose is established.
- A dose increase should not be attempted earlier than the specified timing.
- Effort towards early detection and treatment of skin disorders should be made. Administration of lamotrigine should be discontinued immediately if the following symptoms in addition to a rash occur:
 - Pyrexia (higher than 38 °C)
 - Lip/oral mucosa erosion
 - General malaise
 - Ocular hyperaemia
 - Pharyngodynia
 - Lymphadenopathy
- Delay in the treatment of skin disorders might lead to a poor outcome. Health-

care professionals should consult a dermatologist at an early stage, and appropriate measures should be taken.

- Patients and their family should be advised to see a doctor immediately and inform a doctor or pharmacist that they are being treated with this drug if a rash and/or the above symptoms occur.

Reference:

Revision of Precautions, 16 February 2015, MHLW/PMDA (www.pmda.go.jp/english/)

Memantine hydrochloride

Risk of hepatic dysfunction and jaundice

Japan. The MHLW and the PMDA announced that revision of the package insert for memantine hydrochloride (Memary®) was necessary.

Memantine hydrochloride is used for preventing progression of dementia symptoms in patients with moderate to severe Alzheimer's type dementia.

The MHLW/PMDA stated that cases of hepatic dysfunction and jaundice have been reported in patients treated with memantine hydrochloride in Japan.

Based on expert advice and available evidence, the MHLW/PMDA have recommended the following texts should be added in the "Clinically significant adverse reactions" subsection of the "Adverse reactions" section.

Hepatic dysfunction and jaundice:
Hepatic dysfunction and/or jaundice with elevations of aspartate aminotransferase (glutamate oxaloacetate transaminase), alanine aminotransferase (glutamate

pyruvate transaminase), alkaline phosphatase, bilirubin, etc. may occur. Patients should be carefully monitored. If any abnormality is observed, administration of this drug should be discontinued and appropriate measures should be taken.

Reference:

Revision of Precautions, 17 February 2015, MHLW/PMDA (www.pmda.go.jp/english/)

Metoclopramide

Risk of neurological adverse events

Australia. The TGA has announced that the Product Information for metoclopramide has been updated to include a new contraindication and changes to dosing and duration of use, to reduce the risk of neurological adverse events.

Metoclopramide is a widely used antiemetic and gastro-prokinetic drug. It has a number of approved indications, the most common being to control nausea and vomiting which may be associated with the following conditions:

- intolerance to essential drugs with emetic properties
- uraemia
- radiation sickness
- malignant disease
- postoperative vomiting
- labour
- infectious diseases

The TGA has recently completed an analysis of the findings of an EMA review of metoclopramide.

In December 2013, the European Commission adopted the EMA's recommended changes to restrict the dose and duration of use of metoclopramide, to reduce the risk of potentially serious neurological adverse events,

including extrapyramidal disorders and tardive dyskinesia, as well as rare cardiac conduction disorders. Extrapyramidal disorders, including tardive dyskinesia, may continue even after cessation of metoclopramide and may not be reversible.

From January 1971 to 16 October 2014, the TGA received 2190 adverse event case reports associated with metoclopramide. Among these reports were 16 cases of tardive dyskinesia associated with metoclopramide use, and 86 cases of other extrapyramidal disorders. There were also nine reports of cardiac arrest and a further 63 reports of cardiac arrhythmias.

The TGA has worked closely with the sponsor to update the Product Information (PI) for prescription metoclopramide products and labelling requirements for the over-the-counter metoclopramide products.

The following changes have been made to the PI for prescription metoclopramide:

- It is contraindicated for children aged under one year.
- For young adults (aged under 20 years) and children over one year of age, it is only indicated as second-line therapy.
- The total daily dosage, especially for children and young adults, should not normally exceed 0.5 mg/kg bodyweight, with a maximum of 30 mg daily.
- The maximum dose for adults is 10 mg three times daily.
- The maximum recommended treatment duration is now five days in all age groups.

Reference:

Medicines Safety Update, TGA, Vol. 6, No. 1, February 2015 (www.tga.gov.au)

(See WHO Pharmaceuticals Newsletters No.1, 2015 and

No.5, 2013 for related information)

Montelukast sodium

Risk of thrombocytopenia

Japan. The MHLW/PMDA informed that cases of thrombocytopenia have been reported in patients treated with montelukast sodium (Singulair® and Kipres®) in Japan.

Montelukast sodium is indicated for bronchial asthma and allergic rhinitis.

Based on expert advice and available evidence, the MHLW/PMDA have recommended the following texts should be added in the "Clinically significant adverse reactions" subsection of the "Adverse reactions" section for montelukast.

Thrombocytopenia:

Thrombocytopenia may occur (initial signs and symptoms are: bleeding tendencies including purpura, epistaxis, and gingival bleeding). If these symptoms are observed, administration of this drug should be discontinued and appropriate measures should be taken.

Reference:

Revision of Precautions, 17 February 2015, MHLW/PMDA (www.pmda.go.jp/english/)

Mycophenolates

Risk of bronchiectasis and hypogammaglobulinemia

Canada. Health Canada has announced an update of prescribing information for mycophenolates after a safety review was conducted to evaluate the risk of damage to

the lung airways (bronchiectasis) in patients taking mycophenolates, which are used to prevent transplant rejection. The prescribing information includes the possible risk of bronchiectasis and hypogammaglobulinaemia.

The review evaluated the risk of hypogammaglobulinaemia (decreased quantity of immunoglobulins G (IgG) in the blood), which may occur together with bronchiectasis in patients taking mycophenolates. The assessment was prompted by a growing number of international and literature reports of bronchiectasis in transplant recipients treated with products containing mycophenolates.

Bronchiectasis is a chronic, progressive lung disease characterized by damage to the structure of bronchial tubes (airways). It is associated with respiratory symptoms that include cough, daily sputum or mucus production, and fatigue.

Hypogammaglobulinaemia refers to low levels of IgG in the blood; IgG are antibodies important for fighting infections and a decrease of IgG is often associated with infections. In transplant patients, hypogammaglobulinaemia may increase the risk of respiratory infections, which can trigger bronchiectasis. However, both diseases do not always occur together.

The review considered information from Canadian adverse reaction reports, scientific literature, international safety data as well as what is known about the use of these products in Canada and internationally. The review evaluated the risk and suggested ways to minimize it.

At the time of this review, Health Canada had not received any Canadian reports

of bronchiectasis in transplant patients treated with mycophenolates.

The review concludes that evidence from published medical and scientific literature suggest bronchiectasis might be related to the use of mycophenolates as noted by the following:

- Several studies noted that when patients did not take mycophenolates as part of their immunosuppressive therapy, they did not develop bronchiectasis.
- Patients who stopped taking mycophenolates had less lung complaints and less symptoms related to bronchiectasis.
- Some evidence also indicates that mycophenolates suppress immune system responses including the production of immunoglobulins, especially IgG.

Based on their own reviews, the manufacturers for mycophenolates could not rule out a cause and effect relationship between these drugs and bronchiectasis and/or hypogammaglobulinaemia.

At the time of the review, the WHO Global ICSR Database System (Vigibase®) had 38 reports of bronchiectasis and 36 reports of hypogammaglobulinaemia in patients treated with mycophenolates. Twenty-three of 38 reports of bronchiectasis also reported hypogammaglobulinaemia.

The current evidence suggests that bronchiectasis with or without hypogammaglobulinaemia may occur while taking products containing mycophenolates.

The prescribing information also recommends that treating physicians further investigate patients with persistent lung symptoms and recurrent infections for the possibility of bronchiectasis and

hypogammaglobulinaemia, respectively. Manufacturers of generic versions of these drugs should also update their product information.

Reference:

Safety Reviews, Health Canada, 4 February 2015 (www.hc-sc.gc.ca)

Telaprevir

Risk of renal impairment

Japan. The MHLW and the PMDA announced revisions to the package insert for telaprevir (Telavic®).

Telaprevir is indicated for the following.

- Improvement of viraemia in any of the following patients with serogroup 1 (genotype I [1a] or II [1b]) chronic hepatitis C virus infection:
 - treatment-naïve patients with high blood HCV RNA load
 - patients who have failed to respond to, or have relapsed after, therapy including interferon
- Improvement of viraemia in patients with serogroup 2 (genotype III [2a] or IV [2b]) chronic hepatitis C virus infection who have failed to respond to, or have relapsed after, interferon monotherapy or interferon and ribavirin combination therapy

The MHLW/PMDA informed that an interim analysis of the use-results survey showed that a non-reduced initial dose (full initial dose), higher age, increased baseline creatinine, and diabetes mellitus or hypertension as comorbidities are risk factors for serious renal impairment in patients treated with telaprevir.

Based on expert advice and available evidence, the MHLW/PMDA have recommended the following

texts should be added in the "Precautions for Dosage and Administration".

A reduced initial dose should be considered in geriatrics or in patients with renal impairment, hypertension, or diabetes mellitus because a risk of serious renal impairment may be increased in these patients. It should be noted that the reduced dose may lower the response rate of hepatitis C virus ribonucleic acid turning undetectable. The balance of risks and benefits should be carefully considered.

Reference:

Revision of Precautions, 17 February 2015, MHLW/PMDA (www.pmda.go.jp/english/)

Testosterone Products

Possible increased risk of heart attack and stroke

USA. The Food and Drug Administration (FDA) requested the manufacturers of all approved prescription testosterone products to change their labelling to clarify the approved uses of these medications. FDA also requested these manufacturers to add information to the labelling about a possible increased risk of heart attacks and strokes in patients taking testosterone. FDA cautioned that prescription testosterone products are approved only for men who have low testosterone levels caused by certain medical conditions. The benefit and safety of these medications have not been established for the treatment of low testosterone levels due to aging, even if a man's symptoms seem related to low testosterone.

Testosterone is approved as replacement therapy only for men who have low

testosterone levels due to disorders of the testicles, pituitary gland, or brain that cause hypogonadism.

Based on the available evidence from studies and expert input from an FDA Advisory Committee meeting, FDA has concluded that there is a possible increased cardiovascular risk associated with testosterone use.

FDA advises that health-care professionals should prescribe testosterone therapy only for men with low testosterone levels caused by certain medical conditions and confirmed by laboratory tests. Health-care professionals should make patients aware of the possible increased cardiovascular risk when deciding whether to start or continue a patient on testosterone therapy. Patients using testosterone should seek medical attention immediately if symptoms of a heart attack or stroke are present, such as chest pain, shortness of breath or trouble breathing, weakness in one part or one side of the body, or slurred speech.

Reference:

Drug Safety Communication, US FDA, 3 March 2015 (www.fda.gov)

(See WHO Pharmaceuticals Newsletter No. 2, 2014 for investigating risk of cardiovascular events by testosterone products in USA)

Tiotropium

Risk of cardiovascular side effects

UK. The MHRA has warned health-care professionals to consider the risk of cardiovascular side effects when prescribing tiotropium delivered via Respimat or HandiHaler to patients with certain cardiac conditions, who were excluded from clinical trials of tiotropium (including

the Tiotropium Safety and Performance in Respimat® Trial (TIOSPIR®) clinical trial).

Tiotropium (Spiriva®) is licensed as a maintenance bronchodilator treatment to relieve symptoms of chronic obstructive pulmonary disease (COPD). Tiotropium can be delivered in two ways:

- via the HandiHaler inhaler once daily, from a capsule containing 18 micrograms of tiotropium.
- via the soft-mist Respimat inhaler taken as two puffs once daily (2.5 micrograms of tiotropium delivered per puff).

When using tiotropium delivered via Respimat or HandiHaler to treat COPD, health-care professionals should:

- take the risk of cardiovascular side effects into account for patients with conditions that may be affected by the anticholinergic action of tiotropium, including:
 - myocardial infarction in the last 6 months
 - unstable or life threatening cardiac arrhythmia
 - cardiac arrhythmia requiring intervention or a change in drug therapy in the past year
 - hospitalisation for heart failure (NYHA Class III or IV) within the past year.
- tell these patients to report any worsening of cardiac symptoms after starting tiotropium; patients with these conditions were excluded from clinical trials of tiotropium, including TIOSPIR®.
- review the treatment of all patients already taking tiotropium as part of the comprehensive management plan to ensure that it remains appropriate for them; regularly review treatment of patients at

high risk of cardiovascular events.

- remind patients not to exceed the recommended once daily dose.

The TIOSPIR® clinical trial compared the safety and efficacy of tiotropium delivered via Respimat (2.5 micrograms or 5 micrograms once daily) with tiotropium delivered via HandiHaler (18 micrograms once daily).

In light of the results of TIOSPIR® and other clinical trials, the MHRA have added the warning to use tiotropium with caution in the patients listed above to the tiotropium summaries of product characteristics.

Reference:

Drug Safety Update, MHRA, volume 8, issue 7: 1, February 2015 (www.gov.uk/mhra)

Valproate-related medicines

Risk of abnormal pregnancy outcomes

UK. The MHRA has informed health-care professionals of important new information and strengthened warnings related to safety of medicines related to valproate (sodium valproate, valproic acid (Epilim®) and valproate semisodium (Depakote®). This is based on a Europe-wide review:

- Children exposed in utero to valproate are at a high risk of serious developmental disorders (in up to 30-40% of cases) and/or congenital malformations (in approximately 10% of cases).
- Valproate should not be prescribed to female children, female adolescents, women of childbearing potential or pregnant women unless other treatments are ineffective or not tolerated.

- Valproate treatment must be started and supervised by a doctor experienced in managing epilepsy or bipolar disorder.
- Carefully balance the benefits of valproate treatment against the risks when prescribing valproate for the first time, at routine treatment reviews, when a female child reaches puberty and when a woman plans a pregnancy or becomes pregnant.
- You must ensure that all female patients are informed of and understand:
 - risks associated with valproate during pregnancy
 - need to use effective contraception
 - need for regular review of treatment
 - the need to rapidly consult if she is planning a pregnancy or becomes pregnant.

Valproate is associated with a dose-dependent risk of abnormal pregnancy outcomes, whether taken alone or in combination with other medicines. Data suggest that when valproate is taken for epilepsy with other medicines, the risk of abnormal pregnancy outcomes is greater than when valproate is taken alone.

The risk of congenital malformations is approximately 10 % while studies in preschool children exposed in utero to valproate show that up to 30-40% experience delays in their early development such as talking, and/or walking, have low intellectual abilities, poor language skills and memory problems.

Intelligence quotient (IQ) measured in a study of 6-year old children with a history of valproate exposure in utero was on average 7-10 points lower than those children exposed to other antiepileptics.

Available data show that children exposed to valproate in utero are at increased risk of autistic spectrum disorder (approximately three-fold) and childhood autism (approximately five-fold) compared with the general study population. Limited data suggests that children exposed to valproate in utero may be more likely to develop symptoms of attention deficit/hyperactivity disorder (ADHD).

Given these risks, valproate for the treatment of epilepsy or bipolar disorder should not be used during pregnancy and in women of child-bearing potential unless it is clearly necessary i.e. in situations where other treatments are ineffective or not tolerated.

If health-care professionals decide to prescribe valproate to a woman of child-bearing potential, she must use effective contraception during treatment and be fully informed of the risks for the unborn child if she becomes pregnant during treatment with valproate.

If a woman with epilepsy or bipolar disorder who is treated with valproate plans a pregnancy or becomes pregnant, consideration should be given to alternative treatments.

If valproate treatment is continued during the pregnancy the lowest effective dose should be used and the daily dose should be divided into several small doses to be taken throughout the day - the use of a prolonged release formulation may be preferable to other treatment forms.

The product information will now be updated to reflect the current understanding of the available evidence and to make information as clear as possible.

Reference:
Drug Safety Update, MHRA,

volume 8, issue 6: 1, January 2015 (www.gov.uk/mhra)

(See WHO Pharmaceuticals Newsletters No.1, 2015, No.5, 2014, No. 6, 2013 and No.3, 2013 for related information)

Varenicline

Potential alcohol interaction

USA. The FDA has warned that the prescription smoking cessation medicine varenicline (Chantix®) can change the way people react to alcohol. Interactions between alcohol and varenicline have resulted in some patients experiencing increased intoxicating effects of alcohol, sometimes associated with aggressive behaviour and/or amnesia. In addition, rare accounts of seizures in patients treated with varenicline have been reported. FDA has approved changes to the varenicline label to warn about these risks.

Varenicline is a prescription medicine that is FDA-approved to help adults quit smoking.

FDA has recommended that health-care professionals should weigh the potential risk of seizures against the potential benefits before prescribing varenicline in patients with a history of seizures or other factors that can lower the seizure threshold. Patients should be advised to stop taking varenicline if they develop agitation, hostility, aggressive behaviour, depressed mood, or changes in behaviour or thinking that are not typical for them, or if they develop suicidal ideation or behaviour.

Until patients know how varenicline affects their ability to tolerate alcohol, they should decrease the amount of alcohol they drink. Patients who have a seizure while taking varenicline should stop the

medicine and seek medical attention immediately.

Reference:

Drug Safety Communication, US FDA, 9 March 2015 (www.fda.gov)

Vemurafenib

Risk of pancreatitis

Canada. Health Canada has announced that a safety review was initiated following the identification of 18 cases of vemurafenib-associated pancreatitis in ongoing clinical trials. Among these cases, seven involved sudden-onset (acute) pancreatitis.

Vemurafenib is used in adult patients to treat an aggressive type of skin cancer (unresectable or metastatic melanoma).

A safety review was initiated following the identification of cases of vemurafenib-associated pancreatitis in ongoing clinical trials. A total of 61 reports of pancreatitis associated with the use of vemurafenib were retrieved from different sources (pre-clinical studies, scientific literature, manufacturer's clinical and safety databases, Health Canada's Vigilance Program, the World Health Organization database and Health Canada's Office of Clinical Trials). In 10 of the 61 reports, vemurafenib was deemed to have had a "possible" or "probable" connection in causing the pancreatitis.

The Canadian prescribing information for vemurafenib has been updated to include the risk of pancreatitis. Health Canada has issued a communication to inform patients and health-care professionals of the risk of pancreatitis associated with the use of vemurafenib.

Reference:

Safety Reviews, Health Canada, 12 February 2015 (www.hc-sc.gc.ca)

(See WHO Pharmaceuticals Newsletter No.3, 2014 for association of vemurafenib use with drug induced liver injury (DILI) in Canada)

Atypical Antipsychotics

Potential risk of liver failure

Canada. Health Canada has initiated a safety review to evaluate currently available information regarding the potential risk of liver failure associated with atypical antipsychotics, a class of drugs that are mainly used to treat schizophrenia, bipolar disorder and depression.

Atypical antipsychotics marketed in Canada include: aripiprazole, asenapine, clozapine, lurasidone, olanzapine, paliperidone, quetiapine, risperidone and ziprasidone. These products are approved for different indications, but generally, atypical antipsychotics are used for the treatment of schizophrenia, bipolar disorder and, in some cases, depression.

Liver failure occurs when the liver has been severely damaged and is unable to perform its normal functions. Symptoms of liver failure include: jaundice (yellowing of the skin and the whites of eyes), nausea and vomiting, a general sense of feeling unwell, an accumulation of fluid within the abdomen (ascites), a tendency to bruise and bleed easily and mental disorientation or confusion.

At the time of this review, Health Canada had received several reports of liver failure suspected of being associated with atypical antipsychotics. Some of these cases involved a rapid loss of liver function (acute liver failure). Most of the reports did not provide enough information for a thorough analysis.

Overall, the published evidence linking liver failure with the use of other atypical antipsychotics is limited, with the exception of clozapine and olanzapine,

where the risk of liver failure is recognized and included in their prescribing information.

At the time of this review, the WHO Global ICSR Database System (Vigibase®) contained a number of reports with atypical antipsychotics and liver failure.

Atypical antipsychotics are widely used. A relatively small number of cases of liver failure have been reported in association with these drugs, although cases were serious and sometimes resulted in death. The risk of liver failure is currently included in the prescribing information for clozapine and olanzapine-containing products. With regard to the other atypical antipsychotics, most of the evidence gathered involved quetiapine.

Health Canada has determined that the overall benefits of quetiapine continue to outweigh the risks, when used as recommended but Health Canada has taken the following actions to minimize the risk of liver failure associated with quetiapine:

- In the April 2014 issue of the Canadian Adverse Reaction Newsletter, Health Canada published an article on quetiapine and the risk of acute liver failure.
- The risk of liver failure has been added to the prescribing information of quetiapine.

Evidence linking the other six atypical antipsychotics (aripiprazole, asenapine, lurasidone, paliperidone, risperidone and ziprasidone) is limited. Health Canada will continue its ongoing monitoring of adverse reaction information involving all other atypical antipsychotics to identify and assess potential harms.

Reference:

Safety Reviews, Health Canada, 22 January 2015 (www.hc-sc.gc.ca)

Nitric oxide (INOMax®) cylinders

Valve defect might stop gas delivery early in some cylinders

UK. The MHRA has reminded health-care professionals to always have a full spare nitric oxide cylinder loaded on the delivery device so the cylinders can be switched without delay while valve defects are being investigated.

Nitric oxide, in conjunction with ventilatory support and other appropriate active substances, is licensed:

- for the treatment of newborn infants ≥ 34 weeks gestation with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension, in order to improve oxygenation and to reduce the need for extracorporeal membrane oxygenation.
- as part of the treatment of peri- and post-operative pulmonary hypertension in adults and newborn infants, infants and toddlers, children and adolescents, ages 0-17 years in conjunction to heart surgery, in order to selectively decrease pulmonary arterial pressure and improve right ventricular function and oxygenation.

A defect has been reported and this might cause the valves in some nitric oxide (INOMax®) cylinders to close while in use, before the cylinder is empty. This applies to 400 ppm and 800 ppm cylinders of 2 L and 10 L capacity. It is not possible to identify defective cylinder valves in the hospital setting.

This abruptly stops gas delivery earlier than expected. Unless the cylinder is changed immediately, the following life-

threatening rebound effects can occur:

- increase in pulmonary artery pressure
- decrease in oxygen saturation
- cardiovascular collapse

The MHRA reminded the health-care professionals when using nitric oxide cylinders:

- to always have a full spare cylinder loaded on the delivery device so the cylinders can be switched without delay
- to always deliver INOmax® using devices with pressure sensor monitors and gas monitor alarms - the low pressure alarm will sound if the valve closes
- that devices without low pressure alarms are not safe to use
- purge the regulator of the second cylinder when switching cylinders, before connecting it to the delivery device -this prevents excess NO₂ formation
- to take extra care during patient transfer - always have back-up cylinders available, even for a short transfer

Reference:

Drug Safety Update, MHRA, volume 8, issue 7: 2, February 2015 (www.gov.uk/mhra)

Oral diclofenac

No longer available without prescription

UK. The MHRA has announced that oral diclofenac is no longer available over the counter, as it is associated with a small increased risk of cardiovascular side effects.

Diclofenac is a non-steroidal anti-inflammatory drug used to treat pain and inflammation. The MHRA requires that diclofenac tablets are no longer sold to anyone without a prescription. Diclofenac is associated with a small risk of

serious cardiovascular side effects (e.g. myocardial infarction and stroke).

Therefore it is recommended that patients should have a medical assessment before taking diclofenac to determine if it is suitable for them.

When prescribing or dispensing diclofenac, the following should be considered:

- Oral diclofenac must not be sold without prescription.
- A recall has been issued for non-prescription diclofenac.
- The prescribing advice for diclofenac was updated in June 2013.
- Topical formulations of diclofenac (e.g. gel and cream) remain available for sale over the counter.

Advice to give to patients:

- If you have recently bought diclofenac tablets without a prescription and continue to need pain relief, speak to your prescriber or pharmacist who can advise you on suitable alternatives - there is no problem if you wish to stop taking diclofenac in the meantime.
- If you have been prescribed diclofenac there is no need to stop taking the medicine - speak to your prescriber or pharmacist at your next routine visit if you have any heart problems or other concerns about the treatment.

Reference:

Drug Safety Update, MHRA, volume 8, issue 6: 4, January 2015 (www.gov.uk/mhra)

(See *WHO Pharmaceuticals Newsletters No.5, 2014, No.5, 2013, No.4, 2014 and No.6, 2012 for related information*)

Ustekinumab

Risk of exfoliative dermatitis

UK. The MHRA warned health-care professionals to stop treatment of ustekinumab if

exfoliative dermatitis is suspected to be caused by an adverse drug reaction.

Ustekinumab (Stelara®) is licensed to treat moderate to severe plaque psoriasis and active psoriatic arthritis in adults for whom other non-biological systemic therapies have not worked.

The MHRA have received rare Yellow Card reports of exfoliative dermatitis in patients being treated with ustekinumab for plaque psoriasis. Symptoms reported included widespread erythema, scaling, itching, and skin exfoliation. In some cases skin exfoliation occurred without other symptoms of exfoliative dermatitis. In many cases patients were hospitalised as a result of the symptoms.

In some cases symptoms started within a week of the first dose, suggesting a possible link to ustekinumab.

Symptoms of exfoliative dermatitis may be very similar to those of erythrodermic psoriasis. Erythrodermic psoriasis may develop as part of the natural course of plaque psoriasis. The MHRA advise health-care professionals to consider both exfoliative dermatitis and erythrodermic psoriasis as possible causes if symptoms occur in a patient receiving ustekinumab.

When using ustekinumab to treat plaque psoriasis or active psoriatic arthritis, health-care professionals:

- remain alert for signs and symptoms of exfoliative dermatitis or erythrodermic psoriasis
- start appropriate treatment promptly if a patient develops widespread erythema and skin exfoliation
- stop ustekinumab treatment if you suspect exfoliative dermatitis caused by an adverse drug reaction to ustekinumab

- tell patients to report symptoms of exfoliative dermatitis or erythrodermic psoriasis (e.g. increased redness and shedding of skin over a larger area of the body) to their doctor promptly.

Reference:

Drug Safety Update, MHRA, volume 8, issue 6: 2, January 2015 (www.gov.uk/mhra)

(See WHO Pharmaceuticals Newsletter No.1, 2015 for serious skin disorders (exfoliative dermatitis and erythrodermic psoriasis) associated with ustekinumab in Canada)

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 Individual Case Safety Reports (ICSRs) available in the WHO Global ICSR database, Vigibase®. The database contains over 10 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.

More information regarding the ICSRs, their limitations and proper use, is provided in the UMC Caveat document available at the end of SIGNAL (page 37). 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. UMC's vision is to improve worldwide patient safety and welfare by reducing the risk of medicines. For more information, visit www.who-umc.org. To leave a comment regarding the signals in this Newsletter, please contact: the Uppsala Monitoring Centre, Box 1051, SE-751 40 Uppsala, Sweden. E-mail: signals@who-umc.org.

Brentuximab and Hepatic disorders

Dr Ruth Savage, New Zealand

Summary

Brentuximab is a CD30 directed monoclonal antibody indicated for the treatment of anaplastic large T cell systemic malignant lymphoma and Hodgkin's Lymphoma after failure of prior treatments. Increased hepatic transaminases is a listed adverse reaction for brentuximab in the EMA SPC. Other relevant adverse effects of brentuximab are fever, neutropenia, pancreatitis and increased susceptibility to infection. Recent reports in the WHO Global ICSR database, Vigibase®, of serious hepatobiliary disorder associated with brentuximab use led to a review of all the 55 reports for brentuximab in the liver and biliary WHO-ART System Organ Class. Reports were categorised according to ADR terms into various hepatic pathological categories and assessed for causality. Serious or fatal hepatic clinical events frequently occurred in patients who were seriously ill because of lymphoma progression or infection both of which could have affected the liver. Some were also taking potentially hepatotoxic medicines as well as brentuximab. However, six reports of hepatic disorders occurring in a clear temporal relationship with brentuximab use and without documented alternative explanations are of particular interest: three patients developed an increase in hepatic transaminases and recovered upon discontinuation of brentuximab, while the other three cases provide evidence that brentuximab may lead to more severe hepatic damage. An interaction between brentuximab and fluconazole may have

contributed to the suspected reaction in two reports.

Introduction

Brentuximab vedotin is a CD30 directed monoclonal antibody indicated for the treatment of anaplastic large T cell systemic malignant lymphoma after failure of at least one prior multi-agent chemotherapy regimen and Hodgkin's Lymphoma after failure of autologous stem cell transplant (ASCT) or after failure of at least two prior multi-agent chemotherapy regimens in patients who are not ASCT candidates.¹ Brentuximab vedotin consists of three components: the chimeric IgG1 antibody cAC10 which is specific for human CD30; the microtubule disrupting agent MMAE; and a protease-cleavable linker that covalently attaches MMAE to cAC10. Once the ADC-CD30 complex enters the cell, MMAE is released.² The recommended dose is 1.8 mg/kg administered only as an intravenous infusion over 30 minutes every three weeks. Treatment should be continued until a maximum of 16 cycles, disease progression or unacceptable toxicity.

In the first quarter of 2014 the combination brentuximab - hepatocellular damage was highlighted in the WHO Global ICSR database, Vigibase®, using the vigiRank screening method.³ On examining the eight reports in this combination it became apparent that the WHO-ART preferred

term "hepatocellular damage" included reports recording a range of hepatic reactions from increased serum hepatic transaminases to acute hepatic failure. In the light of this finding it was considered appropriate to consider all of the Vigibase® reports of suspected adverse reactions to brentuximab in the Liver and biliary System Organ Class (SOC) to determine if there was evidence of serious hepatic reactions.

Literature and Labelling

The EMA Summary of Product Characteristics for Adcetris (brentuximab vedotin) indicates that elevations in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) have been reported in > 1/100 to < 1/10 patients and advises that liver function should be routinely monitored in patients receiving brentuximab.¹ The US FDA indicated that it was monitoring brentuximab and hepatotoxicity as a potential safety issue in January 2014.⁴ Other relevant adverse effects of brentuximab are fever and neutropenia and increased susceptibility to infection.¹

Reports in Vigibase®

After the removal of duplicates 55 reports were identified in the Vigibase® SOC Liver and biliary system disorders in which brentuximab was suspect. The reports were divided into pathological categories that allowed a distinction between increased hepatic transaminases and more serious reports and between various types of hepatic pathology. The divisions were as follows, with numbers of reports and fatalities in parentheses.

1. Non-specific hepatic reactions: i.e. the pattern of underlying liver dysfunction or pathology was not described. (10, 6)
2. Increased hepatic enzymes/transaminases with no mention of increased bilirubin, alkaline phosphatase or other hepatic abnormalities. (15, 1)
3. Increased hepatic transaminases together with increased bilirubin and/or alkaline phosphatase or other hepatic abnormalities. (13, 3)
4. Cholestatic hepatitis (2, 0)

Further categories identified were cholelithiasis and gall bladder disorders (eight reports), jaundice or hyperbilirubinaemia (two), hepatic cirrhosis (two), hepatic steatosis (two), hepatomegaly (one). These reports were not thought to be related to brentuximab use either because the duration of use made a causal association

improbable or there were clear alternative explanations.

Table 1 summarises the reports in Groups 1 to 4 and further details are discussed below. The indications and doses are not discussed separately as, where recorded, they were usually in keeping with the product information. Brentuximab is usually administered intravenously at 21 day intervals.

Group 1. Non-specific hepatic reactions

These ten reports included a high proportion of serious reactions, six were fatal. For five of the six reports of death there was an alternative or contributory explanation for the hepatic disorders, including sepsis and disease progression, and for the other insufficient information to establish causality. There was no information on dechallenge outcome for the four patients who survived. However, two did not have obvious alternative explanations. One of these had "cytolytic hepatitis" as well as pancreatitis and cholelithiasis and developed hepatic encephalopathy.

Group 2. Increased hepatic enzymes/transaminases only

There were 15 reports in this group. Two reports for children aged three years were in this group, although it is possible these were duplicate reports. The median age of the adults was 29 years. There was one fatality but the report was insufficiently documented to draw any conclusions about cause of death and causality. These reports represent a documented adverse reaction to brentuximab as discussed above. However, two patients had symptoms suggestive of hepatitis, these were abdominal pain in one and vomiting, diarrhoea and myalgia in the other. Information about outcome was provided in four reports. One patient recovered on stopping brentuximab after four doses. Transaminases had increased three to six fold after each dose. One, who had co-incident abdominal pain, recovered from increased transaminases over two months while brentuximab was continued although extensive investigations did not reveal an alternative cause for the hepatic derangement or the abdominal pain. Another patient developed increased transaminases after the first two cycles of brentuximab but not after the third. One patient did not recover on stopping brentuximab. Finally, two patients had serious infection, a possible alternative explanation for the increase in hepatic enzymes.

Group 3. Increased hepatic transaminases and other hepatic abnormalities

The 13 reports in this group include three fatalities. Alternative explanations for two of the fatalities were pulmonary aspergillosis and necrotising vasculitis. However, one patient who died developed elevated transaminases and severe diarrhoea within three weeks of his first brentuximab infusion. The second infusion was given and he rapidly developed fulminant hepatitis. Although the patient had received chemotherapy and an autologous stem cell transplant previously and was taking other medicines that included fluconazole he had no history of hepatic dysfunction. Of the ten patients who survived five had alternative explanations for hepatic dysfunction including sepsis (two), febrile neutropenia (one), and hepatobiliary disorders unlikely to be causally related to short term brentuximab use (two). Of the five other patients who survived, two recovered or were recovering on stopping brentuximab. One of these patients had a liver biopsy finding suggestive of drug-related disease. Another patient with a similar biopsy finding continued brentuximab and developed severe thrombocytopenia but no further mention was made of the hepatic dysfunction.

Group 4. Cholestatic hepatitis

There were two reports. One was of intrahepatic cholestasis reported with acute cholecystitis. The duration of brentuximab use was not recorded and it is possible that underlying cholelithiasis was the cause. The other patient developed cholestatic hepatitis with abdominal pain and jaundice seven days after starting brentuximab. He had developed a mild cholestasis after the first dose and this was more pronounced seven days after the dose and became severe after the second three-weekly dose. Extensive investigations did not reveal an alternative explanation. He had not recovered at the time of reporting but this was only nine days after the second dose. Clemastine was recorded as co-suspect but was started the day of the second infusion.

Reports of particular interest

Table 2 shows six reports from the groups described above. Three of the reports contain evidence of improvement on brentuximab discontinuation and three reports are of serious or fatal hepatic disorders where confounding factors appear less likely than brentuximab to be the cause.

Reports 1, 2 and 3 describe increased hepatic transaminases improving on brentuximab discontinuation which is in keeping with product

information. However in report 2 the patient also had increased serum bilirubin and symptoms suggestive of hepatitis and in report 3 serum alkaline phosphatase was also increased. In each of these reports there is also a pattern of increases after each administration of brentuximab.

Reports 4, 5 and 6 do not show clear evidence of improvement on brentuximab discontinuation but they do demonstrate hepatitis, one fatal, with little evidence of alternative causes. Fluconazole was listed as a concomitant medicine with no administration dates in the report of rapidly developing fatal fulminant hepatitis. The MMAE component of brentuximab is a substrate for CYP3A4 so that its metabolism may have been inhibited by fluconazole which could be important if the suspected hepatic reactions to brentuximab are dose-related.

Discussion and Conclusion

The pattern of reports in Vigibase® indicates that where there is an increase in hepatic transaminases these tend to occur with each three weekly brentuximab dose. In some patients this reaction subsides despite continued treatment. In others, more rarely, it may persist and quite rapidly lead to hepatitis.

Only one fatality could be assessed as “possibly” related to brentuximab use. Brentuximab is indicated for extremely ill patients with advanced lymphomas and a history of chemotherapy and stem cell transplants. For this reason, sepsis and disease progression were clear alternative explanations in a number of fatal reports. Others were not sufficiently well-documented to make an assessment. However, it is also possible that the patient’s underlying disease and its consequences may obscure a causal association between serious hepatic disorders and brentuximab.

Several patients were taking fluconazole for fungal or yeast infection or prophylaxis. Fluconazole itself is hepatotoxic. Also a small fraction of the MMAE that is released from brentuximab in the cell is a substrate for CYP3A4/5. Caution is advised when using brentuximab together with fluconazole, a moderate CYP3A4 inhibitor, as concomitant use with ketoconazole (a potent CYP3A4 inhibitor) increased MMAE exposure by approximately 34%.⁵ It is possible that fluconazole inhibition of MMAE metabolism may have played a role in Report 5 (Table 2) where the patient became rapidly worse and in Group 3 (Table 1) there was a report of mixed liver injury and icterus. This patient was able to continue brentuximab without further hepatic problems but had received fluconazole with the first dose. However, the dates of administration of the latter were unclear.

Several reports indicated benefit from brentuximab use and it is important not to discontinue it unnecessarily. However, the Vigibase® reports support the manufacturer's recommendation that liver function should be closely monitored. This will identify patients who experience progressive increases in hepatic enzymes and develop other hepatic abnormalities beyond the commonly occurring mild increases in transaminases.

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Response from Takeda and Seattle Genetics

In response to the WHO signal report of Hepatic Disorders associated with brentuximab vedotin, the Marketing Authorization Holders [MAH (Takeda/ Seattle Genetics)] acknowledge the data described in the report and describe below the actions taken to mitigate this risk.

Currently, brentuximab vedotin is authorised for the treatment of adult patients with relapsed/refractory Hodgkin Disease (r/r HL) following autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option, and adult patients with r/r systemic Anaplastic Large Cell Lymphoma (sALCL). Therefore, this product is used in patients with

aggressive malignancies whose disease has not responded to or has progressed through other standard therapies. These patients have extremely limited treatment options.

Hepatotoxicity and liver function abnormalities have been reported during investigational and commercial use of brentuximab vedotin. These events have been continuously monitored by the MAH as part of the safety surveillance and risk management process for the product. Although, in many cases, other alternative causes of hepatotoxicity may have been contributory (e.g. cholestasis from liver lesion compression, graft-versus-host-disease, underlying liver disease, viral hepatitis, sepsis, concomitant medication) the MAH agrees that a possible causal relationship between brentuximab vedotin and hepatobiliary events cannot be excluded. Thus, labelling changes are ongoing in order to inform physicians and patients of the potential risk of hepatotoxicity and to be alert to symptoms that may indicate an early onset of this risk.

The WHO signal report also suggests a potential drug interaction between brentuximab vedotin and fluconazole, a moderate inhibitor of CYP3A4/5 (enzymes that metabolize MMAE). As described in the reference safety information for brentuximab vedotin, the coadministration of strong CYP3A4/5 inhibitors (e.g. ketoconazole) with brentuximab vedotin resulted in a moderate increase in the exposure to MMAE. Therefore, a potential drug interaction with fluconazole cannot be excluded and is being monitored as part of routine pharmacovigilance activities for brentuximab vedotin.

The MAH will continue to closely monitor the severity, frequency and outcome of all future reports of hepatotoxicity and liver function abnormalities through routine pharmacovigilance to assess any further impact on the benefit-risk profile of brentuximab vedotin. Additionally, the MAH has implemented enhanced safety surveillance activities to further characterize hepatotoxicity events associated with brentuximab vedotin use including the following: creation of a hepatic disorders targeted questionnaire for follow-up of reported cases; use of Standard MedDRA Queries and other internal signal detection tools for monthly analysis of cases in the global drug safety database; and quarterly reviews of the FAERS and VigiBase® data for signals of disproportionate reporting. Actions including additional risk minimization measures will be taken should any new and significant safety issue arise that is considered to change the benefit risk.

The potential risk of hepatotoxicity does not alter the overall favourable benefit-risk profile of brentuximab vedotin treatment in patients with r/r HL or sALCL.

Table 1. Groupings of hepatic reactions associated with brentuximab use in VigiBase®

| Group no | Group | No of reports | Sex | Age in years [median] | Hepatic and related adverse drug reactions (WHO-ART/MedDRA) | Brentuximab sole suspect reports | Duration of use (No of reports) | Time to onset (No of reports) | Outcome (No of reports) | Fatal cases | No of reports with confounders* |
|----------|---|---------------|--------------|--------------------------|--|----------------------------------|--|-------------------------------|--|-------------|---------------------------------|
| 1 | Unspecified hepatic reactions | 10 | M(5) F(3) | 24–65 [46.5] (7 reports) | Hepatic failure+ Acute hepatic failure(4) Liver disorder(1) Hepatic function abnormal (3) Bilirubinaemia together with Phosphatase alkaline increased & Prothrombin decreased (1) Hepatic disease(1) | 10 | Single dose(4) 25 to 69 days(2) | - | - | 6 | Fatal(5) Non-fatal (2) |
| 2 | Hepatic transaminases increased without other hepatic abnormalities | 15 | M(6) F(7) | 3–64 [24.5] (12 reports) | Transaminases Increased (5) SGOT increased & SGPT increased (7) Hepatic enzymes increased(3) Indicative of hepatitis: Abdominal pain (1) Vomiting, diarrhoea, myalgia (1) | 14 | Single dose(3) 7 days(2) 63 to 322 (15 cycles) days(3) | 19 days(1) 7 days(1) | Recovered (1) Not recovered(1) Recovered and brentuximab continued (2) | 1 | Fatal(0) Non-fatal (3) |
| 3 | Hepatic transaminases increased and other hepatic abnormalities | 13 | M(9) F(4) | 17–70 [36] (13 reports) | Transaminases Increased (2) SGOT increased & SGPT increased (7) SGOT increased(1) Hepatic enzymes increased(3) Together with: Phosphatase alkaline increased & Bilirubinaemia (2) Phosphatase alkaline increased (2) Bilirubinaemia (3) Cholelithiasis (1) Cholecystectomy (1) Hepatic steatosis(2) Hepatitis fulminant (1) | 12 | Single dose(2) 21 to 98 days(4) 10 months intermittently (1) | 1 day(2) 10 to 30 days(1) | Recovered/ recovering (2) | 3 | Fatal(2) Non-fatal (5) |
| 4 | Cholestatic hepatitis | 2 | M(2) - | 31–51 [41] (2 reports) | Cholecystitis acute with intrahepatic cholestasis (1) Hepatitis cholestatic (1) | 1** | 21 days - | Within 7 days(1) | Not recovered (1)*** | 0 | Non-fatal (1) |

Note; Number of reports shown in parenthesis

*Possible alternative or contributory explanations for the suspected ADR, usually severe infection, disease progression or graft versus host disease

**But in second report co-suspect started after onset of hepatic disorder

***Report submitted within nine days of dechallenge

Table 2. Brentuximab and Liver disorders in VigiBase®: reports of concern and reports with recovery on dechallenge

| Case | Age/ Sex | Reported adverse drug reactions WHO-ART PT/(MedDRA PT) | Other suspected (S) or concomitant (C) drugs | Brentuximab dose | Duration to onset | De/Re-challenge | Outcome | Notes |
|------|-------------|---|---|-------------------|-------------------|-----------------|---|--|
| 1 | -/F | Hepatic enzymes increased, polyneuropathy, hepatocellular damage (hepatotoxicity) | Aciclovir, omeprazole, sulfamethoxazole/ trimethoprim (all C) | - | Within one year | Drug withdrawn | Recovered. Stopped after 4 th dose and recovered from both increased hepatic enzymes and polyneuropathy. | Increased enzymes x 3-6 ULN after each administration, polyneuropathy worsened after each dose. |
| 2 | 26/M | Asthenia, fever SGOT increased, abdominal pain, bilirubinaemia, liver fatty, SGPT increased, toxicity to various agents, serum iron increased, injection site inflammation, hepatocellular damage (biopsy liver abnormal) | Methotrexate, sirolimus, tacrolimus (all C) | 1.8 mg/Kg | 7 days | Drug withdrawn | Recovered | Liver function tests normal pre 1 st dose. ALT and AST increased then improved prior to 2 nd dose. Approximately two weeks after 2 nd dose bilirubin increased then admission for fever, weakness, abnormal liver function tests. Liver biopsy reported as non-specific, probably drug-induced Mild hepatic steatosis, mildly increased iron stores, scattered inflammatory cells |
| 3 | 23/F | Hepatic enzymes increased | Aciclovir, omeprazole, sulfamethoxazole/ trimethoprim (all C) | 50 mg | 10 to 15 days | Drug withdrawn | Recovering | Enzymes increased x 2-3 ULN 10-15 days after each administration |
| 4 | 25/M | Thrombocytopenia, hepatocellular damage (biopsy liver abnormal), graft versus host disease, weight decrease, hepatic function abnormal | - | - | 10 to 40 days | Drug withdrawn | Unknown | Liver biopsy showed no GvHD but "potential drug reaction" |
| 5 | 29/M | Abdominal pain, hepatic enzymes increased (transaminases increased), hepatitis (hepatitis fulminant) | Aciclovir, fluconazole, prednisone, vitamin K (all C) | 135 mg, cyclic al | After first dose | - | Died | Transaminases increased and abdominal pain, then diarrhoea and bilirubin increased. Two days after 2 nd dose developed fulminant hepatitis. No previous hepatic abnormalities despite stem cell transplant, chemotherapy and fluconazole. Aciclovir, fluconazole, prednisone for neoplasm prophylaxis. Vitamin K for INR 1.3 to 1.4 with no evidence of liver disease. |
| 6 | 31/M | Hepatitis cholestatic | Clemastine (S)* Paracetamol (C) | 164.5 mg | Within 7 days | Drug withdrawn | Not recovered at the time of reporting, 9 days after 2 nd dose | Mild cholestasis since day of 1 st dose, more pronounced after seven days, more severe after 2 nd infusion (3 weeks after 1 st) Viral serology negative. |

Note; There are many other serious and fatal reports (see categories of hepatic reactions). However, in these reports the lymphomas that brentuximab was used to treat were advanced and progressing or severe opportunistic infections had occurred all of which could have affected the liver

*Started day of second infusion so not necessarily co-suspect

Desloratadine and QT prolongation

Ms Sarah Watson, Uppsala Monitoring Centre

Summary

Desloratadine is a long-acting selective H1-histamine antagonist that is administered once daily for the relief of symptoms associated with allergic rhinitis and urticaria. The drug-induced long QT syndrome describes a clinical entity in which administration of a drug produces marked prolongation of the QT interval of an electrocardiogram. A prolonged QT interval is also associated with the development of a severe form of ventricular tachycardia, termed torsade de pointes. QT prolongation is not labelled for desloratadine or its parent drug loratadine although there are reports of loratadine interacting with other drugs to cause QT prolongation.

There are nine unique cases of desloratadine and QT prolongation in the WHO ICSR database, Vigibase®. Although confounders exist in some of the reports, there are in total eight positive dechallenges and three reports with a rapid time-to-onset of the same day. The reports in Vigibase® are an indication that there might be a possibility that desloratadine contributes to QT prolongation when interacting with other drugs with QT prolonging potential.

Introduction

Desloratadine

Desloratadine is a long-acting histamine antagonist with non-sedating properties approved in Europe and the United States since 2001.^{1,2} It selectively blocks peripheral histamine H1-receptors which means that the substance does not readily penetrate the central nervous system. Desloratadine is administered once daily for the relief of symptoms associated with allergic rhinitis (including intermittent and persistent allergic rhinitis) and urticaria. The daily dose indicated is 5 mg for adults and children above 12 years of age (and 1,25 mg for children 1-5 years and 2,5 mg for children 5-11 years of age).¹ It is not known which enzyme is responsible for desloratadine's metabolism. QT prolongation is not labelled for desloratadine in the UK summary of product characteristics nor the FDA product label.^{1,2}

QT prolongation

The long QT interval can be congenital or acquired. QT prolongation predisposes to arrhythmia by prolonging repolarization, which

induces early after-depolarisations and spatial dispersion of refractoriness.

This is shown on the electrocardiogram as an undulating QRS axis with the polarity of complexes shifting around the baseline, expressed as the QT interval corrected by the heart rate (QTc). The long QT syndrome is also associated with the development of a distinctive ventricular tachycardia, termed torsade de pointes.^{3,4} Torsade de pointes may cease spontaneously or degenerate into ventricular fibrillation. It causes significant hemodynamic compromise and often death.⁵ Drug-induced long QT syndrome is the most common cause of acquired long QT syndrome. Drugs known to frequently cause long QT syndrome are anti-arrhythmic agents; in particular class Ia, Ic, or III antiarrhythmics. Other drugs that can cause a QT prolongation include tricyclic antidepressants, phenothiazines, certain antivirals and antifungals⁵ as well as some antihistamines such as mizolastine and ebastine.³ Virtually all drugs that cause QT prolongation reduce the delayed rectifier potassium current (IKr) and prolong the cardiac action potential.

Cardiac disorders are also a frequent cause of acquired long QT syndrome, and QT interval prolongation has been reported in chronic heart failure, acute and chronic heart disease, cardiomyopathies, bradycardia due to sinus dysfunction, as well as conduction block. Electrolyte imbalances; mainly hypokalaemia, hypomagnesaemia and hypocalcaemia, are also common causes of prolonged QT intervals as are many metabolic, nutritional, neurological and endocrine pathological conditions.⁶

Patients with a prolonged QT interval often present with syncope because the underlying rate (200 to 250 beats/min) is nonperfusing. Palpitations are also common among conscious patients.

Sometimes the long QT interval is detected after resuscitation. Patients with congenital long QT syndrome should avoid drugs that prolong the QT interval, and patients with exercise-related symptoms should avoid strenuous exercise. If a drug is the cause, it should be stopped, but until drug clearance is complete, patients with frequent or long runs of torsade de pointes require treatment to shorten the QT interval. As an increasing heart rate shortens the QT interval, reducing the rate through temporary pacing, intravenous isoproterenol or both is often effective. Long-term treatment is required for

patients with a congenital long QT interval syndrome.⁵

Literature and Labelling

QT prolongation is not labelled for desloratadine nor for loratadine of which desloratadine is the active metabolite.^{1,7} In a clinical trial where up to 20 mg of desloratadine (four times the indicated dose for adults) was administered daily for two weeks, no cardiovascular effect was observed. In another trial, where desloratadine was administered at a dose of 45 mg daily (which is nine times the clinical dose) for ten days, no prolongation of QTc interval was observed.¹

In three placebo-controlled clinical trials 246 paediatric subjects aged 6 months to 11 years received desloratadine as an oral solution for 15 days. There were no clinically meaningful changes in any electrocardiographic parameter, including the QTc interval.²

Some antihistamines, such as mizolastine and ebastine, can prolong the QT interval and provoke severe arrhythmias. A study performed by Ponte et al compared three non-sedating H1-antagonists' effects on the QT interval, which they assumed were mediated through modulation of cardiac K⁺ channels. The effect of ebastine was compared to terfenadine which at the time of the study had reported cardiotoxicity and loratadine which at the time of the study had not reported cardiotoxicity. Their conclusion was that only H1-antagonists that significantly suppress the K⁺ currents IKr and IK1 (such as terfenadine and astemizole) induce arrhythmogenesis and torsade de pointes, whereas H1-antagonists that have minimal effects on IKr and IK1 (such as loratadine) appear to lack the arrhythmogenic potential.⁸ Although loratadine has not been reported to cause QT prolongations alone, the drug has been reported to cause QT prolongation and torsade de pointes in combination with amiodarone⁹ and other CYP3A4 inhibitors.³

The enzyme responsible for the metabolism of desloratadine has not yet been identified and the product label states that the possibility that desloratadine could interact with other drugs cannot be excluded.¹

Reports in Vigibase®

As of October 2014, there were ten reports of QT prolongation for desloratadine in the WHO Global ICSR database, Vigibase®. Two of the reports are a likely duplicate pair which leaves nine unique reports in total. There are no additional reports in the database for torsade de pointes with desloratadine. For the parent drug loratadine, there are additionally 48 reports of QT prolongation in Vigibase®.

The reports were entered into the database between 2001 and 2014, with all but two reports entered the latest five years. The origin of the reports is four different continents; Europe, North America, Africa and Oceania. The gender distribution among the reports where gender is reported is equal, with four males, four females and there is one patient with unknown gender. The age distribution varies from two years to 89 years of age with a median of 60 years. The reporters are in five cases physicians, one report is from a hospital and the rest are not stated. Positive dechallenges are reported in eight out of the nine cases. All cases are presented in Table 1.

The time to onset is within the same day for three cases and approximately two months, three months and 21 months in the other cases in which this information was provided. For the patients who took desloratadine and had a QT prolongation recorded the same day, two had co-suspected drugs known to cause QT prolongation that were withdrawn at the same time as desloratadine, namely alfuzozin and amiodarone in one case and quetiapine in the other. In one of these cases, case 3, the patient, who was previously on amiodarone, had taken desloratadine and alfuzozin for the first time in the morning of the day of the event. In the other case, case 8, the patient took desloratadine, isotretinoin, quetiapine and loperamide in large doses in an attempt to commit suicide: desloratadine was taken with a dose of 50 mg and quetiapine in a total dose of 2250 mg. The third case that had a time to onset within the same day, case 1, reported ibuprofen as a concomitant drug but had no drugs co-suspected. Although not stated, it is possible that a fourth case, the patient in case 7 who also tried to commit suicide by ingesting 335 mg of desloratadine and 6000 mg of ibuprofen, had a rapid time to onset since the patient assumedly went to hospital quite soon after the suicide attempt and the electrocardiogram was probably taken at this point.

In the overdose cases the reporters assessed all drugs as possibly contributing to the QT prolongation and in case 6 and 9 the reporters assessed desloratadine as the probable cause of the reaction. In case 5 the reporter first assessed desloratadine as possibly related to the reaction but then removed QT prolongation from the list of ADRs with the motivation that it was only slight. In the other reports no causality assessments were made.

Table 1. Case overview of ICSRs in Vigibase® of QT prolongation in association with desloratadine

| Case | Age/Sex | Other suspected (S) or concomitant (C) drugs | Other reported reactions (WHO-ART preferred terms) | Time to onset | Positive dechallenge | Outcome at time of reaction |
|------|---------|--|--|---------------|----------------------|-----------------------------|
| 1 | 66/F | Ibuprofen (C) | - | Same day | Yes | Recovered |
| 2 | 79/M | Diltiazem, fluticasone, glyceryl trinitrate, ipratropium bromide, isosorbide mononitrate, lansoprazole, nicorandil, ramipril, salbutamol (all C) | - | 21 months | Yes | Recovered |
| 3 | 63/M | Alfuzozin* (S) Digoxin, amiodarone*, pyridoxine (all C) | Bradycardia, syncope, dizziness, sweating increased, bundle branch block | Same day | Yes | Recovered |
| 4 | 2/- | - | Arrhythmia | - | - | Unknown |
| 5 | 50/F | Moxifloxacin* (S) Desloratadine (I) | Palpitation, dizziness | - | Yes | Recovered |
| 6 | 60/M | Enalapril, glibenclamide (both C) | - | 2 months | Yes | Recovered |
| 7 | 18/F | Ibuprofen (S) | Intentional overdose | - | Yes | Recovered |
| 8 | 20/F | Isotretinoin, loperamide, quetiapine* (all S) | Tachycardia, somnolence, fever, hallucination, intentional overdose | Same day | Yes | Recovered |
| 9 | 89/M | Levothyroxin, sertraline, vitamins NOS (all C) | AV Block, bradycardia | 3 months | Yes | Recovered |

NOS = Not otherwise specified

* Drugs that are also known to cause QT prolongation.

Discussion

Of the nine unique cases in Vigibase® for desloratadine and QT prolongation three cases had underlying diseases which, if not well treated, could be predisposing factors for QT prolongation or cardiac abnormalities in general. In one case the patient had diabetes, which is a known risk factor for QT prolongation,¹⁰ and the patient was also taking enalapril which is indicated for high blood pressure or heart failure, the latter also a known cause for QT prolongation.⁶ One case was concomitantly taking other drugs, such as ramipril and nicorandil, that indicated underlying heart problems. In one case the patient was taking levothyroxine, presumably for hypothyroidism, which if not well treated can manifest with cardiac abnormalities and there are a few reports in literature of prolonged QT interval in hypothyroid patients.¹¹ Three cases reported a rapid time to onset within one day. In two of these cases other suspected drugs known to cause QT prolongation were co-reported and withdrawn at the same time as desloratadine.

There are eight reported positive dechallenges among the nine cases and although there could be alternative or contributory explanations in at least five reports, three cases do not have a strong alternative explanation for the QT prolongation. Where causality assessments are made, two reporters have assessed the QT prolongation to possibly be related to desloratadine and in two cases the reporters have assessed desloratadine to probably be related to the reactions. In two of the cases ibuprofen was either co-suspected (in a reported overdose) or concomitantly used. Ibuprofen has shown a possible arrhythmogenic potential both in vitro and in vivo.¹² This is however not labelled for ibuprofen¹³ and the clinical significance is unclear. In another case the reporter suspected an interaction between moxifloxacin and desloratadine. It is written in the product label for desloratadine that it is not known which enzyme is responsible for the metabolism of desloratadine and that therefore, some interactions with other medicinal products cannot fully be excluded.

Although desloratadine has not been reported to cause QT prolongations, its parent drug loratadine has been described as causing QT prolongation and torsade de pointes in combination with amiodarone⁹, a drug that is also present in one of these cases.

Conclusion

QT prolongation can have many alternative causes and can either be acquired from e.g. drugs or be congenital. Several of the cases in Vigibase® present alternative or contributory factors to the reaction but eight out of the nine unique cases report a positive dechallenge and three reports have a rapid time to onset recorded the same day as the drug was administered. Two reporters have also assessed the reactions as probably related to desloratadine. The fact that loratadine, the parent drug of desloratadine, has been reported to interact with other drugs, namely amiodarone which was also used as a long term treatment by one of the patients with a rapid time to onset in this case series, makes a possible hypothesis that also desloratadine could have this potential. The product label states that it is not known which enzyme is responsible for the metabolism of desloratadine and that interactions with other medicinal products cannot be excluded. This possibility is highlighted in this signal.

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Golimumab and Migraine

Dr Ian Boyd, Australia

Summary

Golimumab is a human monoclonal antibody that forms high affinity, stable complexes with both the soluble and transmembrane bioactive forms of human tumour necrosis factor (TNF)- α , which prevents the binding of TNF- α to its receptors. It is indicated for the treatment of ulcerative colitis (UC), ankylosing spondylitis (AS), psoriatic arthritis (PsA) and rheumatoid arthritis (RA) in combination with methotrexate (MTX). After the elimination of duplicates there are currently (1 September 2014) 20 ICSRs in the WHO Global ICSR database, Vigibase® of migraine in association with golimumab. The reports are from Australia, Canada, Denmark, Sweden, Switzerland, the United Kingdom and the United States. Golimumab was the only drug suspected in 15 of the 20 cases. The outcome of the migraine was stated in nine reports. Six of these patients were reported as recovered and the remaining three patients had not recovered. In the six cases with recovery, golimumab was withdrawn in five cases and the fate of the drug was unclear in the other case. In the three cases where the patients had not recovered, the drug was withdrawn in two cases and continued in the other case.

Case reports in Vigibase® suggest that there is a possible signal for the association of golimumab and migraine. Although there are alternative explanations such as the use of adalimumab in two reports and the episodic recurrence of migraine in three other reports, the use of golimumab resulting in migraine appears to be a signal. Time to onset is consistent with a drug-induced effect. Migraine is mentioned in the product information of two other TNF- α inhibitors and for one of these drugs as well as an additional TNF- α inhibitor, there are significant reports of the association in Vigibase®. Finally, TNF- α is known to be involved in migraine so a mechanism for the involvement of TNF- α inhibitors in the development of migraine is a possibility.

Introduction

Golimumab is a human monoclonal antibody that forms high affinity, stable complexes with both the soluble and transmembrane bioactive forms of human tumour necrosis factor (TNF)- α , which prevents the binding of TNF- α to its receptors. It is indicated for the treatment of ulcerative colitis (UC), ankylosing spondylitis (AS), psoriatic arthritis (PsA) and rheumatoid arthritis (RA) in combination with methotrexate (MTX). The most

serious ADRs that have been reported for golimumab include serious infections (including sepsis, pneumonia, tuberculosis, invasive fungal and opportunistic infections), demyelinating disorders, lymphoma, hepatitis B virus reactivation, congestive heart failure, autoimmune processes (lupus-like syndrome) and haematological reactions. The adverse reactions which have been reported commonly or very commonly include infections and infestations such as upper respiratory tract infection, bacterial infections, lower respiratory tract infection, viral infections, bronchitis, sinusitis, superficial fungal infections, and abscess; immune system disorders such as allergic reactions and autoantibody positive; nervous system disorders such as dizziness, headache and paraesthesia; gastrointestinal disorders; skin and subcutaneous tissue disorders; general disorders and administration site conditions such as pyrexia, asthenia, and injection site reaction; depression, insomnia, increases in liver function tests, asthma, hypertension and anaemia.¹

Migraine is the second most common form of headache, afflicting approximately 15% of women and 6% of men over a one year period. It is usually an episodic headache associated with certain features such as sensitivity to light, sound, or movement; nausea and vomiting often accompany the headache. A useful description of migraine is a benign and recurring syndrome of headache associated with other symptoms of neurological dysfunction in various admixtures.²

Reports in Vigibase®

As of 1 September 2014 there are 21 ICSRs of migraine and one report of migraine aggravated (WHO-ART preferred terms) in association with golimumab in the WHO Global ICSR database, Vigibase® (Table 1). After the elimination of two duplicates, the reports were submitted from the United States (nine reports), Canada (four reports), Sweden (three reports), and Australia, Denmark, Switzerland and the United Kingdom (one report each). The patients ranged in age from 37 to 77 years with a median of 59 years in the 11 cases which provided the information. There were 18 females and two males.

Golimumab was the only drug suspected in 15 of the 20 cases. There were other drugs also suspected in the remaining five cases and they were mostly drugs probably being used for the same indication as golimumab. These drugs

included adalimumab and hydromorphone in one report each, both infliximab and ibuprofen in one report and adalimumab, etanercept and MTX in another report. In the remaining report, pandemic influenza vaccine was suspected. Concomitant drugs were reported in nine of the 20 cases and apart from asthma treatment in three cases, the concomitant drugs were mostly those which might be expected in a patient population with systemic inflammatory disease and included MTX (five cases), folic acid (four), other immunomodifiers or similar drugs (four), NSAIDs (four) and corticosteroids (three). Drugs used for the treatment of migraine were reported in two cases and in another case the reaction term was migraine aggravated. Golimumab was reported to have been administered subcutaneously, as expected, in all 17 cases which provided this information. The indication for use was stated in 14 reports and included RA in seven reports, AS in four reports, and psoriasis, RA/PsA and RA/osteoarthritis in one report each. In all nine cases which provided information on both dose and dosage regimen, the drug was administered monthly at 50 mg.

Time to onset was reported in five of the reports and ranged from the same day the drug was administered to eight months (median four weeks). Two other reports appeared to indicate that onset was within a month.

The outcome of the migraine was stated in nine reports. Six of these patients were reported as recovered and the remaining three patients had not recovered. In the six cases with recovery, golimumab was withdrawn in five cases and the fate of the drug was unclear in the other case. In the three cases where the patients had not recovered at the time of reporting, the drug was withdrawn in one case, it was reported to only have been given once in one case and continued in the other case.

Other reactions were reported in all but two cases. These included a wide variety of reactions but the most common were those which may be expected to accompany migraine such as headache (five reports), vision abnormal (three), hypoaesthesia (three), paraesthesia (three), fatigue (three), and vomiting (two).

Literature and Labelling

The product literature does not refer to migraine although it does refer to headache. The neurological reactions mentioned include dizziness, headache and

paraesthesia (common), balance disorders (uncommon) and demyelinating disorders (central and peripheral) and dysgeusia (rare). There are no reports in the literature which link migraine with

golimumab. There are also no reports in the literature which link other TNF- α inhibitors with migraine but this reaction is listed as common in the product literature for adalimumab.³ In addition, the product information for another TNF- α inhibitor, certolizumab, indicates that headache, including migraine, is a common reaction.⁴

Discussion

Case reports in Vigibase® suggest that there is a possible signal for the association of golimumab and migraine. Golimumab was the only drug suspected in 15 of the 20 cases. There were other drugs suspected in the remaining five cases and in two of those, adalimumab was also a suspected drug. It could be considered a more likely cause as migraine is a known reaction to this drug. None of the other suspected drugs appear to be a more likely cause than golimumab and in Case 1, the temporal association appears better with golimumab than pandemic influenza vaccine. In Case 19, however, the patient recovered after hydromorphone was withdrawn while golimumab was probably continued. This suggests that hydromorphone is a more likely cause.

Time to onset was reported in five of the reports and ranged from the same day the drug was administered to eight months (median four weeks). Two other reports appeared to indicate that onset was within a month. This would appear consistent with a drug induced effect.

The outcome of the migraine was stated in nine reports. Six of these patients were reported as recovered and the remaining three patients had not recovered. In the six cases with recovery, golimumab was withdrawn in five cases and the fate of the drug was unclear in the other case. This last case is Case 19, mentioned above, in which hydromorphone appears a more likely cause. In the three cases where the patients had not recovered, the drug was withdrawn in two cases and continued in the other case. Dechallenge is usually considered as good evidence of drug association but for a drug which is administered periodically (monthly in this series), this is not necessarily supportive.

As noted above, there are no reports in the literature which link TNF- α inhibitors with migraine but this reaction is listed as common in the product literature for adalimumab and the product information for another TNF- α inhibitor, certolizumab, indicates that headache, including migraine, is a common reaction. In Vigibase®, there are 785 reports of migraine in association with etanercept, 683 with adalimumab, 224 with infliximab and 65 with certolizumab. This information raises the possibility that migraine may be a class effect of TNF- α inhibitors.

It is known that activation in the trigeminal nucleus results in the release of vasoactive neuropeptides, particularly calcitonin gene-related peptide (CGRP) and that CGRP receptor antagonists have been shown to be effective in the treatment of migraine.² Durham noted that TNF- α was implicated in migraine as have a number of others including Robbins and Maides, and Durham further noted that several findings in migraineurs support a role of CGRP in migraine and that TNF- α can stimulate CGRP transcription.^{5,6} These findings suggest that TNF- α inhibitors may be protective against migraine but the involvement of TNF- α in migraine does indicate that a mechanism for the involvement of TNF- α inhibitors in the development of migraine is a possibility.

Conclusion

In summary, there are 20 reports associating migraine with the use of golimumab. Golimumab was the only drug suspected in 15 of the 20 cases. Although there are alternative explanations such as adalimumab in two reports and the episodic recurrence of migraine in three other reports, the use of golimumab in association with migraine appears to be a signal. Time to onset is consistent with a drug induced effect. Dechallenge is supportive of a drug association but for a drug which is administered periodically, this is not compelling evidence. Migraine is mentioned in the product information of two other TNF- α inhibitors and for one of these drugs as well as an additional TNF- α inhibitor, there are significant reports of the association in Vigibase®. Finally, TNF- α is known to be involved in migraine so a mechanism for the involvement of TNF- α inhibitors in the development of migraine is a possibility.

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Table 1. Case overview of reports in Vigibase® of migraine in association with golimumab

| Case | Age/Sex | Other suspected (S) or concomitant (C) drugs | Reactions (WHO-ART preferred terms) | Outcome |
|------|---------|--|---|---------------|
| 1 | 48/F | A/H1N1 Influenza pandemic vaccine (S) Folic acid, meloxicam, methotrexate, decongestants (not further specified) (all C) | Migraine, coughing, eye pain, fever, headache, myalgia, rhinitis, influenza immunisation* | Unknown |
| 2 | 55/F | Budesonide, folic acid, methotrexate (all C) | Migraine | Recovered |
| 3 | 77/F | None | Migraine, arthralgia, depression aggravated, heart murmur, influenza-like symptoms, malaise, oedema peripheral, phlebitis | Unknown |
| 4 | -/F | None | Migraine, infection staphylococcal | Unknown |
| 5 | -/F | None | Migraine, headache, vomiting | Unknown |
| 6 | -/F | Ascorbic acid, ciclosporin, cyanocobalamin, dicycloverine, docusate, ergocalciferol, ergocalciferol/calcium phosphate/calcium sodium lactate, fish oil, fluticasone, hydrocodone, lidocaine, macrogol, methadone, ondansetron, pantoprazole, pyridoxine, salbutamol, sumatriptan, topiramate, vitamins NOS (all C) | Migraine, hypertension, medication error, therapeutic response increased | Not recovered |
| 7 | 53/M | None | Migraine, rash erythematous, vision abnormal | Not recovered |
| 8 | -/F | Adalimumab (S) Ethinylestradiol/desogestrel, fexofenadine, fluticasone, methylprednisolone, oral contraceptive nos, rizatriptan, topiramate (all C) | Migraine, fatigue, gait abnormal, headache, hypoaesthesia, injection site bleeding, medication error, paraesthesia, upper respiratory tract infection, madarosis*, pain in extremity* | Not recovered |
| 9 | 37/F | None | Migraine, hypoaesthesia, hypokinesia, paraesthesia | Unknown |
| 10** | -/F | None | Migraine, visual abnormal | Unknown |
| 11 | 64/M | Antihypertensives (not further specified), methotrexate (both C) | Migraine, malaise, joint fluid drainage* | Recovered |
| 12 | 60/F | None | Migraine | Unknown |
| 13 | -/F | Betamethasone, clonazepam, folic acid, hydrochlorothiazide, ibuprofen, levothyroxine, methotrexate, salbutamol, spironolactone, zolpidem (all C) | Migraine, abdominal pain, allergic reaction, anxiety, asthma, haemorrhage NOS, oedema generalised, oedema peripheral, rhinitis | Unknown |
| 14** | -/F | None | Migraine, vision abnormal | Unknown |
| 15 | -/F | None | Migraine, GI haemorrhage, headache, hypertension | Recovered |
| 16 | -/F | Sulfasalazine (C) | Migraine, hearing decreased, vision abnormal, dysphemia* | Unknown |
| 17 | 60/F | None | Migraine, bronchitis, dizziness, hypoaesthesia, paraesthesia, pharyngitis, vision abnormal | Unknown |
| 18 | -/F | Ibuprofen, infliximab (both S) | Migraine, abdominal pain, pruritus, rash, vomiting | Unknown |

| | | | | |
|-------|------|---|--|-----------|
| 19 | 65/F | Hydromorphone (S) Acetylsalicylic acid, calcitonin, calcitriol, clobetasol, clonazepam, desonide, dimenhydrinate, dorzolamide, ergocalciferol, fentanyl, folic acid, lactulose, methotrexate, prednisolone, prednisone, tacrolimus, teriparatide (all C) | Migraine, arthralgia, arthritis, coma, constipation, fracture, fever, medical device complication, medication error, medicine ineffective, pneumothorax, weight decrease, back injury*, muscle strain* | Recovered |
| 20*** | 57/F | Adalimumab, etanercept, methotrexate (all S) Hydroxychloroquine, meloxicam, vitamins (all C) | Migraine, dyskinesia, fatigue, speech disorder, dysgraphia* | Recovered |
| 21*** | 57/F | Adalimumab, etanercept, methotrexate (all S) Hydroxychloroquine, meloxicam, vitamins (all C) | Migraine, dyskinesia, fatigue, speech disorder, dysgraphia* | Recovered |
| 22 | 59/F | None | Migraine aggravated, constipation, fatigue, headache | Recovered |

NOS = Not otherwise specified

*MedDRA terms

**Cases 10 and 14 are duplicates

***Cases 20 and 21 are duplicates

Response from Janssen

Golimumab is one of several TNF-blocking agents that are available for the treatment of diseases such as rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), and ulcerative colitis (UC). Janssen actively evaluates available safety data from multiple sources to identify new safety signals and works closely with health authorities to accurately inform patients and prescribers about the safety profile of golimumab.

In response to this signal notification, Janssen performed a review of literature, the clinical trial database, and cumulative reports of migraine with golimumab therapy that were contained in the Janssen worldwide safety database. Janssen also conducted searches of the United States Food and Drug Administration Adverse Event Reporting System (FAERS) database/ WHO Global ICSR Database System (Vigibase®) and the Janssen worldwide safety database for reports involving the use of golimumab and coded to a set of MedDRA Preferred terms (PTs) representative of migraine for a signal of disproportionality. The search used the most currently available, cumulative data from the FAERS database through March 31, 2014, and the WHO Vigibase®, through September 30 2014, and the Janssen worldwide safety database cumulatively through 26 November 2014. The results of the analysis are provided below.

A literature search was carried out using PubMed to identify any reports in the literature associating migraine with the use of any TNF- α inhibitors and specifically with the use of golimumab. No reports in the literature were identified associating migraine with the use of golimumab or other TNF- α inhibitors.

Clinical trial data was retrieved from 5 phase 3 subcutaneous studies (3 RA, 1 PsA, 1 AS), 2 phase 3 intravenous RA studies, and 2 phase 2/3 UC studies for the pure placebo-controlled period in which 1,372 subjects were exposed to placebo and 3,513 subjects were exposed to golimumab. Subjects in both golimumab-treated and placebo-treated arms reported the PT of Migraine at a frequency of 0.4%. The frequency of the PT Migraine with aura reported as 0.1% in the placebo arm and 0.0% in the golimumab arm.

The Janssen worldwide safety database was searched for the following PTs: Migraine, Basilar migraine, Retinal migraine, Migraine with aura, Abdominal migraine, Hemiplegic migraine, Ophthalmoplegic migraine, Migraine without aura, Familial hemiplegic migraine, Stroke-like migraine attacks after radiation therapy, Migrainous infarction, or Status migrainosus. The search retrieved 98 reports for the PT of Migraine and 1 report for the PT of Migraine with aura. No disproportionality alerts were observed for either PT in the database. WHO Global Individual Case Safety report database, Vigibase® data mining of

Migraine as of the September 30, 2014 included 22 reports associated with golimumab. No disproportionality was observed for the retrieved dataset. FAERS data mining of Migraine as of the March 31, 2014 included 21 reports associated with golimumab. No disproportionality was observed for the retrieved dataset.

A review of the 99 reports retrieved from the Janssen worldwide safety database elucidated the following details. One report was a duplicate report; 7 reports provided adequate detail without confounding factors; 24 reports involved patients with medical history of headaches/migraines; 10 reports involved patients with co-morbid conditions associated with migraines; and 57 reports provided limited information, including medical history, co suspect/concomitant medications, indication, latency, clinical course of events, treatment, or outcome, precluding an adequate medical assessment. Individual and aggregate review of those reports providing adequate information did not indicate an

association between migraine and golimumab use, either for new onset or worsening of existing conditions of migraine.

Based on this review of data from the Janssen worldwide safety database, the clinical trial database, the literature, the WHO Vigibase®, and FAERS database, migraine is not considered associated with the use of golimumab. Key factors supporting this conclusion include the extensive data from the clinical trials showing a balance between subjects receiving placebo or golimumab, the lack of disproportionality in the various databases, the lack of literature supporting the association, the low reporting rate coupled with the common frequency of migraine in the population as noted by WHO, and the review of individual reports of migraine found in the Janssen worldwide safety database. No changes to the golimumab labelling/prescribing information are warranted at this time, and the benefit-risk ratio for patients treated with golimumab for RA, PsA, AS or UC remains favourable.

Vemurafenib and Sepsis

Dr Geraldine Hill, Uppsala Monitoring Centre

Summary

Vemurafenib is a protein kinase inhibitor with activity against mutated B-Raf protein, which is used in the treatment of metastatic or unresectable malignant melanoma that carries the BRAF V600E mutation. The WHO Global ICSR Database, Vigibase®, contains 22 ICSRs in which vemurafenib is associated with sepsis. Metastatic malignancy is, in itself, a risk factor for sepsis and a number of the ICSRs in the case series include additional risk factors for infection. However, evidence to support a signal includes: a consistent time-to-onset (where stated) among cases without additional risk factors; reports from seven countries and vemurafenib was the only suspected drug in most of cases. In addition, vemurafenib acts in the RAF-MEK-ERK intracellular signalling pathway and this same pathway is involved in neutrophil extracellular trap (NET) formation, a significant host defence mechanism against invading pathogens.

Introduction

Vemurafenib is a serine-threonine protein kinase inhibitor that inhibits the kinase activity of mutated B-Raf protein. The Ras-Raf-MEK-ERK mitogen activated protein kinase (MAPK) cascade is an important cytoplasmic signalling pathway

involved in the regulation of normal somatic cell proliferation. Mutations in the genes encoding components of this pathway have been associated with a number of human cancers.¹ An activating mutation in the BRAF gene, which encodes the serine-threonine protein kinase B-Raf, has been found to be present in 40-60 percent of melanomas, most commonly the BRAF V600E mutation.² Vemurafenib is indicated for the treatment of metastatic or unresectable melanomas that carry the BRAF V600E mutation. The recommended dose is 960 mg twice daily and it is currently available in 240 mg tablets.³

Sepsis is defined as a systemic response to microbes that traverse the epithelial barriers and invade underlying tissues; it is characterized by fever or hypothermia, leukocytosis or leukopenia, tachypnoea and tachycardia; together these clinical signs are known as the systemic inflammatory response syndrome, which may also occur in response to a non-infectious cause. Sepsis represents the early stage of a continuum: when associated with organ dysfunction distant to the site of infection, it is defined as severe sepsis and may be associated with hypotension and hypoperfusion; if perfusion cannot be restored with fluid infusions, the condition is defined as septic shock.⁴

The incidence of sepsis and its associated mortality increases with increasing age and with underlying co-morbidities. Individuals who are immunocompromised due to underlying disease (e.g. metastatic cancer, HIV infection, chronic illness) or medication (cancer chemotherapy, corticosteroids) are at greater risk of sepsis, but immunocompetent individuals are also at risk (e.g. following surgical procedures that breach epithelial barriers). Individuals with a foreign or pathological locus on which infection may seed (e.g. artificial heart valve, indwelling catheter or urinary calculus) are also at risk. Investigations are directed at isolating the causative microorganism from blood or a localized site of infection, and include blood cultures and radiological examinations to identify the source. Treatment requires removal of the source of infection (e.g. removal of indwelling intravenous or urinary catheters, drainage of abscess), circulatory and respiratory support as necessary and correction of metabolic disturbances, in addition to aggressive empirical antimicrobial chemotherapy, which may be tailored to the specific organism once identified.

Reports in Vigibase®

At the time of assessment (August 2014), there were 22 case reports in the WHO Global ICSR Database, Vigibase®, for the combination vemurafenib and sepsis. No duplicates were identified among these 22 reports.

The reports came from seven countries: United States (10), Germany (3), Australia, Italy and United Kingdom (2 each), and Austria and Switzerland (1 each). All of the ICSRs were serious and 12 reports were fatal.

The cases concerned 16 males and 6 females. Age was reported for 18 cases and ranged from 47 to 89 years (median age 63.5 years). The indication for treatment was reported as melanoma for 16 cases but was not stated for the remaining 6 cases. The time-to-onset was reported for 10 cases and ranged from 6 to 132 days, with a median of 17 days. The outcome for sepsis was reported for 18 cases: recovered (6), recovering (1), not recovered (1), died (9), died - reaction may be contributory (1). The outcome was reported as unknown for three cases and was not stated for one case. Three of the patients who recovered continued to take vemurafenib at the same dose, one of whom subsequently developed cellulitis, which was recovering at the time of reporting. A further patient, who continued vemurafenib at a lower dose after developing sepsis, developed a second episode of sepsis; the medication was continued and the infection resolved. Vemurafenib was the sole suspected drug in 19 of the ICSRs and was the only reported drug in ten of the ICSRs.

Of the 22 ICSRs, eight reports were poorly documented. One of these reports concerned a patient with a past medical history of leukaemia and COPD. A further four of these reports concerned patients with co-reported events that suggest a possible source of the sepsis; however, onset dates were not provided so it is not possible to determine the sequence of events. These co-reported events include colitis, cytomegalovirus enteritis, exfoliative dermatitis/blisters/generalized erythema and nasopharyngitis/blisters/erythema.

Of the remaining 14 ICSRs, three patients were reported to have neutropenia, one of whom was also reported to have an intestinal perforation. A further six patients had identifiable sources of infection: one patient with Chronic Hepatitis B developed cholecystitis while on vemurafenib, another patient suffered intestinal perforation, three patients were reported to have pneumonia, one of whom was also reported to have a bronchial obstruction secondary to lung metastases. One patient, with an indwelling suprapubic catheter as a result of Multiple Sclerosis and a known staghorn renal calculus, developed sepsis secondary to a urinary tract infection.

The remaining five patients are summarized below:

A 73 year-old woman with extensive metastases (liver, adrenals, lymph) developed *E. coli* sepsis and hemiparesis while taking Vemurafenib. The exact time-to-onset was not reported, but she had previously experienced fatigue, asthenia and epidermoid cysts on a higher dose (not stated). The dose was halved approximately five months prior to the onset of sepsis (which developed approximately seven months after the drug was started). Vemurafenib was the only suspected drug; the other reported medicine, ibandronic acid, is not known to be associated with sepsis. She recovered following treatment with antibiotics.

A male of unknown age with cerebral metastases developed sepsis of unknown origin (cultures negative; x-ray and CT scan provided no clues as to the source of infection), associated with keratoconjunctivitis, 11 days after starting vemurafenib 1920 mg per day. Vemurafenib was stopped for two days then reintroduced at half the dose. He recovered, but subsequently developed another episode of sepsis of unknown origin, 56 days after treatment initiation, from which he also recovered with appropriate treatment. Both episodes resolved while treatment with vemurafenib continued. Vemurafenib was the only reported drug.

A 47 year-old woman developed sepsis 19 days after starting vemurafenib 1920 mg per day. She recovered quickly with antibiotic treatment and vemurafenib therapy was continued. She

subsequently developed cellulitis, 111 days after treatment initiation, which was resolving at the time of reporting while continuing on vemurafenib. Concurrent medicines were metoclopramide and ramipril; vemurafenib was the only suspected drug.

A 63 year-old male developed Gram-negative sepsis 15 days after starting vemurafenib 3840 mg per day. Vemurafenib was the only suspected and only reported drug. At the time of reporting, the patient was recovering and treatment with vemurafenib continued unchanged.

A 72 year-old male developed sepsis 70 days after starting vemurafenib 1920 mg per day. The patient died. Vemurafenib was the only suspected and only reported drug.

Literature and Labelling

Folliculitis (infection of the hair follicles of the skin) is the only infection labelled on both the UK Summary of Product Characteristics⁵ and the US FDA product label⁶. No other infections are included in the labelling information.

UMC previously signalled granulocytopenia in association with vemurafenib^{7,8}, a condition of impaired immunity that predisposes individuals to sepsis; neutropenia has since been added to the product label.

Discussion

Patients with metastatic malignant disease, such as metastatic melanoma, are at increased risk of sepsis: contributing factors include procedural interventions that breach epithelial barriers (e.g. surgical tumour removal; insertion of intravenous catheters for delivery of chemotherapeutic medicines), blockage of normally patent structures by metastatic tumours (e.g. urinary tract infection secondary to an obstructed ureter; cholangitis secondary to an obstructed gall bladder; pneumonia secondary to an obstructed bronchus) and increased exposure to pathogens during hospitalization. Other host factors that may contribute to sepsis in patients with metastatic malignant melanoma include diminished nutritional status and the use of medications that impair the immune response (e.g. corticosteroids; some chemotherapeutic agents).

Among the 22 cases in this series, six patients had co-morbidities that clearly predisposed them to sepsis: three patients were reported to be neutropenic at the time of developing sepsis (one of whom was also reported to have had an intestinal perforation), one further patient developed sepsis in association with intestinal perforation, one patient developed pneumonia and

sepsis secondary to bronchial obstruction from lung metastases and one patient with an indwelling urinary catheter and staghorn renal calculus developed sepsis in association with a urinary tract infection. Given the nature of the underlying indication for treatment, it is possible that the two further patients who developed sepsis in association with pneumonia and one patient who developed sepsis in association with cholecystitis may have developed these infections as a result of lung and liver metastases, respectively.

Four cases had co-reported events (colitis, viral enteritis, exfoliative dermatitis and nasopharyngitis) that suggest the source of sepsis, although the onset dates for these events were not provided and the sequence is unclear. Five well documented reports did not identify an obvious source of infection but, again given the underlying indication for treatment, these patients do have an increased risk of infection associated with metastatic cancer.

Although dechallenge is essentially meaningless in the context of sepsis (because recovery is determined by the integrity of host defences and the use of appropriate antimicrobial therapy), it is interesting to note that two patients who recovered from the initial sepsis developed subsequent infections while continuing treatment with vemurafenib (in one case at a lower dose).

Vemurafenib was the sole suspected drug in 19 of the ICSRs and was the only reported drug in ten of the ICSRs. Concomitant drugs were reported in 11 patients: two patients were reported to be taking prednisone which may impair the host response to infection; four patients were on proton pump inhibitors, two patients were taking mesalazine, and one patient was taking metamizole (which is associated with agranulocytosis).

When cases with predisposing factors in addition to metastatic melanoma are excluded (neutropenia, intestinal perforation, metastatic obstruction of bronchus, underlying urinary tract pathology), the remaining cases demonstrate a consistent time-to-onset ranging from 11 to 70 days with a median of 17 days.

The question raised by these cases is whether or not vemurafenib further increases the risk of sepsis in patients with metastatic melanoma who are already at risk of developing serious infections. Vemurafenib acts in the RAS-RAF-MEK-ERK intracellular signalling pathway. The RAF-MEK-ERK components of this pathway are involved in Neutrophil Extracellular Trap (NET) formation.⁹ NETs are extracellular chromatin fibres, decorated with granules containing antimicrobial peptides and enzymes, which are released by activated neutrophils to trap and disarm bacteria.¹⁰ Excessive NET formation may play a role in

sepsis.¹¹ Inhibition of the RAS-RAF-MEK-ERK pathway by vemurafenib may thus have an effect on NET formation in patients taking this medicine, potentially making them more susceptible to infection.

Conclusion

Although metastatic melanoma is in itself a risk factor for sepsis, and a number of the patients in this case series had additional factors that predispose to infection, the ICSRs in Vigibase® concerning vemurafenib and sepsis, together with a possible mechanism, suggest a signal for this combination.

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Response from Roche

The WHO Uppsala Monitoring Centre (UMC) notified Roche about a safety signal of sepsis for vemurafenib based on 22 case reports in the WHO Database, Vigibase® as of August 2014.

To date, sepsis is not considered an adverse drug reaction (ADR) for vemurafenib. The relevant ADRs that are listed in the current vemurafenib label are neutropenia and folliculitis.

A review of the Roche global safety database (through 26 August 2014) revealed 33 medically confirmed cases of sepsis based on a diagnostic criteria¹ and includes the 5 unique cases referenced in the WHO report. Of these 33 cases, 28 of them presented with confounding factors that could account for the septic event, including co-morbid conditions (e.g. bowel perforation, urinary tract infection in elderly patients, diabetes, bowel fistula, hemochromatosis, neutropenia) as well as concomitant treatments or procedures (corticosteroids, indwelling catheter, and surgery). Cancer by itself is a risk for sepsis, and is the most common co-morbid medical condition in patients with sepsis.² The remaining five cases with no confounders are summarized in Table 1 below.

Our data showed that the incidence of sepsis was highest among male patients aged 60 years old and above, which is similar to that cited in the literature for cancer patients³. There was no obvious pattern in terms of clinical presentation, with causative pathogens ranging from bacterial, fungal, and viral; the event severity was also varied, ranging from sepsis to severe sepsis, and septic shock; and significantly, there was no consistency observed in the latency period, with time to onset ranging from 5 days to 682 days (median latency is 42 days). In addition, there were no reported cases of sepsis from the Phase III controlled trial, NO25026 (n=336).

Using MarketScan®, a US commercial claims database, the incidence of sepsis among metastatic melanoma patients demonstrated a rate of 23.6 per 1,000 person years. In contrast, the crude reporting rate for the 33 cases in the Roche global safety database was 2.2 per 1,000 person years (estimated exposure of 24,479 patients with an average treatment duration of 8

months) which is significantly lower than the rate of sepsis in metastatic melanoma patients in the claims database, and also lower than the incidence rate cited in the literature for cancer patients in general (14.65 cases per 1,000 person years)³.

The hypothesis for a plausible MOA cited by WHO, i.e. effect on neutrophil extracellular trap (NET) formation through inhibition of the RAS-RAF-MEK-ERK pathway by vemurafenib is not strengthened by our analysis. Although vemurafenib inhibits signalling downstream of mutant RAF, it is known to increase signalling downstream of wild type RAF⁴; in addition there are literature reports showing the opposite effect of the hypothesis, that excessive NET formation is linked to sepsis^{5,6}; plus host defense mechanisms other than NET formation exist, i.e. phagocytosis.

Roche acknowledges this signal considering the potential risk for this event in this patient population together with the known ADR of neutropenia, and will continue to monitor infections, including sepsis. We thank the WHO for this opportunity to comment on this article.

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Table 1. Sepsis Cases With No Confounding Factors, Vemurafenib

| Case No | Age/ Sex | AE Terms | Time to Onset (days) | Reporter Causality | Neutropenia | Outcome |
|---------|----------|-------------------|----------------------|--------------------|-------------|---------------------|
| 1 | 48/F | Grade 3 Sepsis | 18 | Not related | – | Persisting |
| 2 | 73/F | E. coli sepsis | 210 | Not reported | – | Complete Resolution |
| 3 | 73/M | Sepsis | 22 | Not related | – | Persisting |
| 4 | 67/M | Salmonella sepsis | 122 | Not related | – | Resolved |
| 5 | 22/F | Sepsis | 9 | Not related | – | Resolving |

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CAVEAT DOCUMENT

Accompanying statement to data released from the Uppsala Monitoring Centre, WHO Collaborating Centre for International Drug Monitoring

Uppsala Monitoring Centre (UMC) in its role as the WHO Collaborating Centre for International Drug Monitoring receives reports of suspected adverse reactions to medicinal products from National Centres in countries participating in the WHO pharmacovigilance network, the WHO Programme for International Drug Monitoring. Limited details about each suspected adverse reaction are received by the UMC. The information is stored in the WHO Global Individual Case Safety Report database, Vigibase®. It is important to understand the limitations and qualifications that apply to this information and its use.

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

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

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

Some National Centres that contribute information to Vigibase® make an assessment of the likelihood that a medicinal product caused the suspected reaction, while others do not.

Time from receipt of a report by a National Centre until submission to UMC varies from country to country. Information obtained from UMC may therefore differ from those obtained directly from National Centres.

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

Some National Centres strongly recommend that anyone who intends to use their information should contact them for interpretation.

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

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

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

2011

Recommendations from the Thirty-seventh Annual Meeting of National Pharmacovigilance Centres

The thirty-seventh annual meeting of representatives of national pharmacovigilance centres participating in the WHO Programme for International Drug Monitoring was held 14 -17 October 2014, at Tianjin, China. The meeting included eight working groups that discussed various issues in pharmacovigilance. The summary of discussions from each working group is presented below.

Working Group 1: - Challenges and opportunities in facilitating collaboration between public health programmes and national pharmacovigilance (PV) centres

Objectives:

- To discuss the importance of collaboration between programmes (such as TB, Malaria, Immunization programmes etc.) and pharmacovigilance centres
- To discuss challenges to and opportunities for such a collaboration
- To share experiences on how countries have handled these challenges and examples of benefits of such collaborations.

Expected outcomes:

- To present a broad framework for collaboration between public health programmes and national PV centres:
 - What, when and how;
 - Roles and responsibilities
- To provide recommendations to countries, WHO Collaborating Centres (WHO CCs) and / or WHO for promoting collaborations between Public Health Programmes and PV centres.

Discussions: In general, there was agreement within the group that immunization and other public health programmes (PHPs) such as such as TB and HIV treatment programmes are set up as strong, well-resourced, vertical programmes, with limited or no collaboration with the national Pharmacovigilance (PV) centres. The programmes usually do not collect and / or share pharmacovigilance data with the National PV Centre or with the WHO database, Vigibase. PV centres could help integrate PV within the PHPs and also support the routine benefit/harm assessment of treatments within the PHPs. However PV centres are often under resourced or under developed and therefore unable to support PV within these PHPs. This has led to PV being set up programme by programme in many countries, taking away resources and the opportunity to invest in a National PV Centre that can support PV across different programmes. Having a central PV facility will not only remove biases in benefit-harm assessment of products used within the PHPs, but will also improve the public confidence and perception of such PHPs. A Central PV facility will also help standardise PV tools and methodologies across the various programmes, thus ensuring best and consistent practices in safety monitoring in PHPs. In addition, by engaging with the PHPs, the PV centres could gain some visibility within donor communities that support PHPs. PV Centres could also leverage the patient cohorts within PHPs for proof of concept of PV methods and tools.

The Group made the following recommendations:

National PV centres to

- Adopt / further develop guidelines for integrating PV in PHPs, and develop their own competence
- Collaborate with PHPs through joint activities, for example, to develop joint information materials on the safety and safe use of medicines used in in the PHPs; organize joint training materials and courses for PV; develop joint activity plan for PV etc.
- Develop proposals together with PHPs to mobilize funds for joint activities
- Support PHPs in the implementation, monitoring and evaluation of the PV function within the health programmes

WHO and WHO CCs to

- Advocate and facilitate the integration of PV into PHPs
- Develop methodologies, guidelines and tools for PV in PHPs
- Assess training needs and develop training materials for PHP programme managers and staff in PV
- Support regional data aggregation and analysis
- Negotiate with global donors and procurement agencies to include funds for PV for procured / donated medicines

Working Group 2: - Global information sharing during a medicinal product-related crisis

Objectives:

- To share various examples of medicinal product related crisis in recent times
- To reflect on the following, to understand how countries managed the crisis
- Data gathering
- Validation
- Communication
- Regulatory action
- To discuss information sharing, locally and internationally: what, when, how, value added, challenges, opportunities.

Expected Outcomes:

- To identify the core elements of a strategy for information sharing during a medicinal product-related crisis
- To define roles and responsibilities for various stakeholders (governments, public, media, NGOs, health professionals, industry, inter-government agencies, etc.) in information sharing during a medicinal product related crisis.

Discussions: The group agreed that a 'Signal' would rarely lead to a crisis. A rumour about an adverse drug event could easily result in panic and crisis unless there is a routine process for handling and investigating such rumours. It is often seen that countries with weak/no regulatory systems are at higher risk for crises. Every regulator needs a standard protocol that includes an up-to-date internal fact sheet with clear key points on what is known, what are rumours, what is under investigation etc. Communication and media handling are just as critical. Early, and active communication of consistent information through a designated and credible spokesperson with established media relationships are key features of an established drill. Media monitoring for rumour identification and prioritisation of communication based on cognitive factors and other findings from risk psychology research can be usefully exploited to mitigate and manage a crisis. Global information sources such as VigiBase and websites of stringent regulatory authorities should be leveraged, to supplement local information on an event. In some instances frameworks such as the International Health Regulations could be usefully employed to access confidential information from some settings.

The group made the following recommendations:

Countries to:

- Strengthen regulatory systems
- Establish credible media relationships
- Monitor media
- Identify and train a respected spokesperson
- Institute internal processes for communication preparedness
- Initiate stakeholder deliberation and health diplomacy to overcome anti-government sentiments
- Strengthen regional/global information exchange
- Raise awareness of global impact of local communication and local adaptation of global information

WHO / UMC to:

- Develop the definition of crisis and possibly the preferred term: critical incident
- Develop model SOPs for crisis and media management (cf. "Expecting the Worst")
- Include crisis prevention and management exercises in training courses
- Coordinate urgent global information exchange through Vigimed
- Link pharmacovigilance, SSFFC surveillance and quality defect systems at global level

Working Group 3 - Evaluating benefit/risk assessment in drug regulatory decisions: adapting international decisions to local settings

Objectives:

To have a broad understanding of the influence of external factors on regulatory decisions in a country, vis-à-vis the:

- Influence of international decisions
- Availability and quality of local PV data
- Role of local needs (lack of availability of other treatment options), resources (e.g. lack of laboratory to monitor renal / liver functions); characteristics of population (e.g. G6PD deficiency)

- Factors that determine restrictions over suspension versus product withdrawal: when are these appropriate; how are these measures decided, implemented.

Expected Outcomes:

- To outline a broad framework for best practices in benefit-harm assessment
- To list the various factors that influence benefit-harm assessment and regulatory decisions in countries
- To propose recommendations for countries, WHO CCs and / or WHO for promoting best practices in benefit-harm assessment and regulatory decisions.

Discussions: The group noted that factors that influence regulatory decisions making are many and varied. In general, the approach to regulatory decision making needs to be consistent and stepwise. The approach should consider national needs, available data, local experience of data evaluation, and the possibility to generate additional data if needed. Factors that trigger a review and benefit-harm assessment include: the magnitude of risk, strength of evidence, maturity of the PV system and its sensitivity to detect and identify new and emerging issues, thresholds for review, and experience with a product and additional / new information that emerges. The regulatory decision to withdraw, suspend or restrict the use of a product would also depend on population demographics such as genetic predisposition, disease burden, availability of alternative treatment option, capacity to implement the decisions and risk management measures. Transparency and communication with the public, health professionals, media, industry and other international regulatory agencies throughout the decision making process would be essential to mitigate and manage perceptions of conflict of interest and improve compliance with the decisions.

The Group made the following recommendations:

WHO and UMC to:

- Develop a broad, generic framework with a template for benefit-harm assessment that
 - Links clinical trial (safety and efficacy) and post marketing (safety and effectiveness) data
 - Considers existing resources and publicly available assessment reports
- Link with other WHO CCs and Agencies to organize training in benefit-harm assessment for health-care professionals and regulators

National PV Centres and regulators to:

- Support the implementation of recommendations (restricted use, special monitoring etc.) through training and advocacy activities in health-care systems in the country
- Provide relevant platforms and communication channels to promote transparency and share information with public

Working group 4 : - Systematic data collection of drug exposure during pregnancy: "Is there a role for pharmacovigilance centres?"

Objectives:

- To discuss the current activities that are ongoing in PV centres related to drug exposure during pregnancy
- To discuss and come up with minimum requirements (material and tools) for collecting and managing prospective and retrospective data
- To identify the stakeholders of PV
- To list the resources needed by national PV centres for the management of drug-risk during pregnancy

Expected outcomes:

- Short list a few 'feasible' methods to collect data of drug exposure during pregnancy and impact (on fetus, mother, child /neonates)
- Provide recommendations on
 - How PV centres could engage in these methods and with groups collecting data
 - How WHO should support these efforts (develop guidelines; coordinate efforts; establish international platforms?)
 - How WHO CCs could support the process (develop tools, provide training?).

Discussions: Some centres receive reports on adverse pregnancy outcome through the yellow card (ADR reporting form). But the yellow card is not designed to collect information on pregnancy. Most health-care professionals (HCPs) do not report pregnancy status. Some PV Centres collect additional information on drug exposure retrospectively, when there are cases of congenital anomalies, but this works only when there is a good system for keeping health and treatment records. Some centres collaborate with academic researchers to generate information on possible drug exposure and adverse pregnancy outcome.

The group made the following general recommendations:

- Additional fields (example, yes/no check boxes should be added to ADR reporting forms to record pregnancy; and to record date of last menstruation.
- Medicine use data can be approximated for exposure data in a community; use of other health records as additional source of pregnancy outcome and drug exposure could also be considered if available;
- A national centre should design a specific form for prospective data collection on exposure to specific medicines during pregnancy; Use electronic patient management tool to generate data on exposure and outcome
- The PV Centre should advocate expedited reporting of congenital anomalies in fetus/neonates; reports of late fetal death; reports of spontaneous abortion; and reports of ADRs in a newborn/neonate that is fatal, life-threatening, resulting in persistent or significant disability/incapacity or resulting in or prolonging hospitalization
- The PV centre should design an investigation form and a protocol to support relationship assessment between drug exposure and adverse pregnancy outcomes
- PV centres should educate public and health professionals on the appropriate use of medicines and raise awareness to the risk of abortions and fetal abnormalities with some medicines

The group made the following specific recommendations:

WHO to:

- support the efforts of national centres in developing specific guidelines, methods and algorithms for assessment; coordinate PV efforts; establish international platforms and expert committees

WHO CCs to:

- support the process by developing tools, providing training, updating pregnancy data in VigiFlow, and harmonising inter-country data for exchange of information

Working Group 5: Providing information: helping consumers understand benefits versus risks with medicines

The Group exercise had the following objectives and expected outcomes.

Objectives:

- To highlight the importance of providing benefit / risk information to consumers
- To underscore the fact that communicating with consumers is quite different from communicating with health professionals and authorities
- Understand the challenges in providing Benefit /Risk information to consumers: balancing the information (not sensationalising / fear-mongering), balancing right to information, and confidentiality issues; etc.
- Discuss various methods, tools and information products for communicating with consumers
- Understand what countries are doing in this area (legal framework? NGOs? Methods?).

Expected outcomes:

- Key points on what, when and how to communicate Benefit /Risk to consumers
- A mapping of what or if countries are doing to communicate Benefit /Risk to consumers
- Any specific action required of WHO (e.g. Guidelines)
- Any specific recommendations to WHO CC (e.g. develop communication tools; provide communication platforms)
- Any specific recommendations to countries (e.g. to publish experiences, share know-how through WHO PV Toolkit, Vigimed etc.).

Discussions: The group discussed specific aspects of communication in PV: proactive communications approach; planning and message content using appropriate materials for patients; the various channels to use to publicise the materials; the need for a dedicated person/toll-free number for patients and their care givers to contact for information; cultivating good relations between media and the centres; conveying a balanced information to patients.

The group made the following recommendations:

WHO/WHO CCs to:

- Develop a tool kit for communicating with patients that national centres can adapt (a 'pick and choose' menu).
- Provide more in-depth training for PV professionals on how to communicate with patients and care-givers (outside of the PV training)

- Provide a platform for sharing PV information with patients and caregivers

PV Centres to:

- Have an in-house communication professional
- Provide general training to all centre staff in communicating safety information and interacting with the public
- Organize national/regional training in public relations and PV communications.

Working Group 6: Signal detection in low and middle income countries (LMIC): relevance and approach.

Objectives:

- To explore the WHO definition of 'Signal' and the type(s) of Signals implied in this definition
- To understand various PV issues in countries that need 'signalling': ADRs, interactions, misuse, off-label use, quality issues, lack of awareness, programmatic errors, process related issues (e.g. labelling deficiencies) etc.
- To discuss the role and collaboration of various groups in determining such Signals
- To discuss the current Signal detection process at the UMC and how this could be developed in view of the expanding scope of PV to meet country needs.

Expected outcomes:

- To identify priority safety issues related to product, process, use-related and programmatic issues in countries
- To recommend a process for the development of the Signal detection method, to identify the priority issues
- To propose roles and responsibilities for various stakeholders (PV centres, WHO CCs, WHO, health professionals, others) in implementing the full scope of PV and Signal detection.

Discussions: The group discussed the existing definition of Signal and to what extent it applies to the needs of LMIC. In general, in the 1990s, there were many more developed countries with functional PV systems; LMIC on the other hand had little or no engagement in PV. The products in the developed country market were then 'relatively' new, with the potential for new ADRs and Signals. But now, as the LMIC are catching up, the PV activities in these countries are unlikely to pick up any new Signals for the products available since the 1990s. However, it is timely to focus on Signals of products that are being used only in these settings, for example, some of the antimalarial medicines. It is now possible to think of Signal detection in the specific context of LMIC needs because ADR reports are now becoming available from these countries. But on the other hand, there are use-related issues that can be signalled and picked up through PV activities in both LMIC and HIC. Problems of misuse/overuse of antibiotics and injectable products, ignorance or lack of adherence with known contraindications, off-label use, irrational combinations and problems related to quality issues such as decreased or lack of effect, and self-medication can be signalled through an alert PV system. In other words the concept of Signal detection needs to evolve in a manner that is both relevant for the present times and also useful for all Member States (WHO PIDM).

A country should first define and prioritize the medicine-related problems that it wishes to 'Signal' and address: ADRs with medicines (and indications) that are specific to their setting, irrational use, quality issues, and preventable adverse events etc. Some methods may be used in specific situations, for example, the P-method, developed by the WHO CC Rabat, to Signal/ Flag issues of preventable 'ADRs' from a national PV database, and VigiLyze could be used to search the WHO Global database, to validate / strengthen the Signal. Vigimed, the electronic information exchange platform managed by UMC, could also be used by countries to flag and query Signals and information of mutual interest .

The Group made the following recommendations:

National PV Centres to:

- In order to identify issues that are relevant to the country in question, LMIC should utilize their own data instead of fully relying on the UMC and/or big regulatory agencies
- LMIC should NOT only try to detect previously unknown ADRs, but they should also pay attention to Signals of public health concerns and drug related problems in their respective countries.
- The Regulators in LMIC should take regulatory measures according to the identified Signals and alert HCPs as well as public to minimize risks. But,
 - before following the decisions from other countries, regulators in LMIC should carry out their own benefit-harm assessment and validation of the decision for local relevance and decide accordingly.
 - countries should share the decision, together with the basis for the decision, with other Member States and WHO.

WHO-CC (UMC) to:

- Develop the use of disproportionality ratios for Signal detection within national or regional datasets

WHO to:

- Promote the full scope of PV and Signal detection to support also the detection of Signals of all problems associated with medicines, not only new ADRs

Working Group 7: Patient reporting and involvement of civil society in pharmacovigilance: what is the added value?

Objectives:

- Identify additional groups we should engage with
- Learn how (if) countries engage such groups in PV
- Value added, roles and responsibilities
- Framework, rules of engagement, supportive processes and technical solutions to engage these stakeholders.

Expected outcomes:

- A shortlist of groups and ongoing country efforts in this area
- Recommendations to countries, WHO CCs and WHO for relevant action in this area.

Discussions: The group addressed the usual concerns and objections to patient reporting:

- The volume of reports: experience from other countries suggests it is a manageable workload
- Fake reports: this can be a problem but should not stop us accepting reports from patients

On the other hand patients are more likely to report “embarrassing” ADRs that they would not usually share with the HCPs. Patients might be taking herbal or other self-medication that they may not want their doctor to know. Patients provide more information about the impact of ADRs on the quality of life, an aspect only they can report, adding to our understanding of the full significance of an ADR. On the question of whether reports from patients should be stored in a separate database, the group agreed that, to support a comprehensive understanding of the issues, it might be better to store all reports in the same database, but flag the source of the reports (from patients, hospitals, pharmacies etc.).

How to stimulate patient reporting? This is best done through campaigns by patient organizations/ communities. The campaigns need to be regular and sustainable. It should be easy to report, asking least but most essential information from the patient, using a reporting device and format with simple terminologies and adapted to the target group (paper forms, telephone, apps, reporting via a pharmacy or pharmacist).

Feedback is essential to sustain the interest in patients, both to acknowledge the contribution and to provide useful advice on the treatment and the ADRs.

The Group made the following recommendations:

- WHO should issue a statement to encourage patient reporting in countries
- UMC and MedDRA MSSO to collaborate on the development of patient friendly reporting terminologies.
- WHO should develop an easy to use medication guide for patients

Working Group 8: Signal detection in vaccines : What can be learnt from Signal detection of drugs and what needs to be specifically developed for vaccines

Objectives:

- Discuss the definition of Signal
- Define Signals in the context of drugs and vaccines
- Understand current practice in Signal detection:
 - How it is done for medicines (with examples); what have we learnt through this process; how do we communicate Signals
 - How it is done for vaccines (examples); what have we learnt through this process,

Expected outcomes:

- To have a better understanding of Signal detection issues for vaccines and medicines
- To map areas of collaboration and mutual learning for Signal detection (between vaccines and medicines networks)
- To propose recommendations to countries, WHO CCs and / or WHO for improving Signal detection for medicines and vaccines.
- How do we communicate Signals

Discussions: The group compared the CIOMS and WHO definitions of a Signal and noted that the CIOMS definition is more detailed and includes the concept of beneficial as well as adverse effects. Most countries do not consider beneficial effects when characterising a Signal. The group also considered definitions of ADR (WHO), AE (FDA) and AEFI. Some countries still use the term ADR, while some countries are replacing this with AE, as used by the US FDA for medicines, and which is also similar to the AEFI definition. Some countries (e.g. Canada, USA) have separate reporting systems and databases for vaccines and medicines. Some countries have the same reporting system but analyse data separately: of the countries in the working group, Sweden, New Zealand, Australia and Italy use the same data mining tool but compare vaccines with vaccines only; Korea is considering a similar approach. In Malaysia, the PV centre analyses AEFI data together with the immunisation program. Korea collects both medicines and vaccines in the same database but AEFI data are also collected by the public health institute, this has resulted in duplicates; Korea is now considering a project to integrate the two. Many countries have access to vaccine expertise through expert advisory committees while many countries assess AEFI with the help of the Immunisation Programmes.

Exposure or denominator data (=number of individuals given a vaccine or a medicine) are needed when analysing Signals. For medicines this information can be obtained from dispensing databases, and for vaccines information can be obtained from vaccination registers. Italy has a vaccination register which also collects safety data.

Communication strategies/views on publishing information on Signals are different for the Immunization Programmes and for the National PV Centre. The CIOMS Taskforce on Vaccine Safety is working on a guideline on crisis management for vaccines. There are different thresholds for communicating Signals for vaccines and medicines, possibly higher for vaccines so as not to raise unnecessary concerns.

The group concluded that there are many similarities between drugs and vaccines in Signal detection and analysis; however, specific issues that are relevant to vaccines have to be considered. One common database (for medicines and vaccines adverse events) at the national centres is helpful and efficient although it should be possible to share data between PV centre and Immunization programmes. Similarly, analysis and Signal detection and investigations could be managed through a common advisory group that includes vaccines and medicines specialists and experts from the Immunization Programme and PV Centre. Different approaches would be needed for communicating and acting on Signals, for vaccines and medicines.

The group made the following recommendations:

Countries to:

- Establish a separate procedure (even if maintained in the same database) for data analyses of drugs and vaccines

WHO to:

- Promote stronger integration between drug monitoring and immunization programmes at all levels
- Provide more guidance on communication strategies for vaccines

UMC to:

- Improve Vigilize for vaccines e.g. disproportionality analysis only within vaccines

The next annual course in ATC/DDD Methodology
will be held in Oslo 11-12 June 2015.

Please note that the deadline for registration is 25 May 2015.

For more information and registration, please see following website
<http://www.whocc.no/courses/>

Hope to see you in Oslo!