WHO PHARMACEUTICALS NEWSLETTER

Prepared in collaboration with the
WHO Collaborating Centre for
International Drug Monitoring,
Uppsala, Sweden

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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This Newsletter is also available on our Internet website:
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No. 2, 2014

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 from the Uppsala Monitoring Centre's SIGNAL document.

Printed by the WHO Document Production Services, Geneva, Switzerland

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Regulatory Matters

Safety of medicines

Signal

Aliskiren, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers

New warnings regarding blood pressure drugs

Canada. Health Canada informed health-care professionals and patients of the risks associated with combining more than one of the following blood pressure medicines: aliskiren (renin inhibitor), angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs). Recent studies demonstrated that any combination of aliskiren, ACEIs or ARBs increases the risks of hypotension, hyperkalemia and kidney problems.

Furthermore, aliskiren should not be taken in combination with ACEIs or with ARBs in patients with diabetes or kidney disease due to the additional risks of stroke and syncope in these patients. The product labels have been updated to better reflect the new recommendations regarding the safe use of these medicines.

(See WHO Pharmaceuticals Newsletter No.3, 2012 for new warning and contraindication in the US, No.1, 2012 for contra-indication in patients with diabetes taking an ACE inhibitor or an ARB in Canada and No.2, 2012 in Europe).

Reference:
Advisories, Warnings and Recalls, Health Canada, 4 February 2014 (*www.hc-sc.gc.ca*).

Azathioprine and mercaptopurine

Association with Hepatosplenic T-Cell Lymphoma

Canada. Triton Pharma Inc. and Teva Canada Ltd., in consultation with Health Canada, informed the association between the use of purine antagonists azathioprine (Imuran®) or mercaptopurine (Purinethol®) and the development of hepatosplenic T-cell lymphoma (HSTCL), a rare, aggressive and often fatal cancer, mostly in patients where it is used for inflammatory bowel disease (IBD). Azathioprine is a drug used to treat adult rheumatoid arthritis and help prevent kidney transplant rejection. Mercaptopurine is a drug approved to treat leukemias. Azathioprine or mercaptopurine monotherapies are not authorized by Health Canada for the treatment of IBD.

Azathioprine and mercaptopurine labels were updated for HSTCL and physicians should discuss the currently available information regarding risks and benefits of these treatments with their patients.

Reference:
Advisories, Warnings and Recalls, Health Canada, 27 March 2014 (*www.hc-sc.gc.ca*).

Cetuximab

Importance of establishing wild type *RAS* (*KRAS* and *NRAS*) status before treatment of metastatic colorectal cancer

UK. The Medicines and Healthcare products Regulatory Agency (MHRA) announced that, in the treatment of metastatic colorectal cancer, inferior overall survival, progression-free survival, and objective response rates have been shown in people with *RAS* mutations (at exons 2, 3, and 4 of *KRAS* and *NRAS*) who received cetuximab (Erbitux®) in combination with FOLFOX4 (oxaliplatin-containing) chemotherapy versus FOLFOX4 alone. Cetuximab is now indicated for the treatment of people with epidermal growth factor receptor (EGFR)-expressing, *RAS* wild-type metastatic colorectal cancer in combination with irinotecan or oxaliplatin based chemotherapy or as a single agent. Evidence of wild type RAS status at these exons is required before initiating treatment with cetuximab alone or in combination with chemotherapy in metastatic colorectal cancer. Cetuximab combined with oxaliplatin-containing chemotherapy is now contraindicated in people with metastatic colorectal cancer who have mutant RAS at these exons or unknown RAS status. Cetuximab (Erbitux®) is a treatment for people with metastatic colorectal cancer.

It is also advised that *RAS* mutation status should be determined by an experienced laboratory using a validated test method. Prescribing information for cetuximab in the treatment of people with squamous-cell carcinoma of the head and neck is not changed by the new information from this analysis.

Reference:
Drug Safety Update, February 2014, Volume 7, issue 7, A1 MHRA, (*www.mhra.gov.uk*).

Combined hormonal contraceptives

Review confirms risk of venous thromboembolism is small

UK. The MHRA announced that a review of the latest evidence on the risk of thromboembolism in association with combined hormonal contraceptives (CHCs) concluded that:

- the risk of blood clots with all low-dose CHCs is small
- there is good evidence that the risk of venous thromboembolism (VTE) may vary between products, depending on the progestogen
- CHCs that contain levonorgestrel, norethisterone, or norgestimate have the lowest risk of VTE
- the benefits of any CHC far outweigh the risk of serious side effects
- prescribers and women should be aware of the major risk factors for thromboembolism, and of the key signs and symptoms

Health-care professionals are advised to consider such factors and remain vigilant for signs & symptoms.

Health-care professionals are also advised to remind women to read the Patient Information Leaflet that accompanies each pack of CHCs, to read the information provided in user card and information sheet and to mention that they are using a CHC if asked whether they are taking any medicines.

Reference:
Drug Safety Update, February 2014, Volume 7, issue 7, A2 MHRA, (*www.mhra.gov.uk*).

Diacerein-containing medicines

Recommendations to restrict the use of diacerein-containing medicines

Europe. The Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) endorsed recommendations to restrict the use of diacerein-containing medicines in order to manage the risks of severe diarrhoea and effects on the liver. Due to the risks associated with severe diarrhoea, diacerein is no longer recommended in patients aged 65 years and above. It is also advised that patients start treatment on half the normal dose (i.e. 50 mg daily instead of 100 mg) and should stop taking diacerein if diarrhoea occurs.

In addition, diacerein-containing medicines must not be used in any patient with liver disease or a history of liver disease, and doctors should be monitoring their patients for early signs of liver problems. Doctors should also note that, based on available data, the use of diacerein is to be limited to treating symptoms of osteoarthritis affecting the hip or knee. Treatment should only be started by doctors experienced in treating osteoarthritis.

These recommendations are based on the review of the benefits and risks of diacerein conducted by the EMA's Pharmacovigilance and Risk Assessment Committee (PRAC) and follow concerns raised by the French medicines agency (ANSM) about diacerein's gastro-intestinal and liver effects.

Diacerein is a slow-acting medicine of the class 'anthraquinones' used to treat joint diseases such as osteoarthritis.

Reference:
Press release, EMA, 21 March 2013 (*www.ema.europa.eu*).

Doripenem

Risk when used to treat pneumonia on ventilated patients

USA. The U.S. Food and Drug Administration (FDA) concluded that doripenem (Doribax®), an antibacterial drug used to treat patients who develop pneumonia while on ventilators, carries an increased risk of death and lower clinical cure rates compared to use of imipenem and cilastatin for injection (Primaxin®). Doripenem is not approved to treat any type of pneumonia.

Health-care professionals should consider whether the benefits of doripenem treatment are likely to exceed its potential risks in patients who develop pneumonia while on ventilators. Doripenem is still considered safe and effective for its FDA-approved indications - treatment of adults with complicated intra-abdominal infections and complicated urinary tract infections, including kidney infections (pyelonephritis).

(See WHO Pharmaceuticals Newsletters No. 2, 2012 for higher mortality rate and a lower clinical cure rate observed during a comparative clinical trial in Canada)

References:
FDA Drug Safety Communication, US FDA 5 March 2014 (*www.fda.gov*).

Lithium

Risk of hypercalcemia and hyperparathyroidism

Canada. Health Canada informed health-care professionals that it has reviewed the available evidence and scientific

literature, and determined that lithium therapy can cause hypercalcemia which may or may not be accompanied with hyperparathyroidism. The benefits of this drug in the treatment of bipolar disorder continue to outweigh the known risks of this drug.

Lithium is used in the treatment of manic episodes of manic-depressive illness. It is used to treat acute manic episodes, and as a long-term therapy to reduce their frequency and severity.

Health Canada recommends health-care professionals to consider calcium blood levels before starting a patient on lithium treatment, again six months after initiation of the drug, and on an annual basis after that, in long-term treatment. It is also recommended to consider measuring parathormone blood level to identify or rule out hyperparathyroidism if necessary.

Reference:
Advisories, Warnings and Recalls, Health Canada, 5 February 2014 (*www.hc-sc.gc.ca*).

Methysergide-containing medicines

New recommendations follow concerns over association with fibrosis

Europe. The EMA recommended restricting the use of methysergide due to concerns that it could cause fibrosis, a condition in which fibrous tissue accumulates in the body's organs potentially damaging them. Methysergide medicines are now only to be used for preventing severe intractable migraines and cluster headaches when standard medicines have failed.

In addition, treatment should only be started and supervised by a specialist doctor with experience in treating migraine and cluster headaches. Patients should also be screened for fibrosis at the start of treatment and should have additional screenings every 6 months. Treatment must be discontinued if symptoms of fibrosis occur.

The Agency's Committee for Medicinal Products for Human Use (CHMP), which conducted the review, noted that these recommendations were necessary due to the reports of fibrosis seen with methysergide and other medicines of the same class (ergot derivatives). The symptoms of fibrosis often take some time to appear and without screening, the diagnosis may come too late to prevent severe (and potentially life-threatening) damage to organs .

The Committee noted that there is some evidence of a clinically relevant effect of methysergide when used for prevention in patients who regularly get migraines and cluster headaches and for whom treatment options are limited. Methysergide has also been used for treating diarrhoea caused by carcinoid disease. However, there were no data to support this use and methysergide should therefore no longer be used in carcinoid disease.

Methysergide is a medicine that belongs to the class 'ergot alkaloids' that has been used in the EU for preventing migraines (with or without aura) and other types of throbbing headaches.
Reference:
Press release, EMA, 21 February 2013 (*www.ema.europa.eu*).

Orlistat

Interaction with antiretroviral HIV medicines

UK. The MHRA announced that orlistat may theoretically reduce the absorption of antiretroviral HIV medicines. This may be due to retention of lipophilic medicines in the gastrointestinal tract or reduced gastrointestinal tract transit time. This interaction could negatively affect the efficacy of antiretroviral HIV medications. Reports have been received of suspected interactions between orlistat and efavirenz, and between orlistat and lopinavir. However, the theoretical interaction mechanism described above could also apply to other antiretroviral medicines.

Health-care professionals are advised to initiate orlistat treatment only after careful consideration of the possible impact on efficacy of antiretroviral HIV medicines. Pharmacists should advise people who take antiretroviral HIV medicines to consult their doctor before taking non-prescription 60 mg orlistat

Orlistat is a potent, specific, and long-acting inhibitor of gastrointestinal lipases which decreases the amount of fat absorbed from the diet. Orlistat is indicated for weight loss in combination with a low-calorie, low-fat diet. It is available as 120 mg capsules under the brand name Xenical® and as 60 mg capsules under the brand name Alli™. Xenical is only available with a prescription, whereas Alli™ is available without a prescription under the supervision of a pharmacist.

Reference:
Drug Safety Update, March 2014, Volume 7, issue 8, A1 MHRA, (*www.mhra.gov.uk*).

Quetiapine

Risk of QT prolongation

Australia. The Therapeutic Goods Administration (TGA) advised health-care professionals that the Product Information (PI) for quetiapine (Seroquel® and generics) was updated to include additional information regarding risks of QT prolongation. Quetiapine is an atypical antipsychotic drug indicated for the treatment of schizophrenia and bipolar disorder.

The PI for quetiapine products now advises, particularly in elderly patients, to avoid concomitant treatment with antipsychotics and other drugs that are known to prolong the QT interval. These include:

- Class IA antiarrhythmics (such as disopyramide)
- Class III antiarrhythmics (such as amiodarone and sotalol)
- antipsychotics (such as ziprasidone, chlorpromazine and haloperidol)
- antibiotics (such as erythromycin)
- others (such as citalopram, pentamidine and methadone).

The updated information also advises that quetiapine should be avoided in circumstances that may increase the risk of torsades de pointes and/or sudden death, including a history of cardiac arrhythmias, hypokalaemia or hypomagnesaemia, and congenital prolongation of the QT interval.

Additionally, the PI has also been updated to include further information about the risk of venous thromboembolism (VTE), akathisia, neutropenia.

Health-care professionals are encouraged to review the latest PI for quetiapine and particularly the updated information regarding QT prolongation, VTE, akathisia and neutropenia in the precautions section.

Reference:
Medicines Safety Update Vol 5, No. 1, February 2014. (www.tga.gov.au).

Strontium ranelate

Remain available but with further restrictions

Europe. The EMA concluded its review of strontium ranelate (Protelos® and Osseor®) and recommended further restricting the use of the medicine to patients who cannot be treated with other medicines approved for osteoporosis. In addition these patients should continue to be evaluated regularly by their doctor and treatment should be stopped if patients develop heart or circulatory problems, such as uncontrolled high blood pressure or angina. As recommended in a previous review, patients who have a history of certain heart or circulatory problems, such as stroke and heart attack, must not use the medicine.

These final recommendations from the Agency's Committee for Medicinal Products for Human Use (CHMP) come after initial advice from the Pharmacovigilance Risk Assessment Committee (PRAC) to suspend the medicine due to its cardiovascular risk.

The CHMP noted that study data showed a beneficial effect in preventing fractures, including in patients at high risk of fracture. In addition, available data do not show evidence of an increased cardiovascular risk with strontium ranelate in patients who did not have a history of heart or circulatory problems. The CHMP considered that the cardiovascular risk in patients taking strontium ranelate can be managed by restricting its use to patients with no history of heart and circulatory problems and limiting its use to those who cannot take other medicines approved for the treatment of osteoporosis. In addition, patients treated with strontium ranelate should be screened and monitored regularly, every 6 to 12 months.

Additional risk minimisation measures include providing educational material to prescribers to ensure that only the appropriate patients are treated with the medicine. Importantly, the company is required to conduct further research to demonstrate the effectiveness of the new measures.

Strontium ranelate is authorised in the EU to treat severe osteoporosis in women who have been through menopause and who are at high risk of fracture to reduce the risk of fractures' of the spine and the hip. It is also used to treat severe osteoporosis in men who are at high risk of fracture.

Reference:
Press release, EMA, 21 February 2013 (*www.ema.europa.eu*).

Saxagliptin

Review heart failure risk

USA. The US FDA requested clinical trial data from the manufacturer of saxagliptin (Onglyza® and Kombiglyze™ XR) to investigate a possible association between use of the type 2 diabetes drug and heart failure. The US FDA's request resulted from a study published in the New England Journal of Medicine (NEJM), which reported an increased rate of hospitalization for heart failure, when the heart does not pump blood well enough, with use of saxagliptin compared to an inactive treatment. The study did not find increased rates of death or other major cardiovascular risks, including heart attack or stroke, in patients who received saxagliptin. The manufacturer is expected to submit the trial data to FDA by early March 2014, after which FDA will conduct a thorough analysis and report findings publicly.

At this time, the US FDA considered information from the NEJM study to be preliminary. Analysis of the saxagliptin clinical trial data is part of a broader evaluation of all type 2 diabetes drug therapies and cardiovascular risk.

Saxagliptin is used along with diet and exercise to lower blood sugar in adults with type 2 diabetes. It works by increasing the amount of insulin produced by the body after meals, when blood sugar is high.

It is recommended that patients should not stop taking saxagliptin and should speak with their health-care professionals about any questions or concerns.

References:

FDA Drug Safety Communication, US FDA 11 February 2014 (*www.fda.gov*).

St John's wort and hormonal contraceptives, including implants

Reduced contraceptive effect

UK. The Medicines and Healthcare products Regulatory Agency (MHRA) announced that St John's wort interacts with hormonal contraceptives. This interaction reduces the effectiveness of these contraceptives and increases the risk of unplanned pregnancy. This applies to all hormonal contraceptives except intrauterine devices, for which there are currently no data

St John's wort (*Hypericum perforatum* L.) is a herbal medicine traditionally used to relieve slightly low mood and mild anxiety.

The MHRA received two Yellow Card reports in the last quarter of 2013 of suspected interactions in women with implanted contraceptives containing etonogestrel (Nexplanon® and Implanon®). These women started taking St John's wort and then had unplanned pregnancies.

There are warnings about these interactions and their consequences in the product information provided with all contraceptives and the authorised St John's wort products. Some unlicensed products on the UK market or available online do not include the appropriate warnings regarding possible interactions. The lack of warnings does not mean these products do not interact with other products.

Health-care professionals are recommended to advise women taking hormonal contraception for pregnancy prevention that they should not take herbal products that contain St John's wort. This applies to all hormonal contraceptives except intrauterine devices, for which there are currently no data. It is also advised to encourage women to read the Patient Information Leaflet that comes with their hormonal contraceptive.

Reference:

Drug Safety Update, March 2014, Volume 7, issue 8, A2 MHRA, (*www.mhra.gov.uk*).

Testosterone Products

Investigating risk of cardiovascular events

USA. The US FDA is investigating the risk of stroke, heart attack, and death in men taking FDA-approved testosterone products. The US FDA is monitoring this risk and decided to reassess this safety issue based on the recent publication of two separate studies that each suggested an increased risk of cardiovascular events among groups of men prescribed testosterone therapy. The US FDA provided this alert while it continues to evaluate the information from these studies and other available data. The US FDA will communicate final conclusions and recommendations when the evaluation is complete.

Testosterone is a hormone essential to the development of male growth and masculine characteristics. Testosterone products are FDA-approved only for use in men who lack or have low testosterone levels in conjunction with an associated medical condition.

At this time, the FDA has not concluded that FDA-approved testosterone treatment increases the risk of stroke, heart attack, or death. The US FDA advised that patients should not stop taking prescribed testosterone products without first discussing any questions or concerns with their health-care

professionals. Health-care professionals should consider whether the benefits of FDA-approved testosterone treatment is likely to exceed the potential risks of treatment. The prescribing information in the drug labels of FDA-approved testosterone products should be followed.

References:

FDA Drug Safety Communication, US FDA 31 January 2014 (*www.fda.gov*).

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 8 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 on page 29. For information on the UMC Measures of Disproportionate Reporting please refer to WHO Pharmaceuticals Newsletter Issue No. 1, 2014.

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: info@who-umc.org.

Combined Citalopram and Ramipril treatment - Hyponatraemia

Prof. Staffan Hägg, Sweden

Summary

Hyponatraemia is a recognized adverse drug reaction for both citalopram and ramipril even if the documentation for the latter drug is very limited. As of 5 May 2013 there were 56 Individual Case Safety Reports (ICSRs) of hyponatraemia in association with the combination ramipril and citalopram in the WHO Global ICSR Database, VigiBase®. Although not described in the literature a drug interaction between citalopram and ramipril is consistent with known pharmacological properties of the drugs and individuals taking multiple drugs known to cause hyponatraemia is at increased risk. An association is further supported by a plausible time course in some of the ICSRs in VigiBase. This possible effect is probably drug class related rather than substance related and the association should be evaluated further.

Introduction

Hyponatraemia is a common and sometimes serious electrolyte imbalance ascribed to either water retention (most frequent) or loss of effective solute (sodium and potassium) in excess of water.[1-4] Water retention is most often caused by the syndrome of inappropriate antidiuretic hormone (SIADH).[4] Common causes of hyponatraemia are malignancy, pulmonary disorders, central nervous system (CNS) disorders and medications such as diuretics, antiepileptics, non-steroidal anti-inflammatory drugs (NSAIDs), anticancer drugs, antipsychotics and selective serotonin reuptake inhibitors (SSRIs) including citalopram.[1-4] The incidence of SSRI induced hyponatraemia has been reported as varying between 0.5% and 32%.[3] Also angiotensin converting enzyme (ACE) inhibitors have been found to cause hyponatraemia infrequently.[3,5] Izzedine et al. summarized 17 cases of severe hyponatraemia induced by ACE inhibitors previously reported in the literature.[5] In 10 of these cases hyponatraemia occurred in patients receiving combination diuretic therapy.

The risk of drug induced hyponatraemia is highest during the first weeks of treatment[1] and higher in elderly people than in younger people.[1-3] Patients receiving multiple medications known to cause hyponatraemia (most often diuretics) are also at increased risk.[3,6,7] Other important risk factors for hyponatraemia are low body mass index (BMI), low basal levels of hyponatraemia, and female sex.[1-4]

The mechanism by which SSRIs cause hyponatraemia is mainly through SIADH.[1,6,7] The mechanism by which ACE inhibitors induce hyponatraemia is not completely understood but is probably related to the fact that ACE inhibitors can block the conversion of angiotensin I to angiotensin II in the peripheral circulation but not in the brain.[3,5] This can lead to an increased amount of circulating angiotensin I which can enter the brain where it is converted to angiotensin II. Angiotensin II may stimulate thirst

and release antidiuretic hormone (ADH) from the hypothalamus, eventually leading to hyponatraemia.

Reports in VigiBase

Fifty-six Individual Case Safety Reports (ICSRs) of hyponatraemia during treatment with citalopram and ramipril have been entered into the WHO Global ICSR Database, VigiBase® since 2001 (as of 5 May 2013). Both of the drugs were reported as interacting, suspected and/or concomitant. Seven of the ICSRs are duplicates, which leaves 49 cases for assessment.

Citalopram and ramipril were reported together as either interacting or suspected in 18 cases, which should be compared to an expected 3.4. The omega value for these 18 cases is 2.44 with a lower credibility interval limit of 1.76, which indicates a statistically significant association between the combination treatment and the suspected adverse drug reaction (ADR).

Examining the number of reports submitted in VigiBase, hyponatraemia has been reported as an ADR in 0.4% of all reports in which neither citalopram nor ramipril was taken. When looking at the proportion of reports where hyponatraemia is reported for the two drugs separately, one can see that hyponatraemia has been reported in 4.4% when using citalopram alone compared to 1.3% when using ramipril only. The corresponding percentage of reports where hyponatraemia was described when taking both these drugs together was 32%, suggesting that combination treatment might increase the risk of developing this ADR.

The 49 cases originate from nine countries; Germany (15 cases), United Kingdom (12 cases), Canada and France (six cases each), United States (four cases), Italy and Australia (two cases each), Ireland and Sweden (one case each). The cases concern 38 females and 10 males (sex was not specified in one report). Age was reported for 47 patients and ranged between 50 and 92 years with a median of 78 years.

A more comprehensive narrative was available in 11 cases and detailed clinical information regarding the patient and the event was thus lacking in many cases.

Most ICSRs had no complete dates for treatment, and information on time to onset was often lacking for both of the drugs. In 20 cases, the reaction occurred within the first six weeks of treatment with one of the agents. In two cases both drugs were started at the same day and time to onset were 24 days and three years, respectively. In 12 cases treatment with ramipril was started before citalopram (from 10 days to several years) and time to onset (from the first day of treatment with both drugs) could be calculated in nine of these: one day (two cases), three days (four cases), two weeks (two cases) and nine months (one case). In one case, ramipril was started 18 days after citalopram, with a time to onset of 11 days. Another three patients had been treated with both of the drugs together, from unknown dates when the onset of reaction occurred. In two cases the combination treatment was started after onset of hyponatraemia.

Both citalopram and ramipril were reported together as interacting in three cases. In four additional cases, where both drugs were reported as suspected, the WHO-ART terms "drug interaction" or "drug interaction potentiation" were reported. In one case citalopram was reported as interacting and ramipril as suspected, and in another case ramipril was reported as interacting while citalopram was reported as concomitant.

Co-medication was reported for all patients. In 24 cases there were other co-suspected and/or interacting drugs. Thirty-two patients were treated with other drugs (e.g. thiazides, loop diuretics, carbamazepine, cisplatin, valproic acid, mirtazapine, aripiprazole and omeprazole) that have hyponatraemia listed as an ADR in the SPC.

The outcome was stated in 41 cases; the patient had recovered in 27 cases, was recovering in five cases and had not recovered in nine cases. Where the patients had recovered or were recovering, there was a positive dechallenge for both citalopram and ramipril in three cases. In 13 cases, citalopram alone was withdrawn prior to recovery. One positive dechallenge was also seen for ramipril, together with a dose reduction of citalopram.

Two cases had fatal outcome, however, not reported as related to hyponatraemia. In one case worsening of hyponatraemia was described in a 76-year-old male with multiple diseases including recurrent electrolyte imbalance, non-small cell lung cancer, depression, drug abuse, cerebral ischemia, chronic obstructive pulmonary disease (COPD), arterial hypertension, and multiple drug treatment. The drugs citalopram, bromazepam, gemicitabine and cisplatin were all suspected to have caused worsening of hyponatraemia. The patient did not recover from this event and the patient died due to an unknown cause of death. In another case an 83-year- old female with heart failure, COPD and psychotic depression who developed hyponatraemia during treatment with ramipril and citalopram is described. Besides this treatment she was treated with fluticasone, formoterol, enoxaparin, digoxin, acetylsalicylic acid, nebivolol and temazepam. She recovered but

according to the report, she died from an unspecified cause two weeks after hyponatraemia was normalized.

Literature and Labelling

Hyponatraemia is a labelled ADR in the SPC of citalopram,[8] but not a labelled ADR in the SPC of ramipril.[9] The ADR is however described in the literature for ramipril10 and other ACE inhibitors.[5]

Although it has been previously acknowledged that individuals taking multiple drugs known to cause hyponatraemia are at increased risk,[3,6,7] this drug interaction is not described in drug interaction sources such as Stockley's Drug Interactions11 or Swedish Finnish Interaction X-referencing (SFINX),12 possibly since many additive drug interactions are not described in such drug interaction sources. A literature search in PubMed did not reveal any published case reports where hyponatraemia was associated with the combination therapy of citalopram and ramipril.

Discussion

Hyponatraemia is a well-documented ADR to SSRIs including citalopram.[1-4] In addition, ACE inhibitors such as ramipril may induce hyponatraemia.[5,8]

Comparing the proportion of ICSRs in VigiBase where hyponatraemia is reported as an ADR when taking citalopram or ramipril together (32%) to the proportion of reports where the ADR is reported when taking both of the drugs separately (4.4% and 1.3%, respectively), demonstrates that concomitant treatment with the two drugs might increase the risk of developing hyponatraemia. There were 18 cases where the reporter suspected that both citalopram and ramipril played a part in the development of hyponatraemia, and in three of these cases the reporter assessed both of the drugs as interacting.

The analysis of the post-marketing cases revealed a rapid time to onset of hyponatraemia described in several cases. Twelve patients were already on ramipril treatment when citalopram was started, and six of these patients developed hyponatraemia within one to three days after starting citalopram. The quick onset of hyponatraemia in these six cases indicates that the sodium levels might also have been influenced by ramipril.

The information above is suggestive that concomitant treatment of citalopram and ramipril is associated with hyponatraemia. The suggested interaction is consistent with already known pharmacological properties of these drugs. The lack of relevant clinical information in most reviewed cases complicates the assessment.

It is known that individuals taking multiple drugs recognized to cause hyponatraemia are at increased risk. More than half of the patients were co-treated with diuretics or other medication that could possibly have caused or added to the hyponatraemia. A majority of the patients were female and/or elderly, which are both risk factors for hyponatraemia. Whether the risk for hyponatraemia during concomitant treatment of citalopram and ramipril is additively or synergistically increased compared with the risk when these drugs are used separately is not possible to evaluate using the data from these ICSRs.

Conclusion

The proportion of ICSRs where hyponatraemia was reported for citalopram and ramipril taken together in relation to when the drugs were taken separately, together with the cases where the reporter suspected both of the drugs of causing hyponatraemia, suggest that concomitant use of citalopram and ramipril is associated with an increased risk of hyponatraemia. This possible drug interaction is consistent with previously known pharmacological properties of these drugs and is supported by a plausible time course in several cases. It is previously known that individuals taking multiple drugs recognized to cause hyponatraemia is at increased risk. Whether this risk is additively or synergistically increased compared with the risk when using the drugs separately is not possible to evaluate using these data. It seems likely that this potential interaction may occur between other ACE inhibitors and SSRIs and the association should be evaluated further.

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Combined Ibuprofen and Metamizole treatment - Acute renal failure

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Summary

Acute renal failure is an established adverse drug reaction to ibuprofen and has been associated with metamizole treatment in some published case reports. As of 5 May 2013 there were 24 reports of acute renal failure in association with the combination ibuprofen and metamizole in the WHO Global Individual Case Safety Report (ICSR) Database, VigiBase®. The suspected interaction between metamizole and ibuprofen to cause acute renal failure is supported by a plausible time course in several cases and is consistent with previously known pharmacological properties of the drugs. Whether the risk is additively or synergistically increased compared with the risk when using the drugs separately is not known from the literature and is difficult to evaluate using these individual case safety report data. Taking together the information reported in the ICSRs indicates a relevant drug interaction that should be monitored.

Introduction

Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID), a class of medications widely used for their analgesic and anti-inflammatory benefits. Metamizole is a pirazolone derivative of analgesic and antipyretic action, but without an anti-inflammatory effect. Both ibuprofen and metamizole inhibit cyclooxygenase (COX), but metamizole has a different mode of action compared to classical COX-inhibitors.[1] NSAIDs are known to induce several different types of renal injury including acute renal failure.[2] This adverse reaction may occur with any non-selective NSAID or COX-2 specific NSAID[3-6] and is a well-documented adverse reaction to ibuprofen.1 The biological mechanism for acute renal failure during NSAID treatment is inhibition of COX enzymes with consequent decreased synthesis of prostaglandins, which can lead to reversible renal ischemia, a reduction in glomerular filtration, and acute renal insufficiency.[3,4]

The association between acute renal failure and metamizole is less well documented. A number of sporadic cases published in the literature and the pharmacological properties with COX inhibition support an association.[7,8]

Reports in VigiBase

As of 5 May 2013, twenty-four Individual Case Safety Reports (ICSRs) of acute renal failure have been entered into the WHO Global ICSR Database, VigiBase® since 1982 where metamizole and ibuprofen together have been reported as interacting, suspected and/or concomitant (Table 1). In 14 of the ICSRs, the drugs were reported as suspected or interacting which should be compared to an expected 4.2. The omega value for these suspected interacting reports is 1.64 with a lower credibility interval limit of 0.78, which shows a statistically significant association between acute renal failure and the combination treatment of metamizole and ibuprofen in the database.

Table 1. Case overview of ICSRs in VigiBase® of acute renal failure in association with ibuprofen and metamizole

Case	Age/ gender	Other suspected or concomitant drugs	Reactions (WHO-ART)	Outcome of renal failure acute
1	33/F	Cefalexin (S), lincomycin (C)	Oliguria, renal failure acute, rash	Recovered
2	24/F	Spiramycin (C)	Renal failure acute	Recovered
3	70/M	Indapamide (C), tiapride (C), tramadol (C)	Nephritis interstitial, renal failure acute	Recovered
4	75/M	Rabeprazole (C), amitriptyline (C), terbinafine (S), allopurinol (S), pamidronic acid (I), chlortalidone (I), enalapril (I), diclofenac (I)	Rash maculo-papular, renal failure acute	Recovered
5	39/F	Etodolac (S), diclofenac (S), piperacillin sodium/ tazobactam-sodium (C), amoxicillin sodium/clavulanate- potassium (C), paracetamol (C), citalopram (C), isotretinoin (S)	Renal failure acute, cardio-respiratory failure, hepatitis cho- lestatic, hepato-cellular damage	Died
6	86/M	-	Albuminuria, nephritis interstitial, renal failure acute	Not recovered
7	56/F	Tramadol (C), atenolol (C), isosorbide dinitrate (C), enoxaparin(C), pantoprazole (C), etoricoxib (S)	Neoplasm NOS, dysphonia, rash vesicular, oedema periphe- ral, circulatory failure, jaundice, hepatic failure, renal failure acute	Recovered
8	62M	Homeopatics nos (C), calcium carbonate/quercus petr-aea/quercus robur (C), Homeopathic preparation (C), bryophyllum pinnatum (C), homeopatics nos (C), dimetindene (C), amitriptyline (C), tramadol (C), simvastatin (C), furosemide (C), acetylsalicylic acid (C), pantoprazole (C), pregabalin (S)	Renal failure acute	Recovered
9	35/M	Azithromycin (C), NA (C), paracetamol (C)	Renal failure acute	Unknown
10	56/M	Omeprazole (C), ibuprofen (I), fentanyl (I), valproic acid (I), cetuximab (I)	Renal failure acute, hepatitis, myocarditis	Recovered
11	16/M	-	Renal failure acute	Recovered
12	32/M	Acetylsalicylic acid (I), diclofenac (I), naproxen (I)	Intentional overdose, renal failure acute	Recovered
13	41/M	-	Thrombocytopenia, NA, purpura thrombopenic thrombotic, disseminated intravascular coagulation, thrombocytopenia, paraesthesia, LDH increased, dysphonia, haemolysis, hearing decreased, anaemia, renal failure acute	Recovering
14	29/F	Celecoxib (S), ciprofloxacin (S)	Renal failure acute, anaemia normocytic, pharyngitis, sinusitis, fever, agranulocytosis	Recovered
15	77/F	Zoledronic acid (S), antineoplastic agents (C), esome- prazole (C), bromazepam (C)	Renal failure acute, azotaemia, sepsis, marrow depression, condition aggravated	Died- reaction may be contributory
16	45/F	Lithium (I), naproxen (I), quetiapine (I), hyoscine (C)	Speech disorder, ataxia, renal failure acute, drug level increased	Not recovered
17	80/M	Quinapril (S)	Renal failure acute	Recovered
18	24/F	Paroxetine (C), amoxicillin (C), diclofenac (C)	Renal failure acute	Recovered
19	40/M	Ciclosporin (I)	Renal failure acute	Recovered
20	39/M	Tramadol (C), metamizole (S), amoxicillin sodium/ clavulanate potassium (S), paracetamol (C), diclofenac (S), cetirizine (C), ibuprofen (S)	Rash erythematous, rash maculo-papular, renal failure acute, nephrosis, nephritis interstitial	Recovering
21	50/F	Hydrochlorothiazide/metoprolol succinate (C), NA (C), metformin (C), metoclopramide (S), loperamide (S), ramipril (S)	Azotaemia, creatinine clearance decreased, renal failure acute	Recovered
22	71/M	NA (C), NA (C), acetylsalicylic acid (C), ramipril (C), NA (C), clindamycin (S)	NA, creatinine clearance decreased, renal failure acute	Recovered
23	51/M	Astemizole (S), dexketoprofen (S), ciprofloxacin (S)	Renal failure acute	Recovered
24	87/F	Metformin (I), norfloxacin (I)	Renal failure acute	Recovering

Abbreviations: M= male, F= female, S= suspected, I= interacting, C = concomitant, NA = not available

Studying the number of reports submitted in VigiBase, acute renal failure has been identified to be reported as an adverse drug reaction (ADR) in 0.6% of all reports in which neither ibuprofen nor metamizole was taken. When looking at the proportion of reports where acute renal failure is reported for the two drugs separately, one can see that acute renal failure has been reported in 2.0% when using ibuprofen alone compared to 0.9% when using metamizole only. The corresponding percentage of reports where acute renal failure was described when taking both these drugs together, was 7.7% suggesting that combination treatment might increase the risk of developing this ADR.

The ICSRs originate from four countries; Spain (13 cases), Germany (six cases), Switzerland (four cases) and Japan (one case) and concerned 14 males and 10 females. Their age ranged between 16 and 87 years with a median of 48 years.

The time to onset for the reaction generally occurred within the first month of treatment in the majority of the reports. In eight of the ICSRs, both of the drugs were reported as interacting. In three cases only one of the two drugs was reported as interacting while the other drug was reported as suspected or concomitant.

Acute renal failure occurred within the first week of treatment with one of the agents in 13 cases. In four cases (8, 10, 14 and 23) we could identify a time-to- onset pattern. In case 8 and 10, the patient had tolerated ibuprofen separately and after adding metamizole to the treatment, acute renal failure developed within two days of combined treatment. Case 14 and 23 showed an opposite reaction, the patient tolerated metamizole separately and after adding ibuprofen to the treatment, acute renal failure developed.

In three of the cases, the ADR occurred the same day or within a day which indicates that other contributing factors such as dehydration might have influenced the development of acute renal failure. Diclofenac, another NSAID drug, was taken together with ibuprofen and/ or metamizole in four cases, in one case as a long-term treatment with a dose of 75 mg three times a week. This triple treatment might have added even more to the negative effects on the kidney. In one case the patient had diabetes and was treated with metformin. This might have contributed to the suspected ADR since diabetes increases the risk of developing different types of kidney problems.

The outcome was stated in 24 cases and it was reported that the patient had recovered in 16 cases, was recovering in three cases, had not recovered in three cases and that the reaction was fatal in two cases. In one fatal case hepatocellular damage, cholestatic hepatitis and cardio-respiratory failure besides acute renal failure was reported in a 39-year-old female treated with different drugs, among these isotretinoin, which was considered the suspected agent for the liver reactions. In the other case acute renal failure, sepsis, marrow depression, azotaemia, and condition aggravated was reported acute in a 77-year-old female. Zoledronic acid and ibuprofen were reported as suspected agents in this case.

Literature and Labelling

The interaction has not been described in available drug interaction sources such as Stockley's Drug Interactions9 or Swedish Finnish Interaction X-referencing (SFINX).[10] A literature search in Medline has not revealed any published cases where acute renal failure was associated with the combination ibuprofen and metamizole.

Discussion

Acute renal failure is a well-documented adverse reaction to NSAIDs such as ibuprofen. In addition, metamizole has been associated with acute renal failure although the available evidence is limited. Comparing the proportion of reports in VigiBase where acute renal failure is reported as an ADR when taking both the drugs together (7.7%) compare to the proportion of reports where the ADR is reported taking ibuprofen or metamizole separately (2.0% and 0.9% respectively), demonstrates that concomitant treatment with the two drugs might increase the risk for developing acute renal failure.

The review of the post-marketing cases, especially the 14 where the drugs were reported as suspected or interacting together with the eight ICSRs where both ibuprofen and metamizole were reported as interacting, reveals that the reporter suspected a possible interaction between the drugs which should be considered in the assessment. Studying all the ICSRs, a time-to-onset pattern for developing the ADR was identified in four cases after having added either ibuprofen or metamizole to the treatment. Taking this reported information together gives as an association that concomitant treatment with ibuprofen and metamizole could be associated with acute renal failure.

In four cases, diclofenac was used as concomitant drug which can be an additional risk factor for acute renal failure. In three of the recovered cases the drugs were withdrawn at the same time, which makes it difficult to determine which one of the drugs that might have caused the ADR, but at the same time it demonstrates that these drugs together might increase the risk of developing

acute renal failure. Although multi-ingredients drugs with both substances have been launched in some countries, the combination treatment seems irrational from a pharmacological perspective and should therefore probably be avoided.

Whether the risk of acute renal failure during concomi- tant treatment of ibuprofen and metamizole is additi- vely or synergistically increased compared with the risk when these drugs are used separately is difficult to evaluate using spontaneously submitted reports.

Conclusion

The proportion of reports where acute renal failure is included as the reported ADR when taking the two drugs together in relation to taking the drugs separately, together with the ICSRs were the reporter suspected an interaction between the drugs suggest that concomitant use of ibuprofen and metamizole is associated with acute renal failure. The possible interaction is also sup- ported by the four cases where a time-to-onset pattern could be identified when adding either ibuprofen or metamizole together with the plausible time course in several cases which is consistent with previously known pharmacological properties of these drugs. Taking this together, the association is regarded as a valid drug interaction and should be monitored.

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Tocilizumab – Psoriasis and Aggravated psoriasis

Signal strengthening

Dr. Ruth Savage, New Zealand

Summary

Tocilizumab inhibits the activity of the inflammatory cytokine interleukin (IL)-6. Its indications include rheumatoid arthritis and juvenile idiopathic arthritis. In the second quarter of 2013, after exclusion of three duplicates, the WHO Global Individual Case Safety Report (ICSR) Database, VigiBase® held 20 ICSRs of new onset or aggravated psoriasis attributed to tocilizumab. Four published case reports were also identified. This suspected reaction is paradoxical since psoriasis is an autoimmune inflammatory disease primarily affecting the skin. When the published case reports together with VigiBase ICSRs for tocilizumab were combined, there was evidence of improvement with tocilizumab discontinuation or recurrence with each administration in four reports. Report characteristics indicate that there are similarities between reports of psoriasis occurring with tocilizumab and those occurring with TNF inhibitors which have been well-documented in the literature. The VigiBase ICSRs provide additional evidence to the published case histories for tocilizumab.

Introduction

Psoriasis is an autoimmune inflammatory disease that usually presents with the development of inflammatory plaques on the skin. Studies have shown that it is likely that interactions between dendritic cells, T cells, keratinocytes, neutrophils and the cytokines released from immune cells contribute to the initiation and perpetuation of the cutaneous inflammation characteristic of psoriasis.[1] Psoriasis affects about 2% of the population. In about 80% of patients psoriasis occurs as chronic plaque lesions. Palmoplantar variants include plaque psoriasis confined to the palms and soles, and pustular lesions on these surfaces (palmoplantar pustulosis). Rarely, an unrelated generalised and life-threatening pustulosis may develop. Another variant is guttate psoriasis which presents as a rash of drop-like lesions, often after a beta-haemolytic streptococcal infection. About 5% of patients with psoriasis develop an inflammatory arthropathy.[2-4]

Tocilizumab is a humanised anti-human interleukin (IL)-6 receptor antibody. It competes for membrane- bound and soluble forms of human IL-6 receptor, thereby inhibiting the binding of this native inflammatory cytokine to its receptor and interfering with the cytokine's effects. This cytokine has the ability to activate T cells, B cells, macrophages and osteoclasts. Increased synovial fluid IL-6 levels correlate with disease activity in rheumatoid arthritis (RA) and circulating levels are elevated in children with systemic juvenile idiopathic arthritis (JIA). Its approved indications include JIA and RA.[5]

In their respective summaries of product characteristics (SPCs), psoriasis is recognised as a possible adverse effect of tumour necrosis factor (TNF) inhibitors and abatacept, a costimulation blocking soluble fusion protein.[6,7] Like tocilizumab, both are biologic disease-modifying anti-rheumatic agents.

Reports in VigiBase

In the second quarter of 2013, after removal of three duplicates, there were 12 ICSRs for psoriasis (Table 1) and eight for aggravated psoriasis (Table 2) associated with tocilizumab use. The reports were from nine countries, the United States, the United Kingdom, Italy, Belgium, Canada, Spain, Australia, Switzerland and Sweden. The combination tocilizumab/psoriasis aggravated became statistically prominent in the second quarter of 2011 (IC 2.21, IC025 1.04) and tocilizumab/psoriasis in the first quarter of 2013 (IC 0.96, IC025 0.14) when the total number of reports in VigiBase® for tocilizumab was 3,796.

The gender distribution was 15 females and four males in the combined ICSRs for the psoriasis and aggravated psoriasis combinations. In one case gender was not specified. Since the most frequent indication for tocilizumab was RA this observation of female preponderance is not unexpected. Age was documented in only three of the 12 ICSRs for psoriasis but was recorded for seven of the eight patients with aggravated psoriasis. The range for the combined psoriasis and aggravated psoriasis reports was 33 to 60 years and, for aggravated psoriasis, 39 to 58 years with a median of 51 years.

As well as RA, other indications for tocilizumab were psoriatic arthropathy (two cases) and seronegative rheumatoid arthritis (one case) in the aggravated psoriasis group and juvenile arthritis (one case) in the psoriasis group. While none of the patients in the psoriasis group had a reported history of psoriasis, psoriatic arthritis may present as arthritis before psoriasis develops so the patient with juvenile arthritis may have been redisposed.[2]

The recommended dose and dose frequency of tocilizumab is 8 mg/kg monthly for adults with RA and 8 mg/kg two weekly for children weighing more than 30 kg with systemic JIA. Exceeding a dose of 800 mg is not recommended.[8]

The reports indicate that, where recorded, the doses tended to be higher for the aggravated psoriasis group compared with the psoriasis group, although only one patient in the former group received greater than the recommended dose (880 mg). However, two patients whose dose intervals were shorter than recommended (weekly) were in the psoriasis group.

The duration of tocilizumab use to onset of psoriasis was 1 to 85 days, median 19 days, for the psoriasis group (four patients) and 5 to 191 days, median 84 days, for the aggravated psoriasis group (six patients).

One patient had experienced a similar reaction to rituximab, a biologic B-cell depleting agent whose indications include autoimmune disorders, with recurrence on rechallenge. TNF inhibitors had been ineffective in this patient and had not caused psoriasis (Table 2, ICSR1). There was no record of previous exposure to bio- logic antirheumatic medicines in the other reports. Five patients were taking methotrexate and one sulphasalazine, both of which are disease-modifying anti-rheumatic drugs (DMARDs). However, psoriasis is not a recognized reaction to non-biologic DMARDs and one study found no evidence that non-biologic DMARDs caused or aggravated psoriasis in a cohort of 2,880 patients.[9]

There was no consistent use of other medicines, suggesting an alternative explanation for psoriasis or an interaction with tocilizumab. However, some ICSRs were not well-documented and information on concomitant medicines or previous exposures may have been omitted.

The psoriasis was described as guttate in two ICSRs of aggravated psoriasis and pustular in three ICSRs of psoriasis. One patient with psoriasis had a bullous psoriatic reaction affecting the plantar area which was described as "impressive" and occurred several times, always after a tocilizumab infusion, (Table 1, ICSR 9). Two ICSRs indicated serious reactions. One patient with guttate psoriasis required hospital admission and one patient's pustular psoriasis was assessed as disabling or incapacitating.

Of the 12 ICSRs for psoriasis, one patient with pustular psoriasis was recovering after tocilizumab was dis- continued, (Table 1, ICSR 3), and one patient, descri- bed above, developed episodes of psoriasis, described as bullous and plantar, which always occurred after a tocilizumab infusion, (Table 1, ICSR 9). Three other patients recovered or were recovering but the date of stopping tocilizumab in relation to recovery was unclear or not documented.

Of the eight ICSRs for aggravated psoriasis, one patient developed a massive increase in guttate psoriasis and seronegative rheumatoid arthritis five days after one dose of tocilizumab, (Table 2, ICSR 1). This is the patient who had reacted similarly five months previously to rituximab with recurrence on rechallenge. Three patients with aggravated psoriasis had not recovered at the time of reporting and the outcome was unknown for the remaining four.

Literature and Labelling

There are three published articles describing psoriasis or aggravated psoriasis occurring in four patients during tocilizumab use (Table 3).[10-12] The indications were psoriatic and non-psoriatic. One young man also experienced a flare of pre-existing uveitis. The form of psoriasis was palmoplantar in one patient and guttate in another, in keeping with observations in the VigiBase ICSRs. Two patients recovered on dechallenge and one relapsed on rechallenge. However, this patient and one other tolerated further administrations while using topical psoriasis treatment. This suspected reaction does not appear in Martindale, Drugdex, the European Medicines Agency (EMA) Summary of Product Characteristics (SPC), or in the US Food and Drug Administration (FDA) label.

Discussion and Conclusion

The reports in VigiBase do not overlap with published reports (Table 3) and provide additional information. Published articles 1 and 2 in Table 3 indicate recovery when tocilizumab was discontinued, one with recurrence on rechallenge. ICSR 3 in Table 1 indicates recovery on discontinuation and ICSR 9 in the same table notes recurrence with each tocilizumab administration. These provide support for causality. Timing of report submission to national centres with respect to when tocilizumab was discontinued is not clear in some cases so that, for the two patients (Table 2) who had not recovered when tocilizumab was discontinued, sufficient time may not have elapsed for the psoriasis to resolve when the report was submitted. The third report in Table 3 together with ICSR numbers 5 and 8 in the psoriasis group indicate that the patients recovered while tocilizumab was continued, one with topical corticosteroid treatment.

The morphology of psoriasis occurring in association with biologic anti-rheumatic agent use is also of interest. The vast majority of published cases of biologic DMARD-associated psoriasis have occurred with the TNF inhibitors. Analyses of case reports in the US FDA adverse events reporting system (AERS) database and the British Society for Rheumatology Biologics Register (BSRBR) have provided information about the characteristics of these reports.[6,9] In the FDA series of reports of patients taking a TNF inhibitor for non-psoriatic indications about 17% of patients developed palmoplantar and 15% pustular psoriasis. Palmoplantar pustular psoriasis predominated in the BSRBR reports, and guttate psoriasis was also reported. When the VigiBase ICSRs are combined with the published tocilizumab reports, 8 of the 24 ICSRs (33%) describe pustular, palmoplantar or guttate psoriasis. Assuming that the remainder of the patients developed generalised plaque psoriasis (as the nature of their psoriasis was not described), the proportion of patients with other types of lesions with tocilizumab is greater than the 20% expected for psoriasis in general, although a larger case series would be needed to confirm this.

The mechanism whereby TNF inhibitors and tocilizumab might induce or aggravate psoriasis is unknown. Clearly this is a paradoxical reaction as these medicines inhibit the actions of pro-inflammatory cytokines. IL-6 appears to have a role in maintaining inflammation in psoriasis which includes promoting TNF and other cytokine production from T helper 17 cells which are important mediators in autoimmune diseases and host defence against extracellular pathogens.[10]

However, as there is evidence for abatacept and limited evidence for rituximab and anakinra causing psoriasis and these are biologic anti-rheumatic agents with various effects on the immune system,[13] a specific mechanism related to TNF and IL-6 inhibition is less likely. Cytokine imbalance has been proposed as a possible mechanism.[10]

The number of published and VigiBase ICSRs of psoriasis occurring in association with TNF inhibitors far outweighs those for tocilizumab and the other biologic anti-rheumatic agents. This may partly reflect usage and the novelty of the discovery of this reaction with TNF inhibitors leading to a greater likelihood of reporting, but further study to ascertain if there is a real difference between the agents with respect to this adverse reaction would be clinically useful. For tocilizumab the published and VigiBase spontaneous reports do suggest a possible causal relationship with the emergence or aggravation of psoriasis.

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Table 1. Case overview of ICSRs in VigiBase® of psoriasis in association with tocilizumab

ICSR	Sex/Age	Indication	Dose/Dose interval	Duration to onset	Concomitant medicines	Psoriasis description	Outcome
1	M/-	Rheumatoid arthritis	-/-	-	-	Generalised	Not recovered
2	F/-	Rheumatoid arthritis	400 mg/-	-	-	Pustular psoriasis	Unknown
3	F/-	Rheumatoid arthritis	280 mg/week	One day	Methotrexate	Pustular psoriasis	Recovering three weeks after stopping tocilizumab
4	F/-	-	-/-	-	-	Psoriasis	Drug withdrawn, Outcome unknown
5	F/33	Juvenile arthritis	8 mg/kg/week	17 days	Paracetamol	Psoriasis	Recovering
6	M/-	Rheumatoid arthritis	8 mg/kg /month	-	Prednisone Diclofenac	Psoriasis	Recovering
7	F/-	Rheumatoid arthritis	8 mg/kg/-	-	Prednisone	Psoriasis	Unknown.
8	F/-	Rheumatoid arthritis	360 mg/month	85 days Three doses, one each month over 85 days prior to onset.	Loxoprofen Methotrexate Rebamipide	Pustular psoriasis	Recovered
9	-/-	Rheumatoid arthritis	-/-	-	-	Bullous, plantar, psoriatic reaction, "impressive"	Not recorded
10	F/60	Rheumatoid arthritis	650 mg/week	-	Sulphasalazine Hydroxyzine Metronidazole Folic acid	Psoriasis (also folliculitis, conjunctivitis, cyst)	Unknown
11	M/-	-	-/-	-	Methotrexate	Psoriasis	Unknown
12	F/57	Rheumatoid arthritis	400 mg/ -	21 days	Telmisartan Ticlopidine L-thyroxine Methylprednisolone	Scalp psoriasis	Unknown

Table 2. Case overview of ICSRs in VigiBase® of psoriasis aggravated in association with tocilizumab

ICSR	Sex/Age	Indication	Dose/Dose interval	Duration to onset	Concomitant medicines	Psoriasis description	Outcome
1	F/58	Rheumatoid arthritis, seronegative	880 mg/ month One dose given	5 days	Pantoprazole duloxetine, hydrochorothiazide/ valsartan, L-thyroxine,	Massive increase of widespread guttate psoriasis lesions and seronegative rheumatoid arthritis, sweating	Recovered
2	F/49	Psoriatic arthritis	8 mg/kg / month	55 days	Methotrexate	Psoriasis aggravated	Unknown
3	F/41	-	760 mg/-	111 days	Methotrexate	Guttate psoriasis, sharp flare with seeding over body within one week of receiving tocilizumab	Unknown
4	F/56	Rheumatoid arthritis	400 mg/-	191 days	Methylprednisolone, telmisartan, ticlopidine, L-thyroxine, fenofibrate	Psoriasis aggravated	Unknown
5	F/-	Rheumatoid arthritis	-/-	-	-	Psoriasis aggravated, Anaemia	Unknown
6	M/51	Psoriatic arthropathy	-/-	6 days	-	Psoriasis aggravated	Not recovered
7	F/54	Rheumatoid arthritis	800 mg/-	143 days	Codeine/paracetamol, celecoxib, colecalciferol	Psoriasis aggravated	Not recovered
8	F/39	Rheumatoid arthritis, other	800 mg/-	-	-	Psoriasis aggravated	Not recovered

Table 3. Published reports of psoriasis with tocilizumab use[10-12]

ICSR	Sex/Age	Indication	History of Psoriasis	Dose	Duration to onset	Concomitant medicines	Psoriasis description	Outcome
1	F/37	Still's disease	Yes	8 mg/kg/ month	10 days	Prednisone	Scaly erythematous lesions On rechallenge palmoplantar and pubic areas affected	Recovered on dechallenge with increased oral and application of topical corticosteroids. Relapsed on rechallenge
2	F/52	Psoriatic arthritis	Yes	8 mg/kg/ month	5 days	-	Guttate	Recovered on dechallenge within one
3	F/55	Rheumatoid arthritis	No	8 mg/kg/ month	63 days	Prednisone	No description Sites – leg, elbow	Recovered with topical treatment and tocilizumab continuation
4	M/19	Ankylosing spondylitis, uveitis	Yes	8 mg/kg/ month for at least 3 months	Not stated	Predisone, NSAID unspec, methotrexate	Psoriasis "flare"	Not stated

Response from Roche

The Uppsala Monitoring Centre (UMC) of the WHO Collaborating Centre for International Drug Monitoring, identified psoriasis as a technical signal in their Global ICSR database Vigibase® based on calculated Information Component (IC) values. 12 ICSRs for psoriasis and 8 ICSRs for aggravated psoriasis were identified in the second quarter of 2013, after removal of three duplicates. "The combination tocilizumab/ psoriasis aggravated became statistically prominent in the second quarter of 2011(IC 2.21, IC025 1.04) and tocilizumab/psoriasis in the first quarter of 2013 (IC 0.96, IC025 0.14) when the total number of reports in Vigibase® for tocilizumab was 3,796."

Roche has been invited to comment on this technical signal relating to tocilizumab and psoriasis. The safety of patients is of the utmost importance to Roche, and adverse event reports from patients and physicians taking our medicinal products in clinical trials and in the post-marketing setting are continuously monitored and assessed. These events are reported to regulatory authorities in accordance with the respective regulations and safety guidelines.

Roche uses the MedDRA coding dictionary for its Global Drug Safety Database ARISg, which includes spontaneous reports from the post-marketing setting and serious adverse events and non-serious adverse events of special interest from clinical trials. In MedDRA, the High-Level Term (HLT): psoriatic conditions and the HLT: psoriatic arthropathies was used to identify potential cases of psoriasis and then a cumulative review (through 10 April 2013) of these potential psoriasis events was performed.

This cumulative review showed that a majority of reported cases contained minimal information precluding definitive causality assessment. About 20 % of reported cases had a preexisting history of psoriasis and an additional ~15% cases were reported with his- tory of anti-TNF use. As stated in the article above, the vast majority of published cases of biologic DMARD- associated psoriasis have occurred with the TNF inhibitors.

The four cases of psoriasis cited in the literature, that describe evidence on positive re-challenge or positive de-challenge are described as follows: two of the 4 cases had history of anti-TNF use. One case discontinued tocilizumab treatment with resolution of psoriasis symptoms; however, the patient's RA symptoms recurred. She opted to go back to tocilizumab treatment and manage her psoriasis symptoms with topical steroids instead. The last case of psoriasis had prior history of cutaneous eruptions. The patient developed exacerbation of the lesion after the 3rd tocilizumab dose. The status of psoriasis as well as the tocilizumab treatment was not provided. These cases are included in the cumulative review completed by Roche described above.

Of note, in the published literature, there are also case reports describing the successful use of tocilizumab in patients with psoriatic arthritis[1] or anti-TNF induced palmoplantar pustulosis, which is a type of psoriasiform lesion[2].

In conclusion, there does not appear to be a causal relationship between psoriasis and tocilizumab. Roche will continue to monitor this condition. No updates to the product information documents and no changes to the conduct of clinical trials are warranted at this point in time. Roche will continue to monitor and obtain as much information as possible on received reports. The benefit/risk assessment of tocilizumab remains unchanged.

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Vemurafenib and Pancreatitis

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Summary

Vemurafenib is a serine threonine protein kinase inhibitor, which inhibits the kinase activity of mutated B-Raf protein. The drug received FDA approval in August 2011 for use in the treatment of metastatic or unresectable malignant melanoma that is positive for the BRAF V600E mutation. This molecule interferes with the RAS-RAF-MEK-ERK pathway, which is involved in the regulation of cell proliferation, survival, differentiation and apoptosis. As of September 2013, 20 Individual Case Safety Reports (ICSRs) have been submitted from seven different countries to the WHO Global ICSR Database, VigiBase®, in which vemurafenib is associated with pancreatitis. Several reports showed similarities in terms of dosage administered, time to onset, laboratory values, outcome and in many cases vemurafenib was the only drug reported. In the following assessment the evidence for a possible link between vemurafenib and pancreatitis, a serious and potentially life-threatening condition was examined. In addition to the cases identified during the routine screening of VigiBase, we also examined reports for vemurafenib that included related terms for increased amylase and lipase enzymes, which may also indicate pancreatitis. Evidence to support a signal between vemurafenib and pancreatitis included: an analogy with other kinase and BRAF inhibitors suggesting a plausible mechanism of action, coherence in laboratory findings (increased lipase and amylase values) that indicate pancreatic sufferance, consistency in terms of posology and temporal response after drug intake.

Introduction

Vemurafenib (Zelboraf®), a serine threonine protein kinase inhibitor, received FDA approval in August 2011 for use in the treatment of metastatic or unresectable malignant melanoma that is positive for the BRAF V600E mutation. The drug is active in the RAS-RAF-MEK-ERK pathway, which is involved in the regulation of cell proliferation, survival, differentiation and apoptosis. Vemurafenib competes with adenosine-triphosphate (ATP) to reversibly and selectively inhibit the V600E mutated BRAF kinase, by preventing its phosphorylation mediated activation.[1] The drug is administered orally as 240 mg tablets,[2] usually 3-8 tablets per day. Vemurafenib is metabolized by CYP3A4 and mostly excreted in the faeces (94%), up to 5% of its metabolites can be found in plasma.[3] Compared to dacarbazine, the only other FDA approved drug for the treatment of metastatic melanoma, vemurafenib was found to halt the progression of stage III and stage IV previously untreated V600E mutation positive melanomas for a median of 5.4 months versus 1.6 months.[4] Animal studies on vemurafenib did not reveal pancreatitis.5 Reported common adverse reactions during randomized clinical trials were: arthralgia, rash, fatigue, photosensitivity, cutaneous squamous cell carcinoma, keratoacanthoma, nausea, alopecia, pruritus, hyperkeratosis, diarrhoea, headache, and vomiting.[4,6]

Acute pancreatitis is a clinical condition, the annual incidence of which is 4.9 to 35 per 100,000 people, characterized by inflammatory symptoms of individual degrees of manifestation; it can be self-limiting to the point of not requiring treatment but may also be severe (25% of the cases), leading to death due to multi-organ failure (30-50% mortality associated with severe pancreatitis;[7,8] the majority of cases follow an acute course, but 3 to 13% of the cases become chronic).[9] The pathophysiological mechanisms leading to acute pancreatitis have yet to be fully understood. It is accepted that the initial inflammatory response involves the destruction of acinar cells through apoptotic or necrotic mechanisms with consequent leakage of pancreatic digestive enzymes, effectively leading to an autodigestion of the organ. A number of factors may contribute to the development of pancreatitis, including but not limited to gallstones (38% of the cases), alcohol abuse (36%), infectious or toxic causes.[7,10] Laboratory tests for the diagnosis of pancreatitis involve amylase and lipase measurements. Drug induced pancreatitis inci- dence is estimated to be 0.1-2%.[11] Time to onset for drug induced pancreatitis varies greatly as it could range from one day to several months.[12,13]

Table 1. Vemurafenib and pancreatitis – Characteristics of 18 cases retrieved in VigiBase®

Case	Age/ Gender	Time to onset	Duration of treatment	Other suspected (S) or concomitant (C) drugs	Reactions (WHO-ART)	Dechallenge/ Rechallenge	Outcome (pancreatitis)
1	-/F	81 days	126 days	Venlafaxine (C)	Pleuritic pain, pleural effusion, squamous cell carcinoma of skin (MedDRA), pancreatitis	Positive dechallenge/-	Recovered with sequelae
2	-/M	15 days	18 days	-	Pancreatitis, abdominal pain	Drug withdrawn/ Rechallenge	Not recovered
3	-/F	4 days	4 days	Lisinopril, diltiazem (both C)	Lipase increased, pancreatitis	Positive dechallenge/-	Recovered
4	21/F	59 days	64 days	-	Pancreatitis	Drug withdrawn/-	Died (disease progression)
5	-/M	-	-	-	Arthralgia, fatigue, pancreatitis, myalgia, nausea	Unknown/-	Unknown
6	-/F	-	-	Clonidine, omeprazole, potassium, valaciclovir, glipizide, docusate, valsartan/amlodipine besilate, metoprolol, hydrochlorothiazide, metformin (all C)	Renal failure, arthralgia, pyrexia, diarrhoea, rash, pancreatitis	Unknown/-	Unknown
7	35/F	5 days	5 days	-	Pancreatitis	Positive dechallenge/ Re-introduced at lower dose (outcome unknown)	Recovered
8	35/M	-	370 days	-	Pancreatitis, lipase increased	Drug withdrawn/-	Unknown
9	62/M	5 days	-	-	Pancreatitis	-/-	Recovered
10	-/M	-	-	-	Pancreatitis, gastroenteritis viral, Guillain-Barré syndrome, hepatitis	-/-	Unknown
11	76/M	3 days	3 days	Acetylsalicylic acid, iodine, levothyroxine (all C)	Pancreatitis acute	Positive dechallenge/-	Recovered
12	-/M	1-60 days	-	-	Pancreatitis, brain metastases	Dose lowered/-	Unknown, patient died of underlying disease
13	60/M	-	-	-	Hepatitis, hepatic function abnormal, Guillain-Barré syndrome, paraneoplastic syndrome (MedDRA), polyneuropathy chronic (MedDRA), paralysis facial, gastroenteritis viral, pancreatitis	-/-	Not recovered
14	59/M	4 days	> 4 days	-	Pancreatitis, erysipelas	Drug withdrawn/-	Recovering
15	75/M	29 days	30 days	Timolol, Metamizole, Fentanyl, Finasteride, Candesartan, Sodium bicarbonate/potassium chloride/ Sodium chloride/Macrogol 3350 (all C)	Pancreatitis necrotizing, cholecystitis, acute renal failure	Drug withdrawn/-	Unknown
16	80/F	156 days	156 days	Benorilate, Sodium bicarbonate/ Potassium chloride/Sodium chloride/ Macrogol 3350, Sodium picosulfate, acetylsalicylic acid, levothyroxine, pantoprazole, domperidone (all S)	Pancreatitis	Positive dechallenge/-	Recovered
17	67/M	-	-	Codeine phosphate/paracetamol, acetyl l-caretene (all C)	Abdominal pain, pancreatitis	Unknown/-	Unknown
18	70/F	41 days	-	More than 20 drugs, including lisinopril (C), Piperacillin sodium/ Tazobactam sodium (S)	More than 30 terms, including pancreatitis	Unknown/-	Recovered, died from respiratory failure

Reports in VigiBase

A total of 20 Individual Case Safety Reports (ICSRs) of vemurafenib associated with pancreatitis were retrieved from the WHO Global ICSR Database, VigiBase® on 23 September 2013. This combination has been identified as statistically disproportionate with an IC of 1.42 and an IC025 of 0.72. After the exclusion of two duplicates, 18 ICSRs were reviewed case by case (Table 1, page 52). The additional search terms amylase increased and lipase increased yielded a further five cases, two of which had already been captured using the pancreatitis search term, bringing the total number of cases for the assessment. The lipase and amylase results have been summarized in Table 2. All patients were either affected by malignant melanoma or metastatic malignant melanoma.

The 18 ICSRs reporting pancreatitis came from the United States (nine), Australia (three), Germany (two), Austria (one), Switzerland (one), Croatia (one) and Hungary (one). Sex was provided for all cases, 11 of the patients were males. Age was not specified in eight of the cases; of the remaining 10 for which age was provided, three of the patients were between 18-44, three ranged from 45 to 64, three were 65-75 and two were more than 75 years old. Dose regimens were specified in 12 cases, the most common being 1920 mg per day (eight cases). Vemurafenib was the only suspected drug in 16 cases and the only reported drug in 10 cases. Co-suspected drugs were reported in only two ICSRs and those are listed, along with other concomitants, in Table 1. In only three cases concomitants for which pancreatitis is listed in the Summary of Product Characteristics were identified: case 3 and 18 (lisinopril) and case 6 (valsartan/amlodipine besilate and hydrochlorothiazide). However, in case 18, a list of more than 20 drugs was reported but no dates of treatment were provided.

The patient's weight alone was reported in six cases: 64 kg (case 1), 90 kg (case 2), 166 kg (case 3), 99 kg (case 6), 66 kg (case 7), 72 kg (case 18). Sufficient information to calculate Body Mass Index was provided in only one case, (case 11, BMI 28). History of alcohol abuse and gallstones was not reported for any of the patients.

Time to onset was clearly reported in 11 cases and ranged between three days to five months. In one occasion (case 12) the exact start date was not reported although the starting month is known and so is the month of reaction onset. In the remaining six cases, there are no specified dates or only the starting day was reported.

Amylase values were included in four cases, one of which was confounded by metastases, and ranged roughly between 3 and 16 times the upper limit of normal.

Lipase values were included in three reports and ranged from 10 to 30 times the upper limit of normal.

In case 3a (Table 2), the MAH reported an "analysis of similar events" related to lipase increased values. It was stated that three cases were found in the MAH database, one of which was assessed as related to vemurafenib while two were not (due to a prior history of pancreatitis).

In five of 18 cases, a positive dechallenge could be seen. In 10 of the 18 cases the drug was withdrawn; five recovered or were recovering, one recovered with sequelae, one did not recover (in this case the medication was reintroduced but no outcome information was provided), one died (cause of death was said to be disease progression) and in two patients the outcome of the dechallenge was unknown. One of the five patients that recovered was re-exposed at a lower dose and there was no recurrence of pancreatitis.

In one case the dose was lowered and the outcome of pancreatitis was unknown. Of the seven remaining patients no information was provided on the action taken in relation to vemurafenib: the outcome was reported as recovered for two patients, not recovered for one patient and unknown for the remaining four.

Co-morbidities included: pancreatic metastases (case 4), diabetes (case 6 – formally not reported, but patient undergoing diabetes type II therapy, case 18), polyneuropathy, lung metastasis and anaemia (case 11), brain metastasis (case 12), hypertension (case 6, 15, 18).

Causality was assessed as "possible" by the reporters in five cases, two of which were reported by the manufacturer, it was assesed as"certain" in one case and "related" in another two. Where co-suspected drugs were specified, causality was considered as "unlikely".

Table 2. Vemurafenib and lipase and amylase increased – Characteristics of 3 cases retrieved in VigiBase®

Case	Age/ Gender	Time to onset	Duration of treatment	Other suspected (S) or concomitant (C) drugs and underlying conditions	Lipase/Amylase values/Normal reference values	Dechallenge/ Rechallenge	Outcome
1a	44/M	6 days	6 days	Lacosamide, tramadol, mirtazapine, pantoprazole, metamizole, lorazepam, levetiracetam, dexamethasone, calcium (all C)	Lipase: 686 U/L/?	Lowered dose/-	Recovering
2a	46/F	7 days	7 days	Hysterectomy nos, hypertension arterial, smoker	Lipase: 141 U/L/? Amylase: 132 U/L/?	Unknown/-	Unknown
3a	63/F	26 days	26 days	Dexamethasone, etoricoxib, metamizole, gentamicin, bethamethasone valerate/ fusidic acid, pregabalin, zopiclone, lorazepam, ibuprofen, aciclovir, urea-cresol-sulfonate sodium, pantoprazole (all C)	Lipase: 524 IU/L/<60	Positive dechallenge/-	Recovering

Literature and Labelling

Neither the European Medicines Agency (EMA) Summary of Products Characteristis (SPC) nor US FDA labels indicate pancreatitis as a potential adverse reaction; moreover, there was no mention of either increased amylase or increased lipase enzymes. Gamma-glutamyltransferases, potential indicators of pancreatic inflammation, but more commonly associated with hepatobiliary problems, were found to be increased in phase III studies.[3,14] There is one case report in the literature of a 49-year-old male with stage IV melanoma who developed pancreatitis two weeks after starting treatment with vemurafenib. He recovered following withdrawal of the drug, but pancreatitis recurred on rechallenge. His symptoms disappeared after permanent discontinuation of vemurafenib. All other possible causes were ruled out.[15]

Discussion and Conclusion

There are several factors that point towards a causal association between vemurafenib and pancreatitis. Firstly, the evidence of recurring patterns in the reports. Without considering the reports that present underlying conditions such as diabetes,[16] pancreatic metastases or cholecystolithiasis, which can act as con- founders, there are several cases that bear similarities in time to onset: cases 3, 7, 9, 11, 14. The dose was also consistent in these (1920 mg per day), except for case 14 where it was unknown. Although patient 3 was undergoing anti-hypertensive therapy with lisinopril, this drug is considered to have a very rare potential to induce pancreatitis, according to the UK SPC. Drug withdrawal led to recovery in ICSRs 3, 7 and 11.

Secondly, the interruption of the RAS-RAF-MEK-ERK cascade by vemurafenib results in the activation of caspase-9; this enzyme has been found to promote apoptosis.[17] Caspase-induced apoptosis has been pro- posed as one of the pathophysiological mechanisms for acute pancreatitis.[7] Alternatively, low dose vemurafenib can result in paradoxical induction of ERK,[18] which could activate TNF-α dependant transcription factors[17] such as NF-κB that may be linked to acinar cell apo- ptosis and ultimately acute pancreatitis,.[7,19]

In relation to a possible mechanism, it is useful to consider drugs that share similar pharmacodynamic properties with vemurafenib. At least two other kinase inhibitors are known to cause pancreatitis: dabrafenib and sorafenib. The frequency with which sorafenib can induce pancreatitis has been defined as "uncommon" in both the UK SPC and US FDA leaflet, while dabrafenib, according to the US FDA label, induced pancreatitis in less than 10% of the patients. Protein kinase inhibitors interfere with the downstream effects of growth factors, such as VEGF; this inhibition has been linked by some authors to acute pancreatitis of ischemic origin.[20] Sorafenib, a multi kinase inhibitor, acts on a broader spectrum of kinases than vemurafenib, there- fore it is possible that an alternative mechanism may be involved in the development of pancreatitis; however, dabrafenib acts more closely to vemurafenib[21] hence it is plausible that

these drugs share a common mechanism in the development of pancreatitis. It should be borne in mind the pathophysiology of pancreatitis is not yet well understood.[7,10]

It is not possible to rule out obesity as a cause of gallstone-induced pancreatitis, but most ICSRs lack data on essential parameters for a simple assessment, such as BMI calculation.

The elevation of enzymes in cases 1a, 2a, 3a, followed a similar temporal development to the pancreatitis cases, in terms of time to onset, thus the role of vemurafenib cannot be excluded.

Evidence to support a signal include: (i) the temporal association between drug administration and the onset of the reaction is consistent through several cases, (ii) similar drug mechanisms induce the same adverse reaction, (iii) five patients recovered after drug withdrawal. It should also be noted that the malignancy does not commonly metastasize to the pancreas[22] and no evidence of pancreatic metastasis was reported in the majority of the cases. Hence, it is plausible to hypothesize a causal relationship between vemurafenib and the onset of pancreatitis in genetically predisposed individuals, at a dosage of 1920 mg per day.

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Response from Roche

Thank you for providing Roche an opportunity to read and comment on the signal of Pancreatitis.

As early as July 2012, an assessment was conducted by Roche following identification by both Roche and the EMA Pharmacovigilance Risk Assessment Committee of pancreatitis as a potential signal. At that time, eighteen (18) reports of pancreatitis had been received when the estimated exposure worldwide to vemurafenib was 4,500 corresponding to a reporting rate of 0.40%. Of the 18 reports, 12 cases were from clini- cal studies. Overall, these 12 cases did not suggest a particular pattern of time to onset or duration. Four cases were reported in the first week (day 1, 2, 3, and 6) and the rest were distributed across a wide range of time points up to 2 years after start of vemurafenib treatment. Similarly, the duration of the AE ranged from 3 to 158 days. The remaining 6 cases were from spontaneous reports with very limited data available. Case analysis also revealed one or more confounding factors in the 18 cases such as concomitant medications, history of pre-existing pancreatitis, hyperlipidemia, gallstones, and metastases to the pancreas. The review concluded that there was no definitive evidence to show a causal association between vemurafenib and pancreatitis based on the safety information of the 18 case reports. In addition the incidence of pancreatitis seen was within the rate observed among malignant melanoma patients from other databases (Surveillance Epidemiology and End Results (SEER), US Healthcare Claims). This review was presented within the Periodic Safety Update Report covering the period 17 February 2012 to 16 August 2012.

A second assessment on this signal was again undertaken in February to March of this year. Cumulative review of information from pre-clinical, published literature, and the Roche safety database (cut-off date of 04 March 2013) was performed. In this assessment, the Roche global safety database was searched using the Standard MedDRA Query (SMQ) for acute pancreatitis. Overall, 31 cases were retrieved of which 24 cases were reported as pancreatitis and 7 cases were reported as abnormal pancreatic enzymes. Each case was then medically reviewed to assess causal relation- ship. Causality assessment was mainly based on onset latency, absence of major confounding factors and positive rechallenge (if documented). Of the 31 cases, 13 cases were assessed as probable pancreatitis based on a predefined case definition, of which only 5 were assessed to have a likely causal association to vemurafenib. This review was submitted with the Periodic Safety Update Report covering the period 17 August 2013 to 16 February 2013.

Roche also followed up with the authors of the Literature article that the WHO has referenced in their article: Vemurafenib associated pancreatitis: case report. Muluneh, B., Buie, L W and Collichio, F. Feb 22, 2013, Pharmacotherapy. In our conference call with one of the authors, it was confirmed that although the patient was hospitalized for this event, the diagnosis of acute pancreatitis was not supported by CT or ultrasound and that the positive rechallenge diagnosis was not confirmed by either imaging or pancreatic enzymes and was based on an episode of "epigastric pain".

In addition, the number of reported cases of pan- creatitis was compared to the background incidence of pancreatitis among patients with distantly metas- tatic melanoma from 3 databases. Using a conservative analysis, whereby all the 24 reports of pancreatitis (as of 04 March 2013) are considered, and with an estimated exposure worldwide to Zelboraf at 14,283 patients (as of February 2013), this corresponds to a reporting rate of 0.16%. This is in the same range as the incidence seen in the General Practice Research Database, MarketScan and SEER (GPRD database: 0.18%, MarketScan: 0.6% and SEER data (men and women combined): 1.3% (95% CI: 0.4 – 2.3).

The second review also concluded that there was no strong evidence to suggest a causal association between vemurafenib and acute pancreatitis. Roche continues to closely monitor the event of pancreatitis.

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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