WHO PHARMACEUTICALS NEWSLETTER

World Health Organization

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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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.

In addition to the usual features, this issue includes the summary of discussions from the eleventh meeting of the WHO Advisory Committee on Safety of Medicinal Products (ACSoMP).

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Bupropion

Serious cardiovascular adverse events

Australia. The Therapeutic Goods Administration (TGA) informs that the Product Information for bupropion is being updated to provide further information about the risk of serious cardiovascular adverse events.

Bupropion is a selective inhibitor of the neuronal reuptake of catecholamines, noradrenaline and dopamine. It is registered for use in Australia as a short-term adjunctive therapy, used in conjunction with counselling and abstinence, for nicotine dependence to assist in smoking cessation.

The Product Information (PI) for bupropion had previously contained information regarding hypertension. However, the TGA has identified postmarket spontaneous reports of more serious cardiovascular events, including myocardial infarction. To address this, the TGA is working closely with the manufacturer to update and strengthen the precautions for serious cardiovascular adverse events in the PI.

The updated information will advise that there have been reports of patients receiving bupropion (alone and in combination with nicotine replacement therapy) experiencing severe hypertension requiring acute treatment, in patients both with and without pre-existing hypertension.

The updated information will also advise that there is limited clinical experience establishing the safety of bupropion in patients with a recent history of myocardial infarction or unstable heart disease. Therefore, health professionals should exercise care if using bupropion in such patients.

It is recommended that blood pressure be monitored while the patient is taking bupropion, especially in patients with pre-existing hypertension, and consideration be given to discontinuing treatment if a clinically significant increase is observed.

A higher rate of hypertension has been observed when treatment with bupropion is combined with use of nicotine transdermal system products (patches).

If bupropion is used in combination with nicotine patches, caution must be exercised and weekly monitoring of blood pressure is recommended.

Reference: *Medicine Safety Update. October* 2014. (*www.tga.gov.au*)

Diclofenac

Arteriothrombotic events

Australia. The TGA informs that the Product Information documents for prescription-only diclofenac have been updated to provide further information about the increased risk of arteriothrombotic events.

Diclofenac is a non-steroidal anti-inflammatory drug (NSAID). Prescription-only products are available in oral and rectal forms.

Information regarding arteriothrombotic events was previously included in the precaution and adverse reaction sections of the Product Information (PI). However, the updated PI includes details from meta-analyses of individual participant data from randomised trials by the Coxib and traditional NSAID Trialists' Collaboration that estimated, in comparison with placebo, use of diclofenac caused about three additional major vascular events per 1000 patients per year. This information was derived from trials involving long-term (more than 28 days) treatment with high-dose diclofenac (150 mg/day).

To minimise risks, the lowest effective daily dose should be used for the shortest duration necessary to control symptoms.

Patients with cardiovascular disease or other risk factors may be at greater risk. The TGA is undertaking a review of all NSAIDs with regards to their association with cardiovascular risk.

Reference: *Medicine Safety Update. August* 2014. (*www.tga.gov.au)*

Risk of Major Heart and Stroke Related Adverse Events

Canada. Health Canada has reviewed the safety of diclofenac and has found that diclofenac is associated with an increased risk of heart and stroke related adverse events that is comparable to COX-2 inhibitors, and that this risk should be considered when prescribing or taking diclofenac.

Health Canada informs that the overall benefits of diclofenac continue to outweigh the risks, when used as recommended.

However, in order to further reduce the risks associated with diclofenac, additional information is being added to the prescribing information for diclofenac-containing products, which includes:

- Specifying that diclofenac at a higher dose (150 mg per day) is associated with an increased risk of heart and stroke related adverse events that is comparable to COX-2 inhibitors.
- Reducing the maximum daily dose for diclofenac from 150 mg to 100 mg for all indications, excluding VOLTAREN RAPIDE which allows for a 200 mg dose only

on the first day of treatment for dysmenorrhea.

- Recommending that for patients with a high risk of developing heart and stroke related adverse events, other treatment options that do not include NSAIDs, particularly COX-2 inhibitors and diclofenac, should be considered first.

Reference: *Health Canada, Important Safety Information. 06 October 2014. (www.canada.gc.ca)*

Methylphenidate

Priapism

Australia. The TGA warns that in very rare cases, treatment with methylphenidate may potentially lead to prolonged and sometimes painful erections (priapism).

Methylphenidate is a central nervous system stimulant and is indicated for the treatment of attention deficit hyperactivity disorder (ADHD). A US Food and Drug Administration review of methylphenidate products resulted in priapism being added as a class warning to the drug's labelling. Subsequent investigation by the TGA found that, while there had been no reports of this adverse event in Australia, the risk of untreated priapism was potentially serious.

A precaution for priapism has recently been added to the Australian Product Information (PI) for methylphenidate. While this risk applies to all use in males, the greatest concern is regarding pre-pubertal boys, who might not recognise the problem or may be too embarrassed to seek help if it occurs. Health professionals should consider educating parents and caregivers of pre-pubertal boys being treated with methylphenidate about this issue, while reassuring them that it is very rare.

Priapism can develop some time after drug initiation, often subsequent to an increase in dose, and has also been observed during a period of methylphenidate withdrawal.

Health professionals who are considering switching patients to another drug due to this issue are advised that atomoxetine, which is also used to treat ADHD, has been associated with priapism. The PI for atomoxetine lists painful or prolonged erection and male genital pain as potential, but very rare, adverse events.

Reference: *Medicine Safety Update. October* 2014. (*www.tga.gov.au*)

Omalizumab

Slightly elevated risk of cardiovascular and cerebrovascular serious adverse events

USA. The US Food and Drug Administration (FDA) suggests a slightly increased risk of problems involving the heart and blood vessels supplying the brain among patients being treated with the asthma drug omalizumab than in those who were not treated with the drug following a review of safety studies. As a result, FDA has added information about these potential risks to the drug label.

Omalizumab is an injectable medicine for patients 12 years of age and older with moderate to severe persistent allergic asthma whose asthma symptoms are not controlled by asthma medicines called inhaled corticosteroids.

The review found no difference in the rates of cancer between those patients being treated with and those who were not being treated with omalizumab. However, due to limitations in the 5-year study, FDA cannot rule out a potential risk of cancer with omalizumab, so this information was added to the Warnings and Precautions section of the drug label.

Reference: *FDA Safety Communications, US FDA, 26 September 2014. (www.fda.gov)*

Topiramate

Visual field defects

New Zealand. The New Zealand Medicines and Medical Devices Safety Authority (MEDSAFE) has informed that there has been reports of Visual field defects in patients receiving topiramate.

Topiramate is an anticonvulsant (antiepilepsy) drug. The drug had previously been used off-label for weightloss. In clinical trials, most of the side events were reversible after topiramate discontinuation in patients receiving topiramate independent of elevated intraocular pressure.

Visual Field Defects are a recognised adverse reaction for topiramate as described in the Adverse Effects section of the data sheet. Based on cumulative data from a recent review of post-marketing safety databases, and clinical trials, this additional safety Information has now been added in the Warning and Precautions section of the data sheet to increase awareness of this serious risk.

Reference: *Safety Information, MEDSAFE, 05 August 2014. (www.medsafe.govt.nz/)*

Valproate

Fetal exposure and cognitive impairment

Australia. The TGA has reviewed updated information regarding the association between use of valproate during pregnancy and cognitive impairment in children.

Valproate is an anticonvulsant that is indicated for the treatment of primary generalised epilepsy and partial epilepsy. It is also indicated for the treatment of mania, where other therapy has proven inadequate or is inappropriate.

Earlier studies examined the effect of fetal exposure to valproate on cognitive outcomes in children and these risks are reflected in the Australian Product Information (PI).

In 2013, the Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) study published its final analysis, which found that fetal valproate exposure had dose-dependent associations with reduced cognitive abilities across a range of domains at six years of age.

Meanwhile, another study found a link between use of valproate during pregnancy and autism spectrum disorders and childhood autism in the offspring, even after adjusting for maternal epilepsy.

The Product Information for valproate contains a warning about autism spectrum disorders and information about fetal exposure and the risk of developmental delay in the Use in Pregnancy section. However, the TGA's review of the updated information in the NEAD study has concluded that the information about cognitive impairment should be updated to show that cognitive deficits have been observed at six years of age.

The sponsor has agreed to update the PI and intends to also incorporate any recommendations that may result from an ongoing review being conducted in the European Union.

Reference: *Medicine Safety Update. October* 2014. (*www.tga.gov.au)*

Azathioprine

Serious Brain Infection (Progressive Multifocal Leukoencephalopathy)

Canada. Health Canada has warned that there is evidence that suggests a link between azathioprine and Progressive Multifocal Leukoencephalopathy (PML), a rare and serious brain infection.

Azathioprine is an immunosuppressive drug used in organ transplantation and autoimmune diseases. It is used alone or in combination with other immunosuppressive therapy to prevent rejection following organ transplantation, and to treat an array of autoimmune diseases. It is also an important therapy and steroid-sparing agent for inflammatory bowel disease (such as Crohn's disease and ulcerative colitis) and for multiple sclerosis.

A safety review was conducted to evaluate the available information regarding the potential risk of developing PML with azathioprine.

This review was conducted because several cases of PML had been reported worldwide in patients who had received azathioprine.

It is difficult to determine to what extent azathioprine contributes to PML. However, health-care professionals and patients should be aware of the possibility for PML to develop with azathioprine.

Health Canada is working with manufacturers to update the product information for Azathioprine.

Reference: *Health Canada, Important Safety Information. September 30 2014. (www.canada.gc.ca)*

Bo Ying Compound ®

Risk of lead poisoning

USA. The US FDA warns parents and caregivers not to use "Bo Ying compound" manufactured by Eu Yan Sang (Hong Kong) Ltd. due to the potential lead poisoning risk associated with the product.

FDA learned of this risk from the New York City Department of Health & Mental Hygiene after the product was tested and found to contain high levels of lead. FDA has received one adverse event report of lead poisoning in an 18-month-old child who was given this product.

The powdered product is marketed in retail outlets and online for use in infants and children for treatment of a variety of conditions including influenza, fever, sneezing, and nasal discharge. The product is labeled in Chinese and English.

Exposure to lead can cause serious damage to the central nervous system, the kidneys, and the immune system. In children, chronic exposure to lead, even at low levels, is associated with impaired cognitive function, including reduced IQ, behavioral difficulties, and other problems.

Reference: *FDA Safety Communications, US FDA, 26 September 2014 (www.fda.gov).*

Bromocriptine

Restricted use in preventing or stopping lactation

Europe. The European Medicines Agency (EMA's) Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) has endorsed by majority recommendations on the use of oral bromocriptine containing medicines to prevent or suppress breast milk production (lactation) after childbirth.

A review of oral bromocriptine was initiated at the request of France in 2013 of rare but potentially serious or fatal side effects, particularly cardiovascular side effects (such as heart attack and stroke), neurological side effects such as seizures (fits) and psychiatric side effects (such as hallucinations and manic episodes). The review was first conducted by the Pharmacovigilance Risk Assessment Committee (PRAC).

Since lactation is a natural process that eventually stops if the infant is not breastfed, and other means of management are available, the French medicines agency (ANSM) asked the EMA to review the medicines and see if the benefits of such use still outweighed the risks.

The PRAC recommendations were sent to the CMDh, which adopted a final position.

The PRAC's recommendations are based on a review of the available evidence of safety and efficacy of oral bromocriptine for prevention and suppression of lactation.

The CMDh agreed that the medicines should only be used for this purpose (in strengths up to 2.5 mg) when there are compelling medical reasons for stopping lactation, such as the need to avoid further distress after loss of the baby during or just after childbirth, or in mothers with HIV infection, who should not breastfeed.

Bromocriptine should not be used routinely for preventing or stopping milk production, and must not be used in women at increased risk of serious side effects, including women with various disorders that increase blood pressure or

who have or have had heart disease or severe psychiatric disorders. Blood pressure should be monitored so that early signs of an increase can be detected and treatment stopped immediately.

As the CMDh position on bromocriptine was adopted by majority vote, it will now be sent to the European Commission, which will take an EU-wide legally binding decision.

***Reference**: Press Release, EMA, 21 August 2014 (www.ema.europa.eu)*

Denosumab

Updated recommendations on minimising the risk of osteonecrosis of the jaw and hypocalcaemia

UK. The Medicines and Health-care products Regulatory Agency (MHRA) has warned that denosumab is associated with a risk of osteonecrosis of the jaw (ONJ) and with a risk of hypocalcaemia. The risk of hypocalcaemia increases with the degree of renal impairment when using denosumab 120mg for cancer or denosumab 60mg for osteoporosis.

Denosumab 120mg solution for injection is given once every 4 weeks to prevent skeletal related events (pathological fracture, radiation to bone, spinal cord compression, or surgery to bone) in adults with bone metastases from solid tumours.

Denosumab 60mg solution for injection (Prolia) is given once every 6 months to treat osteoporosis in postmenopausal women at increased risk of fractures. It is also indicated for treatment of bone loss associated with hormone ablation in men with prostate cancer who are at high risk of fractures.

To minimize the risk of ONJ and hypocalcaemia, MHRA recommends that calcium levels are to be closely monitored in patients receiving this drug.

Good oral hygiene, routine dental check-ups, and immediate report of any oral symptoms such as dental mobility, pain, or swelling to a doctor and dentist should be made.

***Reference:** Drug Safety Update. September 2014. (www.mhra.gov.uk)*

Ferumoxytol

Risk of serious hypersensitivity reactions

UK. The MHRA has declared that ferumoxytol is now contraindicated in patients with any known history of drug allergy, including hypersensitivity to other parenteral iron products.

This warning came as a result of re-evaluation of the benefits and risks of ferumoxytol. The evaluation focused on the cumulative reports of serious hypersensitivity reactions including life-threatening and fatal anaphylactic reactions to the drug.

Many of the patients who had a life-threatening or fatal anaphylactic reaction also had a known history of drug allergy to a non-iron product. (Hypersensitivity reactions are known to occur rarely with all intravenous (IV) iron products and may be life-threatening). MHRA stated that as with all IV iron products, ferumoxytol should only be administered when resuscitation facilities and staff trained to evaluate and manage anaphylactic or anaphylactoid reactions are immediately available. Furthermore, as with all iron products, the risk of hypersensitivity is increased in patients with immune or inflammatory conditions (e.g. systemic lupus erythematosus, rheumatoid arthritis) and in patients with a history of severe asthma, eczema, or other atopic allergy. In these patients, ferumoxytol should only be used if the benefits are clearly judged to outweigh the risks.

Ferumoxytol should only be administered as an intravenous infusion, in 50 to 250 ml of sterile 0.9% sodium chloride or sterile 5% glucose, and over a minimum period of 15 minutes.

Careful monitoring of patients for signs and symptoms of hypersensitivity reactions, including monitoring of blood pressure and pulse, during and for at least 30 minutes after the infusion is important.

***Reference:** Drug Safety Update. September 2014. (www.mhra.gov.uk)*

Measles, Mumps, Rubella, Varicella (MMRV) vaccine

Reminder of associated fever and febrile convulsion

Australia. The TGA has reminded health professionals that to minimise the risk of fever and febrile convulsion, MMRV vaccine should not be administered as the first dose of measles-containing vaccine to children younger than four years.

This is because the TGA continues to receive reports of such adverse events that suggest an associated risk in children aged 12 months or younger to whom MMRV vaccine has been administered as the first dose of measles-containing vaccine.

MMRV vaccine is a combination live virus vaccine for immunisation against these

four common childhood illnesses.

Like most vaccines, MMRV vaccine can cause some mild adverse events. In rare cases, fever after vaccination can lead to febrile convulsions in young children.

MMRV vaccine administered as a first dose in children aged 9-30 months is associated with an increased rate of fever and febrile convulsions, compared to separate measles, mumps and rubella (MMR) and varicella vaccinations.

On 1 July 2013, MMRV was added to the National Immunisation Program (NIP) schedule to be given at 18 months after an initial dose of measles, mumps and rubella (MMR) vaccine at 12 months of age.

When used as the second measles-containing vaccination, there is no indication of an increased risk with MMRV vaccine.

The overall risk of fever and subsequent febrile convulsion in children is greatly reduced by following the NIP schedule of the initial dose of MMR vaccine at 12 months and the second vaccine dose, as MMRV, at 18 months.

Dosage instructions in the product information recommend an interval of six weeks to three months between the first and second vaccine doses. As with other live virus vaccines, under no circumstances should the interval be less than four weeks.

Reference: *Medicine Safety Update. August 2014. (www.tga.gov.au)*

Nitrofurantoin

Caution in renal dysfunction

UK. The MHRA has warned that nitrofurantoin is now contraindicated in most patients with an estimated glomerular filtration rate (eGFR) of less than 45 ml/min/1.73m^2. However, a short course (3 to 7 days) may be used with caution in certain patients with an eGFR of 30 to 44 ml/min/1.73m^2. It should only be prescribed to such patients to treat lower urinary tract infection with suspected or proven multidrug resistant pathogens when the benefits of nitrofurantoin are considered to outweigh the risks of side effects.

This contraindication allows nitrofurantoin to be used in patients for whom it was previously not recommended.

Nitrofurantoin is an oral antibiotic for the treatment and prevention of urinary tract infections. The antibacterial efficacy in this infection depends on the renal secretion of nitrofurantoin into the urinary tract. In patients with renal impairment, renal secretion of nitrofurantoin is reduced. This may reduce the antibacterial efficacy, increase the risk of side effects (eg, nausea, vomiting, loss of appetite), and may result in treatment failures. Nitrofurantoin was previously contraindicated in patients with a creatinine clearance of less than 60 ml/min.

MHRA has reviewed the evidence for this contraindication in the context of increasing antibiotic resistance of lower urinary tract pathogens to standard therapy (trimethoprim and amoxicillin).

MHRA also considered the risk of *Clostridium difficile colitis* associated with the widespread use of alternative broad-spectrum antibiotics (cephalosporins and flouroquinolones). MHRA concluded that the existing contraindication is no longer supported and that the available evidence justified a revised contraindication against use in patients with an eGFR of less than 45 ml/min/1.73m^2.

Reference: *Drug Safety Update. September 2014.* (*www.mhra.gov.uk)*

Zolpidem

Next day impairment

Australia. The TGA has completed a safety review on zolpidem. Following this review, the TGA reminds health professionals treating patients with zolpidem of the risk of next day impairment.

Zolpidem is an imidazopyridine with relative selectivity for the type 1 benzodiazepine receptor subtype. It has been registered in Australia for the short-term treatment of insomnia in adults since 1999.

There are marketed brands and generics of zolpidem 5mg and 10mg marketed in Australia.

The Product Information (PI) for zolpidem includes a precaution regarding the drug's effect on the patient's ability to drive and use machinery. It warns that patients should not drive or operate machinery for eight hours after taking the drug and that drowsiness may continue the following day.

The PI also includes a black box warning that, among other things, advises health professionals to use caution when this drug is used with other central nervous system (CNS) depressant drugs.

Reference: *Medicine Safety Update.* August 2014. *(www.tga.gov.au*)

Correction: We regret the typographic error in WHO Pharmaceuticals Newsletter No 4, 2014, pg. 6 lines 1-2. The sentence should read "In patients **<75** years of age, the initial IV dose must not exceed **16mg**"

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 7 million reports of suspected adverse drug reactions, submitted by National Pharmacovigilance Centres participating in the WHO Programme for International Drug Monitoring. VigiBase is, on behalf of the WHO, maintained by the Uppsala Monitoring Centre (UMC) and periodic analysis of VigiBase data is performed in accordance with UMC's current routine signal detection process.

More information regarding the ICSRs, their limitations and proper use, is provided in the UMC Caveat document available at the end of SIGNAL (on page 26). 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.

Febuxostat and cardiac failure

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Summary

There are a significant number of reports in the WHO Global Individual Case Safety Report (ICSR) Database, VigiBase® suggesting an association of febuxostat with cardiac failure. The reports of cardiac failure commonly occurred in older individuals with cardiovascular histories who were therefore vulnerable to further cardiovascular events. Sometimes the cardiac failure was reported concomitantly with an ischaemic event, notably myocardial infarction. Cardiac failure is likely to be another manifestation of the association of adverse cardiovascular associations with this drug.

Introduction

Febuxostat is an oral, once daily non-purine inhibitor of xanthine oxidase. It was registered by the US Food and Drug Administration (FDA) in 2009 and by the European Medicines Agency (EMA) in 2008.[1,2] The drug is available in most markets globally. It is indicated for the treatment of hyperuricemia and gout and is particularly useful in patients who have had serious hypersensitivity reactions to allopurinol.[3,4]

Hyperuricemia is a common biochemical abnormality that predisposes affected persons to gout. The clinical manifestations of gout result from deposition of monosodium urate or uric acid crystals from supersaturated body fluids. Allopurinol is the most commonly prescribed treatment, but has side effects that may be severe and that occur more often in patients with renal insufficiency.

The registration labels for febuxostat in the United States and Europe are slightly different. The FDA has approved a dose of 40 and 80 mg per day respectively while the EMA has approved a daily dose of 80 and 120 mg. The EMA has advised to avoid the drug in patients diagnosed with coronary artery disease (CAD) and congestive heart failure (CHF). Adjustment of the dose in patients with renal impairment is not needed. There is no warning for cardiac failure. Febuxostat is not considered cost-effective in comparison to allopuri- nol as first-line therapy but is generally considered equi- valently tolerated and at least similarly effective.[5,6, 7,8]

Reports in VigiBase

As of 3 December 2013, there were 14 Individual Case Safety Reports (ICSRs) of febuxostat associated with cardiac failure in the WHO Global ICSR Database, VigiBase® (Table 1). The association has an IC value of 2.57 and an IC_{025} value of 1.72. In addition, there were eight reports of cardiac failure congestive, and two of cardiac failure acute. Cardiomyopathy was also reported with febuxostat in four cases, and myocarditis in one. Thus a substantial proportion of reports of cardiac dis- orders with febuxostat were identified as cardiac failure or closely related diagnoses.

Focusing on the 14 cases reported with the MedDRA term 'cardiac failure', they were submitted from four different countries; Germany (eight cases), United States (three cases), United Kingdom (two cases) and Finland (one case). The age of the patients was reported in eleven of the ICSRs and ranged from 52 to 83 years with a median age of 72 years. The gender distribution in the reports was nine men and four women, and the sex of one of the patients was not reported. Duration of exposure to febuxostat ranged from four days to nine months. Two of the reports did not offer this information. Time to onset ranged from the same day the drug was started to half a year with a median of 19 days.

Doses reported were 40mg per day (one case), 80 mg per day (eight cases), 120mg per day (two cases), one of the latter being an 83-year-old male patient from United Kingdom who had been taking febuxostat 120mg for 12 days, and had both cardiac and renal failure listed. This patient was one of the three who died with cardiac failure reported as associated with death.

With respect to outcome the patients were reported as recovered or recovering in four cases and not recove- red in two cases. In three of the patients who recovered (case 2, 3 and 11), the patient recovered after the drug was withdrawn. In one of the "not recovered" cases, the patient had stopped taking febuxostat and restarted allopurinol without any improvement. The other "not recovered" patient was still at the hospital at the time of reporting. There were three cases reported as 'unknown' with respect to recovery from cardiac fai- lure, and three had no information at all on outcome. One of these patients was however recorded to have died although there is no information on whether this was attributed to the cardiac failure. Finally two patients were recorded to have died from decompensated heart failure and heart failure respectively.

Causality was assessed in nine cases; related or possibly related to febuxostat in six cases and unlikely, not related or unassessable in three. No patients were re-challenged with febuxostat.

Examining the reactions listed along with cardiac failure in the 14 ICSRs, two had a myocardial infarction (MI) listed that could be the antecedent to the cardiac failure. The majority of these patients (seven cases) were taking

ACE inhibitors, angiotensin II-inhibitors, beta-blockers and/or diuretics that could have preceded the first exposure to febuxostat, indicating previous, probably controlled cardiac failure although these drugs are also indicated for hypertension.

Seven of the 14 cases reported the MedDRA included terms *'decompensation cardiac' (three), 'cardiac failure aggravated' (three) or 'decompensated heart failure'* (one) indicating a previous heart failure. Two of these reports lacked information about concomitant medications indicated for heart failure.

Concomitant pharmacotherapies were reported in nine of the ICSRs. Two cases had antidiabetic drugs and five were taking anticoagulant or antiplatelet medicines. In three of the cases where the patient was taking an anticoagulant drug, atrial fibrillation was listed in the medical history of the patient. In the reports where concomitant drugs had been taken, five of them included a NSAID drug. One of these was listed as acetylsalicylic acid (most likely low dose) well known to induce cardiac failure in those with controlled cardiac failure. Therefore the NSAID history of these patients is critical to understand the antecedents and reasons for the onset of the cardiac failure.

Looking at the eight reports of 'cardiac failure congestive', these were all from the United States. Six of the reports were sent by physicians. In one report, the patient started and stopped the drug the same day while in another the patient was treated for four months. The rest had no information on duration of exposure to febuxostat and there were no times to onset reported. No outcomes were reported, although all reactions were listed as serious and there were two deaths. Two cases had myocardial infarctions.

Table1. Case overview of reports in VigiBase® of cardiac failure in association with febuxostat

Case	Age/Sex	Concomitant drugs (possibly implicated therapies in bold)	Daily Dose (mg)	Duration of treatment	Comorbidity	Dechallenge	Outcome
1	68/M	-	80	51 days	Renal failure	-	Unknown
2	72/M	**Diclofenac**	80	4 days	CHD	Drug withdrawn	Recovered
3	72/M	Ibuprofen, metoprolol, metformin, amlodipine/valsartan, hydrochlorothiazide, doxazosin, phenprocoumon	80	3 months	Renal failure CHD MI Diabetic	Drug withdrawn	Recovered
4	-/M	Spironolactone, furosemide	120	9 months	MI Renal	Drug withdrawn	Not recovered
5	-/-	-	Unknown	-	Unknown	Drug withdrawn	Unknown
6	52/M	**Ibuprofen**	80	6-7 months*	Unknown	Drug withdrawn	Not recovered
7	80/M	-	Unknown	-	Unknown	-	Unknown
8	83/F	**Acetylsalicylic acid** (likely low dose), metoprolol, furosemide, acetylsalicylic acid, simvastatin, enalapril	80	1-5 days*	HF	-	Died
9	77/F	Bisoprolol, phenprocoumon, ramipiril	Unknown	57 days	HF	-	Recovered
10	79/F	**Diclofenac**, flagyl, paracetamol, clopidogrel, esomeprazol, warfarin, escitalopram, clonazepam, simvastatin, candesartan, metoprolol, furosemide	40	6 months	HF	-	Died
11	68/M	"Multiple concominant medication" (not further specified)	80	14 days	HF	Drug withdrawn	Recovered
12	-/F	Torasemide, hydrochlorthiazide, ramipiril, metoprolol, phenprocoumon, amlodipine	80	6 months	HF	-	Unknown
13	65-70*/M	-	Unknown	7 days	HF	-	Unknown
14	83/M	Citalopram, simvastatin, saxagliptin, ramipiril, insulin, furosemide,digoxin, colchicines, codeine phosphate/paracetamol bisoprolol	120	12 days	HF Diabetic	Drug withdrawn	Died

CHD – coronary artery disease history
MI – myocardial infarction occurred with the report of heart failure
HF – history or concomitant medications consistent with heart failure
*More exact age/dates not stated

It appears that two patients had 40 mg febuxostat per day and two others had the dose increased to 80 mg per day.

For the whole system organ class (SOC), there are as of 3 December 2013, 95 ICSRs submitted to VigiBase with febuxostat associated with cardiac disorders. Of these, there are 12 acute myocardial infarctions (AMIs), 19 MIs and one acute coronary syndrome reported. The distinction made between AMI and MI is uncertain and probably of doubtful significance. Any of these MIs may also present as cardiac failure in the future. There were a substantial number, 20 in fact, of atrial and ventricular arrhythmias, and again cardiac failure in association with an arrhythmia would not be unexpected.

Literature and Labelling

Pivotal randomised controlled trials (RCTs) comparing febuxostat with allopurinol leading to registration along with two extension studies indicated a greater incidence of cardiovascular thromboembolic events (sum of cardiovascular death, non fatal myocardial infarction, and non fatal stroke) for febuxostat.[1] EMA advised avoiding the drug in patients with CAD and CHF.[2]

The overall cardiovascular risk of the drug is of known regulatory concern, most focus being the risk of drug-induced MI and stroke. The product label from the US approved by FDA states under Warnings & Precautions; Cardiovascular Events "In the randomized controlled studies, there was a higher rate of cardiovas- cular thromboembolic events (cardiovascular deaths, non-fatal myocardial infarctions, and non-fatal strokes) in patients treated with ULORIC (febuxostat) than allo- purinol. A causal relationship with ULORIC has not been established. Monitor for signs and symptoms of myocardial infarction (MI) and stroke."[1]

A large, randomised, controlled comparison in gout patients with increased cardiovascular risk is recruiting in North America. About 7,500 patients will be entered and followed for up to five years and the study is predicted to close out recruitment in 2018. As per Clinicaltrials.gov; "the primary outcome is the time from randomization to the first occurrence of any predefined major adverse cardiovascular event." The study target is 624 major adverse cardiovascular events (MACE) giving a 90% power to demonstrate non- inferiority to allopurinol for the hazard ratio for MACE less than 1.3 for the upper limit of the confidence interval. Unfortunately, secondary outcomes for this study do not include cardiac failure, cardiac failure aggravated or decompensated heart failure. A positive feature is the targeting of plasma urate to less than 0.36 ug/ml by dose adjustment over the initial weeks while still maintaining the blinding. It is likely that regulatory agencies recommended this study be undertaken. It is hoped that progress with recruitment is satisfactory.[9,10]

A recent analysis of the US FDA post-marketing adverse event reporting system (FAERS) for cardiovascular thrombotic adverse events occurring in gout patients taking febuxostat revealed 21 cardiovascular thrombotic events. This was out of over 900,000 reports on this drug in FAERS since its registration through the end of 2011. Using Bayesian statistics the IC and IC025 values suggested a significant association (IC 4.75; IC025 4.09) with cardiovascular thrombotic adverse events. Of the 31 MedDRA preferred terms selected by the investigators to represent cardiovascular thrombotic events, two cases were labelled "congestive cardiomyopathy" and "cardiomyopathy". Both cases were serious and one patient died as a result of this condition. These two cases may not indicate thrombotic conditions. Cardiac failure was not specifically searched for in this study[11]

Discussion and Conclusion

The risk of cardiac failure associated with febuxostat remains uncertain. Of most concern would be its occurrence in persons with concomitant cardiovascular disease prior to febuxostat therapy, including those with controlled cardiac failure.

EMA advised avoiding the drug in patients with CAD and CHF. The basis for the CHF advice is uncertain. The advice is challenging given the common concurrence of ischaemic cardiovascular disease and cardiac failure with gout, some of the latter related to diuretic use and/or renal impairment. MI and ischaemic cardiac disease are the most common antecedents of cardiac failure. Therefore it is difficult to distinguish drug-induced cardiac failure *per se* such as drug-induced cardiomyopathy from drug-induced cardiac failure on a background of ischaemic heart disease or controlled cardiac failure.

A mechanism why febuxostat might be more prone to possibly causing ischaemic cardiac events and now, cardiac failure, in comparison to allopurinol is speculative, but could be related to the ability of the latter to reduce the production of oxygen free radicals more effectively than febuxostat.[12]

There are a significant number of reports in VigiBase suggesting an association of febuxostat with cardiac failure. The drug is known to be associated with ischaemic cardiovascular disease. The reports of cardiac failure commonly occurred in older individuals with cardiovascular histories who were therefore vulnerable to further cardiovascular events. Sometimes the cardiac failure was reported concomitantly with an ischaemic event, notably MI. Cardiac failure is likely to be another manifestation of the association of adverse cardiovascular associations with this drug and a manifestation of further ischaemia in these patients.

It is reasonable to believe that there is an association for febuxostat with cardiac failure.

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Response from Teijin, Takeda and Menarini

The MAH of febuxostat (Teijin, Takeda, Menarini) agree with WHO-UMC that heart failure (HF) is a very common morbidity in patients with gout, as about 26% had history of infarction/HF [1]. Patients with gout are also predisposed to HF because:

i. Of the presence of other cardiovascular (CV) comorbidities/HF risk factors in about 74% of patients [1].

ii. Gout/hyperuricemia is recognised as an independent risk factor for HF. Accordingly, an analysis on 4989 adults free of HF at baseline, indicated that participants with gout had 2 to 3 fold higher incidence of HF as compared with those without gout. Mortality was also significantly higher in the subgroup of patients with gout and HF [2].

Likewise, data from 734 adults (14-84 years) without prior chronic HF, gout, coronary heart or cerebrovascular disease not taking antihypertensive, antidiabetic, lipid-lowering or serum uric acid (sUA)-lowering drugs, indicated that there is a strong relation between estimated cardiac output and sUA (B=-0.219, p<0.001) and between stroke volume and sUA (B=-3.684, p<0.001) [3].

These results were confirmed in a recent meta-analysis [4] showing that hyperuricemia was associated with an increased risk of incident HF (hazard ratio [HR] 1.65, 95% CI 1.41-1.94), risk of all-cause mortality (HR 2.15, 95% CI 1.64-2.83), CV mortality (HR 1.45, 95% CI 1.18-1.78), and the composite of death or cardiac events (HR 1.39, 95% CI 1.18-1.63) in HF patients. For every 1 mg/dL increase in sUA, the odds of deve- lopment of HF increased by 19% (HR 1.19, 95% CI 1.17-1.21), and the risk of all-cause mortality and the composite endpoint in HF patients increased by 4% (HR 1.04, 95% CI 1.02-1.06) and 28% (HR 1.28, 95% CI 0.97-1.70), respectively.

Therefore HF is a common event in patients with gout, not only because patients with a positive history are at higher risk to relapse, but patients with gout without history of HF are also at higher risk to develop HF. Interestingly some studies [5] indicated that, among patients hospitalised because of acute HF, the survival of allopurinol-treated patients was lower than untreated subjects because patients at higher risk (with a more severe hyperuricemia) were more likely treated with allopurinol than patients with milder hyperuricemia (and there is evidence that febuxostat-treated patients present more comorbidities than those treated with allopurinol, see [6, 7]). Accordingly in 10 of 12 HF cases, where the medical history was reported, patients had CV comorbidities. Concomitant medications, such as nonsteroidal anti-inflammatory drugs can contribute to increase the CV risk in these patients.

A specific warning for patients with medical history of heart ischaemia or congestive heart failure (CHF) is present in the European Union. This was inserted in the EU-labeling before the availability of the final results of CONFIRMS and long-term extension (LTE) studies, when a numeric imbalance of primary Antiplatelet Trialists Collaboration (APTC) events was observed between febuxostat and allopurinol. After the final results of these studies the number of APTC events was more balanced, being the incidence rate (IR) in phase 3 0.74/100 patient years (PY) (95% CI 0.36-1.37) and 0.60/100 PY (95% CI 0.16-1.53), andin LTE studies 1.01/100 PY (95% CI 0.67-1.48) and 0.58/100 PY (95% CI 0.02-3.24), for febuxostat and allopurinol, respectively. Importantly, amongst primary APTC events just 2 events of CHF occurred in patients treated with febuxostat in phase 3 (1 at 80 mg) and LTE studies (1 at 80 mg), respectively. Amongst nonfatal events of CHF collected in phase 3 studies, 7 occurred in the febuxostat and 3 in the allopurinol group, yielding similar IRs (0.52 and 0.45 per 100 PY, respectively). Likewise, no difference was detected in nonfatal events of CHF collected in LTE studies as 7 and 1 event were reported, yielding IRs of 0.40 and 0.58 events per 100 PY in the febuxostat and allopurinol groups, respec- tively. Nevertheless, the above-mentioned warning was maintained and a CV safety comparative trial between febuxostat and allopurinol (FAST study) was mandated by the European Medicines Agency (EMA).

Two CV safety trials are ongoing in the United States and Europe. Both trials include hospitalisation for HF as secondary endpoints; therefore, comparative meaningful information on this event will also be collected. Importantly, independent committees periodically evaluate the interim results of these studies and decide whether the studies can be continued without an excess risk for participating patients. These committees have not risen concerns to date. Likewise, interim

results have been submitted to the Food and Drug Administration and EMA, without concerns being raised.

Despite the warning in the EU-labeling not recommending treatment in patients with ischaemic heart diseases or HF, in some of the postmarketing cases the concerned patients had positive history for these conditions; in a few cases the reporter specified that febuxostat had been prescribed regardless the warning because there were no therapeutic alternatives for these patients. Nevertheless all scientific material continues to point out that febuxostat should not be given to these patients.

Importantly, CV events including HF-related events are part of the continuous safety monitoring that the MAHs conduct for febuxostat. Currently the estimated incidence of postmarketing APTC events is lower than that reported in the literature for allopurinol-treated or untreated patients [8]. Therefore the statement that "febuxostat might cause more ischaemic CV and HF events than allopurinol because of a minor scavenging effect on oxygen radicals" could be argued not only because there is no evidence of a greater rate of CV and HF events under febuxostat, but also because there is evidence that antioxidant properties of febuxostat are actually greater than those of allopurinol [9], even when the sUA lowering activities are comparable [10].

In conclusion, although the most important indications for the causality between CV events in general (including HF-related events) and febuxostat treatment are expected to be collected at the end of the ongoing CV safety studies, this issue is currently under close monitoring and actions will be undertaken by the MAHs and the independent committees if the benefit- risk profile of febuxostat changes.

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Pamidronic acid and Optic Neuritis

Dr. Ian Boyd, Australia

Summary

Pamidronic acid (disodium pamidronate) is a potent inhibitor of osteoclastic bone resorption. The drug is indicated to treat conditions associated with increased osteoclast activity including tumour-induced hypercalcaemia, osteolytic lesions and bone pain in patients with bone metastases associated with breast cancer or multiple myeloma and Paget's disease of bone. In the WHO Global Individual Case Safety Report (ICSR) Database, VigiBase® there are as of October 2013, 11 reports of optic neuritis in association with pamidronic acid. The association has an IC value of 1.32 with an IC025 value of 0.35. The reports are from the United States, Australia, Canada and New Zealand. Of the 10 reports in which the outcome was stated, it was recovered, recovering or recovered with sequelae in four cases, not recovered in two cases and the outcome was fatal in the remaining four cases. Drug withdrawal was unclear in some cases but for a drug which is administered once every three or four weeks, drug withdrawal is not a meaningful parameter. There have been two literature reports of optic neuritis in association with pamidronic acid. The product information indicates that pamidronic acid can be associated with other inflammatory ocular effects.

Introduction

Pamidronic acid (disodium pamidronate) is a potent inhibitor of osteoclastic bone resorption. It binds strongly to hydroxyapatite crystals and inhibits the formation and dissolution of these crystals in vitro. Inhibition of osteoclastic bone resorption in vivo may be at least partly due to binding of the drug to the bone mineral. Pamidronate suppresses the accession of osteoclast precursors onto the bone. However, the local and direct antiresorptive effect of bone-bound bisphosphonate appears to be the predominant mode of action in vitro and in vivo.[1]

Pamidronic acid is indicated in the treatment of conditions associated with increased osteoclast activity including tumour-induced hypercalcaemia, osteolytic lesions and bone pain in patients with bone metastases associated with breast cancer or multiple myeloma and Paget's disease of bone.

Ocular adverse reactions which have been reported include conjunctivitis (common), uveitis (uncommon), scleritis, episcleritis and xanthopsia (very rare) and orbital inflammation (unknown frequency).[1]

Optic neuritis is a common inflammatory disease of the optic nerve.[2] It may cause sudden, reduced vision in the affected eye. The exact cause of optic neuritis is unknown. Conditions that have been linked with optic neuritis include autoimmune diseases, bacterial, fungal, viral and respiratory infections and multiple sclerosis.[3] A number of drugs have been implicated in the development of optic neuritis including ethambutol in particular as well as linezolid, amiodarone and cGMP- specific phosphodiesterase type five inhibitors.[4]

Reports in VigiBase

As of 1 October 2013 there are 11 Individual Case Safety Reports (ICSRs) of optic neuritis in association with pamidronic acid in the WHO Global ICSR Database, VigiBase®. The association has an IC value of 1.32 with an IC025 value of 0.35. The reports were submitted from the US (eight cases), Australia, Canada and New Zealand (one case each). The patients ranged in age from 12 to 88 years with a median of 65 years in the five cases in which this information was provided. In the 10 cases which provided the information, the gender distribution was eight females and two males.

Pamidronic acid was the only drug suspected in seven cases while the other four cases had another bisphosphonate, zoledronic acid, as a suspected drug. Four of the cases had no concomitant drugs reported while in the other six cases, the number of concomitant drugs ranged from three to 28. These indicated a population with considerable morbidity including cancer, depression, hypertension, infection and the requirement for treatment of pain, acid suppression and assistance with sleeping. Pamidronic acid was reported to have been administered intravenously, as expected, in the eight cases which provided this information. The indication for use was included in seven reports and included multiple myeloma (two cases), breast cancer, joint pain and osteoporosis (one case each)

Table 1. Case overview of reports in VigiBase® of optic neuritis in association with pamidronic acid

Case	Age/Sex	Reported reactions (WHO-ART/ MedDRA)	Other suspected (S) or concomitant (C) drugs	Outcome
1	88/F	Optic neuritis, visual impairment, red blood cells CSF positive	Sorbitol, salbutamol, zolpidem, loratadine, magnesium hydroxide, sertraline, celecoxib, lansoprazole, hydrochlorothiazide, letrozole, clonazepam, acetylsalicylic acid(C)	Recovered
2	65/F	Optic neuritis, iritis	Amitriptyline, paracetamol, clonidine(C)	Recovering
3	83/F	Optic neuritis, optic ischaemic neuropathy	Allopurinol, furosemide, nicotinic acid, amlodipine, lisinopril(C)	Recovered with sequelae
4	-/-	Optic neuritis	None	Unknown
5	-/M	Optic neuritis, vision abnormal	None	Not recovered
6	65/F	Optic neuritis, death	None	Died
7	-/F	Optic neuritis, blindness, vitreous floaters, retinal haemorrhage, vision blurred and 59 other reactions	Zoledronic acid(S) 17 concomitant drugs	Died
8	-/F	Optic neuritis, blindness, visual impairment, multiple sclerosis and 86 other reactions	Zoledronic acid(S) 26 concomitant drugs	Not recovered
9	-/M	Optic neuritis and 44 other reactions	Zoledronic acid(S) Acetylsalicylic acid, alprazolam, dexamethasone, duloxetine, esomeprazole, finasteride, lenalidomide, pantoprazole, paracetamol/oxycodone HCl, sulfamethoxazole/trimethoprim, venlafaxine	Died
10	-/F	Optic neuritis, vision blurred, death and 97 other reactions	Zoledronic acid(S) 28 concomitant drugs	Died
11	12/F	Optic neuritis, headache	None	Recovered

Table 2. Inflammatory ocular reactions in VigiBase® in association with bisphosphonates

Drug name	Pamidronic acid	Risedronic acid	Ibandronic acid	Zoledronic acid	Alendronic acid	Clodronic acid	Etidronic acid
Conjunctivitis	94	113	41	330	259	5	14
Scleritis	17	12	10	24	24	0	0
Iridocyclitis	6	7	3	53	14	0	0
Iritis	19	27	8	93	36	0	0
Uveitis	44	26	7	92	69	0	0
Optic neuritis	11	5	2	16	23	1	1

Time to onset was reported with clarity in only two of the reports and ranged from the same day that the drug was most recently administered to one day after admi- nistration. For a drug which is administered once every three or four weeks, as it is in the treatment of bone metastases which is the indication in the majority of reports, time to onset is most meaningful when related to the most recent administration· Of the 10 reports in which the outcome was stated, it was recovered, recovering or recovered with sequelae in four cases, not recovered in two cases and the outcome was fatal in the remaining four cases.

Four of the reports listed a large number of reactions which described a seriously ill population. Other ocular reactions are also described. In five cases, blindness or visual impairment was reported and this may be regarded as a symptom of optic neuritis. In one other case, iritis was reported and in the remaining case, optic ischaemic neuropathy was reported. Three of the four cases in which the outcome was fatal had a large number of reactions reported including cancer progression which was the likely cause of death in these cases.

Literature and Labelling

The product literature does not refer to optic neuritis. As noted above, however, other inflammatory ocular reactions such as conjunctivitis, uveitis, scleritis, episcleritis, xanthopsia and orbital inflammation have been reported.[1] There have also been isolated reports of optic neuritis in association with pamidronic acid.[5,6] Des Grottes et al described a patient who developed reversible retrobulbar optic neuritis after intravenous pamidronate therapy for established osteoporosis.[5] The authors noted that this possible complication had never been previously reported and, since the patient had a history of porphyria, it suggested that bisphosphonates should be administered cautiously in patients with this disease. Stack and Tarr reported three cases of optic neuritis and uveitis in association with bisphosphonates, one case with alendronate and the other two cases with pamidronic acid.[6]

Other bisphosphonates are also associated with inflammatory ocular reactions. Table 2 indicates the numbers of reports in VigiBase of these reactions. The number of reports of optic neuritis with the bisphosphonates is indicative that the frequency of optic neuritis may be similar to that of other inflammatory ocular reactions.

Discussion and Conclusion

Case reports in VigiBase suggest that there is a signal for the association of pamidronic acid and optic neuritis. While most of the cases have pamidronic acid as the sole suspected drug, dechallenge information is lacking as can be the case with a drug administered intravenously and periodically. Time to onset is reported in only two reports but both displayed a close association between the onset of the reaction and the last administration of pamidronic acid.

There have been two literature reports of optic neuritis in association with pamidronic acid. The product information indicates that pamidronic acid can be associated with other inflammatory ocular effects such as conjunctivitis, scleritis, iridocyclitis, iritis and uveitis so it would not be surprising if pamidronic acid can be associated with optic neuritis. In addition, the number of reports of optic neuritis for pamidronic acid and other bisphosphonates also suggests that optic neuritis may occur at a similar frequency to that of other inflammatory ocular reactions.

In conclusion, while it is possible that optic neuritis could arise from other causes in this series of reports, the case reports currently in VigiBase are suggestive that pamidronic acid could be the causative agent.

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Fingolimod and T wave inversion

Signal from Uppsala Monitoring Centre

Summary

Fingolimod is an immunomodulating drug used for treatment of multiple sclerosis. From February 2012 until December 2013, 27 Individual Case Safety Reports (ICSRs) of T wave inversion in association with fingolimod were submitted to the WHO Global Individual Case Safety Report Database, VigiBase®. The drug is known to cause bradyarrhythmias and AV block within the first few hours of the initial dose, but labelling or literature information does not mention the occurrence of inverted T waves. Although there were in some cases concomitant drugs that may affect the heart rate and a few patients had pre-disposing factors, the analysis of the case reports suggests there is cause for further investigation.

Introduction

Fingolimod is an immunomodulating drug used as single treatment of relapsing multiple sclerosis. It was first approved in the US in 2010 and in the EU the following year. The active metabolite fingolimod phosphate binds to sphingosine 1-phosphate receptors and reduces the number of lymphocytes in the peripheral blood. Although the exact mechanism is not known it is believed that fingolimod prevents the lymphocytes from moving into the central nervous system.[1,2] Fingolimod given orally in a daily dose of 0.5 mg has shown to reduce the relapse frequency compared to placebo and interferon beta-1a.[3,4] Common adverse drug reactions are back pain, cough, diarrhoea, head ache, influenza and increased liver enzymes.5,6 Following the unexplained death of a patient within 24 hours of receiving the first dose of fingolimod at the end of 2011, US and European regulatory authorities recommended a baseline electrocardiogram (ECG) before start of treatment and a close cardiac monitoring of all patients in the first six hours after receiving the first dose (a first dose observation, FDO) and in some cases for longer.[7,8]

The T wave in an ECG reflects the repolarization of the ventricles and is normally concordant with the QRS complex. Opposite polarity (i.e. negative T waves in leads with positive QRS complexes) can indicate myocardial ischaemia.9 T wave inversion is also associated with hypertrophic cardiomyopathy, aortic regurgitation, pulmonary embolism, sepsis, hyperventilation syndrome, subarachnoid haemorrhage and severe hypocalcaemia. Patients with pericarditis can show flattened to invert T waves. Anterolateral T wave inversion can be physiological in children and adolescents as well as in well trained athletes (so called athlete's heart).[10]

Multiple sclerosis (MS), the condition being treated with fingolimod, has so far not been associated with an increased incidence of cardiac disease. One recently published cohort study has, however, identified an increased risk of myocardial infarction, stroke and heart failure in MS patients compared to a control group without MS. The study took into account co-morbidities such as diabetes, hypertension, chronic obstructive pulmonary disease (COPD), deep vein thrombosis and others but did not adjust for risk factors such as obesity and smoking.[11]

Reports in VigiBase

Since February 2012 (after the introduction of FDO), 27 Individual Case Safety Reports (ICSRs) on fin- golimod in association with T wave inversion have been reported to the WHO Global ICSR Database, VigiBase®. The majority of the ICSRs are from the USA (17) and the other countries represented are Germany (four), Canada (three), Finland, Ireland and the UK (one each). In December 2013 the IC value was 3.70 and the IC025 was 3.11. Age was mentioned in 23 ICSRs, ranging from 20 to 76 years old with a median age of 47. Women were represented in 22 ICSRs, only four cases were for men and one case had no gender stated.

Concomitant drugs were listed in 18 of the ICSRs and in all but two; the patients were taking drugs that are known to cause cardiac disturbances. The concomitant drugs reported included amantadine amlodipine, atropine sulphate/dephenoxylate HCl, bupropion, celecoxib, citalopram, clonazepam, desipramine, donepezil, doxepin, epinephrine, gabapentin, hydroxychloroquine, interferon beta-1b, ondansetron, oxymorphone, paroxetine, levothyroxine, lorazepam, methylprednisolone-modafinil, naproxen, salbutamol, simvastatin, tadalafil, topiramate, trazodone and venlafaxine. Treatment dates were generally lacking for these drugs.

The dose was given in 25 of the ICSRs, all stating the recommended daily dose. Time to onset was recorded in 20 of the cases, ranging from reaction occurring on the same day up to five months. In 13 cases the reaction occurred on or within two days of FDO, but in seven cases the reaction was

seen at a later stage. The drug was withdrawn in 14 cases and of these five patients had recovered whilst three had not at the time of reporting. For the remaining six patients the outcome was unknown or not recorded. In seven cases the treatment had not been changed, three of these patients recovered and for the other four the outcome was unknown. The remaining six cases lacked information on any action taken regarding the medication and the outcome was recorded as unknown in five cases and not recovered in one case. Two reports listed that a rechallenge was made and in one case there was no recurrence of the event, whilst there was no information about the outcome in the other case.

Only two patients showed clinical signs of myocardial ischaemia (chest pain, dyspnoea) and both had risk factors for coronary artery disease such as heavy smoking and hyperlipidaemia. One further patient had diffuse episodes of chest pain but a concomitant lung infection. All other patients were asymptomatic and in all cases where further investigations such as echocardiogram, cardiac enzymes and/or coronary angiography were reported as performed, the results were negative with the exception of one asymptomatic patient who was found to have extensive obstructive coronary disease and underwent a threefold coronary by-pass.

No ICSR mentioned alternative aetiologies for T wave inversion.

Literature and Labelling

Neither T wave inversion nor myocardial ischaemia is labelled in the UK Summary of Product Characteristics (SPC) or the US FDA Product Label for fingolimod. There is however an increased risk of bradyarrhytmia and AV block and the labelling information specifically recommends that all patients starting on fingolimod treatment should have an initial predose ECG and be further monitored for at least six hours. Clinical trials identified symptomatic bradycardia in 0.5% of patients receiving fingolimod compared to none on placebo. The maximum decrease in heart rate usually occurred after six hours and usually improved after this. In some cases however a second period of heart rate decrease occurred within the first 24 hours and/or after the second dose. With continuous treatment the heart rate returned to baseline within a month. First degree AV block was reported in 0.1% of patients starting treat- ment with fingolimod whilst there were no cases for the placebo group and the same result was recorded for second degree AV block. The AV block was usually resolved within the first 24 hours. The post marketing experience reveals third degree AV blocks, AV blocks with conjunctional delay, transient asystole, syncope and unexplained death although confounders such as concomitant medications or pre-existing disease makes this an uncertain relationship to fingolimod. Patients on drugs that prolong the QT interval should be monito- red closely for the first 24 hours after starting treatment with fingolimod due to the association with torsades de pointes in patients with bradycardia.[5, 6] In a randomized phase IV study of 783 patients where three quarters received fingolimod and one quarter standard disease modifying therapy for six months, one patient was found to have biphasic T waves.[12]

Discussion and Conclusion

Fingolimod is known to affect the heart rate as it may cause bradyarrhythmias and AV block in the initial stages of treatment. The drug's effect on the sphingosine 1-phosphate receptors could theoretically provide an explanation for this as these receptors are also present in the atrial myocytes and nodal cells.[11]

The 27 ICSRs on fingolimod and T wave inversion stand out as statistically significant in the VigiBase dataset and the drug is the sole suspected drug in 26 of these cases. The large proportion of women in the ICSRs may be explained by the disease being more common in women than men. In 13 of the cases where time to onset was recorded, the reaction was seen within two days. 19 out of 27 cases list information on the patients' medical history. Hypertension was mentioned in four cases, three patients were reported as smoking and another three as former smokers. Hyperlipidaemia was reported for three patients and coronary artery disease in two more cases. Of these two patients, one was diagnosed with coronary artery disease after ECG changes were recorded during FDO. Five ICSRs explicitly mention that the patients had no preexisting cardiac morbidity or cardiac risk factors. The lack of treatment dates for the concomitant drugs that can induce arrhythmias complicates the assessment but as all these cases date after the introduction of FDO, it can be assumed that the ECG changes reported were new observations even in those cases where there is no reference to a pre-treatment ECG.

In 14 cases the severity of the ADRs reported, including bradyarrhythmias and signs of myocardial ischemia (two patients), caused a withdrawal of the drug. There was a positive dechallenge on six of the ICSRs, only three patients were reported to have reco- vered without changes to therapy.

The cases in VigiBase suggest that there is a possible causal relationship between fingolimod and T wave inversion and further investigation is warranted.

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Response from Novartis

In response to a WHO signal evaluation on disproportionate reporting of T-wave inversion in patients treated with fingolimod 0.5mg (approved dose in relapsing MS), Novartis presents the Company analysis of this signal. To date, 89,500 patients have been treated with fingolimod including > 15,000 in clinical trials for a total of ~137,000 patient treatment-years. Based on this review, Novartis does not believe the finding of isolated T-wave changes are related to fingolimod treatment.

Background

Fingolimod induces a transient dose-dependent reduction in heart rate and AV conduction upon treatment initiation. Fingolimod's product information recom- mends first-dose monitoring in all patients, which was updated in 2012 to include ECGs before and 6 hours after fingolimod initiation.

Significance of T-wave inversion

In most cases, T-wave inversion is non-specific and associated with physiological conditions. These conditions include orthostatic changes, hyperventilation, electrolyte imbalance, vagal reflex, cold water and anxiety. Food ingestion is one of the most common causes of T-wave inversion in healthy individuals (Okada et al 1994). T-wave inversion can also be associated with myocardial ischemia (with ST suppression), myocardial infarction (with Q waves and ST elevation) or cardiac conditions such as hypertension, left ventricular hypertrophy or cardiomyopathy. Isolated T-wave inversion in asymptomatic adults is usually a normal variant (Fisch, 1997). T-wave changes should be interpreted with caution and should always be correlated with the other clinical and diagnostic findings (echocardiography, coronary angiography, cardiac enzymes etc.)

Preclinical data

In preclinical toxicity testing, no T-wave inversion was observed in rats, guinea pigs, dogs or monkey.

Clinical trial data

Cardiovascular safety including ECGs was extensively assessed in a large number of patients under controlled conditions in fingolimod clinical studies (treatment duration was 6-24 months). Throughout the clinical program, ECGs were read by the treating physician and analyzed by an independent.

Table 1 Adverse events of T-wave inversion in fingolimod controlled clinical trials

	Placebo N = 966	Fingolimod 0.5mg N = 1364	Fingolimod 1.25mg N = 1367
T-wave inversion	2	0	1

Table 2 T-wave inversion in controlled clinical trials

Time of the ECG	Placebo n/N (%)	Fingolimod 0.5mg n/N (%)	Fingolimod 1.25mg n/N (%)
Baseline Day 1 (predose)	7/866 (0.8)	7/1211 (0.6)	7/1312 (0.5)
Day 1 (6h post-dose)	12/855 (1.4)	11/1193 (0.9)	10/1298 (0.8)
Month 1	8/847 (0.9)	18/1184 (1.5)	15/1275 (1.2)
Month 6	8/796 (1.0)	19/1105 (1.7)	19/1156 (1.6)
Month 12	5/635 (0.8)	16/1028 (1.6)	11/976 (1.1)
Month 18	2/344 (0.6)	4/377 (1.1)	7/330 (2.1)
Month 24	9/539 (1.7)	4/574 (0.7)	8/521 (1.5)

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N = number of patients; n = total cases of T-wave inversion; % = total cases of T-wave inversion /number of patients

ECG laboratory. T-wave inversions reported as adverse events (AEs) are presented in Table 1 whereas T-wave inversion detected as ECG abnormality are presented in Table 2. In the majority of cases, the investigators did not consider isolated T-wave inversion clinically relevant, thus warranting reporting as AEs.

In controlled clinical studies, there were no cases of AE related to 'T-wave inversion' with the approved 0.5 mg dose of fingolimod in 1,364 patients.

When data from non-controlled clinical trials is also considered, the frequency of AE reported as T-wave inversion was 2/8,978 patients for the 0.5 mg dose.

ECGs were assessed at predetermined time-points in the placebo-controlled pivotal clinical studies (Table 2). The frequency of T-wave inversion at baseline was similar between the treatment groups and placebo. At 6 hours post-dose on day 1, near the peak cardiac effect of fingolimod (peak bradycardia is observed at 4-5 hours post-dose), Twave inversion on placebo (1.4%) exceeded the frequency of fingolimod 0.5 mg (0.9%) and fingolimod 1.25 mg (0.8%). Overall, as shown in Table 2, T-wave inversion was reported in the placebo group at a range of 0.8% to 1.7%, which was compara- ble to the 0.5 mg dose (0.6% to 1.7%) and the 1.25 mg dose (0.5% to 2.1%), over the 24-month period. The frequency of T-wave inversion on placebo reflects both the baseline prevalence and the range of these abnor- malities in the absence of active drug. There is no indi- cation of a dose-response or a temporal relationship to treatment.

Individual case safety reports from Novartis safety database

There are 26 cases of T-wave inversion out of ~ 89,500 treated patients (spontaneous, clinical trial, literature) in the Novartis safety database. All but two cases were reported after 2012, when the label update for first- dose monitoring (including ECG) was implemented.

The onset latency was known in 23 cases. In about 50% (11/23) of cases, the event occurred during the first two days of treatment, presumably in the context of first-dose monitoring. Only eight events occurred beyond the first month of treatment initiation.

In 17 of 26 cases, the T-wave inversion in ECG was confounded by cardiac disease or preexisting abnormal ECG. In 4 cases, the information was insufficient to assess, and in the remaining 5 cases, "T-wave inversion" was an asymptomatic non-specific finding. Dechallenge and rechallenge evidence was equivocal.

Overall, the review of the 26 cases provides limited additional information.

Conclusions

The thorough analysis of all available evidence presented above does not indicate a causal relationship between T-wave inversion and fingolimod treatment.

- No evidence of T-wave inversion in pre-clinical toxicity studies (across species)
- Extensive ECG monitoring in large controlled clinical trials revealed comparable frequency of
- T-wave inversion between fingolimod and placebo
- In the post-marketing setting, T-wave inversion is rarely reported and two-thirds of reported events are confounded by pre-existing cardiac diseases

Fingolimod product information requires intense ECG monitoring for all patients at treatment initiation which is uncommon. In this context, and in the absence of a signal for ischemic heart disease or other pathologies that may manifest as T-wave inversions, Novartis believes this signal raised by disproportionality analysis can be explained by surveillance and reporting bias.

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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 (UMQ 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.

Eleventh Meeting of the WHO Advisory Committee on Safety of Medicinal Products (ACSoMP)

Geneva, Switzerland

14-16 May 2014

The WHO Advisory Committee on Safety of Medicinal Products (ACSoMP) has been constituted to provide advice on Pharmacovigilance (PV) policy and issues related to the safety and effectiveness of medicinal products. A summary of the discussions from the 11th meeting of ACSoMP is included below.

Safety and Vigilance (SAV) at WHO, Geneva

Safety and vigilance activities related to all medical products fall under the purview of the Safety and Vigilance (SAV) Team in the Department of Essential Medicines and Health Products (EMP). The SAV team is also responsible for the programme on monitoring and surveillance of Substandard/spurious/falsely-labelled/falsified/counterfeit medical products (SSFFCs). The overall goal of SAV team is to provide evidence-based support to countries, to ensure the safe use of health technologies (devices, medicines, vaccines, procedures and systems) in patients. The SAV team works in close collaboration with the three other teams of Medical Products unit (Norms and Standards, Prequalification, and Regulatory Systems Strengthening teams), with WHO public health programmes, with the National Regulatory Authorities, the national Vigilance Centres, the Uppsala Monitoring Centre (UMC) and other relevant WHO Collaborating Centres (in Oslo, Ghana, Morocco, the Netherlands), UN procurement agencies, Advisory Committees, professional associations such as the International Society of Pharmacovigilance (ISoP), groups representing industry (International Federation of Pharmaceutical Manufacturers & Associations (IFPMA), Council for International Organizations of Medical Sciences (CIOMS), control laboratories, manufacturers as well as other internal and external stakeholders. Supporting the development of national vigilance systems and guiding them with relevant norms and standards, advancing the principles and exploitation of a global adverse events database, providing independent safety review and advice on priority products (vaccines and medicines) through committees of experts, strengthening the regulatory oversight for these, and developing effective monitoring tools and systems for SSFFC medical products are some of the key priorities for SAV.

Collaborating centres as core support to the WHO safety and vigilance programmes

There are 5 collaborating centres (CC's) that support SAV in its pharmacovigilance programme goals and objectives: WHO CC in Uppsala (the UMC), Norway (for Anatomical, Therapeutic and Chemical Classification System with Defined Daily Doses (ATC-DDD)), Ghana, Morocco, & Netherlands. WHO SAV is responsible for the PV programme policies, framework, and roadmap. The WHO CCs bring their unique expertise to address specific programme needs. The technical support for implementing WHO PV policies and guidelines is provided by the WHO CCs with a focus on building capacity in the countries for collecting, assessing and acting on pharmacovigilance data within the countries. Each Centre works with a set of core responsibilities, some of which are unique to the Centre in question while some overlap with the activities of other Centres. The UMC is the only Centre responsible for managing and maintaining the WHO global ICSR database, data analysis, signal detection. A side event in future annual meeting of national pharmacovigilance centres will discuss joint strategies and work plans of the WHO CCs and WHO SAV, to allow better coherence and efficiency in their work.

WHO guidance on reporting forms

Public health programmes (PHPs) often request a standard Adverse Drug Reaction (ADR) reporting form from SAV, to collect and report the adverse events associated with treatment within these programmes. WHO SAV has preferred not to be too prescriptive and has directed countries to the CIOMS form for their own adaptation and use. But PHPs are of the opinion that while the CIOMS form is useful for ADR reporting by manufacturers, it is not sufficient to catch all the details that are of importance to PHP, for example, details that would allow identification of programmatic errors. Besides, and in view of the widening scope of PV worldwide, the ADR reporting form needs to support the detection of irrational use, medication errors, include features for recording information on specific products such as herbals and traditional medicines, etc. Some countries are also of the opinion that a WHO endorsed reporting form would be better accepted and promote ADR reporting in some settings. A WHO guidance document on the core information to be captured with the above objectives in view,

together with a prototype reporting form would help PHPs and countries struggling with these issues. The principles for a proposed model reporting form should define the data requirements, data structure, the recording media (paper, electronic or both) and should support data transfer to a database or a computerized repository.

'APPS' for ADR reporting and the value of Electronic Health Records (EHR) in PV

WEB-RADR (Recognizing Adverse Drug Reactions) is a project funded through the private public partnership, the Innovative Medicines Initiative (IMI). The project aims to set policy & guidance and deliver robust information technology tools to address the potential for the reporting of adverse drug reactions (ADRs) through mobile applications and the recognition of drug safety signals from user comments in social media and the internet.

In the USA, RAPID (Real-time Application for Portable Interactive Devices) grew out of the experience with Adverse Events (AE) collection after the experimental drug peramivir during the 2009 H1N1 influenza pandemic. PV departments are encouraged to work with IT departments to optimise the use of such technologies. These are issues of confidentiality because currently, there are no clear policies on traceability of reporters with such interactive devices. Smartphones and 'apps' may hold the key for improving ADR and Adverse Events Following Immunization (AEFI) reporting.

EHR is used in countries like the USA and its use makes the tracking of ADR submission convenient. EHR support the smarter management of information and reduce the inconvenience of paper files. EHR can serve as a nation's public health data, and EHR that includes PV data support patient management and assist signal detection. Information and Communications Technology (ICT) is part of health systems strengthening, and its application in PV can improve standard of care. A working group should investigate the usefulness of EHR in patient care and for collecting PV data in low and middle income countries (LMICs).

Medication errors and risk minimization actions

A Risk Minimization Plan (RMP) defines the steps to minimize the probability and occurrence of harm to patients following the use of medicines. This responsibility (to develop an RMP) lies with the Market Authorization Holder (MAH). The traditional tools applied in routine risk minimization are product leaflets, labelling, Summary and Product Caracteristics (SPC), pack-size and design, prescription status of the product, and in some cases, educational programmes. But in addition, the public health system should build risk minimization plans that complement the RMP from the MAH and through proactive PV activities to minimize harm. Actual risk minimization in practice is the result of good coordination between various stakeholders. A document that provides a step by step guidance on the roles and responsibilities of various stakeholders in managing Medication Errors (ME) through appropriate risk minimization plans and activities should be developed.

Minimal Information Model (MIM) for reporting safety incidents in health care

MIM is an inter-department initiative within WHO. The aim is to understand common information needed to capture patient safety incidents with various healthcare interventions: blood transfusion, herbal medicines, injections, in-vitro diagnostics, medical devices, radiation, medicines, vaccines, etc. There are failures in learning from a patient safety incident. MIM goal is to capture minimal concepts and relationship from a report to elicit learning. The current draft of MIM data elements are: incident identification (patient, age, time and location), type, outcomes, resulting actions and the reporter. Next steps include an in-depth inventory of reporting systems and how they operate at a country level and understanding how the reporting systems lead to learning.

Initiatives for harmonizing PV practice

The African Medicines Regulatory Harmonization (AMRH) aims to improve medicines regulation, through harmonization agreements, including pharmacovigilance, and capacity building. Data sharing would improve regulatory decision-making in the region. However, there is a need to understand the objective of setting up an African PV database that parallels Eudravigilance and to see how best to fulfill any gap in the current WHO global PV database to better address the African PV data needs. Regional networks do fulfill a specific regional need because of common interests, but guidance is needed to explain the concept of good collaboration and how the existing global system could support the regional needs without investing in a parallel system.

The Asia-Pacific Economic Cooperation (APEC) comprises of 21 economies, and, primarily exists for trade facilitation to promote economic growth. Regulatory convergence is one of the end goals. At the November 2013 APEC activity in Korea for PV convergence, the WHO Program was acknowledged

as an important part of global PV. The role of WHO in defining the PV curriculum and defining a minimum set of E2B elements were raised as important issues. There is opportunity for PV to be an economic driver with public health influence. The APEC process helped move up China as a manufacturer of a prequalified vaccine for WHO. One of the major challenges is the variation in languages in the region. The International Conference of Drug Regulatory Authorities (ICDRA) is another platform where the issue of regional harmonization can be raised and resolved among regulators, reinforcing the role of WHO as a coordinator of the process.

CIOMS activity report

The Council for International Organizations of Medical Sciences (CIOMS) acts as a forum to bring regulators and industry together to complement WHO's work. CIOMS' facilitation of communication between the global stakeholders has increased the spread of scientific knowledge and access to new PV data of public concern, and increased preparedness when launching vaccines in new regions or countries. Within the new European Union (EU) PV legislation, the definition of the term Adverse Reaction includes Medication Error. The CIOMS work includes grouping system organ classification with events that lead to medication errors.

Signal detection

Over the years, the UMC has actively revised signal detection processes, refining it to detect duplicate reports, drug-drug interactions and signals specifc to paediatric population. The main goal has been to detect and understand the variety of conditions on the ground, to enable the safer use of medicines as well as to minimize and prevent problems with medicines. In cases where avoidable (preventable) ADRs keep recurring (and surfacing as reports), this may actually be a relevant signal and indicator of medicine misuse, or lack of knowledge of correct medicine utilization. The UMC have now started investigating for "evergreens", that is, known, preventable ADRs that continue to occur and get reported. In other words, a UMC research wing is focusing on "signals of preventable adverse drug reactions". In a wider sense, there is merit in analysing PV data to detect problems of poor quality medicines, medication errors, off-label use, irrational drug use, overuse of injections, overuse of antibiotics etc. from the global database. An ADR with an Anti-Tuberculosis (TB) medicine in Morocco was reported at a disproportionately higher rate than what has been reported in the international community. It is important to follow up known signals because the disproportionate statistics may relate to use, storage, handling, product quality etc.

Reporting ADR in preventive chemotherapy

The WHO Neglected Tropical Disease (NTD) programme is concerned with the quality and safety of medicines for the prevention of lymphatic filariasis (LF), onchocerciasis, trachoma, and schistosomiasis. Currently seasonal malaria chemoprophylaxis is also being added to the program. A WHO handbook on ADR management in preventive chemotherapy was published in 2011, but the implementation remains a challenge. A majority of products within the NTD campaigns are donated by industry and are administered by non-medical personnel in a non-medical setting. Industry is reluctant to take on the PV responsibilities. As a result, ADR reports are not collected or managed systematically or by qualified medical professionals within the national NTD programmes. A more systematic and comprehensive NTD treatment plan is clearly needed. The vaccine safety blueprint for introducing AEFI reporting within Immunization programmes is a good model to introduce and build capacity for PV of medicines within NTD programmes.

Training courses database

A global mapping of available training courses was carried out by WHO through a web-based survey to create a database of available training courses. The database includes information on objectives, key subjects, target audience, venue and duration. Quality assurance of courses through standard setting exists and the evaluation of courses and their impact is the next step in this initiative.

ATC DDD Toolkit

The ATC DDD Toolkit is intended to pool together various reference documents to support drug utilization research. When completed it will serve as a one-stop data source for all reference and guidance material that can support drug utilization research in countries with a view to improving quality of drug use. Results of surveys in EU and Pan-American countries show wide variation in the knowledge and use of ATC DDD protocols. The creation of the of ATC DDD toolkit was recommended at the 34th meeting of the International Working Group for Drug Statistics Methodology in Oslo, Oct

2013. ATC DDD can support pharmacoepidemiology and strengthen PV work. Once developed it will be hosted as part of the PV Toolkit managed by the WHO CC in Ghana.

EudraVigilance (EV)
EV is the European database of suspected adverse reactions reported with medicines authorised in the European Economic Area (EEA). It is managed by the European Medicines Agency (EMA) on behalf of the EU medicines regulatory network. EMA provides data services, makes aggregated data public, sends available cases to the company marketing the medicines, provides monitoring services to identify signals of new or changing safety issues. In line with new EU legislation on pharmacovigilance the EMA is currently working on the addition of the Uppsala Monitoring Centre (UMC), the WHO Collaborating Centre as a new stakeholder group, to be provided with individual case safety reports (ICSRs) originating from within the EEA in electronic format on a weekly basis. The benefits of these arrangements are that all EU case reports are delivered weekly to WHO according to the letter of the law. There are legal and technical conditions underpinning this exchange, in particular, compliance with EU data protection law and new functionalities for the EU national centres that will mean that the pharmaceutical industry needs to report to EudraVigilance only. Until those legal and technical requirements are met, EU national centres will continue to report directly to UMC.

Integrating PV within TB treatment programmes
The introduction of new drugs like bedaquiline into a regimen for adult patient with pulmonary multi drug resistant (MDR)-TB is subject to certain conditions. These are close monitoring, appropriate patient selection and informed consent, use according to set of clinical recommendations and having an active pharmacovigilance in place. Ensuring proper monitoring of effectiveness and safety is particularly important for new drugs, novel regimens and when drugs are used off-label, to prevent avoidable harms. A policy on delamanid use is forthcoming. Studies are ongoing on short regimen. There are projects which have started in Belarus on Cohort Event Monitoring (CEM) of Antiretroviral/Anti-TB drugs and of Linezolid in MDR-TB patients. WHO will assess the drug-safety profile of shorter regimens for MDR-TB in three countries in 2014-2015. PV for TB features prominently in a number of key TB publications, including the Global TB Report 2013, the forthcoming Companion handbook to the WHO guidelines on the programmatic management of drug-resistant TB, the bedaquiline guidance, the post-2015 WHO Global strategy for TB control and the International Standards for TB care.

A new AEFI causality assessment method
Application of the 6-category classification (very likely/certain; probable; possible; unlikely; unrelated; unclassifiable) that is currently used in the assessment of ADRs poses difficulties when applied to AEFI. The non-availability of a standardised methodology to arrive at a final conclusion; difficulty to differentiate between "probable", "possible" and "unlikely" categories; inter-observer disagreement; difficulty in classification of the strength of the relationship and language barriers that hindered standardization were identified as major challenges when applying the WHO ADR causality assessment to AEFI assessment.

According to the revised cause-specific categorization of AEFI by the Council for International Organizations of Medical Sciences (CIOMS) and WHO in 2012, there are 5 types of AEFI;
a. Vaccine product related reaction
b. Vaccine quality defect related reaction
c. Immunization error related reaction
d. Immunization anxiety related reaction
e. Coincidental event

In 2013, the WHO Global Advisory Committee on Vaccine Safety (GACVS) revised AEFI causality assessment methodology and developed a new tool that has a four step process; (i) Eligibility: to determine if the AEFI case satisfies the minimum criteria for causality assessment, (ii) Checklist: to systematically review the relevant and available information to address possible causal aspects of the AEFI, (iii) Algorithm: to obtain a trend to the causality with the information gathered in the checklist and (iv) Classification: to categorize the AEFI's association to the vaccine/vaccination on the basis of the trend determined in the algorithm. At the end of causality assessment, the event will be classified into 3 major categories viz.

- Consistent to immunization: this includes (vaccine product, vaccine quality defect, and Immunization error and immunization anxiety related-reactions)
- Inconsistent to immunization (coincidental events) and
- Indeterminate.

AEFI cases with inadequate information are deemed as unclassifiable. While classifying that the AEFI assessment method is not meant to replace the WHO causality assessment method currently used by countries to assess adverse reactions reported with drugs, a communique explaining the need for and use of the AEFI assessment method and worksheet should be sent from WHO to all countries.

Widening scope of PV

UMC has developed an algorithm for the detection of suspected SSFFC products through the analysis of clusters of suspected product inadequacies in Vigibase. The algorithm has been tested on existing datasets, as a retrospective validation of the method. During 2013-2014, a pilot study has been set up with six national centres to evaluate the algorithm in a more realistic setting. UMC will now perform a 'needs analysis', to determine the prerequisites that need to be in place for a country to be able to effectively detect SSFFC products through its pharmacovigilance system. The ultimate aim is to determine the role of pharmacovigilance networks as additional data sources to detect SSFFC products.

The WHO Expert Committee on Drug Dependence (ECDD) undertakes medical and scientific assessment of dependence producing medicines and their abuse liability. ECDD meets every 4 years and provides recommendations on the level of control of substances. The UMC is exploring the potential use of PV data to inform scheduling decisions. In 2014, upon request, the UMC provided the ECDD committee with pharmacovigilance data on tramadol and ketamine, for the committee to consider in its deliberations. WHO SAV will continue to explore additional ways to support the functions of other WHO Expert Committees with PV data.

Use of hydroxy-ethyl starch (HES) solutions

The EMA has recommended that HES may continue to be used in severe haemorrhage at the discretion of the treating physician, while its continued use in peri-operative setting be put to further research. HES is a polymer of polysaccharide amylopectin, used in hypovolemic conditions. Current information on usage show that 45% of resuscitation cases used HES. In 2008 to 2012, concerns on HES related adverse effects such as renal function in sepsis patients surfaced, prompting a risk-benefit assessment by EMA.

Based on available evidence, the EMA allowed the use of HES in severe haemorrhage at the discretion of the treating physician but contraindicated its use in sepsis and in critically ill patients. Furthermore, risk minimization measures such a limit on dose, limit on duration of use, monitoring renal function within 90 days of use, and asking industry to submit risk management plans to regulators were recommended. Call for more studies on use in peri-operative and trauma settings was made.

The evidence on HES is still evolving. However, in the meantime, and given its use outside Europe, WHO/SAV will develop an Information Note to Member States, to reinforce the conditions of use and safety measures to adopt when using HES. The Information Note will be communicated though the usual WHO communication means such as Drug Alerts, the WHO Pharmaceuticals Newsletter and the WHO Drug Information.

Thalidomide Embryopathy (TE)

A report from a consensus meeting organized by the UK Thalidomide Trust for establishing the criteria and decision tree for diagnosing Thalidomide Embryopathy (TE), and current theories of causative mechanisms in TE formation was discussed. Knowledge about thalidomide has informed certain restrictions on its use to avoid harm in fetus. However, given the wide re-use of this medicine, current controls may not be comprehensive enough to cover the vulnerabilities within the entire supply / use chain. The mechanism for teratogenicity is not fully elucidated.

Although the Consensus meeting was an initiative to develop criteria for TE diagnosis, ACSoMP endorsed the (TE) meeting report and acknowledged that the approach (methods) could be recognized for its utility for a wider capture of pregnancy-drug exposure data. WHO wishes to develop the principles for diagnosing embryopathies due to any medicine and to elucidate the mechanisms. This will complement the WHO work on setting up pregnancy registers to follow effects on children born to mothers who were exposed to medicines during pregnancy.