Signal

Everolimus and osteonecrosis of the jaw (ONJ)

Anna Hegerius, Uppsala Monitoring Centre

Summary

Osteonecrosis of the jaw (ONJ) is a rare but potentially serious and painful condition, originally associated with the use of bisphosphonates. In recent years ONJ has been linked to several other drugs, including the mTOR inhibitor everolimus, used to treat advanced malignancies and to prevent transplant rejection. During a UMC signal detection sprint, held in December 2018, the MedDRA preferred term 'osteonecrosis of jaw' was highlighted for the drug everolimus in VigiBase, the WHO global database of individual case safety reports (ICSRs). As of 3 February 2020, there were 117 reports for this drug–adverse drug reaction (ADR) combination in VigiBase.

ONJ is not labelled for everolimus, but related terms such as stomatitis, jaw pain, oral pain, impaired wound healing and mucositis are. Among the cases in VigiBase and the scientific literature, the vast majority concern patients with concurrent or past therapy with drugs known (or suspected) to cause ONJ, which makes it difficult to identify the offending drug. However, there are a few case reports where neither drugs nor risk factors associated with ONJ were involved, implicating everolimus as an independent cause of ONJ. In 15 of the VigiBase cases, the reaction abated when the drug was withdrawn.

The exact pathophysiology of ONJ remains unclear, but several theories have been proposed and the mechanism is likely multi-factorial. Factors that may cause ONJ are: bone remodelling (osteoclast) inhibition, bone infection/inflammation, angiogenesis inhibition, soft tissue toxicity, and immunity dysfunction. Considering the mechanism of action of everolimus, it is reasonable to assume that it may be involved in the development of ONJ.

Based on current data, the risk of ONJ due to everolimus treatment alone seems very low. However, combined with other drugs with a potential to cause ONJ and risk factors such as diabetes or dental surgery, everolimus may act as a trigger. Further studies in this area are required considering the increasing population of patients at risk of ONJ and the adverse impact on the quality of life for those affected.

Introduction

The antineoplastic agent everolimus is indicated for the treatment of various cancers (breast, pancreatic, gastrointestinal, lung, and renal) and is also used as an immunosuppressant to prevent transplant rejection. In breast cancer treatment, everolimus is combined with the aromatase inhibitor exemestane. Everolimus inhibits the activity of mammalian target of rapamycin (mTOR), a serine-threonine kinase involved in cell growth and metabolism, resulting in a decrease of both hypoxia-inducible factors and vascular endothelial growth factor (VEGF) levels, which reduces tumour growth and angiogenesis. Furthermore, the mTOR and VEGF pathways play a key role in regulating bone homeostasis and immune responses.[1, 2] Everolimus and temsirolimus (the other drug in the same class) are derivatives of sirolimus.

Osteonecrosis of the jaw (ONJ) is characterised as oral lesions of exposed necrotic bone that persist for at least eight weeks, with no previous history of radiation or metastasis to the area. This oral condition is rare but potentially serious and very painful. A number of drugs are known to cause ONJ but it can also occur spontaneously.[3] The condition was first described in 2003, in a case report including 36 patients who had been treated with two different bisphosphonates,[4] and was later determined to be a drug class effect. In the following years, other drugs were also associated with the development of ONJ, such as the monoclonal antibodies denosumab and bevacizumab and the tyrosine kinase inhibitor sunitinib. More recently the mTOR inhibitor everolimus has also been implicated as a risk factor for ONJ.[5] Hence the term 'Medication Related Osteonecrosis of the Jaw' (MRONJ) was established in 2009 by the American Association of Oral and Maxillofacial Surgeons (AAOMS).[3] In addition to the use of antiresorptive and antiangiogenic agents, several other risk factors for ONJ have been identified. These include dental surgery (e.g. tooth extraction), poor oral health, diabetes, smoking, and concomitant use of steroids.[6, 7]

The combination of antiangiogenics and antiresorptives is known to increase the risk of ONJ development,[8, 9] but little is known about the risk of developing ONJ with antiangiogenics alone.

Reports in VigiBase

During a UMC signal detection sprint held in December 2018, the MedDRA preferred term 'osteonecrosis of jaw' was highlighted for the drug everolimus in VigiBase, the WHO global database of individual case safety reports (ICSRs).

As of 3 February 2020, there were 117 reports for this drug–adverse drug reaction (ADR) combination in VigiBase. Based on the overall reporting of adverse reactions for everolimus, and of the adverse reaction ONJ in VigiBase, the expected value for the number of reports on the combination was 35, and the association was highlighted as disproportionally reported, by IC analysis[10].

The reports came from 15 countries across four continents: Europe (76 reports), the Americas (16), Asia (23), and Australia (1). More female than male patients were affected (75% women), since the most common indication for everolimus in the case series was breast cancer, and the age range was 29-82 years, with a median of 64 years. Physicians and other health professionals accounted for 95% of the reports and the rest were submitted by pharmacists and consumers/non-health professionals. More than 90% of the cases were serious, including six fatalities (5%), but all were not caused by the ONJ.

In 18 cases, everolimus was the only reported drug, and in 26 cases it was the only suspected drug. The most frequently co-reported drugs were exemestane (54 cases), zoledronic acid (54), denosumab (38), capecitabine (11) and fulvestrant (11). Zoledronic acid and denosumab are both known to cause ONJ. Exemestane is a potent oestrogen lowering agent, and a reduction in bone mineral density and an increased fracture rate has been observed. Fulvestrant is an oestrogen receptor antagonist and may also cause osteoporosis, but there is no long-term data on the effects on bone. Most co-reported reactions were malignant neoplasm progression (13 cases), stomatitis (12), fatigue (11), pain (10) and metastasis to bone (9). Stomatitis and metastasis to the bone (if located in the jaw) may have contributed to the ONJ.

The vast majority of the patients were administered everolimus due to breast cancer (73 cases) or renal

Table 1. Characteristics of a selection of case reports in VigiBase of everolimus in association with osteonecrosis of jaw (ONJ)

Case	Reporter	Age/Sex	Suspected (S) or concomitant (C) drugs	Reactions (WHO-ART preferred terms)	Time to onset	Action taken
1	Other health professional	76/F	Everolimus (S) Exemestane (C)	Osteonecrosis of jaw	5 weeks	Drug withdrawn, recovering
2	Other health professional	61/F	Everolimus (S)	Osteonecrosis of jaw, aphthous ulcer, oropharyngeal pain, dysphagia, furuncle, hepatotoxicity etc.	9 days	Dose not changed, not recovered
3	Physician	55/F	Everolimus (S) Exemestane (C) Pantoprazole (C) Prednisone (C) Tramadol (C) Colecalciferol (C)	Osteonecrosis of jaw	7 weeks*	Drug withdrawn, recovering
4	Physician	75/F	Everolimus (S) Exemestane (S) Capecitabine (S) Cyclophophamide (S) Fulvestrant (S)	Osteonecrosis of jaw	Unknown	Drug withdrawn, recovering Rechallenge, outcome unknown
5	Other health professional	75/F	Everolimus (S)	Osteonecrosis of jaw, stomatitis	Unknown	Drug withdrawn, outcome unknown for everolimus, recovered for stomatitis

**The patient was treated with the drug for 19 days, halted treatment for a month due to a tooth extraction, and then resumed treatment for only two days before the ONJ occurred and the drug was withdrawn.*

cancer (28 cases), and the dose varied between 5 and 20 mg per day, with 10 mg being the most common daily dose. Most cases had a reasonable time to onset, with a median of 31 weeks, which is shorter than the median time to onset for bisphosphonate-related ONJ (108 weeks) but longer than the median time to onset for non-antiresorptive medications (20 weeks).[11, 12] In 15 cases the reaction abated when the drug was withdrawn.

Since several other drugs are known to cause ONJ, all cases with drugs that have ONJ labelled were excluded from the case series. This resulted in 27 remaining cases, but some of them could also be excluded since the narratives revealed that the patients had taken other ONJ-causing drugs. Some cases had a medical history that may have contributed to the development of ONJ, e.g. stomatitis, dental issues or bone metastasis.

A selection of reports is presented in Table 1. Case 1 concerns a female patient with metastatic breast cancer who developed ONJ five weeks after initiating everolimus (and exemestane) treatment. Both drugs were withdrawn and the patient was recovering when the report was sent. According to a later publication of this case, the patient had no relevant past dental history and metastasis was ruled out. The patient was treated with cephalosporin for two weeks and after two months her condition had improved.[13]

In case 2, a female patient received everolimus for advanced breast cancer and after nine days experienced a range of adverse reactions including aphthae, throat pain and difficulty swallowing. She was also diagnosed with ONJ and had no relevant medical history or concomitant medication. Everolimus treatment was continued and most of the adverse reactions persisted, except for the aphthae

which resolved after laser therapy. The time to onset was very short in this case, but not implausible.[12] The reporter assessed the events as suspected to be related to the drug.

Case 3 describes a female patient with metastatic breast cancer who received everolimus for 19 days and then stopped the drug for one month due to a tooth extraction. The treatment was then resumed but again stopped after only two days due to ONJ onset. The reporter suspected the drug to have caused the adverse reaction since the patient had recovered substantially two weeks after drug withdrawal. However, tooth extraction is also a trigger event for ONJ.

Case 4 concerns a female patient with recurrent breast cancer, treated with everolimus and a few other drugs (see Table 1) who developed ONJ. The time to onset is unknown but the patient was recovering after the drug had been withdrawn. The patient had no related medical history nor past drug therapy.

Case 5 presents a female patient of unknown age who developed ONJ during treatment with everolimus for advanced breast cancer. The time to onset is unknown, but the drug was withdrawn and the stomatitis resolved; the outcome of the ONJ was unknown.

Literature and Labelling

ONJ is not labelled for everolimus (or temsirolimus) in the most recent Summary of Product Characteristics (SPC) in the United Kingdom but related terms such as stomatitis, jaw pain, oral pain, impaired wound healing and mucositis are.[14] ONJ has not been observed in clinical trials, but gingival swelling and jaw pain have been.[6] Osteonecrosis is labelled for sirolimus, and since everolimus mimics sirolimus, it is reasonable to assume that it might have a similar effect.

In addition to the cases in VigiBase, there are several case reports in the literature where everolimus is suspected of causing or contributing to ONJ. However, in some of these cases, it is difficult to establish a causal link since the patient had also taken other drugs known to cause ONJ, for example bisphosphonates.[15-17] Even though many years may have passed since a patient was administered a bisphosphonate, these drugs accumulate in bone and the effect may last more than 10 years,[18] which makes it reasonable to assume that previous intake of these drugs may still be relevant for the development of ONJ.

However, in addition to case 1 above, there are a few other published case reports where bisphosphonates or monoclonal antibodies were not involved, implicating everolimus as an independent cause of ONJ. One case concerns a female breast cancer patient with no medical history of radiation, and metastasis to the mandible was ruled out. The patient had a tooth extracted four months prior to the ONJ diagnosis, which may have contributed to the onset.[19] Another case describes a male patient who had taken everolimus for 1.5 years (after a kidney transplant) when he was diagnosed with ONJ. He had no recent dental trauma, but he had taken steroids, which may also have contributed to the adverse reaction.[20]

There are also case reports where the other mTOR inhibitor temsirolimus has been combined with denosumab or bevacizumab, resulting in ONJ, and the authors describe a potential synergistic effect.[21, 22]

Furthermore, US FDA reviewed all ONJ cases in FAERS on the drugs suspected to cause ONJ. This study was the first to show that the mTOR inhibitors everolimus and temsirolimus were also associated with the risk for ONJ, with 84 and 28 cases respectively. However, compared to other drugs, the risk of mTOR induced ONJ was low (<5%).[23]

The exact pathophysiology of ONJ has still not been fully understood but several theories have been proposed and the mechanism is likely to be multi-factorial. Factors that may cause ONJ are: bone remodelling (osteoclast) inhibition, bone infection/ inflammation, angiogenesis inhibition, soft tissue toxicity, and immunity dysfunction.[24] In relation to everolimus, pre-clinical studies have shown that inhibition of mTOR decreases the maturation of osteoclasts and increases their apoptosis, which may explain how osteonecrosis may occur.[1] Furthermore, when VEGF activity is inhibited, the healing of bone is impaired[6]. The immunosuppression caused by everolimus explains the impaired wound healing and the infection susceptibility of treated patients. However, although infection and inflammation are often present when ONJ is diagnosed, it has not been established whether infection precedes or follows necrosis.[25]

The wide range of time to onset of ONJ can be explained by several factors, for example the potency, route of administration, and cumulative dose of the drug used.[26] One study showed that ONJ caused by non-antiresorptive medications had an earlier time to onset, a higher proportion of cases lacking a trigger event, and greater likelihood of healing and shorter healing time, compared to ONJ caused by bone targeting agents, and the diagnosis of ONJ is often delayed.[12] There is a risk of underdiagnosis of ONJ due to lack of awareness, strict diagnostic criteria, and the fact that early signs and symptoms of the condition are similar to the clinical presentation of stomatitis, which is a very common side effect of everolimus and most other drugs that may also cause ONJ.[6] This means that there is probably under-reporting of ONJ; one study concluded that the occurrence of ONJ in renal cancer patients receiving bisphosphonates and targeted agents might be underestimated.[8]

Discussion and Conclusion

Among the cases in VigiBase, the vast majority concerned patients with concurrent or past therapy with drugs known (or suspected) to cause ONJ, which makes it difficult to identify the offending drug. Furthermore, exemestane and fulvestrant (often co-administered with everolimus), may also play a part in the development of ONJ considering their mechanism of action. Some patients also had potential risk factors such as diabetes and tooth extractions. There are a few case reports of ONJ in patients who neither taken other suspected drugs nor had any known risk factors. Based on current data, the risk of ONJ due to everolimus treatment alone, seems very low. However, combined with other drugs with the potential to cause ONJ and risk factors such as diabetes or dental surgery, everolimus may act as a trigger. Although it is impossible to conclude what role everolimus played in each reported case, VigiBase data and published case reports still point to a potential causal association where the drug may at least have contributed to the development of ONJ. Further studies in this area are required considering the increasing population of patients at risk of ONJ, the seriousness of this condition, and the adverse impact on the quality of life for those affected. Close collaboration between medical doctors and dentists, as well as information to patients at risk, are important aspects for the prevention, prompt recognition and treatment of ONJ.[27]

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NOVARTIS

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Response to WHO

Everolimus (Osteonecrosis of the Jaw)

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Table of contents

Table of contents 2
List of tables 3
1 Introduction 4
2 Novartis response 4
2.1 Everolimus indicated for Oncology and TSC 4
2.1.1 Methodology 4
2.2 Everolimus indicated for prophylaxis of rejection of transplanted organs 6
2.2.1 Methodology 6
3 References (available on request) 7

List of tables

Table 2-1 Case reports of ONJ 5
Table 2-2 Measure of disproportionality 5
Table 2-3 Measure of disproportionality 6
Table 2-4 Case reports of ONJ 6

1 Introduction

On 26 March 2020, Novartis received a request to provide comments on osteonecrosis of the jaw (ONJ) in association with everolimus. Everolimus is marketed by Novartis for three broad indications (Oncology, Tuberous Sclerosis complex (TSC) and Transplant) under brand names Afinitor, Votubia and Certican/Zortress, respectively.

2 Novartis response

2.1 Everolimus indicated for Oncology and TSC

Novartis has been monitoring and providing analysis of ONJ as part of periodic safety update reports (PSURs) in both TSC (since 2014) and oncology indications (since 2017). The Pharmacovigilance Risk Assessment Committee (PRAC) in its most recent assessment report (EMEA/H/C/PSUSA/00010268/201703) concurred with Novartis analysis (cut-off date 31 March 2019) that there is no conclusive evidence of causal association between ONJ and everolimus in oncology and TSC settings and concluded that there was no sufficient data to warrant an update of the SmPC for ONJ. The PRAC requested Novartis to continue monitoring ONJ and present updated analysis in the next PSUR.

2.1.1 Methodology

Novartis is presenting the results of the evaluation of ONJ cases received since the cut-off date of the last PSUR.

2.1.1.1 Novartis global safety database

Between 31 Mar 2019 and 31 March 2020, eight cases were retrieved (seven cases of ONJ and one case of necrosis) using the same MedDRA search strategy with PTs *Chondronecrosis, Necrosis, Osteonecrosis* and *Osteonecrosis of jaw* to the PSURs. All cases were reported in oncology indications.

Noteworthy case definition: Well-documented cases with a HCP-confirmed diagnosis of ONJ with no alternative explanation (concomitant drugs, risk/predisposing factors).

The cases retrieved are presented in Table 2-1 below

Table 2-1 Case reports of ONJ

Case	Reporter	Age /sex	Suspected drugs	Dose	Action taken	PT	TTO (days)
1	non-HCP/SR	65/M	Everolimus Mycophenolate Mofetil, Prednisolone	UKN	UKN	Osteonecrosis of jaw	NR
2	HCP/SR	67/F	Afinitor	UKN	Treatment Discontinued	Osteonecrosis of jaw	44
3	HCP/PMS	35/F	Everolimus, Zoledronic Acid	UKN	Treatment Discontinued	Osteonecrosis of jaw	394
4	HCP/Lit	67/F	Paclitaxel, Carboplatin, Zoledronic Acid Everolimus	2.5 mg	UKN	Osteonecrosis of jaw	NR
5	HCP/PMS	52/M	Everolimus Lenvatinib	5 mg	NR	Necrosis	NR
6	HCP/PMS	64/M	Pazopanib Nivolumab Lenvatinib Zoledronic Acid Everolimus	10mg , 5 mg	Treatment Discontinued	Osteonecrosis of jaw	1669
7	HCP/Lit	46/F	Zoledronic Acid Everolimus, Exemestane	UKN	NR	Osteonecrosis of jaw	455
8	non-HCP/SR	60/F	Everolimus Lenvatinib	5mg	NR	Osteonecrosis of jaw	NR

HCP= Health Care Professional; Lit= Literature, SR=Spontaneous Report, PMS= Post marketing surveillance, PT=Preferred Term, NR=Not reported, UNK= unknown; TTO=Time to onset

Of the eight cases, two were non-HCP and one was necrosis of unknown location. Four cases were confounded by use of bisphosphonates. Anti-angiogenic agent lenvatinib was a co-suspected medication in three cases. Furthermore the cases lacked sufficient information for a meaningful medical assessment. None of the eight cases met noteworthy criteria and hence a causal role could not be established. The review of the new cases is consistent with the conclusion presented in previous PSURs. Novartis will continue to monitor ONJ cases in subsequent PSURs.

2.1.1.2 Empirica Signal

Table 2-2 Measure of disproportionality

Drug	Event	SOC	SP+Lit+POP Total N	SP+Lit+POP EB05
Afinitor	Osteonecrosis of jaw	Musculoskeletal and connective tissue disorders	104	0.617
Votubia	Osteonecrosis of jaw	Musculoskeletal and connective tissue disorders	2	0.146
Afinitor	Osteonecrosis	Musculoskeletal and connective tissue disorders	20	0.617

Drug	Event	SOC	SP+Lit+POP Total N	SP+Lit+POP EB05
Votubia	Osteonecrosis	Musculoskeletal and connective tissue disorders	1	0.11

*SOC=System Organ Class, SP: Lit: POP=Spontaneous: Literature: Patient Oriented Program, EB05= The EB05 is the lower bound of the 90% confidence interval for the EBGM (Empiric Bayes Geometric Mean)

The EB05 (lower bound of the 90% confidence interval for the EBGM (Empiric Bayes Geometric Mean) score was less than one.

2.2 Everolimus indicated for prophylaxis of rejection of transplanted organs

2.2.1 Methodology

In order to assess the association between ONJ and everolimus, Empirica Signal and Novartis Global Safety Database search for ONJ was performed, with a cut-off date of 31 Mar 2020, in transplant patients treated with everolimus by using the MedDRA version 22.1 with the PT *Osteonecrosis of jaw*.

2.2.1.1 Empirica Signal

Table 2-3 Measure of disproportionality

Drug	Event	SOC	SP+Lit+POP Total N	SP+Lit+POP EB05
Certican	Osteonecrosis of jaw	Musculoskeletal and connective tissue disorders	3	0.06

SOC=System Organ Class, SP=Spontaneous: LT=Literature: POP=Patient Oriented Program, EB05=lower bound of the 90% confidence interval for the EBGM (Empiric Bayes Geometric Mean)

2.2.1.2 Novartis Global Safety Database

The search retrieved three LT cases for ONJ. No clinical trial or spontaneous reporting cases were retrieved.

Table 2-4 Case reports of ONJ

Case	Reporter	Age/Sex	Suspected drugs	Dose	Action taken	PT	TTO
1	HCP	69/M	Everolimus	NR	NA	PTLD	NR
			Prednisolone	NR	Unknown	Epstein-Barr virus infection	NR
			Rituximab	NR	Unknown		4 month
			Methylprednisolone	NR	NA	Osteonecrosis of jaw	NR
						Kidney transplant rejection	
2	HCP	65/M	Everolimus	10 mg BD	TD	Osteonecrosis of jaw	18 month
			Prednisolone			Pain in jaw	
				10 mg OD	ongoing	Exposed bone in jaw	18 month
							18 month

Case	Reporter	Age/Sex	Suspected drugs	Dose	Action taken	PT	TTO
3	HCP	65/M	Everolimus	1mg BD and 0.75 mg BD	TD	Osteonecrosis of jaw	NR
						Pain	NR
						Hypophagia	NR
						Weight decreased	NR
			Prednisolone	NR	Unknown	Resorption bone increased	NR
						Sinus perforation	NR
						Oroantral fistula	NR

NR=Not reported, NA=Not applicable, TD=treatment discontinued, PTLD=Post-transplant lymphoproliferative disorders, TTO=Time to onset

In above indicated cases, there is limited information regarding TTO, as well as alternative explanations such as concomitant suspected drugs and/or risk factors (prednisolone in all three cases, rituximab in the first case (1), teeth extractions history in the second case (2), and history of teeth extractions and parathyroidectomy in the third case (3)), therefore, a causal association could not be established.

Up to date, there is no confirmed clinical evidence of an effect of ONJ with everolimus (indicated for prophylaxis of rejection of transplanted organs) alone.

Discussion and Conclusion

Everolimus has been marketed for more than 10 years worldwide. The cumulative post-marketing patient exposure in oncology setting is over 208,393 PTY, in TSC is over 23,522 PTY and in Transplant setting is over 638,081 PTY. Based on analysis of years of clinical and post-marketing data a causal association of everolimus to the event of ONJ could not be established.

3 References (available on request)

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SIGNAL

WHO defines a signal as:

"Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously". An additional note states: "Usually more than one report is required to generate a signal, depending on the seriousness of the event and the quality of the information".*

A signal is therefore a hypothesis together with supporting data and arguments. A signal is not only uncertain but also preliminary in nature: the situation may change substantially over time one way or another as more information is gathered. A signal may also provide further documentation of a known association of a drug with an ADR, for example: information on the range of severity of the reaction; the outcome; postulating a mechanism; indicating an "at risk" group; a dose range which might be more suspect; or suggesting a pharmaceutical group effect or a lack of such an effect by a particular drug.

Signals communicated by UMC are derived from VigiBase, the WHO global database of individual case safety reports. This database contains summaries of individual case safety reports of suspected adverse drug reactions, submitted by national pharmacovigilance centres (NCs) that are members of the WHO Programme for International Drug Monitoring. More information regarding the status of this data, its limitations and proper use, is provided in the Caveat on the last page of this document.

VigiBase is periodically screened to identify drug-ADR combinations that are unknown or incompletely documented. Combinations of such interest that they should be further reviewed clinically are sent to members of the Signal Review Panel for in-depth assessment. The Signal Review Panel consists of experienced international scientists and clinicians, usually affiliated with a governmental or an academic institution. The expert investigates the clinical evidence for the reaction being related to the suspected drug.

The topics discussed in the signals represent varying levels of suspicion. Signals contains hypotheses, primarily intended as information for the national regulatory authorities. They may consider the need for possible action, such as further evaluation of source data, or conducting a study for testing a hypothesis.

The distribution of signals is currently restricted to NCs, regulatory authority staff and their advisers, participating in the WHO Programme. Signals are sent to the pharmaceutical companies when they can be identified as uniquely responsible for the drug concerned. UMC does not take responsibility for contacting all market authorisation holders. As a step towards increased transparency, since 2012 UMC signals are subsequently published in the WHO Pharmaceuticals Newsletter.

National regulatory authorities and NCs are responsible for deciding on action in their countries, including communicating the information to health professionals, and the responsible market authorisation holders, within their jurisdiction.

In order to further debate, we encourage all readers of signals to comment on individual topics.

* Edwards I.R, Biriell C. Harmonisation in pharmacovigilance. Drug Safety 1994;10:93-102.

Responses from industry

Signals on products under patent are submitted to patent holders for comments. Responses from industry are unedited. The calculations, analysis and conclusions are theirs, and should be given serious but critical consideration in the same way as any scientific document. The WHO and UMC are not responsible for their findings, but may occasionally comment on them.

WHO Collaborating Centre for International Drug Monitoring
Box 1051, S-751 40, Uppsala, Sweden
Tel: +46 18 65 60 60 www.who-umc.org

Uppsala Monitoring Centre

Caveat Document

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

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

Tentative and variable nature of the data

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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