Tocilizumab and Pancreatitis

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Summary

Tocilizumab (TCZ) is a humanised monoclonal antibody against interleukin-6 (IL-6) and is indicated in the treatment of rheumatoid arthritis (RA) as well as some other forms of arthritis. TCZ has also been approved for chimeric antigen receptor T-cell therapy induced cytokine release syndrome and has been used recently in the treatment of patients with severe COVID-19 infection. A recent analysis by the UMC of the WHO global database of ICSRs, VigiBase, focused on drugs used in COVID-19 patients. As of 29 November 2020, the UMC analysis identified five individual case safety reports (ICSRs) in VigiBase which reported pancreatitis or pancreatitis acute with the use of TCZ for COVID-19. There are 202 reports (189 de-duplicated) for the combination, regardless of indication, and in respect of the 189 de-duplicated cases the IC is 0.6 and the IC_{025} is 0.4, which indicates a disproportionate association. An analysis of the 189 cases was considered impractical so it was restricted to those 41 cases with more complete information. These reports were from Belgium, Croatia, Denmark, France, Germany, Greece, Japan, Spain, and the United Kingdom.

TCZ appears to be a likely cause as it was the only suspected drug in 31 of the 41 reports. With 25 cases which occurred from one week to ten months, the time to onset is consistent with other well recognised drug causes of pancreatitis. Patients were reported as recovered or recovering in 32 of the 41 cases, not recovered in eight cases, and there was a fatal outcome in the remaining case. In the 32 cases where recovery was reported, TCZ was withdrawn in 25 cases. Recovery after withdrawal is consistent with an effect of the drug. There are also reports of the association in the literature.

Introduction

Tocilizumab (TCZ) is a humanised monoclonal antibody against interleukin-6 (IL-6) and is indicated for the treatment of rheumatoid arthritis (RA) as well as some other forms of arthritis.[1] TCZ has also been approved for chimeric antigen receptor T-cell therapy induced cytokine release syndrome and has been used recently in the treatment of patients with severe COVID-19 infection. The most reported adverse reactions include upper respiratory tract infections, nasopharyngitis, headache, hypertension, and increased liver function tests. More serious adverse reactions include serious infections, complications of diverticulitis, and hypersensitivity reactions.

Acute pancreatitis is an inflammatory disease of the pancreas, characterized by abdominal pain, frequently severe and of sudden onset, and is almost always accompanied by increased pancreatic enzymes in the blood and urine. Although in about 80% of cases the disease is mild to moderate, severe pancreatitis has a mortality rate of 20%. Drug-induced pancreatitis is usually an acute condition.[2,3]

Gallstones are the leading cause of acute pancreatitis (21-33%) with alcohol as the next most common cause (16-27%). Other common causes include hypertriglyceridaemia, hypercalcemia, familial (hereditary) pancreatitis, and viral infections.[4] Approximately 0.1-5% of cases of acute pancreatitis are drug-related.[2,4] More than 500 medications have been implicated as a cause of acute pancreatitis and many of them have been shown to have a definite association.[4] Responsible drugs include azathioprine, 6-mercaptopurine, oestrogens, tetracycline, valproic acid, sulindac, ACE inhibitors, HMG-CoA reductase inhibitors (statins), isoniazid and anti-HIV medications.[3,4]

Reports from VigiBase

A recent analysis by the UMC focused on drugs used in COVID-19 patients. It has been suggested that severe COVID-19 infection is associated with a cytokine storm and pulmonary inflammation secondary to a dysregulated host immune response. As TCZ is indicated for clinical management of cytokine release syndrome, it may be useful to ameliorate the intense inflammatory manifestations associated with severe COVID-19 infection. There were many publications in 2020 which described studies on the use of TCZ in COVID-19 patients, and although the results have been mixed, a recent publication has demonstrated that TCZ reduced the likelihood of progression to the composite outcome of mechanical ventilation or death, but it did not improve survival.[5] As of 29 November 2020, the UMC analysis identified five individual case safety reports (ICSRs) which reported pancreatitis or pancreatitis acute with TCZ for the indications 'COVID-19' or 'Corona virus infection' in the WHO global database of ICSRs, VigiBase. There are 202 reports (189 de-duplicated) for the combination regardless of indication.

With respect to the 189 de-duplicated cases regardless of indication, the Information Component (IC) is 0.6 (189 observed, 125 expected) and the IC_{025} is 0.4 which indicates a disproportionate association. In 148 of these cases, TCZ is the only suspected drug. An analysis of the 189 cases was considered impractical so it was restricted to those cases with more complete information and only those cases with age and gender, start date and action taken with TCZ, date of onset and recovery information were considered. These cases are shown in Table 1.

There were 41 such cases submitted by France (18 cases), Spain and the United Kingdom (both 5), Japan (4), Germany (3), Croatia and Greece (both 2), and Belgium and Denmark (both 1). There was one additional case from Switzerland involving a 30-year-old male which met the criteria, but use of TCZ occurred after onset of the reaction and it was not considered. A majority of the patients were female (26), which is not surprising as the most common indication was RA, a disease which has a predominance of female patients. Ages ranged from 5 to 83 years, with a median age of 54.5 years which is relatively young.

TCZ was the only suspected drug in 31 of the 41 cases. In the remaining ten, there were multiple suspected drugs, but the only other drugs suspected more than once were the closely related corticosteroids, prednisone, prednisolone, and methylprednisolone (in 4 cases), and hydroxychloroquine (in 2 cases). Other commonly occurring concomitant drugs included corticosteroids (13 cases), drugs for the treatment of hypertension (11 cases), proton pump inhibitors and other drugs for the treatment of the gastrointestinal tract (9), methotrexate (8), drugs for the treatment of pain

(7), statins (6), and drugs for the treatment of diabetes (4) and osteoporosis (4). Corticosteroids and methotrexate are commonly used in association with TCZ and the other concomitant drugs were generally reflective of other underlying conditions which accompany the condition for which TCZ was prescribed, particularly RA. In fact, RA was the indication in 28 of the 41 reports. There were a variety of indications in the other 13 reports with Horton's disease, Takayasu's disease, polymyalgia rheumatica, and COVID-19 all being implicated in two reports. Dosages varied greatly depending on the indication and the condition of the patient. The most common dosage (10 patients) was 162-167 mg per week; 400-720 mg per month was reported in seven patients, and 560-800 mg over an unknown period was reported in seven patients.

Time to onset varied significantly from one day to eight years, with a median of five months. Nine cases occurred within a month and nine cases occurred from two to eight years, while almost half the cases (18) had an onset from one to eight months.

Patients were reported as recovered or recovering in 32 of the 41 cases, not recovered in eight cases, and there was a fatal outcome in the remaining case. Two of those patients who recovered were reported as recovered with sequelae but there was no information on the nature of these sequelae. In the 32 cases where recovery was reported, TCZ was withdrawn in 25 cases, continued in three cases, and reported as "not applicable" in the remaining four cases. In the 25 cases in which TCZ was withdrawn, it was the only drug reported in five cases, and the only drug reported withdrawn in 16 cases. In the remaining four cases, there were other drugs which were withdrawn but in three of these cases, they are not known to be associated with pancreatitis. In one case (Case 1), a medicine containing both an ACE inhibitor and a statin (which are possible causes of pancreatitis) was also withdrawn. Patients were reported as not recovered in eight cases. In these cases, TCZ was withdrawn in four cases, continued in three cases and the action with the drug was reported as "not applicable" in the remaining case. The other case had a fatal outcome.

Pancreatitis or acute pancreatitis was the only reaction reported in 28 of the 41 reports. In another four cases, there were additional reactions that related to pancreatitis such as abdominal pain (4 cases), amylase increased (2), and diarrhoea (2). In the remaining nine cases, there was a variety of other reactions but no obvious pattern to these reactions apart from some known to be associated with TCZ use, such as hypertriglyceridaemia (3 cases) and abnormal liver functions tests (3).

Labelling and literature

The product literature does not refer to pancreatitis.[1] It does, however, indicate that hypertriglyceridaemia is an uncommon reaction. As noted above, hypertriglyceridaemia is a possible cause of pancreatitis and three of the cases in this series refer to hypertriglyceridaemia as an additional adverse reaction.

There have, however, been several cases of pancreatitis in association with TCZ reported in the literature. Flaig and co-workers described a 40-year-old male who developed pancreatitis about two weeks after the second dose of TCZ for treatment of RA.[6] The authors ruled out other causes of pancreatitis, TCZ was withdrawn and the patient recovered. The authors also noted that there had been three previous reports of this association. Parekh and colleagues described a patient receiving TCZ for RA who developed acute necrotising pancreatitis, and in a paper on the REACTION study, Takeuchi and colleagues reported acute pancreatitis as an adverse event in one patient.[7,8] In the other case, a 60-year-old man with RA developed severe hepatitis after the use of TCZ for three months. At the same time, he was noted to have developed mild pancreatitis, characterised by elevated lipase levels.[9] Flaig and colleagues also reviewed the FAERS database in the United States and noted 74 pancreatic adverse events in association with TCZ including 52 cases of acute pancreatitis.[6] More recently, in response to the increased use of TCZ in COVID-19, the FAERS database was investigated for the occurrence of statistically significant reporting odds ratios (RORs) for hepatic reactions in association with TCZ.[10] Statistically significant RORs were found for the 61 cases of acute pancreatitis (ROR: 1.99, 95% CI 1.55-2.56) and for the 151 cases of pancreatitis (ROR: 1.65, 95% CI 1.41-1.94). In another recent review of TCZ in COVID-19, Morrison and coworkers reported two cases of acute hypertriglyceridaemia in association with TCZ, one of which had elevated levels of serum amylase.[11]

Discussion and Conclusion

A UMC analysis has identified 189 de-duplicated cases of pancreatitis or pancreatitis acute with TCZ regardless of indication, with an IC of 0.6 and an IC_{025} of 0.4 which indicates a disproportionate association. An analysis of the 189 cases was considered impractical so it was restricted to those cases with more complete information.

TCZ appears to be a likely cause as it was the only suspected drug in 31 of the 41 reports. In the remaining ten reports, there were multiple suspected drugs, but the only other drugs suspected more than once were the closely related corticosteroids, prednisone, prednisolone, and methylprednisolone (in four cases) and hydroxychloroquine (in two cases).

Time to onset varied significantly, from one day to eight years, with a median of five months. Nine cases occurred within a month and another nine occurred from two to eight years, while almost half the cases (18) had an onset of one to eight months. With 25 cases which occurred from one week to ten months, the time to onset is consistent with other well recognised drug causes of pancreatitis. A case control study with ACE inhibitors has shown that the highest risk was during the first six months of therapy while the time to onset with enalapril has been reported to be from five weeks to one year.[4] Two cases of rechallenge with angiotensin receptor antagonists occurred, initially from four days to three months, while pancreatitis rarely occurs within the first three months of treatment with statins.[4] Two cases of rechallenge with tetracycline occurred initially within four days to three months, while time to onset with isoniazid occurred between 11 and 21 days.[4] Onset with azathioprine and mercaptopurine occurred within the first few weeks.[4] It was interesting that the two cases in which TCZ was used for treatment of COVID-19, the time to onset was short at one and eight days, respectively. The time to onset in those other cases (with a lower level of information) in which TCZ was used to treat COVID-19, although unknown, must have also been relatively short due to the short time period from the date TCZ was first used for that indication to the date the most recent cases have been submitted. On the other hand, those cases with a longer time to onset would not have yet occurred so it is not possible to draw any conclusions on this point. There have also been case reports of acute pancreatitis in association with COVID-19, although strong evidence of causality is lacking. If both COVID-19 and TCZ were possible causes, the time to onset may be shortened.[12,13,14]

Patients were reported as recovered or recovering in 32 of the 41 cases, not recovered in eight cases and there was a fatal outcome in the remaining case. In the 32 cases where recovery was reported, TCZ was withdrawn in 25 cases, continued in three cases, and reported as "not applicable" in the remaining four cases. Recovery after withdrawal is consistent with an effect of the drug. When drugs such as TCZ are used periodically, the nature of drug withdrawal may not be straightforward and the reporting of "not applicable" for the action taken with the drug may reflect such difficulties in interpretation. In two of these four cases, the reaction appeared a few days after the completion of a course of TCZ, so the result is the same as if the drug was deliberately withdrawn. In another case, the reaction appeared and resolved in the period between two doses one month apart. The remaining case was difficult to interpret.

In the eight cases where patients were reported as not recovered, TCZ was withdrawn in four cases, continued in three cases and the action with the drug was given as "not applicable" in the remaining case. In one of the four cases in which TCZ was withdrawn, this was only done after a final dose was given a day after onset of pancreatitis so interpretation in this case is difficult. In another case, TCZ was continued on a weekly basis for another three months after the onset of pancreatitis and then for a further three months after a four-month period of no treatment. The remaining two cases describe a lack of recovery despite drug withdrawal. The remaining case where the action with the drug was "not applicable", was difficult to interpret.

The lack of recovery in the three cases in which the drug was continued is consistent with an effect of the drug. In one of the cases, however, the patient died five days after onset of pancreatitis. The cause of death appeared to be complications of COVID-19 disease. The remaining case also had a fatal outcome. The patient developed acute, necrotising pancreatitis three months after commencing TCZ and four weeks after it was withdrawn. The patient died three weeks later. The cause of death was not stated but necrotising pancreatitis has a relatively high rate of mortality and may have been the cause of death.

The product literature does not refer to pancreatitis but there have been several cases of pancreatitis in association with TCZ reported in the literature. The case report by Flaig and coworkers is well documented, with other causes of pancreatitis ruled out, recovery after TCZ withdrawal, and strongly suggests that TCZ is the cause of the pancreatitis.[6] Although not as well documented, the other four publications which describe pancreatitis or increased serum amylase levels in association with TCZ strengthen the proposition that TCZ is a possible cause of pancreatitis. This possibility is further strengthened by the disproportionate ROR of the association in the FDA database.[10]

In summary, there is a signal for the association of pancreatitis and acute pancreatitis in association with TCZ. There are a significant number of reports in VigiBase and those which are well documented have TCZ as the only suspected drug in 76% of the cases. Time to onset supports an association as does recovery after withdrawal. There are reports in the literature and both VigiBase and FAERS show a disproportionation in favour of the association.

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Table 1. Characteristics of selected reports in VigiBase of pancreatitis in association tocilizumab

Case	Age/ Gender	Other suspected (S) or concomitant (C) drugs	Reactions (MedDRA preferred terms)	Outcome	Action taken with drug	Time to onset
1	50/M	Atorvastatin/acetylsalicylic acid/ramipril (S), methotrexate (C)	Pancreatitis	Recovered	Withdrawn	7 m
2	57/F	None	Pancreatitis acute	Recovered	Continued	8 y
3	57/F	Rosuvastatin, sitagliptin (both S), metformin, glimepiride (both C)	Pancreatitis acute, asthenia, abdominal pain upper	Recovered	Not applicable	8 y
4	39/M	Prednisone, atorvastatin, hydrochlorothiazide (all S), clopidogrel, bisoprolol, acetylsalicylic acid, amlodipine/ perindopril, lansoprazole, spironolactone (all C)	Pancreatitis acute	Recovering	Withdrawn	5 m
5	69/F	None	Pancreatitis acute	Recovered	Withdrawn	2 d
6	58/M*	Hydroxychloroquine, ceftriaxone, azithromycin, methylprednisolone, lopinavir/ritonavir (all S)	Pancreatitis acute, hypertriglyceridaemia	Recovered	Withdrawn	7 d
7	21/F*	Hydroxychloroquine, linezolid, amphotericin b (all S)	Pancreatitis acute, acute kidney injury, hepatitis, hypocoagulable state	Not recovered	Continued	1 d
8	59/F	Methotrexate (C)	Pancreatitis	Recovered with sequelae	Withdrawn	9 m
9	53/F	None	Pancreatitis acute	Recovering	Withdrawn	2 m
10	79/F	Colecalciferol, tramadol, bisoprolol, trimebutine, atorvastatin, ramipril, paracetamol, acetylsalicylic acid (all C)	Pancreatitis acute	Recovered	Withdrawn	2 y
11	83/F	None	Pancreatitis	Not recovered	Withdrawn	18 d
12	73/F	Prednisone (S)	Pancreatitis acute	Recovering	Not applicable	2 m
13	66/F	Calcium/colecalciferol, potassium, teriparatide, paracetamol, morphine, metoprolol, promethazine, vancomycin, multivitamins, metoclopramide, prednisolone, minerals (all C)	Pancreatitis, abdominal pain, amylase increased, diarrhoea, weight decreased	Not recovered	Withdrawn	5 m
14	43/F	Methotrexate, leflunomide, etoricoxib, prednisone (all C)	Pancreatitis acute, cholelithiasis, hypercholesterolaemia, hypertriglyceridaemia, pneumonia	Not recovered	Withdrawn	6 w

***COVID-19 cases**

Case	Age/ Gender	Other suspected (S) or concomitant (C) drugs	Reactions (MedDRA preferred terms)	Outcome	Action taken with drug	Time to onset
15	47/F	Alprazolam, atorvastatin, bisoprolol, clopidogrel, pancreatin, valproic acid (all C)	Pancreatitis acute	Recovering	Withdrawn	3 y
16	49/F	Methotrexate, leflunomide, insulin (all C)	Pancreatitis, organising pneumonia	Recovered	Withdrawn	2 m
17	75/M	None	Pancreatitis, transaminases increased	Recovered	Withdrawn	2 m
18	44/F	Methotrexate, tacrolimus (both S)	Pancreatitis acute	Recovering	Continued	16 d
19	37/M	None	Pancreatitis	Not recovered	Continued	3 m
20	61/F	Acetylsalicylic acid, allopurinol, cortisone, insulin, insulin glargine, insulin lispro, methotrexate, omeprazole, torasemide (all C)	Pancreatitis, arthralgia, biliary obstruction, chills, back pain, drug ineffective, blood disorder, fatigue, intervertebral disc protrusion, liver function test abnormal, liver function test increased, musculoskeletal discomfort, pancreatic cyst, spondylolisthesis, stenosis, tendon rupture, white blood cell count increased	Not recovered	Withdrawn	16 m
21	5/M	Inotuzumab, tisagenlecleucel-T (both S)	Pancreatitis, acute lymphocytic leukaemia, blood bilirubin increased, blood fibrinogen decreased, lipase increased, lymphocyte count decreased, neutrophil count decreased, platelet count decreased, white blood cell count decreased	Not recovered	Not applicable	8 m
22	66/M	Indapamide, lansoprazole, sulfasalazine (all C)	Pancreatitis acute	Recovering	Not applicable	5 m
23	47/M	Prednisone (C)	Pancreatitis acute	Recovered	Withdrawn	4 y
24	59/F	Levothyroxine (C)	Pancreatitis, abdominal discomfort, diarrhoea, pustule	Recovered	Withdrawn	6 m
25	56/M	Prednisolone (S), acetylsalicylic acid, altizide/ spironolactone, anagrelide, levothyroxine, potassium, sotalol (all C)	Pancreatitis acute	Recovered	Withdrawn	16 d
26	41/M	Methotrexate (C)	Pancreatitis, hypertriglyceridaemia	Recovering	Withdrawn	3 w
27	28/F	Clopidogrel, lansoprazole, prednisone, rosuvastatin (all C)	Pancreatitis	Recovered	Not applicable	4 m
28	46/M	Brinzolamide, bisoprolol, latanoprost, prednisone (all C)	Pancreatitis acute	Not recovered	Continued	4 y

***COVID-19 cases**

Case	Age/ Gender	Other suspected (S) or concomitant (C) drugs	Reactions (MedDRA preferred terms)	Outcome	Action taken with drug	Time to onset
29	53/M	Leflunomide (S)	Pancreatitis acute	Recovered	Withdrawn	2 y
30	35/F	Folic acid, loxoprofen, methotrexate (all C)	Pancreatitis acute	Recovering	Withdrawn	17 m
31	49/F	None	Pancreatitis acute	Recovered	Withdrawn	13 m
32	67/F	None	Pancreatitis	Recovered	Withdrawn	5 w
33	35/F	Prednisolone (C)	Pancreatitis acute	Recovered	Continued	6 y
34	81/F	Amlodipine/atorvastatin, bucillamine, eldecalcitol, lansoprazole, minodronic acid, pilocarpine, prednisolone, sulfasalazine, tacrolimus (all C)	Pancreatitis acute	Recovering	Withdrawn	3 y
35	35/M	Azathioprine (C)	Pancreatitis acute, acute abdomen, amylase increased	Recovered	Withdrawn	3 m
36	71/F	Omeprazole, prednisolone, risedronic acid (all C)	Pancreatitis acute	Recovering	Withdrawn	11 m
37	28/M	Azathioprine, prednisolone (both C)	Pancreatitis, abdominal distension, abdominal pain, abdominal sepsis, abdominal tenderness, back pain, blood pressure decreased, body temperature increased, condition aggravated, heart rate increased, immunosuppression, oxygen saturation decreased, respiratory rate increased, splenic infarction, Takayasu's arteritis	Recovered with sequelae	Withdrawn	11 d
38	57/F	Deflazacort, oxandrolone (both C)	Pancreatitis	Recovered	Withdrawn	1 m
39	40/M	Metamizole, prednisolone, ramipril, calcium/ colecalciferol, omeprazole (all C)	Pancreatitis acute	Recovering	Withdrawn	6 w
40	73/F	Blinded methotrexate (S), alfacalcidol, amlodipine, clopidogrel, folic acid, hydroxychloroquine, ibandronic acid, metformin, sitagliptin, simvastatin, valsartan (all C)	Pancreatitis acute	Recovered	Withdrawn	14 m
41	62/F	Amlodipine, citalopram, iron, lisinopril, naproxen, omeprazole, simvastatin, tramadol (all C)	Pancreatitis acute, pancreatitis necrotising	Died	Withdrawn	3 m

***COVID-19 cases**

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.

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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.

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Caveat Document

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

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

Tentative and variable nature of the data

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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