Medicines Adverse Reactions Committee

Meeting date	9/03/2023	Agenda item	3.2.1
Title	**Interleukin inhibitors and the risk of pancreatitis**		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice

Active ingredient	**Product name**	**Sponsor**
Tocilizumab	Actemra	Roche Products (NZ) Ltd
Ustekinumab	Stelara	Janssen-Cilag (New Zealand) Ltd
Mepolizumab	Nucala	GlaxoSmithKline NZ Limited
Canakinumab	Ilaris	Novartis New Zealand Ltd
Secukinumab	Cosentyx	Novartis New Zealand Ltd
Siltuximab	Sylvant	Pharmacy Retailing (NZ) Ltd t/a Healthcare Logistics
Risankizumab	Skyrizi	AbbVie Limited
Benralizumab	Fasenra	AstraZeneca Limited
Basiliximab	Simulect	Novartis New Zealand Limited

PHARMAC funding	Refer to Table 2.
Previous MARC meetings	The topic of interleukin inhibitors and pancreatitis has not previously been reviewed by the MARC.
International action	Pancreatitis has been added to the interleukin inhibitor tocilizumab prescribing information in the United States of America (USA) and Australia. It is listed as a clinical trial adverse drug reaction in the Canada product information.
Prescriber Update	Medsafe have previously published articles relating to drug-induced pancreatitis: • Drug-Induced Pancreatitis: An Unlucky Dip (December 2005) • Acute pancreatitis – Sometimes triggered by Medicines (June 2019)
Classification	Prescription medicine
Usage data	Refer to Table 3.

Advice sought	**The Committee is asked to advise:**
	• Whether there is evidence for an association between pancreatitis and tocilizumab?
	  ○ If yes, are data sheet updates are required (for example, to align with recent updates requested by the TGA)?
	• Whether there is evidence for an association between pancreatitis and the IL inhibitor class.
	  ○ If yes, is further action required?
	• Does the topic require communication, other than MARC's remarks in *Prescriber Update?*

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1 PURPOSE

Medsafe was notified by a sponsor of a signal of pancreatitis in patients treated with tocilizumab.

The signal originated from a review of this association in the World Health Organization (WHO) Pharmaceuticals newsletter from reports derived from the WHO global database of individual cases safety reports, Vigibase.

[redacted]

Pancreatitis is not listed in the EU or UK Summary of Product Characteristics (SmPC) for tocilizumab, however, is listed in the US, Canadian and the Australian product information. The sponsor does not plan to update the core data sheet, nor the New Zealand data sheet at present.

This paper outlines the information available regarding tocilizumab and the risk of pancreatitis. In addition, whether there is information to support a possible class effect of pancreatitis with interleukin inhibitors.

2 BACKGROUND

2.1 Immune system

The immune system fights foreign substances (referred to as antigens) that enter the body. Activation of the immune system can lead to inflammation [1].

Figure 1 highlights the two main parts of the immune system, the innate immune system and adaptive immune system, and which cells play a role in each immune response.

Figure 1: Cells in the innate and adaptive immune system

Source: Cellpedia. Immune Cell. URL: https://cellpedia.org/en/immune-cells/ (accessed 10 February 2023).

The innate immune system is the first line barrier of defence and acts quickly to activate immune cells on recognition of foreign antigens. Cells of the innate immune system include neutrophils, macrophages, granulocytes, and macrophages [1].

The adaptive immune system is made up of T and B cells, and antibodies. There are different types of T cells, and they have many roles, including activating other immune cells and to detect and destroy cells that are infected or tumorous. Both T and B cells become specialised to target different antigens and multiply to mount a specific immune response. When B cells are activated, they transform into plasma cells and release antibodies, which bind to antigens. Antibodies help to neutralise antigens, activate other immune cells and assist with the immune response [2, 3].

Cells of the immune system communicate via chemical messengers called cytokines. There are many types of cytokines including interleukins (IL), tumour necrosis factor (TNF), chemokines and interferons (IFN). Cytokines play an integral role in the initiation, perpetuation and subsequent downregulation of the immune response [2].

Table 1 outlines several IL and their critical functions in the body. IL are secreted by different cells and either act on the same cell or nearby cells to modulate growth, differentiation and activation of immune cells [2].

Table 1: Contributions of important interleukins to immunological responses, by source and critical functions

IL	Source	Critical functions
IL-1	Macrophages Many cells	Induce other cytokines, T cell stimulation, induce metalloproteinases and prostaglandins, increase adhesion molecule expression.
IL-2	T cells	Increase T cell proliferation, activate B cells.
IL-4	T cells	Signal for immunoglobulin switch, increase IgE, decrease production of proinflammatory cytokines, suppress delayed-type hypersensitivity cells (Th1 cells).
IL-5	T cells	Increase eosinophil production.
IL-6	Many cells	T and B proliferation, acute-phase reactants, induce natural protease inhibitor.
IL-12	Macrophages	Increase IFN-gamma production and Th1 cell differentiation.
IL-13	T cells	Similar to IL-4.
IL-15	T cells, macrophages	Induces TNF-alpha release from synovial macrophages, induces mitogenesis, inhibits apoptosis.
IL-17	T cells, innate lymphoid cells	Activates neutrophils and a variety of stromal cells to regulate host defence and also matrix disruption.
IL-23	Macrophages, dendritic cells	Promotes T cells differentiation particularly of the Th17 type.

Source: Heimall J. 2023. The adaptive cellular immune response: T cells and cytokines. In: *UpToDate*. 30 January 2023. URL: https://www.uptodate.com/contents/the-adaptive-cellular-immune-response-t cells-and-cytokines (accessed 10 February 2023).

2.1.1 Autoimmune diseases

Abnormal functioning of the immune system can occur, in which immune cells are produced to target healthy body cells (self-antigens). Immune cells which target self-antigens are referred to as autoreactive [4].

The immune system carries out several functions to ensure that T and B cells identify target antigens correctly. This process is known as immune tolerance and happens at several stages of the cell life cycle [4].

Autoimmune disease is caused by an adaptive autoimmune response against a self-antigen. It represents a breakdown in the normal mechanisms that prevent autoreactivity of both T and B cells. The response may be induced by a foreign or self-antigen. Such a response causes chronic inflammation [4].

There are different types of autoimmune diseases that affect different parts of the body, including inflammatory bowel disease (IBD), psoriasis and rheumatoid arthritis (RA) [4].

Management of autoimmune disease requires agents to decrease the activity the immune system (immunosuppressants) or block the inflammation (anti-inflammatory) [4].

2.2 Interleukin inhibitors

IL inhibitors are a class of medicines that inhibit the action of one or more ILs [5].

IL inhibitors work by either binding to the IL molecule or to the IL target receptor. Both mechanisms inhibit cell signalling and release of pro-inflammatory cytokines, therefore dampening down the immune response and subsequent inflammation [2, 5].

IL inhibitors are used in a wide range of inflammatory diseases. Table 2 outlines the approved IL inhibitors in NZ, including their funding status and approved indication. Other IL inhibitors that are not approved in NZ include anakinra, satralizumab and sarilumab [6, 7].

Tocilizumab is used in the treatment of several autoimmune disorders including RA [8]. RA is a chronic form of inflammatory arthritis and is thought to be caused from complex interactions between genes and the environment, leading to a breakdown of immune tolerance and synovial inflammation. IL-6 has been implicated in the pathogenesis of RA. Elevated levels have been found in the synovial fluid and serum of patients with RA, and higher levels have been found to correlate with disease activity and joint destruction [9].

Tocilizumab is also used to treat cytokine release syndrome (CRS), an unapproved indication in NZ [8, 10]. CRS is condition that may occur after treatment with some types of immunotherapies, such as chimeric antigen receptor (CAR)-T cell therapy. It is caused by a large, rapid release of cytokines into the blood from immune cells affected by the immunotherapy. Cytokines contribute to many of the clinical manifestations of CRS, including IL-6 [2].

Several studies have shown that the level of inflammatory cytokines is also increased in COVID-19, including IL-6, and is associated with severe COVID-19 disease. Cytokine blockage has been implicated in treatment options, including use of tocilizumab [11]. Tocilizumab is included in the NZ COVID-19 Clinical Management of COVID-19 in hospitalised adults and is funded for one dose in moderate to severe COVID-19 [12].

Table 2: Approved interleukin inhibitors in New Zealand, by type, route of administration, availability, funding status and indication

Substance (product name) *(First approval date NZ)*[a]	Mechanism of action[a]	Route	Marketed	Funded[b]	Indication (as per NZ data sheet)[a]
Tocilizumab (Actemra) *(23 July 2009)*	Monoclonal antibody targets IL-6 receptor	IV, SC	Yes	Yes	Rheumatoid arthritis, giant cell arteritis, COVID-19, polyarticular juvenile idiopathic arthritis, systemic juvenile idiopathic arthritis
Ustekinumab (Stelara) *(1 February 2018)*	Monoclonal antibody targets IL-12 and IL-23	IV, SC	Yes	Yes	Psoriatic arthritis, plaque psoriasis, Crohn's disease, ulcerative colitis
Mepolizumab (Nucala) *(22 June 2017)*	Monoclonal antibody targets IL-5	SC	Yes	Yes	Eosinophilic asthma
Canakinumab (Ilaris) *(24 April 2011)*	Monoclonal antibody targets IL-1 beta	SC	No	No	Cryopyrin-associated periodic syndromes[c]
Secukinumab (Cosentyx) *(14 January 2016)*	Monoclonal antibody targets IL-17A	SC	Yes	Yes	Plaque psoriasis, psoriatic arthritis, ankylosing spondylitis
Siltuximab (Sylvant) *(2 July 2015)*	Monoclonal antibody targets IL-6	IV	Yes	Yes	Multicentric Castleman's disease
Risankizumab (Skyrizi) *(24 September 2020)*	Monoclonal antibody targets IL-23	SC	Yes	No	Psoriatic arthritis, plaque psoriasis
Benralizumab (Fasenra) *(13 February 2020)*	Monoclonal antibody targets IL-5 receptor	SC	Yes	Yes	Eosinophilic asthma
Basiliximab (Simulect) *(17 September 1998)*	Monoclonal antibody targets IL-2 receptor	IV	Yes	Yes[d]	Prophylaxis of acute organ rejection in *de novo* renal transplantation

Key: IV – intravenous, SC – subcutaneous.
Notes:
a. Medsafe. Data sheets and Consumer Medicine Information. URL: medsafe.govt.nz/Medicines/infoSearch.asp (accessed 22 December 2022).
b. PHARMAC. 2022. Hospital and Community funding schedule. URL: pharmac.govt.nz/pharmaceutical-schedule/ (accessed 10 February 2023) (Must meet criteria required for funding).
c. The Ilaris data sheet is not published. Indication accessed from Medsafe's Product/Application Search. URL: medsafe.govt.nz/regulatory/DbSearch.asp (accessed 25 January 2023).
d. Funded in hospital only.

Eosinophilic inflammation is an important component in the pathogenesis of asthma. IL-5 is the major cytokine responsible for the growth and differentiation, recruitment, activation and survival of eosinophils [13]. Mepolizumab blocks the binding of IL-5 to the IL-5 receptor expressed on the eosinophil cell surface, thereby inhibiting IL-5 signalling and reducing the production and survival of eosinophils [14].

IBD is comprised of two major disorders, ulcerative colitis (UC) and Crohn's disease (CD). Both are chronic inflammatory conditions affecting the gastrointestinal tract. IBD results from a dysregulated response by the mucosal immune system to the microbiota within the intestinal lumen. Abnormal levels of cytokines, including IL had been identified in IBD [15]. In patients with Crohn's disease (CD), IL-12 and IL-23 are elevated in the intestines and lymph nodes. Both IL-12 and IL-23 can stimulate TNF-alpha production by T cells, resulting in chronic intestinal inflammation and epithelial cell injury. A potential causal role for IL-12/23 signalling has been suggested [16].

Comments: There are a range of approved IL inhibitors that may be used for a wide range of inflammatory conditions. Some IL inhibitors have been approved recently by Medsafe.

ILs are targets in these conditions to suppress inflammation resulting from a hyperactive immune response.

2.3 Pancreatitis

2.3.1 The pancreas

The pancreas is an organ in the body located in the upper abdomen behind the stomach and is part of the digestive system. The main functions of the pancreas are to produce enzymes that break down food in the intestine, and hormones that regulate blood sugar levels [17].

Within the pancreas there are two main types of cells: exocrine cells and endocrine cells [17].

Exocrine cells of the pancreas, called acinar cells, produce digestive enzymes. There are three main types of enzymes: lipases (break down fat), proteases (break down protein) and amylases (break down carbohydrates). These enzymes are secreted into the small intestine through the pancreatic duct, where they become activated and help to break down the contents of the intestine [17].

Islets of Langerhans cells are endocrine cells in the pancreas that produce hormones, including insulin and glucagon. These hormones help to regulate blood sugar levels in the body. Insulin is released when blood sugar levels rise, allowing glucose to be absorbed from the bloodstream into the cells. On the other hand, low blood sugar stimulates glucagon to be released, which triggers the liver to convert glycogen (stored glucose) in the liver to a usable form [17].

2.3.2 Definition

Pancreatitis is a condition characterised by inflammation of the pancreas. It is classified into two forms: acute or chronic pancreatitis [18].

Acute pancreatitis (AP) is a sudden onset of inflammation, which may arise from a number of cases (discussed below) [18].

Chronic pancreatitis relates to persistent inflammation in the pancreas, where permanent damage and subsequent loss of pancreatic function has occurred [18].

Most patients with AP have a mild episode and recover within several days. However, approximately 20% of patients experience a severe episode with complications [19]. Such complications may involve local effects on the pancreas (eg, acute peripancreatic fluid collection or necrotising pancreatitis) and/or other organ systems (eg, acute respiratory failure or renal failure). The overall mortality of acute pancreatitis is approximately 5%. [20]. Serious outcomes may be more likely in certain subgroups of patients, such as the elderly and those with were more severe episodes [21].

Comment: This report will focus on acute pancreatitis/pancreatitis, as opposed to chronic pancreatitis.

2.3.3 Causes

Figure 2 outlines potential causes of AP. The two most common causes of AP are gallstones (up to 40% of cases) and alcohol (30% of cases). Although medicines appear to cause less than 5% of all cases of AP, many medicines have been reported to cause pancreatitis.

It is generally accepted that levels of triglycerides >11.3 mmol/L may increase the risk of precipitating AP [22]. Hypertriglyceridemia-induced AP has been reported to be responsible for worse outcomes when compared with other causes of AP [19].

Figure 2: Causes of acute pancreatitis

Source: Forsmark CE, Vege SS and Wilcox CM. 2016. Acute Pancreatitis. *New England Journal of Medicine* 375(20): 1972-1981. DOI: 10.1056/NEJMra1505202 (accessed 9 February 2023).

In some cases, the cause of AP cannot be established, and is referred to as idiopathic AP. A number of potential factors many contribute to idiopathic AP, such as exposure to toxins and the effects of co-existing diseases that are commonly associated with AP (eg, obesity and diabetes, or smoking history) [23]. The risk of pancreatitis may be higher in those with inflammatory disease, such as IBD and RA [24, 25].

2.3.3.1 Drug-induced pancreatitis

Drug-induced pancreatitis (DIP) is rare, however, has become increasingly recognised that DIP represents an important cause of AP [22, 26].

The mechanism by which medicines cause pancreatitis is not clearly understood. Potential theories have been identified from case reports, case-control studies and animal studies [27]. A number of mechanisms have been postulated (see Figure 3). Hypertriglyceridemia resulting from medicines has also been identified as a rare potential cause for AP [19]. When it is not known how the medicine causes pancreatitis, this is referred to as an idiosyncratic response. Idiosyncratic reactions to medicines are adverse effects that are not directly related to the pharmacodynamic mechanisms [22].

The majority of cases of DIP are mild, but severe and even fatal cases may occur, thus making identification of the offending agent critical [22].

Figure 3: Proposed mechanisms for drug-induced pancreatitis

Source: Weissman S, Aziz M, Perumpail RB, et al. 2020. Ever-increasing diversity of drug-induced pancreatitis. *World J Gastroenterol* 26(22): 2902-2915. DOI: 10.3748/wjg.v26.i22.2902 (accessed 15 February 2023).

Most of the available information for DIP is derived from case reports or case control studies. Case reports with the strongest evidence are those that clearly diagnose pancreatitis and exclude common aetiologies, provide the dose and time interval between the start of treatment with the suspected drug and the development of pancreatitis, and demonstrate recurrent pancreatitis upon rechallenge of the medicine [28].

The diagnosis of DIP is often challenging because there are no unique clinical characteristics to distinguish medicines from other causes of pancreatitis. It is often difficult to determine whether the medicine is responsible due to the presence of other, more common causes of AP. This is especially relevant in patients with multiple comorbidities and underlying risk factors. Patients may also be taking other medicines that are associated with pancreatitis, and it is challenging to determine which medicines may be contributory. Diagnosis may be difficult in elderly patients due to polypharmacy and multiple comorbidities [28].

The exact mechanism for AP with tocilizumab is unknown but may be due to hypertriglyceridemia and IL-6 inhibition [29].

As per the tocilizumab data sheet, elevations in lipid parameters including total cholesterol, low density lipoprotein (LDL), high density lipoprotein (HDL) and triglycerides (TG) were observed in patients treated with tocilizumab. The data sheet recommends that assessment of lipid parameters should be performed in patients 4 to 8 weeks following initiation of therapy and managed accordingly [8].

Nakamura et al discussed a case report where the administration of tocilizumab for CRS with COVID-19 affected the lipid profile. Serum TG levels greatly increased, and serum amylase level gradually increased in accordance with TG elevation. Serum trypsin and lipase levels were also elevated. While in this case, the patient did not experience AP, the potential for AP was likely elevated, given elevation of pancreatic enzymes [30].

Even though IL-6 is mostly known as a proinflammatory agent, some anti-inflammatory capacities have been associated with IL-6. A pancreatitis model found a more severe inflammation when IL-6 was absent, posing the question whether blockage of this molecule might induce or at least aggravate the course of AP [29].

Comment: The potential mechanisms whereby IL inhibitors could induce pancreatitis are unknown.

Of note, elevations of blood cholesterol and triglyceride levels were reported in patients receiving secukinumab in clinical trials for psoriatic arthritis and non-radiographic axial spondylarthritis.

Hypertriglyceridemia was also reported in clinical trials with siltuximab, and hypercholesterolaemia is listed in section 4.8 in the basiliximab data sheet.

2.3.4 Pathogenesis

Regardless of the cause, AP occurs due to damage to acinar cells and/or injury to the pancreatic duct, causing abnormal activation of digestive enzymes in the pancreas [22, 27].

Activated digestive enzymes are released into the surrounding pancreatitis tissue and accumulate, causing damage to the pancreas through the breakdown of tissue membranes, apoptosis, necrosis, oedema, vascular damage, haemorrhage and localised inflammatory response. An extensive inflammatory response is mounted, due to pancreatic cells synthesising and secreting inflammatory cytokines [22].

Gallstones trigger AP when they become impacted and obstruct the outflow from the pancreatic duct. This leads to increased pancreatic pressure and induces acinar cell injury [18].

Elevated plasma levels of TG are proposed to increase blood viscosity, leading to local ischemia in pancreatic tissues [18]. Proinflammatory free fatty acids generated from TG may lead to the release of inflammatory mediators, further contributing to pancreatic damage [27].

Although the exact mechanism of DIP is not always known, the pathogenesis likely does not differ from other causes of AP [22].

2.3.5 Symptoms

Individuals who experience AP most likely develop acute onset of persistent, severe epigastric and left upper quadrant pain, and associated nausea and vomiting. Those with severe pancreatitis may have fever, tachypnoea, hypoxemia and hypotension [20].

The pancreatic digestive enzymes amylase and lipase may be elevated on laboratory findings. An elevation of serum lipase or amylase 3 times or greater that the upper limit of normal is suggestive of AP [20].

A number of cytokines and inflammatory mediators are released during acute pancreatitis, resulting in elevations in C-reactive protein (CRP), IL-6, IL-8, IL-10 and TNF [20].

Metabolic abnormalities, including elevated blood urea nitrogen (BUN), hypocalcaemia, hyperglycaemia and hypoglycaemia, may also occur [20].

AP may have a multi-system inflammatory response in up to 25% of patients [20].

2.3.6 Diagnosis and management

The diagnosis of AP requires the presence of 2 of the following 3 criteria [23]:

- acute onset of pain consistent with AP
- elevation in serum lipase or amylase to 3 times or greater than the upper limit of normal
- characteristic findings of AP on imaging.

Initial management of patients presenting with AP focuses primarily on the acute symptoms [21].

All patients with pancreatitis are initially treated with fluids and pain control. Initially, patients are made nil by mouth, meaning no food or water is consumed, allowing the pancreas to rest and recover. Patients with severe AP may require a feeding tube on the basis that symptoms continue to be severe, or they are unable to tolerate normal eating [21].

Management of drug-induced AP requires withdrawal of the offending agent and supportive care. Early diagnosis and discontinuation of the offending drug can reduce complications [21, 27].

Comments: AP is a condition that may be triggered by numerous causes; however, most cases are caused by alcohol or gallstones.

While the majority of cases are mild, some cases may become severe and lead to complications. Certain subpopulations may be more at risk of worse outcomes.

Drug-induced AP counts for a small number of cases, however the mechanisms are not well understood.

Distinguishing between a medicine cause where other causes of AP are present may be challenging.

2.4 Usage

The Pharmaceutical Web Tool provides information about medicines that are dispensed in community pharmacies.

Administration of IL inhibitors most often takes place within a hospital or outpatient clinics, and medicines are provided by a hospital pharmacy. Such dispensing information is not included in the Pharmaceutical Web Tool and is therefore not available.

Table 3 outlines the IL inhibitors that have been dispensed in the community as recorded in the Pharmaceutical Web Tool.

Table 3: Number of people dispensed mepolizumab and secukinumab in the community, 2017–2021

Interleukin Inhibitor	2017	2018	2019	2020	2021
Mepolizumab (Nucala)	n/a	n/a	n/a	156	470
Secukinumab (Cosentyx)	N/a	109	404	658	1190

Source: Ministry of Health. 2022. Pharmaceutical Data web tool version 7 November 2022 (data extracted from the Pharmaceutical Collection on 10 August 2022). URL: https://tewhatuora.shinyapps.io/pharmaceutical-data-web-tool/ (accessed 10 February 2023).

Comments: The number of people dispensed mepolizumab and secukinumab has increased from 2017 to 2021. This likely reflects funding changes for these medicines. For example, mepolizumab became funded from April 2020.

The use of tocilizumab may be increasing due to use in COVID-19 disease, as recommended in NZ guidelines.

3 SCIENTIFIC INFORMATION

3.1 New Zealand and international prescribing information

Table 4 shows whether or not pancreatitis is listed in the prescribing information for IL inhibitors, by country.

Of the class of IL, only tocilizumab (Actemra) has pancreatitis listed as a post-market adverse event (Australia and US), and a clinical trial adverse reaction (Canada). It is not listed in the Actemra company core data sheet nor the NZ data sheet.

Table 4: Listing of pancreatitis in interleukin inhibitor prescribing information, by country (Dec 2022)

Product	NZ	Australia	UK	Canada	US	EU
Tocilizumab (Actemra)	No	**Yes***	No	**Yes****	**Yes***	No
Ustekinumab (Stelara)	No	No	No	No	No	No
Mepolizumab (Nucala)	No	No	No	No	No	No
Canakinumab (Ilaris)	not available	not available	No	No	No	No
Secukinumab (Cosentyx)	No	No	No	No	No	No
Siltuximab (Sylvant)	No	not available	No	No	No	No
Risankizumab (Skyrizi)	No	No	No	No	No	No
Benralizumab (Fasenra)	No	No	No	No	No	No
Basiliximab (Simulect)	No	No	No	No	No	No

Key: *Post market ADR; **Clinical trial ADR (reported in <1% of participants on tocilizumab in RA + COVID-19 trials)

Sources:

New Zealand data sheets: Medsafe. *Data sheets and Consumer Medicine Information*. URL: medsafe.govt.nz/Medicines/infoSearch.asp (accessed 22 December 2022)

Australian Product Information: Therapeutic Goods Administration (TGA). *PI/CMI search facility*. URL: tga.gov.au/how-we-regulate/labelling-and-packaging/medicines-and-biologicals/picmi-search-facility (accessed 22 December 2022)

UK SmPC: Electronic Medicines Compendium (emc). *UK SmPC information*. URL: medicines.org.uk/emc/ (accessed 22 December 2022)

Canadian labels: Health Canada. *Drug Product Database: access the database*. URL: canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html (accessed 22 December 2022).

USA labels: Food and Drug Administration (FDA). *FDA Online Label Repository*. URL: labels.fda.gov/ (accessed 22 December 2022).

EU SmPC: European Medicines Agency (EMA). URL: https://www.ema.europa.eu/en (accessed 20 February 2023)

3.2 Published literature

This section includes information available in the literature, and mostly consists of spontaneous reporting.

Comment: Some of the literature articles relate to disproportionality analysis within adverse event reporting data bases.

A disproportionality analysis determines whether there is disproportional reporting of a drug-adverse event combination compared with the occurrence of the adverse event with other drugs in the database. In other words it detects a signal but cannot confirm a side effect. Terms used in disproportionality analysis include the reporting odds ratio (ROR) and information component (IC).

ROR is the ratio of the odds of an adverse event in those who received the suspected medicine, compared with those who did not receive the suspected medicine. A ROR with the lower bound 95% confidence interval >1 is considered to be a signal.

IC involves the calculation of the observed to expected ratio; it may provide erroneous results when the observed or expected number is extremely low. If a particular drug-adverse event is reported more often than expected from the rest of the database, then value of IC will be positive. The IC_{025} is the lower limit of the 95% confidence interval for IC.

3.2.1 Tocilizumab-induced pancreatitis: a case report and review of data from the FDA Adverse Event Reporting System – Flaig et al, 2016 [29]

Case report

The authors present a case report of a 40-year-old male who was taking tocilizumab (720mg IV) for RA, of which he had received two doses, who was admitted to hospital and diagnosed with AP.

Patient history included CKD, hypertension, hypercholesterolaemia and hepatic steatosis. He had a smoking history, a daily consumption of approximately one litre of beer and BMI of 27.2 Kg/m^2 (overweight). His other medicines included ramipril, calcium and vitamin D.

Tocilizumab was stopped and changed to anakinra. The patient has not presented with AP again.

The association between tocilizumab and AP in this case was judged as probable, according to the WHO causality assessment.

United States Food and Drug Administration Adverse Event Reporting System (FAERS)

The FAERS database was searched between 2009 and 2013 for an association between tocilizumab use and pancreatic adverse events, where tocilizumab was listed as the primary suspect medicine.

74 cases were found (see Table 5). Most of the cases are in women. The mean age of cases was 55.5 years. AP was the most frequently reported pancreatic adverse event, and 12% of AP cases were fatal.

Table 5: Pancreatic adverse events in the Food and Drug Administration Adverse Event Reporting System (FAERS) associated with tocilizumab between 2009 and 2013

Comments: A number of reports relating to an association between tocilizumab and pancreatitis were identified in the FAERS database. Unfortunately, further details of these cases were not reviewed, and therefore it cannot be determined if tocilizumab was the cause of pancreatitis in these cases.

The authors present a case report, which they believe to be AP caused by tocilizumab. It is noted that information provided in this case includes other potential causes or contributory factors to AP, including his alcohol intake, weight and ramipril, a drug known to cause AP.

3.2.2 Assessment of pancreatitis associated with tocilizumab use using the United States Food and Drug Administration Adverse Event Reporting System database – Kamath et al, 2021 [25]

This was a retrospective database review using the US FAERS database to identify individual case safety reports (ICSR) between January 2013 to December 2019. The aim of the review was to determine whether pancreatitis is reported more often with tocilizumab compared with other drugs, by performing a disproportionality analysis, and to describe the clinical and demographic characteristics of the cases.

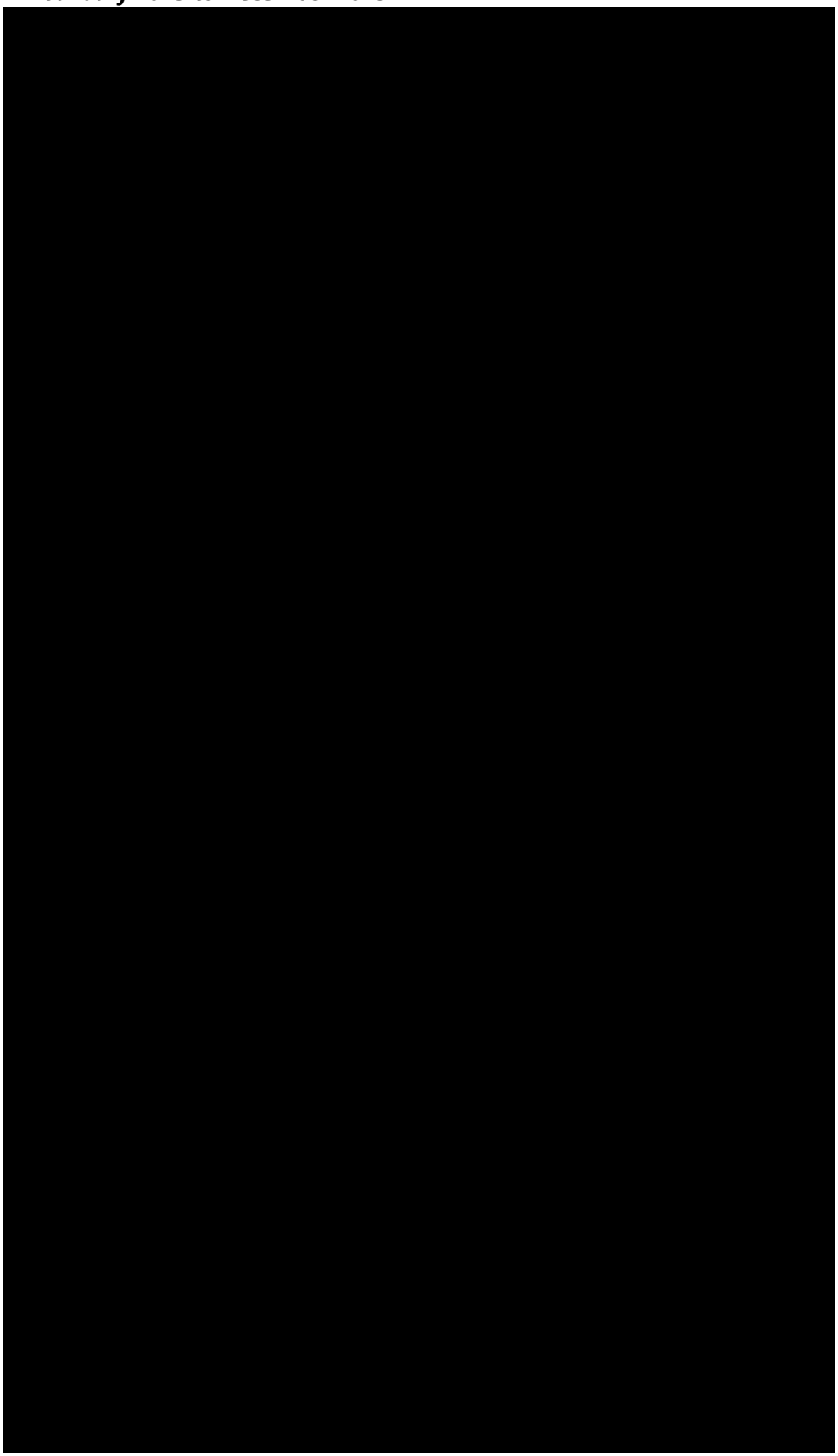
Cases were included if they reported pancreatitis-related MedDRA terms, and where tocilizumab was mentioned as the primary or secondary suspect medicine.

144 cases of pancreatic adverse events were identified (see Table 6). The median age of the patients was 56 years, and females represented 53% of cases. The most frequently reported pancreatic adverse event was pancreatitis.

The majority of cases fulfilled the criteria for a serious adverse event, of which 10% were fatal. The median duration of onset from time of initiation of tocilizumab was 4 months.

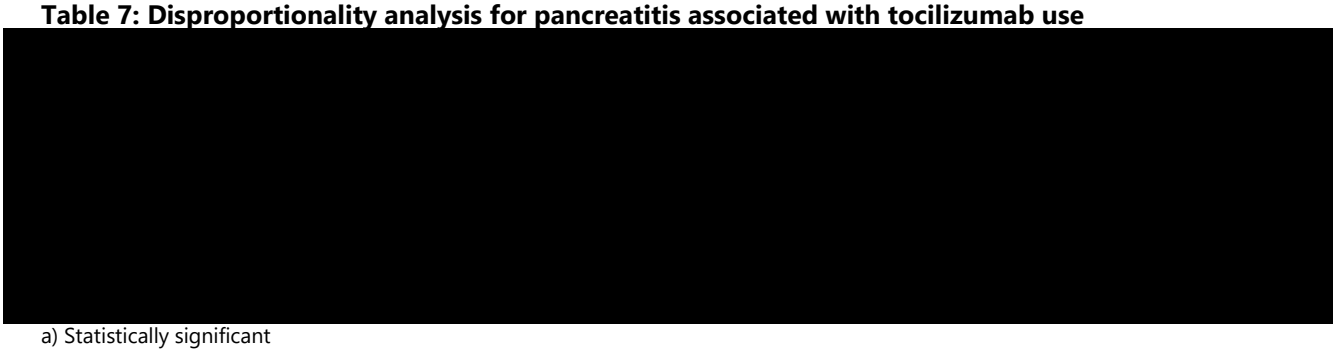
Concomitant medicines were reported in 107 cases. Among these, 74 patients received medicines that can cause pancreatitis, of which, 38 patients received more than one such medicine.

Table 6: Characteristics of case reports relating to pancreatitis and tocilizumab, in FAERS database, January 2013 to December 2019



Disproportionality analysis showed that the likelihood of reporting pancreatic events compared with any other adverse event with tocilizumab was 1.32 times higher than with other drugs (Table 7). The results did not show significant reporting for the MedDRA term 'pancreatitis acute'.

Table 7: Disproportionality analysis for pancreatitis associated with tocilizumab use



a) Statistically significant

Comment: A signal of pancreatitis was detected for tocilizumab in the FAERS database.

This review by Kamath et al provided more up-to-date information relating to reports of pancreatitis with tocilizumab in the FAERS database. The Flaig review above identified 74 reports between 2009 and 2013, whereas Kamath identified 144 reports between 2013 and 2019. This may represent increased use of tocilizumab over time.

Limitations of the FAERS database include missing or incomplete data in the cases, duplicate reports, under reporting and reporting errors. In addition, individual case information is not provided, which could contribute to the development of pancreatic events. While fatal cases were identified, individual factors such as age and comorbidities were likely influential.

The authors note that given the limitations of the FAERS database, the signal should be interpreted cautiously, and further analysis is needed to confirm findings.

3.2.3 Serious adverse events with tocilizumab: Pharmacovigilance as an aid to prioritise monitoring in COVID-19 – Gatti et al, 2020 [31]

An observational, retrospective disproportionality analysis was performed to characterise adverse events with higher-then-expected increased reporting using the US FAERS database.

A total of 39,572 reports with tocilizumab as a suspect agent were found, of which, 78.8% were serious. Table 8 outlines the cases relating to pancreatitis only, where a statistically significant reporting odds ratios (ROR) was identified (other adverse events were reported, but are not included here).

Table 8: Pancreatic adverse events reported with tocilizumab showing statistically significant disproportionality

Adverse Event	No. cases	No. deaths	Proportion of deaths	ROR (95% CI)	Most frequently reported indication	Predictability
Pancreatitis	151	17	11.3%	1.65 (1.51-1.94)	75.5% RA, 14.6% NA, 4.6% CRS, 3.3% TIA, 1.3% JIA, 0.7% PR	Unpredictable
Pancreatitis acute	61	4	6.6%	1.99 (1.55-2.56)	77.1% RA, 13.2% NA, 3.3% TA, 1.6% CD, 1.6% JIA, 1.6% SD, 1.6% PR	Unpredictable

Key: Reporting odds ratio (ROR), rheumatoid arthritis (RA), cytokine release syndrome (CRS), not available (NA), juvenile idiopathic arthritis (JIA), temporal arteritis (TA), polymyalgia rheumatica (PR), Castleman's disease (CD), Still's disease (SD).

Comments: A review of the US FAERS database for serious adverse events of tocilizumab identified increasing reporting of pancreatic reactions, confirming previous reviews.

The majority of reports were in patients using tocilizumab for RA. However, cases also occurred in CRS patients where the duration of treatment with tocilizumab is short term only. Use of tocilizumab for COVID-19 is also for short durations.

Some reports for pancreatitis and acute pancreatitis were fatal, reinforcing the potential seriousness of the condition.

As previously mentioned, there are limitations with the FAERS data. Causality cannot be established between drug exposure and occurrence of the adverse event. In addition, given the lack of denominator, and potential for under reporting, the ROR and its magnitude cannot quantify the real risk in clinical practice.

3.2.4 Tocilizumab and pancreatitis – Boyd, 2021 [32]

(Full text available in Annex 1)

As of 29 November 2020, there are 189 de-duplicated individual case safety reports (ICSRs) of tocilizumab and pancreatitis or pancreatitis acute, in the WHO global database of ICSRs, Vigibase.

The IC was 0.6 (189 observed, 125 expected) and the IC_{025} was 0.4, indicating a disproportionate association. Tocilizumab was the only suspect drug in 148 cases.

An analysis was undertaken for 41 cases with more complete information, and included age, gender, start date, action taken with tocilizumab, date of onset and recovery information. Further information on these cases is outlined in Annex 1, and a summary is provided below.

The majority of the cases were female, and RA was the most common indication for tocilizumab. The ages of the cases ranged from 5 to 83 years, with a median age of 54.5 years. Tocilizumab was the only suspected drug in 31 of the 41 cases. In the remaining 10 cases, there were other suspected drugs present. Corticosteroids were listed as suspect medicines in more than one case. These medicines are often used in conditions for which tocilizumab is prescribed, such as RA. The dosage of tocilizumab varied. Two cases reported that tocilizumab was used for COVID-19.

Time of onset varied significantly. However, 25 cases occurred from one week to ten months after starting treatment, which is consistent with other well-recognised medicine causes of pancreatitis.

Patients were reported as recovered or recovering in 32 of the 41 cases, not recovered in 8 cases, and one case had a fatal outcome. In the 32 cases where recovery was reported, tocilizumab was withdrawn in 25 cases. In the fatal case, the patient developed acute, necrotising pancreatitis 3 months after commencing tocilizumab, and 4 weeks after tocilizumab was withdrawn. The patient died 3 weeks later. The cause of death was not stated, however necrotising pancreatitis has a relatively high rate of mortality and may have been the cause of death.

Pancreatitis or acute pancreatitis was the only reaction reported in 28 of the 41 reports. In 4 cases, there were additional reactions related to pancreatitis, such as abdominal pain (4 cases), amylase increased (2) and diarrhoea (2). There was a variety of other reactions in the remaining 9 cases, but no obvious pattern to these reactions apart from some known to be associated with tocilizumab use, such as hypertriglyceridemia (3) and abnormal liver function tests (3).

Comments: A signal of pancreatitis and pancreatitis acute in associated with tocilizumab has been identified in Vigibase.

The review further supports the signal, previously identified in the FAERS database.

While the author provides analysis of case reports where more complete information is available, potential other causes of pancreatitis may have been confounding. However, tocilizumab was listed as the only suspected medicine in the majority of the cases analysed.

Some patients recovered after withdrawal of the medicine, consistent with a medicine-induced effect.

3.2.5 Drug-induced acute pancreatitis: results from the hospital-based Berlin case-control surveillance study of 102 cases – Douros et al, 2013 [33]

A hospital-based Berlin case-control surveillance study was undertaken from October 2002 to December 2011 to determine the risk of pancreatic toxicity with a wide range of medicines.

Patients with a minimum age of 18 years and a new diagnosis of idiopathic acute pancreatitis (IAP) within the last 6 months were included. At least 2 of the following 3 criteria had to be met:

- elevation of lipase or amylase at least threefold above the upper limit of normal
- characteristic upper abdominal pain
- signs of pancreatitis in imaging.

Cases were excluded if other potential causes of acute pancreatitis were present, such as but not limited to, biliary aetiology, obstruction-related aetiologies, alcoholic, ischaemic or trauma-induced AP, hypertriglyceridemia >11.2 mmol/L or an endoscopic retrograde cholangiopancreatography in the last 48 hours.

284 cases of IAP were notified to the study centre, of which 116 cases were analysed. A possible medicine aetiology was assessed for each case. In relation to tocilizumab, one case was identified, which was considered 'probable'.

Comments: While only one case was found, this study identified a potential risk of pancreatic toxicity for tocilizumab.

Tocilizumab was first approved by the EMA in 2009. Given the study period, use of tocilizumab for approved indications may have been low, which may have influenced case reports.

An advantage of this study is that other causes of pancreatitis were mostly ruled out due to the exclusion criteria.

3.2.6 Pharmacovigilance assessment of drug-induced acute pancreatitis using a spontaneous reporting database – Niinomi et al, 2019 [34]

A review of the drugs most frequently implicated in the occurrence of AP using the Japanese Adverse Drug Event Report (JADER) database was undertaken between April 2004 and January 2017.

Cases included for analysis were those that were classified as a suspected medicine, with the MedDRA PT 'pancreatitis acute', and excluded patients with a history of chronic or autoimmune pancreatitis.

3,443 reported cases of AP were identified, 431 different medicines were suspected. Cases of the 70 most frequently reported medicines were further examined, of which, 39 medicines generated a signal.

A signal was detected for ustekinumab (16 cases; ROR: 5.35, 95% CI 3.27–8.76), but not for tocilizumab (39 cases; ROR: 1.00, 95% CI 0.73–1.37).

Comments: Analysis of the Japanese adverse event reporting database identified a signal for ustekinumab and acute pancreatitis. Although cases of tocilizumab were identified, no signal was detected.

3.2.7 Additional literature case reports

Table 9: Literature case reports

Author (s), date	Case details
Parekh at el, 2013 [35]	67-year-old presented with AP complicated by pancreatic pericardial fistulisation. He was receiving tocilizumab for RA. The patient died. The cause of the patient's AP was not fully understood. Tocilizumab has been implicated in the setting of necrotising pancreatitis, although the literature is limited. It is possible that tocilizumab played a role in this case, however there is insufficient evidence.
Mekinian et al, 2020 [36]	A case of AP was reported in a prospective open-labelled trial in 13 tocilizumab-naïve patients with Takayasu arteritis (TAK). No interruption of treatment or dose reduction was required.
Decker et al, 2018 [37]	A systemic review of the literature (105 cases) of tocilizumab in the treatment of Takayasu disease identified one case of pancreatitis. The pancreatitis occurred 2 weeks after the first tocilizumab infusion in a patient who had been treated with azathioprine and corticosteroids.
Wazir et al, 2013 [38]	Two case reports of patients who developed acute pancreatitis during treatment with tocilizumab for RA. Case 1: 35-year-old Caucasian male with RA, one month after his monthly dose of tocilizumab (800mg, 8mg/Kg), he developed AP with high serum amylase, CRP 30, WCC 30. CT findings: AP. No history of excess alcohol or cholelithiasis. Other medicines: prednisolone, azathioprine, opiates, omeprazole, alendronic acid. Case 2: 70-year-old Caucasian female with RA, 2 weeks after 8th infusion of tocilizumab admitted with AP. No history of risk factors. Other medicines included prednisolone, minocycline, lisinopril, omeprazole and levodopa/carbidopa.
Righetti et al, 2019 [39]	Analysis of 10 patients who had received tocilizumab treatment for large vessels vasculitis (8mg/kg IV monthly). One case of haemorrhagic pancreatitis was reported after 24 weeks. Report not further classified.
Takeuchi et al, 2011 [40]	Analysis of 232 consecutive RA patients who began tocilizumab in 3 rheumatology centres in Japan for 52 weeks. One case of necrotising pancreatitis was reported. Report not further classified.
Conway et al, 2018 [41]	In a study of ustekinumab in 25 patients for giant cell arteritis. 11 adverse events were recorded, included one case of pancreatitis. Report not further classified.
Diana et al, 2021 [42]	Case report of possible alithiasic pancreatitis after treatment of psoriatic arthritis with secukinumab (abstract only).
Casale F and Jan I, 2021 [43]	Case report of a 49-year-old female with severe persistent asthma, gastroesophageal reflux disease, diabetes mellitus, post-traumatic stress disorder, hypoadrenalism and obesity, who developed AP likely secondary to delayed-hypersensitivity reaction with mepolizumab.

Summary of literature

From the literature reviewed, a large majority of reports of pancreatitis with IL inhibitors relate to tocilizumab and are from case reports and spontaneous reporting.

A signal has been identified for tocilizumab and pancreatitis within FAERS and Vigibase. Within the FAERS database reviews, most cases were in RA patients aged around 55 years. However, cases have also been reported where tocilizumab was used in COVID-19 treatment, where the duration of treatment is much shorter than the continuous dosing in chronic inflammatory conditions.

AP has a variety of different causes, most of which are not medicine related. The significance of the signal with tocilizumab in clinical practice may need to be taken with caution. There is confounding present in some of the cases reviewed, whereas other cases may have not had enough information required to make a causality assessment. However, some of the Vigibase cases with more complete information were able to be analysed.

A signal was identified for ustekinumab in the Japanese adverse event reporting database. However, there are very few case reports of pancreatitis with other IL inhibitors.

3.3 Company information

3.3.1 [redacted]

[redacted]

[redacted]

3.4 Regulatory action

3.4.1 Australia

[redacted]

In August 2022, the sponsor agreed to update the Australian PI, but will not be updating the core company data sheet.

Comment: The Australia Product Information for tocilizumab was updated in September 2022 to include pancreatitis as a post-marketing adverse effect.

3.5 Spontaneous reporting

3.5.1 Centre for Adverse Reactions Monitoring (CARM) New Zealand

Up to 26 January 2023, CARM had received one case of pancreatitis with the IL inhibitor, tocilizumab.

CARM ID 136299 involved a 48-year-old [redacted] male [redacted] who experienced pancreatitis [redacted] other reported medicine was atorvastatin [redacted]

[redacted]

Comments: Similar to other case reports in the literature, they may be confounding factors present in the case. [redacted]

[redacted]

There have been no other cases of pancreatitis associated with IL inhibitors reported to CARM.

3.5.2 Database of adverse event notifications (DAEN) Australia

On 13 January 2023, the Australian database of adverse event notifications (DAEN) was searched for reports of IL inhibitor medicines and pancreatitis (see Table 10).

A small number of reports were identified for ustekinumab, mepolizumab and secukinumab.

Tocilizumab had the most reports (11 reports). None of the reports were fatal. In 10 out of the 11 reports, tocilizumab was listed as the single suspected medicine.

Table 10: Reports of pancreatitis with interleukin inhibitor medicines, reported in the Australian database of adverse event notifications (DAEN), as at 13 January 2023

Product	Number of reports PT 'pancreatitis'
Tocilizumab (Actemra)	11
Ustekinumab (Stelara)	1
Mepolizumab (Nucala)	1
Canakinumab (Ilaris)	0
Secukinumab (Cosentyx)	5
Siltuximab (Sylvant)	0
Risankizumab (Skyrizi)	0
Benralizumab (Fasenra)	0
Basiliximab (Simulect)	0

Source: Therapeutic Goods Administration. Database of Adverse Event Notifications – medicines. URL: apps.tga.gov.au/PROD/DAEN/daen-entry.aspx (accessed 13 January 2023).

Comments: There have been reports of pancreatitis with four different IL inhibitors in Australia. Tocilizumab had the most reports.

3.5.3 World Health Organization Global Database

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
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	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

4 DISCUSSION AND CONCLUSIONS

Pancreatitis is potentially serious condition that may arise due to multiple causes, including from medicines.

The Actemra (tocilizumab) PI in Australia has been recently updated with pancreatitis as a post-market ADR. Pancreatitis is also listed as a post-market ADR in the FDA label. There have been case reports of pancreatitis with tocilizumab in Australia, in which, most cases list tocilizumab as the only suspect medicine.

At present, pancreatitis is not listed in the NZ Actemra (tocilizumab) data sheet. There has been one local case report of pancreatitis and tocilizumab in NZ. It is not currently known how many people are using tocilizumab in NZ; however, its use has been recently included in NZ COVID-19 treatment guidelines.

Available information of reports of pancreatitis with tocilizumab consist of case reports and spontaneous reporting. Cases were identified when tocilizumab was used in long term chronic conditions, such as RA, and also for short term use, such as in COVID-19 and CRS. A signal was identified on analysis of cases in the FAERS and Vigibase databases for pancreatitis and tocilizumab. Further analysis of selected cases in Vigibase identified tocilizumab as the single suspect medicine in a number of cases. However, the risk cannot be further quantified with spontaneous reporting. Additionally, causality cannot be assessed in cases where there is insufficient information.

Identifying medicines as the cause of pancreatitis may be challenging in patients who may have other aetiologies for AP present, have underlying risk factors and/or taking concomitant medicines.

[redacted].

Other than with tocilizumab, there is currently very limited literature that describes an association with the IL inhibitor class of medicines. There have been a small number of cases of pancreatitis from spontaneous reporting for several IL inhibitors. A review of the Japanese reporting database found disproportional reporting for ustekinumab. [redacted] Pancreatitis is not currently listed as an adverse event in the prescribing information for IL inhibitors (excluding tocilizumab) in New Zealand or internationally.

5 ADVICE SOUGHT

The Committee is asked to advise:

- Whether there is evidence for an association between pancreatitis and tocilizumab?
    - If yes, are data sheet updates are required (for example, to align with recent updates requested by the TGA)?
- Whether there is evidence for an association between pancreatitis and the IL inhibitor class?
    - If yes, is further action required?
- Does the topic require communication, other than MARC's remarks in *Prescriber Update?*

6 ANNEXES

Annex 1: World Health Organization (WHO) Pharmaceutical Newsletter 2021 No.3

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