Signal

Gastric perforation due to Tocilizumab

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Summary

Tocilizumab (TCZ), a humanized monoclonal antibody acting as an interleukin6 (IL-6) receptor antagonist, belongs to an important group of biological agents that has revolutionized the anti-inflammatory therapy of rheumatoid arthritis (RA). However, drugs that block IL-6 are reported to be associated with increased risk of gastrointestinal perforation, mainly intestinal. Gastric perforation associated with TCZ was identified as a potential signal in a screening of VigiBase, the WHO global database of individual case safety reports. As of March 2020, there were 20 unique cases (compared to three expected), from nine countries, reporting gastric perforation with TCZ as a suspected medicine, in VigiBase. Seventeen of the 20 cases (85%) were considered as serious, one with a fatal outcome, and occurred with a time to onset from 0.5 to 36 months (median five months). The indication (known in 18 cases) for TCZ treatment was RA in 16 and temporalis arthritis, or giant cell arthritis (GCA), in two cases. The outcome was unknown for seven cases, but eleven patients recovered or were recovering, including four where a surgical procedure was mentioned, while two did not recover, including the fatal case. In ten patients known risk factors for gastric perforation existed, including e.g. co-mobilities or a history of GI disorders, smoking; and concomitant treatment with methotrexate (MTX), rituximab, steroids, NSAIDs, or combination of these. There seem to be more cases with a higher body weight than with a lower, where information was available. Considering the seriousness of this reaction, it would be prudent to recommend close monitoring of patients when treated with TCZ, in particular those with risk factors for GI perforation as well as those with a high body weight, as its dose is determined by the patient's total body weight.

Signal

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Introduction

Tocilizumab (TCZ) is a humanized monoclonal antibody that acts as an interleukin6 (IL-6) receptor antagonist. Thus, it is an immunosuppressive and interleukin repressive medicine, indicated for adult treatment of severe active and progressive rheumatoid arthritis, especially in combination with methotrexate (MTX)[1], and giant cell arteritis (GCA)[2, 3]. TCZ is often given to patients responding inadequately or being intolerant to previous therapy with disease-modifying anti-rheumatic drugs or tumour necrosis factor (TNF) antagonists.[4] Further, it can be given as monotherapy in case of intolerance to, or inappropriate continued treatment with glucocorticoids and/or MTX. TCZ reduces joint progression rate damage and improves physical function when given in combination with MTX. It is also indicated for treatment of juvenile idiopathic polyarthritis in patients from two years of age who have not responded to previous therapy with MTX. More recently, TCZ has been discussed and tested as an alternative treatment for COVID-19 patients with a risk of cytokine storms, since IL-6 has been suggested as one of the most important cytokines in the storms[5].

GI perforation is a hole in the wall of GI tract which could include the oesophagus, stomach, small intestine and large intestine. Underlying causes of GI perforation may be gastric ulcers, duodenal ulcers, appendicitis, GI cancer, diverticulitis, inflammatory bowel disease, and use of medicines such as NSAIDs. Surgical intervention is usually required for haemostasis, and closure of perforation and conservative treatment is indicated only in selected patients who are clinically stable[6].

Gastrointestinal perforation is mentioned in both the EMA and FDA labelling. However, the labelling is focused on INTESTINAL perforation, and as complications of diverticulitis. This was why GASTRIC perforation was identified as a potential signal in a screening of VigiBase.

The objective of this study was to analyze the pattern and clinical features of gastric perforation associated with TCZ in the VigiBase cases, and to assess the causality alongside literature findings.

Reports in VigiBase

A clinical review of reports with gastric perforation (PT) associated with TCZ retrieved from VigiBase up to March 2020 was performed.

VigiBase contained 20 unique cases (expected three) reporting gastric or stomach perforation with TCZ as a suspected or interacting medicine. Table 1 shows the patient demographics and the characteristics of the cases. The reports came from nine countries (5 from Japan, 5 USA, 3 Colombia, 2 Austria, and 1 from UK, Ireland, Greece, Portugal and Hungary). The indications of TCZ were – when the information was available (n=18) - RA (n=16) and GCA (n=2). There were 13 females, 6 males and one lacking gender information, which reflects the population treated under the indications. Patient age ranged from 37 to 83 (median = 61 years). When reporter category information was available, the vast majority of the cases came from physicians (n=16). Of the 20 cases, 17 (85%) were serious, including four life-threatening and one with a fatal outcome. In 11 cases (55%) there were narratives, although some of these were considered less informative.

In addition to gastric perforation, seven cases had co-reported reactions such as acute coronary syndrome, pulmonary embolism, cerebrovascular accident, neutropenia, transaminases increased, respiratory or urinary tract infections, while some patients had multiple co-reported reactions. In 15 cases (75%), TCZ was the only suspected drug. In the remaining five cases the co-reported suspected drugs included MTX, prednisolone, hormones (unspecified) and celecoxib, and two of these patients, on NSAIDs or steroid, no gastroprotection (such as antacids) was mentioned. Where information was provided, concomitant medications were given to 12 patients.

Eight cases had information on TCZ dosing: mean dose, corresponding to four-weekly intervals, was 7.9 (SD 1.1; median 8.0) mg/kg, ranging 6.0 to 10.0 mg/kg, based on the highest dose if different doses had been given. When information was available (n=8), the mean body weight was 80 (SD 24; median 89) kg, ranging 49 to 114 kg (49, 52, 53, 75, 88, 90, 98, 100 and 114 kg, respectively).

The time to reaction onset (TTO) was reported in 13 cases, ranging from 0.5 to 36 months (mean 10; SD 11; median 5). The reaction led to withdrawal of

TCZ in seven cases when information was available. The outcome was reported as recovery in eleven cases, no recovery in one, fatal in one, and unknown in seven. Positive dechallenge was reported in four cases and there was one case with rechallenge, where no gastric symptoms were reported two weeks after the restart of TCZ at the time of reporting. Surgery was specifically mentioned in the management of the reaction in four cases.

Where information on the medical history and concomitant medications was available, known risk factors for gastric perforation existed in ten patients, including e.g. GI disorders, smoking; concomitant treatment with MTX, rituximab, steroids, NSAIDs, or a combination of these.

Literature and labelling

Tocilizumab (RoActemra) EU summary of product characteristics (SPC)[4]

Posology and method of administration

Treatment should be initiated by healthcare professionals experienced in the diagnosis and treatment of RA, systemic juvenile idiopathic arthritis (sJIA), juvenile idiopathic polyarthritis (pJIA) or cytokine release syndrome (CRS). TCZ should be administered as an intravenous infusion over one hour.

For RA patients, the recommended posology is 8 mg/kg body weight, given once every four weeks.

For individuals whose body weight is more than 100 kg, and doses exceeding 800 mg per infusion are not recommended. Dose adjustments are needed if laboratory abnormalities (liver enzyme abnormalities, low absolute neutrophil count, and low platelet count) are found. No dose adjustment is required in elderly patients >65 years of age, or in patients with mild renal impairment.

Special warnings and precautions for use

Complications of diverticulitis: perforations as complications of diverticulitis have been reported uncommonly with TCZ in RA patients (see section 4.8). TCZ should be used with caution in patients with a previous history of intestinal ulceration or diverticulitis. Patients presenting with symptoms potentially indicative of complicated diverticulitis, such as abdominal pain, haemorrhage and/or unexplained change in bowel habits with fever should be evaluated promptly for early identification of diverticulitis, which can be associated with gastrointestinal perforation.

Gastrointestinal perforation: during the 6-month controlled clinical trials, the overall rate of gastrointestinal perforation was 0.26 events per 100 patient years with TCZ therapy. In the long-term exposure population the overall rate of gastrointestinal perforation was 0.28 events per 100 patient years. Reports of gastrointestinal perforation on TCZ were primarily reported as complications of diverticulitis including generalised purulent peritonitis, lower gastrointestinal perforation, fistulae and abscess.

Discussion

TCZ, as a monoclonal antibody targeting the IL-6 receptor, has been reported to increase the GI perforation risk (see review by Jagpal & Curtis 2018)[7]. Xie et al. (2016) [8] estimated that the risk for lower GI perforation associated with TCZ was more than twice that for anti-tumour necrosis factor agents. Strangfield et al. (2017)[9] in a registry of lower intestinal perforation (LIP) showed that the crude incidence rate of LIP was significantly increased in TCZ (2.7/1000 PYs) as compared with all other treatments (0.2–0.6/1000 PYs). In the literature, more data are available regarding the risk of perforation for lower GI tract. More recently, Jagpal and Curtis (2018) have reviewed the issue of GI perforations

Table 2 Undesirable effects (relevant to the signal, selected by the authors)

MedDRA System Organ Class	Frequency categories with preferred terms
Infections and infestations	**Uncommon**: diverticulitis
Gastrointestinal disorders	**Common**: abdominal pain, mouth ulceration, gastritis **Uncommon**: stomatitis, gastric ulcer

among RA patients receiving targeted therapies with updated data. It was stated that although data are limited, drugs that block IL-6 are associated with an increased risk of GI perforation, more so than other RA therapies. In our current study, 20 cases of gastric perforation in VigiBase were reviewed with a focus on the clinical features. TTO ranged from 0.5 to 36 months (mean 10; median 5). About 2/3 of the cases were females, reflecting the treatment indication of RA where a female to male prevalence ratio of 2-3:1 was reported[10].

When TCZ (RoActemra) was approved in the EU (2009), the Member States were required to implement an educational pack to inform physicians and patients about the risks of serious infections and complications of diverticulitis[11]. In the summary of the Risk Management Plan (RMP)[12] it was stated that the rate of serious infections appears to increase with body weight. TCZ is dosed according to body weight: 8 mg/kg body weight, given once every four weeks. For individuals whose body weight is more than 100 kg, doses exceeding 800 mg per infusion are not recommended[13].

In the current study, the body weight was about 80 kg on average. However, no case had this body weight reported: only one patient had a body weight of 75 kg, which was close to the average body weight, while five patients had higher body weight (88.2, 90, 98, 100 and 113.5 kg) and three patients had lower body weight (49, 52.2 and 53 kg). It seems that patients with higher body weight are over-represented in this study. It has been reported that chronic dosing using total body weight can lead to drug toxicity in obese adults[14]. Although the body composition (lean versus adipose weight) and the body mass index were not reported, it seems prudent to recommend close monitoring of patients, in particular those with a high body weight when the drug is dosed according to total body weight.

The findings in the present case series are in line with the literature regarding the commonly used concomitant medicines in RA, e.g. MTX, NSAIDs, and corticosteroids, all known to present risks for GI disorders, in particular gastric perforation[7]. As shown in Table 1, in five cases patients used MTX, in five cases NSAIDs, and in six cases steroids, including one with higher dose of steroids. In addition, one patient concomitantly used rivaroxaban which is known for increasing the risk of GI bleeding. These drugs may all therefore have further impacted the adverse events. Moreover, six patients also had concomitantly used PPI. Whether this was used to prevent GI problems, or for treatment of the same, is however unknown.

The case reports did not specifically mention diverticulosis, apart from two: one where it was stated as present, and another where its absence was noted. Ghorai et al. (2003)[15] identified 0.8% of patients, who underwent colonoscopy and lacked symptoms or clinical evidence of diverticulitis, to have diverticular inflammation. According to Storz et al. (2019)[16], up to 40% of the Western population may have diverticulosis. Giang et al. (2016)[17] question whether patients with known severe diverticulosis should be excluded, or if they should have a colonoscopy before starting TCZ to assess whether they have diverticulosis. Jagpal & Curtis 2018 also suggested IL-6 blockers are best avoided in patients with a history of diverticulitis, as they are known to increase the risk of subsequent intestinal perforation. The impact of diverticulitis on gastric perforation is unclear.

In one case, the patient was a smoker, which according to Li et al. (2014)[18], can induce pathogenic and carcinogenic processes in the GI tract. This is because active compounds in cigarette smoke can damage GI tract structure through cellular apoptosis induction, and hamper the mucosal cell renewal. Cigarette smoke further interferes with protective mechanisms of the GI tract through modulating the mucosal immune system, and reducing the mucosa blood flow. In addition, it inhibits the synthesis and release of EGF and polyamines, resulting in mucus secretion decrease, which may harm the defence of mucosal integrity.

It should be noted that 11 patients, when information was provided, had at least one factor that may have contributed to the occurrence of gastric damage, such as concomitant drugs (e.g. MTX, NSAIDs, steroids, rivaroxaban), or conditions (e.g., smoking, high body weight and associated high dose). In most of these cases (n=8) there were two or more of the above factors, suggesting compounded risks for the reaction to occur.

Only four cases specifically mentioned surgery as an action taken for the ADR. The current treatment of perforated peptic ulcer is surgical repair, although conservative treatment can be adopted in selected

patients[6]. It is unclear in our case series whether the perforations without surgery mentioned in the reports were "microperforation" (see definition of GI perforation[7] by Jagpal & Curtis 2018) where surgery was not indicated, or surgery was performed but such information was not given in the reports.

Conclusion

Gastrointestinal perforation is an important identified risk of TCZ treatment which may be life-threatening. However, the current labelling is focused on intestinal perforation, and as a complication of diverticulitis. In VigiBase, cases of gastric perforation have been reported, in particular in patients with concomitant medications known to cause gastric perforation and with high body weight. Health care professionals should be aware of this possible risk and closely monitor patients, in particular those with risk factors for GI perforation, as well as those with high body weight, during treatment with TCZ, which is dosed according to total body weight.

We acknowledge with thanks the pharmacovigilance centres which have contributed to additional case information upon request.

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Table 1. Patient demographics and case characteristics of gastric perforations associated with tocilizumab in VigiBase.

Case	Age/sex/ body weight	Indication/ Dose (mg /4 w)	Other suspected (S) drugs than TCZ or concomitant drugs	Time to onset in (months)	Outcome Recovery: Yes/No/ unknown	Co-reported adverse events	Relevant medical history and concomitant medicines
1	-/-/-	Unknown / -	-	Unknown	Unknown	-	-
2	55/F/ 88 kg	RA / -	Calcium carbonate, levothyroxine, losartan, omeprazole, vitamin D nos	Unknown	Unknown	Acute coronary syndrome, UGI haemorrhage	PPI; BW 88 kg
3	53/F/-	RA / 560	-	5	Yes (sequelae)	-	-
4	70/F/-	RA / 400	-	3	Yes (sequelae)	-	-
5	50/F/-	RA / 504	-	36	Yes	-	-
6	37/F/ 98 kg	RA / 780	Etoricoxib leflunomide hydroxychloroquine tramadol	2	Yes, after surgery	-	NSAID, diverticulitis, BW 98 kg
7	-/F/-	RA / -	-	Unknown	Unknown	¬¬¬-	-
8	67/-/-	RA / -	Rituximab (S), beclometasone, budesonide, fluticasone, folic acid, formoterol, furosemide, gabapentin, ipratropium, metformin, MTX, montelukast, pantoprazole, prednisone, ranitidine, salbutamol, salmeterol, simvastatin, sitagliptin, warfarin	Unknown	Unknown	Oesophagitis, pulmonary embolism, tongue ulceration	Steroid high dose, MTX, PPI, rituximab, higher than max dose
9	65/F/-	RA / 400		13	Yes	-	-
10	49/F/ 52 kg	RA / -	DMARDs, NSAIDs	17	Unknown	GI haemorrhage, neutropenia	NSAID
11	55/M/ 90 kg	RA / 680/35-40	Folic acid (S), hydroxy-chloroquine (S), MTX. Corticosteroids, PPI	27	Yes, after surgery	Transaminases increased, URTI	Smoking, MTX, steroids; PPI; high dose; BW 90 kg
12	58/M/ 49 kg	RA / 400	MTX (S), Prednisol (S), alfacalcidol allpurinol, aspartate calcium, diclofenac, dimeticone, etizolam, iron, lansoprazol, mizoribine, risedronic acid, tacrolimus, zopiclone	3	Yes	-	MTX, steroids, max dose

Case	Age/sex/ body weight	Indication/ Dose (mg /4 w)	Other suspected (S) drugs than TCZ or concomitant drugs	Time to onset in (months)	Outcome Recovery: Yes/No/ unknown	Co-reported adverse events	Relevant medical history and concomitant medicines
13	46/M/ 100 kg	RA / 800	Diclofenac, leflunomide omeprazole, prednisolone	3	Yes, after surgery	Abscess, (probably tamponated)	NSAID, steroids, PPI, BW 100 kg
14	-/F/-	Unknown / -	-	Unknown	Unknown		-
15	73/M/ 75 kg	RA / 600	Meloxicam, MTX, PPI.	11	Yes, after surgery	-	NSAID, PPI, MTX. ***No*** *history of GI disorders (ulcers, diverticulosis etc).*
16	62/F/ 113 kg	RA / -	Folic acid, metoprolol, oxybutynin, pravastatin, rivaroxaban, omeprazole	Unknown	Unknown	UTI, influenza	(Rivaroxaban), PPI, BW 113.5 kg. Mg/ kg unknown.
17	79/M/-	GCATemp. art/-	-	Unknown	No	-	-
18	83/M/-	RA/162/ 1or2v =	Hormones (S), iguratimod, Sulfasalazine	8	Yes	-	-
19	76/F/-	Temp.art / 162/1v (=648?) s.c./i.m.	Prednisone	3	Death	Cerebrovascular accident	Steroids; fatal
20	50/F/ 53 kg	RA /162/2v (= 324 mg?)	Celecoxib (S), prednisolone (S), folic acid, MTX, paracetamol, tramadol	0.5	Yes	-	NSAID, steroids, MTX

BW: Body weight; DMARDs: Disease-modifying antirheumatic drugs; F:Female; GCA: Giant Cell Arteritis; GI: Gastrointestinal; M: Male; MTX: Methotrexate; NSAIDs: Nonsteroidal anti-inflammatory drugs; PPI: Proton pump inhibitor; RA: Rheumatoid arthritis; TCZ: Tocilizumab; URTI: upper respiratory tract infection;

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.

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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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