Signal

# Tocilizumab and Cutaneous Vasculitis

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## Summary

Tocilizumab is a biological agent that inhibits interleukin-6 that is indicated in rheumatoid arthritis, and recently, polymyalgia rheumatica and giant cell arteritis. Administration intravenously or subcutaneously leads to a rapid decline in C-reactive protein. The medicine is corticosteroid-sparing in polymyalgia and giant cell arteritis. Sixteen reports from VigiBase of cutaneous vasculitis, an inflammation of small blood vessels, the majority labelled as serious, occurred after a median of 60 days treatment but with a wide range for time to onset. Reports were entered in VigiBase from June 2012 until April 2019. Reactions were more prevalent in men and with higher dose rates of 8 mg/kg monthly intravenously. Fifteen of these cases were in patients with rheumatoid arthritis. A number of medicines taken in addition to tocilizumab were listed as 'suspected' contributors to the cutaneous vasculitis reaction, including other biological medicines, namely tumour necrosis factor inhibitors, abatacept, anakinra and leflunomide, all these in one case. Dechallenge was successful in six cases and rechallenge led to recurrence in the one subject re-exposed providing reasonable evidence for an association between tocilizumab and cutaneous vasculitis, although the standard of the 16 reports were generally poor. This potential adverse drug reaction, however, is not listed in the drug label approved by FDA.

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## Introduction

Tocilizumab is one of an important group of biological agents that have revolutionized the treatment of rheumatoid arthritis. It is a fully human monoclonal antibody that inhibits the inflammatory cytokine, interleukin-6 (IL-6). IL-6 synthesis is driven by interleukin-1(IL-1) and tumour necrosis factor-alpha, up-stream cytokines that are also targets for inhibitory therapies, including IL-1 receptor antagonist (anakinra) and a number of tumour necrosis factor inhibitor recombinant proteins, including etanercept, adalimumab, infliximab and golimumab. Tocilizumab also has an indication for juvenile idiopathic arthritis, and more recently, polymyalgia rheumatica (PMR)[1], and giant cell arteritis.[2]

Tocilizumab therapy is administered parenterally, either intravenously or subcutaneously (SC), and results in rapid reduction of C-reactive protein (CRP) concentrations, the preferred biomarker for systemic inflammation. IL-6 promotes the production of CRP from the liver. Optimally, the drug is given with concomitant methotrexate in patients with rheumatoid arthritis (RA) or juvenile idiopathic arthritis (JIA), since the combination is more effective at slowing disease progression as manifest by joint bone erosions. In PMR, tocilizumab is corticosteroid-sparing, beneficial in reducing the dose and duration related adverse effects of corticosteroids, notably osteoporosis, type 2 diabetes mellitus, weight gain, muscle loss and sleep disturbance.

A number of cases of cutaneous vasculitis associated with tocilizumab have now been reported, including reports submitted to VigiBase.[3] Cutaneous vasculitis is inflammation of small blood vessels and is confined to the skin. Typically, it presents with palpable purpura and/or petechiae, essentially small haemorrhages that have formed small blood clots. However, it is also a recognised manifestation of rheumatoid arthritis.

## Reports in VigiBase

Sixteen cases of apparent cutaneous vasculitis have been reported in association with tocilizumab from the middle of June 2012 up until April 2019. The cases were from nine countries (UK 4, USA 3, France 2, Japan 2 and one each from Germany, Belgium, Slovakia, Hungary and Canada). Fifteen cases had a diagnosis of RA and there was one person with JIA. There were 11 men and 5 women affected, an unexpected distribution given RA is more prevalent in women at around 75%.[4] Patients were aged 16 to 78 (median 63; n = 13). There were 13 of the 16 cases that were labelled serious. Four were associated with prolonged hospitalization with one of these described as a life-threatening condition. One case was described as disabling/incapacitating. Eight individual's reactions were labelled as 'other'. Only two subjects were participants in clinical trials. One patient was rechallenged with tocilizumab and the vasculitis recurred. This person had also been exposed to rituximab, but ultimately this was not considered as related to the vasculitis, an opinion in keeping with the result of the rechallenge.

The quality of the reports as assessed by 'completeness scores' were poor, range 0.2 to 0.9. Fourteen of the reports were submitted by physicians.

The drug was administered as an intravenous infusion monthly or, with a more recent formulation, via weekly or second weekly SC. Only two of the reports indicated administration via the SC, the dose being 162 mg and these cases were reported recently (2017 and 2018). The reported doses of tocilizumab were 8 mg/kg (2 cases), 4 mg/kg (1 case) and actual doses of 480 mg (female), 560 mg (male), 440 mg (female), 400 mg (male) and 580 mg (male), these latter five likely to be equivalent to 8mg/kg given that an individual patient would need to weigh 100 kg for a dose of at least 400 mg if the dose rate was 4 mg/kg. In six subjects, the dose was not reported. Therefore, for the 8 cases of 11 where the drug was delivered intravenously and the dose reported, seven of the eight were given 8 mg/kg. There is divergence in the 'label' regarding the recommended dose of RA. In some jurisdictions e.g. USA it is 4 mg/kg every 4 weeks (or 162 mg SC every 2 weeks)[5] and in others it is 8 mg/kg every 4 weeks (or 162 mg SC every week). The one case dosed with 4 mg/kg came from the USA.

Data on duration of therapy with tocilizumab until the onset of the vasculitis from the VigiBase reports is limited (6 of 16 case reports) and some reports only note 'start' and 'stop' months, not the day of the month, the reaction commenced. Median duration of therapy was 161 days however in the few cases [6] where 'time to onset' of reaction was recorded, the median was 60 days, but the range was from 2 to 540 days.

**Table 1. Cases of cutaneous vasculitis associated with tocilizumab in VigiBase**

| Case | Age/ Sex | Seriousness criteria* | Other suspected (S) or concomitant (C) drugs | Time to onset | Action drug | Outcome |
|---|---|---|---|---|---|---|
| 1 | 70/M | - | Tocilizumab (S) | - | - | Not recovered |
| 2 | 67/M | - | Tocilizumab, rituximab (S) | - | Drug withdrawn/ Reaction abated<br>Rechallenge/ Reaction recurred | Recovered |
| 3 | -/F | - | Tocilizumab (S) | - | - | Unknown |
| 4 | 48/M | Other | Tocilizumab (S)<br>Folic acid, methotrexate, metoclopramide, naproxen, omeprazole, sildenafil, tramadol (C) | 7 days | Drug withdrawn/ Reaction abated | Recovering |
| 5 | 55/M | Prolonged hospitalization | Tocilizumab (S) | 18 months | Drug withdrawn/ Reaction abated | Recovering |
| 6 | 63/F | Other | Tocilizumab, etanercept, adalimumab, abatacept, anakinra, leflunomide (S)<br>Tofacitinib (C) | | Drug withdrawn | Unknown |
| 7 | 55/M | Other | Tocilizumab (S) | - | - | Recovering |
| 8 | -/F | Life threatening, prolonged hospitalization | Tocilizumab (S)<br>Methylprednisolone (C) | - | - | Unknown |
| 9 | 78/M | Other | Tocilizumab, certolizumab pegol (S) | 2 days | Drug withdrawn/ Reaction abated 3.5 months after cessation of drug | Recovered |
| 10 | 16/F | Prolonged hospitalization | Tocilizumab, methotrexate, cortisone (S) | 10 months | Drug withdrawn | Unknown |
| 11 | 65/M | Other | Tocilizumab (S)<br>Sulfasalazine, bucillamine, isoniazid, prednisolone, omeprazole, celecoxib, nateglinide, alfacalcidol (C) | 2 months | Drug withdrawn/ Reaction abated | Recovering |
| 12 | 74/M | Disabling, incapacitating | Tocilizumab (S)<br>Methotrexate, folic acid, prednisolone, lansoprazole, metformin, acetylsalicylic acid, simvastatin, senna, furosemide, ramipril, doxazosin, bisoprolol, isosorbide monohydrate (C) | 2 months | Drug withdrawn/ Reaction abated | Recovered |
| 13 | 54/M | Prolonged hospitalization | Tocilizumab (S) Dihydrocodeine, paracetamol, omeprazole, nitrazepam, folic acid, diazepam (C) | | Drug withdrawn | Unknown |
| 14 | 67/M | Other | Tocilizumab (S) | - | - | Recovering |
| 15 | 52/F | Other | Tocilizumab (S) | - | - | Recovered |
| 16 | -/M | Other | Tocilizumab (S) | - | - | Recovered |

**Seriousness is classified in accordance with the criteria defined in the ICH E2A guideline*

Regarding medications preceding and/or during and/or immediately following the period of exposure to tocilizumab, some were suspected as contributing to the vasculitis. There were three cases prescribed methotrexate, which was suspected as contributing in one of these. In one case rituximab, and in another, certolizumab, was suspected, along with tocilizumab, as contributing. One patient had been taking sulfasalazine and bucillamine but these were not suspected contributors to the vasculitis. One patient was described as having 'RA aggravated' and 'condition aggravated'. This patient was treated (in order of administration) with etanercept, then adalimumab, then abatacept, then tocilizumab, then anakinra, then leflunomide and finally, tofacitinib. It is uncertain if this patient's cutaneous vasculitis occurred in relation to tocilizumab, as all of the aforementioned drugs including leflunomide were recorded as suspected contributors. Glucocorticosteroids were noted as concomitant medications for three patients, one given 1000 mg methylprednisolone possibly for their cutaneous vasculitis, another person, doses of oral prednisone ranging from 15 to 45 mg/day for the six months following cessation of tocilizumab, suggesting treatment for the cutaneous vasculitis and one a therapeutic dose for RA of prednisone 5 mg/day. A patient who had JIA and suspected tocilizumab caused vasculitis was taking cortisone that was listed as 'suspected' as a cause of the vasculitis.

There were patchy reports of reactions, features or investigations accompanying the cutaneous vasculitis. Complement C4 was noted as decreased in two patients and one of these also had reduced C3, thus suggesting immune complex aetiology. The person with JIA exhibited splenomegaly, fever, Sweet's syndrome (acute febrile neutrophilic dermatosis) and Stevens-Johnson syndrome. In this person, cutaneous vasculitis occurred while taking methotrexate and about 6 months later, tocilizumab was commenced, and a rash was reported. Both drugs were continued for about nine months. The diagnoses of Sweet's syndrome and Stevens-Johnson syndrome occurred together, about the time both methotrexate and tocilizumab were ceased. Therefore, there is significant doubt that the presumed vasculitis was caused by tocilizumab in this case.

## Literature and Labelling

Sakaue et al reported the first case of leukocytoclastic vasculitis in 2014.[3] There do not appear to be further publications in the literature. The case described by Sakaue and colleagues was a Japanese woman aged 62 years with RA for 25 years. Treatment with infliximab for five years was followed with etanercept but control was not achieved, and tocilizumab was commenced. The initial dose was 8 mg/kg for one month, then 4 mg/kg along with prednisone 3 mg/day, and good control of her RA was achieved for five years. An inflammatory disease flare along with palpable purpura on limbs and buttocks led to a skin biopsy that showed leukocytoclastic vasculitis without IgA deposition, and not fulfilling criteria for Henoch-Schönlein purpura. There were no other relevant laboratory findings apart from an elevated CRP. The prednisone dose was increased and abatacept commenced with good effect. There was no recurrence and no rechallenge with tocilizumab. Sakaue et al noted that the vasculitis in association with TNFI occurs on average around 30 weeks (210 days) compared to the median of 8 weeks (60 days) in the VigiBase cases. However, in Sakaue et al's case it was over five years and there were two VigiBase cases occurring after one year's tocilizumab therapy.

The FDA label notes that serious hypersensitivity reactions, including anaphylaxis, have occurred with tocilizumab but without further information. Cutaneous vasculitis is not listed as an adverse drug reaction.[5]

## Discussion and Conclusion

Tocilizumab has been generally well tolerated. As with other biologic medicines there is a risk of serious infections including reactivation of tuberculosis (TB), hepatitis B and C, and opportunistic infections including disseminated fungal infections. Testing for latent TB and hepatitis infection prior to commencement is mandatory. The drug is associated with elevations of serum cholesterol in adults. The label indicates that elevations of hepatic enzymes can occur, and recently a warning regarding liver failure, transplantation and deaths has been published by Canadian and US regulatory agencies, and other agencies are considering their own responses.

Sakaue et al (2014) note that biologic agents used for inflammatory rheumatic conditions such as RA, psoriasis and psoriatic arthritis have been associated with autoimmune adverse events, especially the tumour necrosis factor inhibitor (TNFI) group of biologics. The most frequent conditions reported

have been SLE but vasculitis and skin involvement in these conditions is common.

This series from VigiBase of 16 cases of associations between tocilizumab therapy, mainly for RA, and cutaneous vasculitis add to only one in the literature. There is an unusual proportion of males with RA in these cases. Regarding the strength of the association and possible causation, there is only one report with a rechallenge. In this case the vasculitis recurred, providing strong evidence of causality. Also, six of the cases responded positively to dechallenge, adding further strength to the case for an association. The stated treatment duration with tocilizumab had a median of 161 days, and median time to onset of reaction in six of the cases of 60 days, but both medians have a very wide range. This is quite long for drug-induced cutaneous vasculitis that is often in the order of 7-14 days until onset.[6] However, vasculitis induced by anti-TNF agents has been noted to occur after 30 weeks exposure.[7] It has been suggested that the immunogenic stimulus for autoimmune reactions such as vasculitis may be less for tocilizumab compared to TNF inhibitors.[3]

The doses of tocilizumab noted most commonly were high, at 8 mg/kg. Some guidelines groups and regulatory labels recommend 4 mg/kg monthly (162 mg SC second weekly), stating that the lower dose rate is better tolerated without substantial reduction in efficacy.

Unfortunately, there are no biopsy reports for any of the VigiBase cases. Although there are very few cases, there may be a predilection for males, the elderly and dosing at the higher end of the recommended range. Given the new indications of PMR and giant cell arteritis, prevalent and important conditions, in the light of these reports, vigilance is recommended.

In summary, the review of the 16 cases reported in VigiBase provides good evidence that tocilizumab, like TNF inhibitor biological agents, is associated with cutaneous vasculitis. The possible risk factors for the association are possibly male sex, duration of exposure of many months and higher dose rates namely 8 mg/kg monthly intravenously. The case for a causal relationship between the drug and vasculitis is quite strong with six of 16 responding to 'dechallenge' and one patient subject to a rechallenge manifesting the vasculitis again.

## References


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## SIGNAL

WHO defines a signal as:

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

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

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

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

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

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

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

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

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

## Responses from industry

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

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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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