Tocilizumab in the Management of Immune-Related Adverse Effects (irAEs)

A guide for members on the prescribing and monitoring of Tocilizumab when used in the management of irAEs caused by treatment with immune-checkpoint inhibitors.

It should be noted that this use is considered off-label use; relevant governance processes within each organisation should be followed to ensure the risks associated with this are mitigated.

British Oncology Pharmacy Association in Collaboration with The Immuno-oncology Clinical Network

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1. Introduction

- Tocilizumab is a humanised anti-interleukin-6 (IL-6) receptor monoclonal antibody that has an anti-inflammatory effect. Tocilizumab binds to soluble and membrane bound IL-6 receptors, preventing IL-6 mediated inflammation. Within its licensed indication it is used to treat moderate to severe rheumatoid arthritis, juvenile idiopathic polyarthritis, coronavirus disease 2019 and cytokine release syndrome (CRS) associated with some types of immunotherapy and chimeric antigen receptor T cell therapy (CAR-T). Off licence is can be used as a steroid sparing agent to treat multiple immune-related adverse events (irAEs), which can present as a **result of immune-checkpoint inhibitor (ICI) treatment.**

- Evidence exists for the use of tocilizumab in a variety of ICI irAEs such as hepatitis, cholangitis, interstitial lung disease, pneumonitis and CRS as per the ESMO and ASCO guidelines. In addition, there are case reports in a variety of other ICI irAEs including immune-related myocarditis.

- This document is intended to be used as a monograph to provide prescribing and monitoring advice once the decision has been made to initiate tocilizumab for **ICI irAEs.**

- It is not a clinical guideline, but a consensus view of current use of tocilizumab when used for **irAEs as a result of immune-checkpoint inhibitors.** It should be used in conjunction with any local policies/procedures/guidelines and should be approved for use according to the trust clinical governance processes.

2. Prescribing and Monitoring Advice

2.1 Contraindications

- Active, severe infections with the exception of COVID-19.
- Hypersensitivity to Tocilizumab.
- Hypersensitivity to any of the excipients.

2.2 Precautions

- Risk of serious infection - Increased risk of serious infection including tuberculosis, bacterial, invasive fungal, viral, and other opportunistic infections.
- Caution with patients with a history of recurring or chronic infections or underlying conditions which may predispose to infection.
- Risk of reactivation of Hepatitis B and C – screening and prophylaxis as per local policy.
- Serious drug-induced liver injury has been reported - avoid or treat with cautious in patients with active hepatic disease or liver impairment.
- Patients with a history of gastrointestinal ulceration and diverticulitis may be at higher risk for gastrointestinal perforation
- Immunisations - Avoid live immunisations. Contact specialist for advice.

2.3 Pre-treatment assessment

- Urea and electrolytes (U&Es), liver function tests (LFTs)
- Full blood count (FBC)
- Hepatitis B and C serology
- Chest X ray and T spot test to exclude tuberculosis if required (as per local policy)

2.4 Pharmaceutical form

- Tocilizumab is available as two forms. Either a solution for intravenous(IV) infusion (20mg/ml), or a subcutaneous(SC) injection (162mg) via a pre-filled pen or syringe.
- Tocilizumab concentrate for solution for infusion is the choice of formulation when treating ICI irAEs.
- Two brands of tocilizumab are available within the United Kingdom (RoActemra® and Tyenne®). Tocilizumab biosimilar (Tyenne®) is available in the same formulations as RoActemra® (IV and SC).
- As the clinical efficacy, safety profile and immunogenicity of tocilizumab biosimilar and the reference product are similar, brands can be used interchangeably.
- Branded prescribing is not required for tocilizumab.

2.5 Dosage

- For grade 2 or higher CRS, tocilizumab should be prescribed at 8mg/kg (maximum 800mg/dose). Based on a reassessment of the patient's response, repeat doses may be given every 8 hours, with a maximum of 3 doses in a 24-hour period. No more than 4 doses should be given during a CRS episode (maximum 800mg/dose).
- For other irAEs, tocilizumab should be prescribed at a dose of 8mg/kg for one dose and repeated after 2 weeks if required.
- Tocilizumab can be administered alongside IV methylprednisolone.
- Dose adjustments are not required in patients with mild renal impairment. Tocilizumab has not been studied in patients with severe renal impairment or hepatic impairment, therefore dose adjustments cannot be recommended.

2.6 Method of administration

- Tocilizumab should be given as an IV infusion over 60 minutes. Tocilizumab dose should be diluted in a 100ml bag of sodium chloride 0.9%, after removing an equivalent volume of sodium chloride (total end volume 100ml).
- Serious hypersensitivity reactions have been reported with tocilizumab.
- Consider pre-medication with analgesics, antihistamines, and corticosteroids if there is evidence of previous reactions to tocilizumab.

2.7 Is there therapeutic Drug Monitoring?

- Therapeutic drug monitoring is not required for tocilizumab.

2.8 Other monitoring

- Pulse, blood pressure, temperature and respiratory rate should be monitored for any signs of hypersensitivity reactions during the infusion. Observations to be checked every 15 minutes and every 30 minutes until 1-hour post infusion.
- FBC, U&Es, LFTs

Blood Test Results	**Advice**
Baseline Neutrophils < 1.0 x 10^9 /l	Do not initiate. Discuss with specialist team
Baseline Platelets < 50 x 10^9 /l	Do not initiate. Discuss with specialist team
Baseline ALT or AST > upper limit of normal.	Initiate with caution; discuss with specialist team. Use may be appropriate if raised LFTs are associated with the underlying irAE e.g. when being used to treat immune-related CRS.
Lipids	Discuss abnormal result with specialist team.
Symptoms	
Unexplained rash	Withhold until discussed with specialist team.
Signs of sepsis or infection	Withhold until infection has resolved. Discuss with specialist team.
Signs or symptoms of liver impairment - tiredness, abdominal pain, and jaundice	Withhold until discussed with specialist team.

2.9 Adverse effects

- The table below outlines the broad range of adverse events that patients can experience with Tocilizumab.
- This is not an exhaustive list. See SmPC for further details.

System	**Adverse Effects**
Infections and infestations	Upper respiratory tract infections, Cellulitis, Pneumonia, Oral herpes simplex, Herpes zoster.
Blood and lymphatic system disorders	Leukopenia, Neutropenia, Hyperfibrinogenemia
Metabolism and nutrition disorders	Hypercholesterolaemia
Nervous system disorders	Headache, Dizziness
Eye disorders	Conjunctivitis
Vascular disorders	Hypertension
Respiratory, thoracic and mediastinal disorders	Cough, Dyspnoea
Gastrointestinal disorders	Abdominal pain, Mouth ulceration, Gastritis
Skin and subcutaneous tissue disorders	Rash, Pruritus, Urticaria

General disorders and administration site conditions	Peripheral oedema, Hypersensitivity reactions
Investigations	Hepatic transaminases increased, Weight increased, Total bilirubin increased

2.10 Drug interactions

- The expression of CYP450 enzymes is suppressed by IL-6 which stimulates chronic inflammation. Therefore, CYP450 expression may be reversed when tocilizumab is administered.
- When starting or stopping tocilizumab, patients taking medicines which are metabolised via CYP450 3A4, 1A2 or 2C9) should be monitored as doses may need to be increased to maintain therapeutic effect.
- Given its long elimination half-life the effect of tocilizumab on CYP450 enzyme activity may continue for several weeks after stopping therapy.
- In addition, due to the risk of hepatic toxicity there is a risk of additive toxicity with other hepatotoxic drugs, so these should also be avoided.

- The table below lists the most common interactions but is not exhaustive. The SmPC and other drug interactions resources should be further consulted.

Drug	**Interaction**
Live vaccines	Avoid. Increase risk of infections.
Alprazolam	Decreased exposure to Alprazolam
Aminophylline	Decreased exposure to Aminophylline
Amlodipine	Decreased exposure to Amlodipine
Atorvastatin	Decreased exposure to Atorvastatin
Ciclosporin	Decreased exposure to Ciclosporin
Dexamethasone	Decreased exposure to Dexamethasone
Diazepam	Decreased exposure to Diazepam
Diltiazem	Decreased exposure to Diltiazem
Felodipine	Decreased exposure to Felodipine
Filgotinib	Increased exposure to Filgotinib
Fosphenytoin	Decreased exposure to Fosphenytoin
Lacidipine	Decreased exposure to Lacidipine
Lercanidipine	Decreased exposure to Lercanidipine
Methylprednisolone	Decreased exposure to Methylprednisolone
Midazolam	Decreased exposure to Midazolam
Nicardipine	Decreased exposure to Nicardipine
Nifedipine	Decreased exposure to Nifedipine
Nimodipine	Decreased exposure to Nimodipine
Phenytoin	Decreased exposure to Phenytoin

Simvastatin	Decreased exposure to Simvastatin
Theophylline	Decreased exposure to Theophylline
Verapamil	Decreased exposure to Verapamil
Warfarin	Decreased exposure to Warfarin

2.11 Advice to patients

- Tocilizumab is a medication used to manage adverse events associated with immune checkpoint inhibitors. It is administered via an IV infusion over 60 minutes.
- Drug monitoring is not required whilst receiving tocilizumab.
- Tocilizumab can affect their liver. Patients and their carers should be advised to contact their acute oncology team for immediate medical attention if signs and symptoms of liver injury, such as tiredness, abdominal pain, and jaundice, occur.
- There are several significant interactions with tocilizumab. Patients should confirm with their oncology team before any new medicines are started, including those they buy over-the-counter.
- Effective contraception required during and 3 months after treatment.
- An example patient information leaflet is available in Appendix 1.

3. Appendix 1 Example Patient Information Leaflet

What is Tocilizumab?

Tocilizumab is a medication used to manage adverse events associated with immune checkpoint inhibitors, which are treatments that help your immune system fight cancer. Tocilizumab works by blocking a specific protein in your body that can cause inflammation and immune-related side effects.

How do I take Tocilizumab?

Tocilizumab is usually administered as an infusion into a vein (intravenously) by a healthcare professional in a hospital or clinic setting. The frequency and dosage will be determined by your oncology team based on your specific needs and response to treatment.

Drug level monitoring.

Drug monitoring is not required for tocilizumab. Regular monitoring of your condition and response to Tocilizumab will be conducted by your healthcare team. Blood tests may be required to check your liver function, blood cell counts, and other parameters to ensure the medication is working effectively and safely.

How long will I need to take Tocilizumab for?

The duration of your treatment with Tocilizumab will depend on your individual response and the specific immune-related adverse events being managed. Your oncology team will regularly review your treatment plan and make any necessary adjustments.

Does Tocilizumab have any side-effects?

There are several possible side effects that you may notice, although many people do not experience any of these. Side effects include:

- Increased risk of infections: if you develop ‘flu-like symptoms’, cough, sore throat or high temperature contact your oncology team immediately.
- Upper respiratory tract infections (common cold, sinus infections)
- Headache
- High blood pressure
- Liver enzyme elevations
- Injection site reactions (redness, swelling, itching)
- Hypersensitivity reaction to infusion
- Cold sores

It is important to tell your doctor about any side effects or unusual symptoms you experience.

Can I still be vaccinated?

You should avoid live vaccines whilst receiving tocilizumab. Inactivated vaccines are generally safe, but always check with your oncology team before receiving any vaccinations.

Is it safe to become pregnant while I am receiving Tocilizumab?

Tocilizumab can be harmful to an unborn baby. It is crucial not to plan a pregnancy whilst receiving this medication. Use effective contraception if you are sexually active. Discuss your options with your oncology team.

Can I take other medicines whilst I am taking Tocilizumab?

Always inform your oncology team or pharmacist about any new medications you are taking, including over-the-counter drugs and supplements. Tocilizumab can interact with some medications and affect their efficacy or increase the risk of side effects.

Supply of Tocilizumab?

It will be prescribed, supplied and administered by the hospital, and it is essential to plan ahead to avoid interruptions in your treatment.

Who can I contact for further information?

If you have any questions about your Tocilizumab treatment, the best people to speak to are:

- Your oncology team
- The team of specialists who prescribed Tocilizumab for you
- An oncology pharmacist

Your healthcare team is there to support you throughout your treatment and address any concerns you may have. Always reach out to them for guidance and information.

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5. Acknowledgements

Nil

6. Document control

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