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

A guide for members on the prescribing and monitoring of infliximab when used in the management of irAEs because of treatment immune-checkpoint inhibitors.

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

Version 1.0

Nov 2024

Contents

1. Introduction

- Infliximab is an anti-tumour necrosis factor-alpha (TNF-α) inhibitor.
- It is a chimeric human-murine monoclonal antibody, composed of 75% of the human constant region and 25% of the variable murine region. It is the murine region that increases the risk of infusion related reactions.
- TNF-α is a pro-inflammatory cytokine which plays an important role within the regulation of inflammatory responses and when dysregulated e.g., increased TNF-α production it leads to inflammatory and immune conditions.
- Within the UK, infliximab is licensed for inflammatory bowel disease, rheumatoid arthritis, ankylosing spondylitis and psoriasis, for both children and adults. Please refer to the SmPC for full licensing details.
- For immune related adverse events, evidence exists for the utility of infliximab for the treatment of immunotherapy induced colitis and rheumatoid arthritis for patients refractory to corticosteroid therapy.
- In addition, there are case reports of the use of infliximab in a variety of other immune-related adverse events e.g., immunotherapy induced pulmonary toxicities.
- This document is intended to be used as a monograph to provide prescribing and monitoring advice once the decision has been made to initiate infliximab. It is not a clinical guideline, but a consensus view of current use of infliximab when used for irAEs. 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

- Hypersensitivity to infliximab
- Hypersensitivity to any of the excipients
- Hypersensitivity to murine proteins
- Patients with active and latent tuberculosis (TB)
- Patients with severe infections and at high risk of opportunistic infections e.g., aspergillosis
- Abscess
- Patient with moderate or severe heart failure e.g., NYHA class III/IV or ejection fraction <20%
- Pregnancy
- Breastfeeding

2.2 Precautions

- Immunisations - Avoid live immunisations. Contact specialist for advice.
- Infliximab infusion reactions/hypersensitivity.

- Concurrent administration with other biological agents which will increase risk of serious infections e.g., abatacept, anakinra.
- Hepatitis B reactivation.

2.3 Pregnancy Advice

- The available clinical experience is limited. Infliximab should only be used during pregnancy if clearly needed.

2.4 Pre-treatment assessment

- Weight
- Confirmation of negative stool culture (colitis patients only)
- Full blood count (FBC), urea and electrolytes (U&Es), liver function tests (LFTs)
- Full TB history, including family and travel history.
- Chest X-ray or CT
- Hepatitis A, B and C serology
- HIV serology
- VZV serology
- QuantiFERON-TB Gold test
- Informed consent
- Echocardiogram for patients with suspected heart failure
- Urine pregnancy test for women of childbearing potential

2.5 Pharmaceutical form

- Infliximab is available as a biosimilar and all are available as 100mg powder for concentrate for solution for infusion.
- However, the brand Remsima is also available as a 120 mg solution for injection in pre-filled pen.

2.6 Dosage

Colitis

- 5mg/Kg at week 0, then followed by a second dose 2 weeks later if symptoms persist.
- A third dose can be administered 2 to 4 weeks later depending on symptoms.

Refractory colitis.

- 10mg/kg (unlicensed dose) can be considered for refractory colitis.
- Doses can be repeated after 1 or 2 weeks.
- Once symptoms improve infliximab dosing can be reduced back to 5mg/kg.

The need to administer more than 3 doses of infliximab is rare, however, in some cases subsequent dosing via monthly administrations can be considered. At this point it would be prudent to seek gastroenterology advice.

Rheumatoid arthritis

- 3mg/Kg at weeks 0, 2 and 6 weeks, then every 8 weeks thereafter.
- For on-going maintenance treatment to seek advice from rheumatologist.

2.7 Method of administration

- Hydrocortisone 100mg INTRAVENOUS bolus to be administered 30 minutes prior to infliximab (see pre-medication below)

- Infliximab 100mg vials for solution are administered via intravenous infusion only.

- Infliximab 100mg vials should be reconstituted and prepared as per product information.
    - For Remicade®, Remsima®, Inflectra® and Flixabi® a final concentration of 0.4 to 4mg per 1mL needs to be prepared using sodium chloride 0.9%.
    - For Zessly® the equivalent volume of the reconstituted vials should be removed from 250mL sodium chloride 0.9% bag, and then the required dose should be slowly added remaining infusion bag and mixed gently.

- Administer over 2 hours using an in-line, low protein binding filter (1.2 micron or less) using an infusion pump.

- For the prefilled 120mg Remsima brand, please refer to the summary of product characteristics for full details.
- The name and batch number of the product should be clearly recorded to improve traceability of biological medicinal products.

Pre-medication

- Infliximab is associated with infusion related reactions which includes anaphylactic shock and delayed hypersensitivity reactions.

- Take baseline observations, observe the patient every 30 minutes during the infusion, and for at least 2 hours after the infusion for signs of infusion-related reactions:

    - Observations: temperature, blood pressure, oxygen saturations, pulse and respiratory rate.

- Hydrocortisone 100mg INTRAVENOUS bolus to be prescribed 30 minutes prior to infliximab

- Other Supportive pre-medications to be prescribed and given as required:
    - Chlorphenamine 10mg INTRAVENOUS bolus up to 3 times per day
    - Chlorphenamine 4mg oral up to 3 times per day
    - Paracetamol ORAL 1 gram FOUR times a day
    - Salbutamol 2.5mg NEBULISER

Extravasation

- Infliximab is a non-vesicant however all the brands contain the excipient called **polysorbate 80** which can cause pain and irritation at the injection site.

- If extravasation suspected, follow your local protocol but below is a suggested treatment pathway:

- Inject 1500 i.u. hyaluronidase subcutaneously around the site
- Apply a warm pack to aid hyaluronidase absorption and warm pack to remain on site for 2 to 4 hours
- Elevate limb
- Apply hydrocortisone cream 1% to prevent local inflammation
- Contact plastics for further advice.

2.8 Therapeutic Drug Monitoring

There is no recommended therapeutic drug monitoring guidance or data to support measuring anti-infliximab antibodies when infliximab is used for the management of irAEs.

2.9 Other monitoring

Blood Test Results	Advice
WBC ≤3 x 10^9/L	Withhold until discussed with specialist team
Neutrophils ≤1.0 x 10^9 /l	Withhold until discussed with specialist team
Platelets ≤100 x 10^9 /l	Withhold until discussed with specialist team
≥ 3 x ULN in AST, ALT (from upper limit of reference range)	Withhold until discussed with specialist team
GFR <10 mL/min	Dose as in normal renal function

2.10 Adverse effects

- The most common adverse effects are listed below.
- This is not an exhaustive list and clinicians should refer to SmPC related to the infliximab brand being used for further details.

System	Common Adverse Effects
General disorders and administration site conditions	Infusion-related reaction, pain, chest pain, fatigue, fever, injection site reaction, chills, oedema.
Infections	Bacterial and viral infections.
Blood and lymphatic system disorders	Neutropenia, leukopenia, anaemia, lymphadenopathy.
Immune system disorders	Allergic respiratory symptoms.
Nervous system disorders	Headaches, vertigo, dizziness, hypoaesthesia, paraesthesia.
Eye disorders	Conjunctivitis.
Cardiac disorders	Tachycardia, palpitations.
Vascular disorders	Hypotension, hypertension, ecchymosis, hot flush, flushing.

Respiratory, thoracic and mediastinal disorders	Upper respiratory tract infection, sinusitis, lower respiratory tract infection (e.g. bronchitis, pneumonia), dyspnoea, epistaxis.
Gastrointestinal disorders	Abdominal pain, nausea, gastrointestinal haemorrhage, diarrhoea, dyspepsia, gastroesophageal reflux, constipation.
Hepatobiliary disorders	Hepatic function abnormal, transaminases increased.
Skin and subcutaneous tissue disorders	New onset or worsening psoriasis including pustular psoriasis (primarily palm & soles), urticaria, rash, pruritus, hyperhidrosis, dry skin, fungal dermatitis, eczema, alopecia.
Musculoskeletal and connective tissue disorders	Arthralgia, myalgia, back pain.
Renal and urinary disorders	Urinary tract infection.
Psychiatric disorders	Depression, insomnia.

2.11 Drug interactions

- No formal drug interaction studies have been performed.
- Corticosteroids have not shown to affect infliximab pharmacokinetics.

Additive toxicity

- Concomitant administration of drugs which increase the risk of immunosuppression or myelosuppression should be avoided where clinically appropriate.

- If treatment with another immunosuppressive or myelosuppressive drug is unavoidable, supportive care to reduce the risk of opportunistic infections can be considered with careful considerations of risk-benefit profile e.g., increased risk of side effects when using fungal prophylactic treatment.

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

Drug	**Interaction**
Live vaccines	Predicted to increase the risk of generalised and/or life threatening infections.
Systemic anti-cancer therapies e.g., chemotherapy	Increased risk of myelosuppression and/or immunosuppression.
Monoclonal antibodies	Increased risk of myelosuppression and/or immunosuppression.

2.12 Advice to patients

- Risk of infusion or injection site reactions e.g., redness, swelling or pain.
- If treatment being administered within an outpatient setting with the recommended observation period as described in section 2.6, it is recommended to advise patients/relatives to contact a nurse/doctor or emergencies services if at home if the patient has any of the following symptoms:
    - Difficulty breathing or swallowing
    - A rash or raised, itchy patches on your skin, known as hives
    - Swelling of your face, lips, mouth, throat, hands, feet or ankles
    - Feeling dizzy or light-headed
    - Your heart starts beating very fast

Appendix 1 Example Patient Information Leaflet

What is INFLIXIMAB?

- Infliximab is an antibody which targets a protein called tumour necrosis factor-alpha, also known as TNF-α.
- TNF-α is naturally made within your body to help regulate your immune system and fight infections. When treated with immunotherapy, your body can respond by producing lots of TNF-α causing too much inflammation, which leads to the side effects such as colitis or rheumatoid arthritis.
- Infliximab is an antibody drug which binds to the TNF-α to block its effects to reduce the inflammation.
- Before treatment, your oncology team will a take a blood test before you start treatment to make sure infliximab is safe for you. They will also ask you questions on any past or current infections as infliximab can make it harder to fight off infections.

How is infliximab administered?

Infliximab is administered as a drip into your vein in your arm, this is also known as an intravenous infusion. In some hospitals the infliximab can be administered under the skin as an injection using a pre-filled syringe.

If you are receiving the infusion, the infliximab will be administered over 2 hours with another 2 hours of monitoring time. During this 4 hour period you regularly have your observations monitored to check for any signs of allergic reaction. These observations will include measurements of your blood pressure, pulse, breathing rate and temperature.

How long will infliximab be prescribed for?

The number of doses administered will be based on how you respond to infliximab. In many cases up to 3 doses of infliximab can be administered. Some patients may need 1 dose and others may need more than three doses. Infliximab can be administered every 1 or 2 weeks. Sometimes this interval can be longer or shorter, but your oncology team will explain your treatment plan with you. This is because your infliximab treatment will be tailored to you and your symptoms.

Does infliximab have any side-effects?

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

The main side effects include:

- Redness, swelling and/or pain at the site of injection

- Difficulty breathing or swallowing
- A rash or raised, itchy patches on your skin, known as hives
- Swelling of your face, lips, mouth or throat
- Swelling of the hands, feet or ankles
- Feeling dizzy or light-headed
- Your heart starts beating very fast
- Chest pain
- Tiredness
- Feeling cold
- Headache
- Dizziness
- Feeling sick
- Diarrhoea.

It is important to tell your doctor of any side effects or unusual symptoms that you are experiencing.

Can I still be vaccinated?

It is advisable to avoid live vaccinations 4 weeks before and during treatment with infliximab. Before being treated with infliximab your oncology team will ask you for your vaccination history and will explain when it is safe to have a vaccine. Always check with your medical team before a vaccine is given to you.

Is it safe to become pregnant while on infliximab?

You may have already had these conversations with your oncology team before starting immunotherapy. It is important that you do not plan a pregnancy if you are on infliximab and should use effective contraception if sexually active for at least 6 months after completing the treatment.

Can I take other medicines whilst I am taking infliximab?

You should always check with your oncology team or pharmacist if you are started on any new medicines, including anything you may buy over the counter.

It is advised that you AVOID taking any herbal supplements whist being treated with infliximab due to the risk of serious side effects to the liver.

Who can I contact for further information?

If you have any queries about infliximab the best people to speak to is the team who you are under or the team of specialists who have prescribed the infliximab for you or your pharmacist.

3. References

- Summary of Product Characteristics for Flixabi 100mg powder for concentrate for solution for infusion. Accessed at https://www.medicines.org.uk/emc/product/7265/smpc last reviewed July 2024

- Summary of Product Characteristics for Inflectra 100mg powder for concentrate for solution for infusion. Accessed at https://www.medicines.org.uk/emc/product/3710/smpc last reviewed May 2024

- Summary of Product Characteristics for Remicade 100mg powder for concentrate for solution for infusion. Accessed at https://www.medicines.org.uk/emc/product/3831/smpc last reviewed December 2024

- Summary of Product Characteristics for Remsima 100mg powder for concentrate for solution for infusion. Accessed at https://www.medicines.org.uk/emc/product/3709/smpc last reviewed September 2024

- Summary of Product Characteristics for Remsima 120mg solution for injection in pre-filled pen. Accessed at https://www.medicines.org.uk/emc/product/11101/smpc last reviewed September 2024

- Summary of Product Characteristics for Zessly 100mg powder for concentrate for solution for infusion. Accessed at https://www.medicines.org.uk/emc/product/12497/smpc last reviewed August 2022

- Medusa IV Monograph, infliximab, version 9 https://www.medusaimg.nhs.uk/IVGuideDisplay.asp accessed October 2024

- Jang, D. I., Lee, A. H., Shin, H. Y., Song, H. R., Park, J. H., Kang, T. B., Lee, S. R., & Yang, S. H. (2021). The Role of Tumor Necrosis Factor Alpha (TNF-α) in Autoimmune Disease and Current TNF-α Inhibitors in Therapeutics. *International journal of molecular sciences*, *22*(5), 2719. https://doi.org/10.3390/ijms22052719

- Smolders, E. J., Benoist, G. E., Smit, C. C. H., & Ter Horst, P. (2020). An update on extravasation: basic knowledge for clinical pharmacists. *European journal of hospital pharmacy : science and practice*, *28*(3), 165–167. Advance online publication. https://doi.org/10.1136/ejhpharm-2019-002152

- Dougan M. (2023). Gastrointestinal mucosal toxicities from immune checkpoint inhibitors: Current understanding and future directions. *Immunological reviews*, *318*(1), 11–21. https://doi.org/10.1111/imr.13239

- Haanen, J., Obeid, M., Spain, L., Carbonnel, F., Wang, Y., Robert, C., Lyon, A. R., Wick, W., Kostine, M., Peters, S., Jordan, K., Larkin, J., & ESMO Guidelines Committee. Electronic address: clinicalguidelines@esmo.org (2022). Management of toxicities from immunotherapy: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Annals of oncology : official*

journal of the European Society for Medical Oncology, *33*(12), 1217–1238. https://doi.org/10.1016/j.annonc.2022.10.001

- The Clatterbridge Cancer Centre NHS Foundation Trust, Infliximab for immune mediated toxicities, version 3.0 https://www.clatterbridgecc.nhs.uk/application/files/8217/0126/0625/Infliximab_For_Immune-Mediated_Toxicities.pdf last reviewed August 2023

- Crohn's and Colitis UK, Infliximab patient information leaflet, https://crohnsandcolitis.org.uk/info-support/information-about-crohns-and-colitis/all-information-about-crohns-and-colitis/treatments/infliximab last reviewed June 2024

4. Acknowledgements

- BOPA immunotherapy specialist interest group

5. Document control

Title	**Infliximab in the Management of Immune-Related Adverse Effects (irAEs)**		
Authors / Editors version 1.0	Dharmisha Chauhan, Lead Genomic Pharmacist | North Thames Genomic Medicine Service Alliance Bethan Mortley, Advanced Cancer Pharmacist, Swansea Bay University Healthboard Alice Tew, Consultant Pharmacist Oncology, University Hospital Birmingham NHS Foundation Trust		
Owner	BOPA		
Change History			
Draft	**Date**	**Lead Author/Editor**	**Summary of Change**

Proposed Target Audience	Any healthcare professional involved in the care of patients treated with immune-checkpoint inhibitors.
Proposed Circulation List	BOPA members, IOCN members
Contact details	Alice.tew@uhb.nhs.uk