WAHT-KD-019

Treatment of Inflammatory Bowel Disease with Biologics (in patients over 15 years of age)

INFLIXIMAB PRESCRIBING AND SCHEDULE INFORMATION (Remicade, inflectra, remsima)

Mode of action of Anti TNFa

Infliximab is an anti TNFα monoclonal antibody, which binds to Tumour Necrosis Factor alpha (TNFα). TNFα is an inflammatory cytokine and is found at relatively high concentrations in patients with Inflammatory Bowel Disease. There is evidence that treatment with Anti TNFα reduces the infiltration of inflammatory cells into diseased parts of the intestine and also reduces inflammatory markers.

Infliximab is given as an intravenous infusion in either the medical daycase unit for patients over 18 years of age, or in the childrens clinic for patients aged 15-18years.

Prescribers should prescribe by brand name; Remicade, Inflectra, Remsima using either the pre-printed prescription chart (or on a fluid chart if unavailable)

Induction regime

Infusions are given at week 0, 2 and 6 (from the first date) to induce remission. All outpatient dates are arranged by the IBD clinical nurse specialist or if unavailable the consultants secretary.

Dose is 5mg/kg in 250ml Sodium Chloride 0.9% over 2 hours (with an observation period of 2hours afterwards).

Before each induction dose 200mg hydrocortisone I.V should also be given, (evidence suggests this reduces antibody formation and thus the risk of anaphylaxis).

Maintenance regime

Infusions are given at a 5mg/kg dose every 8 weeks over one hour for the first 2 maintenance infusions (with a 1 hour observation period).

If no reaction has occurred during these infusions, all following infusions can be given over 30minutes (with an observation period of 30minutes).

The 8 week interval may be increased to 9 or 10 weeks in stable patients if trough levels of infliximab are high (over 10 mg/L).

Managing loss of response

Ensure symptoms are due to active disease by performing faecal calprotectin or other investigations such as endoscopy, MRI, CT or VCE.

Obtain Infliximab trough levels and antibodies with a blood test taken immediately prior to their infusion.

Dependant on the results the patient should then be managed as per the following table.

DRUG LEVEL	ANTIBODIES	POSSIBLE ACTION
Low (<3.5mg/L)	Negative	Intensify regime by increasing dose to 10mg/kg and/or decrease interval to 6 or 7 weekly. If low levels persist, consider changing to another Anti TNFα or out of class.
Low (<3.5 mg/L)	Positive, low level titre (<40 AU/ml)	Intensify regime as above. Also consider adding in or optimising immunosuppression. If low levels persist, consider changing to another Anti TNFα or out of class.
Low (<3.5 mg/L)	Positive, high level titre (>41 AU/ml	Switch to another Anti TNFα or out of class.
Therapeutic (>3.5 mg/L)	Negative	Switch to another biologic

out of class.

Evidence on interpreting infliximab drug levels is at present based on observational studies only and so the above is intended as guidance only, some patients may require higher levels to achieve therapeutic response. There is some evidence that patients with fistulating disease should aim for an infliximab level of over 10 until fistulas are healed/resolved. In these patients a trough level should be obtained before their first maintenance infusion, if this is low and the fistula has not healed their treatment should be optimised by increasing the dose to 10mg/kg and/or decreasing the interval to 6weekly.
The effectiveness of any changes should be assessed after 8 to 16 weeks by reviewing current symptoms and rechecking levels and when possible the dosage or interval returned to the standard maintenance schedule.
Patients on a 10mg/kg dose should receive the first two doses over 2 hours and then stay for 1 hour observation, if no reaction occurs they can receive future doses over 1 hour with a 30 minute observation after.

Before each infusion

- Patients will have blood tests for U&Es, LFTs, CRP, FBC and ESR before each Infliximab infusion, no longer than 4 days prior for induction doses and 7 days prior for maintenance doses.

For outpatients, if abnormal these blood tests must be reviewed by the IBD CNS (or Team D doctor) before the infusion can be commenced.
For patients in the childrens clinic, these blood tests must be reviewed by the nurse in charge, if they have any concerns they will discuss this with either the IBD CNS, Team D doctor or paediatrician.

- All patients to be asked before each infusion if they have any signs of active infection, if they do they must be discussed with IBD CNS or Team D doctor before the infusion can be commenced
- Full set of observations to be taken, any concerns to discuss with IBD CNS or Team D doctor before the infusion can be commenced (in particular any pyrexia)
- Female patients pre or peri menopause to have pregnancy test before each infusion, if positive IBD CNS to be informed

Daycase staff to complete form A and file in patient notes for each infusion, to be printed from eZ notes, or LINK 7

Pregnancy and breast feeding
Several studies have shown that treatment with anti-TNFα does not increase the risk of adverse pregnancy outcomes. The drug does cross the placenta in the third trimester and so where possible Infliximab should be stopped by week 24-26 of gestation, with timing of the last dose as close to this as possible. If the patient has severe disease treatment can be continued throughout pregnancy after discussion with the patient with regards to the unknown long term risks.
As Infliximab has been detected in infants up to 6months after birth, the infant should not receive any LIVE vaccinations until it is 6months of age. With the normal vaccine programme, this should only affect the rotovirus vaccine, which cannot be given at all. They can receive all non-live vaccines as per the normal vaccination strategy. This information should be given to the patient and their GP in writing.
There is currently limited data on the safety of treatment with Anti-TNFα whilst breastfeeding, but it is probably low risk. Patients should be informed of this.

Storage of Infliximab
Store in a refrigerator (2°C - 8°C) before reconstitution. After reconstitution use within 3 hours the stability of the reconstituted solution has been demonstrated for 24 hours at 25 °C.

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Reconstitution and administration of Infliximab (irrespective of the brand used)
Pharmacy will generally provide pre-made infusion bags, however if vials are supplied please use the following instructions.

How to reconstitute infliximab.
Add 10mls sterile water for injection to each vial taking care to aim the stream of water at the side of the vial to prevent damage to the antibody.
DO NOT shake or agitate the vial, rotate each vial gently between the palms of the hands (excess foaming will result in drug wastage, shaking will destroy the antibody and may render the infusion inactive).
Leave to stand for 5 minutes.
Check solution for discoloration or foreign particles. Discard if any present.
Carefully withdraw solution from the vial using a green needle and sterile syringe, and add to a bag of Sodium Chloride (0.9%) for infusion, to a **total volume of 250mls**
(You will have to remove the equivalent amount of saline from the 250ml bag as you are going to add, so the total volume after reconstituting is 250mls).
For example, if the infliximab dose is 150mg, it would equal 15mls once reconstituted, so you would have to remove 15mls of sodium chloride from the bag before adding the infliximab.

The reconstituted and diluted Anti TNFa solution should be infused using a volumetric pump through a filter (<1.2 microns).
Commence infusion within 24 hours of reconstitution.
How to administer Infliximab
Commence infusion at 60ml/hour for the first 10 minutes, and then re-check patient observations.
If observations satisfactory and patient reporting no side effects, increase rate as follows
For a 2hour infusion – increase rate to 125ml/hour for remainder of infusion
For a 1 hour infusion – increase rate to 250ml/hour for remainder of infusion
For a 30 minute infusion – increase the rate to 500ml/hour for remainder of infusion
Check observations every half hour throughout infusion and at the end of the observation period.
If the patient reports any side effects please manage as per instructions below, you will also find these on the reverse of the pre-printed prescription sheet.

Managing infusion related events

Mild hypersensitivity reaction:
Clinical signs: Pruritus, mild rash, headaches. No respiratory or cardiovascular distress.
Action:

- Stop infusion and administer 10mg IV chlorphenamine (for pruritus/rash) and/or 1gram paracetamol (for headache)
- If improvement, restart infusion at half the previous rate and monitor closely for further signs of hypersensitivity
- If symptoms return or worsen, STOP infusion and administer 100-200mgs hydrocortisone IV and further 10mgs IV chlorphenamine and treat as moderate hypersensitivity reaction.
- Advise patient to seek IMMEDIATE medical advice if hypersensitivity symptoms recur after discharge.

Moderate hypersensitivity reaction:
Clinical signs: Urticaria/rash, mild hypotension, tachycardia, mild wheeze, nausea
Action:

- STOP infusion.
- Administer 200mgs IV Hydrocortisone & 20mgs IV chlorphenamine by slow IV injection.
- Check vital signs, including oxygen saturations.
- Seek medical advice (or advice from IBD CNS bleep 469 or 228) before restarting the infusion.

- Call medical assistance if continued/worsening symptoms

 If reaction worsening – treat as SEVERE REACTION.

Severe hypersensitivity reaction:

Clinical signs: Anaphylactic reaction**,** Hypotension/respiratory distress, swollen lips, airways, reduced/loss of consciousness/reduced oxygen saturations, flushed/pale.

Action:

- STOP infusion permanently
- CALL 2222 and state it is a medical emergency
- Lay patient flat and secure airway
- Administer 0.5ml 1:1000 adrenaline IM found in resus trolley in the anaphylaxis pack and then give 20mgs IV Chlorphenamine and 200mgs IV hydrocortisone.
- Give oxygen via non rebreathe face mask and monitor oxygen saturations/pulse, BP
- Repeat adrenaline if no improvement at 5 minute intervals

- Administer 1 litre Glucose 5%/ Sodium Chloride 0.9% rapidly if hypotension persists.