Infliximab Tips

Infliximab (Remicade®) is a chimeric (part mouse, part human) monoclonal antibody that blocks activity of a key biologic response mediator called "tumor necrosis factor (TNF) alpha". The action of infliximab is to bind to and neutralize TNF-α on the cell membrane, soluble TNF-α and to destroy TNF-α producing cells, thus inhibiting inflammation. Infliximab is supplied as a sterile, white lyophilized powder for intravenous infusion. It is an infusible medication that has been approved for home IV therapy, hospital outpatient administration or physician office administration.

Pre Screening
1. Should be done prior to first and subsequent infusions.
2. Patient Counseling Information
   a. Patient advised of potential benefits and risks
      i. Major Risks:
         1. Infections (like TB, blood infections, pneumonia)—fever, tiredness, cough, flu, or warm, red or painful skin or any open sores. Infliximab can make you more likely to get an infection or make any infection that you have worse.
         2. Lymphoma or any other cancers in adults and children.
         3. Skin cancer—any changes in or growths on your skin.
         4. Heart failure—new or worsening symptoms, such as shortness of breath, swelling of your ankles or feet, or sudden weight gain.
         5. Reactivation of HBV—feeling unwell, poor appetite, tiredness, fever, skin rash and/or joint pain.
         6. Liver injury—jaundice (yellow skin and eyes), dark brown urine, right-sided abdominal pain, fever, or severe tiredness.
         7. Blood disorders—fever that doesn't go away, bruising, bleeding or severe paleness.
         8. Nervous system disorders—numbness, weakness, tingling, and changes in your vision or seizures.
         9. Allergic reactions during or after the infusion—hives, difficulty breathing, chest pain, high or low blood pressure, swelling of face and hands, and fever or chills.
         10. Lupus-like syndrome—chest discomfort or pain that does not go away, shortness of breath, joint pain, rash on the cheeks or arms that gets worse in the sun. The more common side effects with Infliximab are respiratory infections (that may include sinus infections and sore throat), headache, rash, coughing and stomach pain.
         11. Psoriasis—new or worsening psoriasis such as red scaly patches or raised bumps on the skin that are filled with pus.

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ii. Benefits:

1. A greater percentage of patients in both infliximab groups UC and CD achieved clinical response, clinical remission and mucosal healing than in the placebo group.\(^1\)

2. Of patients on corticosteroids at baseline, greater proportions of patients in the infliximab treatment groups were in clinical remission and able to discontinue corticosteroids at Week 30 compared with the patients in the placebo treatment groups.\(^1\)

3. Healed Fistulas: Fistula response (≥50% reduction in number of enterocutaneous fistulas draining upon gentle compression on at least 2 consecutive visits without an increase in medication or surgery for Crohn’s disease) was seen in 68% (21/31) of patients in the 5 mg/kg infliximab group (\(P=0.002\)) and 56% (18/32) of patients in the 10 mg/kg infliximab group (\(P=0.021\)) vs. 26% (8/31) of patients in the placebo arm. The median time to onset of response and median duration of response in infliximab (Infliximab)-treated patients was 2 and 12 weeks, respectively. Closure of all fistulas was achieved in 52% of infliximab (Infliximab)-treated patients compared with 13% of placebo-treated patients (\(P<0.001\)).\(^1\)

4. The safety and effectiveness of infliximab for reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients aged 6 years and older with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy are supported by evidence from adequate and well-controlled studies of infliximab in adults.\(^1\)

b. Document counseling in the patient’s record
   i. e.g. “The nature, indication, alternatives, material risks and benefits of chronic use of anti-TNF therapy were discussed. Specific complications discussed included but were not limited to life threatening bacterial or mycobacterial infection, hepatitis B reactivation, hepatotoxicity, cytopenia, hypersensitivity, heart failure, certain types of cancer, nervous system disorders, Psoriasis and Lupus-like syndrome.”

   c. Patient provided resource MEDICATION GUIDE\(^1\) to be read before starting and re-read prior to each infusion (available for download online, Janssen also provides a colored hard copy for patients of this same information, for reference). The label on the infliximab 100 mg box indicates that this is a requirement.

3. Tuberculosis Screening
   a. Verify latent tuberculosis infection screening has been performed
      i. Detailed history of patient tuberculosis exposure risk factors
      ii. Confirm the following
         1. Negative tuberculin skin test /PPD (<5mm induration) and/or Negative QuantiFERON TB Gold.\(^2,3\)
a. Consider chest x-ray in patients with TB risk factors but negative screening tests -OR-
2. Positive tuberculin skin test/PPD or positive QuantiFERON test with negative chest x-ray
   a. Consider infectious disease consult and/or treating with INH if tuberculosis history risk factors are present (TB may be in other tissues and may have negative chest x-ray) -OR-
3. Patient is at least 4 weeks post initiation of INH
   b. Consider repeating screening tests if patient has had recent travel to TB endemic country or change in risk factors for TB exposure

4. Screen for Hepatitis B⁴
   a. Surface Ag
   b. Surface Ab
5. Screen for Hepatitis C⁵
6. Verify vaccine status/update if indicated⁶
   a. MMR* Note this is a live vaccine, if indicated, give prior to initiating infliximab
   b. Hepatitis A
   c. Hepatitis B
   d. Influenza
   e. Pnuemovax and Prevnar
   f. Tdap
   g. HPV
   h. Zoster (Shingles) * live vaccine
7. Evaluate for history of heart failure, consider cardiac echo on patients over the age of 65⁶
   a. Notify the patient’s PCP or cardiologist
   b. The results of a randomized study evaluating the use of infliximab in patients with heart failure (NYHA Functional Class III/IV) suggested higher mortality in patients who received 10 mg/kg infliximab, and higher rates of cardiovascular adverse events at doses of 5 mg/kg and 10 mg/kg.¹
8. Skin cancer screening

Start the Patient Assistance Process
1. At the time the decision is made to start treatment with Infliximab
2. Designate dedicated office personnel to manage infliximab patient assistance
   a. Have process in place e.g., Receive orders for infliximab, initiate patient assistance, notify infusion nurse
3. If infliximab dose or frequency is changed, you may need a new patient assistance approval

Patient Assistance
1. Advise each family to inquire about Remistart Program and determine eligibility
2. ACESSONE: 1 888 ACCESS 1 (222-3771) Monday –Friday 8am to 8pm ET

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ACCESSONE supports the benefits investigation process, and offers coding, billing and reimbursement support for healthcare providers, and care coordination services for patients.

3. Patient Assistance Program: Johnson and Johnson Foundation. For patients with no insurance for infliximab. They must meet certain medical and financial criteria.

**Further Assistance through Janssen**

1. janssenaccessone.com Web Site
2. **Billing**: provides state specific information for all key areas of reimbursement
3. **References**: listing of documentation and reference material to help guide health care professionals through the reimbursement process.
4. **eBIF**: Access to the electronic benefit investigation process.
5. **Indications and Important Safety Information**: Links to full Prescribing Information and Medication Guide
6. **Patient Assistance**: your patients may be eligible for these prescription assistance and affordability options
7. **Infusion Record for infliximab**: This record is for office use only. May aid in documenting the patient’s infusion. Can be a guide for EMR infusion forms.

**Initial Infusion Therapy**

1. Obtain written orders for Infliximab infusion therapy and pre medications if indicated
2. Order medication, know the dosage required
3. Schedule infusion

**Dosing**

1. Induction is week 0, 2 and 6. Thereafter every 8 weeks
2. Initial dosing is 5mg/kg in most cases
3. Response to infliximab usually occurs during the first 3 doses
4. When patient is not responding or losing response before 8 weeks, may increase dose to 10mg/kg; this is to be discussed/evaluated by gastroenterologist; and usually requires insurance authorization for dose escalation
5. Continued loss of response before 8 weeks, decrease frequency to every 6 weeks; this is to be discussed/evaluated by gastroenterologist; and usually requires insurance authorization for dose change

Based on which assay used, you can check drug and antibody level at any time.

**Labs**

1. CBC, Liver panel, BMP, may be drawn at every infusion or predetermined times.
2. Consider checking infliximab levels and antibodies prior to the next infusion if the patient experienced a reaction or is losing response to the Infliximab. Depending on which assay used, you can check drug and antibody level at any time.

**Yearly Screening**

1. Refer to Crohn’s & Colitis Foundation Health Maintenance Checklist

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INFUSING INFlixIMAB

Infliximab is supplied as a sterile, white lyophilized powder for intravenous infusion. It is an infusible medication that has been approved for home IV therapy, hospital outpatient administration or physician office administration.

Evaluate patient for: (review affirmative answers with ordering provider)
  o Any current or recent bouts of fever, illness or infection
  o Taking any antibiotics
  o Recent or upcoming surgeries
  o Recent or planned live virus vaccinations (live virus vaccinations are not recommended during therapy with infliximab)
Vital Signs Monitoring
Obtain weight to calculate dose.
Obtain vital signs (patient temperature, blood pressure, respiration, and pulse) upon arrival, after start of medication, upon discontinuing infusion and before the patient departs the facility. However, if prior history of an acute infusion reaction, monitor vitals every 10 minutes for 30 minutes, then every 30 minutes and for 30 minutes after infusion.

Review Orders and Obtain IV Access
1. FDA-Approved Indications and Dosing:
   - Crohn's Disease and Fistulizing Crohn's Disease: 5 mg/kg (10mg/kg may be considered if initial response is lost); Patients that lose response prior to 8 weeks may have frequency decreased to every 6 weeks. May need insurance authorization/approval for this.
   - Ulcerative Colitis: 5mg/kg. Dose escalation may also be indicated/needed for UC patients, as with CD patients.
   - Treatment at weeks 0, 2 and 6 weeks, then every 8 weeks.
   - Patients who do not respond by week 14 are unlikely to respond with continued dosing and consideration should be given to discontinue infliximab in these patients. To be discussed and evaluated by gastroenterologist; consider therapeutic drug monitoring with drug and antibody level at this point as well.
2. Prime filtered tubing (20 drops/mL) with normal saline (NS). A “Y” connection or piggy back set up is recommended so that isotonic saline solution can be infused as an alternate to infliximab infusion if required. Start IV using aseptic technique, smaller IV needles may be used in this medication administration setting, e.g. # 22 or #24 catheters. Patient may like administration of topical anesthetic spray or cream.
3. Begin infusing with 100mL NS bag; set rate to TKO. Check for pre-medications. Give pre-medications if ordered. Pre-medications could include antihistamines, acetaminophen and/or corticosteroids
4. Consider IV fluid hydration for diarrhea flares, prior to starting the infliximab. E.g.1000 cc NS.
5. May combine blood draw prior to infusion.
6. ***Do not reconstitute vials until after successfully obtaining intravenous access***

Drug Preparation
Infliximab is intended for use under the guidance and supervision of a physician. The reconstituted infusion solution should be prepared by a trained medical professional using aseptic technique by the following procedure:
1. Calculate the dose per provider’s medical order, total volume of reconstituted Infliximab solution required and the number of infliximab vials needed. Each infliximab vial contains 100 mg of the infliximab antibody. Be aware which insurers require wasting of drug. Appropriately document the correct dose given to the patient.
2. Reconstitute each infliximab vial with 10 mL of Sterile Water using a syringe equipped with a 21-gauge or smaller needle as follows:
   1. Remove the flip-top from the vial and wipe the top with an alcohol swab.
2. Insert the syringe needle into the vial through the center of the rubber stopper and direct the stream of Sterile Water gently to the glass wall of the vial.
3. Gently swirl the solution by rotating the vial to dissolve the lyophilized powder. Avoid prolonged or vigorous agitation.
4. **DO NOT SHAKE.** Foaming of the solution on reconstitution is not unusual.
5. Allow the reconstituted solution to stand for 5 minutes. The solution should be colorless to light yellow and opalescent, and the solution may develop a few translucent particles as infliximab is a protein.
6. Do not use if the lyophilized cake has not fully dissolved or if opaque particles, discoloration, or other foreign particles are present.
7. The infliximab infusion should begin within 3 hours of preparation.

3. Dilute the total volume of the reconstituted infliximab solution dose to 250 mL with sterile 0.9% Sodium Chloride Injection, USP, by withdrawing a volume equal to the volume of reconstituted infliximab from the 0.9% Sodium Chloride Injection, USP, 250 mL bottle or bag.
4. More than 10 vials of infliximab will require more than 250 ml NS to achieve proper concentration of 0.4-4mg/ml.
5. Slowly add the total volume of reconstituted infliximab solution to the 250 mL infusion bottle or bag. Gently mix.
6. The infusion solution should be administered over a period of not less than 2 hours and must use an infusion set with an in-line, sterile, non-pyrogenic, low-protein-binding filter (pore size of 1.2 μm or less). The vials are single use and do not contain antibacterial preservatives. Therefore, any unused portion of the infusion solution should not be stored for reuse.
7. No physical biochemical compatibility studies have been conducted to evaluate the co-administration of infliximab with other agents. Infliximab should not be infused concomitantly in the same intravenous line with other agents.

### Standard Infusion Checklist

1. **Recommended Rate Titration Schedule** slower infusion will decrease adverse events
   1. 10ml/hr x 15 min, increase to
   2. 20ml/hr x 15 min, increase to
   3. 40 ml/hr x 15 min, increase to
   4. 80 ml/hr x 15 min, increase to
   5. 150 ml/hr x 30 min, increase to
   6. 250 ml/hr x 30 min to the end of infusion
2. **Alternate titration schedule**
   1. 40 cc/hr x 30 minutes
   2. 80cc/hr x 30 minutes
   3. 160cc/hr for the duration of infusion
3. Push 20cc NS flush into bag once bag is nearly empty to clear all medication in the IV tubing.


*Safety Accelerated Infliximab Infusions in Patients with Inflammatory Bowel Disease (IBD). Clinical Trials.gov. This study is ongoing, but not recruiting participants.*
Managing Acute Infusion Reactions
Acute infusion reaction can occur during the administration of this agent. If patient reports mild reactions (such as flushing, chills, etc.), slow down the infusion rate and assess patient. For more severe reactions (such as hives, difficulty breathing, chest pain, high or low blood pressure, swelling of face and hands, fever, chills or anaphylaxis) or where mild reactions persist, stop the infusion and treat the acute reaction. Then notify the supervising provider immediately to coordinate next plan of action. For mild reactions, consider adding additional pre-medications for subsequent doses.
Prior to infusion of infliximab, premedication may be administered at the physician’s discretion.
Premedication could include antihistamines (anti-H1 +/- anti-H2), acetaminophen and/or corticosteroids.

In the event of an infusion reaction
  1. Stop or slow infusion
  2. Give Benadryl 25-50 po/IV
  3. Give Acetaminophen 650-1000 mg po
  4. Give Prednisone 40 mg po or IV
  5. Resume infusion at 10ml/hr and follow Recommended Rate Titration Schedule
     1. Reaction resolved, complete infusion
     2. Reaction unresolved or more severe, stop infusion. Treatment should be dictated by the signs and symptoms of the reaction. Appropriate personnel and medication should be available to treat anaphylaxis if it occurs. The initial management of anaphylaxis includes a focused examination, procurement of a stable airway and intravenous access, and administration of epinephrine.
        1. Epinephrine 1:1,000 dilution, 0.2 to 0.5 mL (0.2 to 0.5 mg) in adults, should be injected subcutaneously or intramuscularly, usually into the upper arm.
        2. Administer O2
        3. Transfer to Emergency Care Facility if indicated

Post Infusion
  1. Observe patient for an additional 30 minutes after conclusion of infusion
  2. Patient Education: Educate patient on infliximab possible side effects, allergic reactions, delayed allergic reactions and when to contact MD
     1. Most common side effects of infliximab: respiratory infections, such as sinus infection and sore throat, headache, rash, coughing, stomach pain
     2. Educate patient to contact MD with following allergic reactions (may occur during or shortly after infusion): hives, difficulty breathing, chest pain, high or low BP, fever, chills
     3. Educate patient about signs and symptoms of delayed infusion reactions which may occur 3 to 12 days after receiving infliximab infusion and notifying MD immediately if following occur: fever, rash, headache, sore throat, muscle or joint pain, swelling of the face and hands, difficulty swallowing

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Drug Holidays

1. Treatment with infliximab can be associated with the development of antibodies to infliximab. A higher incidence of antibodies to infliximab was observed in patients receiving infliximab after drug free intervals >16 weeks. The majority of the antibody-positive patients were more likely to have higher rates of clearance, reduced efficacy and to experience infusion reactions.  

2. Medications for the treatment of hypersensitivity reactions should be available.
3. Consider automatically pre medicating this patient group.
4. Update live vaccines if indicated.

**Equipment**

- Infusion chair
- Infusion pump
- Blood pressure monitor, thermometer
- Patient entertainment equipment
- Locking medication refrigerator - Must keep log of the temperature of the medication refrigerator (logs available on line)
- Back up generator
- Other supplies (initiation/maintenance of IV access)
  - IV catheters (#22, # 24 gauge)/supplies to secure/alcohol wipes/2X2s
  - IV poles
  - IV tubing with extension/with filters
  - 0.9% Normal Saline Bags: 250 ml and 50 ml, also 500 ml or 1000 ml for hydration
  - Gloves, latex free
  - Needles, Sharps container
  - Syringes: various sizes 50ml, 10 ml, 5 ml, 3ml

**Supplies to Manage Complications**

- Epinephrine (1:1000)
- Antihistamines
- Corticosteroids
- Acetaminophen
- Normal saline
- Crash Kits
- Defibrillator
- Oxygen
- Nasal cannula
- Ambu bag

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4. Esteve M. Chronic Hepatitis B reactivation following infliximab therapy in Crohn’s Disease patients. Gut. 2004 Sep; 53 (9); 1363-1365.