Infliximab Reactions

Reminder: Document all infusion reactions in the patient record.

Infliximab has been associated with hypersensitivity reactions (acute or delayed), anaphylactoid or anaphylactic reactions and serum sickness. Hypersensitivity reactions include urticaria, dyspnea, and/or hypotension.

The TNF-alfa inhibitor infliximab (IFX) is generally well tolerated in patients with inflammatory bowel disease (IBD) but infusion reactions occur. An infusion reaction is defined as any adverse event occurring during the infusion or immediately after the infusion. Like other foreign protein-derived agents, infliximab may lead to infusion reactions during and after infusion. Acute infusion reactions to IFX are reported in up to 40% of IBD patients, acute severe reactions in less than 5% of patients, and delayed reactions in approximately 2%. An anaphylactic reaction is defined as an acute systemic reaction caused by the massive release of histamine and other cytokines from mast cells, mediated by IgE. Bronchospasms and urticaria are typical symptoms of an IgE-mediated anaphylactic reaction, or type 1 hypersensitivity reaction. Acute infusion reactions may be seen during administration and can be mild to moderate, or severe: Severe reactions necessitate immediate discontinuation because of hypotension, chest tightness, respiratory distress, and/or urticaria, and may necessitate hydrocortisone and antihistamine therapy. Mild to moderate reactions are usually self-limiting and resolve spontaneously after temporary cessation or reduction of infusion rate; typical symptoms are nausea, headache, fever, erythema, and itching.

Delayed reactions occur 1–14 days after drug administration and are commonly associated with myalgias, arthralgias, headache, fever, rash, and fatigue.

Serum sickness is a type III hypersensitivity reaction. The disease is the result of tissue deposition of circulating antigen-antibody complexes. Typical symptoms of serum sickness are rash, fever, and polyarthralgias or polyarthritis. These symptoms begin 1-2 weeks after first exposure to the agent responsible and resolve within a few weeks after discontinuation. A delayed infusion reaction to infliximab clinically imitates serum sickness.

Serious reactions involve respiratory symptoms or a symptomatic blood pressure drop. A severe infusion reaction can be anaphylactic or anaphylactoid and should be treated as such. An anaphylactic reaction is defined as an acute reaction caused by massive release of histamine. Bronchospasms and urticaria are
typical symptoms. Nevertheless, they may lead to discontinuation of treatment with infliximab. In clinical trials serious infusion reactions occurred in < 1% of patients and included anaphylaxis, convulsions, erythematous rash and hypotension. Approximately 3% of patient’s discontinued infliximab because of infusion reactions, and all patients with treatment and/or discontinuation of the infusion.

Acute reactions are defined as those that occur during the infusion or in the first 24H afterwards. The majority of acute reactions occur during or in the first 2H after the infusion.

In some cases serum-sickness reactions have been observed in patients after initial infliximab therapy (e.g., as early as after the second dose), and when infliximab was reinstituted following an extended period without infliximab treatment. Symptoms associated with these reactions include fever, rash, headache, sore throat, myalgias, polyarthralgias, and facial edema and/or dysphagia. These reactions were associated with a marked increase in antibodies to infliximab, loss of detectable serum concentration of infliximab, and possible loss of drug efficacy.

Premedication is often given before infusions, consisting of acetaminophen, antihistamine and/or corticosteroids, to prevent the occurrence of infusion reactions. However, solid evidence that prophylactic medication can prevent infusion reactions is lacking.

After a mild to moderate infusion reaction there is usually no reason to stop infliximab treatment. Precautions can be taken to diminish the chance of a new infusion reaction, such as pre-medications.

Infusion reactions may occur more in patients that go longer than the proposed every 8 weeks maintenance dose and in some cases would be an indication for pre-medications (e.g. > 16 weeks).

Use of treatment protocols resulted in rapid resolution of almost all acute reactions to infliximab.

A number of studies have identified protective factors that may minimize adverse reactions, presumably related to the immune response against infliximab. Concomitant immunosuppressive therapy with azathioprine, 6-mercaptopurine, or Methotrexate may result in improved outcomes due to reduction in frequency of antibody formation, acute infusion reactions and reduced risk of delayed hypersensitivity-like reactions. Significant reduction of ATI formation was also achieved by co-medication with prednisone ≥20mg daily.13

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12 Han PD; Cohen RD. Concomitant immunosuppressive therapy with azathioprine, 6-mercaptopurine, or Methotrexate may result in improved outcomes due to reduction in frequency of antibody formation, acute infusion reactions and a reduced risk of delayed hypersensitivity-like reactions. Drugs. 2004; 64 (16): 1767-77


Other references:


Remicade (infliximab) Prescribing Information. Janssen Biotech, Inc. 2013

The following infliximab reaction management strategies are suggestions only, cumulated from resources as well as several infusion nurses’ experiences.

MILD REACTION
• Pruritus or rash
• Lightheadedness/Dizziness
• Hypo/Hypertension
• Chest tightness without SOB/wheezing
• Headache
• Flushing with no throat tightness

TREATMENT FOR MILD REACTION
• Slow rate to 10ml/hr (4 gtts/min). If symptoms do not resolve STOP Infliximab.
• Infuse NS KVO
• Give diphenhydramine 25 mg po x 1 dose or 25-50 mg IVP ( Slow IV Push 25 mg/min)
• Give acetaminophen 650 mg po x 1 dose (if patient able to tolerate)
• Monitor vital signs every 10 minutes
• Wait 20 minutes then increase Infliximab restart at 10cc/hr X 15 min
• Then increase to 20 ml/hr (7 gtts/min) X 15 min
• Then increase to 40 ml/hr (14 gtts/min) X 15 min
• Then increase to 80 ml/hr (27 gtts/min) to complete infusion

MODERATE REACTION
• Pruritis and/or rash
• Hives
• Wheezing without dyspnea
• Shortness of breath
• Hypertension or hypotension with greater than 20-point, but less than 40-point drop or rise in systolic blood pressure
• Chest discomfort (tightening)/pressure
• Palpitations

TREATMENT FOR MODERATE REACTION
• Stop Infliximab infusion, start NS @ 500 cc/hr
• Give diphenhydramine 25-50 mg IVP x 1 dose (dose depends on whether patient pre-medicated)
• Give acethaminophen 650 mg po x 1 dose (if patient able to tolerate)
• If wheezing present: Give Hydrocortisone 100mg or Solumedrol 40 mg IV push x 1 dose
• Wait 20 minutes then increase Infliximab restart at 10cc/hr X15 min
• Then increase to 20 ml/hr (7 gtts/min) X 15 min
• Then increase to 40 ml/hr (14 gtts/min) X15 min
• Then increase to 80 ml/hr (27 gtts/min) to complete infusion
• Monitor vital signs every 5 minutes, until normal then every 30 minutes

SEVERE REACTION (NOTIFY ORDERING PROVIDER)
• Symptoms as above with progression
• Elevated temperature with rigors
• Dyspnea with wheezing
• Dyspnea requiring ventilator support
• Chest discomfort (tightening)/pressure
• Hypotension with greater than 40-point drop in systolic blood pressure
• Stridor (call for emergency support)
TREATMENT OF SEVERE REACTION

- Stop Infliximab
- Maintain NS at 100 ml/hr
- Call for emergency support
- Maintain airway, if available: Start oxygen to keep saturation greater than 90%
- Give diphenhydramine (Benadryl) 25-50 mg slow IVP (25mg/min) x 1 dose
- Give Hydrocortisone 100 mg or Solumedrol 40 mg IVP x 1 dose (onset of action 1 hour)
- If no improvement within 5-10 minutes. (5-10 minutes is the onset of action for diphenhydramine)
- Administer Epinephrine (1:1000) 0.1 mL - 0.5 mL subcutaneous; may repeat every 5 minutes x 3
- Administer acetaminophen 650 mg if tolerated
- Demerol 25 mg IV ONLY IF RIGORS SEVERE
- Monitor vital signs every 2 minutes
- If patient stabilizes, follow infusion rate protocol for subsequent dosing up to 80 ml/hr
- If patient requires second dose of Epinephrine – call 911 to transfer to ER

If the patient experiences a second reaction during the Infliximab infusion

- Stop Infliximab
- Infuse NS 500 -1000 cc/hr
- Give Hydrocortisone 100 mg or Solumedrol 40 mg IVP x 1 dose
- Give diphenhydramine 25-50 mg IVP x 1 dose
- Consider administering Ranitidine 50 mg IV
- Test dose @ 10 ml/hr (4 gtts/min) X 15
- Then increase to 20 ml/hr (7 gtts/min) X 15 min
- Then increase to 40 ml/hr (14 gtts/min) X 15 min
- Stop increasing rate at the rate the patient experienced the reaction

Upon completion of Infliximab infusion

- Discharge patient home on the following
- Fexofenadine, Loratadine, Cetirizine po every HS X 5 days
- Prescribe Medrol Dose Pack to be filled if symptoms of joint pain or myalgias

Managing Subsequent Infusions:

- All patients should receive NS @ 100cc/hr throughout subsequent doses

MILD REACTION:

- Pre-medicate with diphenhydramine 25-50 mg IVP, plus
• Acetaminophen 650 mg PO 1 hour prior to infusion
• Test dose Infliximab: @ 10 ml/hr (4 gtts/min) X 15 min.
• Then increase rate to infuse over 3 hours

**MODERATE REACTION:**
• Pre-medicate with diphenhydramine 50 mg IVP, plus
• Acetaminophen 650 mg PO 1 hour prior to infusion
• If Hydrocortisone or Solumedrol used to manage last reaction, administer as pre-med IVP.
• Test dose Infliximab @ 10 ml/hr (4 gtts/min) X 15 min
• Then increase to 20 ml/hr (7 gtts/min) X 15 min
• Then increase to 40 ml/hr (14 gtts/min) X15 min
• Then increase to 80 ml/hr (27 gtts/min) X 15 min
• Then increase to 100 ml/hr (34 gtts/min) X 15 min
• Then increase to 125 ml/hr (41gtts/min) through completion
  *(drip factor based on 20 drop/ml tubing)*

**SEVERE REACTION** (and/or if patient experienced a second reaction within a dose):
• Cetirizine QD X 5 days
• Ranitidine 150 mg PO the PM prior and morning of infusion or Ranitidine 50 mg IV as premed
• Prednisone 40-50 mg PO BID X 3 days prior to infusion or Prednisone 20 mg daily for 2 days, day of infusion and for 2 days after infusion
• Pre-medicate with diphenhydramine 50 mg IVP, plus
• Acetaminophen 650 mg PO
• Administer Hydrocortisone 100 mg IV or Solumedrol 40 mg IV as pre-med 20 min prior to infusion
• Test dose Infliximab @ 10 ml/hr (4 gtts/min) X 15 min
• Then increase to 20 ml/hr (7 gtts/min) X 15 min
• Then increase to 40 ml/hr (14 gtts/min) X15 min
• Then increase to 80 ml/hr (27 gtts/min) X 15 min
• Then increase to 100 ml/hr (34 gtts/min) X 15 min through completion of the infusion

**DELAYED REACTION SYMPTOMS:**
• Muscle aches
• Rash/Urticaria
• Flu like symptoms
• Joint stiffness and pain

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Note: The Crohn's & Colitis Foundation provides information for educational purposes only. The Foundation does not provide medical or other health care opinions or services. The inclusion of another organization's resources or referral to another organization does not represent an endorsement of a particular individual, group, company or product. Please contact the company associated with these medications for more information and refer to the prescribing insert.
Treatment:
- For rash only: Diphenhydramine 25-50 mg PO every 4 hours for 1-2 days
- Begin Medrol Dose Pack as soon as onset of body aches, stiffness or pain
- Follow MODERATE REACTION for subsequent dosing
- Can consider adding steroid IVP and/or Ranitidine
- Instruct patient to take 2nd generation antihistamine (Fexofenadine, Loratadine, Cetirizine, Chlorpheniramine) QD X 5 days pre infusion and 14 days post infusion
- Acetaminophen 650 mg PO QID X 3 days
- For more severe arthritis: give analgesics at maximum dose acetaminophen, ibuprofen or tramadol.
- If unsatisfactory results add prednisone 40 mg daily, which should be reduced in a few weeks or
- Consider ordering a Medrol Dose Pack and instruct to take if patient experiences, joint malaise or rash

When patient returns after hiatus from Infliximab of more than 4 months
- CAUTION RE INDUCTION: re-administration of Infliximab after a period of no treatment resulted in a higher incidence of infusion reactions relative to regular maintenance treatment. In general, the benefit risk of re-administration of Infliximab after a period of no-treatment, especially as a re induction regimen given at weeks 0, 2 and 6, should be carefully considered.
- If re induction not done: Infliximab should be reinitiated as a single dose followed by maintenance therapy.
- Usually the second dose is 4-8 weeks after the first infusion
- Treat as if patient had mild infusion reaction and pre-medicate:
  - Pre-medicate with diphenhydramine 25- 50 mg IVP and
  - Instruct the patient on symptoms of delayed reaction
- Provide patient with prescription and instructions for Medrol Dose Pack and Benadryl usage as needed

**INFUSION RATES:**  

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Remicade (infliximab) for Intravenous (IV) injection Detailed View: Safety Labeling Changes Approved By FDA Center for Drug Evaluation and Research (CDER) – December 2010. Page Last Updated: 02/02/2011