UNC INFLAMMATORY BOWEL DISEASE DRUG PROTOCOL

INFLIXIMAB (REMICADE)

TREATMENT PROTOCOL:

Infliximab is a chimeric IgG1 monoclonal antibody that binds tumor necrosis factor alpha (TNF α) with high affinity and neutralize its effect in promoting inflammatory response. It is comprised of 75% human and 25% murine sequences. It has a half-life of 7-12 days.

Current IBD indications for infliximab at UNC

- **Crohn's disease:**
  1. Induction and maintenance therapy in adult patients with moderate to severe active disease who have had an inadequate response to conventional therapy.*
  2. Reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adult patients with fistulizing disease.*
  3. Post-operative prophylaxis for high risk patients.
  4. Can be considered for severe, refractory extraintestinal manifestations (arthritis, pyoderma gangrenosum, and iritis/uveitis).
  5. Induction and maintenance therapy in **pediatric patients** with moderately to severely active disease who have had an inadequate response to conventional therapy.*

- **Ulcerative Colitis:**
  1. Induction and maintenance therapy for adult patients with moderate to severe disease who have had an inadequate response to conventional therapy.*
  2. Salvage therapy for patients with severe colitis refractory to steroid.
  3. Can be considered for severe, refractory extraintestinal manifestations (arthritis, pyoderma gangrenosum, and iritis/uveitis).
  4. Induction and maintenance therapy for **pediatric patients** with moderate to severe disease who have had an inadequate response to conventional therapy.*

Dosage and Route of Administration

- **Route of administration:** Intravenous (IV).

* FDA-approved indications

- **Dose and intervals:**
  - Induction: 5 mg/kg at weeks 0, 2, and 6.
  - Maintenance: 5 mg/kg every 8 weeks.

Higher dose or shorter intervals can be used based on the clinical situation.

Time for Response

- Patients may feel better within 48-72 hours of the first infusion. It may take up to 6 weeks for a definitive clinical response.

Contraindications

- **Absolute:**
  1. Moderate or severe HF (New York Heart Association [NYHA] class III/IV)
  2. Previous severe hypersensitivity to infliximab
  3. Active solid or hematological malignancies
  4. Active systemic infection
  5. Untreated latent TB

- **Relative/may use with caution:**
  1. Mild heart failure (NYHA functional class I or II)†
  2. History of demyelinating disease (MS, optic neuritis)‡
  3. Family history of demyelinating disease (MS, optic neuritis)
  4. History of solid or hematological malignancy within the past 5 years
  5. History of malignant melanoma
  6. Patients with multiple comorbid conditions that may increase risk of infections (tobacco use, DM, COPD)

† Baseline echocardiogram with ejection fraction documentation and cardiology consultation are needed prior to initiation of anti-TNF therapy. In this situation, should avoid high doses of anti-TNF therapy and provide close follow-up with prompt discontinuation of anti-TNF-alpha therapy if HF worsens.

‡ Can only be used under the discretion of treating neurologist.

Administration and Safety Monitoring

Before initiation of therapy:

- Careful medical history to assess for any absolute and relative contraindications.
- Evaluate immunization status and provide any indicated vaccines (influenza, pneumonia, hepatitis B, HPV)
- Prior authorization: Email IBD nurse the patient's information
  - Anthea Darling, RN (Dr. Isaacs, Dr. Sartor, and Dr. Jain)
  - Laurie Powers, RN (Dr. Herfarth, Dr. Hansen)
  - Christina Womble, RN (Dr. Long, Dr. Sheikh)
- Pre-treatment laboratory evaluation:
  1. Screen for latent Tuberculosis (Quantiferon gold TB test or Tuberculin skin test + chest X-ray)[§]
  2. Screen for chronic infections (HBs-Ag, HBs-Ab, HBc-Ab, HCV Ab, HIV testing)
  3. Baseline LFTs, albumin, CBC, renal function and CRP

Therapy administration:

- IBD nurse assists in placing treatment plan and arranging infusions
- *Pre-treatment:*
  - Standard:
    - Methylprednisolone sodium succinate (Solu-MEDROL) 40mg/ml injection: 20 mg IV once
    - Cetirizine (Zyrtec) tablet 10 mg: 10 mg, oral once
  - Optional/alternative:

[§] Tuberculosis testing and anti-TNF therapy:

- Tuberculin skin test (TST) can be falsely negative in patients with (1) severe malnutrition and (2) receiving immunosuppressive drug (corticosteroids, anti-TNF therapy, and chemotherapy).
- Neither Quantiferon gold TB test nor TST can provide 100% sensitivity for detecting latent TB.
- **In patients at high risk for TB, both tests should be considered with treatment if either one is positive.**
- In patients with latent TB, anti-TNF therapy can be started after 4 weeks of TB therapy. In patients with active TB, anti-TNF therapy should be delayed until completion of TB therapy is possible.

- Acetaminophen (TYLENOL) tablet 650 mg, oral, once
- Diphenhydramine PO or IV:
  - Diphenhydramine 25 mg capsule, oral, once
  - Diphenhydramine injection, 25 mg, IV, once**

- *Infliximab (Remicade)* in sodium Chloride 0.9% 250 ml. The determined dose (5mg/kg or 10 mg/kg) is given via IV infusion over 120 minutes. Dose is titrated as follows:
  - 10 ml/hour x15 minutes, 20 ml/hour x15 minutes, 40 ml/hour x15 minutes, 80 ml/hour x15 minutes, 150 ml/hour x30 minutes, 250 ml/hour until the bag is empty

- *Monitoring during infusion:* Vitals before starting therapy and every 30 minutes during and post infusion

- *Emergency orders for infusion reaction (part of the order set)††:*

  - Nasal Cannula oxygen sats >/= 92%: Liters per minute: 2 LPM, Wean FIO2 to keep: Sats >/= 92%. For acute infusion reaction: Grade 2 - Moderate symptoms and Grade 3 - Severe/Anaphylaxis symptoms

  - Sodium Chloride (NS) 0.9% infusion: 20 ml/hour, IV, continuous PRN for infusion reaction: Grade 3 - Severe/Anaphylaxis symptoms

  - Sodium Chloride (NS) 0.9% bolus 1000 ml: IV bolus for acute infusion reaction: Grade 3 - Severe/Anaphylaxis symptoms

  - Diphenhydramine (Benadryl) 25 mg, IV injection once as needed for acute infusion reaction: Grade 2 - Moderate Symptoms or Grade 3 - Severe/Anaphylaxis Symptoms. Dilute 20 mg to 5 mL with 0.9% NaCl for IV push, give over at least 2 minutes**

** Patient should have driver if IV Diphenhydramine is given.

†† Grades of acute allergic reaction:

Grade 1- Mild (Skin and subcutaneous tissues only)	Generalized erythema, urticaria, periorbital edema, or angioedema
Grade 2- Moderate (Features suggesting respiratory, cardiovascular, or gastrointestinal involvement)	Dyspnea, stridor, wheeze, nausea, vomiting, dizziness (presyncope), diaphoresis, chest or throat tightness, or abdominal pain
Grade 3- Severe (Hypoxia, hypotension, or neurologic compromise)	Cyanosis or SpO2 ≤ 92% at any stage, hypotension (SBP < 90 mm Hg in adults), confusion, collapse, LOC, or incontinence

- Famotidine (Pepcid) 20 mg IV injection, once as needed for acute infusion reaction: Grade 2 - Moderate Symptoms or Grade 3 - Severe/Anaphylaxis Symptoms.
- Meperidine (Demerol) 25 mg/ml, 25 mg IV injection as needed for rigors
- Methylprednisolone sodium succinate (Solu-MEDROL) 125 mg/2 ml injection. 125 mg IV once for infusion reaction: Grade 2 - Moderate Symptoms or Grade 3 - Severe/Anaphylaxis Symptoms
- Epinephrine (Adrenalin) 0.3 mg, intramuscular injection once as needed for acute infusion reaction: Grade 3 - Severe/Anaphylaxis Symptoms.

Laboratory monitoring while on therapy:

- Standing order is placed as part of the therapy plan.
  - CBC with differential, ALT, and creatinine with the first 3 infusions. Subsequent intervals per the treating physician
  - Periodic TB testing‡‡
  - CRP if clinically indicated
  - Infliximab trough level/antibody if clinically indicated

Special Considerations

- **Accelerated induction for patients with acute severe ulcerative colitis:**
  - May be considered when infliximab is used as a rescue therapy in hospitalized patients with severe refractory ulcerative colitis
  - After the initial dose of 5-10 mg/kg, patients are closely monitored for a number of clinical and laboratory parameters (stool diaries, pain, albumin, and C-reactive protein)→ if no significant improvement or worsening after initial improvement → the second induction dose can be given as soon as 5 days after the first dose. In patients with poor response to the first 2 induction infusions, the third induction dose can be attempted but those patients will likely require colectomy.

‡‡ Patients should be assessed for risk of TB exposure at each clinic visit with repeat testing based on the risk. Patients at high risk include: 1. Exposure to patients with active TB, 2. History of travel to high-risk countries- Mexico, Philippines, Vietnam, India, China, Haiti, and Guatemala. For complete list of high risk countries visit: http://www.stoptb.org/countries/tbdata.asp .3. Patients who live or work in a high-risk environment- homeless shelter, prison or jail, or long-term care facility, and 4. Health-care workers. **Some infusion centers require annual testing regardless of the risk.**

- **Restarting infliximab in patients with previous exposure to infliximab (High-risk protocol):**

    - Patients who previously discontinued infliximab secondary to disease remission or patient's preference are better candidate for reinitiating infliximab as compared to those who stopped therapy secondary to loss or response or drug-related reactions

    - When possible concomitant immunosuppressive (thiopurines or methotrexate) therapy should be used

    - **First three infusions provided in the GI clinic:**

        - Pre-medications:
            - Prednisone 60 mg the day before the infusion and the day of the infusion, then reduce by 10 mg every 2 days to complete taper over 12 days
            - Hydrocortisone sodium succinate (Solu-Cortef) 200 mg IV injection prior to the infusion
            - Acetaminophen (Tylenol) 650 mg orally prior to the infusion
            - Cetirizine (Zyrtec) tablet 10 mg: 10 mg, oral once

        - *Infliximab (Remicade)* in sodium Chloride 0.9% 250 ml. The determined dose (5mg/kg or 10 mg/kg) is given via IV infusion over 4 hours. Dose is titrated as follows:
            - 10 ml/hour x15 minutes, 20 ml/hour x15 minutes, 40 ml/hour x15 minutes, 60 ml/hour x15 minutes, 75 ml/hour until the bag is empty

    - **The fourth infusion** is given with the standard premedication and infusion rate in the GI clinic for close monitoring. If tolerated, subsequent infusions can be arranged in the infusion center as per the usual protocol

    - Obtain trough infliximab level/antibodies before the second infusion. In patients with undetectable/low level and positive antibodies, infliximab should be discontinued.

- **Other safety considerations:**

- Infliximab is pregnancy Category B and should be continued during pregnancy. It can cross the placenta during the third trimester and therefore live or live-attenuated vaccines should not be given to infants born to mothers receiving infliximab within the first 6 months of life.

- The limited data available suggests that anti-TNF therapies are compatible with breastfeeding and therefore the anti-TNF therapy should not influence the decision to breast-feed, and breast-feeding should not influence the decision to use these medications

- Live vaccines are contraindicated if patient receiving anti-TNF agents or planning to initiate therapy within 4-6 weeks

- Patients should be advised to comply with general cancer screening protocols: mammograms, annual pap smears, CRC/dysplasia surveillance

- Protect against UV radiation (sunscreen) and annual dermatological screening

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