CAREPATHrx™
Specialty Pharmacy & Infusion Solutions

GUIDELINES FOR OUTPATIENT INTRAVENOUS ACTEMRA (TOCILIZUMAB) THERAPY

Section: Nursing
Compliance: ACHC Infusion Pharmacy
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I. BACKGROUND

ACTEMRA (Tocilizumab) is a recombinant humanized anti-human interleukin 6 (IL-6) receptor monoclonal antibody of the immunoglobulin IgG1κ (gamma 1, kappa) subclass with a typical H2L2 polypeptide structure. Tocilizumab binds specifically to both soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R), and has been shown to inhibit IL-6-mediated signaling through these receptors. IL-6 is a pleiotropic pro-inflammatory cytokine produced by a variety of cell types including T- and B-cells, lymphocytes, monocytes, and fibroblasts. IL-6 has been shown to be involved in diverse physiological processes such as T-cell activation, induction of immunoglobulin secretion, initiation of hepatic acute phase protein synthesis, and stimulation of hematopoietic precursor cell proliferation and differentiation. IL-6 is also produced by synovial and endothelial cells leading to local production of IL-6 in joints affected by inflammatory processes such as rheumatoid arthritis. The following outlines clinical guidelines for servicing patients in need of outpatient intravenous Tocilizumab.

II. PATIENT ACCEPTANCE CRITERIA

A. All candidates for home care service must be evaluated by the clinician(s) and deemed appropriate to receive home care based upon dispensing pharmacy's admission criteria.

B. The decision to administer a first dose in the home by a field nurse will be determined on a case-by-case basis and reviewed by nursing and pharmacy management. The following criteria will be evaluated:
   1. Prescriber preference
   2. Allergy profile
   3. Age ≥18 years
   4. Ability to secure contracted nursing for subsequent infusions
   5. Other relevant social and/or medical history
   6. Treatment indicated for arthritis or arteritis

C. Patients must have documentation of TB screening and be free from active infection

D. Evidence of baseline bloodwork including ANC, platelets, AST/ALT and total bilirubin, lipid panel

E. Patient is up to date on recommended vaccinations prior to therapy initiation

F. Prescriber orders shall include:
    1. Drug and dose
    2. Route of administration
    3. Frequency of administration
    4. Emergency medications per protocol
    5. Line care protocol
    6. Laboratory monitoring and frequency, if applicable
    7. Premedication orders, if applicable

G. Dispensing pharmacy treatment protocol for anaphylaxis will be instituted unless patient-specific orders are provided by physician. See policy NUR012 (Appendix A).

III. PHARMACOLOGIC OVERVIEW

Refer to manufacturer's full Prescribing Information for most up to date information

A. Indications for Intravenous Administration
**Subcutaneous dosing and administration will not be discussed in the scope of this guideline*
    1. Rheumatoid Arthritis
        a. Adult patients with moderately-to severely- active rheumatoid arthritis who have had an inadequate response to one or more TNF antagonist therapies
    2. Giant Cell Arteritis
        a. Adult patients
    3. Polyarticular Juvenile Idiopathic Arthritis
        a. Patients 2 years of age and older with active disease
    4. Systemic Juvenile Idiopathic Arthritis
        a. Patients 2 years of age and older with active disease

B. Dosage
    1. Rheumatoid Arthritis
        a. 4 mg/kg once every 4 weeks; may be increased to 8 mg/kg once every 4 weeks based on clinical response (maximum dose: 800 mg)
    2. Giant Cell Arteritis
        a. 6 mg/kg once every 4 weeks
    3. Polyarticular Juvenile Idiopathic Arthritis
        a. Patients < 30 kg: 10 mg/kg every 4 weeks
        b. Patients $\geq$ 30 kg: 8 mg/kg every 4 weeks
    4. Systemic Juvenile Idiopathic Arthritis
        a. Patients < 30 kg: 12 mg/kg every 4 weeks
        b. Patients $\geq$ 30 kg: 8 mg/kg every 4 weeks

C. Contraindications
    1. Tocilizumab is contraindicated in patients with a known hypersensitivity

D. Warnings and Precautions
    1. Serious Infections
        a. Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral, protozoal, or other opportunistic pathogens have been reported in patients receiving immunosuppressive agents including Tocilizumab for rheumatoid

arthritis. Tocilizumab should not be administered in patients with an active infection, including localized infections. Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with Tocilizumab, as signs and symptoms of acute inflammation may be lessened due to suppression of the acute phase reactants. Tocilizumab should be interrupted if a patient develops a serious infection, an opportunistic infection, or sepsis.

   i. Tuberculosis - Patients should be evaluated for tuberculosis risk factors and tested for latent infection prior to initiating Tocilizumab.
   ii. Viral Reactivation - Viral reactivation has been reported with immunosuppressive biologic therapies and cases of herpes zoster exacerbation were observed in clinical studies with Tocilizumab.

2. Gastrointestinal Perforations
   a. Events of gastrointestinal perforation have been reported in clinical trials, primarily as complications of diverticulitis. Tocilizumab should be used with caution in patients who may be at increased risk for gastrointestinal perforation. Patients presenting with new onset abdominal symptoms should be evaluated promptly for early identification of gastrointestinal perforation.
3. Laboratory Parameters
   a. Neutrophils - Treatment with Tocilizumab was associated with a higher incidence of neutropenia.
      i. It is not recommended to initiate Tocilizumab treatment in patients with a low neutrophil count i.e., absolute neutrophil count (ANC) <2000/mm3.
   b. Platelets - Treatment with Tocilizumab was associated with a reduction in platelet counts.
      i. It is not recommended to initiate Tocilizumab treatment in patients with a platelet count below 100,000/mm3.
   c. Liver Function Tests - Treatment with Tocilizumab was associated with a higher incidence of transaminase elevations, especially when used with other hepatotoxic drugs (e.g., MTX).
      i. It is not recommended to initiate Tocilizumab treatment in patients with elevated transaminases ALT or AST > 1.5x ULN.
   d. Lipids - Treatment with Tocilizumab was associated with increases in lipid parameters such as total cholesterol, triglycerides, LDL cholesterol, and/or HDL cholesterol
4. Immunosuppression
   a. The impact of treatment with Tocilizumab on the development of malignancies is not known but malignancies were observed in clinical studies. Tocilizumab is an immunosuppressant, and treatment with immunosuppressants may result in an increased risk of malignancies.
5. Hypersensitivity Reactions
   a. Serious hypersensitivity reactions, including anaphylaxis, have been reported in association with infusion of Tocilizumab. Appropriate medical treatment should be available for immediate use in the event of an anaphylactic reaction during administration of Tocilizumab.
6. Demyelinating Disorders
   a. The impact of treatment with Tocilizumab on demyelinating disorders is not known, but multiple sclerosis and chronic inflammatory demyelinating polyneuropathy were reported rarely in clinical studies. Patients should be closely monitored for signs and symptoms potentially indicative of demyelinating disorders. Prescribers should exercise caution in considering the use of Tocilizumab in patients with preexisting or recent onset demyelinating disorders.

7. Active hepatic disease and hepatic impairment
    a. Treatment with Tocilizumab is not recommended in patients with active hepatic disease or hepatic impairment.
8. Vaccinations
    a. Live vaccines should not be given concurrently with Tocilizumab as clinical safety has not been established. Because IL-6 inhibition may interfere with the normal immune response to new antigens, patients should be brought up to date on all recommended vaccinations, except for live vaccines, prior to initiation of therapy with Tocilizumab.

E. Pharmacokinetics
1. Half-life of 11-13 days
2. Vd of 6.4L

F. Adverse Reactions
1. Upper respiratory tract infection, nasopharyngitis, bronchitis, headache, hypertension ALT increased, transaminase increased, dizziness, rash, mouth ulceration, upper abdominal pain, gastritis

G. Drug Interactions
1. Concomitant immunosuppressants due to additive effects
2. CYP 450 substrates - increased metabolism of drugs that are CYP450 substrates when co-administered with Tocilizumab.

IV. ADMINISTRATION GUIDELINES

A. Administration
1. Allow the fully diluted Tocilizumab solution to reach room temperature prior to infusion.
2. Tocilizumab should not be infused concomitantly in the same intravenous line with other drugs. No physical or biochemical compatibility studies have been conducted to evaluate the co-administration of Tocilizumab with other drugs.
3. The infusion must be administered with an infusion set. Do not administer as an intravenous push or bolus.
4. IV infusions should be given immediately after dilution. Use within 1 hour of preparation per current USP Immediate-Use Guidelines.

B. Dose Adjustment
1. The safety and efficacy of Tocilizumab have not been studied in patients with hepatic impairment, including patients with positive HBV and HCV serology
2. Tocilizumab has not been studied in pregnant or breast-feeding patients and has not been studied in children.
    a. To monitor the outcomes of pregnant women exposed to Tocilizumab, a pregnancy registry has been established. Physicians are encouraged to register patients and pregnant women are encouraged to register themselves by calling 1 (877) 311-8972.
3. No dose adjustment is required in patients with mild renal impairment.

4. Dose adjustment based on toxicities

Liver Enzyme Abnormalities *[see Warnings and Precautions (5.3)]:*	
Lab Value	**Recommendation**
> 1 to 3x ULN	Dose modify concomitant DMARDs if appropriate For persistent increases in this range, reduce ACTEMRA dose to 4 mg/kg or interrupt ACTEMRA until ALT/AST have normalized
> 3 to 5x ULN (confirmed by repeat testing)	Interrupt ACTEMRA dosing until < 3x ULN and follow recommendations above for >1 to 3x ULN For persistent increases > 3x ULN, discontinue ACTEMRA
> 5x ULN	Discontinue ACTEMRA

Low Platelet Count *[see Warnings and Precautions (5.3)]:*	
Lab Value (cells/mm^3)	**Recommendation**
50,000 to 100,000	Interrupt ACTEMRA dosing When platelet count is > 100,000 cells/mm^3 resume ACTEMRA at 4 mg/kg and increase to 8 mg/kg as clinically appropriate
< 50,000	Discontinue ACTEMRA

Low Absolute Neutrophil Count (ANC) *[see Warnings and Precautions (5.3)]:*	
Lab Value (cells/mm^3)	**Recommendation**
ANC > 1000	Maintain dose
ANC 500 to 1000	Interrupt ACTEMRA dosing When ANC > 1000 cells/mm^3 resume ACTEMRA at 4 mg/kg and increase to 8 mg/kg as clinically appropriate
ANC < 500	Discontinue ACTEMRA

C. Patient Monitoring
   1. Monitor for signs and symptoms of infections
   2. Monitor for signs and symptoms of CNS demyelinating disorders
   3. Monitor for new onset abdominal symptoms

V. NURSING PROCEDURE

A. Supplies may include but are not limited to:
   1. Alcohol Swabs
   2. Gloves
   3. Tocilizumab vials
   4. 50 mL or 100 mL bag of sodium chloride 0.9% for dilution
   5. Dressing change kit

6. IV Pole
7. IV Start Kit
8. Peripheral IV catheter
9. Port access needle
10. Tape
11. Extension set 8”
12. IV injection cap
13. IV administration set (dial-a-flow or gravity)
14. Syringes with needles
15. Normal Saline (0.9%) Flushes
16. Sharps container

B. How Supplied
    1. Tocilizumab is supplied as a sterile, preservative-free solution for intravenous (IV) infusion at a concentration of 20 mg/mL. Tocilizumab is a colorless to pale yellow liquid, with a pH of about 6.5. Single-use vials are available containing 80 mg/4 mL, 200 mg/10 mL, or 400 mg/20 mL of Tocilizumab.

C. Storage and Handling
    1. Do not use beyond expiration date on the container. Tocilizumab must be refrigerated at 2ºC to 8ºC (36°F to 46°F). Do not freeze. Protect the vials from light by storage in the original package until time of use.

D. Compatibility
    1. Fully diluted Tocilizumab solutions are compatible with polypropylene, polyethylene and polyvinyl chloride infusion bags and polypropylene, polyethylene and glass infusion bottles.
    2. Stable in 0.9% sodium chloride

E. Procedures - Preparation of product, infusion rates, post infusion monitoring time.
    1. Explain the reasoning for visit and use of Tocilizumab
    2. Don gloves.
    3. Establish venous access prior to preparation of drug.
    4. Counsel patient on warnings, precautions, and potential side effects.
    5. Prepare Product
        a. For pediatric patients <30 kg, utilize 50mL 0.9% sodium chloride bag; for patients ≥ 30 kg, utilize 100mL 0.9% sodium chloride bag.
        b. For adult patients at or above 30 kg, utilize 100mL 0.9% sodium chloride bag
        c. From a 50 mL or 100 mL 0.9% sodium chloride infusion bag, withdraw a volume of 0.9% Sodium Chloride Injection, USP, equal to the volume of the Tocilizumab solution required for the patient’s dose.
        d. Slowly add Tocilizumab for intravenous infusion from each vial into the infusion bag. To mix the solution, gently invert the bag to avoid foaming.
        e. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If particulates and discolorations are noted, the product should not be used.
        f. Allow the fully diluted Tocilizumab solution to reach room temperature prior to infusion.
    6. Infusion Rates
        a. The infusion should be administered over 60 minutes
    7. Nurse to remain with patient for at least 30 minutes following medication administration to monitor vital signs and response to therap

VI. CLINICAL MONITORING

A. Labs
   1. Neutrophils, platelets - prior to therapy, 4 to 8 weeks after start of therapy, and every 3 months thereafter
   2. ALT/AST, alkaline phosphatase, and total bilirubin - every 4 to 8 weeks after start of therapy for the first 6 months, and every 3 months thereafter
   3. lipid panel - 4 to 8 weeks following initiation of therapy, then subsequently according to current guidelines

B. Monitor patients for signs and symptoms of infection, signs and symptoms of CNS demyelinating disorders, and new onset abdominal symptoms.

Please refer to the package insert for the most up to date guidance on this medication.

REFERENCES:

ACTEMRA (Tocilizumab) Package insert. South San Francisco, CA. Genentech Inc. 2019.

Acheson, Emily E. et al. "Tocilizumab: Drug Information." UpToDate, Accessed Sep 15, 2022. https://www.uptodate.com/contents/tocilizumab-drug-information?search=actemra.

APPENDIX A: ANAPHYLAXIS KIT INTRUCTIONS

Emergency Medication After Your Infusion

Please call your pharmacy if you have any questions or concerns. In the event of an emergency, always call 911.

Your nurse will tell you when you need to use Emergency Medications.
The epinephrine dose will be noted on the Anaphylaxis Protocol included with your kit.

Start with a clean work surface and clean hands.

Open the supply bag labeled Anaphylaxis Kit Contents.

You will need:

1. Bag containing Pills (2 Acetaminophen and 2 Diphenhydramine)
2. Bag containing Alcohol Prep Pads
3. Bag labeled IM Epinephrine

All other contents will not be needed.

Open the IM Epinephrine Bag

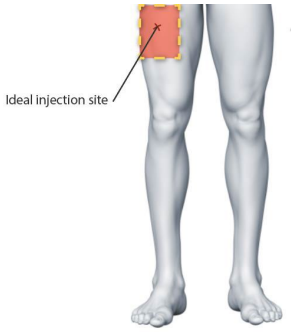
1. Remove 1 of each item
    a. 1 -syringe
    b. 1 – brown labeled filter needle (BD Filter Needle)- **for ampule use only**
    c. 1 – black labeled safety needle (Magellan Hypodermic Safety Needle 22G x 1”)
    d. 1 ampule of epinephrine

Prepare IM (intramuscular) injection of Epinephrine:

1. Attach the brown filtered needle to syringe
    a. Be careful to not touch the tip of the syringe or the needle.
2. Using an alcohol swab, wipe the neck of the epinephrine ampule.
3. Holding the ampule upright, swirl and flick the ampule until all fluid flows to the bottom chamber (the top chamber should be empty).
4. Using a new alcohol wipe, grasp the neck of the ampule and with your other hand grasp the bottom chamber of the ampule. Quickly snap the top of the ampule off, directing the snap way from you.
5. Place the tip of the brown filter needle inside the ampule. Tilting the ampule, withdraw dose of medication into the syringe by gently pulling back on the plunger. Be careful to not pull the plunger out of the syringe.
6. Remove the needle from the ampule and hold the syringe upright with the needle pointing upward. Gently tap the side of the syringe to bring any air to the top of the syringe.
7. Push the air out of the syringe by gently pushing on the plunger.

8. Replace the cap on the brown filter needle. Discard remainder in ampule.
9. Remove the brown filter needle and place the black safety needle onto the syringe.

Give your IM Epinephrine injection



1. Grasp your leg muscle at the outer mid-thigh and cleanse the area with a new alcohol wipe.
2. Push the needle into your leg muscle straight in at a 90-degree angle.
3. Inject the medication by depressing the plunger in a slow and steady motion.
4. Remove the needle and wipe the site with the alcohol wipe.
5. May repeat dose every 5 minutes (maximum 3 doses) if ordered per protocol.

Take the pills by mouth.

a. 2 – Acetaminophen
b. 2 – Diphenhydramine

Place all trash in the bag the pills came in and take with you when you seek medical care. **Give the bag to the nurse or EMT**, so your doctor will know what medication you already took. They will properly dispose of the syringe and needles.
Call 911 or have someone drive you to the emergency department.

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Nothing within these Clinical Guidelines is intended to supersede or interfere with any individual clinician's decision-making or professional judgment with respect to either (1) prescribing or dispensing the drug or product in question or (2) the overall treatment plan for an individual patient.