Positive Quality Intervention: Siltuximab (Sylvant®) in Patients with Idiopathic Multicentric Castleman Disease

Description:
The purpose of this PQI is to discuss the use of siltuximab (Sylvant®) in idiopathic multicentric Castleman disease (MCD).

Background: Siltuximab, a monoclonal antibody that targets inhibiting interleukin-6 (IL-6), has emerged as a significant therapeutic option in the management of idiopathic MCD, a rare and complex disorder primarily affecting the lymph nodes. The drug exerts its therapeutic effect by selectively inhibiting IL-6, a crucial cytokine implicated in the pathogenesis of Castleman disease. The United States Food and Drug Administration (FDA) granted approval for siltuximab in 2014, marking a pivotal development in the treatment landscape for this challenging condition. The approval was based on compelling evidence derived from a multicenter, randomized, double-blind clinical trial (NCT01400503). This trial compared siltuximab plus best supportive care to placebo plus best supportive care. Durable tumor and symptomatic responses occurred in 34% of patients randomized to siltuximab compared to 0% in the placebo arm. This trial played a crucial role in establishing the efficacy of siltuximab in reducing the symptoms associated with Castleman disease. In a post-hoc analysis, siltuximab demonstrated improved progression-free survival (PFS) compared to placebo with a median PFS of 14.5 months in the placebo arm while median PFS was not reached for patients receiving siltuximab. Siltuximab is listed as the National Comprehensive Cancer Network (NCCN) preferred first-line treatment option for idiopathic MCD that is HIV and HHV8 negative.

PQI Process: Upon ordering Siltuximab
Indication: Treatment of MCD in patients who are human immunodeficiency virus (HIV) and human herpesvirus-8 (HHV-8) negative

Dosing
- FDA approved: 11 mg/kg IV over 1 hour every 3 weeks until treatment failure
- Off-label (severe disease in critically ill patients): 11 mg/kg IV once weekly x 4 then every 3 weeks until treatment failure
- Dosing Considerations

Prior to First Infusion
- Absolute neutrophil count ≥1000 cells/mL
- Platelet count ≥75 cells/mL and 50 cells/mL for retreatment
- Hemoglobin ≤17 g/dL
- Severe impairment (Child-Turcotte-Pugh class C): No dosage adjustments provided in the manufacturer’s labeling (has not been studied)

Initial Disease Control
- Adjunctive corticosteroids may be also administered for 4 to 8 weeks, followed by a corticosteroid taper; patients who are more symptomatic may require higher initial dose corticosteroids and a more gradual taper

Altered Kidney Function
- CrCl < 15 mL/min/End stage renal disease: No dosage adjustments provided in the manufacturer’s labeling (has not been studied)

Cytokine Release Syndrome
- Permanently discontinue

Hematologic Toxicity
- Consider delaying treatment until ANC ≥1,000 cells/mL, platelets ≥50,000 cells/mL, and hemoglobin <17 g/dL

Severe Infection
- Withhold siltuximab until infection resolves

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### Infusion Related Reactions

<table>
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<tr>
<th>Immediate interrupt infusion for reaction of any severity and manage symptoms as clinically appropriate</th>
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<td><strong>Grade 1 or 2 (mild to moderate) infusion reactions:</strong> Once symptoms resolve, resume infusion at a lower infusion rate; consider antihistamines, acetaminophen, and corticosteroids; if patient does not tolerate infusion following intervention, permanently discontinue</td>
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<td><strong>Grade 3 (severe) or Grade 4 (anaphylactic reaction or life-threatening) infusion reactions:</strong> Permanently discontinue</td>
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### Monitoring
- Complete blood count (CBC) with differential should be reviewed prior to each dose for the first 12 months and every 3 dosing cycles thereafter

### Warnings and precautions
- Do not administer with concurrent active severe infections; hold until resolution
- Avoid administration of live vaccinations to patients or infants born to patients receiving siltuximab
- Administer in setting able to provide resuscitation in event of infusion related reaction
- Increased risk of gastrointestinal perforation; promptly evaluate at first signs/symptoms

### Admixture
- Available in 100 mg and 400 mg single dose vials
- Prepare using a 21-gauge, 1.5" needle; infusion bag 250 mL D5W, polyvinyl chloride (PVC), polyurethane (PU), or polyethylene (PE) set which contains a 0.2-micron inline polyethersulfone (PES) filter
  - **Note:** only stable with D5W
- Allow vial to come to room temperature (approximately 30 min), reconstitute using sterile water for injection (SWFI), and gently swirl (do not shake) (approximately 60 min to fully dissolve)
  - 100 mg vial – 5.2 mL SWFI (reconstituted concentration 20 mg/mL)
  - 400 mg vial – 20 mL SWFI (reconstituted concentration 20 mg/mL)
- Inject calculated volume for final concentration into 250 mL D5W and invert bag gently

### Administration
- Administer IV over 1 hour
- Do not infuse in the same line as other medications
- Complete the infusion within 4 hours of dilution of the reconstituted solution to the infusion container
- Administer in a setting to provide resuscitation equipment in case of an infusion related reaction; bronchodilators, antihistamines, and corticosteroids should be readily available

### Patient-Centered Activities:
- Educate patients on siltuximab therapy and recommend appropriate interventions
  - Counsel on most common side effects: skin disorders (rash, pruritis), respiratory tract infection, edema, weight gain, hyperuricemia, fatigue, diarrhea
  - Avoid live vaccinations
  - Report signs of infection (fever, chills, cough, or sore throat) to your care team immediately
  - Increased risk of fetal harm; discuss risk/benefits; patients who could become pregnant should use effective contraception during treatment and for 3 months after the last dose of siltuximab
- Patient Assistance: [NCODA Financial Assistance Tool](https://www.ncoda.org/), [Recordati Patient Liaison](https://www.recordati-us.com/contactus/patientliaison.html)

### References:
1. Sylvant (siltuximab) [prescribing information].