Vedolizumab Tips

Vedolizumab (Entyvio®) is a humanized monoclonal antibody that binds to the α4β7 integrin receptor and blocks the interaction of the α4β7 integrin with MAD-CAM-1 (mainly expressed in gut tissues), thereby inhibiting the movement of the discrete subset of T-lymphocytes that preferentially migrate into inflamed GI tissue. Vedolizumab is the first biologic with a specific binding action that inhibits the movement of gut-directed white blood cells into the GI tract, thereby controlling inflammation and symptoms of Ulcerative Colitis (UC) and Crohn’s Disease (CD). As part of the natural immune response, white blood cells are programmed to travel to different body tissues, defending against disease. Certain white blood cells are directed to the GI tract. In people with UC and CD, the increased number of these cells causes inflammation. Vedolizumab is supplied as a sterile, white to off white, preservative free, lyophilized (freeze-dry) cake for intravenous infusion. It is an infusible medication that has been approved for home IV therapy, hospital outpatient administration or physician’s office administration.

Pre-Screening

1. Should be done prior to first and subsequent infusions (see 4-8 below).
2. CBC, liver and renal function prior to initiating therapy and periodic monitoring.¹
3. Patient Counseling Information
   a. Patient advised of potential benefits and risks
      i. **Benefits²**
         1. Clinical trials evaluated safety in over 3300 adults
         2. Offers consistent, predictable dosing
         3. Adult Crohn’s Disease (CD). For patients with moderately or severely active CD, patients who received Vedolizumab:
            a. Achieved remission
            b. Achieved clinical response
            c. Achieved clinical remission without steroids
      4. Adult Ulcerative Colitis (UC). For patients with moderately or severely active UC, Vedolizumab offers:
         a. Rapid and lasting efficacy
         b. Helps patients achieve remission without steroids
         c. Provides visible mucosal improvement
   ii. **Major Risks²**
      1. Infusion and serious allergic reactions. Allergic reactions including dyspnea, bronchospasm, urticaria, flushing, rash and increased blood pressure and heart rate have been reported. The majority were mild to moderate which consist of nausea, headache, and pruritus. Experience with other biologic medications suggest that hypersensitivity reactions and anaphylaxis to Vedolizumab may vary in their time of onset from during infusion or immediately post-infusion to occurring up to several hours post-infusion.

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2. **Infections.** Patients treated with Vedolizumab may be at an increased risk of developing infections. The most commonly reported involved the upper respiratory and nasal mucosa (e.g., nasal pharyngitis and upper respiratory tract infections). Serious infections have also been reported including anal abscess, sepsis (some fatal), tuberculosis, salmonella sepsis, listeria meningitis, giardiasis and cytomegalovirus colitis. Vedolizumab is not recommended in patients with active, severe infections until the infection is controlled. Exercise caution when considering the use of Vedolizumab in patients with a history of recurring severe infections.

3. **Progressive Multifocal Leukoencephalopathy.** Another integrin receptor antagonist (natalizumab (Tysabri)) has been associated with Progressive Multifocal Leukoencephalopathy (PML), a rare and often fatal opportunistic infection in the central nervous system (CNS). PML is caused by the John Cunningham (JC) virus and typically occurs in patients who are immunocompromised. In Vedolizumab trials, patients were actively monitored for PML with frequent and regular screenings. While zero cases of PML were identified among patients with at least 24 months of exposure, a risk of PML cannot be ruled out. Monitor patients on Vedolizumab for any new onset, or worsening, of neurological signs and symptoms. Typical signs and symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body or clumsiness of the limbs, disturbance of vision, and changes in thinking and memory, and orientation leading to confusion and personality changes. If PML is suspected, hold Vedolizumab and refer to neurologist; if confirmed, discontinue dosing permanently.

4. **Liver Injury.** There have been reports of elevations of transaminases and/or bilirubin in patients receiving Vedolizumab. It is unclear if the reactions indicated drug-induced or autoimmune etiology. *

5. **Malignancies.** In the trials, malignancies (excluding dysplasia and basal cell carcinoma) including colon cancer (n=2), transitional cell carcinoma (n=1), breast cancer (n=1), carcinoid tumor of the appendix (n=1) and squamous cell carcinoma (n=1). Malignancy was reported in one of 297 (0.3%) patients treated with placebo (squamous cell carcinoma).²

6. **Adverse Reactions.** Adverse reactions were reported in 52% (n=1434) of patients treated with Vedolizumab and 45% (n=297) of patients treated with placebo. The following adverse reactions were reported in ≥ 3% of patients treated with Vedolizumab: nasopharyngitis, headache, arthralgia, nausea, pyrexia, upper respiratory infections, fatigue, cough, bronchitis, influenza, back pain, rash, pruritus, sinusitis, oropharyngeal pain, and pain in extremities.
7. **Immunogenicity.** In blinded trials, the frequency of antibodies detected in patients who received Vedolizumab was 13% at 24 weeks. *Positive antibody detection prevented clinical remission.

   b. Document counseling in the patient’s record
      i. e.g. The nature, indication, alternatives, material risks and benefits of chronic use of vedolizumab therapy were discussed. Specific complications discussed included but were not limited to hypersensitivity reactions, infections, progressive multifocal leukoencephalopathy, liver injury, malignancies, adverse reactions and/or immunogenicity.”

   c. Patient provided resource MEDICATION GUIDE² to be read before starting and re-read prior to each infusion (available for download online).

4. **Tuberculosis screening**²
   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. ³,⁴
            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 on 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.

5. **Screen for Hepatitis B**⁵
   a. Surface Ag
   b. Surface Ab

6. **Screen for Hepatitis C**⁶

7. **Verify vaccine status/update if indicated²,⁷**
   a. MMR * this is a live vaccine and not indicated <4 weeks before first infusion
   b. Hepatitis A
   c. Hepatitis B
   d. Influenza
   e. Pneumovax and Prevnar

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8. Live and Oral Vaccines ²
   a. Patient receiving Vedolizumab may receive non-live vaccines (e.g. influenza vaccine injection) and may receive live vaccines if the benefits outweigh the risks. (eg. Zoster, MMR)
   b. There are no data on the secondary transmission of infection by live vaccines in patients receiving Vedolizumab.

9. Skin Cancer screening ⁸
   a. Annual visual exam of skin by dermatologist if immunocompromised and recommend sun exposure precautions.

Start the Prior Authorization (PA) Process

   1. At the time of the decision to start treatment with Vedolizumab.
   2. Designate dedicated office personnel to manage Vedolizumab PA.
       a. Have process in place e.g. Receive orders for Vedolizumab, initiate PA, notify infusion nurse, set up schedule, order medications.
   3. If Vedolizumab frequency is changed, you may need a new PA.

Patient Assistance

   1. Entyvio Connect is a patient assistance program that puts patients in touch with insurance and financial assistance experts called case managers. They will have a small case manager team—no more than 3 people—who are personally dedicated to each account.
   2. Once the patient is prescribed Vedolizumab, healthcare provider’s office staff should help patients enroll in Entyvio Connect. A case manager team starts processing information when they receive enrollment.
   3. Case managers are trained to:
       a. Determine eligibility for financial assistance options
       b. Work with insurance companies on the patient’s behalf to identify how their Vedolizumab treatment is covered
       c. Help enroll patients in an appropriate financial assistance program, if available
       d. Entyvio Connect offers out-of-pocket financial assistance for eligible patients.
       e. Determine what information and support the healthcare provider needs from insurance companies before starting treatment

4. If there are any questions about enrollment into Entyvio Connect, call 1-855-ENTYVIO (1-855-368-9846). Call Monday to Friday, from 8 AM to 8 PM EST (except holidays) to speak to an Entyvio Connect case manager.

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1. Benefit Investigation and Co-pay Consent Form/Instructions
2. Co-pay assistance-only Enrollment Form/Instructions
3. Sample Summary of Benefits /Instructions
4. Physician Office Samples CMS-1500 Claim Form/Instructions
5. Hospital Outpatient Sample UB -04 Claim Form/Instructions
6. Sample Letter of Medical Necessity Form/Instructions
7. Sample Letter of Appeal Form/Instructions
8. Diagnosis Code Quick Reference Guide Form
   a. Product Specific J-code J3380 for Vedolizumab, 1mg\textsuperscript{10} Effective January 1, 2016, the Centers for Medicare and Medicaid Services has assigned a product-specific J-code for Vedolizumab. Vedolizumab will no longer be classified under “Miscellaneous” (J3590/J3490).
   b. It is important that your office conducts a patient specific benefit investigation with each insurance provider to ensure use of the correct code.
9. Prescribing Information
10. Medication Guide

**Initial Infusion**

1. Obtain written orders for Vedolizumab infusion therapy and pre-medication if indicated
2. Order medication
3. Schedule infusion

**Dosing**

1. Induction is week 0, 2 and 6. Thereafter every 8 weeks.
2. For adults with moderate to severe active UC or CD, the recommended dose of Vedolizumab is 300 mg
3. Response is usually determined by week 14
4. When patient is not responding or losing response, frequency may be increased, e.g. every 4 weeks with insurance authorization

**Yearly Screening**

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1. Refer to **Crohn’s & Colitis Foundation Health Maintenance Checklist**¹
   a. Labs
   b. Bone Density
   c. Vaccine Update
   d. Cancer screening
   e. Pregnancy evaluation

2. Designated follow up with Gastroenterology Provider

**Special Populations**²

1. **Pregnancy Evaluation**: ask the patient if she has intentions of getting pregnant within the next year, if the answer is no, ask her what she is doing to prevent pregnancy. Certain medications should be discontinued or adjusted when the patient with UC/CD becomes pregnant.

2. **Nursing Women**: It is not known whether Vedolizumab is excreted in human milk or absorbed systemically after ingestion. Vedolizumab was detected in the milk of lactating monkeys. Exercise caution when administering Vedolizumab to a nursing woman.

3. **Pediatrics (< 18 years of age)**: The safety and efficacy of Vedolizumab in pediatric patients below the age of 18 has not been established, although clinical trials in pediatric population are in process. **Geriatrics (> 65 years of age)**: Clinical trials of Vedolizumab did not include sufficient numbers of subjects aged 65 and over (46 patients 65 years of age or older were treated with Vedolizumab in the Phase 3 clinical trials) to determine whether they respond differently from younger subjects. The efficacy and safety of Vedolizumab should be interpreted with caution in patients older than 65 years of age.

4. **Renal and Hepatic Insufficiency**: No formal studies have been conducted to examine the effects of either renal or hepatic impairment on the pharmacokinetics of Vedolizumab. No dose recommendation can be made.

**INFUSING VEDOLIZUMAB**

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**Evaluate patient for**: (review affirmative answers with ordering provider)

- Any current or recent bouts of fever, illness or infection
- Any change in medical history

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Vital Signs Monitoring

Obtain vital signs prior to initiating infusion and thereafter according to infusion center protocol. However, if prior history of an acute infusion reaction, monitor vital signs 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: Intravenous infusion 300 mg
   - Ulcerative Colitis: Intravenous infusion 300 mg
   - Treatment at weeks 0, 2 and 6 then every 8 weeks.
   - Patients that do not respond by week 14 are unlikely to respond with continued dosing and consideration should be given to discontinue Vedolizumab in these patients.¹ This should be discussed or evaluated further by their primary gastroenterologist.

2. Consider IV fluid hydration for diarrhea flares, prior to starting the Vedolizumab e.g. 1000 cc NS

3. If patient requires laboratory monitoring related to their disease or medications, if appropriate, combine blood draw with the IV start.

***Do not reconstitute vials until after successfully obtaining intravenous access***

Drug Preparation²

DOSAGE AND ADMINISTRATION

Vedolizumab is administered as an intravenous infusion over 30 minutes. Vedolizumab must be reconstituted and diluted prior to administration (see Instructions for Reconstitution and Infusion). Do not administer as an intravenous push or bolus.

Vedolizumab should be administered by a healthcare professional prepared to manage hypersensitivity reactions including anaphylaxis, if they occur.

Missed Dose

Patients who miss their scheduled infusion should be advised to contact their healthcare professional and to schedule another appointment as soon as possible.

Reconstitute Instructions

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Reconstitute Vedolizumab at room temperature, this would involve taking out of the refrigerator ahead of time (eg. 30 minutes). Vedolizumab should be reconstituted and prepared by a trained medical professional using aseptic technique by the following procedure:

1. Remove the flip-off cap from the single dose vial and wipe with alcohol wipe. Reconstitute Vedolizumab vail containing lyophilized powder with 4.8 mL of Sterile Water for injection, using a syringe with a 21 to 25 gauge needle.
2. Insert the syringe needle into the vial through the center of the stopper and direct the stream of sterile water for injection to the glass wall of the vial to avoid excessive foaming.
3. Gently swirl the vial for at least 15 seconds to dissolve the lyophilized powder. Do not vigorously shake or invert.
4. Allow the solution to sit for up to 20 minutes at room temperature to allow for reconstitution and for any foam to settle; the vial can be swirled and inspected for dissolution during this time. If not fully dissolved after 20 minutes, allow another 10 minutes for dissolution. Do not use the vial if the drug product is not dissolved within 30 minutes.
5. Visually inspect the reconstituted Vedolizumab solution for particulate matter and discoloration prior to administration. Solution should be clear to opalescent, colorless to light brownish yellow and free of visible particulates. Do not administer reconstituted solution showing uncharacteristic color or particulates.
6. Prior to withdrawing the reconstituted Vedolizumab solution for the vial, gently invert vial three times.
7. Withdraw 5 ml (300mg) of reconstituted Vedolizumab solution using a syringe with a 21 to 25 gauge needle. Discard any remaining portion of the reconstituted solution in the vial.

**Dilution Instructions**

1. Add the 5ml (300mg) of reconstituted Vedolizumab solution to 250 ml of sterile 0.9% sodium chloride and gently mix the infusion bag.
2. Do not add other medicinal products to the prepared infusion solution or intravenous infusion set.
3. Once reconstituted and diluted, use the infusion solution as soon as possible.
4. Infuse over 30 minutes.
5. After the infusion is complete, flush with 30 mL of sterile 0.9% Sodium Chloride injection.

**Storage**

Vedolizumab is supplied in sterile 20 ml single-use glass vials, containing 300 mg of Vedolizumab as a white to off-white cake.

Refrigerate unopened vials at 2° to 8° (36° to 46°). Retain in original package to protect from light.

If necessary, the infusion solution may be stored for up to four hours at 2° to 8° (36° to 46°). Do not freeze. Discard any unused portion of the infusion solution.
Infusion Related Reactions and Hypersensitivity

In clinical trials with Vedolizumab, infusion related reactions (IRR) and hypersensitivity reactions have been reported, with the majority being mild to moderate in severity (see Adverse Reactions). Experience with other biologic medications suggest that hypersensitivity reactions and anaphylaxis may vary in their time of onset from during infusion or immediately post infusion to occurring up to several hours post infusion.

If a severe infusion-related reaction, anaphylactic reaction, or other severe reaction occurs, administration of Vedolizumab must be discontinued immediately and appropriate treatment initiated (e.g. epinephrine and antihistamines).

If a mild to moderate IRR occurs, the infusion rate can be slowed or interrupted and appropriate treatment initiated. Once the mild or moderate IRR subsides, the healthcare professional may continue the infusion with monitoring. Pre-treatment with standard medical treatment (e.g., antihistamine, hydrocortisone and/or acetaminophen) may be considered prior to the next infusion for patients with a history of mild to moderate IRR to Vedolizumab, in order to minimize their risks (see Dosage and Administration).

In the event of an infusion reaction

1. Stop or slow infusion
2. Give Benadryl 25-50 po/IV (IV is given slowly 25mg/min)
3. Give Acetaminophen 650-1000 mg po
4. Give Prednisone 40 mg po or IV
5. Resume infusion
   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 Education²: Educate patient on Vedolizumab possible side effects, allergic reactions, delayed allergic reactions and when to contact MD
   1. Most common side effects of Vedolizumab: nasopharyngitis, arthralgia, headache, nausea, fever, upper respiratory tract infection, fatigue and cough. 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 [see Major Risks]

2. Educate patient about signs and symptoms of delayed allergic reactions which may occur 3 to 12 days after receiving Vedolizumab 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

3. Inform patients that they may be more likely to develop infections when taking Vedolizumab. Instruct patients to tell their health care provider if they develop any signs or symptoms of an infection. [see Major Risks]

4. Inform patients that progressive multifocal leukoencephalopathy (PML) has occurred in patients who received different integrin receptor antagonist product. Instruct patients to report if they experience any new or worsening of neurological signs and symptoms immediately, as these could be indicative of PML. [see Major Risks]

5. Inform patients that elevated transaminase levels with or without elevated bilirubin has occurred in patients who received Vedolizumab. Instruct patients to report promptly any symptoms that may indicate liver injury including fatigue, anorexia, right upper abdominal discomfort, dark urine, jaundice. [see Major Risks]

**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
Supplies to Manage Complications

- Epinephrine
- Antihistamines
- Corticosteroids
- Acetaminophen
- Crash Kits
- Defibrillator
- Oxygen
- Ambu bag

References

2. Entyvio (vedolizumab) Prescribing Information. Deerfield, IL: Takeda Pharmaceuticals America, Inc.
10. Centers for Medicare and Medicaid Services. CMS-1633-FC; CMS-1607-F2. https://www.cms.gov/Medicare/Medicare-Fee-for-Service-