INFORMATION FOR MEDICAL PROFESSIONALS

CAD FOUNDATION CARES

Information provided by the Cold Agglutinin Disease Foundation (CADF) https://coldagglutinindisease.org/ A non-profit foundation dedicated to creating healthier lives for the CAD community of patients and committed to educating them, their care partners and the medical profession about this rare disease.

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All four are notable and recognized in the field of CAD treatment and research.

ABOUT - COLD AGGLUTININ DISEASE:
Cold agglutinin disease (CAD) is a rare form of autoimmune hemolytic anemia, in which cold agglutinins can cause clinical symptoms related to agglutination (clumping) of red blood cells and hemolytic anemia.
Cold agglutinins – Cold agglutinins are antibodies that recognize antigens on red blood cells (RBCs) at temperatures below normal core body temperature, agglutinating autoantibodies with an optimum temperature of 3 to 4°C. They can cause agglutination of the RBCs and hemolysis, resulting in anemia.
Cold agglutinins may be seen with primary cold agglutinin disease or secondary cold agglutinin disease. The antibodies are typically immunoglobulin M (IgM), and much less frequently IgG or IgA .

- Primary CAD – Primary CAD is used to refer to cold agglutinins that cause RBC agglutination and extravascular hemolysis in the absence of an underlying disorder. Note: Despite the lack of an underlying malignancy, most cases of primary CAD produce a monoclonal cold agglutinin, suggesting these individuals have a clonal B-cell Lymphoproliferative Disorder (LPD).
- Secondary CAD – When cold agglutinins arise in the setting of an underlying disorder such as a viral infection, autoimmune disorder, or lymphoid malignancy, the syndrome is referred to as secondary CAD.

SYMPTOMS:

Cold-induced symptoms in the acral areas are extremely common in CAD. These symptoms can range from mild to disabling and include the following:

- Acrocyanosis – dark purple to gray discoloration of the skin in acral areas such as fingertips, toes, nose and ears.
- Livido reticularis – it makes the skin, usually legs, look mottled and purplish, in a netlike pattern with distinct borders.
- Raynaud phenomenon – sharply demarcated color changes of the skin or digits, frequently painful.
- Cutaneous ulceration or even necrosis in severe cases.
- Pain or discomfort on swallowing cold food or liquids.

Additional symptoms may include:

- Fatigue (Lack of stamina)
- Shortness of breath
- Sore back, legs, or joints
- Dizziness
- Pale skin
- Nausea and diarrhea
- Irregular and fast heartbeat
- Muscle weakness
- Chest pain
- Ringing or whooshing in the ears
- Headaches
- Tea colored or Dark urine
- Jaundice
- Blood Clots

Hemolytic anemia is common in CAD. The severity can range from compensated hemolysis without anemia to severe hemolytic anemia requiring transfusion.

Some individuals have chronic compensated hemolytic anemia with episodes of more severe anemia due to increased hemolysis precipitated by cold temperatures or inflammatory responses

- Episodes of hemolysis may be precipitated by exposure to colder ambient temperatures.
- Episodes of hemolysis may also be exacerbated by febrile or other acute illnesses.

DIAGNOSIS:

Generally accepted diagnostic criteria include the following:

- CBC - Evidence of hemolysis (eg, low hgb, high reticulocyte count, high LDH, high indirect bilirubin, low haptoglobin) *
- Coombs Test – an antiglobulin test which is almost always positive for immunoglobulin M (IgM).
- Cold Agglutinin Titer of ≥64 at 4°C . The titer is the number of dilutions after which the antibody can still cause agglutination; it reflects antibody concentration and avidity.
- Thermal Amplitude Test - The cold agglutinin thermal range reflects the temperature range over which the antibody will bind to the RBC antigen. The thermal amplitude (TA) is the highest temperature at which the antibody will bind the antigen. Most clinically significant cold agglutinins have a thermal amplitude that exceeds 28° to 30°C.

***Orders for usable CBC blood draws for CAD patients.**

MUST BE KEPT AT 37 °C.

1. Warm the test tube with a baby heel warmer or other warming device. Continue the blood draw with the tube wrapped in the heel warmer.

2. Take to the lab immediately and have the blood tested stat.

Improper handling of blood samples is a problem often experienced by CAD patients. Hospital personnel and labs may be unfamiliar with the procedures for proper blood draws and testing because CAD is so rare, resulting in unusable blood samples and incorrect test results.

Testing for underlying disorders — Evaluation for an underlying disorder that could be responsible for cold agglutinins is appropriate in most individuals, especially older adults and those who have evidence of an infectious, autoimmune, or lymphoproliferative disorder. Further testing often includes Bone Marrow Biopsy and CT Scans or MRI.

GENERAL MANAGEMENT:
Treatment is directed at minimizing cold-induced symptoms, maintaining an acceptable hemoglobin level, and addressing underlying disorders. For secondary CAD patients, treating and resolving the underlying condition may result in resolving or improving the CAD.

Cold-induced symptoms – The main therapy is avoidance of cold temperatures. Avoidance of cold demands constant vigilance to avoid cold rooms or environments including air-conditioned rooms in summer and ice water, cold drinks and foods. Space heaters may be necessary to keep room temperature at adequate levels.

Warm clothing should protect all areas outdoors and in cold indoor spaces, freezers and refrigerators, including warm socks, shoes, gloves, scarves, and hats. All extremities, particularly the nose, ears, hands and feet should be protected.

There are many disposable hand and toe warmers as well as battery heated handwarmers, gloves, scarves and socks available for purchase. In winter, cars should have blankets, warm clothing and warming aids available in case of emergency.

Maintaining an acceptable hemoglobin level – A daily dose of 1 MG Folic Acid is recommended.

MANAGEMENT IN MEDICAL SETTINGS:
Avoidance of cold is especially important during hospitalization and surgery, when the affected individual may have less control over their ambient temperature and the temperature of intravenous solutions. Many medical professionals are unfamiliar with Cold Agglutinin Disease and proper care procedures.

- Intravenous solutions and blood products should be warmed to an appropriate temperature before infusion. For blood transfusions, the temperature must be warmed to body temperature but cannot be above 40°C.
- Space heaters and warm blankets should be provided and liquids without ice should be available for drinking.
- Fever should be treated with medications, NOT with ice or cooling blankets.
- Infections should be treated promptly.
- Medical ID bracelets should be worn identifying Cold Agglutinin Disease and with information such as: No ice, warm all IV's and Blood Transfusions, Keep me warm

TREATMENTS:
Enjaymo FDA Approved February 4, 2022

Enjaymo is the first and only approved treatment in CAD and works by inhibiting the destruction of red blood cells (hemolysis) and helps address a serious unmet need for people living with this rare blood disorder. Enjaymo is a humanized monoclonal antibody that is designed to selectively target and inhibit C1s in the classical complement pathway, which is part of the innate immune system. By blocking C1s, Enjaymo inhibits the activation of the complement cascade in the immune system and inhibits C1-activated hemolysis in CAD to prevent the abnormal destruction of healthy red blood cells. Enjaymo does not inhibit the lectin and alternative pathways.

INDICATION

ENJAYMO is a prescription medicine used to decrease the need for red blood cell transfusion due to the breakdown of red blood cells (hemolysis) in adults with cold agglutinin disease (CAD).

It is not known if ENJAYMO is safe and effective in children.

IMPORTANT SAFETY INFORMATION

Do not receive ENJAYMO if you are allergic to sutimlimab-jome or any of the ingredients in ENJAYMO.

ENJAYMO can cause serious side effects, including:

- **Serious Infections:** ENJAYMO is a prescription medicine that affects your immune system. ENJAYMO can lower the ability of your immune system to fight infections. People who take ENJAYMO may have an increased risk of getting infections caused by certain kinds of bacteria such as *Neisseria meningitides*, *Streptococcus pneumoniae*, and *Haemophilus influenzae*. These infections may be serious or life-threatening. Some infections may quickly become life-threatening or cause death if not recognized and treated early.
    - You need to receive vaccinations against infections caused by certain kinds of bacteria at least 2 weeks before your first dose of ENJAYMO. You may need to have additional vaccinations during treatment
    - If your healthcare provider decides that urgent treatment with ENJAYMO is needed, you should receive vaccinations as soon as possible.
    - Vaccinations may reduce the risk of these infections, but do not prevent all infections. Call your healthcare provider or get medical help right away if you get any new signs and symptoms of an infection, including:
        - Fever
        - cough or difficulty breathing
        - severe headache with stiff neck or back
        - flu-like symptoms
        - pain during urination or urinating more often than usual
        - pain, redness or swelling of the skin
- **Infusion-related reactions:** Treatment with ENJAYMO may cause infusion-related reactions, including allergic reactions that may be serious or life-threatening. Your healthcare provider may slow down or stop your ENJAYMO infusion if you have an infusion-related reaction, and will treat your symptoms if needed. Tell your healthcare provider right away if you develop symptoms during your ENJAYMO infusion that may mean you are having an infusion-related reaction, including:
    - shortness of breath
    - rapid heartbeat
    - nausea
    - flushing
    - headache
- **Risk of autoimmune disease:** ENJAYMO may increase your risk for developing an autoimmune disease such as systemic lupus erythematosus (SLE). Tell your healthcare provider and get medical help if you develop any symptoms of SLE, including:
    - joint pain or swelling
    - rash on the cheeks and nose
    - unexplained fever
- If you have CAD and you stop receiving ENJAYMO, your healthcare provider should monitor you closely for return of your symptoms after you stop ENJAYMO. Stopping ENJAYMO may cause the breakdown of your red blood cells due to CAD to return. Symptoms or problems that can happen due to red blood cell breakdown include:
    - tiredness
    - shortness of breath
    - rapid heart rate
    - blood in your urine or dark urine

The most common side effects of ENJAYMO include:

- respiratory tract infection
- diarrhea
- cough
- joint inflammation (arthritis)
- viral infection
- indigestion
- joint pain
- swelling of the lower legs, ankles, and feet

These are not all the possible side effects of ENJAYMO. Call your doctor for medical advice about side effects.

Before receiving ENJAYMO, tell your healthcare provider about all of your medical conditions, including if you:

- have a fever or infection, including a history of human immunodeficiency virus (HIV), hepatitis B, or hepatitis C.
- have an autoimmune disease such as systemic lupus erythematosus (SLE), also known as lupus.
- are pregnant or plan to become pregnant. It is not known if ENJAYMO will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if ENJAYMO passes into your breast milk.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.
Please see Full Prescribing Information, including Medication Guide.

Rituximab (aka Rituxan) is a drug given by IV infusion which has been found effective in treating CAD, and in some cases, it is administered in combination with other drugs. It is an anti-CD20 monoclonal antibody created to deplete B cells. The depletion interferes with the production of Cold Agglutinins and can result in a significant improvement in the hemoglobin levels for some CAD patients. A course of treatment is normally four infusions that are given one per week for four weeks. Sometimes, a second course of four infusions is prescribed. There can be a risk with the initial dose due to the possibility of a serious allergic reaction.
Blood transfusions of washed red cells are sometimes necessary as a temporary measure when the hemoglobin gets too low, seven to eight (US) and 70 to 80 (Outside US), or below, and the antibody titer (antibody load) is high. The transfused blood should be warmed to prevent new red cells from being coated with antibodies.
Plasmapheresis (PP), which involves filtering blood to remove antibodies, is sometimes helpful for the short term when other treatments fail. In some cases, it has been useful prior to drug therapy and/or surgery to reduce the CA antibody load, resulting in a better outcome.

NOT RECOMMENDED TREATMENTS:
Splenectomy and corticosteroids are not effective treatments for Cold Agglutinin Disease. The use of erythropoietins (EPO) such as Procrit, Epogen, and Aranesp are also not recommended**.**

DRUG TRIALS:
Currently a number of drug trials and studies are being conducted. For more information visit https://coldagglutinindisease.org/clinical-trials

PATIENT SUPPORT:
Cold Agglutinin disease is an isolating disease, as patients may look normal except for a pale, sometimes yellowish complexion and blue coloration when exposed to cold temperatures. It is a difficult condition to explain to others, including family and friends. Fatigue is a constant companion and can be debilitating. Vigilant monitoring of temperatures can be stressful, as can dealing with medical staff who are unfamiliar with CAD. The Cold Agglutinin Disease Foundation supplies information and links to studies and research through their website, peer support through a private Facebook Group, Zoom Seminars, education, and newsletters with information on the latest developments in drug treatments and drug trials. Please visit our website for additional information and please share with your CAD patients. Thank you for your help in treating and supporting Cold Agglutinin Disease patients.