Science of CRVO

www.scienceofcrvo.org

An Informational Guide to CENTRAL RETINAL VEIN OCCLUSION

This brochure will guide you in understanding CRVO and the treatment options available to prevent vision loss. Know how to take an active role in managing CRVO and choosing the best treatment.

The Angiogenesis Foundation

INTRODUCTION: The Science of CRVO

Central retinal vein occlusion (CRVO) is the highest form of retinal vein occlusion (RVO). RVO is the second most common cause of vision loss from retinal vascular disease. It is estimated that 16.4 million people are affected by RVO worldwide, with 2.5 million global cases of CRVO. Prevalence of CRVO increases with age.

The Angiogenesis Foundation built this resource to provide accurate, easy to understand, and useful information about the evidence supporting anti-VEGF therapy for CRVO. We believe that patients, their advocates, and eye care professionals can be empowered with the knowledge of relevant treatments and the practical steps they can take to fight vision loss.

Use this resource to learn:

- How CRVO can lead to severe or even permanent vision loss
- Why early treatment is important for saving vision
- The role of VEGF in vision loss due to CRVO
- Evidence on the benefits of anti-VEGF therapies for CRVO patients
- Future directions for treating CRVO

The Science of CRVO focuses on increasing global public awareness of central retinal vein occlusion (CRVO), the role of VEGF (vascular endothelial growth factor) in vision loss due to CRVO, and the benefits of anti-VEGF treatments for patients with CRVO.

WHAT IS CRVO?

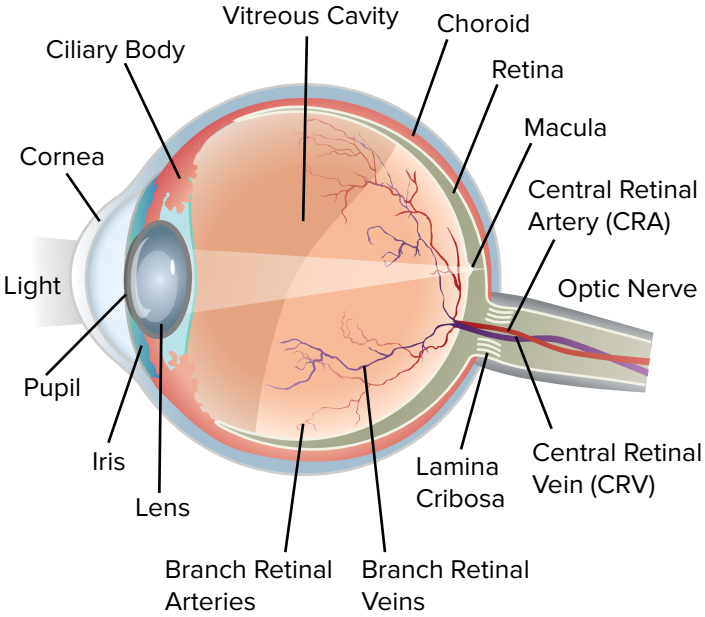
CRVO occurs when the central retinal vein is occluded, or blocked, obstructing retinal blood flow from the eye.

CRVO can lead to a number of complications that affect visual acuity, the sharpness or clarity of vision. Loss of vision in CRVO is commonly caused by a condition called macular edema, which is the accumulation of fluid in the center and most visually sensitive portion of the retina, known as the macula. Other complications of CRVO that can lead to vision loss include vitreous hemorrhage, neovascularization and neovascular glaucoma.

If left untreated, people affected by CRVO can experience severe eye complications, which can cause significant vision loss. The major cause of vision loss in CRVO is swelling and thickening of the macula caused by the accumulation of fluid from leaky blood vessels, resulting in macular edema.

CRVO can occur where the central retinal vein exits the retina, or by the back of the lamina cribrosa.

The retina is a layer of tissue at the back of the eye that processes objects in the visual field and sends signals to the brain. A small part of the retina, called the macula, is critical for seeing fine details clearly. CRVO involves the entire retina.

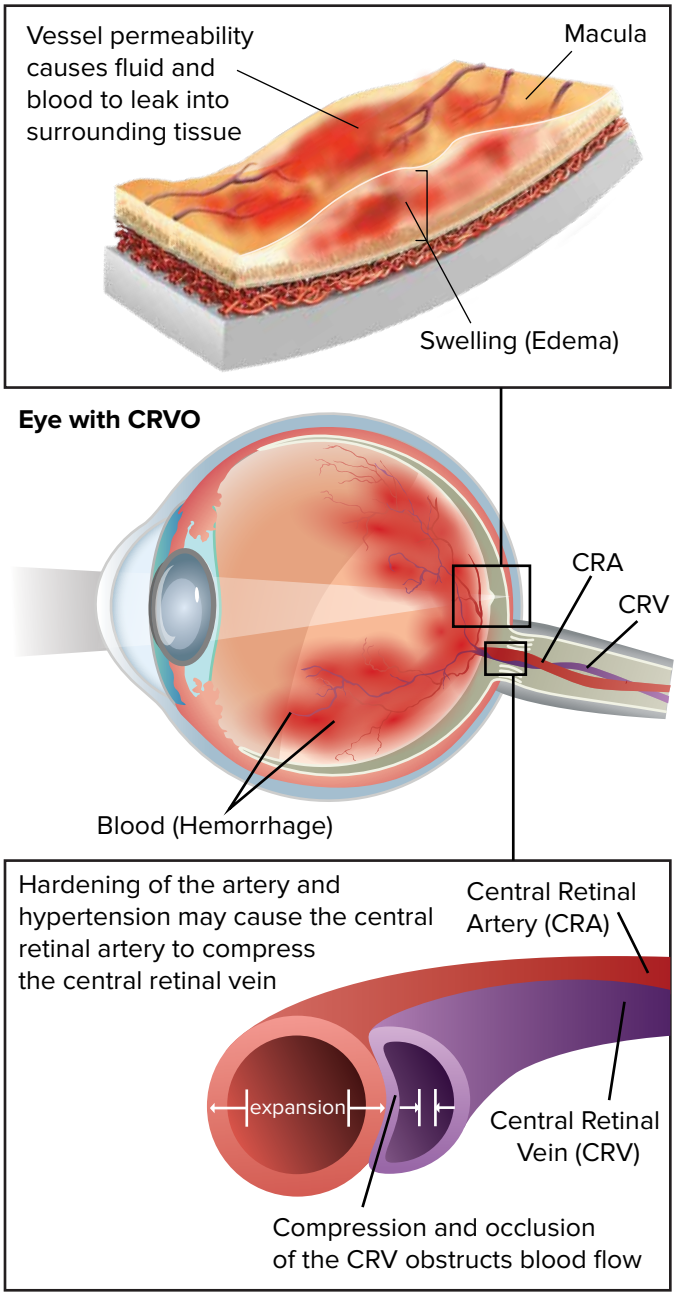


LEARN: The Science of CRVO

CRVO DEVELOPMENT

The outer layer of the retina receives nutrients from the choroid, while the inner layer of the retina receives nutrients from the central retina artery (CRA). The central retinal vein (CRV) drains blood from the retina. The CRV generally runs the same course as the CRA and they share a connective tissue. Occlusion typically begins when the central retinal artery compresses the central retinal vein. The compression of the CRV causes the vein to narrow and leads to increased intravascular pressure, sluggish or turbulent blood flow, endothelial cell damage and, ultimately, occlusion of the central retinal vein.

The vein occlusion causes an upregulation (increase) in the glycoprotein **vascular endothelial growth factor (VEGF)**, which weakens the vessel wall and increases vascular permeability. This results in blood vessels that leak fluid and blood into the retina, causing retinal and macular edema. Most CRVO patients have signs of swelling in the macula at diagnosis.



Non-Ischemic CRVO

CRVO is subtyped into non-ischemic, or perfuse, if there is very limited obstruction of blood flow in the capillaries. Complications such as macular edema can occur in the non-ischemic (or perfuse) form.

Ischemic CRVO

CRVO is considered to be ischemic, or nonperfuse, when blood flow in the retinal capillaries is more widely obstructed. This is a more severe form of CRVO in which vision is more likely to be poor and complications, such as neovascularization, are more likely to occur, depending on the degree of the ischemia.

SYMPTOMS AND IMPORTANCE OF EARLY DIAGNOSIS

Vision loss or distortion in vision in CRVO patients is typically sudden and painless.

The later CRVO is diagnosed, the more advanced the condition is likely to be, and the greater the likelihood is for visual impairment. The severity of visual impairment will also depend on the extent to which the retina and macula are involved. The risk of developing permanent structural damage to the macula increases with the duration of the edema.

Normal Vision

Blurry Vision

Distorted Vision

YOUR ROLE: Become Empowered

RISK FACTORS

A risk factor is anything that affects the chances of getting a disease. The major global risk factors for CRVO include:

- Age
- Hypertension
- Glaucoma

The association between CRVO and other medical conditions is not yet clearly understood. Other factors that are commonly associated with the risk for CRVO include cardiovascular disease, hypercoagulability, and end-organ damage from hypertension or diabetes.

FOR PATIENTS: WHAT YOU CAN DO

There are steps that you can take to prevent or delay vision loss, and manage your condition and treatment:

- If you have not been diagnosed with CRVO but suspect that some of the risk factors may apply to you, go see the appropriate doctors and get tested for hypertension, vascular disorders, and glaucoma.
- Control any modifiable risk factors that you may have.
- If you are diagnosed with CRVO, get tested for systemic risk factors, such as hypertension or diabetes. Treating systemic conditions is critical for preventing serious health complications in the future.
- If diagnosed with CRVO, get regular check-ups to monitor progression of the condition.
- Get regular check-ups to test for and measure the presence of edema with an eye care professional.

TESTING

Three common tests can detect and identify the extent of CRVO: funduscopy, fluorescein angiography and optical coherence tomography.

Fundoscopy: This test uses a hand-held ophthalmoscope to identify retinal hemorrhage or other abnormalities that indicate the presence of CRVO. A non-specialist can perform a funduscopy.

Fluorescein angiography (FA): If CRVO is found, an eye care specialist will perform a fluorescein angiography (FA). FA is a test that takes images of the eye to evaluate the blood flow in the back of the retina. FA can identify the areas of capillary nonperfusion, leakage, and hemorrhage, which can affect treatment strategies. This procedure involves pupil dilation and an injection of a special vegetable dye called fluorescein into the arm.

Optical Coherence Tomography (OCT)
OCT is a non-invasive imaging test that measures the thickness of the retina and identifies the extent of edema in the retina and macula. It is a special camera that uses light to take cross section images of the inner parts of the eye.

ANTI-VEGF TREATMENTS

In recent years, new treatments have emerged to address CRVO and its complications. The development of macular edema is the most common cause of vision loss in people with CRVO and is a key target for treatment.

ANTI-VEGF THERAPY

A major development in treating vision loss in people with CRVO has been the introduction of anti-VEGF drugs, which leverage recent advances in our understanding of the different mechanisms that cause CRVO. These drugs are designed to attack specific factors that contribute to CRVO development and are improving our ability to treat this condition.

Anti-VEGF agents target and block the glycoprotein VEGF (vascular endothelial growth factor). Lower levels of VEGF in the retina decrease its effects on retinal blood vessels, resulting in a reduction in macular edema and other complications, such as the growth of abnormal vessels (neovascularization). Anti-VEGF agents have been effective in treating macular edema for many CRVO patients, demonstrating improved visual acuity without the risk of developing other major eye conditions.

Approved Anti-VEGF Therapies:

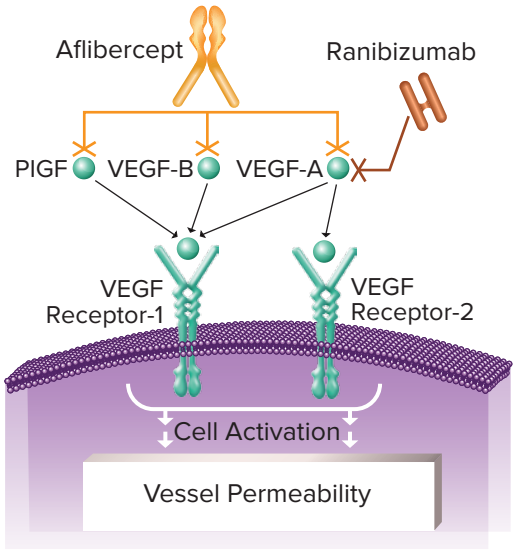
Currently, two anti-VEGF agents are approved for treating macular edema in CRVO patients:

➔ **Eylea (Aflibercept)** is a type of anti-VEGF drug known as a fusion protein which can stabilize and even improve vision in patients with retinal disease. For CRVO patients, it is directly injected into the eye at a recommended dose of 2 mg once a month.

➔ **Lucentis (Ranibizumab)** is a type of anti-VEGF drug called a monoclonal antibody fragment that was developed to treat retinal diseases and can stabilize and even improve vision. For CRVO patients, it is injected directly into the eye at a recommended dose of 0.5 mg once a month.

Anti-VEGF treatment is relatively safe when administered correctly by a trained retinal specialist. Patients and physicians should discuss whether anti-VEGF therapy is the best option to treat the symptoms of CRVO.

How Treatments Work



Eylea (Aflibercept): Dosing Schedule*

The recommended dose for Eylea is 2 mg aflibercept equivalent to 50 microlitres. After the initial injection, treatment is given monthly. The interval between two doses should not be shorter than one month. If there is no improvement in visual and anatomic outcomes over the course of the first three injections, continued treatment is not recommended. Monthly treatment continues until visual and anatomic outcomes are stable for three monthly assessments. Thereafter the need for continued treatment should be reconsidered. If necessary, treatment may be continued with gradually increasing treatment intervals to maintain a stable visual and anatomic outcome. If treatment has been discontinued, visual and anatomic outcomes should be monitored and treatment should be resumed if these deteriorate.

Usually, monitoring should be done at the injection visits. During treatment interval extension through to completion of therapy, the monitoring schedule should be determined by the treating physician based on the individual patient's response and may be more frequent than the schedule of injections.

*European

Source: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002392/WC500135815.pdf

Lucentis (Ranibizumab): Dosing Schedule*

The recommended dose for Lucentis is 0.5 mg given monthly as a single intravitreal injection. This corresponds to an injection volume of 0.05 ml. Treatment is given monthly and continued until maximum visual acuity is achieved, i.e the patient's visual acuity is stable for three consecutive monthly assessments performed while on ranibizumab treatment. Thereafter patients should be monitored monthly for visual acuity. If there is no improvement in visual acuity over the course of the first three injections, continued treatment is not recommended.

Treatment is resumed when monitoring indicates loss of visual acuity due to macular oedema secondary to RVO. Monthly injections should then be administered until stable visual acuity is reached again for three consecutive monthly assessments (implying a minimum of two injections). The interval between two doses should not be shorter than 1 month.

*European

Source: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000715/WC500043546.pdf

ANTI-VEGF TREATMENTS: Clinical Data

Eylea Clinical Trials

Eylea (Aflibercept)

The pivotal phase III **COPERNICUS** and **GALILEO** studies involved nearly 360 patients with macular edema from CRVO and demonstrated that after 24 weeks of treatment, monthly injections of 2 mg of Eylea had greatly improved vision compared to patients without treatment. At 24 weeks, 56% of patients in the COPERNICUS study and 60% of patients in the GALILEO study gained at least 15 letters in vision (compared to 12% of patients without treatment in the COPERNICUS study and 22% of patients without treatment in the GALILEO study). Retinal thickness decreased by an average of 457.2 µm in the COPERNICUS study, and by an average of 448.6 µm in the GALILEO study (compared to a reduction of only 144.8 µm in patients without treatment in the COPERNICUS study and a reduction of only 169.3 µm in the GALILEO study).

These benefits were maintained in the COPERNICUS trial at 52 weeks with injections of 2 mg of Eylea given between week 24 and week 52 on an as-needed basis to both groups of patients (those who did receive treatment for the first 24 weeks and those who did not in the COPERNICUS study). The benefits were also maintained at 52 weeks with injections of 2 mg of Eylea given between weeks 24 and 52 in GALILEO, where only the patients in the Eylea group were treated on an as-needed basis. The need for further injections was determined by the retreatment criteria: certain changes in visual acuity or in OCT findings.

At week 52, 55% of patients in the COPERNICUS study and 60% of patients in the GALILEO study gained at least 15 letters in visual acuity (compared to only 30% of control patients who began Eylea injections at week 24 on an as-needed basis in the COPERNICUS study, and 32% of control patients not converted to Eylea in GALILEO). Retinal thickness decreased from the initial level of thickness by an average of 413 µm (compared to a reduction of 381.8 µm in control patients who began Eylea injections at week 24) in the COPERNICUS study, and by an average of 423.5 µm (compared to a reduction of 219.3 µm in control patients at week 24) in the GALILEO study.

The COPERNICUS study demonstrated that injections of Eylea were still beneficial at week 100 with 49% of patients gaining at least 15 letters in visual acuity (compared to only 23% in patients who began Eylea injections at week 24 on an as-needed basis). The GALILEO study demonstrated that injections of Eylea were still beneficial at 76 weeks, with 57% of patients gaining at least 15 letters in visual acuity (compared to only 29% in patients who began Eylea injections at week 52).

Side effects were rare. The most commonly reported side effects for Eylea include conjunctival hemorrhage, eye pain, reduced visual acuity, and increased intraocular pressure.

The earlier the treatment is administered, the better the outcomes are likely to be.

Lucentis Clinical Trials

Lucentis (Ranibizumab)

The pivotal phase III **CRUISE** study involved nearly 400 patients with macular edema from CRVO and demonstrated that after six months of treatment, monthly injections of 0.5 mg of Lucentis had greatly improved vision compared to patients without treatment.

At 6 months, 48% of patients had gained at least 15 letters in vision (compared to 17% in patients without treatment), and retinal thickness had reduced on average by 452 µm (compared to a reduction of only 168 µm in patients without treatment).

These benefits were maintained at 12 months with injections of 0.5mg of Lucentis given between months 6 through 12 on an as-needed basis to both groups of patients (those who did receive treatment for the first 6 months and those who did not). The need for continuous injections was determined by the retreatment criteria: poor visual acuity or changes in retinal thickness as measured by OCT.

At 12 months, 51% of patients gained at least 15 letters in visual acuity (compared to only 33% of patients who began Lucentis injections at 6 months on an as-needed basis). Commonly reported side effects of Lucentis injections include conjunctival hemorrhage and eye pain.

OTHER TREATMENTS

OTHER AVAILABLE TREATMENTS

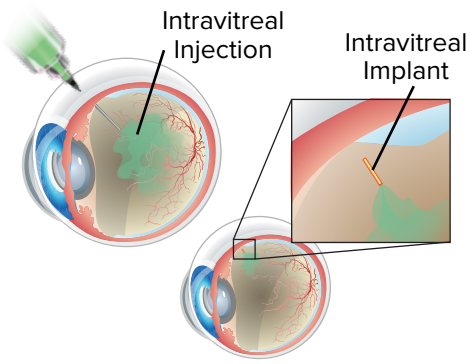
Steroids
Steroids can stabilize the vessel wall, reduce vascular permeability and inhibit VEGF-expression—a promoter of macular edema. They can be received as an intravitreal injection or through a sustained-release implant.

- **Intravitreal Triamcinolone Acetonide (IVTA)**
  IVTA has been shown to offer temporary visual improvement in CRVO patients in the short-term. IVTA can significantly improve visual acuity within one year in CRVO patients when compared to no treatment. These benefits are temporary and subsequent treatment every few months may be required to maintain them.

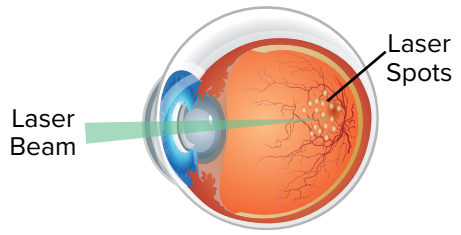
- **Sustained Corticosteroid Delivery Devices**
  Biodegradable sustained-release devices have been designed to prolong the benefit of corticosteroid therapy, and can provide medication for up to 6 months when implanted in the vitreous cavity in the back of the eye.

Laser Photocoagulation
Laser photocoagulation has been used in the past for treating macular edema in CRVO patients, and may be appropriate for certain complications of the disease.

Corticosteroid Therapy



Laser Coagulation



FUTURE DIRECTIONS

The advent of anti-VEGF therapy has shifted the approach to treating retinal disease and offers new promise for maintaining a high quality of life for CRVO patients. However, further studies are needed to better understand the benefits and limitations of anti-VEGF therapy, and clinical trials for different anti-VEGF agents are ongoing. The long-term effects of anti-VEGF agents need to be examined further.

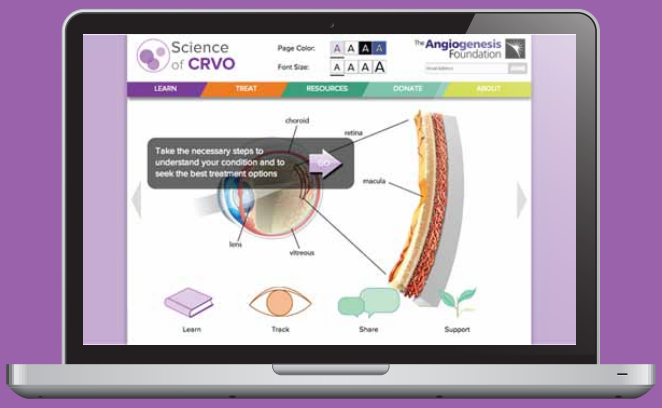
Therapy may evolve to reduce the frequency of injections and visits required, which currently presents a burden to patients and their families. Combination approaches for treating CRVO are likely to develop and improve patient outcomes. Factors that play a role in CRVO formation other than VEGF are potential targets for treatment and need to be studied further.

Risk factors for CRVO have yet to be understood clearly. Understanding the role of various risk factors in CRVO development, identifying individuals with a higher risk for this condition, and treating and monitoring individual risk factors, when possible, would help to prevent the development of CRVO, its complications and vision loss.

Pursuing these questions further holds significant promise for providing each patient with the most effective treatment and greatly improving patient outcomes and quality of life.

WHAT NOW?

By reading this brochure, you've just taken the first step to understanding CRVO and learning about available treatment options. Patients should work with their doctors to select the most effective therapeutic approach.



The Angiogenesis Foundation is the world's first and leading nonprofit organization dedicated to conquering diseases using a groundbreaking approach based on angiogenesis, the growth of new blood vessels in the body. Angiogenesis is the "common denominator" in overall health.

Our mission at the Angiogenesis Foundation is to improve health globally, through education and advocacy, and to empower patients to take an active role in fighting vision loss. Understanding the science behind CRVO and its treatment empowers patients, their advocates, doctors and everyone affected by CRVO to take concrete action steps in preventing and effectively treating CRVO. We work with CRVO patients, their advocates and healthcare providers around the world to disseminate knowledge about anti-VEGF treatments for CRVO in order to improve patient outcomes.

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