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UVEITIS

WHAT IS UVEITIS?

Ocular inflammatory disease (OID) is a general term for inflammation affecting any part of the eye or surrounding tissue. Inflammation involving the eye can range from the familiar allergic conjunctivitis of hay fever to rear, potentially blinding conditions such as: anterior or posterior uveitis; scleritis; episcleritis; optic neuritis; keratitis; orbital pseudotumor; retinal vasculitis and chronic conjunctivitis.

Uveitis may affect primarily the front part(s) of the eye (anterior uveitis) including inflammations such as iritis (inflammation of the iris: iridocyclitis (inflammation of the iris and ciliary body) and scleritis (inflammation of the sclera). Uveitis can also affect the middle and back part of the eye (posterior uveitis) such as pars planitis (inflammation of the pars plana); vitritis (inflammation of the vitreous gel); vasculitis (inflammation of retinal blood vessels); retinitis (inflammation of the retina); choroiditis (inflammation of the choroid) and optic neuritis (inflammation of the optic nerve).

Uveitis is often a chronic disease that can affect both eyes. If unrecognized and not treated aggressively, uveitis often results in significant vision loss or blindness.

WHAT CAUSES UVEITIS?

Uveitis can be caused by:

A: INFECTIONS—from a virus (e.g. Herpes), bacteria (Syphilis, Tuberculosis), fungus or a parasite (e.g. Toxoplasmosis).

B: AUTOIMMUNE INFLAMMATORY DISEASE such as Rheumatoid Arthritis (RA), Systemic Lupus, Erythematosus, Wegener's Granulomatosis etc.

C: INJURY to the eye.

In the United States and other developed countries, the vast majority of Uveitis cases are believed to be autoimmune in origin, while infections are responsible for the majority of Uveitis cases in developing countries.

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WHAT ARE AUTOIMMUNE DISEASES AND WHAT TYPE OF DAMAGE CAN THEY CAUSE TO THE EYE?

Autoimmune diseases are characterized by the body's immune responses being directed against its own tissues, causing prolonged inflammation and subsequent tissue destruction. A number of autoimmune diseases exist, the most familiar of which is Rheumatoid Arthritis (RA). In Rheumatoid Arthritis, the dysregulated immune system attacks the joints and damages their function.

The eye can be attacked in many systemic autoimmune diseases such as Rheumatoid Arthritis, systemic Lupus, Erythematosus, Polyarteritis Nodosa, relapsing Polychondritis, Wegener's Granulomatosis, Scleroderma, Behcet's Disease, inflammatory bowel disease (Crohn's Disease and Ulcerative Colitis) Sarcoidosis, Ankylosing Spondylitis etc.

In addition, eye tissues may themselves be the only objects of the autoimmune attack. Classic examples are ocular cicatricial pemphigoid; Moorens's corneal ulcer (including Birdshot Retinochoroidopathy); Vogt-Koyanagi-Harada syndrome; primary retinal vasculitis and sympathetic ophthalmia.

WHAT ARE THE SYMPTOMS OF UVEITIS?

The symptoms of Uveitis include light sensitivity, blurring of vision, pain, and redness of the eye. Uveitis may come on suddenly with redness and pain, or it may be slow in onset with little pain or redness but gradual blurring of vision. Uveitis arising in the front or middle part of the eye (iritis or cyclitis) is commonly more sudden in onset, more painful, and generally last six to eight weeks. In the early stages it can usually be controlled by the frequent use of eye drops. Often, this type of Uveitis cannot be given a specific cause. Uveitis in the back part of the eye (intermediate Uveitis, retinitis, choroiditis and optic neuritis) is commonly slower in onset, causes more visual blurring that pain, and may last longer. It is often more difficult to treat and more commonly associated with other systemic inflammatory conditions. Inflammation inside the eye can permanently affect sight, at times even leading to blindness.

HOW IS UVEITIS DIAGNOSED?

A careful eye examination by an eye care specialist is extremely important when symptoms occur. The eye care specialist will use instruments to examine the inside of the eye and sometimes can make a diagnosis on that basis alone. In many circumstances blood tests, skin tests, X-rays, and sometimes even biopsy specimens taken surgically from the eye, may assist the diagnosis. Many times, the layers in the back of the eye are more closely studied using a

photographic test (fluorescein angiography). In this test, a synthetic yellow dye called fluorescein is injected into an arm vein and then photographed as it flows through the vessels in the back of the eye. Some types of Uveitis result in a characteristic pattern of dye leakage. Since Uveitis can be associated with a disease in the rest of the body, the patient's overall medical health is important. This may involve consultation with other medical specialists.

HOW IS OCULAR INFLAMMATORY DISEASE TREATED?

It is crucial to stop the inflammation before delicate tissues in the eye are damaged in order to prevent secondary complications and permanent vision loss. The goal of the treatment of ocular inflammatory disease is the elimination of the inflammation and the prevention of recurrence without chronic use of steroids. This in return will alleviate pain, stop formation of new floaters, and normalize any acute changes in vision. The long-term goal is total remission of the ocular inflammatory disease without the use of medication. Prompt treatment is necessary to minimize any loss of vision. Treatment is often very lengthy and associated with multiple remissions and exacerbations. With the use of new immunomodulatory drugs, many cases of Uveitis can be cured or brought into durable remission. Medical therapy often requires a stepladder approach consisting of topical medications (eye drops); non-steroidal anti-inflammatory drugs (NSAIDS) and immunomodulatory drugs (immunomodulatory therapy IMT).

Eye drops, especially steroids and pupil dilators, are medications used to reduce inflammation and pain. For deeper inflammation, oral medication or injections may be necessary. Complications such as glaucoma (high pressure in the eye), cataracts (clouding of the lens of the eye), or ocular neovascularization (new blood vessel formation) may also occur and need treatment in the course of the disease. If complications are advanced, laser surgery or conventional surgery in the operating room may be necessary. Your doctor will discuss specific treatment recommendations with you.

The road to long-term remission is often very long and unpredictable because many forms of ocular inflammatory diseases can be very aggressive and "stubborn" to control. In understanding the treatment of OID, one has to remember that the mechanisms of the immune attack reside in the body (immune system), not in the eye.

THE STEPLADDER APPROACH

For noninfectious causes of inflammation, including idiopathic (having an unknown cause), treatment will follow a stepladder approach. The object of the stepladder approach is to modify the immune system and stop if from inappropriately attacking the eye and causing inflammation.

The first step is the use of steroid medication (s). A steroid is an anti-inflammatory immunosuppressive medication that can be administered in many forms: drops, oral, injection, or intravenous infusion. The form of steroid that is prescribed depends on the severity and type of OID. Steroids are an effective medication in quickly aborting acute inflammation, but used long-term, can result in its own set of complications such as stomach ulcer, osteoporosis (bone thinning), diabetes, cataract, glaucoma, cardiovascular disease, weight gain, fluid retention and Cushing's syndrome.

If inflammation continues to recur after weaning off of steroids, your doctor will move to the next step; non-steroidal anti-inflammatory drugs (NSAIDS). Some examples of NSAIDS include Indocin, Celebrex and Naprosyn. NSAIDS are a non-steroidal type of medication aimed at suppressing inflammation. Certain types of oral NSAIDS, if used long-term, will need additional medication for protection against stomach ulcers.

IMMUNOMODULATORY THERAPY (IMT)

When inflammation persists despite the use of a NSAID, immunomodulatory therapy (IMT) is indicated. Medications used in this treatment modality include Methotrexate, CellCept, Imuran, Cyclosporine, Cytoxan and Leukeran. IMT is a specific immunosuppressive therapy which, when done properly, has minimal side effects and an excellent record in curing autoimmune disease (durable remission). For many forms of chronic and severe ocular inflammatory diseases, IMT is the only treatment that can provide "durable remission" cure. Above mentioned medications have been used by rheumatologist and internal medicine specialists for many years to treat autoimmune diseases such as rheumatoid arthritis, lupus etc. Regrettably, many people (including a surprising number of ophthalmologists) are unaware of the very favorable risk-to-benefit ratio in treating uveitis. Since some of the above-mentioned medications were used to treat cancer in the past, some people refer to this therapy as "chemo therapy'. In addition, many people equate the use of such medications with the high doses given in cancer chemotherapy, with all the risks and side effects that occur at those high doses. This is not the case for IMT used to treat uveitis. Doses of IMT drugs are much smaller than those used to treat cancer. Consequently, side effects and complications are very rear and mild.

Your doctor will always start with the type of IMT treatment that he or she believes is most appropriate for you and your type of OID. In addition, the medication that has the least potential for side effects is favored. The use of such medication requires special, regular monitoring (blood tests) in order to ensure that no hidden side effects occur. Used correctly, by a physician who is an expert in such matters, the patient with OID who is treated with IMT

should look and feel normal. Patients do not lose their hair, do not have to wear a mask or stay away from other people for fear of getting opportunistic infections. In other words, they should be able to lead normal lives. One of the most common side effects is feeling more tired than usual. Patients complain about fatigue for approximately six months. This side effect can often be prevented by making some adjustments in lifestyle-going to bed earlier at night, sleeping longer in the morning, taking a nap during the daytime, reducing one's workload at work/home, avoiding competitive sports and strenuous activities. If an IMT medication disagrees with a patient, that medication should be stopped and another tried so that the goal of resolved inflammation with no significant IMT side effects is achieved.

BIOLOGIC RESPONSE MODIFIERS

A newer category of medications employed for the treatment of autoimmune diseases called "biologic response modifiers (BRM)" or "biologics" now exists. The biologics more specifically target certain elements of the immune system and, in so doing, avoid some of the potential risks of the more conventional IMT medications. These medications include Enbrel, Humira, Remicade, Zenapax, Orencia, Rituximab and Immunoglobulin (IgG).

A BRM medication may be added to a conventional IMT medication in the stepladder approach in aggressiveness of therapy for stubborn inflammation.

"OFF-LABEL USE" OF MEDICATIONS

It should be noted here that none of the medications mentioned in this pamphlet, including corticosteroids, IMT and BRM medications, are "approved for treating OID by the United States Food and Drug Administration (FDA). That is to say, the pharmaceutical companies who manufacture these medications have never conducted the randomized clinical trials required by the FDA in order for the companies to include treatment of OID in the package insert or "label". **Off-label use is perfectly legal and appropriate, if, in the doctor's opinion, it is in the patient's best interest to proceed with such treatment**. There is a wealth of data supporting the use of above-mentioned drugs in the treatment of uveitis.

In addition to immunosuppressants or antibiotics, other medication may be used. Eye drops that dilate the pupil may be prescribed, if inflammation is in the iris to prevent spasm of the muscles of the iris and ciliary body that cause pain. You doctor may recommend sunglasses because bright light may cause discomfort.

Additional treatment may also be required for complications of OID, such as glaucoma, cataract and macular edema (swelling of the retinal center)

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EXPECTED DURATION OF TREATMENT

The duration of treatment varies person to person and depends on the type and cause of ocular inflammatory disease. Simple forms of uveitis, for example, may respond to treatment within days and may not recur. Chronic (long-term, recurring) forms of ocular inflammatory disease that threaten vision can be very difficult to cure and require persistence on the part of the treating physician(s) and patient. The length of time required to get the disease into a durable remission on IMT is difficult to quantify and is very individualistic, but a minimum of two years is a reasonable estimate. During treatment on IMT, one can expect visits to the ophthalmologist every 4-6 weeks. Those visits have two purposes: 1) to assess the activity of the ocular inflammation and 2) to assess blood counts, liver and kidney function. All patients will need to have specific blood tests performed a day or two before every visit so that the physician will have updated lab results to review with them at each visit.

With appropriate, targeted treatment, most patients with ocular inflammatory disease will become well controlled and progress into remission. Once in remission from ocular inflammatory disease, you should expect to have regular follow-up visits to your doctor to make sure that the disease remains in remission.

VERY IMPORTANT PLEASE READ VERY CAREFULLY!!!

Problems that are discussed below are unique in treating patients with uveitis who require IMT. Those problems can result in enormous patient frustration and disappointment, often leading to mistrust. Some patients start "shopping around" trying to find another doctor who may have a simple and easy solution to their problem(s) such as eye drops or "stronger glasses". In doing so, many patients lose precious time and their disease may not be adequately treated leading to further vision loss.

1. **Any type of uveitis may have a different course in different patients.** Specific disease may occur only once, be mild and respond well to short-term treatment in one patient, while in the next patient it may have a long, aggressive and protracted course that responds poorly to any available treatment modality leading to severe vision loss. **It is impossible to predict how aggressive a form of uveitis will affect an individual patient. Therefore it is impossible to predict neither the length nor aggressiveness of the treatment (topical medications vs. IMT).**
2. The goal of uveitis treatment is to abolish any intraocular inflammation, to prevent further loss of vision and to bring the patient into durable remission. **Adequate response to treatment does not often lead to immediate improvement in vision!!!**

Other pre-existing ocular problems such as cataract, glaucoma, floaters etc. may still be a cause of decreased vision and they have to be addressed separately at a later date. In addition, some surgical procedures such as cataract surgery should be done in uveitis patients only after the uveitis has been kept under excellent control with immunomodulatory therapy for at least 3 months (sometimes 6 months). This long wait for visual improvement inevitably leads to patient frustration because often patients expect immediate improvement in vision.

3. **Different patients respond differently to the same immunomodulatory drug.** While Methotrexate, for instance, may work beautifully for one patient (bringing the disease easily to durable remission), it may not work at all in the next patient with the same (or different) disease**. It is impossible to predict which patient will respond well to medication prescribed** and different drugs are often tried before the "right drug" is found that works for that individual patient. Evidently, both the patient and the treating physician must have a significant amount of patience during the initial phase of treatment.
4. If medications such as eye drops, periocular or intraocular injections of steroids are unable to control the intraocular inflammation, the patient must understand that he/she will need systemic therapy. **Therapy that did not work in the past will not work in the future.** There is often a misunderstanding about this. Some patients think that another doctor may give them "stronger glasses" or different eye drops that "will work this time". Unfortunately, this fear of systemic therapy leads to long delays in the patient's treatment.
5. Immunomodulatory therapy is not "experimental, highly dangerous therapy". Most of the drugs used to treat severe intraocular inflammation (Methotrexate, CellCept, Imuran Cyclosporine, alkylating agents, biological drugs etc.) have been used successfully for many years by rheumatologists and other internal medicine specialists to treat diseases such as rheumatoid arthritis, systemic lupus erythematosus, Wegener's Granulomatosis etc. In the hands of an experienced physician, those medications are the only medications that can save and improve vision! It is well known that patients who need systemic immunomodulatory therapy for their eye disease have a much better prognosis if that therapy is started promptly than if therapy is delayed for months and years.
6. **Although very useful, all immunomodulatory drugs can have serious side effects if used without close supervision of the treating physician.** Those serious side effects can be numerous. They include (but are not limited to) serious infections liver or kidney toxicity, development of malignancy and death. **With proper monitoring those side effects are very, very rare.** If those (or other side effects) do develop, they can be

reversed by lowering the dose of the medication or stopping the medication altogether for several weeks. Proper monitoring includes follow-up visits every 4-6 weeks with frequent monitoring of blood counts, liver function tests and kidney function**. Patients who cannot or do not want to schedule regular appointments and have their blood drawn every 4-6 weeks should inform the treating physician and should not use immunomodulatory therapy at all!!!**

7. **If a patient has any new systemic symptoms or problems (nausea, diarrhea, high fever, weakness etc.) immunomodulatory drugs should be stopped and the treating physician should be notified immediately!!!** Our phone number is **910-254-2023.** The physician will most likely order additional blood tests right away and will want to see the patient as soon as possible. In addition, patients with any new systemic symptoms while on immunomodulatory drugs can always walk-in at any of our offices and they will be seen the same day on emergency add-on basis. Patients must understand that help or answers to his/her questions(s) are only a phone call away.
8. Even though a drug, Methotrexate for example, has brought a disease into remission does not necessarily mean that the drug will work well forever. **Any drug (or combination of drugs) may lose effectiveness at any time during the long treatment and new drugs(s) may have to be started. It is impossible to predict when and/or to whom that may happen.** This often leads to patient frustration and disappointment in the whole treatment process. Your uveitis specialist will place you on a different medication that will keep the inflammation under control.
9. **If immunomodulatory therapy is started, treatment generally lasts for two to two and one half years.** For patients whose disease does not respond to IMT as expected, treatment may last even longer. Very few patients can be well served by only one specific dose of a medication during their IMT. In the vast majority of patients, the medication dosage may need to be adjusted based on their blood test results and status of intraocular inflammation**. In addition, almost no uveitis patient achieves excellent uveitis control right away with the first medication prescribed and stays well controlled for two years.** Obviously, this requires significant dedication on the patient's part in treating uveitis. In some patients, ocular inflammation is very stubborn and the patient may never be brought into long-term remission. They may need very prolonged IMT.
10. Many patients mat need a combination of several immunomodulatory drugs.
11. It takes an average of 6-8 weeks of treatment with oral medications such as Methotrexate, Imuran or CellCept before the treating physician can be sure that the "drug is truly effective." Patients need to be patient during the first 2 months and not expect immediate improvements.

12. If a disease has been kept inactive (or brought under control) with specific immunomodulatory therapy for two years or longer, it is very likely that the patient is getting into durable remission (equivalent of cure). **However, reoccurrences are possible at any time.** Luckily, it is rare that a patient who has been kept inactive with proper immunomodulatory therapy for two years will have reactivation. Two years of clinical inactivity should be a goal of every treatment with immunomodulatory drugs.
13. **Women of childbearing age who are about to start IMT or are currently on it <u>SHOULD NOT BECOME PREGNANT</u> during the therapy. This <u>therapy can lead to spontaneous abortion or multiple and severe birth defects</u> if the unborn child is exposed to these drugs, especially in very early pregnancies. If a patient thinks that she could be pregnant, she must inform her treating physician.**

    Every effort on the part of the patient and her partner should be made to prevent pregnancy during IMT. It is usually recommended that two methods of contraception be used in conjunction with each other (example: using both birth control pills and condoms).

    Women who are about to start IMT should have <u>two (2) negative pregnancy tests done two weeks apart</u> before starting this therapy, regardless of the type of contraception used before starting IMT. Pregnancy testing can be done in a physician's office (primary care or OB/GYN) or at home with home pregnancy tests that can be purchased at a local pharmacy.

    All questions concerning pregnancy and IMT should be discussed with your treating physician and/or OB/GYN as soon as possible.

<u>What should a patient on IMT do if he develops a cold/flu or bacterial infection?</u>

Patients who are properly monitored and have normal white blood cell counts are not immunosuppressed like cancer patients or AIDS patients. If such a patient gets what feels and behaves like a "regular cold," they should continue IMT without any changes. If, however, the cold is not improving within 5-7 days, the patient should temporarily stop IMT then restart the medication when he/she feels healthy again**. In addition, if a patient develops a very severe cold/flu and is feeling very sick, he should stop IMT right away. If the patient develops a fever or any bacterial infection such as bronchitis, pneumonia, strep throat, urinary tract infection,**

etc., he/she should stop IMT immediately until the infection is properly treated with antibiotics.

Call your physician with any questions.

What should a patient do if immunization is needed while receiving IMT?

This is a common problem with children and adolescents. It is important to mention that there are two types of vaccines:

"First type" vaccines are prepared from bacterial toxins, dead bacteria or dead viruses (inactivated vaccine).

"Second type" vaccines are prepared from weakened or attenuated bacteria nad viruses that are still alive (live attenuated vaccine).

In general, first type vaccines (dead vaccines) can be used on patients undergoing IMT. Second type (live attenuated vaccines) should not be used while patient is on IMT. In those cases, the patient must temporarily stop IMT and receive the vaccine or postpone the vaccine, if possible, until the IMT is finished. **We believe that only those vaccines that are absolutely necessary should be used on IMT patients. Your infectious disease specialist should decide about the need for a specific vaccine.**

Lists of all vaccines (and their characteristics) that are used in the USA today can be found at: http:www.cdc.gov/vaccines/pubs/pinkbook/downloads/appendices/B/us-vaccines.pdf (Source: Center for Disease Control)

Every IMT patient who is to receive a vaccine should:

1. Inform the health care provider that is administering the vaccine that he/she is using immunomodulatory therapy. In addition, he should ask about possible complications of the specific vaccine. A physician should answer those questions.
2. Call our office to discuss those issues.

Does a patient who is using IMT need any antibiotic pre-treatment before dental cleaning?

Yes. All patients who are using IMT need to have antibiotic pre-treatment before any dental work. Patients should inform his/her dentist about using IMT drugs.

Obviously, patients with uveitis face many difficult problems directly related to the nature of his/her uveitis and/or to the nature of therapy. **There are no guarantees that any medication used will work fast enough or well enough to prevent further loss of vision. However, if treated early enough and aggressively enough, most patients with chronic uveitis can achieve durable remission (70-90%).** Treating any uveitis entity is often very frustrating for both the patient and the treating physician.

We strongly encourage all of our patients to read this pamphlet very carefully and to feel free to express any concerns at any time before or during treatment. Patients may call our office at **910-254-2023.** Our technical staff will relay all questions or concerns to one of our doctor(s) who will respond to your call in as quickly as possible.

All patients are strongly encouraged to read more about their disease, uveitis, and its treatment options online at: www.uveitis.org