Managing uveitis in children involves unique challenges,” says Gary N. Holland, M.D., the Vernon O. Underwood Family Professor of Ophthalmology at UCLA, and Chief of the Cornea–External Ocular Disease & Uveitis Division. About 30 children per 100,000 in the United States have uveitis, making it less common than uveitis in adults. Nevertheless, uveitis in children can be a greater problem for various reasons: their smaller size, poor cooperation, and increased risk of disease complications and treatment side effects. Children, for example, are more likely to have corticosteroid-induced elevation of intraocular pressure, and systemic corticosteroids can cause growth retardation.

Coordination of Care

Both Dr. Holland and colleague Ralph D. Levinson, M.D., Associate Clinical Professor of Ophthalmology, evaluate, treat and monitor children with uveitis, but the overall management of these children often requires collaboration with other subspecialists from ophthalmology (retina and glaucoma specialists) and pediatrics (pediatric immunologists or rheumatologists). Such collaborations are facilitated through a special clinical program created by Dr. Holland for children with uveitis. “This program has allowed us to provide children with the close attention they need,” notes Dr. Holland.

Uveitis specialists generally coordinate treatment with a child’s pediatrician or with a pediatric rheumatologist who actually administers the drug(s). These are complicated, time-consuming management problems, says Dr. Holland, and some ophthalmologists may not be prepared to undertake the level of care that is required. Many patients come long distances for their appointments. “Whenever possible, we try to coordinate visits so that our patients can see their pediatric rheumatologists on the same day they see us, if they are also receiving their medical care at UCLA,” comments Dr. Levinson. Both Drs. Holland and Levinson also follow children who receive their treatments elsewhere; they have established good working relationships with pediatric rheumatologists at various facilities throughout Southern California.

Treatment: A Balancing Act

“Uveitis” is a non-specific term; it can have many causes and can take many forms. Non-infectious anterior uveitis is the most common category of uveitis seen in children. Juvenile idiopathic arthritis (JIA, more commonly known as juvenile rheumatoid arthritis [JRA] in the United States) is the most commonly identified cause of such uveitis in children, but the same type of uveitis can be seen in children without joint problems. Too often, Drs. Holland and Levinson
see children whose uveitis smolders chronically at a low level. Although affected children may be asymptomatic, chronic inflammation, even at a low level, can eventually lead to vision-threatening complications, such as glaucoma or macular edema.

In some cases, persistence of low-grade inflammation is attributable to fear on the part of referring clinicians about the complications of corticosteroids or immunosuppressive drugs in children. With appropriate doses and careful monitoring, however, these drugs can be used safely in children, according to Drs. Holland and Levinson. “Immunomodulatory therapy, in particular, plays a critical role in the management of children with non-infectious forms of uveitis,” notes Dr. Holland. “Without such treatment, many children will be at substantial risk of vision loss.” A key to success is balancing the risks of treatment against the advantages of better disease control.

An Arsenal of Drugs
Kerry T. Gallagher, M.D., Clinical Instructor in the UCLA Department of Pediatrics, is one of the pediatric rheumatologists working with Drs. Holland and Levinson to manage medications for children with uveitis. “We certainly have more options than were previously available for controlling inflammation, using drugs with better safety profiles and tolerance levels,” comments Dr. Gallagher. “Clinical experience is crucial because approaches [for treatment of children] are often extrapolated from adult data, since many drugs are not studied in children.”

Dr. Gallagher feels that aggressive treatment is warranted. “When the ophthalmologist is not able to rapidly get control of uveitis with topical corticosteroids and requests help, we rheumatologists try to begin systemic immunomodulatory therapy as early as possible, rather than risk the side effects of high-dose systemic corticosteroids (including weight gain, mood swings, high blood pressure, poor growth and striae). It has been my experience with these children, as with arthritis patients, that it takes time for the immune system to re-regulate itself, so to speak, and to stop causing inflammation in areas like the eye, where it’s actually causing harm. It may take a few weeks before beneficial effects of immunomodulation are seen.”

Methotrexate is the immunomodulatory agent used most commonly for the long-term control of JIA-associated uveitis. It acts as a potent anti-inflammatory agent in children, and it is better tolerated in terms of gastrointestinal and hepatic effects than in adults. Liver biopsies in children who had received methotrexate for five years showed some minor histological changes, but no fibrosis or other pathologic changes, notes Dr. Gallagher.

In addition, other immunomodulatory drugs, listed below, are used successfully to control uveitis in some children.

- **Mycophenolate mofetil** (Cellcept®), like methotrexate, is an antimetabolite that suppresses B- and T-lymphocyte activity, and is generally well tolerated.
- **Cyclosporine**, which also suppresses T-lymphocyte activity, is effective, but can cause hypertension, hirsutism, and has potential for renal toxicity. It is therefore used selectively in cases of uveitis that are not controlled with an antimetabolite alone. The combination of an antimitabolite and cyclosporine has been particularly effective in some cases of severe uveitis.
- **Biologic agents** that block the activity of tumor necrosis factor (TNF, a cytokine that plays a key role in inflammatory reactions) are being used increasingly by uveitis specialists, and initial experience in children has been very promising. The most extensive experience has been with **infliximab** (Remicade®), a monoclonal antibody against TNF. Patients are at risk for serious side effects with the drug, however, including reactivation of infections (such as tuberculosis) and allergic reactions to the drug. It is also expensive and must be given as an intravenous infusion; thus, it is not used as a “first-line” agent. **Adalimumab** (Humira®) is another monoclonal antibody against TNF that appears to be effective, but there has been less experience with it than with infliximab for treatment of uveitis. There can be a differential effect between anti-TNF agents, depending on the site of
inflammation. Another agent, etanercept (Enbrel®), which is a soluble TNF-receptor, rather than an antibody against TNF, is effective against joint inflammation, but seems to have little effect against uveitis.

Currently, the choice of agents for a given patient depends to a great extent on which is best tolerated. Yet to be identified is whether any agent or combination of agents is the most effective in the long term for prevention of vision loss.

**An Approach to Treatment**

Immunomodulatory drugs are felt to be safer for chronic therapy than high-dose topical or oral corticosteroids. “We know that in the long run, excessive amounts of corticosteroids in children can cause local problems, like cataracts or glaucoma, or a host of systemic problems, if given orally,” according to Dr. Levinson. Immunomodulatory agents will not have the rapid effect of corticosteroids, however. The usual strategy is to bring disease into control with corticosteroids, then transition to immunomodulation, if long-term therapy is needed to maintain disease control.

Clinicians are traditionally taught to taper the dose of corticosteroids as soon as inflammation subsides, but the approach to treatment with immunomodulatory drugs is different. “If immunomodulatory therapy is having a beneficial effect, and is tolerated medically, we generally continue treatment for at least one to two years, to maintain good control for an extended period of time, before trying to discontinue treatment,” says Dr. Holland.

**Long-term Concerns**

The benefits of immunomodulatory therapy must be weighed against its long-term risks, especially with regard to two persistent concerns: secondary infections and development of malignancies. Treatment of children has generally been without complications, though, probably because doses used to suppress inflammation are lower than doses used for other indications, such as cancer chemotherapy or prevention of transplant rejection. Also, the duration of treatment for uveitis is generally shorter.

 Patients are screened for infections prior to initiation of immunomodulatory agents, and will be vaccinated against infectious diseases to which they are susceptible. Children who are candidates for anti-TNF agents will be screened for prior exposure to tuberculosis. With this approach, most patients do not develop serious infections during therapy.

The issue of malignancy attributable to immunosuppressive drug therapy is more complex, and remains unresolved, in part because its occurrence may not be seen for years after treatment. Secondary malignancies are known to occur in other groups of patients receiving these drugs, but several factors have to be kept in mind when comparing different populations. Transplant recipients and adult patients with rheumatoid arthritis are at an increased risk of malignancy independent of immunosuppressive drug therapy. These patients tend to be on therapy longer, using multiple drugs and at higher doses than patients with uveitis. Although the risk of secondary malignancies among patients with uveitis is thought to be small, it remains a subject of investigation.

**Unanswered Questions**

Although the effects of current treatment are clearly beneficial in the short term, a challenge for the future will be to confirm that those short-term benefits translate into the preservation of vision over a lifetime. “Most uveitis specialists believe that methotrexate is effective in about 60 percent of children with uveitis,” according to Dr. Holland. “Although it is well accepted that immunomodulation helps to preserve vision, there is surprisingly little information in the literature documenting the long-term success of treatments objectively.” He goes on to explain that he and his colleagues have been impressed with infliximab as a treatment for uveitis, but there is not enough long-term experience with it to know how successful its use for the management of uveitis will be ultimately.

**Making a Commitment**

Dr. Holland’s message to referring clinicians is the same one he shares with parents: uveitis is a long-term management problem, and an under treated disease that can have life-altering consequences. Dr. Gallagher agrees, “Some physicians may be wary of using systemic medications as being too aggressive when really the potential damage from the uveitis is more concerning. We do know that if you stop treatment too early, inflammation just comes right back.”

Drs. Holland and Levinson have made a commitment to improving the future management of uveitis in children through continued study. One focus of concern for Dr. Holland is the appropriate choice of patients for immunomodulatory therapies. He feels that an important refinement will be to determine which children are at greatest risk for vision-threatening complications, and thus have the greatest need for such treatments. Although under treatment is clearly the bigger problem, at the other end of the spectrum, the indiscriminate use of
medications can also be a mistake. Because of associated toxicities, drugs should not be used at higher doses or for longer durations than is necessary to control inflammation and prevent complications.

Although Dr. Holland would like to target treatment for those who need it most, there is currently little way to predict who is at greatest risk for vision-limiting complications. As one approach to answering this question, he and his colleagues are studying levels of aqueous humor protein (“flare”) in children with uveitis, which can be quantified by a non-invasive technique called laser flare photometry. Assessing flare is more specific and objective than counting cells in the anterior chamber (another measure of inflammation) using the slit lamp biomicroscope, which is the traditional method of assessing inflammation. “It has been our impression that children with low flare are at a lower risk of problems and, in fact, a cross-sectional study that we performed did confirm a relationship between flare and complications of uveitis,” Dr. Holland says. “We have not determined whether that relationship is causal; that is, whether protein plays a direct role in the development of complications, or whether it is simply a marker for their occurrence.”

He and his colleagues are planning additional studies to determine the predictive value of flare in children when they present with uveitis. “If we eventually show that high flare is related to the future development of complications and that protein levels can be lowered with treatment, then treatment can be targeted accordingly,” he says. Such efforts, he notes, are being supported in part by the Maggi Kelly Vision Fund, a gift from an anonymous donor that honors one of Dr. Holland’s patients, and serves as an endowment for a host of activities related to inflammatory eye disease in children, including patient care, education and research. The continued study of uveitis in children is being conducted not only on the UCLA campus, but through collaborations with other specialists in the United States, Europe and South America. Through these efforts, the challenge of uveitis in children is being met.

REFERENCES
