

UVEITIS

No Time to Lose: Rethinking Arthritis Treatment

BY LINDA ROACH, CONTRIBUTING WRITER

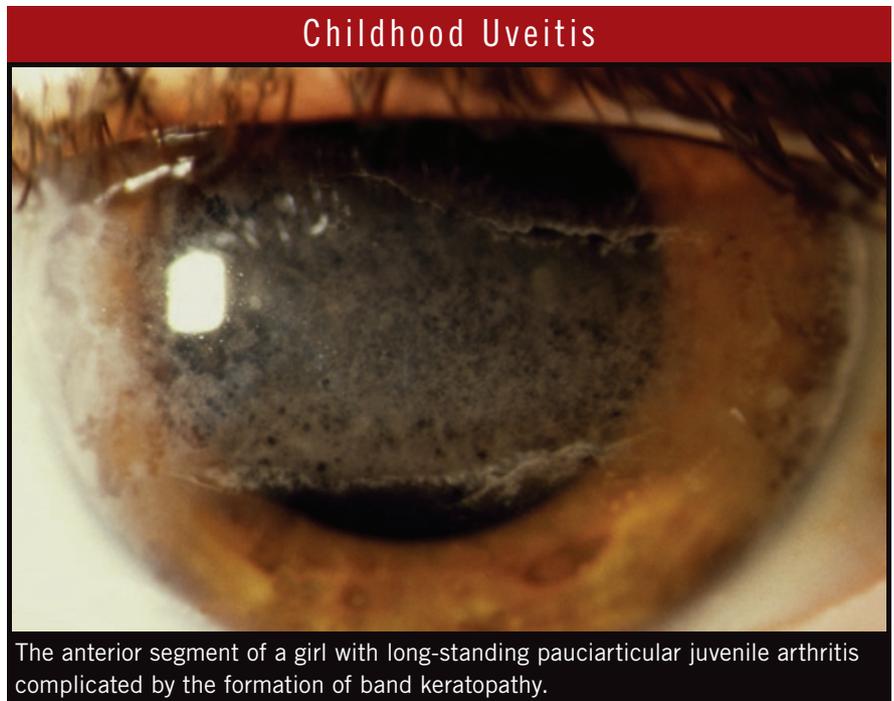
When it comes to treating patients with juvenile arthritis, getting stuck in the steroid rut can prove costly. The discovery of early macular damage in a majority of patients with juvenile idiopathic arthritis (JIA, once known as juvenile rheumatoid arthritis) reinforces the aggressive treatment recommendations that pediatric uveitis experts have been trying to disseminate to general ophthalmologists for a number of years now.

Their message: Childhood uveitis requires intensive medical therapy, careful and frequent follow-up and the expertise and willingness to use long-term immunosuppressive therapy if an initial course of topical corticosteroids does not work.

Jump to Immunosuppressants
Rheumatologists, ocular immunologists and uveitis specialists recommend switching children with JIA promptly—within a few weeks of initial therapy—to systemic, corticosteroid-sparing immunosuppressant therapy when there are signs that the corticosteroids are not working, said uveitis specialist C. Stephen Foster, MD.

Dr. Foster, clinical professor of ophthalmology at Harvard, said that the switch to immunosuppressants should take place if:

- ocular inflammation rebounds when tapering of the corticosteroid dose begins,



The anterior segment of a girl with long-standing pauciarticular juvenile arthritis complicated by the formation of band keratopathy.

- examination reveals the formation of new synechiae and
- the corticosteroids raise the child's IOP uncontrollably, putting him or her at risk for losing vision to glaucoma.

However, the message to move quickly has been slow to filter into comprehensive ophthalmic practices, where many children with JIA are first examined and treated, said Dr. Foster, who's also the founder and director of the Ocular Immunology and Uveitis Foundation.

As a result, while children represent only about 10 percent of the uveitis cases in a comprehensive ophthalmology practice, about a third of the patients who suffer a significant visual

loss from the disease are children with JIA-associated uveal inflammation, he said.

Dr. Foster said that, in his tertiary care practice, he regularly sees children in whom subtherapeutic corticosteroid doses were continued for many months, or even years, before the children were referred.

"It's nothing short of a disgrace that we still see instances where people involved in the child's care have gotten stuck in the steroid rut," he said.

"One of the saddest things I see in the course of a day's work is the new patient referral, the 5-year-old girl with JIA-associated uveitis who has had JIA three years, and now she's coming to

me with cataract and glaucoma as a result of three years of corticosteroids.”

Treatment Algorithm

For a busy comprehensive ophthalmology practice, the JIA undertreatment problem can be easily solved by co-managing the children with a rheumatologist, ocular immunologist or uveitis specialist familiar with systemic immune suppression, said Dr. Foster.

And for a general overview, Dr. Foster has developed a treatment algorithm for detecting and managing uveitis in juvenile arthritis patients and posted it on the Ocular Immunology and Uveitis Foundation’s Web site (go to www.uveitis.org/medical/treatment/algo3.html).

Which Drug?

To begin with, methotrexate is the immunosuppressive drug of choice. Biologic response modifier drugs also can be used to block inflammatory activity by T cells or by cytokines such as tumor necrosis factor (TNF).

There is a growing belief that TNF inhibitors should be second-line therapy for JIA, said Emmett T. Cunningham Jr., MD, PhD, MPH, director of the uveitis service at California Pacific Medical Center in San Francisco and adjunct clinical professor ophthalmology at Stanford. Thus, he said, the treatment regimen would be an anti-metabolite first, followed thereafter by one of the TNF inhibitors.

“In my experience, most children with JIA-associated uveitis require an immunosuppressive agent to completely control their inflammation,” Dr. Cunningham said. “For me, the first choice has been—and continues to be—methotrexate. What to use in those children who continue to have inflammation on a maximally tolerated dose of methotrexate is, however, a matter of some debate. Some might change to another antimetabolite, say, to something like mycophenolate mofetil [CellCept]. Others might add cyclosporine. More and more, however, people are turning to the TNF inhibitors, which have been showing great promise for the treatment of

Key Facts

Juvenile Idiopathic Arthritis:

One in 250 U.S. children under age 18 (total: 294,000) have been diagnosed with arthritis or another rheumatologic condition.¹

Eye inflammation can occur up to one year before, at the same time as, or up to 15 years after JIA is diagnosed.

Inflammation can also occur several years after JIA is in remission.

The severity of the child’s joint disease does not correlate with severity of the uveitis.

An international rheumatology consortium renamed juvenile rheumatoid arthritis (JRA) as JIA in the mid-1990s and classified JIA cases into seven categories. These are based on onset before age 16 and groups of symptoms lasting more than six continuous weeks.²

Oligoarthritis:

Afflicts about 50 percent of children who have JIA.

More likely than other six types of juvenile idiopathic arthritis to cause uveal inflammation, although any type of JIA can do so.

Causes uveitis most frequently in young girls with positive ANA test (anti-nuclear antibodies).

Affects four or fewer joints during the first six months of disease, but in some children additional joints are affected later.

Usually affects the large joints: knees, ankles or wrists.

Often affects a joint on one side of the body only, particularly the knee.

Sometimes called by its earlier name, pauciarticular juvenile arthritis.

1 Sacks, J. J. et al. *Arthritis Rheum* 2007;57(8):1439–1445.

2 Minden, K. and M. Niewerth. *Z Rheumatol* 2008;67(2):100, 102–106, 108–110.

JIA,” Dr. Cunningham noted.

The most commonly used TNF inhibitors are infliximab (Remicade), etanercept (Enbrel) and adalimumab (Humira). However, Dr. Cunningham cautioned, “We need to remember that these are very potent agents with the potential for serious adverse events, and so parents and guardians need to be appraised of the risks and benefits of therapy.”

OCT Finds Early Macular Damage

The increasing use of OCT has proved instrumental in making the case that damage occurs much earlier than once thought.

For instance, a study published in 2008—which found macular lesions in JIA patients with chronic uveitis—showed maculopathy in children as young as 5 years, said Bahram Bodaghi MD, PhD, professor of ophthalmology at University of Pierre and Marie Curie

in Paris. Dr. Bodaghi, a uveitis specialist, was the senior author on the paper.¹

Dr. Bodaghi and his colleagues used OCT to examine 62 eyes of 38 patients (with a mean age of 13.7 years) with chronic uveitis and a diagnosis of JIA. All but four of the eyes showed maculopathy on the OCT scans. “Until our study, macular involvement was thought to occur only in about 5 or 10 percent of children with uveitis caused by JIA. People thought the late complications and visual loss were because of cataract and glaucoma,” Dr. Bodaghi said. “But almost 85 percent of the patients we examined presented with early macular alterations that can eventually lead to visual loss.”

A History of Poor Outcomes

Although children with JIA can reach adulthood without long-term effects on their joints, the same cannot be said for their vision. Before the use of

methotrexate and biologic response modifiers to suppress the immune system, published studies reported generally negative visual outcomes for JIA patients who did not receive systemic immunosuppression.

For instance, in an analysis of 75 adults, 64 percent had at least one ocular complication from their childhood diseases. The most frequent were band keratopathy (32 percent), posterior synechiae (28 percent) and cataract (22 percent).²

In a separate report, the same group found that immunosuppressive drug therapy reduced the risk of hypotony in JIA uveitis patients by 74 percent. It also reduced the risk of epiretinal membrane formation by 86 percent and the risk of blindness in the better eye by 60 percent.³

One of the largest studies of visual outcomes after juvenile uveitis, published last year, found that ocular complications of childhood uveitis were common. The retrospective, longitudinal study of 527 children with a 10-year history of chronic uveitis found that cystoid macular edema and hypotony had the most significant impact visual impact overall. Posterior uveitis and panuveitis caused the most severe loss of acuity.⁴

Inflammatory Damage

If there has been an impression among ophthalmologists that JIA only affects the anterior segment, it was based on what ophthalmologists could see at the slit lamp, Dr. Bodaghi said.

Often, however, chronic uveitis occurs painlessly and before an arthritis diagnosis, allowing posterior synechiae to form and obscure the view of the retina.

Dr. Bodaghi said the macular damage his study found suggests that, if a child with JIA-associated uveitis develops a cataract, the clinician should rule out visual loss from maculopathy before considering surgery. The ocular inflammation also must be treated successfully prior to any surgery, he said.

“The later you operate on the lens of a child who has JIA, the better the

results. And if you implant an IOL without first strictly controlling the inflammatory disease, you are very likely to have a catastrophe,” Dr. Bodaghi said. “The worst situations occur in very young children, 2 or 3 years old, with JIA. Their eye can react very badly, and they may lose the eye.”

In contrast, Lam and associates found that, if intraocular inflammation is well controlled, children under age 12 can emerge from cataract surgery and IOL implantation with lasting improvements in their visual acuity. Methotrexate, other immunosuppressives and an intensified regimen of topical corticosteroids before and after surgery were credited for the lack of complications.⁵

It is unclear how much of the macular involvement in JIA-associated uveitis is caused directly by the underlying disease and how much is a secondary effect of the uveitis. Dr. Foster favors the latter explanation.

“The longer inflammation in the front part of the eye persists, the higher the likelihood that cytokines from the inflammatory cells are going to reach the retinal cells, most particularly those responsible for keeping it from developing macular edema,” he said. “And we know that macular edema is the most common cause of loss of vision in kids with uveitis.”

Dr. Foster summarized, “Get off the steroid pony before it’s too late. Don’t keep flogging that horse and expect to get a different result. You have to come in bold and put out the fire. If you don’t do it that way, matters simply will get worse.”

1 Ducos de Lahitte, G. et al. *Br J Ophthalmol* 2008;92:64–69.

2 Woreta, F. et al. *Am J Ophthalmol* 2007; 143(4):647–655.

3 Thorne, J. E. et al. *Am J Ophthalmol* 2007; 143(5):840–846.

4 Smith, J. A. et al. *Ophthalmology* 2009; 116(8):1544–1551.

5 Lam, L. A. et al. *Am J Ophthalmol* 2003; 135(6):772–778.

Drs. Bodaghi, Cunningham and Foster have no related financial interests.

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