AMERICAN ACADEMY
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Teleglaucoma

Multiple Models, Much Promise, Many Challenges

ROP: Evolving Perspectives on Anti-VEGF Therapy

Glaucoma and Exercise
What to Tell Your Patients

PEARLS
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Protecting Sight. Empowering Lives.®

INDICATION[1]

HUMIRA is indicated for the treatment of non-infectious intermediate, posterior, and panuveitis in adults and pediatric patients 2 years of age and older.

IMPORTANT SAFETY INFORMATION[1]

SERIOUS INFECTIONS

Patients treated with HUMIRA are at increased risk for developing serious infections that may lead to hospitalization or death. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

Discontinue HUMIRA if a patient develops a serious infection or sepsis.

Reported infections include:

- **Active tuberculosis (TB), including reactivation of latent TB. Patients with TB have frequently presented with disseminated or extrapulmonary disease. Test patients for latent TB before HUMIRA use and during therapy. Initiate treatment for latent TB prior to HUMIRA use.**
- **Invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis. Patients with histoplasmosis or other invasive fungal infections may present with disseminated, rather than localized, disease. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Consider empiric anti-fungal therapy in patients at risk for invasive fungal infections who develop severe systemic illness.**
- **Bacterial, viral, and other infections due to opportunistic pathogens, including Legionella and Listeria.**

Carefully consider the risks and benefits of treatment with HUMIRA prior to initiating therapy in patients: 1. with chronic or recurrent infection, 2. who have been exposed to TB, 3. with a history of opportunistic infection, 4. who resided in or traveled in regions where mycoses are endemic, 5. with underlying conditions that may predispose them to infection. Monitor patients closely for the development of signs and symptoms of infection during and after treatment with HUMIRA, including the possible development of TB in patients who tested negative for latent TB infection prior to initiating therapy.

- Do not start HUMIRA during an active infection, including localized infections.
- Patients older than 65 years, patients with co-morbid conditions, and/or patients taking concomitant immunosuppressants may be at greater risk of infection.
- If an infection develops, monitor carefully and initiate appropriate therapy.
- Drug interactions with biologic products: A higher rate of serious infections has been observed in RA patients treated with rituximab who received subsequent treatment with a TNF blocker. An increased risk of serious infections has been seen with the combination of TNF blockers with anakinra or abatacept, with no demonstrated added benefit in patients with RA. Concomitant administration of HUMIRA with other biologic DMARDs (e.g., anakinra or abatacept) or other TNF blockers is not recommended based on the possible increased risk for infections and other potential pharmacological interactions.

MALIGNANCY

Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, including HUMIRA. Postmarketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have been reported in patients treated with TNF blockers, including HUMIRA. These cases have had a very aggressive disease course and have been fatal. The majority of reported TNF blocker cases have occurred in patients with Crohn's disease or ulcerative colitis and the majority were in adolescent and young adult males. Almost all of these patients had received treatment with azathioprine or 6-mercaptopurine concomitantly with a TNF blocker at or prior to diagnosis. It is uncertain whether the occurrence of HSTCL is related to use of a TNF blocker or a TNF blocker in combination with these other immunosuppressants.

- Consider the risks and benefits of HUMIRA treatment prior to initiating or continuing therapy in a patient with known malignancy.
- In clinical trials, more cases of malignancies were observed among HUMIRA-treated patients compared to control patients.
- Non-melanoma skin cancer (NMSC) was reported during clinical trials for HUMIRA-treated patients. Examine all patients, particularly those with a history of prolonged immunosuppressant or PUVA therapy, for the presence of NMSC prior to and during treatment with HUMIRA.
- In HUMIRA clinical trials, there was an approximate 3-fold higher rate of lymphoma than expected in the general U.S. population. Patients with chronic inflammatory diseases, particularly those with highly active disease and/or chronic exposure to immunosuppressant therapies, may be at higher risk of lymphoma than the general population, even in the absence of TNF blockers.
- Postmarketing cases of acute and chronic leukemia were reported with TNF blocker use. Approximately half of the postmarketing cases of malignancies in children, adolescents, and young adults receiving TNF blockers were lymphomas; other cases included rare malignancies associated with immunosuppression and malignancies not usually observed in children and adolescents.

HYPERSENSITIVITY

- Anaphylaxis and angioneurotic edema have been reported following HUMIRA administration. If a serious allergic reaction occurs, stop HUMIRA and institute appropriate therapy.

HEPATITIS B VIRUS REACTIVATION

- Use of TNF blockers, including HUMIRA, may increase the risk of reactivation of hepatitis B virus (HBV) in patients who are chronic carriers. Some cases have been fatal.
- Evaluate patients at risk for HBV infection for prior evidence of HBV infection before initiating TNF blocker therapy.
- Exercise caution in patients who are carriers of HBV and monitor them during and after HUMIRA treatment.
- Discontinue HUMIRA and begin antiviral therapy in patients who develop HBV reactivation. Exercise caution when resuming HUMIRA after HBV treatment.

NEUROLOGIC REACTIONS

- TNF blockers, including HUMIRA, have been associated with rare cases of new onset or exacerbation of central nervous system and peripheral demyelinating diseases, including multiple sclerosis, optic neuritis, and Guillain-Barré syndrome.
- Exercise caution when considering HUMIRA for patients with these disorders; discontinuation of HUMIRA should be considered if any of these disorders develop.
- There is a known association between intermediate uveitis and central demyelinating disorders.

HEMATOLOGIC REACTIONS

- Rare reports of pancytopenia, including aplastic anemia, have been reported with TNF blockers. Medically significant cytopenia has been infrequently reported with HUMIRA.
- Consider stopping HUMIRA if significant hematologic abnormalities occur.

CONGESTIVE HEART FAILURE

- Worsening and new onset congestive heart failure (CHF) has been reported with TNF blockers. Cases of worsening CHF have been observed with HUMIRA; exercise caution and monitor carefully.

AUTOIMMUNITY

- Treatment with HUMIRA may result in the formation of autoantibodies and, rarely, in development of a lupus-like syndrome. Discontinue treatment if symptoms of a lupus-like syndrome develop.

IMMUNIZATIONS

- Patients on HUMIRA should not receive live vaccines.
- Pediatric patients, if possible, should be brought up to date with all immunizations before initiating HUMIRA therapy.
- Adalimumab is actively transferred across the placenta during the third trimester of pregnancy and may affect immune response in the *in utero* exposed infant. The safety of administering live or live-attenuated vaccines in infants exposed to HUMIRA *in utero* is unknown. Risks and benefits should be considered prior to vaccinating (live or live-attenuated) exposed infants.

ADVERSE REACTIONS

- The most common adverse reactions in HUMIRA clinical trials (>10%) were: infections (e.g., upper respiratory, sinusitis), injection site reactions, headache, and rash.

References: 1. HUMIRA Injection [package insert]. North Chicago, IL: AbbVie Inc. **2.** Ramanan AV, Dick AD, Benton D, *et al.* STUDY PROTOCOL: A randomised controlled trial of the clinical effectiveness, safety and cost-effectiveness of adalimumab in combination with methotrexate for the treatment of juvenile idiopathic arthritis associated uveitis (SYCAMORE Trial). *Trials.* 2014;15(14),1-13.

Please see Brief Summary of full Prescribing Information on the following pages.

abbvie

1ST AND ONLY FDA-APPROVED ANTI-TNF FOR AGES 2 & OLDER FOR TREATING NI UVEITIS*

*Non-infectious (NI) intermediate, posterior, and panuveitis.

Now approved

For pediatric non-infectious (NI) intermediate, posterior, and panuveitis in patients 2 years of age and older[1]

In a clinical trial of pediatric patients 2 years of age or older with JIA-associated NI uveitis†

HUMIRA + MTX was proven to:

- **Extend time controlling ocular inflammation and/or ocular comorbidities as defined by treatment failure[1]:**
  - –Treatment failure was a composite measure defined by worsening or sustained non-improvement in ocular inflammation, and/or worsening of ocular co-morbidities (reduction in vision, raised IOP, hypotony, disc swelling, or CME)[2]
- **Provide topical steroid-sparing efficacy[1]**

†HUMIRA is not indicated for anterior uveitis.

CME=cystoid macular edema; IOP=intraocular pressure; JIA=juvenile idiopathic arthritis.

HUMIRA® adalimumab

HUMIRA® (adalimumab)

PROFESSIONAL BRIEF SUMMARY
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

WARNING: SERIOUS INFECTIONS AND MALIGNANCY

SERIOUS INFECTIONS

Patients treated with HUMIRA are at increased risk for developing serious infections that may lead to hospitalization or death *[see Warnings and Precautions]*. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

Discontinue HUMIRA if a patient develops a serious infection or sepsis.

Reported infections include:

- **Active tuberculosis (TB), including reactivation of latent TB. Patients with TB have frequently presented with disseminated or extrapulmonary disease. Test patients for latent TB before HUMIRA use and during therapy. Initiate treatment for latent TB prior to HUMIRA use.**
- **Invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis. Patients with histoplasmosis or other invasive fungal infections may present with disseminated, rather than localized, disease. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Consider empiric anti-fungal therapy in patients at risk for invasive fungal infections who develop severe systemic illness.**
- **Bacterial, viral and other infections due to opportunistic pathogens, including Legionella and Listeria.**

Carefully consider the risks and benefits of treatment with HUMIRA prior to initiating therapy in patients with chronic or recurrent infection.

Monitor patients closely for the development of signs and symptoms of infection during and after treatment with HUMIRA, including the possible development of TB in patients who tested negative for latent TB infection prior to initiating therapy *[see Warnings and Precautions and Adverse Reactions]*.

MALIGNANCY

Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers including HUMIRA *[see Warnings and Precautions]*. Post-marketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have been reported in patients treated with TNF blockers including HUMIRA. These cases have had a very aggressive disease course and have been fatal. The majority of reported TNF blocker cases have occurred in patients with Crohn's disease or ulcerative colitis and the majority were in adolescent and young adult males. Almost all these patients had received treatment with azathioprine or 6-mercaptopurine (6–MP) concomitantly with a TNF blocker at or prior to diagnosis. It is uncertain whether the occurrence of HSTCL is related to use of a TNF blocker or a TNF blocker in combination with these other immunosuppressants *[see Warnings and Precautions]*.

INDICATIONS AND USAGE

Rheumatoid Arthritis

HUMIRA is indicated for reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active rheumatoid arthritis. HUMIRA can be used alone or in combination with methotrexate or other non-biologic disease-modifying anti-rheumatic drugs (DMARDs).

Juvenile Idiopathic Arthritis

HUMIRA is indicated for reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis in patients 2 years of age and older. HUMIRA can be used alone or in combination with methotrexate.

Psoriatic Arthritis

HUMIRA is indicated for reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with active psoriatic arthritis. HUMIRA can be used alone or in combination with non-biologic DMARDs.

Ankylosing Spondylitis

HUMIRA is indicated for reducing signs and symptoms in adult patients with active ankylosing spondylitis.

Adult Crohn's Disease

HUMIRA is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy. HUMIRA is indicated for reducing signs and symptoms and inducing clinical remission in these patients if they have also lost response to or are intolerant to infliximab.

Pediatric Crohn's Disease

HUMIRA is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active Crohn's disease who have had an inadequate response to corticosteroids or immunomodulators such as azathioprine, 6-mercaptopurine, or methotrexate.

Ulcerative Colitis

HUMIRA is indicated for inducing and sustaining clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to immunosuppressants such as corticosteroids, azathioprine or 6-mercaptopurine (6-MP). The effectiveness of HUMIRA has not been established in patients who have lost response to or were intolerant to TNF blockers.

Plaque Psoriasis

HUMIRA is indicated for the treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less appropriate. HUMIRA should only be administered to patients who will be closely monitored and have regular follow-up visits with a physician *[see Boxed Warning and Warnings and Precautions]*.

Hidradenitis Suppurativa

HUMIRA is indicated for the treatment of moderate to severe hidradenitis suppurativa in patients 12 years of age and older.

Uveitis

HUMIRA is indicated for the treatment of non-infectious intermediate, posterior, and panuveitis in adults and pediatric patients 2 years of age and older.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Serious Infections

Patients treated with HUMIRA are at increased risk for developing serious infections involving various organ systems and sites that may lead to hospitalization or death *[see Boxed Warning]*. Opportunistic infections due to bacterial, mycobacterial, invasive fungal, viral, parasitic, or other opportunistic pathogens including aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, histoplasmosis, legionellosis, listeriosis, pneumocystosis and tuberculosis have been reported with TNF blockers. Patients have frequently presented with disseminated rather than localized disease.

The concomitant use of a TNF blocker and abatacept or anakinra was associated with a higher risk of serious infections in patients with rheumatoid arthritis (RA); therefore, the concomitant use of HUMIRA and these biologic products is not recommended in the treatment of patients with RA *[see Warnings and Precautions and Drug Interactions]*.

Treatment with HUMIRA should not be initiated in patients with an active infection, including localized infections. Patients greater than 65 years of age, patients with co-morbid conditions and/or patients taking concomitant immunosuppressants (such as corticosteroids or methotrexate), may be at greater risk of infection. Consider the risks and benefits of treatment prior to initiating therapy in patients:

- with chronic or recurrent infection;
- who have been exposed to tuberculosis;
- with a history of an opportunistic infection;
- who have resided or traveled in areas of endemic tuberculosis or endemic mycoses, such as histoplasmosis, coccidioidomycosis, or blastomycosis; or
- with underlying conditions that may predispose them to infection.

Tuberculosis

Cases of reactivation of tuberculosis and new onset tuberculosis infections have been reported in patients receiving HUMIRA, including patients who have previously received treatment for latent or active tuberculosis. Reports included cases of pulmonary and extrapulmonary (i.e., disseminated) tuberculosis. Evaluate patients for tuberculosis risk factors and test for latent infection prior to initiating HUMIRA and periodically during therapy.

Treatment of latent tuberculosis infection prior to therapy with TNF blocking agents has been shown to reduce the risk of tuberculosis reactivation during therapy. Prior to initiating HUMIRA, assess if treatment for latent tuberculosis is needed; and consider an induration of ≥ 5 mm a positive tuberculin skin test result, even for patients previously vaccinated with Bacille Calmette-Guerin (BCG).

Consider anti-tuberculosis therapy prior to initiation of HUMIRA in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent tuberculosis but having risk factors for tuberculosis infection. Despite prophylactic treatment for tuberculosis, cases of reactivated tuberculosis have occurred in patients treated with HUMIRA. Consultation with a physician with expertise in the treatment of tuberculosis is recommended to aid in the decision whether initiating anti-tuberculosis therapy is appropriate for an individual patient.

Strongly consider tuberculosis in the differential diagnosis in patients who develop a new infection during HUMIRA treatment, especially in patients who have previously or recently traveled to countries with a high prevalence of tuberculosis, or who have had close contact with a person with active tuberculosis.

Monitoring

Closely monitor patients for the development of signs and symptoms of infection during and after treatment with HUMIRA, including the development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy. Tests for latent tuberculosis infection may also be falsely negative while on therapy with HUMIRA.

Discontinue HUMIRA if a patient develops a serious infection or sepsis. For a patient who develops a new infection during treatment with HUMIRA, closely monitor them, perform a prompt and complete diagnostic workup appropriate for an immunocompromised patient, and initiate appropriate antimicrobial therapy.

Invasive Fungal Infections

If patients develop a serious systemic illness and they reside or travel in regions where mycoses are endemic, consider invasive fungal infection in the differential diagnosis. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Consider appropriate empiric antifungal therapy, taking into account both the risk for severe fungal infection and the risks of antifungal therapy, while a diagnostic workup is being performed. To aid in the management of such patients, consider consultation with a physician with expertise in the diagnosis and treatment of invasive fungal infections.

Malignancies

Consider the risks and benefits of TNF-blocker treatment including HUMIRA prior to initiating therapy in patients with a known malignancy other than a successfully treated non-melanoma skin cancer (NMSC) or when considering continuing a TNF blocker in patients who develop a malignancy.

Malignancies in Adults

In the controlled portions of clinical trials of some TNF-blockers, including HUMIRA, more cases of malignancies have been observed among TNF-blocker-treated adult patients compared to control-treated adult patients. During the controlled portions of 39 global HUMIRA clinical trials in adult patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), Crohn's disease (CD), ulcerative colitis (UC), plaque psoriasis (Ps), hidradenitis suppurativa (HS) and uveitis (UV), malignancies, other than non-melanoma (basal cell and squamous cell) skin cancer, were observed at a rate (95% confidence interval) of 0.7 (0.48, 1.03) per 100 patient-years among 7973 HUMIRA-treated patients versus a rate of 0.7 (0.41, 1.17) per 100 patient-years among 4848 control-treated patients (median duration of treatment of 4 months for HUMIRA-treated patients and 4 months for control-treated patients). In 52 global controlled and uncontrolled clinical trials of HUMIRA in adult patients with RA, PsA, AS, CD, UC, Ps, HS and UV, the most frequently observed malignancies, other than lymphoma and NMSC, were breast, colon, prostate, lung, and melanoma. The malignancies in HUMIRA-treated patients in the controlled and uncontrolled portions of the studies were similar in type and number to what would be expected in the general U.S. population according to the SEER database (adjusted for age, gender, and race).

In controlled trials of other TNF blockers in adult patients at higher risk for malignancies (i.e., patients with COPD with a significant smoking history and cyclophosphamide-treated patients with Wegener's granulomatosis), a greater portion of malignancies occurred in the TNF blocker group compared to the control group.

Non-Melanoma Skin Cancer

During the controlled portions of 39 global HUMIRA clinical trials in adult patients with RA, PsA, AS, CD, UC, Ps, HS and UV, the rate (95% confidence interval) of NMSC was 0.8 (0.52, 1.09) per 100 patient-years among HUMIRA-treated patients and 0.2 (0.10, 0.59) per 100 patient-years among control-treated patients. Examine all patients, and in particular patients with a medical history of prior prolonged immunosuppressant therapy or psoriasis patients with a history of PUVA treatment for the presence of NMSC prior to and during treatment with HUMIRA.

Lymphoma and Leukemia

In the controlled portions of clinical trials of all the TNF-blockers in adults, more cases of lymphoma have been observed among TNF-blocker-treated patients compared to control-treated patients. In the controlled portions of 39 global HUMIRA clinical trials in adult patients with RA, PsA, AS, CD, UC, Ps, HS and UV, 2 lymphomas occurred among 7973 HUMIRA-treated patients versus 1 among 4848 control-treated patients. In 52 global controlled and uncontrolled clinical trials of HUMIRA in adult patients with RA, PsA, AS, CD, UC, Ps, HS and UV with a median duration of approximately 0.7 years, including 24,605 patients and over 40,215 patient-years of HUMIRA, the observed rate of lymphomas was approximately 0.11 per 100 patient-years. This is approximately 3-fold higher than expected in the general U.S. population according to the SEER database (adjusted for age, gender, and race). Rates of lymphoma in clinical trials of HUMIRA cannot be compared to rates of lymphoma in clinical trials of other TNF blockers and may not predict the rates observed in a broader patient population. Patients with RA and other chronic inflammatory diseases, particularly those with highly active disease and/or chronic exposure to immunosuppressant therapies, may be at a higher risk (up to several fold) than the general population for the development of lymphoma, even in the absence of TNF blockers. Post-marketing cases of acute and chronic leukemia have been reported in association with TNF-blocker use in RA and other indications. Even in the absence of TNF-blocker therapy, patients with RA may be at a higher risk (approximately 2-fold) than the general population for the development of leukemia.

Malignancies in Pediatric Patients and Young Adults

Malignancies, some fatal, have been reported among children, adolescents, and young adults who received treatment with TNF-blockers (initiation of therapy ≤ 18 years of age), of which HUMIRA is a member *[see Boxed Warning]*. Approximately half the cases were lymphomas, including Hodgkin's and non-Hodgkin's lymphoma. The other cases represented a variety of different malignancies and included rare malignancies usually associated with immunosuppression and malignancies that are not usually observed in children and adolescents. The malignancies occurred after a median of 30 months of therapy (range 1 to 84 months). Most of the patients were receiving concomitant immunosuppressants. These cases were reported post-marketing and are derived from a variety of sources including registries and spontaneous postmarketing reports.

Postmarketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have been reported in patients treated with TNF blockers including HUMIRA *[see Boxed Warning]*. These cases have had a very aggressive disease course and have been fatal. The majority of reported TNF blocker cases have occurred in patients with Crohn's disease or ulcerative colitis and the majority were in adolescent and young adult males. Almost all of these patients had received treatment with the immunosuppressants azathioprine or 6-mercaptopurine (6–MP) concomitantly with a TNF blocker at or prior to diagnosis. It is uncertain whether the occurrence of HSTCL is related to use of a TNF blocker or a TNF blocker in combination with these other immunosuppressants. The potential risk with the combination of azathioprine or 6-mercaptopurine and HUMIRA should be carefully considered.

Hypersensitivity Reactions

Anaphylaxis and angioneurotic edema have been reported following HUMIRA administration. If an anaphylactic or other serious allergic reaction occurs, immediately discontinue administration of HUMIRA and institute appropriate therapy. In clinical trials of HUMIRA in adults, allergic reactions (e.g., allergic rash, anaphylactoid reaction, fixed drug reaction, non-specified drug reaction, urticaria) have been observed.

Hepatitis B Virus Reactivation

Use of TNF blockers, including HUMIRA, may increase the risk of reactivation of hepatitis B virus (HBV) in patients who are chronic carriers of this virus. In some instances, HBV reactivation occurring in conjunction with TNF blocker therapy has been fatal. The majority of these reports have occurred in patients concomitantly receiving other medications that suppress the immune system, which may also contribute to HBV reactivation. Evaluate patients at risk for HBV infection for prior evidence of HBV infection before initiating TNF blocker therapy. Exercise caution in prescribing TNF blockers for patients identified as carriers of HBV. Adequate data are not available on the safety or efficacy of treating patients who are carriers of HBV with anti-viral therapy in conjunction with TNF blocker therapy to prevent HBV reactivation. For patients who are carriers of HBV and require treatment with TNF blockers, closely monitor such patients for clinical and laboratory signs of active HBV infection throughout therapy and for several months following termination of therapy. In patients who develop HBV reactivation, stop HUMIRA and initiate effective anti-viral therapy with appropriate supportive treatment. The safety of resuming TNF blocker therapy after HBV reactivation is controlled is not known. Therefore, exercise caution when considering resumption of HUMIRA therapy in this situation and monitor patients closely.

Neurologic Reactions

Use of TNF blocking agents, including HUMIRA, has been associated with rare cases of new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disease, including multiple sclerosis (MS) and optic neuritis, and peripheral demyelinating disease, including Guillain-Barré syndrome. Exercise caution in considering the use of HUMIRA in patients with preexisting or recent-onset central or peripheral nervous system demyelinating disorders;

discontinuation of HUMIRA should be considered if any of these disorders develop. There is a known association between intermediate uveitis and central demyelinating disorders.

Hematological Reactions

Rare reports of pancytopenia including aplastic anemia have been reported with TNF blocking agents. Adverse reactions of the hematologic system, including medically significant cytopenia (e.g., thrombocytopenia, leukopenia) have been infrequently reported with HUMIRA. The causal relationship of these reports to HUMIRA remains unclear. Advise all patients to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias or infection (e.g., persistent fever, bruising, bleeding, pallor) while on HUMIRA. Consider discontinuation of HUMIRA therapy in patients with confirmed significant hematologic abnormalities.

Use with Anakinra

Concurrent use of anakinra (an interleukin-1 antagonist) and another TNF-blocker, was associated with a greater proportion of serious infections and neutropenia and no added benefit compared with the TNF-blocker alone in patients with RA. Therefore, the combination of HUMIRA and anakinra is not recommended *[see Drug Interactions]*.

Heart Failure

Cases of worsening congestive heart failure (CHF) and new onset CHF have been reported with TNF blockers. Cases of worsening CHF have also been observed with HUMIRA. HUMIRA has not been formally studied in patients with CHF; however, in clinical trials of another TNF blocker, a higher rate of serious CHF-related adverse reactions was observed. Exercise caution when using HUMIRA in patients who have heart failure and monitor them carefully.

Autoimmunity

Treatment with HUMIRA may result in the formation of autoantibodies and, rarely, in the development of a lupus-like syndrome. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with HUMIRA, discontinue treatment *[see Adverse Reactions]*.

Immunizations

In a placebo-controlled clinical trial of patients with RA, no difference was detected in anti-pneumococcal antibody response between HUMIRA and placebo treatment groups when the pneumococcal polysaccharide vaccine and influenza vaccine were administered concurrently with HUMIRA. Similar proportions of patients developed protective levels of anti-influenza antibodies between HUMIRA and placebo treatment groups; however, titers in aggregate to influenza antigens were moderately lower in patients receiving HUMIRA. The clinical significance of this is unknown. Patients on HUMIRA may receive concurrent vaccinations, except for live vaccines. No data are available on the secondary transmission of infection by live vaccines in patients receiving HUMIRA.

It is recommended that pediatric patients, if possible, be brought up to date with all immunizations in agreement with current immunization guidelines prior to initiating HUMIRA therapy. Patients on HUMIRA may receive concurrent vaccinations, except for live vaccines.

The safety of administering live or live-attenuated vaccines in infants exposed to HUMIRA *in utero* is unknown. Risks and benefits should be considered prior to vaccinating (live or live-attenuated) exposed infants *[see Use in Specific Populations]*.

Use with Abatacept

In controlled trials, the concurrent administration of TNF-blockers and abatacept was associated with a greater proportion of serious infections than the use of a TNF-blocker alone; the combination therapy, compared to the use of a TNF-blocker alone, has not demonstrated improved clinical benefit in the treatment of RA. Therefore, the combination of abatacept with TNF-blockers including HUMIRA is not recommended *[see Drug Interactions]*.

ADVERSE REACTIONS

The most serious adverse reactions described elsewhere in the labeling include the following:

- Serious Infections *[see Warnings and Precautions]*
- Malignancies *[see Warnings and Precautions]*

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The most common adverse reaction with HUMIRA was injection site reactions. In placebo-controlled trials, 20% of patients treated with HUMIRA developed injection site reactions (erythema and/or itching, hemorrhage, pain or swelling), compared to 14% of patients receiving placebo. Most injection site reactions were described as mild and generally did not necessitate drug discontinuation.

The proportion of patients who discontinued treatment due to adverse reactions during the double-blind, placebo-controlled portion of studies in patients with RA (i.e., Studies RA-I, RA-II, RA-III and RA-IV) was 7% for patients taking HUMIRA and 4% for placebo-treated patients. The most common adverse reactions leading to discontinuation of HUMIRA in these RA studies were clinical flare reaction (0.7%), rash (0.3%) and pneumonia (0.3%).

Infections

In the controlled portions of the 39 global HUMIRA clinical trials in adult patients with RA, PsA, AS, CD, UC, Ps, HS and UV, the rate of serious infections was 4.3 per 100 patient-years in 7973 HUMIRA-treated patients versus a rate of 2.9 per 100 patient-years in 4848 control-treated patients. Serious infections observed included pneumonia, septic arthritis, prosthetic and post-surgical infections, erysipelas, cellulitis, diverticulitis, and pyelonephritis *[see Warnings and Precautions]*.

Tuberculosis and Opportunistic Infections

In 52 global controlled and uncontrolled clinical trials in RA, PsA, AS, CD, UC, Ps, HS and UV that included 24,605 HUMIRA-treated patients, the rate of reported active tuberculosis was 0.20 per 100 patient-years and the rate of positive PPD conversion was 0.09 per 100 patient-years. In a subgroup of 10,113 U.S. and Canadian HUMIRA-treated patients, the rate of reported active TB was 0.05 per 100 patient-years and the rate of positive PPD conversion was 0.07 per 100 patient-years. These trials included reports of miliary, lymphatic, peritoneal, and pulmonary TB. Most of the TB cases occurred within the first eight months after initiation of therapy and may reflect recrudescence of latent disease. In these global clinical trials, cases of serious opportunistic infections have been reported at an overall rate of 0.05 per 100 patient-years. Some cases of serious opportunistic infections and TB have been fatal *[see Warnings and Precautions]*.

Autoantibodies

In the rheumatoid arthritis controlled trials, 12% of patients treated with HUMIRA and 7% of placebo-treated patients that had negative baseline ANA titers developed positive titers at week 24. Two patients out of 3046 treated with HUMIRA developed clinical signs suggestive of new-onset lupus-like syndrome. The patients improved following discontinuation of therapy. No patients developed lupus nephritis or central nervous system symptoms. The impact of long-term treatment with HUMIRA on the development of autoimmune diseases is unknown.

Liver Enzyme Elevations

There have been reports of severe hepatic reactions including acute liver failure in patients receiving TNF-blockers. In controlled Phase 3 trials of HUMIRA (40 mg SC every other week) in patients with RA, PsA, and AS with control period duration ranging from 4 to 104 weeks, ALT elevations ≥ 3 x ULN occurred in 3.5% of HUMIRA-treated patients and 1.5% of control-treated patients. Since many of these patients in these trials were also taking medications that cause liver enzyme elevations (e.g., NSAIDS, MTX), the relationship between HUMIRA and the liver enzyme elevations is not clear. In a controlled Phase 3 trial of HUMIRA in patients with polyarticular JIA who were 4 to 17 years, ALT elevations ≥ 3 x ULN occurred in 4.4% of HUMIRA-treated patients and 1.5% of control-treated patients (ALT more common than AST); liver enzyme test elevations were more frequent among those treated with the combination of HUMIRA and MTX than those treated with HUMIRA alone. In general, these elevations did not lead to discontinuation of HUMIRA treatment. No ALT elevations ≥ 3 x ULN occurred in the open-label study of HUMIRA in patients with polyarticular JIA who were 2 to <4 years.

In controlled Phase 3 trials of HUMIRA (initial doses of 160 mg and 80 mg, or 80 mg and 40 mg on Days 1 and 15, respectively, followed by 40 mg every other week) in adult patients with CD with a control period duration ranging from 4 to 52 weeks, ALT elevations ≥ 3 x ULN occurred in 0.9% of HUMIRA-treated patients and 0.9% of control-treated patients. In the Phase 3 trial of HUMIRA in pediatric patients with Crohn's disease which evaluated efficacy and safety of two body weight based maintenance dose regimens following body weight based induction therapy up to 52 weeks of treatment, ALT elevations ≥ 3 x ULN occurred in 2.6% (5/192) of patients, of whom 4 were receiving concomitant immunosuppressants at baseline; none of these patients discontinued due to abnormalities in ALT tests. In controlled Phase 3 trials of HUMIRA (initial doses of 160 mg and 80 mg on Days 1 and 15 respectively, followed by 40 mg every other week) in patients with UC with control period duration ranging from 1 to 52 weeks, ALT elevations ≥3 x ULN occurred in 1.5% of HUMIRA-treated patients and 1.0% of control-treated patients. In controlled Phase 3 trials of HUMIRA (initial dose of 80 mg then 40 mg every other week) in patients with Ps with control period duration ranging from 12 to 24 weeks, ALT elevations ≥ 3 x ULN occurred in 1.8% of HUMIRA-treated patients and 1.8% of control-treated patients. In controlled trials of HUMIRA (initial doses of 160 mg at Week 0 and 80 mg at Week 2, followed by 40 mg every week starting at Week 4), in subjects with HS with a control period duration ranging from 12 to 16 weeks, ALT elevations ≥ 3 x ULN occurred in 0.3% of HUMIRA-treated subjects and 0.6% of control-treated subjects. In controlled trials of HUMIRA (initial doses of 80 mg at Week 0 followed by 40 mg every other week starting at Week 1) in adult patients with uveitis with an exposure of 165.4 PYs and 119.8 PYs in HUMIRA-treated and control-treated patients, respectively, ALT elevations ≥ 3 x ULN occurred in 2.4% of HUMIRA-treated patients and 2.4% of control-treated patients.

Immunogenicity

Patients in Studies RA-I, RA-II, and RA-III were tested at multiple time points for antibodies to adalimumab during the 6- to 12-month period. Approximately 5% (58 of 1062) of adult RA patients receiving HUMIRA developed low-titer antibodies to adalimumab at least once during treatment, which were neutralizing *in vitro*. Patients treated with concomitant methotrexate (MTX) had a lower rate of antibody development than patients on HUMIRA monotherapy (1% versus 12%). No apparent correlation of antibody development to adverse reactions was observed. With monotherapy, patients receiving every other week dosing may develop antibodies more frequently than those receiving weekly dosing. In patients receiving the recommended dosage of 40 mg every other week as monotherapy, the ACR 20 response was lower among antibody-positive patients than among antibody-negative patients. The long-term immunogenicity of HUMIRA is unknown.

In patients with polyarticular JIA who were 4 to 17 years of age, adalimumab antibodies were identified in 16% of HUMIRA-treated patients. In patients receiving concomitant MTX, the incidence was 6% compared to 26% with HUMIRA monotherapy. In patients with polyarticular JIA who were 2 to <4 years of age or 4 years of age and older weighing <15 kg, adalimumab antibodies were identified in 7% (1 of 15) of HUMIRA-treated patients, and the one patient was receiving concomitant MTX.

In patients with AS, the rate of development of antibodies to adalimumab in HUMIRA-treated patients was comparable to patients with RA.

In patients with PsA, the rate of antibody development in patients receiving HUMIRA monotherapy was comparable to patients with RA; however, in patients receiving concomitant MTX the rate was 7% compared to 1% in RA.

In adult patients with CD, the rate of antibody development was 3%.

In pediatric patients with Crohn's disease, the rate of antibody development in patients receiving HUMIRA was 3%. However, due to the limitation of the assay conditions, antibodies to adalimumab could be detected only when serum adalimumab levels were < 2 mcg/mL. Among the patients whose serum adalimumab levels were < 2 mcg/mL (approximately 32% of total patients studied), the immunogenicity rate was 10%.

In patients with moderately to severely active UC, the rate of antibody development in patients receiving HUMIRA was 5%. However, due to the limitation of the assay conditions, antibodies to adalimumab could be detected only when serum adalimumab levels were < 2 mcg/mL. Among the patients whose serum adalimumab levels were < 2 mcg/mL (approximately 25% of total patients studied), the immunogenicity rate was 20.7%.

In patients with Ps, the rate of antibody development with HUMIRA monotherapy was 8%. However, due to the limitation of the assay conditions, antibodies to adalimumab could be detected only when serum adalimumab levels were < 2 mcg/mL. Among the patients whose serum adalimumab levels were < 2 mcg/mL (approximately 40% of total patients studied), the immunogenicity rate was 20.7%. In Ps patients who were on HUMIRA monotherapy and subsequently withdrawn from the treatment, the rate of antibodies to adalimumab after retreatment was similar to the rate observed prior to withdrawal.

Anti-adalimumab antibodies were measured in clinical trials of subjects with moderate to severe HS with two assays (an original assay capable of detecting antibodies when serum adalimumab concentrations declined to < 2 mcg/mL and a new assay that is capable of detecting anti-adalimumab antibody titers in all subjects, independent of adalimumab concentration). Using the original assay, the rate of anti-adalimumab antibody development in subjects treated with HUMIRA was 6.5%. Among subjects who stopped HUMIRA treatment for up to 24 weeks and in whom adalimumab serum levels subsequently declined to < 2 mcg/mL (approximately 22% of total subjects studied), the immunogenicity rate was 28%. Using the new titer-based assay, anti-adalimumab antibody titers were measurable in 61% of HS subjects treated with HUMIRA. Antibodies to adalimumab were associated with reduced serum adalimumab concentrations. In general, the extent of reduction in serum adalimumab concentrations is greater with increasing titers of antibodies to adalimumab. No apparent association between antibody development and safety was observed.

In adult patients with non-infectious uveitis, anti-adalimumab antibodies were identified in 4.8% (12/249) of patients treated with adalimumab. However, due to the limitation of the assay conditions, antibodies to adalimumab could be detected only when serum adalimumab levels were < 2 mcg/mL. Among the patients whose serum adalimumab levels were < 2 mcg/mL (approximately 23% of total patients studied), the immunogenicity rate was 21.1%. Using an assay which could measure an anti-adalimumab antibody titer in all patients, titers were measured in 39.8% (99/249) of non-infectious uveitis adult patients treated with adalimumab. No correlation of antibody development to safety or efficacy outcomes was observed.

The data reflect the percentage of patients whose test results were considered positive for antibodies to adalimumab or titers, and are highly dependent on the assay. The observed incidence of antibody (including neutralizing antibody) positivity in an assay is highly dependent on several factors including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to adalimumab with the incidence of antibodies to other products may be misleading.

Other Adverse Reactions

Rheumatoid Arthritis Clinical Studies

The data described below reflect exposure to HUMIRA in 2468 patients, including 2073 exposed for 6 months, 1497 exposed for greater than one year and 1380 in adequate and well-controlled studies (Studies RA-I, RA-II, RA-III, and RA-IV). HUMIRA was studied primarily in placebo-controlled trials and in long-term follow up studies for up to 36 months duration. The population had a mean age of 54 years, 77% were female, 91% were Caucasian and had moderately to severely active rheumatoid arthritis. Most patients received 40 mg HUMIRA every other week.

Table 1 summarizes reactions reported at a rate of at least 5% in patients treated with HUMIRA 40 mg every other week compared to placebo and with an incidence higher than placebo. In Study RA-III, the types and frequencies of adverse reactions in the second year open-label extension were similar to those observed in the one-year double-blind portion.

Table 1. Adverse Reactions Reported by ≥5% of Patients Treated with HUMIRA During Placebo-Controlled Period of Pooled RA Studies (Studies RA-I, RA-II, RA-III, and RA-IV)

	HUMIRA 40 mg subcutaneous Every Other Week	Placebo
	(N=705)	(N=690)
Adverse Reaction (Preferred Term)		
Respiratory		
Upper respiratory infection	17%	13%
Sinusitis	11%	9%
Flu syndrome	7%	6%
Gastrointestinal		
Nausea	9%	8%
Abdominal pain	7%	4%
Laboratory Tests*		
Laboratory test abnormal	8%	7%
Hypercholesterolemia	6%	4%
Hyperlipidemia	7%	5%
Hematuria	5%	4%
Alkaline phosphatase increased	5%	3%
Other		
Headache	12%	8%
Rash	12%	6%
Accidental injury	10%	8%
Injection site reaction **	8%	1%
Back pain	6%	4%
Urinary tract infection	8%	5%
Hypertension	5%	3%

* Laboratory test abnormalities were reported as adverse reactions in European trials
** Does not include injection site erythema, itching, hemorrhage, pain or swelling

Juvenile Idiopathic Arthritis Clinical Studies

In general, the adverse reactions in the HUMIRA-treated patients in the polyarticular juvenile idiopathic arthritis (JIA) trials (Studies JIA-I and JIA-II) were similar in frequency and type to those seen in adult patients *[see Warnings and Precautions, Adverse Reactions]*. Important findings and differences from adults are discussed in the following paragraphs.

In Study JIA-I, HUMIRA was studied in 171 patients who were 4 to 17 years of age, with polyarticular JIA. Severe adverse reactions reported in the study included neutropenia, streptococcal pharyngitis, increased aminotransferases, herpes zoster, myositis, metrorrhagia, and appendicitis. Serious infections were observed in 4% of patients within approximately 2 years of initiation of treatment with HUMIRA and included cases of herpes simplex, pneumonia, urinary tract infection, pharyngitis, and herpes zoster.

In Study JIA-I, 45% of patients experienced an infection while receiving HUMIRA with or without concomitant MTX in the first 16 weeks of treatment. The types of infections reported in HUMIRA-treated patients were generally similar to those commonly seen in polyarticular JIA patients who are not treated with TNF blockers. Upon initiation of treatment, the most common adverse reactions occurring in this patient population treated with

HUMIRA were injection site pain and injection site reaction (19% and 16%, respectively). A less commonly reported adverse event in patients receiving HUMIRA was granuloma annulare which did not lead to discontinuation of HUMIRA treatment.

In the first 48 weeks of treatment in Study JIA-I, non-serious hypersensitivity reactions were seen in approximately 6% of patients and included primarily localized allergic hypersensitivity reactions and allergic rash.

In Study JIA-I, 10% of patients treated with HUMIRA who had negative baseline anti-dsDNA antibodies developed positive titers after 48 weeks of treatment. No patient developed clinical signs of autoimmunity during the clinical trial.

Approximately 15% of patients treated with HUMIRA developed mild-to-moderate elevations of creatine phosphokinase (CPK) in Study JIA-I. Elevations exceeding 5 times the upper limit of normal were observed in several patients. CPK levels decreased or returned to normal in all patients. Most patients were able to continue HUMIRA without interruption.

In Study JIA-II, HUMIRA was studied in 32 patients who were 2 to <4 years of age or 4 years of age and older weighing <15 kg with polyarticular JIA. The safety profile for this patient population was similar to the safety profile seen in patients 4 to 17 years of age with polyarticular JIA.

In Study JIA-II, 78% of patients experienced an infection while receiving HUMIRA. These included nasopharyngitis, bronchitis, upper respiratory tract infection, otitis media, and were mostly mild to moderate in severity. Serious infections were observed in 9% of patients receiving HUMIRA in the study and included dental caries, rotavirus gastroenteritis, and varicella.

In Study JIA-II, non-serious allergic reactions were observed in 6% of patients and included intermittent urticaria and rash, which were all mild in severity.

Psoriatic Arthritis and Ankylosing Spondylitis Clinical Studies

HUMIRA has been studied in 395 patients with psoriatic arthritis (PsA) in two placebo-controlled trials and in an open label study and in 393 patients with ankylosing spondylitis (AS) in two placebo-controlled studies. The safety profile for patients with PsA and AS treated with HUMIRA 40 mg every other week was similar to the safety profile seen in patients with RA, HUMIRA Studies RA-I through IV.

Adult Crohn's Disease Clinical Studies

HUMIRA has been studied in 1478 adult patients with Crohn's disease (CD) in four placebo-controlled and two open-label extension studies. The safety profile for adult patients with CD treated with HUMIRA was similar to the safety profile seen in patients with RA.

Pediatric Crohn's Disease Clinical Studies

HUMIRA has been studied in 192 pediatric patients with Crohn's disease in one double-blind study (Study PCD-I) and one open-label extension study. The safety profile for pediatric patients with Crohn's disease treated with HUMIRA was similar to the safety profile seen in adult patients with Crohn's disease.

During the 4-week open label induction phase of Study PCD-I, the most common adverse reactions occurring in the pediatric population treated with HUMIRA were injection site pain and injection site reaction (6% and 5%, respectively).

A total of 67% of children experienced an infection while receiving HUMIRA in Study PCD-I. These included upper respiratory tract infection and nasopharyngitis.

A total of 5% of children experienced a serious infection while receiving HUMIRA in Study PCD-I. These included viral infection, device related sepsis (catheter), gastroenteritis, H1N1 influenza, and disseminated histoplasmosis.

In Study PCD-I, allergic reactions were observed in 5% of children which were all non-serious and were primarily localized reactions.

Ulcerative Colitis Clinical Studies

HUMIRA has been studied in 1010 patients with ulcerative colitis (UC) in two placebo-controlled studies and one open-label extension study. The safety profile for patients with UC treated with HUMIRA was similar to the safety profile seen in patients with RA.

Plaque Psoriasis Clinical Studies

HUMIRA has been studied in 1696 subjects with plaque psoriasis (Ps) in placebo-controlled and open-label extension studies. The safety profile for subjects with Ps treated with HUMIRA was similar to the safety profile seen in subjects with RA with the following exceptions. In the placebo-controlled portions of the clinical trials in Ps subjects, HUMIRA-treated subjects had a higher incidence of arthralgia when compared to controls (3% *vs.* 1%).

Hidradenitis Suppurativa Clinical Studies

HUMIRA has been studied in 727 subjects with hidradenitis suppurativa (HS) in three placebo-controlled studies and one open-label extension study. The safety profile for subjects with HS treated with HUMIRA weekly was consistent with the known safety profile of HUMIRA.

Flare of HS, defined as ≥25% increase from baseline in abscesses and inflammatory nodule counts and with a minimum of 2 additional lesions, was documented in 22 (22%) of the 100 subjects who were withdrawn from HUMIRA treatment following the primary efficacy timepoint in two studies.

Uveitis Clinical Studies

HUMIRA has been studied in 464 adult patients with uveitis (UV) in placebo-controlled and open-label extension studies and in 90 pediatric patients with uveitis (Study PUV-I). The safety profile for patients with UV treated with HUMIRA was similar to the safety profile seen in patients with RA.

Postmarketing Experience

The following adverse reactions have been identified during post-approval use of HUMIRA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to HUMIRA exposure.

Gastrointestinal disorders: Diverticulitis, large bowel perforations including perforations associated with diverticulitis and appendiceal perforations associated with appendicitis, pancreatitis

General disorders and administration site conditions: Pyrexia

Hepato-biliary disorders: Liver failure, hepatitis

Immune system disorders: Sarcoidosis

Neoplasms benign, malignant and unspecified (including cysts and polyps): Merkel Cell Carcinoma (neuroendocrine carcinoma of the skin)

Nervous system disorders: Demyelinating disorders (e.g., optic neuritis, Guillain-Barré syndrome), cerebrovascular accident

Respiratory disorders: Interstitial lung disease, including pulmonary fibrosis, pulmonary embolism

Skin reactions: Stevens Johnson Syndrome, cutaneous vasculitis, erythema multiforme, new or worsening psoriasis (all sub-types including pustular and palmoplantar), alopecia, lichenoid skin reaction

Vascular disorders: Systemic vasculitis, deep vein thrombosis

DRUG INTERACTIONS

Methotrexate

HUMIRA has been studied in rheumatoid arthritis (RA) patients taking concomitant methotrexate (MTX). Although MTX reduced the apparent adalimumab clearance, the data do not suggest the need for dose adjustment of either HUMIRA or MTX.

Biological Products

In clinical studies in patients with RA, an increased risk of serious infections has been seen with the combination of TNF blockers with anakinra or abatacept, with no added benefit; therefore, use of HUMIRA with abatacept or anakinra is not recommended in patients with RA *[see Warnings and Precautions]*. A higher rate of serious infections has also been observed in patients with RA treated with rituximab who received subsequent treatment with a TNF blocker. There is insufficient information regarding the concomitant use of HUMIRA and other biologic products for the treatment of RA, PsA, AS, CD, UC, Ps, HS and UV. Concomitant administration of HUMIRA with other biologic DMARDS (e.g., anakinra and abatacept) or other TNF blockers is not recommended based upon the possible increased risk for infections and other potential pharmacological interactions.

Live Vaccines

Avoid the use of live vaccines with HUMIRA *[see Warnings and Precautions]*.

Cytochrome P450 Substrates

The formation of CYP450 enzymes may be suppressed by increased levels of cytokines (e.g., TNFα, IL-6) during chronic inflammation. It is possible for a molecule that antagonizes cytokine activity, such as adalimumab, to influence the formation of CYP450 enzymes. Upon initiation or discontinuation of HUMIRA in patients being treated with CYP450 substrates with a narrow therapeutic index, monitoring of the effect (e.g., warfarin) or drug concentration (e.g., cyclosporine or theophylline) is recommended and the individual dose of the drug product may be adjusted as needed.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Available studies with use of adalimumab during pregnancy do not reliably establish an association between adalimumab and major birth defects. Clinical data are available from the Organization of Teratology Information Specialists (OTIS)/MotherToBaby HUMIRA Pregnancy Registry in pregnant women with rheumatoid arthritis (RA) or Crohn's disease (CD). Registry results showed a rate of 10% for major birth defects with first trimester use of adalimumab in pregnant women with RA or CD and a rate of 7.5% for major birth defects in the disease-matched comparison cohort. The lack of pattern of major birth defects is reassuring and differences between exposure groups may have impacted the occurrence of birth defects *(see Data)*.

Adalimumab is actively transferred across the placenta during the third trimester of pregnancy and may affect immune response in the *in-utero* exposed infant *(see Clinical Considerations)*. In an embryo-fetal perinatal development study conducted in cynomolgus monkeys, no fetal harm or malformations were observed with intravenous administration of adalimumab during organogenesis and later in gestation, at doses that produced exposures up to approximately 373 times the maximum recommended human dose (MRHD) of 40 mg subcutaneous without methotrexate *(see Data)*.

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-associated maternal and embryo/fetal risk

Published data suggest that the risk of adverse pregnancy outcomes in women with RA or inflammatory bowel disease (IBD) is associated with increased disease activity. Adverse pregnancy outcomes include preterm delivery (before 37 weeks of gestation), low birth weight (less than 2500 g) infants, and small for gestational age at birth.

Fetal/Neonatal Adverse Reactions

Monoclonal antibodies are increasingly transported across the placenta as pregnancy progresses, with the largest amount transferred during the third trimester *(see Data)*. Risks and benefits should be considered prior to administering live or live-attenuated vaccines to infants exposed to HUMIRA *in utero [see Use in Specific Populations]*.

Data

Human Data

A prospective cohort pregnancy exposure registry conducted by OTIS/MotherToBaby in the U.S. and Canada between 2004 and 2016 compared the risk of major birth defects in live-born infants of 221 women (69 RA, 152 CD) treated with adalimumab during the first trimester and 106 women (74 RA, 32 CD) not treated with adalimumab.

The proportion of major birth defects among live-born infants in the adalimumab-treated and untreated cohorts was 10% (8.7% RA, 10.5% CD) and 7.5% (6.8% RA, 9.4% CD), respectively. The lack of pattern of major birth defects is reassuring and differences between exposure groups may have impacted the occurrence of birth defects. This study cannot reliably establish whether there is an association between adalimumab and major birth defects because of methodological limitations of the registry, including small sample size, the voluntary nature of the study, and the non-randomized design.

In an independent clinical study conducted in ten pregnant women with IBD treated with HUMIRA, adalimumab concentrations were measured in maternal serum as well as in cord blood (n=10) and infant serum (n=8) on the day of birth. The last dose of HUMIRA was given between 1 and 56 days prior to delivery. Adalimumab concentrations were 0.16-19.7 µg/mL in cord blood, 4.28-17.7 µg/mL in infant serum, and 0-16.1 µg/mL in maternal serum. In all but one case, the cord blood level of adalimumab was higher than the maternal serum level, suggesting adalimumab actively crosses the placenta. In addition, one infant had serum levels at each of the following: 6 weeks (1.94 µg/mL), 7 weeks (1.31 µg/mL), 8 weeks (0.93 µg/mL), and 11 weeks (0.53 µg/mL), suggesting adalimumab can be detected in the serum of infants exposed *in utero* for at least 3 months from birth.

Animal Data

In an embryo-fetal perinatal development study, pregnant cynomolgus monkeys received adalimumab from gestation days 20 to 97 at doses that produced exposures up to 373 times that achieved with the MRHD without methotrexate (on an AUC basis with maternal IV doses up to 100 mg/kg/week). Adalimumab did not elicit harm to the fetuses or malformations.

Lactation

Risk Summary

Limited data from case reports in the published literature describe the presence of adalimumab in human milk at infant doses of 0.1% to 1% of the maternal serum level. Published data suggest that the systemic exposure to a breastfed infant is expected to be low because adalimumab is a large molecule and is degraded in the gastrointestinal tract. However, the effects of local exposure in the gastrointestinal tract are unknown. There are no reports of adverse effects of adalimumab on the breastfed infant and no effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for HUMIRA and any potential adverse effects on the breastfed child from HUMIRA or from the underlying maternal condition.

Pediatric Use

Safety and efficacy of HUMIRA in pediatric patients for uses other than polyarticular juvenile idiopathic arthritis (JIA), pediatric Crohn's disease and pediatric uveitis have not been established. Due to its inhibition of TNFα, HUMIRA administered during pregnancy could affect immune response in the *in utero*-exposed newborn and infant. Data from eight infants exposed to HUMIRA *in utero* suggest adalimumab crosses the placenta *[see Use in Specific Populations)]*. The clinical significance of elevated adalimumab levels in infants is unknown. The safety of administering live or live-attenuated vaccines in exposed infants is unknown. Risks and benefits should be considered prior to vaccinating (live or live-attenuated) exposed infants.

Post-marketing cases of lymphoma, including hepatosplenic T-cell lymphoma and other malignancies, some fatal, have been reported among children, adolescents, and young adults who received treatment with TNF-blockers including HUMIRA *[see Boxed Warning and Warnings and Precautions]*.

Juvenile Idiopathic Arthritis

In Study JIA-I, HUMIRA was shown to reduce signs and symptoms of active polyarticular JIA in patients 4 to 17 years of age. In Study JIA-II, the safety profile for patients 2 to <4 years of age was similar to the safety profile for patients 4 to 17 years of age with polyarticular JIA *[see Adverse Reactions]*. HUMIRA has not been studied in patients with polyarticular JIA less than 2 years of age or in patients with a weight below 10 kg.

The safety of HUMIRA in patients in the polyarticular JIA trials was generally similar to that observed in adults with certain exceptions *[see Adverse Reactions]*.

Pediatric Crohn's Disease

The safety and effectiveness of HUMIRA for reducing signs and symptoms and inducing and maintaining clinical remission have been established in pediatric patients 6 years of age and older with moderately to severely active Crohn's disease who have had an inadequate response to corticosteroids or immunomodulators such as azathioprine, 6-mercaptopurine, or methotrexate. Use of HUMIRA in this age group is supported by evidence from adequate and well-controlled studies of HUMIRA in adults with additional data from a randomized, double-blind, 52-week clinical study of two dose levels of HUMIRA in 192 pediatric patients (6 to 17 years of age) with moderately to severely active Crohn's disease. The safety and effectiveness of HUMIRA has not been established in pediatric patients with Crohn's disease less than 6 years of age.

Pediatric Uveitis

The safety and effectiveness of HUMIRA for the treatment of non-infectious uveitis have been established in pediatric patients 2 years of age and older. The use of HUMIRA is supported by evidence from adequate and well-controlled studies of HUMIRA in adults and a 2:1 randomized, controlled clinical study in 90 pediatric patients. The safety and effectiveness of HUMIRA has not been established in pediatric patients with uveitis less than 2 years of age.

Hidradenitis Suppurativa

Use of HUMIRA in pediatric patients 12 years of age and older for HS is supported by evidence from adequate and well-controlled studies of HUMIRA in adult HS patients. Additional population pharmacokinetic modeling and simulation predicted that weight-based dosing of HUMIRA in pediatric patients 12 years of age and older can provide generally similar exposure to adult HS patients. The course of HS is sufficiently similar in adult and adolescent patients to allow extrapolation of data from adult to adolescent patients. The recommended dose in pediatric patients 12 years of age or older is based on body weight.

The use of HUMIRA has not been established in patients less than 12 years of age with HS.

Geriatric Use

A total of 519 RA patients 65 years of age and older, including 107 patients 75 years of age and older, received HUMIRA in clinical studies RA-I through IV. No overall difference in effectiveness was observed between these patients and younger patients. The frequency of serious infection and malignancy among HUMIRA treated patients over 65 years of age was higher than for those under 65 years of age. Because there is a higher incidence of infections and malignancies in the elderly population, use caution when treating the elderly.

OVERDOSAGE

Doses up to 10 mg/kg have been administered to patients in clinical trials without evidence of dose-limiting toxicities. In case of overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions or effects and appropriate symptomatic treatment instituted immediately.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies of HUMIRA have not been conducted to evaluate the carcinogenic potential or its effect on fertility.

PATIENT COUNSELING INFORMATION

Patient Counseling

Provide the HUMIRA "Medication Guide" to patients or their caregivers, and provide them an opportunity to read it and ask questions prior to initiation of therapy and prior to each time the prescription is renewed. If patients develop signs and symptoms of infection, instruct them to seek medical evaluation immediately.

Advise patients of the potential benefits and risks of HUMIRA.

- **Infections**
  Inform patients that HUMIRA may lower the ability of their immune system to fight infections. Instruct patients of the importance of contacting their doctor if they develop any symptoms of infection, including tuberculosis, invasive fungal infections, and reactivation of hepatitis B virus infections.
- **Malignancies**
  Counsel patients about the risk of malignancies while receiving HUMIRA.
- **Allergic Reactions**
  Advise patients to seek immediate medical attention if they experience any symptoms of severe allergic reactions. Advise latex-sensitive patients that the needle cap of the HUMIRA 40 mg/0.8 mL Pen and 40 mg/0.8 mL, 20 mg/0.4 mL and 10 mg/0.2 mL prefilled syringe may contain natural rubber latex.
- **Other Medical Conditions**
  Advise patients to report any signs of new or worsening medical conditions such as congestive heart failure, neurological disease, autoimmune disorders, or cytopenias. Advise patients to report any symptoms suggestive of a cytopenia such as bruising, bleeding, or persistent fever.

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Ref: 03-B819/20029585 Revised December, 2018

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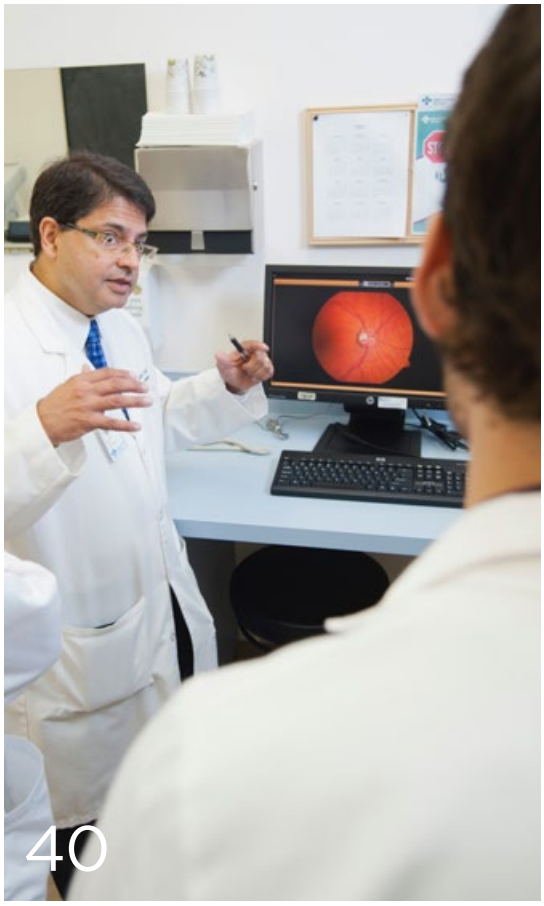

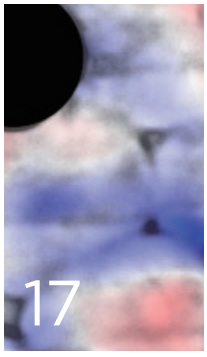

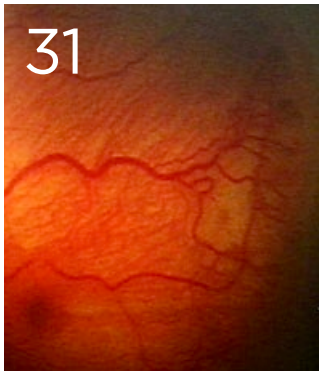

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MARCH 2019
VOLUME 23 • NUMBER 3

AMERICAN ACADEMY OF OPHTHALMOLOGY®

EyeNet*® *Magazine (ISSN 1097-2986) is published monthly by the American Academy of Ophthalmology, 655 Beach St., San Francisco, CA 94109-1336, as a membership service. Subscription is included in U.S. members' annual dues. International Member, IMIT, $135 per year. Nonmember in U.S., $150 per year. Nonmember outside U.S., $210 per year. Periodicals Postage Paid at San Francisco, CA, and at additional mailing offices. POSTMASTER: Send address changes to *EyeNet*, P.O. Box 7424, San Francisco, CA 94120-7424.

COVER PHOTOGRAPH

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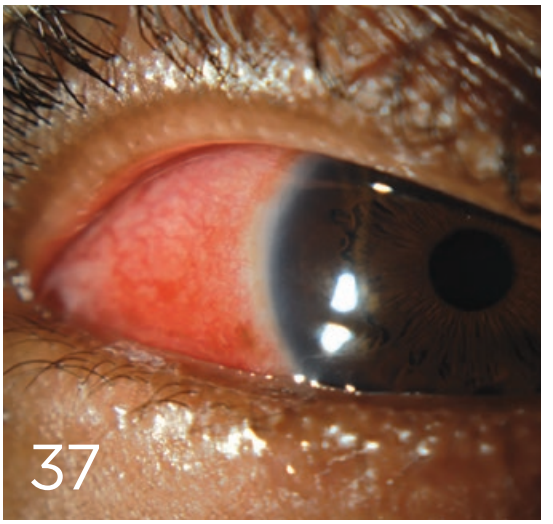

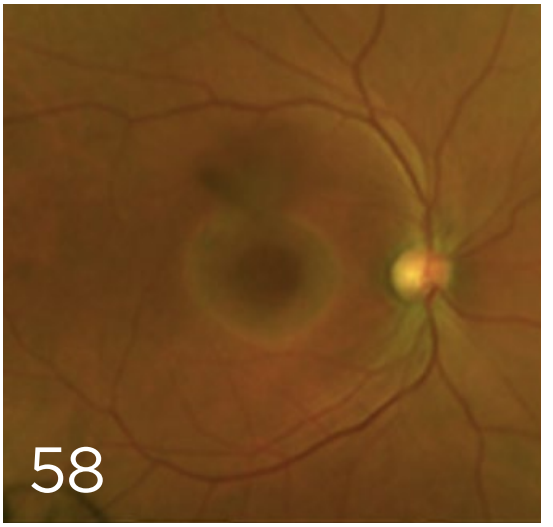

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References
1. Alcon Data on File (Jul 2016). 2. AcrySof® IQ ReSTOR® +2.5 D Multifocal Toric IOL Directions for Use. 3. Vega F, Alba-Bueno F, Millán MS, Varon C, Gil MA, Buil JA. Halo and through-focus performance of four diffractive multifocal intraocular lenses. *Invest Ophthalmol Vis Sci.* 2015;56(6):3967-3975 (study conducted with corneal model eye with 0.28µ spherical aberration). 4. Wirtitsch MG, Findl O, Menapace R, et al. Effect of haptic design on change in axial lens position after cataract surgery. *J Cataract Refract Surg*. 2004;30(1):45-51 5. Visser N, Bauer NJ, Nuijts RM. Toric intraocular lenses: historical overview, patient selection, IOL calculation, surgical techniques, clinical outcomes, and complications. *J Cataract Refract Surg*. 2013;39(4):624-637. 6. Potvin R, Kramer BA, Hardten DR, Berdahl JP. Toric intraocular lens orientation and residual refractive astigmatism: an analysis. *Clin Ophthalmol*. 2016;10;1829-1836.

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Opinion

RUTH D. WILLIAMS, MD

What Is Patient-Centered Care?

Isn't all ophthalmic care patient-centered? Isn't the outcome for an individual patient the whole point of what we do every day? The array of acronyms—including PREM (patient-reported experience measures), PROM (patient-reported outcome measures), PRO (patient-reported outcomes), and SDM (shared decision-making)—can add a sense of confusion around what ophthalmologists have done well for decades.

The emerging buzz about patient-centered care and outcomes seems like a lot of fuss about the obvious. Anne Coleman, MD, the Academy's President-Elect and former Secretary for Quality of Care, suggested that we take a step back, noting that these efforts reflect attempts "to measure what we're already doing."

Evidence-based medicine incorporates the best evidence in making decisions about the care of individual patients. Much of our evidence has been developed through randomized clinical trials. But as we develop research instruments, we sometimes measure things that matter more to the ophthalmologist than to the patient. Patient-centered outcomes are an attempt to measure what's important to the patient, and these priorities can be difficult to quantify.

Patient-centered outcomes research has been around for a long time. In 1999, the Collaborative Initial Glaucoma Treatment Study was the first randomized clinical trial in glaucoma to use PROMs. Now, regulatory science is developing many sophisticated instruments for evaluating patient experience. This seems especially relevant for ophthalmology, which is all about preserving and enhancing a sensory function. PROWL (patient-reported outcomes with LASIK) was developed by the FDA, NEI, and Department of Defense and was validated as a tool to measure what the patient experiences before and after LASIK. The Academy is working with the FDA to develop a PROM for evaluating novel IOLs, and the American Glaucoma Society is working with the FDA to develop a PROM for evaluating the patient experience with minimally invasive glaucoma surgery devices.

PROMs are created by convening focus groups of patients and determining what is important to them in their own words. Flora Lum, MD, the Academy's Vice President for Quality and Data Science, said, "We want to do what makes a difference for patients from their perspective. It has to be in their language." For this reason, focus groups need to be established for each patient population. It's difficult to communicate a visual experience with words. As Anne pointed out, "what one person means by glare might be very different than what another person means." Letting patients put things into their own words without input from the ophthalmologist is important.

Ruth D. Williams, MD
Chief Medical Editor, EyeNet

Patient-centered care is a corollary to patient-centered outcomes. Perhaps previous generations of patients were comfortable when the physician made decisions and dispensed directions. Today, we are expected to be diligent about sharing evidence when it's available. Shared decision-making is a collaborative model for engaging patients in health care decisions, especially when there are multiple treatment options without one obviously superior choice.

In 1996, when HIPAA was introduced, it seemed cumbersome to implement a law around something we already did well. Yet HIPAA has been important on many levels, as it holds all of us to a high and verifiable standard of privacy. Similarly, creating reasonable standards and validated tools for measuring what we do might also increase our awareness of the patient perspective. Requiring PROMs in clinical trials certainly refocuses research on what the patient wants and not merely on the evidence that we imagine is most important.

Now, we must integrate the individual patient experience with evidence-based medicine and outcomes. Even as we are trying to save money and time, we are developing expensive instruments for measuring patient experience and emphasizing shared decision-making, which is a time-consuming process. It's a tricky tightrope to walk.

Current Perspective

DAVID W. PARKE II, MD

EyeWiki, Do You Wiki?

One of the Academy's most popular educational resources almost didn't happen.

Academy educational tools, whether the *Basic and Clinical Science Course (BCSC), Focal Points, EyeNet*, or the ONE Network, go through a rigorous editorial process. This results in a high level of member trust in the accuracy and integrity of the Academy products. In 2009 Academy educational leaders noted the success of a new learning tool that violated the core principle of this process—the wiki.

A wiki is a website on which users collaboratively post and modify articles from within the web browser itself. Once the articles are initially written, registered visitors can make changes, contributions, or corrections. Wikis first emerged in 1995 after computer programmer Ward Cunningham posted his software WikiWikiWeb. ("Wiki" is Hawaiian for "quick.")

Mr. Cunningham is also reputed to have made the statement, "The best way to get the right answer on the internet is not to ask a question; it's to post the wrong answer." Although he denies the attribution, it's now known as Cunningham's Law.

The strength of a wiki is also one of its weaknesses; it is a living document that is posted without initial editorial review. But with a sufficiently committed web community, any errors or omissions are rapidly remediated.

The question was, "Should the Academy embrace an educational process that ignored rigorous editing and instead depended on the ophthalmic community for content development after posting?" In June 2009 the Academy Board of Trustees, intrigued by a wiki's potential, approved its development as a free, public online repository of knowledge that would cover the spectrum of eye disorders. Authorship would be limited to ophthalmologists or ophthalmologists-in-training, and a committee of ophthalmologists would be tasked with reviewing articles after they were posted and contribute to them as needed to ensure content quality.

EyeWiki launched in July 2010 with Drs. Aaron Miller and Brad Feldman as the original editor-in-chief and deputy editor-in-chief. (The current editors-in-chief are Drs. Marcus Marcet and Penny Asbell.) Shortly afterward the new EyeWiki had nearly 100 articles covering a spectrum of common clinical topics in ophthalmology.

Where is EyeWiki now? As of Feb. 1, 2019, EyeWiki has 818 user-contributed articles and 70 active volunteer content reviewers. In 2018 there were 7.2 million page views by 3.1 million visitors. Of these, 62%, are from outside the United States and 52% access Eye Wiki from a mobile device. It is the most popular single web-based educational resource in the Academy's armamentarium! As I was writing this column on Feb. 5, I typed "glaucoma" into my search engine, and the first nonadvertising site listed was EyeWiki.

David W. Parke II, MD
Academy CEO

A total of 1,526 ophthalmologists and ophthalmologists-in-training have contributed content to the site. The majority, 65%, come from the United States, 12% are from the Asia Pacific region, 9% are from Europe, and 7% each are from Latin America and the Middle East/Africa. Once a page exists on EyeWiki, anyone with an author account can edit and contribute to it. Volunteer ophthalmologist editors review all content on the site every six months.

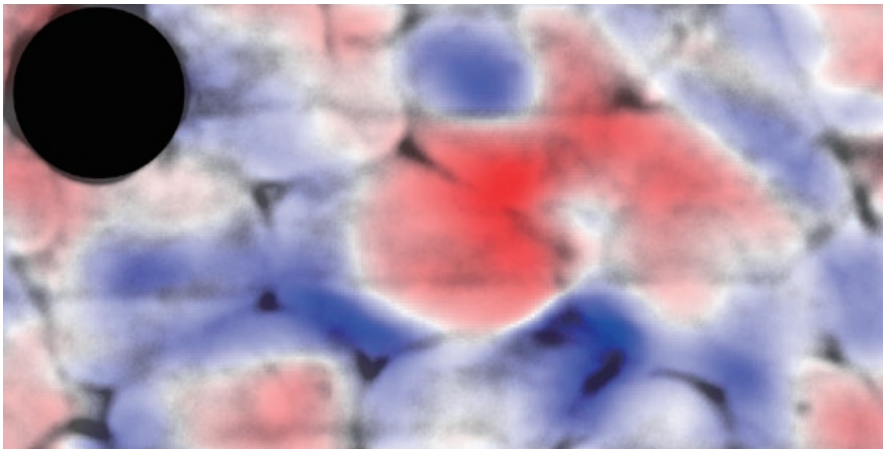
EyeWiki supports U.S residents and fellows, and international contributors. Each year it sponsors contests for the best new EyeWiki entries from these groups; since 2011, it has sent 30 U.S. winners to the Mid-Year Forum (all expenses paid) and has awarded free ebook subscriptions to the *BCSC* and *Focal Points* to international winners.

What are the hottest EyeWiki topics as searched by readers? Herpes zoster ophthalmicus, bacterial conjunctivitis, and hypertensive retinopathy. But it's not just common entities. Also, in the Top 20 are dacryocystorhinostomy, Horner's syndrome, and glaucomatocyclitic crisis!

So, if you've never been there before, I encourage you to visit http://eyewiki.org. See why millions of people visit it annually, and (if you've got a favorite topic) go to the "Getting Started Page," type in the topic, hit "Create," and become an author!

IMAGING

Watching Nerve Cells Deform as They Fire



IN VITRO. *Color overlay of firing nerve cells shows membrane deformation at the peak of the action potential. (Gray = nerve cells; red = movement toward viewer; blue = movement away from viewer; black dot = opaque electrode.)*

Palanker Laboratory, Stanford University

CALIFORNIA SCIENTISTS HAVE DEVEL-oped a noninvasive method to detect nanometer-scale changes in the shape of human nerve cells as they fire, a development that could someday enable ophthalmic researchers to assess and quantify the eye's neural functioning at the cellular level.

Using an interferometric microscope and a high-speed camera that imaged in vitro cells at up to 50,000 frames per second, the researchers assembled videos showing the membranes rounding slightly as they fired, then returning to normal.[1]

The genetically altered human cell line used in their experiments, called HEK-293, was chosen because it has regular, spontaneous electrical spikes. To separate the minuscule deformations from noise in the data, the scientists combined 50 frames at a time, averaged each pixel to strengthen the signal, and then used a self-reinforcing algorithm to boost the signal further.

In this way, they determined that the cells' outer dimensions changed by between 1 and 3 nm, fluctuating as the action potentials propagated across the cells. These surrogate optical measurements of electrical activity corresponded precisely to the signals detected conventionally with electrodes placed near the cells.

"This nanometer-scale shape change is very difficult to see—but with ultrafast quantitative phase imaging, it actually turns out to be visible," said Daniel Palanker, PhD, who led the investigation.

Advantage: noninvasive. The technique's major potential advantage compared to existing methods of measuring in vivo neuronal activity in the eye is that it is noncontact and noninvasive, said study coauthor Kevin C. Boyle, MS, a PhD student in Dr. Palanker's laboratory at Stanford University in Palo Alto, California.

"Nothing needs to be added to the cells—no fluorescent dyes, no optogenetic viruses, no markers, no additional preparation. It's all done optically," Mr. Boyle said. "It's also high throughput. You're getting much more information about what's happening across an individual cell and also across multiple cells in a field of view."

Deformation of nerve cells when they fire was first described decades ago, based on observations of large nerves from crustaceans, he said. "But no one has been able to see the real thing in mammalian cells because the deformations are much smaller," Mr. Boyle said.

But why do the membranes deform at all? "Based on our current hypothesis, which is from a model developed by others who have studied this effect, we believe that when the action potential happens the electrical potential generated across the cell membrane changes the membrane tension. This change tends to minimize the surface area of the cell membrane, causing the cell to become more spherical during the action potential," he said.

Ultimate goal. The NEI views better imaging as essential for the advancement of regenerative therapies for retinal diseases, and it is funding five such projects through its Audacious Goals Initiative. This new technique, along with adaptive optics and optical coherence tomography, may eventually be used to build a device to noninvasively assess the electrical activity of the optic nerve and retinal cells.

—Linda Roach

1 Ling T et al. *Light Sci Appl.* 2018;7:107.

Relevant financial disclosures—Mr. Boyle and Dr. Palanker: None.

DRUG SAFETY

Fungal Outbreak Posed Difficult Treatment Issues

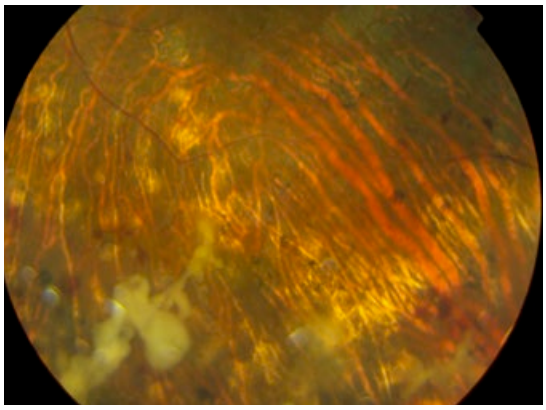
SEVEN YEARS AFTER AN OUTBREAK of fungal endophthalmitis from contaminated triamcinolone, ophthalmologists whose patients were infected have reached some sobering conclusions about the difficulties of treating such cases.

In 2012, 30 eyes nationwide were infected with a plant fungus, *Bipolaris hawaiiensis,* from intravitreal injections of contaminated triamcinolone.[1,2] The drug had been compounded by the now-defunct Franck's Compounding Pharmacy in Ocala, Florida.

Five-year outcomes. Ophthalmologists who treated 23 of these patients (25 eyes) in Los Angeles and New York City have now reported their five-year follow-up outcomes.[3]

Treatment challenges. The outbreak started as an acute crisis but evolved into a chronic, puzzling management problem, the retrospective chart review revealed. For example:

- Some infections presented as late as 10 months postinjection.
- Despite appearing sterile after treatment, eyes that were enucleated still had hyphae present. (Because the organism is difficult to culture, the hyphae's viability could not be determined, the authors reported.)
- Intravitreal antifungal injections, vitreous tap, and pars plana vitrectomy did not resolve the infections. Nor did a standard, on-label systemic regimen for treating fungal infections (200 mg oral voriconazole twice a day for six weeks). "With all the patients, as soon as the oral voriconazole was stopped after six



PRESENTATION. *This patient's visual acuity was 20/50 at onset of fungal endophthalmitis. He eventually underwent enucleation.*

GLAUCOMA

Asymmetric Pattern of VF Loss Found in POAG

RESEARCHERS WHO PREVIOUSLY FOUND THAT PRIMARY open-angle glaucoma (POAG) and primary angle-closure glaucoma (PACG) have different patterns of visual field damage[1] now report yet another difference between the two glaucomas. An asymmetric rate of visual field (VF) loss seems to be a feature of eyes with POAG—but not those eyes with PACG.[2]

"This difference further promotes our understanding of mechanisms of visual field loss underlying both glaucoma types," said Ryo Asaoka, MD, at the University of Tokyo in Japan.

Study goal. The researchers set out to determine and compare global, region-wise, and point-wise rates of VF loss in POAG and PACG eyes, with the goal of identifying whether POAG and PACG eyes progress at different rates and/or with different patterns.

To do so, they reviewed the medical records of 282 patients (440 eyes) with POAG and 49 patients (79 eyes) with PACG who were treated at two university hospitals in Japan between 1998 and 2016. All had at least six reliable visual field tests with Humphrey Field Analyzer II. Glaucoma was the only disease that caused VF damage.

Asymmetric findings. In POAG, the rate of VF loss was faster in the superior hemifield compared to the inferior hemifield, particularly in the central, paracentral, and peripheral arcuate 2 regions. This asymmetry was not observed in PACG eyes. "This was not necessarily surprising because we already knew there were considerably different patterns in visual field damage between POAG and PACG," Dr. Asaoka commented.

In a separate finding, PACG eyes had a consistently faster global rate of VF loss compared to POAG eyes; however, this difference was not statistically significant.

Questions remain. Dr. Asaoka wants to better understand the disease mechanisms related to VF loss and how they might differ between POAG and PACG eyes.

For example, VF loss in PACG appears to be purely due to an elevated IOP, he said, whereas loss in POAG is more complex. Another possible contributing factor is corneal hysteresis; this "is very closely associated with the progression of glaucoma in POAG," he said. In a separate study, Dr. Asaoka and his colleagues confirmed that concept in a Japanese population with a very high prevalence of normal-tension glaucoma,[3] and they plan to continue to look at these contributing factors, he said.

In the clinic. Dr. Asaoka advised clinicians to consider that superior VF is likely to progress faster in POAG, whereas both superior and inferior hemifields can progress relatively quickly in PACG. *—Miriam Karmel*

1 Yousefi S et al. *Invest Ophthalmol Vis Sci.* 2018;59(3):1279-1287.
2 Yousefi S et al. *Invest Ophthalmol Vis Sci.* 2018;59(15):5717-5725.
3 Matsuura M et al. *Sci Rep.* 2017;7:40798.

Relevant financial disclosures—Dr. Asaoka: None.

weeks, the infection came back with a vengeance," said lead author Kent W. Small, MD, who practices in Los Angeles and Glendale, California.

- Patients required prolonged systemic off-label, high-dose treatment with oral voriconazole (300 mg twice daily for six to 12 months) to eliminate clinical signs of infection.
- Despite apparently successful treatment, some of the eyes continued to deteriorate, most frequently from hypotony. Only eight of the 25 eyes had final visual acuity (VA) of 20/50 or better. Five eyes had to be enucleated, and the VA in an additional five eyes was light perception or no light perception.

Need for prompt communication. In addition to such clinical lessons, the endophthalmitis outbreak was an example of the importance of the need for meticulous oversight of compounding (and other) pharmacies as well as the importance of professional transparency among ophthalmologists when an outbreak occurs, Dr. Small said.

In Dr. Small's own practice, 17 eyes were infected with *B. hawaiiensis*. "No practice—private, academic, or governmental—is immune to receiving contaminated medication from any pharmacy. But when this sort of incident happens, a feeling of isolation is overwhelming because you realize you are on your own in unchartered waters," Dr. Small said. After his initial feelings of dismay and embarassment, he said, "I soon realized I did nothing wrong. There is nothing I could have done differently to have prevented this."

He concluded, "The ophthalmic community needs to know about these kinds of incidents. We need to alert each other and learn from each other how to handle them." *—Linda Roach*

1 Mikosz CA et al., and the Fungal Endophthalmitis Outbreak Response Team. *Emerg Infect Dis.* 2014;20(2):248-256.

2 MMWR *Morb Mortal Wkly Rep.* 2012;61(17):310-311.

3 Small KW et al. *Ophthalmol Retina.* 2019;3(2):133-139.

Relevant financial disclosures—Dr. Small: None.

RETINA

After Anti-VEGF: When Patients Don't Return

RESEARCHERS AT WILLS EYE HOSPITAL have added to their growing body of evidence that too many patients are lost to follow-up after receiving an anti-VEGF injection.

In their most recent study of nonadherence, one-fourth of patients with nonproliferative diabetic retinopathy (DR) and diabetic macular edema (DME) did not return for follow-up within 12 months after receiving an injection.[1] Hispanics, lower income patients, and those with poorer baseline vision were among those most likely to be lost to follow-up.

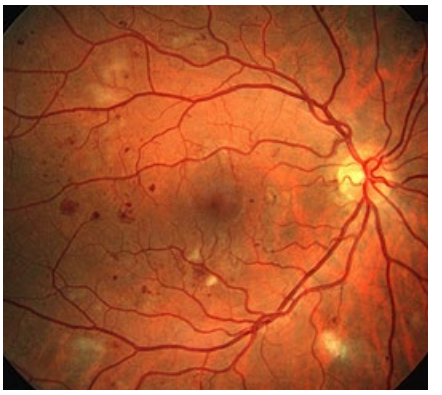
Recalcitrant problem. This finding was consistent with the group's previous studies of patients receiving anti-VEGF injections for wet AMD, retinal vein occlusion, and proliferative DR.[2]

"Almost across the board, with all diagnoses we have looked at, about a quarter of patients are lost to follow-up immediately after receiving an anti-VEGF injection," said Jason Hsu, MD, at Wills Eye Hospital in Philadelphia. "Given the importance of ongoing therapy to prevent vision loss, these real-world findings are of significant concern."

Parsing risk factors. In this retrospective cohort study, 1,632 patients received a total of 10,884 anti-VEGF injections over 15,803 clinical visits. Of these patients, 355 had no further visits for more than 12 months after the last injection.

The researchers also found the following:

- By self-identified racial group, 35% of Hispanic patients were lost to follow-up, followed by 30.6% of Asian patients, 29.1% of black patients, and 21.3% of white patients.
- Patients living in zip codes with lower-than-average adjusted gross income were more likely to miss the next appointment. For instance, 32.4% of those in a low-income zip code (defined as less than $50,000 per year) were lost to follow-up. In contrast, 18.4% of those in a higher-income zip code (defined as more than $75,000 per year) did not return for treatment.
- Decreasing baseline vision also was significantly associated with risk of nonadherence. In a subgroup of the 923 DME patients, the lowest rate of attrition (12.4%) was found in those with a baseline VA that was 20/50 or better; the highest rate of attrition (32.5%) occurred in those with a baseline VA of 20/80 or worse.
- The patient's stage of nonproliferative DR did not significantly predict the risk of loss to follow-up or interact with other factors.



***NONCOMPLIANCE**. Approximately 1 in 4 patients with nonproliferative DR (shown here) and macular edema had no follow-up visit for at least a year postinjection.*

Clinical implications. Dr. Hsu urged physicians to track patients carefully. He also suggested making phone calls or sending letters to encourage patients to return for care. "I worry that many patients with preventable vision loss are losing their sight as a result of nonadherence with follow-up." (See also page 22.) *—Miriam Karmel*

1 Gao X et al. *Ophthalmol Retina.* 2019;3(3):230-236.

2 Obeid A et al. *Ophthalmology.* Published online Aug. 2, 2018.

Relevant financial disclosures—Dr. Hsu: Genentech/Roche: S.

See the financial disclosure key, page 13. **For full disclosures,** including category descriptions, view this News in Review at aao.org/eyenet.

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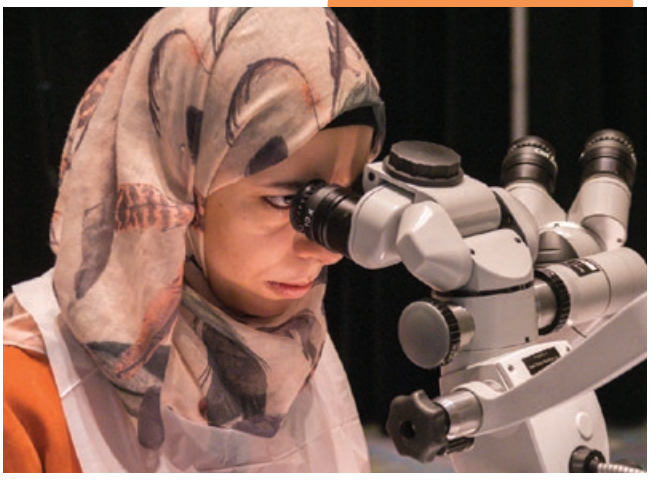

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Journal Highlights

NEW FINDINGS FROM THE PEER-REVIEWED LITERATURE

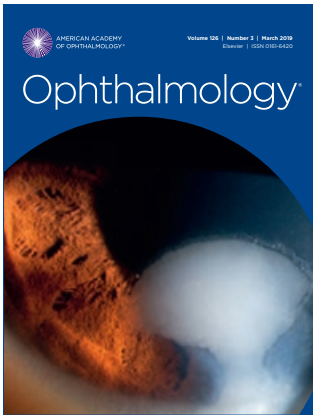
Ophthalmology

Selected by Stephen D. McLeod, MD

Dig Rush Binocular Game for Children With Amblyopia

March 2019

Studies of binocular games in children with amblyopia have been hampered by noncompliance, perhaps due to the mundane nature of the games. **Holmes et al.** prescribed treatment with the dichoptic binocular Dig Rush game, which appeared engaging in a pilot study. They also compared visual outcomes between amblyopic children who played the Dig Rush game and those who continued with spectacle correction only. They found that the game did not result in better visual acuity (VA) or stereoacuity within four or eight weeks of treatment.



This multicenter randomized study included 138 children between the ages of 7 and 12 with amblyopia (resulting from strabismus, anisometropia, or both). Participants were required to have at least 16 weeks of optical treatment in spectacles, if needed, or to exhibit no improvement in the VA of the amblyopic eye for at least eight weeks leading up to enrollment.

The children were assigned randomly either to receive eight weeks of treatment with the game and, if needed, spectacle wear (n = 69) or to continue with spectacle correction alone (n = 69). The game, which was played on an iPad, was prescribed for one hour each day, five days per week.

The main outcome measure was VA change in the amblyopic eye from baseline through week 4, assessed by a masked examiner. Secondary outcomes included changes from baseline through eight weeks.

By the four-week mark, the mean VA letter score of amblyopic eyes had improved by 1.3 with binocular game treatment and by 1.7 with spectacle correction alone. After adjusting for baseline VA, the difference in letter score between the groups (binocular minus control) was –0.3. After eight weeks of treatment, there was no difference in letter scores. Among the binocular group, adherence data obtained from the iPad indicated that just over half of the participants completed more than 75% of prescribed treatment (58% for four weeks; 56% for eight weeks).

Although the authors found no VA benefit from the binocular game, there is evidence that such treatment may help some younger children, particularly those who have not been treated previously. The issue is being evaluated in an ongoing study of children between the ages of 4 and 6.

Uncorrected Myopia's Impact on Productivity

March 2019

Naidoo et al. aimed to estimate the loss of productivity associated with the global burden of myopia. They found that, even by conservative estimation, the potential loss in productivity linked to uncorrected myopia outweighs the cost of correction.

For their study, the authors performed a systematic review and meta-analysis to estimate the number of people with myopia and myopic macular degeneration (MMD), stratified by visual acuity thresholds. The percentages of myopes who had spectacle correction were compared with country-level variables for the year of data collection (2015). Variation in spectacle correction was represented by a model based on the human development index, with adjustment for age and urbanization.

The authors combined data for spectacle correction with myopia data, from which they estimated the number of people with each predefined visual-impairment level of uncorrected myopia (from mild myopia to blindness). They applied disability weights, employment rates, labor-force participation rates, and gross domestic product per capita to estimate the degree of productivity loss among individuals with each level and type of myopia-related visual impairment in 2015, expressed in U.S. dollars.

Their analyses showed that adequate correction of myopia is less common for older people who live in rural areas

of less-developed countries. In 2015, the estimated global productivity loss associated with visual impairment was $244 billion for uncorrected myopia (95% confidence interval [CI], $49 billion to $697 billion) and $6 billion for MMD (95% CI, $2 billion to $17 billion). The regions with the greatest burden as a proportion of their economic activity were Southeast Asia, South Asia, and East Asia. The region with the greatest absolute burden was East Asia.

Understanding the economic burden of uncorrected visual impairment is crucial for addressing public health problems such as myopia. The authors emphasized that the productivity effects of myopia should be considered in a broader framework by policymakers. Findings of their study highlight the economic value of interventions.

When Diabetic Eyes Are Lost to Follow-Up

March 2019

Although panretinal photocoagulation (PRP) greatly reduces the risk of severe vision loss from proliferative diabetic retinopathy (PDR), it has side effects that might be avoided by using anti-VEGF treatment. Studies of intravitreal injection of anti-VEGF agents have shown that this treatment produces similar (and possibly superior) outcomes, but strict adherence to the follow-up schedule is crucial. Little information exists on eyes that are lost to follow-up after either treatment. **Obeid et al.** compared anatomic and functional outcomes for eyes with PDR that were lost to follow-up for more than six months after treatment. They observed better outcomes for eyes treated with PRP than for those that received anti-VEGF injections.

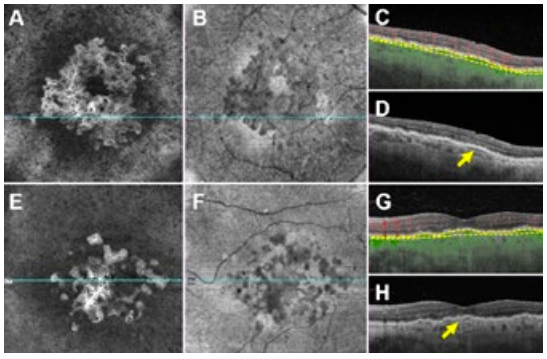
For their study, the authors identified 59 patients (76 eyes) who were lost to follow-up immediately after treatment and returned more than six months later. Documented data included visual acuity (VA) and anatomic outcomes at the last visit before the patients were lost to follow-up, at their return visit, six months later, 12 months later, and at the final visit. The authors compared outcomes for the treatments, including functional changes that occurred between visits.

Of the 76 treated eyes, 46 underwent PRP, and 30 received anti-VEGF treatment. Results were as follows:

- In the PRP group, mean VA worsened significantly between the last visit before patients were lost to follow-up and when they returned (0.42 ± 0.34 vs. 0.62 ± 0.64 logMAR; p = .03). However, the difference in mean VA from the visit before being lost to follow-up to the final visit was not significant (0.46 ± 0.47 logMAR; p = .38).
- For the anti-VEGF group, the decline in mean VA was significant from the visit before being lost to follow-up to the return visit (0.43 ± 0.38 vs. 0.97 ± 0.80 logMAR; p = .001) and to the final visit (0.92 ± 0.94 logMAR; p = .01).
- At the final visit, the incidence of tractional retinal detachment and of iris neovascularization was higher in the anti-VEGF group. Four anti-VEGF eyes experienced iris neovascularization, and 10 experienced retinal detachment—versus none and one, respectively, of the PRP eyes.

These findings suggest that when patients are lost to follow-up, anatomic outcomes are better for PRP than for anti-VEGF treatment. Although the difference in functional outcomes also appears to favor PRP, the study lacked randomization. The authors recommend considering the sequelae related to follow-up noncompliance when selecting a treatment for PDR. They encourage studies of noncompliance predictors, which may help guide personalized treatment strategies. *(Also see related commentary by Andrew P. Schachat, MD, in the same issue. For another study on this topic, see page 19.)*

—Summaries by Lynda Seminara



AGREEMENT. *Graders agreed on the presence of the double-layer sign (yellow arrows) in these two eyes with iAMD and MNV. En face angiographic (A, E) and structural (B, F) images show the CNV pattern. Structural B-scans through the MNV (C, G) are color-coded for flow (red = retinal microvasculature; green = flow under the retinal pigment epithelium [RPE]). The yellow dashed lines represent the slab boundaries from the RPE to Bruch membrane.*

Ophthalmology Retina

Selected by Andrew P. Schachat, MD

Using the Double-Layer Sign to Predict Subclinical Macular Neovascularization

March 2019

Can the double-layer sign on optical coherence tomography (OCT) images be used to predict the presence of subclinical macular neovascularization (MNV) in cases of dry age-related macular degeneration (AMD)? **Shi et al.** found that the sign on OCT B-scans was associated with subclinical type 1 MNV and can be used to identify these lesions with good predictive values.

For this prospective observational study, the researchers evaluated 100 eyes from 94 patients. Of these, 64 eyes had intermediate AMD (iAMD) and 36 eyes had late AMD. Thirty-three eyes had subclinical MNV (20 of the 64 eyes with iAMD and 13 of the 36 eyes with late AMD). All eyes were initially scanned with swept-source OCT angiography (SS-OCTA), using a 6 × 6 mm scan pattern centered on the fovea. All eyes included in the study had no evidence of exudation. Eyes with geographic atrophy (GA) that was not fully contained within the scan area were excluded.

Two groups of graders—including junior graders who had no prior knowledge of the cases—evaluated the B-scans for the presence of the double-layer sign. The senior and junior graders

agreed on the presence of a double-layer sign in 24 of the 33 eyes with subclinical MNV and on the absence of the sign in 52 of the 67 eyes without subclinical MNV. For junior graders, the sensitivity, specificity, positive predictive value, and negative predictive value were 73%, 84%, 69%, and 86%, respectively; and for the senior grader, 88%, 87%, 76%, and 94%, respectively. The two gradings also showed that the double-layer sign was a better predictor of subclinical MNV in eyes with drusen than in eyes with GA.

The authors note that the development of a machine-learning algorithm to identify subclinical MNV based on structural OCT is under way. This would be of particular benefit to clinical practices that do not have SS-OCTA capabilities. —*Summary by Jean Shaw*

American Journal of Ophthalmology

Selected by Richard K. Parrish II, MD

Glaucoma Study Results and Masked Adjudication of Endpoints

March 2019

The commingling of glaucomatous and nonglaucomatous endpoints in clinical trials can lead to overestimation of glaucoma incidence or progression, underestimation of treatment effect, or reduction in statistical power. The FDA and the European Medicines Agency recommend centralized adjudication if treatment assignment is unmasked or if endpoints are subjective or involve complex definitions. **Gordon et al.** evaluated the effect of a masked Endpoint Committee on estimates of the incidence of primary open-angle glaucoma (POAG), treatment efficacy, and statistical power in the Ocular Hypertension Treatment Study–Phase 1, an unmasked randomized trial of the safety and efficacy of ocular hypotensive medication for preventing or delaying POAG onset. Their new research showed that masked adjudication of endpoints improved POAG incidence estimates, increased statistical power, and increased the calculated treatment effect by 23%.

The Endpoint Committee comprised three practicing clinicians who decided independently whether an endpoint was "most probably due to POAG" or "most probably not due to POAG." For optic disc deterioration, each member specified whether the change was clinically significant. The Committee reviewed 267 first endpoints from 1,636 participants and attributed 155 (58%) of them to POAG. The incidence of all-cause endpoints versus POAG endpoints was 19.5% versus 13.2% (respectively) for the observation group and 13.1% versus 5.8% (respectively) for the medication group. Treatment effect for all-cause endpoints was a 33% reduction in risk (relative risk, 0.67) and a 56% reduction in risk for POAG endpoints (relative risk, 0.44). Post-hoc statistical power for detecting treatment effect was 0.94 for all-cause endpoints and 0.99 for POAG endpoints.

The authors advocate endpoint adjudication for clinical trials in which common ocular or systemic comorbidities could compromise the results. Given the strong treatment effect in this trial, the increased power was not crucial. However, it could be important in studies of interventions that have less robust effects.

Kalman Filtering Can Forecast NTG Disease Trajectory

March 2019

Unlike most types of open-angle glaucoma, normal-tension glaucoma (NTG) often includes dense visual field (VF) loss, which may occur close to central fixation and early in the disease. Because common activities such as reading and driving can be difficult for patients with central or paracentral VF loss, it would help to personalize the forecasting of disease trajectory, allowing identification of patients at high risk for progression before the damage occurs. The Kalman filtering (KF) algorithm, which has been used for decades by the aerospace industry to guide planes and shuttles, recently has been applied to the trajectory of chronic diseases. The KF model accounts for underlying disease dynamics among patient populations, as well as unique patient-specific characteristics. Personalized forecasts are derived, which can be updated whenever the patient has additional testing. **Garcia et al.** previously tested the model in patients with high-tension open-angle glaucoma and found it effective in forecasting disease progression. In a new study, they established its utility for patients with NTG.

Initially, the authors validated a KF model, named KF-NTG, to forecast mean deviation (MD) and other parameters. The algorithm was used for 263 eyes (263 Japanese patients) with NTG. The proportion of patients with MD forecasts within 0.5, 1.0, and 2.5 dB of the actual values was determined, and the root mean squared error (RMSE) was calculated for each forecast. Results of KF-NTG were compared with those of the KF model used for patients with high-tension OAG. Of this group, 242 eyes had enough data to forecast two years into the future.

Twenty-four months in advance, KF-NTG was able to forecast MD values that fell within 0.5, 1.0, or 2.5 dB of actual values for 78 eyes (32.2%), 122 eyes (50.4%), and 211 eyes (87.2%), respectively. The percentage of eyes with forecasted MD values within 2.5 dB of actual values (87.2%) was similar to that with the model for high-tension OAG (86.0%) and with the null model (86.4%), and much better than data from two linear regression models (72.7%-74.0%). KF-NTG achieved a lower RMSE than the other models in this study, denoting the superiority of its performance.

These findings suggest that KF holds promise for personalizing disease trajectory forecasts. The authors continue to refine their KF models by incorporating additional variables and validation studies.

—*Summaries by Lynda Seminara*

JAMA Ophthalmology

Selected and reviewed by Neil M. Bressler, MD, and Deputy Editors

Endothelial Cell Loss: Donor, Recipient, and Operative Factors

February 2019

For the Cornea Preservation Time Study (CPTS), researchers looked at the effect

of donor preservation time (PT) on graft survival and endothelial cell loss after Descemet stripping automated endothelial keratoplasty (DSAEK). Results showed a small difference in endothelial cell loss at 3 years. In a secondary analysis of data from this prospective trial, **Lass et al.** found that donor diabetes, recipient diagnosis of pseudophakic/aphakic corneal edema (PACE), lower screening endothelial cell density, and operative complications were associated with lower endothelial cell density three years after DSAEK, potentially affecting long-term graft success.

In CPTS, 1,330 eyes (1,090 participants; median age, 70 years) underwent DSAEK for Fuchs dystrophy or PACE. Of these, 913 eyes (749 patients) with a functioning graft and analyzable preoperative and endothelial images at the three-year mark were included in the secondary analysis. Preoperative endothelial cell density was used as the baseline. Recipient and donor characteristics were similar to those of the full CPTS population.

In the final multivariable model, the following factors were associated with lower endothelial cell density at three years: donors with diabetes (−103 cells/mm^2), lower screening endothelial cell density (−234 per 500 cells/mm^2), PACE diagnosis (−257 cells/mm^2), and operative complications (−324 cells/mm^2). Mean endothelial cell loss from baseline to year 3 was 47% in participants with tissue from donors with diabetes versus 43% without; 53% in recipients with PACE versus 44% with Fuchs dystrophy; and 55% with surgical complications versus 44% without.

Among the factors linked to lower endothelial cell density in this study, surgical complications are the most modifiable.

The authors urged additional study of the effects of diabetes on long-term DSAEK outcome, coupled with improved characterization of diabetes in donors and recipients by means of multiple methodologies. Although findings of this study do not prove causation, they may help to optimize donor selection, minimize surgical trauma, and improve outcomes.

Effects of Low Self-Perception in Children With Amblyopia

February 2019

The self-esteem of school-aged children is affected by their scholastic, social, and athletic competence. Limitations caused by amblyopia may impede children's ability to demonstrate their knowledge and participate in physical activities, which in turn may reduce self-esteem.

In a cross-sectional study, **Birch et al.** explored this matter further and found that low self-perception among children with amblyopia is associated with slower reading speed and poorer motor skills than their peers.

For this study, which was conducted in 2016 and 2017, the researchers enrolled 68 healthy participants in grades 3 through 8. Of these, 50 had amblyopia and 18 served as controls. Self-perception was assessed using the Self-Perception Profile for Children, which includes five domains (behavioral conduct, physical appearance, and scholastic, social, and athletic competence) and a separate scale for global self-worth. In addition, reading speed, eye-hand task performance, visual acuity, and stereoacuity were evaluated.

Compared with controls, children with amblyopia scored much lower scholastically (mean, 2.93 vs. 3.58; $p = .004$), socially (mean, 2.95 vs. 3.62; $p < .001$), and athletically (mean, 2.61 vs. 3.43; $p = .001$). Among children with amblyopia, lower self-perception of scholastic competence was associated with slower reading speed ($r = 0.49$; $p = .002$), and lower self-perception of scholastic, social, and athletic competence was linked to poorer catching and aiming skills (scholastic: $r = 0.48$; $p = .007$; social: $r = 0.63$; $p < .001$; athletic: $r = 0.53$; $p = .003$). There were no meaningful differences between the control and amblyopia groups in regard to conduct, self-perception of physical appearance, or global self-worth.

It is noteworthy that most of the participants with amblyopia wore eyeglasses, versus none of the healthy controls. Therefore, it is possible that the stigma of wearing glasses may contribute to the lower social and athletic self-perceptions of children with amblyopia.

Findings of this study suggest that the impaired visual development related to amblyopia may have wide-ranging negative consequences for affected children. *(Also see related commentary by Joseph L. Demer, MD, PhD, in the same issue.)*

Do Glaucoma Staging Systems Underestimate the Severity of Macular Damage?

February 2019

Although recent studies have found that loss of macular function is more common in early glaucoma than originally thought, 24-2 and 30-2 standard automated perimetry (SAP) tests may routinely miss macular damage in the central 10 degrees of the visual field. This can lead to underestimation of glaucoma severity. In a cross-sectional study, **de Moraes et al.** demonstrated that most participants with glaucoma and 24-2 mean deviation (MD) better than −6 dB were classified by 24-2 and 30-2 SAP as having no or early-stage defects despite matching evidence of macular damage. The research was conducted at a New York glaucoma referral center and included 57 eyes of 57 participants with confirmed glaucoma (mean age, 57 years; 57% women). Macular damage was defined by 10-2 SAP and spectral-domain optical coherence tomography (SD-OCT) evidence of retinal ganglion cells plus inner plexiform layer probability maps.

Findings of glaucoma staging according to Hodapp-Parrish-Anderson (HPA) criteria, visual field index (VFI), and the Brusini Glaucoma Staging System 2 were then compared with visual field and SD-OCT results.

Forty-eight (84%) of the 57 eyes were confirmed to have macular damage. For the affected eyes, the mean (standard deviation [SD]) of the 24-2 MD was −2.5 (1.8); the mean (SD) of the 10-2 MD was −3.0 (2.4) dB; and the mean (SD) of the VFI was 94.2% (4.5%). In contrast, according to the HPA criteria, VFI, and Brusini systems, early defects were apparent in 70%, 81%, and 68% of the eyes that had

macular damage, respectively.

The authors' observations suggest that glaucoma staging systems based exclusively on 24-2 or 30-2 visual fields risk underestimating disease presence, location, and extent; moreover, they also may result in suboptimal care that ultimately may affect patients' visual-related quality of life. If these results are confirmed and found to be generalizable to other patients, the authors would advocate using at least a 10-2 visual field and high-resolution macular SD-OCT scans in the classification of glaucoma.

—Summaries by Lynda Seminara

OTHER JOURNALS

Selected by Deepak P. Edward, MD

Causes and Outcomes of Misdiagnosed Optic Nerve Sheath Meningioma

JAMA Neurology
Published online Dec. 17, 2018

Kahraman-Koytak et al. documented the reasons for initial misdiagnosis of optic nerve sheath meningioma (ONSM). They found that misdiagnosis occurs often, with optic neuritis being the most common erroneous label. Factors contributing to misdiagnosis were inaccurate funduscopic exams, biased pre-established diagnoses, failure to order correct tests, and incorrect interpretation of magnetic resonance imaging (MRI) results.

For this retrospective study, the authors reviewed records of 35 patients (mean age, 45 years) with unilateral ONSM who were seen at Emory University's neuro-ophthalmology practice during a 15-year period. To ascertain causes of diagnostic errors, the Diagnosis Error Evaluation and Research taxonomy tool was applied to cases of missed or delayed diagnosis.

Of the 35 patients, 25 (71%) had a delayed or initially missed diagnosis, the mean of which was 63 months. The most common diagnostic error (n = 19) was clinician assessment failure (errors in hypothesis generation and weighing), followed by errors in diagnostic testing (n = 15). The most common initial misdiagnosis was optic neuritis (n = 12). Another common contributor to diagnostic delay or inaccuracy was failure to recognize optic neuropathy in patients with ocular disorders. Sixteen (64%) of the 25 patients had poor visual outcomes.

Of the 16 patients with a missed diagnosis, five had unnecessary lumbar puncture, 12 received inappropriate lab tests, and six had unwarranted steroid treatment. Eleven of the 16 had previous MRI results that were considered healthy: Five showed ONSM but were misread by a clinician other than a neuroradiologist, and six were performed improperly (without orbital sequence or contrast).

Compressive optic neuropathy should be considered in the differential diagnosis of monocular vision loss that is painless and progressive. Diagnostic delays and errors are costly and often lead to suboptimal visual outcomes in patients with ONSM.

The authors emphasized that various efforts can minimize diagnostic difficulty, including effective neuroimaging education, better diagnostic strategies, and easier access to neuro-ophthalmologists.

Refractive Outcomes: IOL Formulas for Patients With Previous PPV

Journal of Cataract & Refractive Surgery
Published online Dec. 21, 2018

Although refractive surprises after phacoemulsification have become less common with newer formulas for calculating the power of IOLs, estimates can be inaccurate for some patients, including those with previous ocular surgery. **Lamson et al.** looked at refractive outcomes of cataract surgery in previously vitrectomized eyes and compared the accuracy of various formulas for calculating IOL power. They found that, regardless of the calculation method, refractive outcomes after cataract extraction in vitrectomized eyes were more variable and hyperopic than the predicted outcomes. Of the formulas used in their study, Holladay 2 provided the best estimates.

This retrospective study involved a record review of phacoemulsifications performed from 2013 to 2017 (61 eyes of 57 patients; mean age, 60 years). Patients with previous pars plana vitrectomy (PPV) in the same eye were included. However, patients with a history of refractive surgery or silicone oil in the eye—or with any other factor that could preclude accurate calculation of IOL power—were excluded from the study.

The mean postoperative spherical equivalent was –0.16 D. Mean prediction errors were as follows: 0.30 ± 0.82 D for Holladay 1; –0.09 ± 0.76 D for Wang/Koch adjusted (WKA) Holladay 1; 0.23 ± 0.76 D for Holladay 2; 0.25 ± 0.81 D for SRK/T; 0.04 ± 0.85 D for WKA SRK/T; 0.33 ± 0.80 D for Hill-Radial Basis Function; 0.45 ± 0.80 D for Ladas; and 0.30 ± 0.82 D for Barrett.

The formula with the highest percentage of predictions within ±0.50 D of the postoperative outcome was Holladay 2 (60.42%). Significant differences between the predicted and actual refractive outcomes were found with all methods ($p < .05$) except WKA Holladay and WKA SRK/T. Intraclass correlation showed low repeatability (<0.50) for all formulas.

The authors acknowledged that the study is limited by its retrospective nature and small size, which did not allow for subgroup analyses by axial length or other parameters.

Moreover, the indications for vitrectomy varied widely, and differences in retinal pathology may have resulted in anatomic differences that affected formula performance.

Predicting refractive outcomes for this population is challenging, and patients should be counseled accordingly. Larger studies are needed to determine the best methods for choosing IOLs for patients who have previously undergone eye surgery.

—Summaries by Lynda Seminara

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Glaucoma and Exercise: What to Tell Your Patients

Can I or can't I? Should I or shouldn't I? Ophthalmologists are often asked about the effects of exercise—particularly yoga—on glaucoma. As the science is continuing to unfold, considerable uncertainty remains. But a combination of evidence-based recommendations and common sense can go a long way when talking with glaucoma patients about exercise.

Aerobic Exercise: Definitely

There's no question that aerobic exercise is crucial to overall good health. As for glaucoma, Robert Ritch, MD, at New York Eye & Ear Infirmary of Mount Sinai in New York City, tells his patients, "It's simple. If it's good for your heart, it's good for glaucoma. If it's good for your brain, it's good for glaucoma."

Dr. Ritch advises 45 minutes of aerobic exercise three to four times a week. The research supports this guidance:

- In one study, aerobic exercise (such as walking, swimming, biking, or working out on stationary machines) at a brisk level for 30 to 45 minutes three to four times a week lowered intraocular pressure (IOP) and improved blood flow to the brain and the eye.[1]
- In a recent study, all measures of physical activity—average steps per day, minutes of basic (nonsedentary) movement, and greater time spent doing moderate-to-vigorous physical activity—were associated with slower rates of visual field (VF) loss in a treated group of glaucoma patients.

At baseline, participants walked an average of 5,313 steps and averaged 148 minutes of nonsedentary activity and 11 minutes of moderate-to-vigorous activity per day. Each incremental increase in activity was associated with less decline in VF, although the observed effects were small. But significantly boosting those levels each day—walking an additional 5,000 steps, engaging in an additional 2.6 hours of nonsedentary activity, or exercising for 120 minutes at a moderate-to-vigorous level—decreased the average rate of VF loss by approximately 10%.[2]

- Results of a meta-analysis showed that exercise in sedentary people had a greater IOP lowering effect than it did in people who were already active.[3] "It's important for clinicians to tell their patients who are not motivated to exercise that it's actually the patients who have not been active who do the best in terms of lowering eye pressure with exercise," said Yvonne Ou, MD, at the University of California, San Francisco.

EXERCISE CAUTION. *Patients with glaucoma may need to modify or skip certain poses, such as downward-facing dog.*

Clues from animal research. According to Dr. Ou, recent animal studies add to the evidence that physical activity protects against glaucoma damage.

In a murine study that examined the role of exercise in a transient ocular hypertension model, exercise was able to reverse signs of age-related vulnerability to optic nerve injury, such that the signs of injury in older mice that had completed the exercise regimen were similar to young mice that were not exercised.[4] The investigators then went on to show that exercise may prevent the injury-induced loss of brain-derived neurotrophic factor (BDNF) in the retina. (The group also has recently demonstrated that a high-fat high-sucrose diet made the mouse optic nerve more vulnerable to injury, but that exercise did not offset the negative effects of this diet.[5])

Strength Training: Maybe

Lack of clarity. Relatively few studies have been conducted on weight training's effect on IOP. Moreover, the results have been contradictory:

BY GABRIELLE WEINER, MS, INTERVIEWING **ROGER COLE, PHD, YVONNE OU, MD,** AND **ROBERT RITCH, MD.**

- Several years ago, Dr. Ritch's group evaluated the effect of bench pressing on IOP in 29 normal subjects, and a number of them experienced rises in IOP during the exercise.[6] "The study hasn't been done in people with glaucoma, but I presume that glaucoma patients would have a more exaggerated response," Dr. Ritch said.
- In another study of 30 healthy individuals, the opposite occurred: Dynamic resistance exercises (chest and leg presses) induced moderate postexercise decreases in IOP.[7]

Advice for patients? Given the lack of clarity, Dr. Ritch's guidance for glaucoma patients comes down to the amount of weight being lifted. Is a patient working with 10-, 20-, or 30-pound weights—or much more than that? "I caution patients with glaucoma about bench pressing 200 pounds, but a definitive study has not been done. If a patient has mild glaucoma, I tell them to go ahead with their routine unless they [experience] severe damage. I had one patient who lost his 3-degree island of vision in the middle of doing a crunch, and IOP can also rise in patients doing push-ups. I basically tell them to use common sense."

Avoid the Valsalva maneuver. It's crucial that the person continues to exhale during periods of maximum exertion. This helps the patient avoid the Valsalva maneuver, in which a person exhales forcefully with a closed mouth and nose and the windpipe is blocked by the closed epiglottis—which can increase IOP dramatically.

Yoga: It Depends

There's no clear evidence to suggest that certain yoga poses—especially if they are held for short periods—are detrimental to people's glaucoma, but there is reason for caution.

Just say no to headstands. Back in 1980, Dr. Ritch saw a 45-year-old woman with normal-tension glaucoma who had 5-degree fields. She had continued to progress despite consultation with clinicians at 12 institutions.

As it turned out, she had been standing on her head for 20 minutes a day for 20 years. When her IOP was measured while she was performing a headstand, it was 60 mm Hg. In contrast, it was 15 mm Hg while she was sitting. Dr. Ritch proceeded to take all of his lab colleagues and stand them on their

Analyzing Asana

Modifications of yoga poses allow practitioners to experience many of the benefits of the full poses without pushing, overstretching, and incurring injuries. (Modifications are also used to help yoga students recover from illnesses and injuries.) The following modifications may be appropriate for some glaucoma patients, as they help the person achieve gradation from minimal to large increases in IOP by attending to the relative heights of the eyes, heart, and the rest of the body.

Inversions

Legs-up-the-wall pose (Viparita Karani). If a patient goes from sitting on the floor to lying on her back with her legs up a wall, IOP rises only a little, Dr. Cole said, and even that can be partially reversed by elevating the head on a folded yoga blanket.

For a slightly steeper version of this inversion, which can be more calming, at the possible expense of slightly higher pressure in the eyes, he recommended adding a folded blanket or two under the pelvis and rolling the shoulders back to lift the chest (lifting the chest elevates the heart a little).

Plow pose (Halasana) and shoulderstand (Sarvangasana). For a strong inversion that is expected to produce only a moderate increase in IOP, consider plow pose or full shoulderstand. "Although these poses raise the heart, abdomen, and pelvis [and in the case of shoulderstand, the legs] quite high—and you can't mitigate these factors by raising the head because that would flex the neck too strongly—they are unlikely to raise IOP to an extreme," Dr. Cole said. This is because the flexed position of the neck raises the eyes somewhat relative to the heart.

By contrast, headstand (Sirsasana) is likely to increase IOP maximally because it places the eyes as far as possible below the heart while lifting the abdomen, pelvis, and legs as far as possible above the heart.

Forward Bends

Forward seated bend pose (Paschimottanasana). In the full version of this pose, the person sits on the floor, bends forward, and rests the head on the knees. But modifying the pose—by having the person rest the forehead on a padded chair seat—keeps the eyes above the heart and most of the rest of the body below it, presumably keeping IOP low.

Forward standing bend pose (Uttanasana). As with the seated version, the person bends forward from the waist and the head is brought toward the knees. Standing in front of a chair that has a high stack of blankets on the seat, bending forward, and resting the forehead on the stack will likely raise IOP much less than bending forward without support and hanging the head.

Downward-facing dog pose (Adho Mukha Svanasana). Two modifications to consider in practicing downward-facing dog pose: 1) Rest the hands on a chair (on the seat or on the top of the chairback), or 2) place the hands on the floor while elevating the forehead on a yoga block or on one or more folded blankets. Either modification will probably prevent IOP from rising as much as it would if the head were allowed to dangle downward or rest on the floor.

Another option: Practice the pose at the wall. In this variation (commonly known as half dog), the hands are placed on the wall, and the person steps back from the wall, bending forward at the hips. The head is kept in line with the arms and not allowed to drop down toward the floor.

heads. Everyone's IOP roughly doubled.

Subsequent studies and case reports tested headstand pose, demonstrating a twofold rise in IOP.[8] "Doing headstands and shoulderstands is a real no-no for glaucoma patients, especially if you're going to do them for 20 minutes a day," Dr. Ritch said.

What about downward-facing dog? But what about other head-down positions? Yoga students routinely practice a number of poses in which the head is positioned below the heart.

In a recent study, Dr. Ritch and his colleagues had glaucoma patients and a cohort of healthy participants perform a series of four inverted yoga positions—downward-facing dog, standing forward bend, plow, and legs-up-the-wall poses.[9] The researchers captured the IOP in each group at five time points: 1) at baseline, while seated, 2) immediately after assuming the pose, 3) two minutes later, while still holding the pose, 4) immediately after performing the pose, in a seated position, and 5) 10 minutes later, after resting in the seated position.

Both groups of participants showed a rise in IOP in all four yoga positions, with the greatest increase of pressure—almost 10 mm Hg—occurring during downward-facing dog. After a few minutes of rest, all eye pressures returned to normal.

Can modifications help? For glaucoma patients, the safest way to practice yoga is to avoid inversions altogether, said Roger Cole, PhD, a research scientist and Iyengar yoga instructor based in Del Mar, California. However, he said, when a patient who has mild glaucoma also has a passion for yoga, their ophthalmologist and yoga teacher may be able to help them design a modified practice that diminishes the potential effects on IOP.

"The most important factor determining an inverted posture's effect on IOP appears to be the vertical distance of the eyes below the heart," said Dr. Cole. "Elevating the legs, pelvis, and abdomen above the heart may also raise IOP but seems to have a smaller effect."

For example, he noted, "in Dr. Ritch's yoga study, the two postures that placed the eyes furthest below the heart [downward-facing dog and standing forward bend poses] raised IOP by about 10 mm Hg even though the feet remained on the floor." In contrast, he said, "the two postures that kept the eyes at or only slightly below heart level while lifting the legs, pelvis, or abdomen the most [plow and legs-up-the-wall poses] raised IOP by 4 mm Hg, on average." Knowing this makes it easier to select and modify inversions based on their likelihood of raising IOP (see "Analyzing Asana").

Take-Home Message

The last thing a clinician wants to do is discourage patients from exercising. Rather, it's critical to ask patients about their activities and discuss limits and modifications when necessary.

Finally, what about Dr. Ritch's patient, who had been standing on her head for 20 minutes a day for 20 years? She stopped doing headstand pose—and her glaucoma stopped progressing.

Advice to Yoga Practitioners

Dr. Cole offers the following advice to yoga students with glaucoma:

- Have your glaucoma medically treated before practicing.
- Get your doctor's OK before practicing inverted postures or any pose that places your head below your heart.
- Modify or substitute inverted poses to reduce their effects on eye pressure.
- Enter inverted postures slowly.
- Avoid strenuous inversions. Yoga is not about "no pain, no gain."
- Exhale gently and slowly. Avoid holding the breath or restricting the exhalation. If you practice pranayama (yoga breathing techniques), avoid the classical exhalation phase of the Ujjayi breath, as it involves making a "haaaah" sound through a restricted throat. Instead, exhale normally.
- Practice a form of yoga that has you move slowly, provides props, and adapts postures to your needs. Iyengar yoga is the best-known example of this approach.
- Find a teacher who is compatible with you, willing to work with special needs, and knowledgeable about adapting postures.
- Practice mindfully. "Relax your mind and body everywhere you can, then do whatever it takes to get into the pose as far as is reasonable for you at that moment, without disturbing your mind," Dr. Cole said.

1 Schmidt KG et al. *Graefes Arch Clin Exp Ophthalmol.* 1996;234(8):527-532.

2 Lee MJ et al. *Ophthalmology.* Published online Oct. 10, 2018.

3 Roddy G et al. *Clin J Sports Med.* 2014;24(5):364-372.

4 Chrysostomou V et al. *Aging Cell.* 2016;15(6):1082-1091.

5 Chrysostomou V et al. *Exp Eye Res.* 2017;162:104-109.

6 Vieira GM et al. *Arch Ophthalmol.* 2006;124(9):1251-1254.

7 Chromiak JA et al. *J Strength Cond Res.* 2003;17(4):715-720.

8 Baskaran M et al. *Ophthalmology.* 2006;113(8):1327-1332.

9 Jasien JV et al. *PLoS One.* Published online Dec. 23, 2018.

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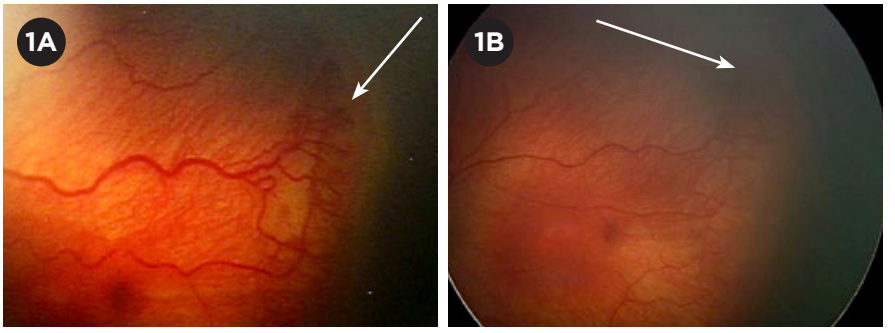
Fighting ROP With Anti-VEGF Therapy

In a major shift for pediatric ophthalmic care, drugs to inhibit aberrant intraocular angiogenesis have largely supplanted laser photocoagulation as first-line treatment for the most severe cases of retinopathy of prematurity (ROP).

"This is done fairly commonly now by many practitioners in the United States and throughout the world. It is becoming increasingly recognized and accepted, because it enables us to preserve the retina in children with very advanced zone 1 ROP or aggressive posterior disease," said Stephen J. Kim, MD, at Vanderbilt University in Nashville, Tennessee. "In the past, if you lasered these eyes at this stage, you would destroy much of their peripheral vision."



BEFORE AND AFTER. *In this case of stage 3 ROP, dilated tortuous vessels (plus disease) are evident before anti-VEGF treatment (1A). One week later, there is less tortuosity, reduced stage 3 ROP, and regrowth of physiologic vascularization (1B).*

Where We Are Now

Guidance on how and when to use anti-VEGF medications in ROP patients has emerged over the past several years from a few prospective clinical studies and some clinical trials comparing drug and laser treatment. (There also is an ongoing prospective, phase 1 dose de-escalation study sponsored by the Pediatric Eye Disease Investigator Group [PEDIG] and the NEI.[1]) And while most of the studies have investigated the use of bevacizumab (Avastin), attention to ranibizumab (Lucentis) has begun to rise.

Guidance statements. In 2017, the Academy's Ophthalmic Technology Assessment Committee (OTAC) reported finding Level II and III evidence in the literature that intravitreal therapy to inhibit VEGF is at least as effective as laser photocoagulation for achieving regression of acute ROP.[2]

And in an updated policy statement published in December, the American Academy of Pediatrics prominently included intravitreal anti-VEGF therapy among the recommendations for managing some types of ROP.[3] The statement was developed with representatives from the Academy, the American Association for Pediatric Ophthalmology and Strabismus, and the American Association of Certified Orthoptists.

Fear of systemic problems. The onset of off-label usage of VEGF inhibitors sparked concerns that circulation of the drugs elsewhere in the body might reduce systemic VEGF sufficiently to hamper organ development, and these concerns are still being debated today, said Amy K. Hutchinson, MD, at Emory University in Atlanta.

"There's a lot of controversy at the heart of this topic," Dr. Hutchinson said. "Some physicians are reluctant to use bevacizumab until more is known about its effects outside the eye on developing organs like the brain, kidney, and lungs. In addition, we are still studying bevacizumab to determine the smallest effective dosage to minimize such risks."

Residence time in the body. M. Elizabeth Hartnett, MD, at the University of Utah's John A. Moran Eye Center in Salt Lake City, said that the full-length antibody bevacizumab inactivates multiple VEGF isoforms and persists in the body for weeks. But, as a smaller antibody fragment, ranibizumab blocks fewer VEGF receptors and disappears from circulation faster, she noted.

"If you inject bevacizumab into the eye, it gets into the circulation and can be detected for several months after a

BY LINDA ROACH, CONTRIBUTING WRITER, INTERVIEWING **M. ELIZABETH HARTNETT, MD, AMY K. HUTCHINSON, MD,** AND **STEPHEN J. KIM, MD.**

Melissa Chandler, CRA, OCT-C

single dose," she said. In contrast, preliminary data from a large, multicenter trial showed that serum VEGF levels in infants treated with ranibizumab returned to baseline within two weeks after a single intravitreal treatment,[4] she said. "Nonetheless, the studies suggest that more than one treatment with ranibizumab may be needed, and the repetition of use may extend the inhibition longer than the two weeks," she said.

"We need more information before advocating either drug for all types of treatment-warranted ROP. However, the evidence for zone 1 treatment-warranted ROP seems to favor consideration for anti-VEGF treatment," Dr. Hartnett said.

Variations in clinician preference. It is too early to know how the speed of anti-VEGF drug clearance from the body might affect safety or long-term outcomes of therapy, but on the premise that less systemic exposure is better, Dr. Kim prefers ranibizumab for treating ROP. "At Vanderbilt we have moved almost entirely to ranibizumab, and we generally avoid bevacizumab. The reasons are theoretical at this time but are based on ranibizumab's faster clearance and reduced chance for systemic inhibition of VEGF," he said.

In contrast, Drs. Hartnett and Hutchinson said they tend to use bevacizumab for zone 1 treatment-warranted ROP at a dose of 0.25 mg, or at lower doses as part of the PEDIG de-escalating dose study, for two reasons: 1) The literature on bevacizumab's effectiveness and apparent safety is deeper than it is for ranibizumab, and 2) bevacizumab is both cost-effective and widely available around the world.

A Look at Early Outcomes

Resolution and recurrence. Results from clinical trials have shown that a single intravitreal injection of either medication successfully resolved ROP in many eyes. But bevacizumab's greater potency compared with ranibizumab appears to result in fewer cases that required late retreatment for recurrent disease by six months postinjection.

For instance, in the RAINBOW trial (a randomized trial comparing low-dose ranibizumab with laser), preliminary analysis found that 31% of the ranibizumab infants had recurrent ROP requiring retreatment in the six months after the initial injection, Dr. Hartnett said.[4] That compares to a 23% retreatment rate at the same time point in children treated with bevacizumab during the ROP1 study.[5]

In addition, a study in 241 infants treated with bevacizumab found late reactivation of proliferative disease in 8.3% of the children, and retreatments had to be performed as long as 65 age-adjusted weeks after initial treatment.[6]

Anti-VEGF plus laser. "Given the risk of late recurrence of ROP with ranibizumab and loss to follow-up, we have a policy at Vanderbilt of performing laser treatment to avascular retina in all ranibizumab-treated eyes after normal retinal vascularization has ceased" and before the infants are discharged, Dr. Kim said.

More normal structure? Anti-VEGF therapy in eyes with zone 1 (the most posterior) ROP has a potential advantage over laser photocoagulation: the possibility that it can nondestructively enable healthy intraretinal blood vessels to mature and extend a bit across formerly avascular retina, Dr. Hartnett said. "Anti-VEGF offers an ability to extend normal retinal vascularization into zone 2 in some eyes. I think that's exciting," Dr. Hartnett said. Some case studies also suggest that anti-VEGF-treated eyes may be less myopic.[7]

Risk of avascular retina. Investigators in the CARE-ROP study have reported a high incidence of avascular retina in ranibizumab-treated eyes, Dr. Hartnett said. The rate was 84% in the higher-dose eyes, compared to 18% of eyes treated with bevacizumab in the ROP1 study.

"We can't directly compare these trials, of course, since they are not head-to-head studies and they had different enrollment criteria, [evaluated] different zones of disease, were from different regions of the world, and had different outcomes, but we can make observations about them." Nonetheless, she said, "We don't know what the observations mean in the long term." For instance, she said, "The avascular retina could stimulate VEGF and cause recurrent ROP. There also have been some reports of recurrent retinal detachment even up to 2.5 years after a single anti-VEGF treatment."

Difficulties evaluating developmental delays. To alleviate concerns about potential damage to the brain and other organs from systemic anti-VEGF exposure, researchers must find ways to tease out any VEGF-related anomalies from the natural history of prematurity, Dr. Hutchinson said.

"A handful of studies have been published with conflicting conclusions about whether bevacizumab is associated with poorer neurodevelopmental outcomes than laser. Since patients in these studies were not randomized, there is a strong potential for bias," she said.

Are Outcomes Improved?

The question of whether anti-VEGF therapy improves outcomes takes clinicians into unknown territory. Pediatric ophthalmologists are hoping that, as treated children enter their school years, normalized retinal structure will translate into better visual functioning than if they had been treated with laser monotherapy. But, like so much else in the anti-VEGF treatment field, this possibility remains to be demonstrated scientifically. "This is all anecdotal and theoretical," Dr. Kim said. "We don't know what will happen in five years or beyond with these children."

Dr. Hutchinson concurred. "I think most of us would agree that the published literature suggests that for zone 1 ROP, anatomical outcomes, recurrence rates, and rates of high myopia are better with bevacizumab than with laser. However, since we have not yet carefully studied retinal function in bevacizumab-treated eyes, we cannot say for certain that bevacizumab is the best treatment for zone 1 ROP," she said.

One of the first infants Dr. Hutchinson treated with bevacizumab is now 7 years old and appears to have overcome early developmental delays, she said. "He performed poorly on the Bayley infant skill and development test at age 2 and was labeled at having 'severe impairment,' but he is now excelling in school."

To progress beyond the anecdotal, it

would be helpful if future anti-VEGF trials for ROP included objective tests of retinal function, such as visual field and electrophysiological testing, Dr. Hutchinson said. "On the other hand, the longer we go without seeing obvious differences in the health and development in our formerly premature patients treated with bevacizumab, the more comfortable we start to feel," she said. But—as she acknowledged—"that might be a false sense of security."

1 www.ClinicalTrials.gov Identifier: NCT02390531. Accessed Jan. 7, 2019.
2 VanderVeen DK et al. *Ophthalmology*. 2017; 124(5):619-633.
3 Fierson WM et al. *Pediatrics*. 2018;142(6). http://pediatrics.aappublications.org/content/142/6/e20183061. Accessed Jan. 9, 2019.
4 Hartnett ME. "Anti-VEGF treatment for ROP: Clinical trials and phenotypic differences worldwide." Presented at: Retina Subspecialty Day; Oct. 26, 2018; Chicago.
5 Wallace DK et al. *JAMA Ophthalmol.* 2017; 135(6):654-656.
6 Mintz-Hittner HA et al. *Ophthalmology*. 2016; 123(9):1845-1855.
7 Mintz-Hittner HA, Geloneck MM. *Eye Brain.* 2016;8:135-140.

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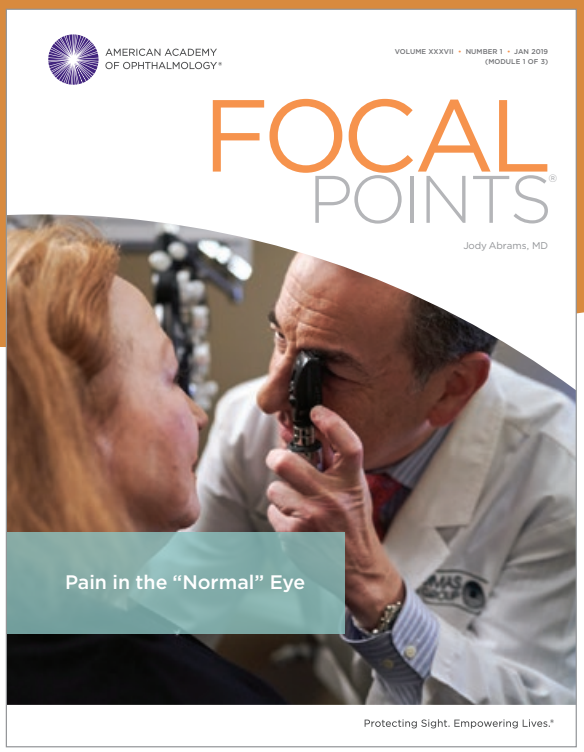

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Microspherophakia: Genetics, Diagnosis, and Management

Microspherophakia is a rare abnormality of the crystalline lens, marked by reduced equatorial diameter and increased lens thickness. The prevalence of this disorder is unknown, but it is reportedly more common in persons of Asian and North African descent.[1]

Although classically described in association with Weill-Marchesani syndrome (WMS), microspherophakia may occur with various ocular and systemic conditions, and in isolation.

Genetic Link to WMS

WMS is a rare inherited disorder of connective tissue, characterized by short stature, brachydactyly, brachycephaly, joint stiffness, maxillary hypoplasia, cardiovascular abnormalities, and ocular conditions. The latter include ectopia lentis, glaucoma, microspherophakia, and severe myopia.

Responsible mutations. Mutations in the *ADAMTS10* and *FBN1* genes have been identified in WMS. Another implicated mutation is that of the latent TGF-beta-binding protein 2 (LTBP2).[1,2]

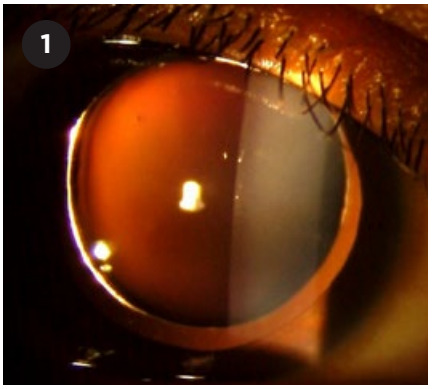
ADAMTS10 mutation is known to cause the autosomal-recessive variant of WMS. The *ADAMTS10* gene belongs to the ADAMTS family of zinc-dependent proteases associated with connective-tissue organization, coagulation, angiogenesis, and cell migration. These proteases play a major role in growth and in the development of the skin, heart, and crystalline lens.

The *FBN1* gene encodes instructions for the protein fibrillin-1, which is an important component of connective tissue, giving it strength and flexibility. Mutations are inherited in an autosomal-dominant pattern and result in an unstable fibrillin-1, which weakens connective tissue and produces the syndrome's ocular and systemic features.

Some cases of autosomal-recessive microspherophakia have been linked to mutations of the LTBP2.[2] Structurally homologous to fibrillins, LTBPs are highly expressed in the lens capsule, lens epithelium, and ciliary body. *ADAMTS17* is from the matrix metalloproteinase family of proteins that bind to the extracellular matrix and sequester TGF-beta. A number of mutations in the *ADAMTS17* gene have been shown to disrupt the organization of the extracellular matrix, resulting in microspherophakia.[1-3]

Pathophysiology

It has been observed that the human crystalline lens is almost spherical at birth, with an equatorial diameter of 6.5 mm and a sagittal diameter of 3.5 to 4.0 mm.[4] As the child grows, the equatorial diameter increases rapidly, reaching about 9 to 10 mm by adulthood. The sagittal diameter is approximately 3.7 mm at 20 years of age and 4.0 mm at 50 years of age; the sagittal growth causes the lens to become more spherical with age.[4]



EDGE OF MICROSPHEROPHAKIC LENS. *Pupil is fully dilated and the lens equator is visible. The patient had lenticular myopia of –11 D and features of angle-closure glaucoma. A clear lens extraction was performed, followed by in-the-bag IOL placement, which helped achieve better glaucoma control.*

It has been postulated that weakness of the zonular fibers leads to lack of tension in the equatorial plane; thus, the lens remains spherical and does not acquire a biconvex shape.[4] This spherical configuration of the lens results in a high degree of lenticular myopia in affected eyes. It also causes a shallow anterior chamber and, often, angle-closure glaucoma. Late subluxation of the lens may occur because of weak zonules.

Systemic and Ocular Links

Apart from WMS, microspherophakia has been associated with Alport syndrome, homocystinuria, Klinefelter

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syndrome, mandibulofacial dysostosis, and Marfan syndrome. It also has been linked to GEMSS syndrome (glaucoma, ectopia lentis, microspherophakia, stiff joints, and short stature). See Table 1 online for more associations.

Familial microspherophakia is not associated with any systemic defect and is thought to be autosomal-recessive.

Identifying Microspherophakia: Key Features

- Abnormally increased lens thickness
- Defective accommodation
- Features of angle closure
- Glaucomatous optic atrophy
- Isolated or syndromic association
- Lens edge seen in fully dilated pupils
- Lens subluxation or dislocation
- Low equatorial lens diameter
- Moderate or high myopia
- Shallow anterior chamber

Clinical Features

Microspherophakia is usually bilateral. The edges of these small-diameter lenses generally can be observed when pupils are fully dilated (Fig. 1). Frequently, subluxation is present as well. Other common clinical observations are a high degree of lenticular myopia, defective accommodation, and angle-closure glaucoma.

Most patients who present to an ophthalmologist with microspherophakia will complain of low vision; however, some cases exhibit acute angle-closure glaucoma at initial presentation.[5]

Mechanisms of Glaucoma

Glaucoma associated with microspherophakia can result from various mechanisms. Pupillary block is a common mechanism leading to angle-closure glaucoma in patients with microspherophakia. Other reported mechanisms include crowding of the angle by the spherophakic lens, chronic pupillary block without complete angle closure, and angle abnormalities with agenesis of angle structures.

It is difficult to estimate the prevalence of glaucoma among patients with microspherophakia given the latter's rarity. However, in a series of 36 eyes of patients with microspherophakia, glaucoma was present in 16 (44.4%).[6]

Examination

Ocular examination should include:

- Comprehensive slit-lamp exam: look at lens morphology and angle of the anterior chamber; look for preexisting subluxation
- Fundus exam: check for any glaucomatous damage to the disc
- Peripheral fundus exam: may rule out coexisting retinal pathology
- Intraocular pressure: measure, monitor, and manage appropriately
- Ultrasound biomicroscopy and anterior-segment optical coherence tomography: may help to elucidate biomechanics of angle crowding and angle closure in some patients
- Detailed systemic evaluation: mandatory to rule out syndromic association
- Measure lens thickness and axial length

Management

Lenticular myopia. Patients with microspherophakia who present with only lenticular myopia (without any other manifestation) need early refractive correction to avoid irreversible vision loss due to amblyopia. Routine follow-up will ensure that spectacle prescriptions are changed to coincide with the refractive status of the eye.

If glaucoma is present. Pupillary block can be relieved or prevented with Nd:YAG laser peripheral iridotomy. Cycloplegics are useful for managing acute attacks of pupillary block glaucoma. These drugs relax the ciliary muscle and tighten the zonules, in turn "pulling back" the iris-lens diaphragm, thus relieving the pupillary block.

If angle-closure glaucoma develops, it may require antiglaucoma medications. Eyes that do not respond to these medications may need glaucoma filtration surgery or a glaucoma drainage device. Primary trabeculectomy has a good success rate in such cases.[7]

As evidence mounts in support of early lensectomy in cases of primary angle closure, this approach could be considered in patients with microspherophakia, as well. However, it is important to note that recent studies looking at this issue did not include patients with secondary causes of angle closure.[8]

Lens subluxation. Clear lens extraction followed by in-the-bag intraocular lens (IOL) placement may relieve crowding of the angle by the spherophakic lens.[9] However, this may be difficult to achieve in the presence of a small capsular bag and zonular instability. Therefore, capsular tension rings often are used in conjunction with the IOL. Other indications for lens extraction include subluxation, cataract, lenticulocorneal touch, and intermittent pupillary block.

Lensectomy by the limbal route is done in cases of severe lens subluxation and anterior dislocation.[10] For posterior dislocation, a pars plana lensectomy is required.

Lifelong care. Most patients with microspherophakia will need lifelong ophthalmologic follow-up. It is important to make them aware of this.

1 Bitar MS et al. *JSM Ophthalmol.* 2016;4(1):1040.
2 Kumar A et al. *Hum Genet.* 2010;128(4):365-371.
3 Morales J et al. *Am J Hum Genet.* 2009;85(5):558-568.
4 Chan RT, Collin HB. *Clin Exp Optom.* 2002;85(5):294-299.
5 Kaushik S et al. *BMC Ophthalmol.* 2006;6:29.
6 Muralidhar R et al. *Eye.* 2015;29(3):350-355.
7 Senthil S et al. *Indian J Ophthalmol.* 2014;62(5):601-605.
8 Azuara-Blanco A et al. *Lancet.* 2016;388:1389-1397.
9 Lu Y, Yang J. *J Clin Exp Ophthalmol.* 2016;7:532.
10 Rao DP et al. *Br J Ophthalmol.* 2018;102(6):790-795.

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EXTRA **MORE ONLINE.** For supplemental materials, find this article at aao.org/eyenet.

The Case of Red Eyes and Red Ears

Jack Hanson,* a 57-year-old African-American man, presented to his local ophthalmologist's clinic with a two-week history of red, profoundly light-sensitive, painful eyes. In addition, both of his ears hurt badly and were tender. He had experienced ear pain twice previously and told his physician that he felt the eye and ear problems were connected somehow—and he really wanted to determine the cause of his symptoms so he could avoid future episodes.

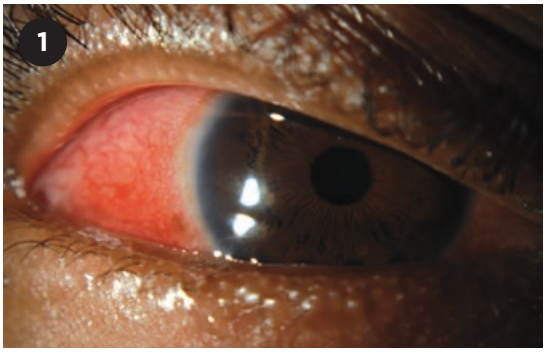
What We Saw

History. Mr. Hanson's medical history included hypertension controlled with hydrochlorothiazide and an ocular history of presbyopia. His family history was remarkable for glaucoma in his maternal grandmother.

When we asked about other health problems, Mr. Hanson reported that the auricles of his ears seemed swollen and painful on two occasions in the past, but that these episodes had not involved eye inflammation. The first episode had occurred three years earlier and was resolved with steroids prescribed by his family physician. The second episode of auricular inflammation occurred a year ago and was associated with fever, myalgia, and joint pain as well as a 30-lb weight loss.

He specifically denied prior tuberculosis, immunocompromised state, sinus pain, ulcers, joint pain, and any difficulty breathing.

Exam. Our examination revealed that his visual acuity was 20/20 in both eyes with no afferent pupillary defect in either eye. Visual fields by confrontation were normal, as were ocular motility, intraocular pressure, and color vision. The external examination was remarkable for thickened, tender auricles bilaterally and 2+ diffuse scleritis of both eyes without proptosis (Fig. 1). Both of his globes were tender to light touch.



SCLERITIS. *Bilateral eye redness that did not blanch with phenylephrine.*

The anterior segment examination showed a clear cornea without thinning or keratic precipitates. We saw no cellular reaction in the anterior chamber, and no iris nodules or atrophy were present. Mr. Hanson had trace nuclear sclerosis and no vitritis.

The fundus examination was normal in both eyes, without serous retinal detachments, disc edema, or retinal vasculitis. He had no facial deformity, apart from his ear swelling, and no joint tenderness.

Differential Diagnosis

Given his auricular involvement, a diagnosis of relapsing polychondritis (RP) was at the top of our differential. During a thorough workup, we also evaluated Mr. Hanson for other causes of scleritis, including infectious diseases and vasculitis. Laboratory testing for rheumatoid factor, syphilis serologies, antinuclear antibody (ANA), and antineutrophilic cytoplasmic antibodies (ANCA) were negative, and a chest x-ray was normal. A biopsy of the auricular cartilage was performed for definitive diagnosis. The pathology report confirmed a mixed perichondral infiltrate of lymphocytes and other inflammatory cells at the chondrodermal junction consistent with RP.

Discussion

RP is an inflammatory disorder believed to be caused by antibodies against type II collagen.[1,2] Sudden onset of ear involvement is frequently the presenting symptom, although patients may also present with concomitant arthritis. Other common manifestations include recurrent inflammation of cartilaginous tissues: ears, nose, peripheral joints, eyes, and the laryngotracheobronchial tree. Patients may develop cardiovascular disease, and one-third of patients

BY **ASHVINI K. REDDY, MD,** AND **CHRISTOPHER WEAVER, MD.** EDITED BY STEVEN J. GEDDE, MD.

Christopher Weaver, MD

have vasculitis and autoimmune rheumatic disease.

Diagnostic criteria for RP include recurrent chondritis of both auricles, nonerosive inflammatory polyarthritis, chondritis of nose cartilage, ocular inflammation (keratitis, scleritis, episcleritis, uveitis), laryngotracheitis, and vestibulocochlear inflammation and damage. Although not diagnostic, patients often have anemia, elevations in erythrocyte sedimentation rate and C-reactive protein, and leukocytosis. Antibodies to collagen II are found in 40% to 50% of patients.

Eye involvement. Ocular involvement occurs in 60% of reported patients with RP and usually manifests as scleritis, episcleritis, keratitis, or conjunctivitis, but it can present with multiple findings.[3] Scleritis and episcleritis often occur concomitantly with nose and joint inflammation. Compared with scleritis associated with other systemic immune diseases, scleritis associated with RP is more often bilateral, necrotizing, recurrent, and associated with decreased vision. Furthermore, over 60% of patients with RP-associated scleritis also have another systemic immune disease.[3] Patients can also develop retinal vasculitis and optic neuritis.

The classic sign of scleritis is edema in the episcleral and scleral tissues with injection in the superficial and deep episcleral vessels. Ocular complications of scleritis include interstitial keratitis, marginal corneal ulcers, peripheral ulcerative keratitis, anterior uveitis, and glaucoma. Posterior scleritis may be associated with a higher risk of macular edema, exudative retinal detachment, and vitritis.

Evaluation. Because scleritis can be associated with various underlying disorders, the evaluation may include chest x-ray, urinalysis, serum creatinine, ANCA, syphilis serology, and Quantiferon testing (for tuberculosis). Other tests may be indicated as dictated by history and examination findings: radiographic imaging of the sinuses (for granulomatous polyangiitis involving the sinuses), ANA and complement proteins C3 and C4 (for systemic lupus erythematosus), rheumatoid factor and anticyclic citrullinated peptide (for rheumatoid arthritis), and imaging of the trachea (for RP). Additional imaging may be indicated to evaluate for associated orbital inflammation. Ultrasound can confirm posterior involvement, if suspected.

Management. RP-related scleritis should be managed with a multidisciplinary team, given the risk of systemic disease. The team may include rheumatologists and otolaryngologists. Treatment for RP-related scleritis may involve use of nonsteroidal anti-inflammatory drugs, steroids, or immunosuppressants. Indications for immunosuppression include failure to control disease with steroids, health-threatening steroid adverse effects, or an autoimmune condition requiring steroid-sparing therapy.

Specific agents may include the following:

- Indomethacin 25 mg orally, four times daily or naproxen 500 twice daily
- Prednisone 1 mg/kg orally daily
- Antimetabolites: methotrexate, azathioprine, or mycophenolate
- Biologics: adalimumab or infliximab
- Alkylating agents: cyclophosphamide or chlorambucil

Some patients may achieve remission following therapy. With appropriate medication and follow-up, the prognosis can be good.

Lethal sequela. It is important for physicians to be aware of RP because respiratory involvement can be fatal. Up to 25% of patients present initially with respiratory symptoms. Laryngotracheobronchitis can manifest with hoarseness, nonproductive cough, dyspnea, wheezing, and inspiratory stridor with tenderness over the thyroid cartilage and trachea. Patients are at risk for upper airway collapse and infections.

Our Patient's Course

Mr. Hanson was educated about RP, especially the risk of life-threatening tracheal involvement and the need to seek emergency care if he suspected any problems. Once the diagnosis was confirmed, he was referred to the rheumatology and pulmonary services for coordinated care and was started on treatment with oral prednisone and methotrexate with folic acid. This regimen resulted in good control of his inflammatory disease, and he had no further episodes of scleritis or auricular inflammation. He continues to be followed for any signs of inflammation.

Conclusion

RP is a rare inflammatory disorder directed against type II collagen that can present as ocular inflammatory disease. It is important to recognize the condition early because respiratory involvement can be fatal if untreated. Multidisciplinary involvement with immunosuppression is generally needed to control systemic disease.

*Patient name is fictitious.

1 Borgia F et al. *Biomedicines.* 2018;6(3):E84.
2 Zampeli E, Moutsopoulos HM. *Rheumatology* (Oxford). 2018;57(10):1768.
3 Sainz-de-la-Maza M et al. *Br J Ophthalmol.* 2016;100(9):1290-1294.

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The Promise of Teleglaucoma:

Increasing Outreach, Expanding Access to Care

Can teleglaucoma reach patients whom traditional eye care has missed?

By Annie Stuart, Contributing Writer

First you heard of telemedicine, then teleophthalmology. Thanks to an abundance of technology, the evolution continues. Today it takes many forms. Remote screenings can be done at drugstore kiosks and on personal computers and smartphones. And distance management can happen with home-monitoring devices and apps or in optometry offices via real-time or asynchronous consultation with an ophthalmologist. And the options are only proliferating.

Now a band of glaucoma experts is making the concept their own with teleglaucoma. Chronic, progressive, and largely silent, glaucoma poses challenges for patients and eye care providers alike. Teleglaucoma—the use of electronic technologies to remotely find and enhance management of patients with or at risk of glaucoma—has the potential to help ensure continuity of care and preserve vision in an aging population, said Albert S. Khouri, MD, in Newark, New Jersey.

"The patient-physician relationship in glaucoma is really critical," said Karim F. Damji, MD, in Edmonton, Alberta. "But not every patient needs to be seen for everything, and there are smart ways to leverage technology to improve holistic care."

Benefits

Access to care. Teleglaucoma could increase access to eye care for people in medically underserved areas, said Paula Anne Newman-Casey, MD, in Ann Arbor, Michigan. "This includes impoverished populations and people living in rural or remote areas or countries where they wouldn't otherwise have access to medical expertise."

It also offers the potential to shift the paradigm from first-come, first-served to needs based, said Dr. Khouri. "We can develop teleglaucoma standards where patients with more advanced or progressive disease cut the line and are seen first, literally saving the vision of those patients."

Of course, said Dr. Damji, "not all patients are good candidates for teleglaucoma. For example, patients experiencing acute angle-closure glaucoma or those with concomitant mental health issues are better seen in person."

Efficiency and convenience. Patients may appreciate that telemedicine allows them to be seen quickly, rather than waiting months for an appointment in a big eye center, said Dr. Damji. In one northern Alberta program, optometrists work in teleconsultation with a glaucoma specialist to handle ongoing patient management.[1,2]

We can't underestimate the patient's need for convenience, for which some patients may even be willing to pay extra, said Lama A. Al-Aswad, MD, MPH, in New York City. Today, many glaucoma patients must take time off work and spend a couple of hours for testing. "In the future," she said, "home monitoring and ophthalmology kiosks may allow patients greater control over their time."

Cost. As an added benefit, this approach is

TEACHING. *Dr. Damji leverages remote fundus images when he teaches residents and fellows.*

expected to save money. A cost-effectiveness analysis of teleglaucoma screening in Canada demonstrated that implementing teleglaucoma in rural Alberta and targeting an at-risk population was cost-effective when compared with an in-person exam.[3]

Resident education. Teleglaucoma may also have a superb application in resident education, said Dr. Khouri, who is program director of the ophthalmology residency at Rutgers New Jersey Medical School. "For example, it can make it possible for the attending physician to give direct feedback based on objective data—images and readings—through telemedicine, not just a description over the phone."

Implementation Challenges

Telemedicine has come a long way since it was introduced in the 1960s and '70s, yet in today's Internet-enabled world, teleglaucoma still faces challenges.

A complex disease. Diabetic retinopathy (DR) is ideal for a telemedicine-based approach because it requires only a single modality of imaging for diagnosis, said Dr. Newman-Casey. In contrast, "glaucoma requires multiple imaging modalities and ancillary testing to make a good diagnosis." This includes structural assessment of the optic nerve through photographs or optical coherence tomography (OCT), as well as functional assessment through visual field testing. When evaluating a patient's risk of disease progession and deciding on the ideal treatment regimen, ophthalmologists take into account other parameters as well, such as central corneal thickness, intraocular pressure (IOP), and family history, she said.

"Because the diagnosis and management of glaucoma are more complex, it's more difficult to do remotely," said Dr. Newman-Casey. "That being said, it's not impossible."

Validation and standardization. "If you ask doctors to begin using a new technology," said Michael F. Chiang, MD, in Portland, Oregon, "they will often ask, 'Can you prove to me that I'm going to get the right answer?'" The same holds true for teleglaucoma. "You need to demonstrate that you can get the right diagnosis at a distance."

Notably, teleglaucoma needs "models or standards that are validated for image acquisition, transfer, and interpretation as well as tonometry and structure and function testing," said Dr. Khouri. In addition, agreement is needed on questions such as when to refer patients for follow-up, said Dr. Al-Aswad.

Another challenge? "Sometimes the technology evolves so fast that by the time you construct and complete a clinical trial, the technology has evolved, making the data obsolete," said Dr. Khouri, who is currently conducting a clinical trial at Rutgers to compare findings from teleglaucoma evaluations (visual acuity, tonometry, optic nerve, and OCT readings) to a standard clinical exam.[4]

Medical liability. Another need is clear-cut regulation. "There is a range of liability issues in telemedicine, including HIPAA and confidentiality concerns," said Dr. Khouri, "and all of these need to be sorted out for the field to progress." An umbrella license for telemedicine is also urgent, added Dr. Al-Aswad, who cited her inability to read images of New Jersey patients when her mobile eye van crosses into that state from New York, where she has her practice.

Reimbursement. Widespread adoption of teleglaucoma also won't happen without legislation concerning reimbursement, said Dr. Al-Aswad.

"An ongoing challenge of telemedicine in the United States is reimbursement, which has been limited, particularly for the store-and-forward models that are most common in ophthalmology," said Dr. Chiang. Dr. Newman-Casey noted that the reimbursement code used for picture-based store-and-forward screening or diagnosis is not enough to cover the equipment or services provided. "However," she said, "this is now undergoing scrutiny as the patient's burden for monitoring chronic disease becomes more apparent."

To improve reimbursement models for telemedicine, said Dr. Chiang, "we'll need evidence of diagnostic accuracy to demonstrate for providers that these technologies work, evidence of cost-effectiveness to demonstrate for payers that they should be covered, and discussion with policymakers, which the Academy has been involved with. In some diseases like DR and retinopathy

John Ulan

of prematurity, there is fairly extensive literature demonstrating diagnostic accuracy and cost-effectiveness. For other diseases, there has been far less work."

Reimbursement needs to be carefully thought out, Dr. Newman-Casey pointed out. "We don't want to incentivize patients to not come in to see their provider when it's important that they do so. We want to have some contact with people to make sure they're not having trouble taking their medications—that cost and side effects aren't a barrier and that they know how to put eyedrops in."

Continuity of care. In fact, lack of follow-up and face-to-face contact can be one of the biggest challenges with teleglaucoma, said Dr. Khouri. "Once you identify patients through screening, many may not present back to doctors for continuity of care." However, he said, continued improvements in technology may help remove some of these obstacles. For example, telepresence now allows a remote physician to have access to data in real time. "With synchronous audiovisual communication, you can more comfortably evaluate the patient and make recommendations," he said.

An Array of Teleglaucoma Models

Teleglaucoma has multiple arms, said Dr. Al-Aswad. In addition to synchronous and asynchronous relay of data, a variety of models can be used for screening and management.

Screening. Given that more than 50% of Americans with glaucoma don't know they have the disease,[5] screening may be the lower-hanging fruit for teleglaucoma. "With effective tools, teleglaucoma has the potential to detect the disease early, critically important given that severe damage can occur despite a lack of symptoms," said Felipe A. Medeiros, MD, PhD, in Durham, North Carolina.

One model is consultation-based telehealth. For example, a rural ophthalmologist might remotely collect data to transmit to the nearest glaucoma subspecialist, said Dr. Chiang.

Another model is community-based screening. Dr. Al-Aswad and her team have developed a real-time (synchronous) teleophthalmology program in New York City, where they use a mobile van to screen individuals for the four leading causes of blindness, including glaucoma. This includes video consultation with an eye care provider. (See sidebar, "An Urban Model for Teleophthalmology.") Densely populated areas like this can help facilitate community-based screening, said Dr. Newman-Casey.

Dr. Khouri and his team have also developed and reported on a protocol to detect eye disease in high-risk populations in Newark and other parts of New Jersey.[6,7] "Our teleophthalmology protocols rely on high-resolution imaging and software filters that enhance the detection of vision-threatening diseases," said Dr. Khouri. "Imaging the ganglion cell and nerve fiber layers is important in the early detection of glaucoma. We do screening events at soup kitchens, community centers, churches, temples, and mosques. When we identify patients with pathology, we make recommendations and refer patients to the university hospital for management."

Monitoring. Another strength for telemedicine is monitoring. "As long as we have effective teleglaucoma methods to monitor these patients, they don't need to be coming to the hospital all the time for follow-up," said Dr. Medeiros. An alternative is to have a trained technician conduct tests on glaucoma suspects or patients who are stable, a method that has been piloted in the United Kingdom.[8] "The physician then reviews the data online, reports and signs off, and alternates a virtual visit with an in-person visit," said Dr. Damji.

Home monitoring. "I think the future of teleglaucoma is patients becoming active participants in monitoring their disease," said Dr. Al-Aswad. "I envision that the patient will do home testing—measuring IOP and visual fields, for example—and transmit that data to me. If the patient is stable, I will only see him or her once a year."

Dr. Al-Aswad refers to a study she was involved in using home tonometry to understand disease progression and fluctuation of IOP. Home testing allowed her to spot and treat high IOP in a patient whose test results in the office had all appeared normal.

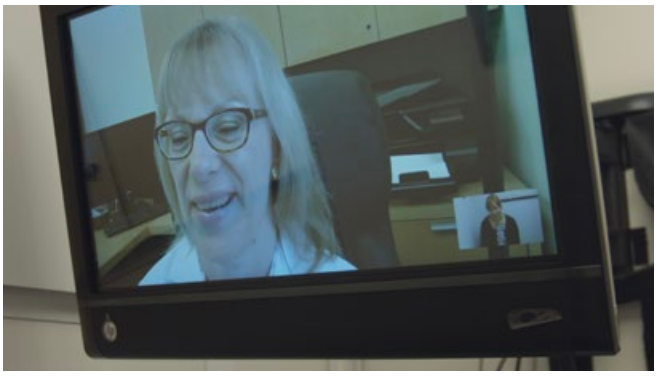
There are still lots of logistics to work out with home monitoring, said Dr. Chiang. Should patients self refer or be responsible for calling their doctor if their pressure is above a certain cutoff? Or should the data automatically trans-

GRADING. *Dr. Damji in the process of teleglaucoma grading.*

John Ulan

mit to some central service and flag the system if there is a concern?

Information overload is another risk with home monitoring. "You can get an overwhelming amount of data with a lot of noise built in," said Dr. Khouri. "But as the technology improves, you will be able to filter out the noise. Or with a product such as iCare HOME, for example, you could ask patients to monitor once a day or customize testing, as needed."



CONSULTING. *In Dr. Al-Aswad's mobile unit, a physician at an academic center speaks with a patient.*

Collaborative care. Shared management, another model, can take several forms.

ODs. In Northern Alberta, we've developed shared-care guidelines,[9] said Dr. Damji. "We collaborate with a large network of optometrists, who manage the patient on the front line. They provide us with structured information, using an asynchronous, store-forward system. We then provide feedback on the particular patient based on the history, exam, and testing, and we advise how soon a patient needs to be seen."

Techs. In Atlanta, April Maa, MD, has created and implemented a collaborative screening program called Technology-Based Eye Care Services, which allows the Veterans Affairs to reach underserved veterans. A trained ophthalmology technician is stationed in a primary care clinic. This person follows a detailed protocol to collect information about the patient's eyes, which is then interpreted remotely. Patients with likely abnormal findings are scheduled for a face-to-face exam in the eye clinic.[10]

Dr. Newman-Casey said she thinks this model works well because screening doesn't take up much space in the family practice office and nonophthalmic staff members aren't expected to capture the ocular data. "If this model were expanded to provide glaucoma monitoring in low-risk patients, the ophthalmic technicians' role could be expanded to provide glaucoma education as well," she said.

SCREENING. *A patient is examined in Dr. Al-Aswad's mobile unit.*

Portable Technologies

A variety of types of portable technologies are being developed for remote screening and monitoring of glaucoma. "It's incumbent upon us to test these devices more thoroughly before rolling them out for patient care," said Dr. Newman-Casey. "I would love to see industry take a greater role in validating new instruments in the population in which they'll be used."

Portable cameras. In fact, Dr. Newman-Casey recently conducted an instrument validation study in Nepal to compare the reliability of information that clinicians could obtain from either a traditional tabletop fundus camera or a portable, lightweight, less expensive fundus camera that requires no dilation. The researchers found no clinically significant difference in reliability between the two cameras.[11] "This lays the groundwork for using the portable camera as part of population-based screening for glaucoma," said Dr. Newman-Casey.

Smartphones. Smartphones are another way to visualize the optic nerve. When equipped with special lenses, they can get very good pictures of the back of the eye, said Dr. Medeiros.[12]

"I can foresee the day where patients can obtain a selfie of their own eyes," added Dr. Damji, "and obtain more than just structural information. The device could take photographs of the front and back of the eyes, assist in visual acuity/visual field and eventually other aspects of testing, and provide a template for structured history taking. The patient could then send all this data through a patient electronic portal into an artificial intelligence (AI) filter and then very quickly receive feedback from an eye care professional."

Tablets. "There's also the potential to use the portable camera on a tablet in conjunction with perimetry software, such as the iPad-based Visual Fields Easy App, which is being used in Nepal," said Dr. Newman-Casey. (On the computer, Peristat is a free, web-based visual field test that can be used on monitors 17 inches or larger.)

Lama A. Al-Aswad, MD, MPH

The iCare HOME tonometer can be connected to a tablet, thus making it possible for that data to be transmitted to your office, something that Dr. Al-Aswad is doing with her patients.

Virtual reality goggles. Taking the next step in technology, Dr. Medeiros' lab has done an initial validation of a portable approach using virtual reality goggles to assess visual field defects. Called the nGoggle, it consists of a brain-computer interface that uses a wireless, dry electroencephalogram, electrooculogram systems, and a head-mounted display.[13] (See "The New World of Virtual Reality," *EyeNet*, October 2018.)

"We have optimized the nGoggle's algorithm for testing and incorporated eye tracking to better detect loss of fixation and ensure testing reliability," said Dr. Medeiros. He hopes to soon begin studies to validate the home-based application.

Artificial Intelligence

Dr. Medeiros is also working with AI. He predicts that AI will be implemented in primary care practices for opportunistic screening of eye diseases within the next five years. "The future is AI and doctors working together to provide better care for our patients," said Dr. Al-Aswad. "It will help us practice at the top of our license, manage disease, and prevent blindness—not replace us."

Optic disc photos. "A model that excites me is the Pegasus system," said Dr. Damji. The retinal analysis decision support system can provide quick grading of the nerve and additional aspects for DR, he said. "Using deep learning, it has the potential to develop a comparable ability in assessing optic disc photographs for glaucoma."

Using OCT to train AI. One challenge in using AI to evaluate fundus photographs for glaucoma, said Dr. Medeiros, is that an AI algorithm—when taught by using human-based grading as reference—will simply replicate the doctors' errors, which are especially common in the early stages of the disease. "We know that ophthalmologists, even glaucoma specialists, tend to perform poorly when trying to detect glaucoma based on a photograph of the optic disc. Therefore, an AI algorithm trained on that is not going to be different," he said.

"An alternative is to use an objective instrument such as OCT, which can give us a much more accurate, precise, and quantifiable assessment of structure," said Dr. Medeiros. "An AI algorithm trained to predict OCT measures from optic disc photographs can give you a quantitative and precise measurement of the amount of nerve damage." Dr. Medeiros and his team have used

An Urban Model for Teleophthalmology

Between 2007 and 2014, Dr. Al-Aswad conducted a screening program in high-risk communities of New York City—and did so without the help of teleglaucoma. "Whether or not they had insurance, 57% had never previously been seen by an eye doctor, which was astonishing to me," she said.

MOBILE UNIT. *Dr. Al-Aswad's mobile center brings screening for glaucoma and other blinding conditions to at-risk communities in the New York area.*

This became the seed for what she and her team ultimately built—telemedicine to screen for leading causes of blindness in high-risk, poor communities in the city. "In 12 months, we've screened close to 1,300 individuals for the four leading causes of blindness," said Dr. Al-Aswad.

It took two to three years to build the program, which included creating the team, acquiring a mobile unit with state-of-the-art equipment for ophthalmology, building a data-capturing system, and ensuring connectivity and security. The free screening includes visual fields, anterior and posterior segment OCT images of the optic nerve, and retina and fundus photographs of the retina.

Recently, Dr. Al-Aswad collaborated with GlobeChek to add the first GlobeChek kiosk to her screening program. "In addition, we screen for comorbidities of eye disease, checking hemoglobin A_{1C}, blood pressure, and body mass index," said Dr. Al-Aswad. "After the technicians complete the screening, the individuals go to a private area in the mobile unit, where they have a videoconference with an ophthalmologist or optometrist to discuss the results."

The eye care physician then gives a recommendation for follow-up. "If it's an emergency, like angle-closure glaucoma, we send them directly to an ER at a safety net hospital," she said. "If it's not an emergency, we send them to the community ophthalmologist or optometrist in their area. This has not only been helpful to the patients, but we're also learning a lot about these eye diseases."

Lama A. Al-Aswad, MD, MPH

more than 30,000 pairs of optic disc photos and spectral-domain OCT (SD-OCT) retinal nerve fiber layer retinal (RNFL) scans to train AI to assess the photos and predict the actual estimate of nerve damage.[14] "In a validation study, we found a very strong correlation between the predicted and observed RNFL thickness values—between what the AI algorithm could see in the photo and the SD-OCT result," said Dr. Medeiros.

Although the researchers have not yet implemented this AI approach in a teleglaucoma setting, Dr. Medeiros is optimistic about its potential. An AI algorithm trained this way to assess optic nerve damage from photographs would be much less expensive than an OCT system and, therefore, potentially suitable for large-scale deployment, he added. "Because it provides a quantitative estimate of nerve damage—not just a 'yes' or 'no' diagnosis—it may also be used for monitoring over time," he said, adding that the algorithm has not yet been tested for this kind of follow-up.

More is better? Currently, most AI models rely on either optic nerve head photos or OCTs to determine pathology, said Dr. Khouri. "But, in time, I predict they will integrate both structure and function, and the accuracy of detection will be even better."

1 Arora S et al. *Telemed J E Health.* 2014;20(5):439-445.
2 Verma S et al. *Can J Ophthalmol.* 2014;49(2):135-140.
3 Thomas S et al. *PLoS One.* 2015;10(9):e0137913.
4 Khouri AS, Szirth BC. Feasibility of teleglaucoma versus clinical evaluation for diagnostic accuracy and management recommendations in patients with glaucoma. ClinicalTrials.gov NCT03587454.
5 aao.org/newsroom/news-releases/detail/half-of-those-with-glaucoma-don-t-know-it-are-you-.
6 Kolomeyer AM et al. *Telemed J E Health.* 2013;19(1)2-6.
7 Al-Aswad LA et al. Poster #407, Ophthalmic screening for high-risk population using mobile tele-ophthalmology (pilot study). Presented at AAO 2018, Monday, Oct. 29, 2018.
8 Kotecha A et al. *Clin Ophthalmol.* 2015;9:1915-1923.
9 Kassam F et al. *Clin Exp Optom.* 2013;96(6):577-580.
10 Maa AY et al. *Ophthalmology.* 2017;124(4):539-546.
11 Miller SE et al. *Am J Ophthalmol.* 2017;182:99-106.
12 Mohammadpour M et al. *Int J Ophthalmol.* 2017;10(12):1909-1918.
13 Nakanishi M et al. *JAMA Ophthalmol.* 2017;135(6):550-557.
14 Medeiros FA et al. *Ophthalmology.* Published online Dec. 20, 2018.

EXTRA **MORE ONLINE.** See this article at aao.org/eyenet for a sidebar on prerequisites for a successful teleglaucoma program.

MEET THE EXPERTS

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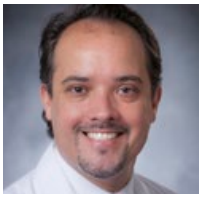

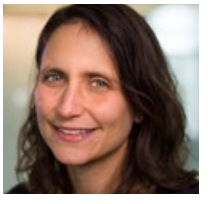

See the disclosure key, page 13. **For full disclosures,** see this article at aao.org/eyenet.

Code-a-Palooza: Money Talks, But Can You Make It Sing?

With a game show format, prizes, and a soundtrack of golden oldies, Code-a-Palooza lives up to its name! At each year's annual meeting, two teams of volunteers compete against each other *and* against the crowd, which is equipped with audience-response units.

How would you do at Code-a-Palooza? Try tackling some of the most challenging questions from last year's event. (Answers on page 57.)

Turn Up the Music and See How You Do!

Q1: "I Heard It Through the Grapevine." The No. 1 question currently submitted to aao.org/coding is: "Does Medicare reimburse us for both services if we perform GDx imaging (CPT code 92133) and an extended visual field exam (92083) on the same patient on the same day?"

A. Yes.
B. No.

Q2: "Happy Together?" "We submitted the Eye visit code for an intermediate established patient (92012), along with codes for fundus photography (92250), serial tonometry (92100), and corneal pachymetry (76514). The commercial BlueShield plan paid all but serial tonometry. Why was serial tonometry denied?"

A. It is bundled with the other tests.
B. Its CPT description states "separate procedure."
C. It is payable with an E&M code, not an Eye visit code.

Q3: "Do Wah DiddY DiddY" (DiddY). You are researching a surgical code in the Medicare database, and you notice that its global period is listed as "YYY." Why the "YYY"?

A. Why, why, why does it matter?
B. Because the surgical code is an add-on code, as in strabismus surgery (e.g., +67320).
C. Because it is a code for an unlisted procedure, such as 66999 *Unlisted procedure, anterior segment of the eye.*
D. Because it is a Category III CPT code, such as 0191T, which is used for iStent and Hydrus inserts.

Q4: "Yesterday." One day before a patient is due to have surgery (which could be major or minor), she presents for a problem unrelated to that surgery. Which of the following statements is true?

A. No issues; the exam is payable.
B. The exam will be denied because it is a preoperative service that is included in the global surgical payment.
C. The exam requires a modifier.

Q5: "For What It's Worth." A physician spent 25 minutes talking to the patient and his daughter. No elements of the exam were performed. Which code should you submit to insurance?

A. 99212.
B. 99214.
C. 92002.
D. Submit nothing.

Q6: "Every Breath You Take" (They'll Be Watching You). You perform an exam (99205) and find that the patient has a retinal tear in the left eye and a detachment in the right. Later that morning, you perform extended ophthalmoscopy (92225) and laser (67105) in the office; in the afternoon, you take the patient to the operating room to repair the retinal detachment with vitrectomy (67108). The payer is Medicare Part B.

Q6a: What modifier(s) should be appended to the exam code?

A. 99205–25.
B. 99205–57.
C. 99205–25–57.

Q6b: What modifier(s) should be appended to the surgical codes?

A. 67105–LT, 67108–RT.
B. 67105–LT, 67108–79–RT.
C. 67105–LT, 67108–59–79–RT.

Q7: "Help!" "A hospital inpatient is seen in our office. An exam and test were performed. I billed from the inpatient family of E&M codes with hospital as the place of service. I got paid for the exam but not the test. Why?"

A. The test may have been bundled with the exam.
B. The practice should have submitted only the technical component since the equipment is owned by the practice.
C. The practice should have submitted only the professional component.

BY **SUE VICCHRILLI, COT, OCS,** AND **MATTHEW BAUGH, MHA, COT, OSC, OCS, OCSR.**

Ms. Vicchrilli is Academy director of Coding and Reimbursement; **Mr. Baugh** is program manager of Revenue Cycle Integrity and Quality Improvement Programs at the John A. Moran Eye Center in Salt Lake City.

Indications and Usage

BromSite® (bromfenac ophthalmic solution) 0.075% is a nonsteroidal anti-inflammatory drug (NSAID) indicated for the treatment of postoperative inflammation and prevention of ocular pain in patients undergoing cataract surgery.

Recommended Dosing

One drop of BromSite® should be applied to the affected eye twice daily (morning and evening) 1 day prior to surgery, the day of surgery, and 14 days postsurgery.

Important Safety Information

- **Slow or Delayed Healing:** All topical nonsteroidal anti-inflammatory drugs (NSAIDs), including BromSite®, may slow or delay healing. Topical corticosteroids are also known to slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.
- **Potential for Cross-Sensitivity:** There is the potential for cross-sensitivity to acetylsalicylic acid, phenylacetic acid derivatives, and other NSAIDs, including BromSite®. Therefore, caution should be used when treating individuals who have previously exhibited sensitivities to these drugs.
- **Increased Bleeding Time of Ocular Tissue:** With some NSAIDs, including BromSite®, there exists the potential for increased bleeding time due to interference with platelet aggregation. There have been reports that ocularly applied NSAIDs may cause increased bleeding of ocular tissues (including hyphemas) in conjunction with ocular surgery. It is recommended that BromSite® be used with caution in patients with known bleeding tendencies or who are receiving other medications which may prolong bleeding time.
- **Keratitis and Corneal Effects:** Use of topical NSAIDs may result in keratitis. In some susceptible patients, continued use of topical NSAIDs may result in epithelial breakdown, corneal thinning, corneal erosion, corneal ulceration or corneal perforation. Patients with evidence

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FOR YOUR CATARACT SURGERY PATIENTS

Defend against ocular pain and combat postoperative inflammation with the penetrating power of BromSite® formulated with DuraSite®[1]

- DuraSite® increases ocular surface retention time, resulting in increased bromfenac absorption[2-5]
- Provides 24-hour coverage with BID dosing[1]
- Available in 5 mL bottle

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BromSite®
(bromfenac ophthalmic solution) 0.075%
Formulated with DURASITE® DELIVERY SYSTEM

of corneal epithelial breakdown should immediately discontinue use of topical NSAIDs, including BromSite®, and should be closely monitored for corneal health. Patients with complicated ocular surgeries, corneal denervation, corneal epithelial defects, diabetes mellitus, ocular surface diseases (e.g., dry eye syndrome), rheumatoid arthritis, or repeat ocular surgeries within a short period of time may be at increased risk for corneal adverse events which may become sight threatening. Topical NSAIDs should be used with caution in these patients. Post-marketing experience with topical NSAIDs also suggests that use more than 24 hours prior to surgery or use beyond 14 days postsurgery may increase patient risk for the occurrence and severity of corneal adverse events.

- **Contact Lens Wear:** BromSite® should not be administered while wearing contact lenses. The preservative in BromSite®, benzalkonium chloride, may be absorbed by soft contact lenses.
- **Adverse Reactions:** The most commonly reported adverse reactions in 1% to 8% of patients were anterior chamber inflammation, headache, vitreous floaters, iritis, eye pain, and ocular hypertension.

Please see brief summary of Full Prescribing Information on the adjacent page.

NSAID=nonsteroidal anti-inflammatory drug.

References: 1. BromSite® [package insert]. Cranbury, NJ: Sun Pharmaceutical Industries, Inc.; 2016. **2.** Hosseini K, Hutcheson J, Bowman L. Aqueous humor concentration of bromfenac 0.09% (Bromday™) compared with bromfenac in DuraSite® 0.075% (BromSite™) in cataract patients undergoing phacoemulsification after 3 days dosing. Poster presented at: ARVO Annual Meeting; May 5-9, 2013; Seattle, Washington. **3.** ClinicalTrials.gov. Aqueous humor concentration of InSite Vision (ISV) 303 (bromfenac in DuraSite) to Bromday once daily (QD) prior to cataract surgery. https://clinicaltrials.gov/ct2/show/results/NCT01387464?sect=X70156&term=insite+vision&rank=1. Accessed March 2, 2017. **4.** Si EC, Bowman LM, Hosseini K. Pharmacokinetic comparisons of bromfenac in DuraSite and Xibrom. *J Ocul Pharmacol Ther.* 2011;27(1):61-66. **5.** Bowman LM, Si E, Pang J, et al. Development of a topical polymeric mucoadhesive ocular delivery system for azithromycin. *J Ocul Pharmacol Ther.* 2009;25(2):133-139.

SUN-OPH-BRO-219 03/2017

SUN OPHTHALMICS

BromSite® (bromfenac ophthalmic solution) 0.075%
Brief Summary

INDICATIONS AND USAGE
BromSite® (bromfenac ophthalmic solution) 0.075% is indicated for the treatment of postoperative inflammation and prevention of ocular pain in patients undergoing cataract surgery.

CONTRAINDICATIONS
None

WARNINGS AND PRECAUTIONS
Slow or Delayed Healing
All topical nonsteroidal anti-inflammatory drugs (NSAIDs), including BromSite® (bromfenac ophthalmic solution) 0.075%, may slow or delay healing. Topical corticosteroids are also known to slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.

Potential for Cross-Sensitivity
There is the potential for cross-sensitivity to acetylsalicylic acid, phenylacetic acid derivatives, and other NSAIDs, including BromSite® (bromfenac ophthalmic solution) 0.075%. Therefore, caution should be used when treating individuals who have previously exhibited sensitivities to these drugs.

Increased Bleeding Time of Ocular Tissue
With some NSAIDs, including BromSite® (bromfenac ophthalmic solution) 0.075%, there exists the potential for increased bleeding time due to interference with platelet aggregation. There have been reports that ocularly applied NSAIDs may cause increased bleeding of ocular tissues (including hyphemas) in conjunction with ocular surgery.

It is recommended that BromSite® be used with caution in patients with known bleeding tendencies or who are receiving other medications which may prolong bleeding time.

Keratitis and Corneal Reactions
Use of topical NSAIDs may result in keratitis. In some susceptible patients, continued use of topical NSAIDs may result in epithelial breakdown, corneal thinning, corneal erosion, corneal ulceration or corneal perforation. These events may be sight threatening. Patients with evidence of corneal epithelial breakdown should immediately discontinue use of topical NSAIDs, including BromSite® (bromfenac ophthalmic solution) 0.075%, and should be closely monitored for corneal health.

Post-marketing experience with topical NSAIDs suggests that patients with complicated ocular surgeries, corneal denervation, corneal epithelial defects, diabetes mellitus, ocular surface diseases (e.g., dry eye syndrome), rheumatoid arthritis, or repeat ocular surgeries within a short period of time may be at increased risk for corneal adverse events which may become sight threatening. Topical NSAIDs should be used with caution in these patients.

Post-marketing experience with topical NSAIDs also suggests that use more than 24 hours prior to surgery or use beyond 14 days postsurgery may increase patient risk for the occurrence and severity of corneal adverse events.

Contact Lens Wear
BromSite® should not be administered while wearing contact lenses. The preservative in BromSite®, benzalkonium chloride, may be absorbed by soft contact lenses.

ADVERSE REACTIONS
The following serious adverse reactions are described elsewhere in the Brief Summary:
- Slow or Delayed Healing
- Potential for Cross-Sensitivity
- Increased Bleeding Time of Ocular Tissue
- Keratitis and Corneal Reactions
- Contact Lens Wear

Clinical Trial Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The most commonly reported adverse reactions in 1–8% of patients were: anterior chamber inflammation, headache, vitreous floaters, iritis, eye pain and ocular hypertension.

USE IN SPECIFIC POPULATIONS
Pregnancy
Risk Summary
There are no adequate and well-controlled studies in pregnant women to inform any drug associated risks. Treatment of pregnant rats and rabbits with oral bromfenac did not produce teratogenic effects at clinically relevant doses.

Clinical Considerations
Because of the known effects of prostaglandin biosynthesis-inhibiting drugs on the fetal cardiovascular system (closure of ductus arteriosus), the use of BromSite® during late pregnancy should be avoided.

Data
Animal Data
Treatment of rats with bromfenac at oral doses up to 0.9 mg/kg/day (195 times a unilateral daily human ophthalmic dose on a mg/m^2 basis, assuming 100% absorbed) and rabbits at oral doses up to 7.5 mg/kg/day (3243 times a unilateral daily dose on a mg/m^2 basis) produced no structural teratogenicity in reproduction studies. However, embryo-fetal lethality, neonatal mortality and reduced postnatal growth were produced in rats at 0.9 mg/kg/day, and embryo-fetal lethality was produced in rabbits at 7.5 mg/kg/day. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Lactation
There are no data on the presence of bromfenac in human milk, the effects on the breastfed infant, or the effects on milk production; however, systemic exposure to bromfenac from ocular administration is low. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for bromfenac and any potential adverse effects on the breast-fed child from bromfenac or from the underlying maternal condition.

Pediatric Use
Safety and efficacy in pediatric patients below the age of 18 years have not been established.

Geriatric Use
There is no evidence that the efficacy or safety profiles for BromSite® differ in patients 65 years of age and older compared to younger adult patients.

NONCLINICAL TOXICOLOGY
Carcinogenesis, Mutagenesis and Impairment of Fertility
Long-term carcinogenicity studies in rats and mice given oral doses of bromfenac up to 0.6 mg/kg/day (129 times a unilateral daily dose assuming 100% absorbed, on a mg/m^2 basis) and 5 mg/kg/day (540 times a unilateral daily dose on a mg/m^2 basis), respectively revealed no significant increases in tumor incidence.

Bromfenac did not show mutagenic potential in various mutagenicity studies, including the bacterial reverse mutation, chromosomal aberration, and micronucleus tests.

Bromfenac did not impair fertility when administered orally to male and female rats at doses up to 0.9 mg/kg/day and 0.3 mg/kg/day, respectively (195 and 65 times a unilateral daily dose, respectively, on a mg/m^2 basis).

Rx Only
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SUN-OPH-BRO-017-1 03/2017

SUN OPHTHALMICS

How to Manage Your Malpractice Risk

Malpractice lawsuits are more common than you might think. During a typical 30-year career cycle, "31% of physicians will have three or more claims filed against them, with only 5% having none," said Hans Bruhn, MHS, risk manager at Ophthalmic Mutual Insurance Company (OMIC) in San Francisco.

What's more, plaintiff payout amounts are increasing. "There has been more volatility with regard to claims over the last several years because most attorneys who represent damage-seeking plaintiffs are taking on cases that have compelling merit and therefore result in larger settlements," said Ryan Bucsi, OMIC claims manager. However, he added, while there were "more million-dollar plaintiff verdicts awarded than ever in 2017, the frequency of claims and lawsuits filed has remained stable during the past six years."

In the current malpractice environment, risk management experts advise that ophthalmic practices take a few basic steps to help prevent and mitigate claims.

Purchase Comprehensive Malpractice Insurance

With so much at stake, it is essential to purchase insurance that covers patient liabilities resulting from direct patient care and the risks associated with that treatment. Medical malpractice insurance works by putting in place substantial safeguards against allegations of medical negligence directed toward a physician or practice.

Make sure that your malpractice carrier understands the work you do, said Linda D. Harrison, PhD, director of risk management at OMIC. "Risk management staff should possess both a depth and breadth of knowledge in general health care risk management as well as issues specific to the field of ophthalmology." They should also assist you with the less critical issues that may arise in your daily encounters. Whether you are confronted by patients who are dissatisfied with their LASIK procedure or patients who have major objections to their most recent bill, incidents should be managed in tandem with your insurer to avert or mitigate the threat of a claim, she said.

Keep insurance documentation current. Some ophthalmology practices may undergo changes that could affect their professional liability, such as addition of satellite locations, surgical suites, or new procedures. Even if the changes do not necessarily require a change to the type of insurance policy, they may need to be specifically underwritten and endorsed to the policy, Mr. Bucsi said. "It is always best to have a conservative view of insurance coverage and contact your carrier to verify requirements since it will often be too late to add coverage after an incident has occurred."

Identify and Manage Your Risk

Purchasing insurance is not your only line of defense, however. Knowing the risks for patient dissatisfaction and litigation can help your practice address potential issues before they turn into a lawsuit.

Prioritize patients. Of course, excellent patient care is central to effective risk management. "A breakdown in any of the multiple processes involved in patient care can result in patient dissatisfaction, patient harm, and a claim being filed against the insured. When dealing with patients, staff must listen carefully, communicate clearly and promptly, act with integrity, and be exquisitely sensitive to patient confidentiality," said Dr. Harrison.

Recognize the warning signs. It's also important to know which patients are more likely to bring a suit. Ellen Adams, MBA, compliance officer at Ophthalmic Consultants of Boston, has observed several characteristics that indicate you might be dealing with a litigious patient. "Noncompliance [e.g., when the patient has a high frequency of missed appointments or refuses to follow physician instructions], failure to pay copays and other out-of-pocket expenses, displaying disruptive behavior in the office, and having unrealistic treatment expectations and unreasonable demands are clues—sometimes subtle, sometimes overt."

In addition, Ms. Adams said, "Notes in a patient's chart that indicate a level of dissatisfaction that does not correlate with the patient's vision is an automatic 'red flag' for me." She offered the

BY LESLIE BURLING, CONTRIBUTING WRITER, INTERVIEWING **ELLEN ADAMS, MBA, HANS BRUHN, MHS, RYAN BUCSI,** AND **LINDA D. HARRISON, PHD.**

example of a patient with a premium intraocular lens and 20/20 vision who was complaining bitterly about having poor vision. She said that practices should heed these cues and promptly respond by following practice protocols and involving their insurance carrier when necessary.

Educate staff. The ability to quickly ask for advice is often effective in preventing a situation from escalating into a formal claim, Mr. Bucsi said. To best prepare your staff for the wide variety of situations they may face regarding malpractice risk, he suggested prominently displaying your insurer's number in your office where all staff (and not patients) can see it, and giving verbal instructions about using the service to staff. He also recommended posting those instructions in writing on a bulletin board or common area of your office. It is particularly important for ancillary personnel to know whom to call if the physicians are not present or available, he said.

Work Cooperatively With the Insurer

If you have a potentially litigious patient, it's best to call your insurer so that they can help you proactively manage the issue.

Call every time questions arise. There is a common misconception that if an insured calls their insurance company frequently or reports multiple incidents, the insurer will no longer cover them. That simply is not the case, said Mr. Bruhn. "Call early and call often. Insureds should call at the very first sign that a patient is dissatisfied so the incident can be resolved before a claim is initiated."

If the situation has escalated, never respond to a third party, particularly attorneys working on behalf of plaintiffs or patients, without first consulting with your malpractice insurance carrier. Responding without a consultation could negatively impact defensibility of a claim. Furthermore, Mr. Bruhn said that insurance policies often have requirements for the timely reporting of an incident, so you should always report claims promptly to your insurer.

Remember that your medical malpractice insurer is there to help, and the advice they can offer is extremely valuable.

Contact the insurer. Queries can be submitted to most risk management teams either by telephone or email, said Mr. Bruhn. Some insurers, like OMIC, offer risk management hotlines that can and should be used anytime practices have concerns related to potential incidents, existing claims, or lawsuits, said Mr. Bucsi.

OMIC's records show that hotline calls tend to fall into two categories: administrative/procedural and legal.

Administrative calls. The most common topics insureds inquire about include "dealing with difficult patients, patient termination protocols, informed consent, responding to patient complaints (with and without a monetary demand), and developing office policies and procedures," said Dr. Harrison.

She added, "When there is an issue in the national lay or scientific press, such as the recent CyPass stent recall by the U.S. Food and Drug Administration, or a state-specific issue that impacts ophthalmologists, we tend to receive a higher volume of inquiries from our insureds."

Legal calls. Mr. Bucsi detailed the types of legal calls OMIC typically receives. These include requests for legal advice and questions about deposition representation in cases in which the physician is not the target of a lawsuit but was involved in the patient's care; handling of medical board complaints; precautionary reporting of unanticipated outcomes that could result in a claim; and actual claims or lawsuits.

OMIC's Data: Settlements by Subspecialty

To be awarded damages in a malpractice claim, an injured patient must demonstrate that a physician acted negligently when rendering care and that the negligence resulted in an injury with demonstrable damages. Although a claim can be filed against any ophthalmic office, OMIC's data reveal trends that may indicate an increased risk for certain subspecialties.

The majority (73%) of OMIC's claims are related to comprehensive ophthalmology, cataract, and retina cases. However, pediatric cases account for 11% of OMIC's total indemnity payments and garner the highest settlement payouts, even though they account for only 2% of the total claims and suits filed. "This group averages over $400,000 per claim, with the highest paid claim peaking at $3.375 million for a case of retinopathy of prematurity," Mr. Bruhn reported.

Other examples of frequency and severity rates among ophthalmic subspecialties include the following:

- Oculoplastics. 7% percent of cases and 8% of indemnity payments
- Refractive. 7% of both cases and indemnity payments
- Glaucoma. 5% of cases and 4% of indemnity payments
- Cornea. 3% of both cases and indemnity payments.

About OMIC. OMIC is the largest insurer of ophthalmologists in the United States. Since OMIC's establishment in 1987, approximately 20% of claims made against its clients have been resolved with an indemnity payment, while the remaining 80% have been successfully mitigated.

More on Malpractice Lawsuits

Be sure to read this month's "Academy Notebook" section. The "Ask the Ethicist" column (page 56) investigates whether it is acceptable to serve as an expert witness in a malpractice case if you have not recently practiced the procedure in question. The article discusses the responsibilities and implications of malpractice testimony according to the Academy Code of Ethics.

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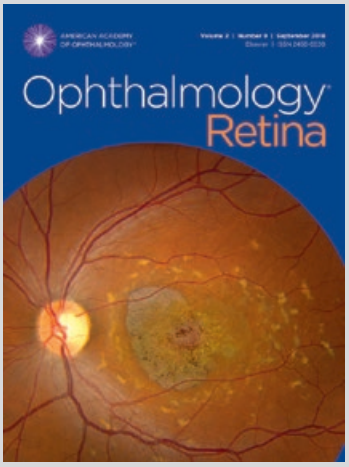
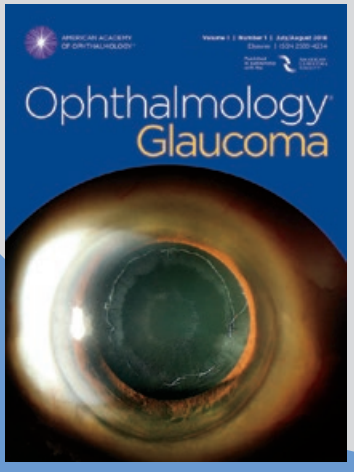
Ophthalmology® *Glaucoma*, published in partnership with the American Glaucoma Society, is the newest and most promising journal for this dynamic subspecialty.

*Source: Kantar Media





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- Play a key role in driving the highest quality of care for your patients.

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- The registration fee is $225 ($325 after March 6).
- There is no fee for Congressional Advocacy Day.
- Academy members in training receive complimentary registration to all events.
- Pre-registration ends March 25, 2019.

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Academy Notebook

NEWS • TIPS • RESOURCES

OPAL AT OBS. *This year's OPAL cohort will attend the Ophthalmology Business Summit on March 23-24, following an OPAL behavioral workshop on March 22.*

WHAT'S HAPPENING

Practice Administrators Participate in AAOE Pilot Leadership Program

A select group of American Academy of Ophthalmic Executives (AAOE) practice managers will meet in Chicago later this month as part of a pilot leadership development program called Ophthalmic Practice Administrators Leadership Program (OPAL), which AAOE launched at AAO 2018.

This first cohort will attend the Academy's Ophthalmology Business Summit (OBS) on March 23 and 24—a business-focused "boot camp" designed to address the volatile and complex challenges facing ophthalmic practices. During the summit, participants will attend sessions on emotional intelligence, strategic management, and building a culture of collaboration. Additionally, the cohort will attend a special kick-off Insights Discovery session on March 22, when they will learn a powerful behavior-style tool designed to teach people how to perform at their highest level.

Program objectives. OPAL focuses on professional development in the areas of communication, time management, collaboration, and change management with the goal of fostering participants' leadership skills to drive practice efficiency and encourage meaningful contributions to the field of ophthalmology.

Learning opportunities. Classroom-style learning is one key part of the program. In addition to the sessions at OBS, the OPAL program featured courses at AAO 2018, which participants attended in conjunction with an OPAL-specific session on mentorship. The group has also been engaging in bimonthly conference calls that use media, such as TED Talks and news articles, to spark discussions about leadership trends.

Individual projects. The capstone of the OPAL program is completion of individual leadership projects that address a specific gap or need within each participant's practice and/or community. After submitting project proposals in December, participants were paired with mentors who have experience in their proposed project area. They meet monthly with mentors via teleconferences. Participants have also supported each other during monthly teleconferences by providing different perspectives on each other's projects and sharing their struggles, triumphs, and useful tips.

In October, this year's OPAL cohort will present their projects at the AAOE Practice Management Program and welcome the incoming 2020 cohort.

Hone your leadership potential. If you are an AAOE practice administrator or work with an AAOE practice administrator who could benefit from this program, consider an application for the 2020 OPAL class. The deadline is May 1. For more information, visit aao.org/opal.

Be Heard at Mid-Year Forum 2019

The Mid-Year Forum (MYF) brings ophthalmologists together to advocate for political change on behalf of patients and the profession. This year's program, held April 10-13 in Washington, D.C., offers a variety of opportu-

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nities to learn and to make an impact, including the following:

- sessions on hot topics such as attempting to control drug spending, creating an inclusive practice, and understanding private equity in relation to ophthalmology;
- Congressional Advocacy Day, when attendees and Academy facilitators visit Congress and their staff members to speak on key ophthalmic issues; and
- the Academy Council meeting, when the Board of Trustees will speak about its goals and priorities as well as give Academy members a chance to offer feedback.

Register today. To find more information on the program and to reserve your spot, visit aao.org/myf. The registration fee increases from $225 to $325 on March 7, and preregistration is available through March 25; Congressional Advocacy Day's lobbying events on April 11 are free to Academy members.

TAKE NOTICE

Ask the Ethicist: The Nonoperating Expert Witness

Question. *I was asked to serve as an expert witness in a malpractice case involving visual loss related to cataract surgery. Although I am a general ophthalmologist and have performed many cataract surgeries in my career, I have not operated in several years. Is it ethical to serve as an expert?*

Answer. The trial judge will review your qualifications and determine whether you may testify. Typically, expert witnesses are practicing ophthalmologists who hold a current, valid, and unrestricted license. Considering that the opposing counsel will question your testimony and credentials as an expert witness, you must be very clear about your qualifications and the fact that you no longer operate.

Despite your status as a nonoperating physician, you are responsible for knowing about the accepted surgical techniques and standard of care relevant to the time and place of the case in question. The judicial process relies on expert witnesses to establish standard of care and therefore deviation from the standard of care. To help others understand the case and distinguish between malpractice and maloccurrence, it is your role to present truthful, unbiased information supported by the literature.

OPHTHALMOLOGY'S ADVOCATES. *Advocacy Ambassador Program members prepare for meetings with their House representatives during Congressional Advocacy Day, April 19, 2018.*

The Academy does not wish to influence which cases you choose to serve on as an expert witness. However, if your testimony is challenged, the Academy will enforce Rule 16 of its Code of Ethics:

"Expert testimony should be provided in an objective manner using medical knowledge to form expert medical opinions. Nonmedical factors (such as solicitation of business from attorneys, competition with other physicians, and personal bias unrelated to professional expertise) should not bias testimony. It is unethical for a physician to accept compensation that is contingent upon the outcome of litigation. False, deceptive, or misleading expert testimony is unethical. For purposes of this Rule, expert testimony shall include oral testimony provided under oath; affidavits and declarations used in court proceedings; and certificates of merit signed, ratified, or otherwise adopted by the physician."

Learn more at the Redmond Ethics Center, aao.org/clinical-education/redmond-ethics-center. Send questions to the Ethics Committee at ethics@aao.org.

Academy Year in Review

Academy leadership, staff, and countless volunteers work hard to provide you with the best member experience. Find out what the Academy achieved in the last year on all fronts, including advocacy, education, and public service. The *2018 Year in Review* highlights some of the Academy's greatest achievements, including the following:

- establishing a permanent research fund to advance the practice of pediatric ophthalmology;
- launching a campaign to build a new Museum of Vision;
- lobbying for ophthalmology's best interests in state and federal government affairs; and
- developing an award-winning public education campaign.

Learn more at aao.org/yearinreview.

Submit Your Research to *Ophthalmology Retina*

Ophthalmology Retina seeks to publish original research that will be of strong interest to retina specialists globally. The selection process favors papers that teach clinicians how to make better diagnoses, implement preferred treatments, and follow accepted practice patterns with the goal of delivering the best outcomes for patients.

Submit your research at www.evise.com/profile/#/ORET/login.

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MEETING MATTERS

Submit an AAO 2019 Abstract

Want to contribute your expertise to the world's most comprehensive ophthalmology meeting? The online submitter for AAO 2019 paper/poster and video abstracts opens March 7 and closes on April 9.

Posters. Starting in 2019, all posters will be electronic. Posters will be available to view on terminals in the convention center, online, and through the Mobile Meeting Guide. Selected poster authors will present their posters onsite at the Poster Theater.

Submit your video and paper/poster abstract at aao.org/abstracts. **Find abstract guidelines** at aao.org/presentercentral.

Important Dates

Registration and hotel. Mark your calendar: Academy and American Academy of Ophthalmic Executives members can register and make hotel reservations for Subspecialty Day (Oct. 11-12) and AAO 2019 (Oct. 12-15) in San Francisco starting June 12. Non-members can do so starting June 26.

Find more information at aao.org/registration and aao.org/hotels.

Event reservations. The annual meeting is a great opportunity to connect with colleagues. Hold your 2019 alumni or related group event in an official Academy hotel. You can now explore available locations, determine function hours, and reserve hotel meeting space through the Academy by using aao.org/meetingspace.

International Attendees

If you are traveling to the United States to attend AAO 2019, you may need a visitor visa. There are several steps to apply for a visa, so get started early. To help you obtain travel documents, the Academy has created an online tool that will create a personalized letter of invitation to attend AAO 2019.

Visit aao.org/visa.

D.C. REPORT

Academy to CMS: Make Part B Demonstration Voluntary, Well-Defined

The Academy is urging the Centers for Medicare & Medicaid Services (CMS) to take several important steps to ensure that its new Part B drug demonstration is a success for both patients and physicians.

As part of this national test, which is slated to begin in 2020, Medicare would adopt lower prices based on what foreign countries already pay through an International Pricing Index. It also would separate physicians' payments for handling and inventory costs from the price of the drugs.

As CMS continues to discuss the program's design, the Academy has urged the agency to carefully define expectations of vendors who would now purchase and deliver drugs, and to ensure that the demonstration will not lower average sales price–based payments for those physicians not participating.

Additionally, in response to CMS' recent statement that the program will be mandatory, the Academy has issued comments stressing that the demonstration must be voluntary. The Academy objects to CMS making this program mandatory because previous attempts to establish competitive acquisition programs failed to demonstrate their viability.

Although some of this proposal's broad details are known thanks to Academy conversations with the agency and published reports, CMS is still working to determine additional important details and tactics for implementation. Throughout the planning process, the Academy has been engaging in a dialogue with Administrator Seema Verma and her staff to try to ensure that this concept works for our profession. Thus far, Academy efforts have been met with assurances that the demonstration would be designed in a way to limit disruption to physicians and patients.

SAVVY CODER

Code-A-Palooza Answers

For the questions, see Savvy Coder on page 47.

1: A—yes. CCI does not currently bundle 92133 and 92083, which are therefore both payable. **Tip:** Each test can have frequency edits that may vary by payer, so be sure to check your payer's policy. Furthermore, some payers may not consider it medically necessary to perform both tests—optic nerve evaluation and visual fields—together or separated by a short period of time. However, they may consider it appropriate to alternate use of these tests at the proper time intervals.

2: B—CPT description. Some non-Medicare payers may not allow payment the same day as an exam because of the "separate procedure" wording in the code's description.

3: C—unlisted procedure. Unlisted procedure codes may have "YYY" listed as the global period. This means that the carrier, rather than CMS, determines whether the global concept applies and establishes a postoperative period, if appropriate, at the time of pricing.

4: B—denied. Unfortunately, there is no modifier available to indicate that the exam is unrelated to the procedure. Even listing the unrelated diagnosis wouldn't be enough; to get paid, you would need to go to review.

5: D—submit nothing. You can't submit an exam code when no medically necessary elements of the exam have been performed.

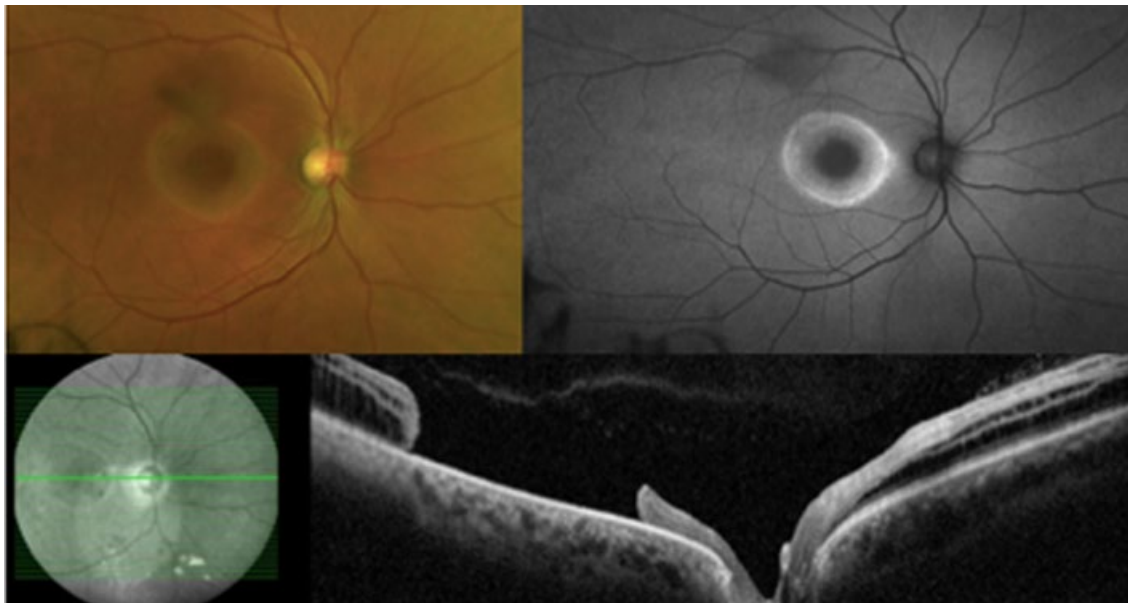
6a: C—99205–25–57. Because the exam was performed the same day as a minor surgery (67105), append modifier –25 to indicate that the exam was a significant and separately identifiable service. Modifier –57 indicates that the decision to perform major surgery (67108) was made at this exam. (Note: You cannot use –25 if the exam was performed solely to confirm the need for the minor surgery.)

6b: B—67105–LT + 67108–79–RT. CCI bundles 67105 with 67108, which may tempt you to use modifier –59 to unbundle them. But the two procedures were performed on different eyes; therefore there is no need to unbundle them.

7: C—only the professional component. Because the patient is currently an inpatient, it is as if the hospital owned the equipment. Remember to use place of service code 21 to indicate inpatient hospital.

MYSTERY IMAGE

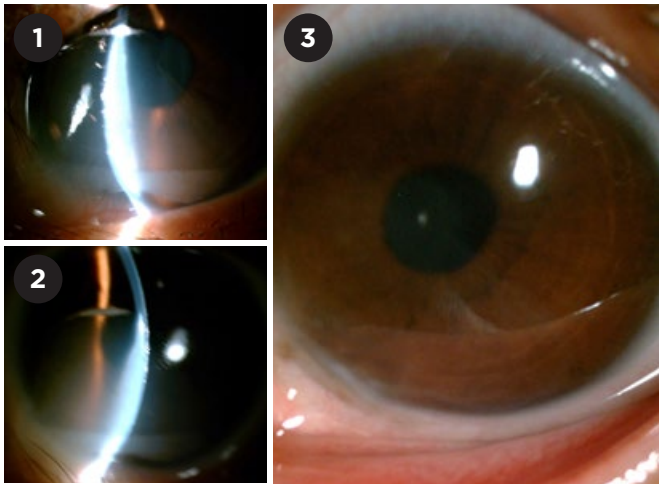
BLINK



WHAT IS THIS MONTH'S MYSTERY CONDITION? *Visit aao.org/eyenet to make your diagnosis in the comments section.*

LAST MONTH'S BLINK

Corneal Cyst



An active, otherwise healthy 6-year-old girl presented with a "white spot" on her left eye that had been slowly growing over the past few years. She had not complained about her eye or shown signs of discomfort. Neither the girl nor her parents could remember any incidence of ocular trauma.

On examination, visual acuity (VA) was 20/25 and 20/200 in the right and left eyes, respectively. There was no afferent pupillary defect or strabismus. Slit-lamp biomicroscopy revealed conjunctival thickening inferonasally with vascularization encroaching upon the limbus in the left eye only. Adjacent to the limbus was an oval area of corneal thickening 6 mm wide by 5 mm high, extending from the limbus up into the visual axis (Fig. 1). The corneal stroma contained turbid fluid, with white material settling dependently (Figs. 1 and 2).

These findings suggested a corneal stromal cyst communicating from conjunctival epithelium as the result of a developmental or unrecognized traumatic etiology. The risk of amblyopia in a 6-year-old prompted surgical rather than conservative management.

We performed surgical incision and drainage through a partial-thickness clear corneal incision into the stromal cyst with a microkeratome blade. We applied 1.6% 5-fluorouracil for chemodestruction of the involved epithelial cells and then dissected conjunctiva away from the limbus to disrupt any potential communication with the corneal stroma. Cytological review of the cyst fluid revealed epithelial cells that were consistent with our clinical diagnosis. At her one-month postoperative visit, the patient's VA had improved to 20/100 in the left eye; her cornea remained clear without recurrence (Fig. 3); and she was beginning treatment for amblyopia.

WRITTEN BY **LEE E. MOORE, MD, DO THUY HANG, MD,** AND **KENNETH L. COHEN, MD.** PHOTOS BY **DR. COHEN.** DR. HANG IS AT VIETNAM NATIONAL INSTITUTE OF OPHTHALMOLOGY, HANOI, AND DRS. MOORE AND COHEN ARE AT THE UNIVERSITY OF NORTH CAROLINA, CHAPEL HILL.

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BRIEF STATEMENT

Rx only. **Indications for Use:** The Crystalens is intended for primary implantation in the capsular bag of the eye for the visual correction of aphakia secondary to the removal of a cataractous lens in adult patients with and without presbyopia. The Crystalens provides approximately one diopter of monocular accommodation which allows for near, intermediate, and distance vision without spectacles. **Warnings:** Careful preoperative evaluation and sound clinical judgment should be used by the surgeon to decide the risk/benefit ratio before implanting a lens in a patient. Some adverse events which have been associated with the implantation of intraocular lenses are: hypopyon, intraocular infection, acute corneal decompensation, and secondary surgical intervention. **Precautions:** Do not resterilize; do not store over 45°C. **ATTENTION:** Refer to the Physician Labeling for complete prescribing information.

References: 1. Ang R. Comparison of 3 presbyopia-correcting IOLs used in cataract surgery. Presented at: XXIX Congress of the European Society of Cataract & Refractive Surgeons (ESCRS); September 17-21, 2011; Vienna, Austria. 2. Pepose JS, Qazi MA, Davies J, et al. Visual performance ofpatients with bilateral vs combination Crystalens, ReZoom, and ReSTOR intraocular lens implants. *Am J Ophthalmol.* 2007;144(3):347-357.