REVIEW® of Ophthalmology

August 2016

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ANNUAL RETINA ISSUE

CUTTING-EDGE APPROACHES TO TREATMENT

New Indication. New Dosing Regimen.

HUMIRA is administered by subcutaneous injection

INITIAL DOSE

80 mg

FOLLOWED BY

40 mg given every other week starting 1 week after the initial dose

The first injection should be given under the supervision of a healthcare professional. A patient may self-inject HUMIRA after appropriate training and monitoring by a healthcare professional.

Visit www.HumiraPro.com to learn more about our education programs for NI uveitis.*

***Intermediate, posterior, and panuveitis.**

Indication[1]

Uveitis: HUMIRA is indicated for the treatment of non-infectious intermediate, posterior, and panuveitis in adult patients.

IMPORTANT SAFETY INFORMATION FOR HUMIRA® (adalimumab)[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 rheumatoid arthritis patients treated with rituximab who received subsequent treatment with a TNF blocker. Concurrent use of HUMIRA with 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.

NOW APPROVED

F1RST AND ONLY FDA-APPROVED ANTI-TNF **FOR TREATING NON-INFECTIOUS (NI) UVEITIS***

HUMIRA® adalimumab *destination you*™

HUMIRA for NI intermediate, posterior, and panuveitis*

A steroid-sparing option proven to prolong time to a combination of disease flare† and decrease of visual acuity.[1]

†Disease flare is defined by an increase in 1 or more inflammatory markers: AC cells, vitreous haze, and/or development of new chorioretinal, and/or retinal vascular lesions.

- 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 or new onset congestive heart failure (CHF) may occur; 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.
- 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.

Reference: 1. HUMIRA Injection [package insert]. North Chicago, IL: AbbVie Inc.

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

 North Chicago, IL 60064 64C-1859319 June 2016 Printed in U.S.A.

abbvie

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.

Uveitis

HUMIRA is indicated for the treatment of non-infectious intermediate, posterior and panuveitis in adult patients.

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.

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. 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.

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. 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. 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

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, 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 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.

In subjects with moderate to severe HS, the rate of anti-adalimumab antibody development in subjects treated with HUMIRA was 6.5%. However, because of the limitation of the assay conditions, antibodies to adalimumab could be detected only when serum adalimumab levels were < 2 mcg/mL. 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%.

In 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 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
Adverse Reaction (Preferred Term)	(N=705)	(N=690)
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 and 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 patients with uveitis (UV) in placebo-controlled and open-label extension studies. 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

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

Limited clinical data are available from the Humira Pregnancy Registry. Excluding lost-to-follow-up, data from the registry reports a rate of 5.6% for major birth defects with first trimester use of adalimumab in pregnant women with rheumatoid arthritis (RA), and a rate of 7.8% and 5.5% for major birth defects in the disease-matched and non-diseased comparison groups *[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. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and miscarriage is 15-20%, respectively.

Clinical Considerations

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

In a prospective cohort pregnancy exposure registry conducted in the U.S. and Canada between 2004 and 2013, 74 women with RA treated with adalimumab at least during the first trimester, 80 women with RA not treated with adalimumab and 218 women without RA (non-diseased) were enrolled. Excluding lost-to-follow-up, the rate of major defects in the adalimumab-exposed pregnancies (N=72), disease-matched (N=77), and non-diseased comparison groups (N=201) was 5.6%, 7.8% and 5.5%, respectively. However, this study cannot definitely establish the absence of any risk because of methodological limitations, including small sample size and non-randomized study design. Data from the Crohn's disease portion of the study is in the follow-up phase and the analysis is ongoing.

In an independent clinical study conducted in ten pregnant women with inflammatory bowel disease 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.

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. 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) and pediatric Crohn's disease 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 *[see Clinical Studies]*. 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 *[see Clinical Studies]*. The safety and effectiveness of HUMIRA has not been established in pediatric patients with Crohn's disease less than 6 years of age.

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 prefilled syringe contains 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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US License Number 1889

Ref: 03-B374 Revised July 2016

64C-1865519 **MASTER**

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REVIEW NEWS
Volume XXIII • No. 8 • August 2016

Tecnis Symfony IOL Secures FDA Approval

In July, regulators approved Abbott Medical Optics' Symfony intraocular lens in both monocular and toric powers. The approval also marks the arrival of a new category of IOLs in the United States: extended depth of focus lenses.

The idea of an EDOF lens is to enhance near and intermediate vision without hurting distance vision or inducing as many issues with glare and halo as might be experienced with a multifocal IOL. Sioux City, Iowa, surgeon Jason Jones, who participated in Symfony's clinical trial, explains the design: "It's still a single-piece acrylic lens that we're familiar with from Abbott on the Tecnis platform," Dr. Jones says. "It has the spherical aberration correction that's shared across that family of lenses, so the overall design and injection system is familiar. It has a diffractive grating which, on its face, reminds us of a multifocal lens, but there are some significant differences. The ring structures have an echelette formation that elongates the focus area rather than splitting the light.

"The design also allows for less chromatic dispersion," Dr. Jones continues. "Instead of dispersing it as another lens design might, it helps collapse it to a tight region of focus. This helps improve contrast sensitivity and balance out some of the issues that you might get from elongating the focal length and splitting the light."

What this design translates into in the clinical study is patients in the Symfony group seeing 1.7 lines better on average at intermediate distances, monocularly uncorrected vs. the Tecnis monofocal IOL group. Monocular distance-corrected intermediate vision is 20/25 or better in 70 percent of the Symfony patients vs. 14 percent of the monofocal patients. At near, 62 percent of the Symfony patients saw 20/40 or better monocularly, distance corrected vs. 16.2 percent of control patients. Average distance vision was slightly better with the monofocal controls, but Dr. Jones says the difference wasn't statistically significant.

In terms of distance-corrected near vision, Dr. Jones says Symfony patients got a little over two lines of improvement vs. the monofocal lens. "At the 20/40 or better level of distance-corrected near vision, monocularly, you'd see a little over 60 percent of the Symfony patients," he says. "This compares with 16 percent of the monofocal patients." Dr. Jones says that, at the six-month visit, 85 percent of the Symfony patients reported wearing glasses "a little or none of the time" in the week prior to the visit.

"There's also the concern of dysphotopsias with a lens like this," Dr. Jones says. "Some patients report some dysphotopsias, but it's a very low rate, perhaps slightly more than a monofocal lens. In comparison to what we're used to with a multifocal lens, this lens appears to have what I would call a 'softer' profile in terms of halo and glare formation. There were no decentrations or glistenings reported."

The lens was also approved for toric correction. The toric models correct from 0.69 D at the corneal plane up to 2.57 D, in 0.5-D steps.

"For this lens, you want a patient who's interested in at least reducing his dependence on spectacles," Dr. Jones says. "If someone wants to wear their glasses, this isn't a lens you want to choose for them. They also have to be willing to incur some extra cost. At this stage, without a lot of experience with this lens, I'd be more comfortable approaching it as a lens that will give an enhanced range of near and intermediate vision without glasses, but may not give you complete performance without glasses for everything. It should significantly reduce the amount the patient uses his glasses, though. It's also worth telling the patient he might have some halo and glare that could potentially affect his quality of, and level of comfort with, his vision, just to prepare him for this possibility."

Shire's Xiidra Is Approved

On July 11, 2016, Shire (Lexington, Mass.) announced Food and Drug Administration approval of lifitegrast

(continued on page 10)

Ophthalmic Product Development Insights

Matthew Chapin and David A. Hollander, MD, MBA • Ora Inc., Andover, Mass.

An Interdisciplinary Approach to Addressing an Unmet Need

Since this column often explores topics related to funding, development strategy, and the identification and filling of unmet needs in the marketplace, this month's installment explores the case of the dry-eye device-maker Oculeve, which sits at the intersection of all these elements. Oculeve started with only one mission—to recognize an unmet need through a blank-slate observation of clinical practice—and leveraged an interdisciplinary approach to think out-of-the-box for addressing it. If you're working on a new device or therapy and looking to gain traction with it, the Oculeve story is a great example of managing the early stage funding process, moving a project through the development cycle and driving the program to a point where it registers with large pharma.

Oculeve was born out of the Stanford University Biodesign Fellowship program, a mentored program in which physicians and scientists are put into small teams and assigned an area in which to innovate. The focus of this particular team, including scientist/engineer Michael Ackermann, PhD, was ophthalmology. The team, consisting of a biomaterials scientist/engineer (Garrett Smith), a board-certified surgeon (Victor McCray, MD) and a mechanical engineer (Brandon Felkins), along with Dr. Ackermann, were new to ophthalmology, and set out to embed themselves in a busy clinical ophthalmology practice. They observed the physicians and patients in the office and operating room daily and tracked such things as the flow of patients and reasons for their office visits. After about a month, they had accumulated a list of approximately 350 unmet needs. Recognizing that almost one in every three patients who were seen had dry eye, that's what they focused on.

To determine how they were going to approach dry-eye therapy, the team broke down the disease into two basic components: decreased production of the critical components of the tear film, and inflammation, the latter leading to further breakdown of the body's ability to create tears from the lacrimal glands. They identified the unmet clinical need—and gap in therapy—for an immediate restoration of the tear film. Leveraging their background in neuroengineering, and after evaluating many different approaches, the team focused on neurostimulation for creating tears.

The initial focus for stimulating tear production was with an implant to directly stimulate the lacrimal gland, which they tested in more than 40 subjects. To carry out this testing, however, the new business needed funding.

In order to fund the early stages of proof-of-concept testing, a start-up company should be open to seeking funding from alternative sources, which may be grants, friends and family, seed investors, service-in-kind investments from development partners or even prize money from winning business-plan competitions. Early data generation can then drive subsequent larger rounds from the traditional VCs or pharma partners. This is an important point for the new entrepreneur to recognize. Many times we see early-stage start-ups that attempt to pursue large rounds of financing from the start but don't gain traction. However, when possible and appropriate given the nature of the project, leveraging off-the-shelf devices, or already approved and marketed drugs of a similar pharmacologic class with a repurposing approach, can facilitate small, pilot clinical testing to generate the required proof-of-principle, and a reason for others to believe in it.

In Oculeve's case, its early development was funded through winning business plan competitions, which brought in up to $50,000. After that, Oculeve was formed, and attracted seed capital of $100,000 from Kleiner, Perkins, Caufield and Byers, and $100,000 from "sophisticated angel investors." This supported the development of a prototype off-the-shelf stimulator that they used to directly stimulate the lacrimal gland via a needle electrode through the eyelid. The data supported raising $500,000 additional capital through debt financing, followed by closing a Series A sale of preferred stock in the company of $7.59 million in August 2012, from Kleiner, NEA and Versant. This allowed them to spin-out the technology from the university and with the capital, run additional studies outside of the United States, including studies in Mexico, New Zealand and Australia.

Early data from the orbital implant were promising in some patients, but inconsistent in others. During the clinical trials of the implant, Oculeve identified an interesting finding that patients with the best response had tearing in both eyes despite a unilateral implant. This led to the realization that tearing could be more powerfully stimulated by activating a reflex. Oculeve changed its tack and developed a nasal stimulation device that activates the nasolacrimal reflex. The device is handheld, non-invasive and doesn't involve an implant or needle. Of course, that realization and evolution of the product delivery transformed the nature of the device into a product that was acceptable to an even greater number of patients.

In reflecting on the impetus of going outside the United States with the implant, Dr. Ackermann indicated that the main driver behind going to Mexico and the Philippines was speed, given that the timeline for opening an investigational device exemption in the United States was prohibitive for them. However, after the evolution to the non-invasive nasal stimulator, which is considered a non-significant risk device and therefore didn't need an IDE in the United States, he chose to keep running the studies in Mexico, despite a more straightforward institutional review board approval that would have been needed in the United States. This was done mainly to stay under the radar until the patent portfolio was locked down and the scientific foundation of the treatment was better understood. In Oculeve's case, the technology is disruptive in the way in which it is delivered, and protection of intellectual property was a main driver of the decision.

In prior columns, we've discussed situations where going outside the country for studies is warranted and have explored other case studies. In the case of Oculeve, partnering with an investigator with whom there is a relationship and trust, and setting up the study so the sponsor could be on-site in a collaborative fashion, helped ensure success and quality data.

In March 2014, Oculeve completed a larger round of $16 million in financing. This infusion funded a large, well-controlled Phase II dry-eye study with a focus on precise endpoints designed to support the regulatory process and build value for partner discussions. As a result, Oculeve was acquired by Allergan in August 2015. Allergan's CEO Brent Saunders has espoused the open-science model of research and development, in which innovation is sought from both internal laboratories and external start-ups and university settings

in order to increase R&D efficiency. The company then follows through with the clinical development and regulatory process in order to bring these innovative products to patients. To that end, Allergan has 70 programs in mid- to late-stage development. Oculeve was a great strategic fit for Allergan, which markets Restasis and Refresh tears and has multiple clinical development programs in dry eye. "At Allergan we use our open-science model to harness the power of the new innovation ecosystem," Mr. Saunders states. "This approach allows us to develop de-risked, late-stage assets and cutting-edge early-stage programs within our targeted therapeutic areas, such as eye care. This provides significant rewards to the entrepreneurs and higher return on our R&D investments and is a true win-win for the innovation ecosystem."

The Oculeve story shows the value of first seeking an unmet need as opposed to a product, building a company around a structured process of mentorship, and throwing in a little serendipity, as well. Leveraging expertise from other areas of development, Oculeve's researchers and owners drove efficient pilot testing with off-the-shelf products, raised seed funds to support prototyping and then, when things didn't go as planned, they learned from their observations and adapted effectively, creating a superior, less-invasive approach to delivering the neurostimulation.

An important take-home point from Oculeve's story is the value of early proof of concept, built around efficiently executing small, high-quality studies that both prove the concept and demonstrate the basic science—which was needed, given the novelty of the approach. The testing was designed to ensure that their data would inform decision-making, shifting and revision of plans, and the ability to secure additional capital to run the definitive Phase II clinical trial that supported industry partnering.

Mr. Chapin is senior vice president of the Corporate Development Group and Dr. Hollander is chief medical officer at Ora Inc. and assistant clinical professor of ophthalmology at the Jules Stein Eye Institute, UCLA. Ora provides a comprehensive range of development, clinical-regulatory and product consulting for developers, investors and buyers; preclinical and turnkey clinical trial services and regulatory submissions; and integration with asset, business partnering and financing support in ophthalmology. They welcome your product development comments or questions. Please send correspondence to mchapin@oraclinical.com or visit www.oraclinical.com.

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ophthalmic solution 5% (Xiidra), a twice-daily eye drop indicated for the treatment of the signs and symptoms of dry-eye disease in adult patients. Shire notes that Xiidra is the only prescription eye drop indicated for the treatment of both signs and symptoms of dry eye.

According to the company, the inflammation associated with dry eye is thought to be primarily mediated by T-cells and associated cytokines. One effect of this process may be overexpression of intracellular adhesion molecule 1 in corneal and conjunctival tissues, which may contribute to T-cell activation and migration to target tissues. Although the exact mechanism of action of lifitegrast is not known, *in vitro* studies demonstrated that it may inhibit T-cell adhesion to ICAM-1 in a human T-cell line and the secretion of cytokines in human peripheral blood mononuclear cells.

The safety and efficacy of Xiidra were studied in 1,181 patients in four placebo-controlled 12-week trials; 1,067 patients received lifitegrast 5%. Each of the four studies assessed the effect of Xiidra on both the signs and symptoms of dry eye at baseline and weeks two, six and 12. In all four studies, a larger reduction in eye dryness score was observed with Xiidra at six and 12 weeks; in two of the four studies, an improvement in EDS was also seen with Xiidra at two weeks. At week 12, a larger reduction in inferior corneal staining score, favoring Xiidra, was observed in three of the four studies. The most common adverse reactions reported in 5 to 25 percent of patients were instillation site irritation, altered taste sensation (dysgeusia) and reduced visual acuity.

Edward Holland, MD, professor of clinical ophthalmology at the University of Cincinnati and a clinical trial investigator for Xiidra, says the approval is a boon to clinicians. "There have been more than 20 dry-eye trials that failed to reach significance in both signs and symptoms," he says. "Credit goes to the Shire folks for designing a trial that got across the finish line with both signs and symptoms of dry eye."

Dr. Holland explains that the reason Shire succeeded where others failed was their trial design. "Everyone else tried to achieve significance in both signs and symptoms in the same patient population," he says. "Shire realized that wasn't going to work. So the Shire scientists analyzed the data and saw that one group of patients did very well clearing the clinical sign of corneal staining, while another group had symptoms significantly reduced. So they did two separate trials and then repeated both of them. This was a totally new strategy. It made the timetable much longer and the number of patients much greater, but it certainly worked for them, and it might work for other formulations as well."

Asked how he expects Xiidra to fit into his armamentarium, Dr. Holland says he expects it to be first-line. "Artificial tears are palliative," he notes. "This is a very effective anti-inflammatory that gets at the pathogenesis of dry eye. For me it will be primary therapy."

Shire expects to launch Xiidra in the United States in the third quarter of 2016.

Humira Cleared for Uveitis

In mid-July, the FDA approved AbbVie's non-steroidal immunomodulatory agent Humira (adalimumab) for use in non-infectious intermediate uveitis, posterior uveitis and panuveitis. This approval finally gives ophthalmologists an approved immunomodulatory option, obviating the headaches involved with using such agents off-label.

The approval was based on the results of two large-scale, Phase III studies, VISUAL-1 and -2. "VISUAL-1 was designed to test Humira in patients with active uveitis, with the goal of seeing if patients with active inflammation—despite being on steroids—could be tapered off their steroids while Humira helped fight the inflammation," explains Glenn Jaffe, MD, chief of the retina division at Duke University, and Robert Machemer, MD, professor of ophthalmology at Duke and consultant to AbbVie. "The other study, dubbed VISUAL-2, recruited uveitis patients whose eyes were quiet because they were currently on steroids, with the goal being to get them off the steroids and to substitute the Humira." The main endpoint in VISUAL-1 was the time until treatment failure. In VISUAL-2, the researchers wanted to see how likely a flare-up would be as patients were tapered off the steroids and kept on Humira.

"The way I think of the results of the VISUAL-1 study is the phrase, 'twice as long or half as likely,' " says Dr. Jaffe, "meaning that the time to treatment failure was about twice as long—24 weeks for the treatment group vs. 13 for the placebo—and the likelihood of getting failure was approximately half for the Humira group. In many cases, the Humira group didn't fail. So, not only did it take longer, in general, for them to get a flare-up, but they were half as likely to get one, as well.

"Similarly, in VISUAL-2, the study in which the patients' inflammation was quiet with systemic steroids to begin with, the idea was to see if patients were less likely to get a flare-up if they were treated with Humira than if they weren't," Dr. Jaffe continues. "Both studies mandated a steroid taper over 15 weeks. In VISUAL-2, the patients who were switching over to Humira were significantly less likely to have treatment failure when the steroids were tapered, and they had less of a

chance of visual acuity going down."

In terms of the best patients for the use of Humira, Dr. Jaffe notes that a risk of infection always lurks whenever an immunomodulatory agent is used. "Certainly, if someone has a history of tuberculosis, especially if it's not treated, you don't want to put him on one of these agents," he avers. "However, you can cautiously treat someone with TB as long as it's been completely treated, but that's something you have to confirm before starting these agents. Also, in general, I'd say patients with an underlying infectious cause of the uveitis wouldn't be good candidates.

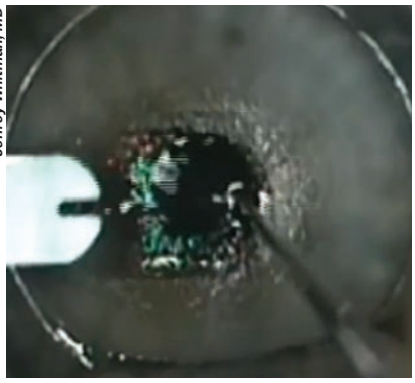
"The tumor necrosis factor inhibitors like Remicade and Humira can potentially cause a flare-up of multiple sclerosis or other demyelinating diseases," adds Dr. Jaffe. "Also, individuals who have intermediate uveitis are at an increased risk of having MS as an association with the inflammation. In intermediate uveitis patients, I'd recommend a brain MRI to ensure there's no evidence of MS."

FDA Approves The Raindrop

Surgeons now have a new option for their presbyopic patients, thanks to the Food and Drug Administration approval of ReVision Optics' Raindrop Near Vision Inlay in July. The inlay is designed to give patients improved near and intermediate visual performance, and was approved based on the results of a one-year prospective, nonrandomized, multicenter clinical trial.

Dallas surgeon and Raindrop investigator Jeffrey Whitman, MD, says the inlay did give presbyopes a wider focal range. "The question is, does it work for reading?" he says. "Yes. It does well for intermediate, as well. In this day and age people aren't really looking for just distance and close up. They're looking at their phones and computers, and the inlay does well at that distance."

Jeffrey Whitman, MD



The Raindrop inlay is implanted beneath a LASIK flap, and its presence steepens the cornea, yielding greater depth of focus.

The inlay uses corneal shape change—not refractive power—to get its effect. "It's a 2-mm-diameter, meniscus-shaped inlay with an index of refraction that's equal to the cornea's," explains Dr. Whitman. "It's 30 µm thick in the center. The Raindrop works by steepening the center of the cornea, which gives you a greater depth of focus." It's approved for use in the non-dominant eye of patients with a manifest refraction spherical equivalent of -0.5 to +1 D, with 0.75 D or less of cylinder. The inlay is approved for implantation beneath a LASIK flap at one-third corneal depth, and a corneal pocket study is imminent. Though it's not approved for it, surgeons may opt to perform LASIK beforehand to get patients in the emmetropic range and then implant the inlay.

The study looked at 373 non-dominant eyes of emmetropic, presbyopic subjects that received the Raindrop at 11 sites. During the one-year follow-up visit, researchers studied 340 of the nondominant eyes.

"By one year 93 percent of subjects were 20/25 or better at near. They gained an average of 5.1 lines of reading vision," Dr. Whitman says. "So, it was pretty dramatic; 97 percent of subjects saw 20/30 at intermediate distance postop. The inlay is clear, so there's very little loss of contrast sensitivity and no loss of binocular vision."

At one year in the treated eye, uncorrected intermediate visual acuity improved by 2.5 lines while best-corrected distance visual acuity decreased by 1.2 lines. From three months through one year, 93 percent of subjects achieved uncorrected near visual acuity of 20/25 or better, 97 percent achieved UIVA of 20/32 or better and 95 percent achieved UDVA of 20/40 or better. Binocularly, the mean UDVA exceeded 20/20 from three months through one year.

Dr. Whitman says the procedure is straightforward. "You lift the flap up and place the device over the light-constricted pupil. Wait about a minute for it to dry in place before putting the flap down. Then let it dry as you would a normal flap. Then, there's the recommended drop regimen afterward that's similar to LASIK's."

In terms of candidates for the inlay, Dr. Whitman states, "If they're not healthy enough to be a LASIK candidate, they aren't a good candidate for this. Because, basically, the issues relate to flap technology."

Dr. Whitman says adverse events were low in the study. "Visual symptoms such as glare and halo had less than a 4-percent incidence," he says. "Eighteen inlays were replaced, most of those for decentration. After replacement, they had the same uncorrected near vision as the rest of the study population. Eleven cases required explantation, for reasons such as decentration, dissatisfaction with vision and foreign-body reaction. Only one eye experienced the foreign-body reaction. The foreign-body reaction can usually be treated with steroids, but if it persists, in the study we recommended removal of the inlay. You can remove it and patients get back to within one line, on average, of their best-corrected vision within three months." REVIEW

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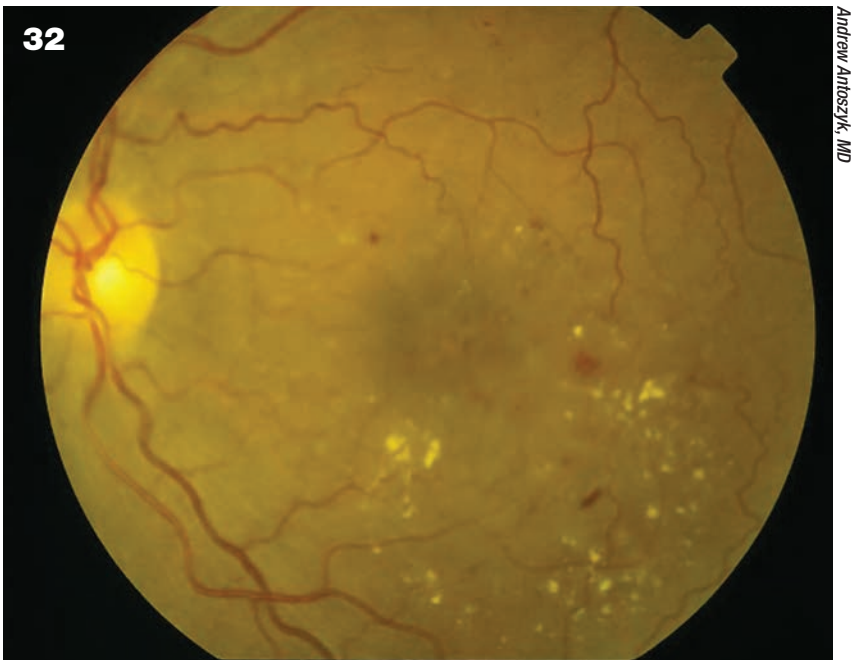

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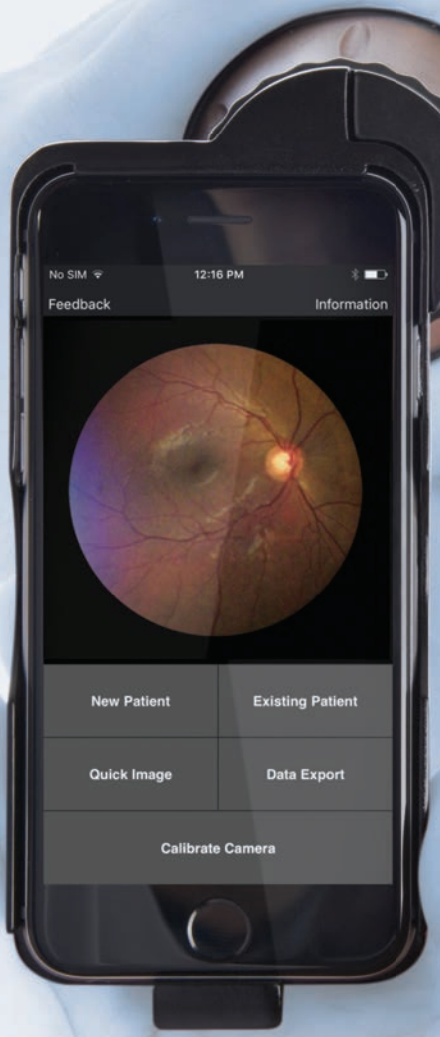

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Here's to Repurposing

Reading through the retina specialists' comments in this month's articles on treatments for diseases like wet AMD and DME, you get a sense of how completely anti-VEGF drugs have changed ophthalmology.

For years, laser therapy was the best treatment for wet age-related macular degeneration, even though it sometimes left patients with blind spots in their visual fields. Genentech's clinical trial of Lucentis changed all that. Building upon the success clinicians were having with Macugen, Lucentis—and, later, Eylea—showed that anti-VEGF drugs could actually allow patients to recover vision, an effect unheard of with laser treatments. It was a drug innovation success story.

However, at the same time, the dawn of anti-VEGF in ophthalmology was also a story about innovative repurposing.

As the Lucentis trial was compiling its impressive data, groups of intrepid physicians decided to take Genentech's cancer drug Avastin and repurpose it for use in the eye, with similarly impressive results. Though this sparked controversy, this use of compounded Avastin gave ophthalmology at-large its first taste of the ability of these drugs to change people's lives.

Lucentis and Eylea were eventually approved, and have been embraced by retina specialists, but Avastin remains an option for patients with insurance issues for whom the companies' co-pay assistance doesn't help for one reason or another. The Avastin option wouldn't be there for them, though, if certain creative ophthalmologists didn't step back, ask "What if ..?" and repurpose it to fight blindness.

Drugs aren't the only thing that can be repurposed: people can be, too. In 1994, I started on *Review* as a production editor for the magazine's second issue, laying out other editors' articles and making sure everything looked pretty—or at least not ugly—on the page. In his wisdom, the founding editor of *Review*, Stan Herrin, knew I could do more, and I was repurposed into a writer and associate editor. Since then, the repurposing continued, and I entered various new roles on the magazine, ensuring that I was always researching and writing more about this fascinating specialty, that I was always learning. Stan's successor, Chris Glenn came on in 1999, and followed suit.

In June, Chris retired after 17 years at *Review*, and he's now in the enviable position of being able to repurpose himself as often as he wants, to follow his bliss. I want to wish him well, and thank him for sharing his knowledge, experience and, most of all, friendship.

I'm proud to say this cycle of repurposing has culminated with me being named *Review*'s new editor in chief. I'd like to take this opportunity to make a pledge that the one purpose that will never change is the one at the heart of *Review*: To provide readers with the timely, practical information they've come to expect, with an abiding respect for editorial integrity instilled in me by the editors that have gone before.

—Walt Bethke, Editor in Chief

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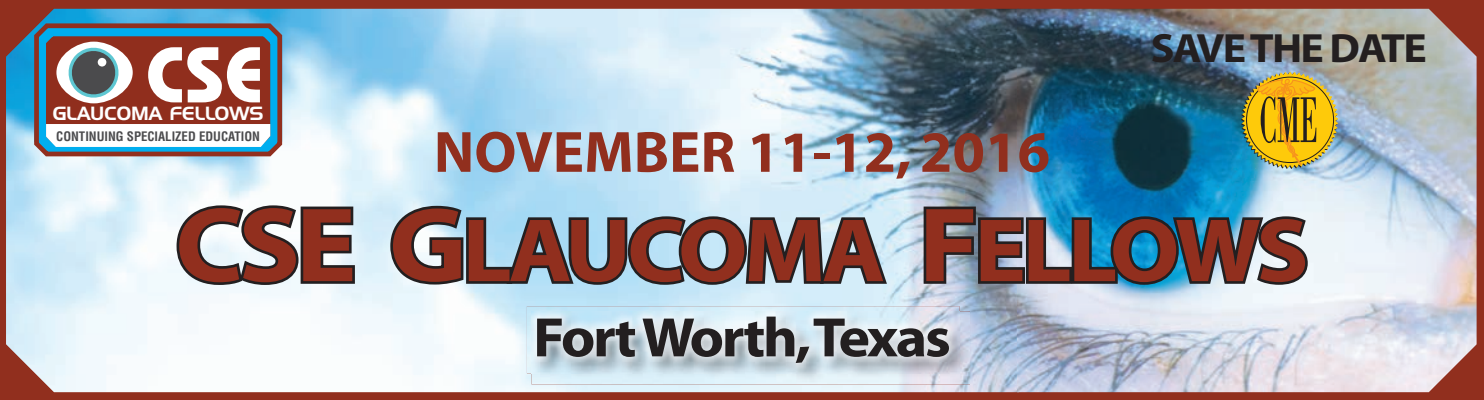

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Creating Great Surgical Videos (for less money)

Capturing live surgery for simultaneous viewing—or later viewing—can be done in 2-D or 3-D without breaking the bank.

Christopher Kent, Senior Editor, and Walter Bethke, Editor in Chief

Today, it's become increasingly important to be able to share what you see through the oculars during surgery. Digital technology has made that easier than ever, but technology can be costly. Here, Samaresh Srivastava, DNB, of the Raghudeep Eye Hospital in Ahmedabad, India, shares some secrets for capturing, displaying and recording high-quality video—in 2-D or 3-D—without breaking the bank.

Recording with an SLR Camera

Dr. Srivastava notes that taking high-resolution video using a digital single-lens reflex camera connected to your surgical microscope can be far less expensive than using a standard video camera. "Most of the new digital SLRs have HD digital recording capability," he says. "Some, like Sony's a7R II, have 4K recording ability as well. A full-frame DLSR camera costs about $2,000; a ballpark cost for the video mount to connect it to your microscope is $1,500 to $2,000 if you buy it directly from the microscope manufacturer, and less-expensive off-brand mounts are available as well. That means you're investing about $4,000 for the whole setup, which is a third of what you might pay for a full-HD video camera with a C-mount [the connector that joins the beam-splitter of the operating microscope to the camera].

"Once the SLR is plugged in, you can record directly onto the SLR camera, or you can use the camera's live video-out port to export the video onto another device such as a computer with a video capture card or a digital recorder," he says. "File size is limited on a camera, but a separate recording device should allow you to record streaming video for as long as you want—maybe a two- or three-hour surgery, for example.

"If you're using a computer, you'll need a good video-capture card, such as the one made by Blackmagic Design," he adds. "The card goes into a PCI slot on the motherboard; because it's directly connected to the motherboard it doesn't lose any frames and produces a high-quality video. You also can choose the compression, file size and format you want, such AVI or PAL. Most of these capture cards can take video input from any camera."

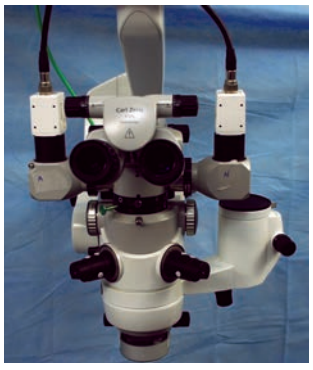
Using Your Smartphone

Another option is recording a surgical video using your smartphone. "There are many free apps available through the Android store and Apple App store that will allow you to do the recording," he notes. "The special features of these newer phones can also be used: We've used an iPhone's slow-motion mode to capture the stages of phaco and phacodonesis.

"Unlike an SLR or other camera, you can't mount a smartphone on your microscope's beam splitter," he continues. "To do that, the microscope would need a video adapter tube. However, a smartphone can be mounted on an assistant's viewing scope, which most microscopes have. To do this, you can use any adapter for a smartphone that's available off the rack, such as one designed for slit lamp attachment; some ophthalmic companies also make them, and one person in India designed a mount you can make at home for $10 to $15." [Instructions for making one are available on the website of the *Journal of Mobile Technology in Medicine* at http://www.journalmtm.com/2014/

diy-smartphone-slit-lamp-adaptor/)

Dr. Srivastava notes that it can be tricky to export live video from a smartphone. "Most of these phones have an attachment that allows you to duplicate the phone's screen on a smart TV or computer screen," he says. "This is called screen mirroring. If you don't have a computer available, you can insert an Android Dongle into your TV's HDMI port to allow it to mirror the smartphone screen. With an iPhone, you can use Apple TV."



Samaresh Srivastava, DNB

Above, left: Two similar cameras mounted on either side of a microscope's beam splitter using video adapter tubes of the same focal length. Above, right: Two stackable projectors with their projected images aligned. A pair of polarized eyeglasses has been broken in half, with one lens placed in front of each projector's lens to polarize the projected images.

Working Live in 3-D

Dr. Srivastava says it's possible to do both 3-D recording and live 3-D video displays without investing in expensive equipment. "All 3-D videos work the same way," he explains. "Your left eye sees one image while your right eye sees a similar but slightly different image; your mind fuses them to create a perception of depth. When you mount one camera on the left side of a beam splitter and another camera on the right side, you're capturing slightly dissimilar images, like those your eyes perceive. These two images can then be sent to two different projectors. By polarizing the light emitted by each projector, you can throw two different images with different polarizations onto a silver polarized screen. Then a viewer can use polarized glasses to see very good 3-D images—better quality than what you'd see at the movies.

"To do this, you need two identical cameras with identical video adapter tubes so the optics are the same," he continues. "To project the resulting images, you need two projectors, referred to as stackable projectors. Most multimedia companies use stackable projectors to increase the brightness of their presentations. In this case, you run the video from the left side of the beam splitter through one projector and the video from the right side through the other projector."

Dr. Srivastava explains how polarization makes 3-D viewing possible. "When you watch 3-D movies, each lens in the glasses you wear has a different polarization," he says. "If the left eye has a vertical polarization, the right eye will have a horizontal polarization. As a result, your left eye will only see things that are vertically polarized, and your right eye will only see things that are horizontally polarized. Now, if you polarize the light coming from each projector differently, the left eye will see only one of the two images and the right eye will see only the other.

"Accomplishing this is easy; just order some 3-D glasses," he continues. "Break one pair in half and place the left lens in front of the first projector and the right lens in front of the second projector. That will polarize the light from each projector in a different direction. Then, when you wear that same type of 3-D glasses and watch the video, you'll see the video in 3-D."

Dr. Srivastava adds that this will only work if you project the two images onto a silver screen. "A silver screen will reflect the polarization back; a white screen will just absorb the polarization, causing you to see both images in both eyes," he says. "Silver screens are readily available; mine was shipped from China, from aliexpress.com, a big, online shopping portal. It cost less than $800 dollars. I also ordered my 3-D glasses from that site."

Recording in 3-D

"Recording your surgery in 3-D is a little different, but it's not complicated," says Dr. Srivastava. "Your recording device needs to have a 3-D capture card. Instead of projecting the video, you send the two video feeds to the video capture card; it simultaneously records both the left and right views of the surgery. Once completed, you'll have a large digital file; the software will then let you send the left image to one projector and the right image to the other. A 3-D capture card costs about $1,500, but other than the computer itself—which needs to have a good processor that can buffer a large video file—that's the only added expense. In my experience, as with a standard video card, the best 3-D video capture card is the one available from Blackmagic Design.

"To project the surgery recording, you just need to connect your computer to the two projectors, as described above," he concludes. "If you want to view the video in 3-D on your computer screen, you'll need a special 3-D monitor." REVIEW

Donna McCune, CCS-P, COE, CPMA

Understanding HEDIS For Ophthalmology

An overview of HEDIS, covering insurance plans and the role of ophthalmologists and optometrists.

Q What does HEDIS stand for?

A HEDIS is an acronym for Healthcare Effectiveness Data and Information Set; a set of healthcare performance measures. The National Committee for Quality Assurance oversees the development, implementation and all facets of the HEDIS tool. HEDIS consists of 81 measures across five domains of care. The measures compare how well a health plan performs in areas of quality of care, access to care and member satisfaction with the plan itself.

Q Who utilizes the HEDIS tool?

A Health plans primarily use HEDIS, collecting and reporting data on the various HEDIS measures. With a defined set of measures, HEDIS permits a comparison of health-plan performance that's consistent from plan to plan.

Health plans combine their HEDIS scores with Consumer Assessment of Healthcare Providers and Systems scores and NCQA Accreditation standards scores to receive a Health Insurance Plan Rating from the NCQA. The NCQA ratings list includes commercial payers, Medicare and Medicaid plans.

Q What type of rating do insurance plans receive?

A Health Insurance Plan Rating is a score from one to five in 0.5 increments, with five being the highest possible rating. This system is similar to CMS' Five-Star Quality Rating System, although the CMS system only rates nursing homes.

Compared with other plans in their category, those that get a five are in the top 10 percent, those that get a four are above average, those that get a three are average, those that get a two are below average and those that get a one are in the bottom 10 percent.

Q What is the significance of the rating to a health plan?

A Consumers analyze the ratings of different health plans when either selecting a plan for the first time or considering switching plans. The ratings provide consumers with a clear picture of how the various plans perform in key quality areas.

Individual health plans can use their star ratings as marketing tools. For example,

"XYZ Medicare Preferred HMO plans and the XYZ Health Plan Senior Care Options Plan earned a 5 out of 5 Star Rating from Medicare for 2016. This is Medicare's highest rating and makes these plans among the best in the country! In fact, out of nearly 400 plans rated for 2016, only 12 received a 5-star rating!"

Q How does the Centers for Medicare & Medicaid Services use HEDIS scores?

A CMS can impose financial and contractual penalties on health plans that score poorly on HEDIS measures and Star Ratings, while health plans with high ratings benefit with potential financial bonuses from the federal government. Plans with a score of four or higher are eligible for federal bonuses that run from millions to billions. A recent article from Kaiser Health News, also published in USA Today, describes some of the ways health plans improved their ratings and the return on investment for having done so.

Good or bad results provide a health plan with the opportunity to analyze its results and make improvements in the quality of care and ser-

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vices it provides to its members.

Q Are third party-payers required to submit HEDIS data to the NCQA?

A Yes. Private insurance plans with Medicare and Medicaid contracts are required to collect and submit HEDIS data as a component of their contracts. Without the data, a payer will not receive a rating, which is critical to its ability to sell its insurance plans.

Q How do ophthalmology and optometry play a role in HEDIS scores and Health Insurance Plan Ratings?

A One of the HEDIS measures is "Comprehensive Diabetes Care." This measure requires health plans to gather data showing that their subscribers (patients) with diabetes get recommended screenings and exams. The 2016 measure includes:

- Hemoglobin A1c testing (HbA1c poor control >9, HbA1c control <8);
- Blood pressure control (<140/90 mmHg);
- Eye exam (retinal) performed; and
- Medical attention for nephropathy.

Because a retinal exam is required to meet this quality measure, ophthalmologists and optometrists are an integral part of achieving the quality measure.

Q How does the health plan know that the patient received these services?

A Claims submission data provides the necessary information to the payer to validate meeting the HEDIS measure. For example, a claim for a lab test with CPT 83036 or 83037 confirms that the patient's A1c was tested. There are several other ways that the health plan confirms performance of an eye exam. Per HEDIS, any provider may submit codes to substantiate the retinal exam. Eye exam codes (920xx) or evaluation and management codes (992xx), paired with a diabetes ICD-10 code as well as the CPT Category II codes used in PQRS reporting of this measure all suffice to support that this component of the measure was satisfied. The Category II codes are:

- CPT II 2022F: Dilated retinal eye exam with interpretation by an ophthalmologist or optometrist documented and reviewed;
- CPT II 2024F: Seven standard field stereoscopic photos with interpretation by an ophthalmologist or optometrist documented and reviewed;
- CPT II 2026F: Eye imaging validated to match diagnosis from seven standard field stereoscopic photos results documented and reviewed; and
- CPT II 3072F: Low risk for retinopathy (no evidence of retinopathy in the prior year).

In addition, payers request provider medical records and conduct chart reviews to gather necessary data to report to the NCQA.

Q How do primary-care providers fit into this matrix if the primary objective is to have the plan receive a high rating?

A A provider can be removed from the payer's provider panel for not participating in HEDIS data collection. Most, if not all, participation contracts require providers to make available the medical record information necessary for the payer to meet regulatory and accreditation requirements.

Q If ophthalmologists and optometrists can report on the eye exam component of the HEDIS measure, why are primary-care providers concerned about insufficient data being reported to the health plan for this measure?

A According to the Centers for Disease Control and Prevention, "The age-adjusted percentage of adults aged 18 years or older with diagnosed diabetes receiving a dilated eye exam in the last year was 57 percent in 1994 and 62.8 percent in 2010." Other organizations report less than 50 percent of diabetics receiving an eye exam.

If 85 percent of diabetic patients see a physician regarding their diabetes, and, according to the CDC, only 63 percent of diabetics receive an eye exam, there's a large gap in reporting to satisfy the HEDIS measure.

Q How are primary-care providers working to achieve compliant results to report?

A Some primary-care providers are incorporating technology in their offices that takes a retinal photograph. An ophthalmologist or an optometrist interprets the photograph remotely. This approach assures the primary-care provider that his diabetic patients are receiving the required component of the HEDIS measure. REVIEW

Ms. McCune is vice president of the Corcoran Consulting Group. Contact her at DMcCune@corcoranccg.com.

Treating Wet AMD With Anti-VEGF Drugs

Christopher Kent, Senior Editor

It's becoming clear that the treat-and-extend protocol works well—and may be needed indefinitely.

Anti-VEGF agents are proving to be useful for addressing a number of conditions, including diabetic macular edema and proliferative diabetic retinopathy, but today they are most often used to treat wet age-related macular degeneration. As experience with bevacizumab (Avastin), ranibizumab (Lucentis) and aflibercept (Eylea) grows, our understanding of how best to use these agents to treat wet AMD in the short and long run keeps expanding.

Here, three retina specialists with extensive experience using these agents share the latest thinking about the pros and cons of using anti-VEGF drugs; the different treatment protocols being used; differences between the drugs; what to do when they don't work; and what the future may hold.

Using Treat-and-Extend

"Today, the standard of care for a patient who has been identified as having wet macular degeneration is to treat with a potent anti-VEGF agent monthly until the patient is dry on OCT," notes David M. Brown, MD, FACS, who practices at Retina Consultants of Houston, is clinical professor of ophthalmology at Baylor College of Medicine and runs the Greater Houston Retina Research Center. "If you treat with any of these agents, even with aflibercept—which the studies suggest is probably the best drying agent—about 20 percent of patients still have fluid after three monthly shots. In that situation you just keep treating. If it takes 10 or 20 shots to dry them out, you keep going until they're dry."

"Once the eye is dry, you have a decision to make with the patient," he continues. "You can try treating PRN, or you can begin a treat-and-extend protocol. Some patients—maybe 10 or 20 percent—dry out after several injections and don't need any more injections for a while. If you're willing, once the patient is totally dried out, you can choose to just watch the patient closely—see the patient at four weeks and six weeks and eight weeks and look for new leakage. Once you find leakage, though, you know the patient still needs treatment. At that point we typically begin treating the patient at an interval a little shorter than the amount of time that has passed since the last injection."

Dr. Brown says that not all patients want to take this wait-and-see approach. "Most patients would rather start the treat-and-extend protocol at the beginning of their dryness," he says. "If I've dried them out and the shot was four weeks ago, I'd say, 'Let's

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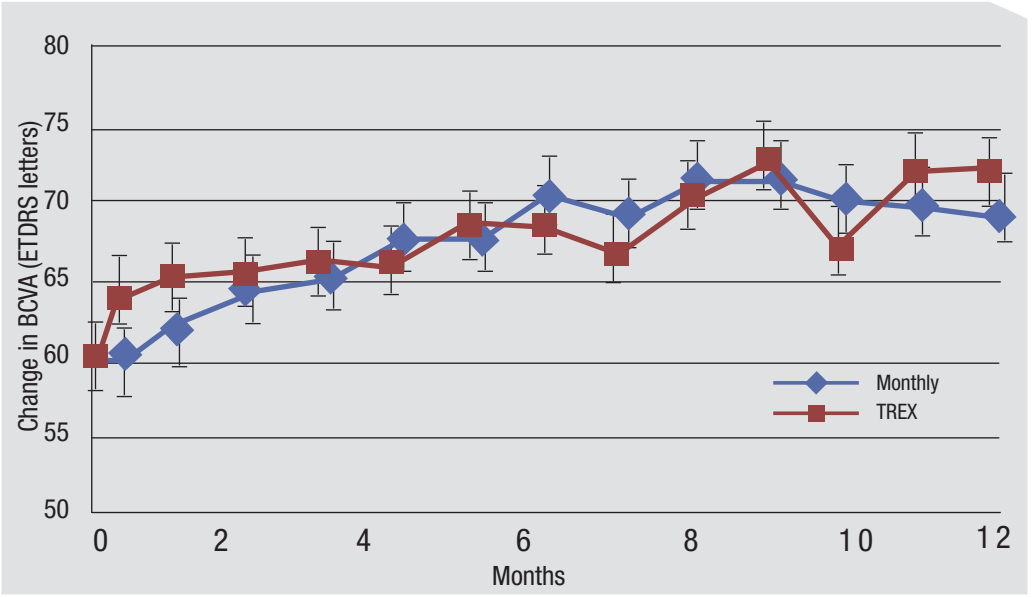
give you another shot and I'll see you in six weeks.' Then, when I see them six weeks later, I give them another shot and try extending the interval to seven weeks, eight weeks, etc., until they re-leak. If the patient re-leaks at nine or 10 weeks, I tell him that I'll be treating him every eight weeks for the rest of his life. The goal in all of these treatment paradigms is to treat patients with the smallest number of injections that gives them the least amount of recurrent disease, leakage or hemorrhage. It's unusual for a patient to dry out and stay dry over time.

Comparing Monthly Treatment of AMD to Treat-and-Extend



Patients in the TREX-AMD trial were randomized to receive intravitreal 0.5-mg ranibizumab either monthly or according to a treat-and-extend protocol. Mean BCVA gains were similar at 12 months (p=0.60).[5]

"Most of the time we do a fluorescein angiogram at the beginning, but sometimes we don't," he adds. "If it walks and talks and quacks like a duck, it's probably a duck. On the other hand, if we treat with an anti-VEGF agent and it's not getting better, we look harder. At that point, if we haven't already done a fluorescein angiogram, we certainly do one then."

According to Dr. Brown, a recent subanalysis of the VIEW studies by Glenn Jaffe, MD, and colleagues, [in press] found that only 20 percent of the patients still had fluid after three shots of Eylea, meaning they would probably need monthly therapy. "Of the patients in the Q8 arm of VIEW, 55 percent were dry at each visit, so another 35 percent of these patients probably needed injections more frequently than every eight weeks, but maybe not as frequently as monthly," he says. "That gives you some sense of how many patients need this frequency of injection—at least with Eylea."

Charles Wykoff, MD, PhD, a partner at Retina Consultants of Houston, co-director of the Greater Houston Retina Research Foundation and deputy chair of ophthalmology at the Blanton Eye Institute, Houston Methodist Hospital, also favors treat-and-extend. "My goal is to get the patient out to about 12 weeks," he says. "Occasionally there are lesions that are well outside of the fovea on the periphery of the macula that I might choose to observe or laser, but in all other cases I start with monthly dosing and continue that until the macula is completely dry. The number of months that takes is variable; generally, larger lesions with more fluid at the outset take longer to dry out, although that isn't always the case. Once the macula is dry, I typically pursue a treat-and-extend protocol.

Dr. Wykoff notes that fluid is not the only consideration. "At baseline I typically perform a fluorescein angiogram in the majority of my wet AMD patients," he says. "If I have any suspicion of an alternate diagnosis, I also obtain an indocyanine green angiogram. If I get them out to a 12 to 16-week interval with treat-and-extend dosing and there is no evidence of recurrent exudative disease activity, I'll repeat the fluorescein angiogram and evaluate the choroidal neovascular lesion compared to what it was at the beginning. If a lesion is present on angiography, typically I continue dosing the patient. If the lesion appears larger on the angiogram, then I have a discussion with the patient; I may decrease the interval to eight weeks to try to prevent further growth of the lesion, even if the OCT shows no fluid. Sometimes I don't see much evidence of a lesion; maybe just some staining. In those patients I'll have a discussion with the patient and sometimes try withholding injections and changing over to a PRN follow-up pattern, where I don't necessarily inject the patient every time I see him."

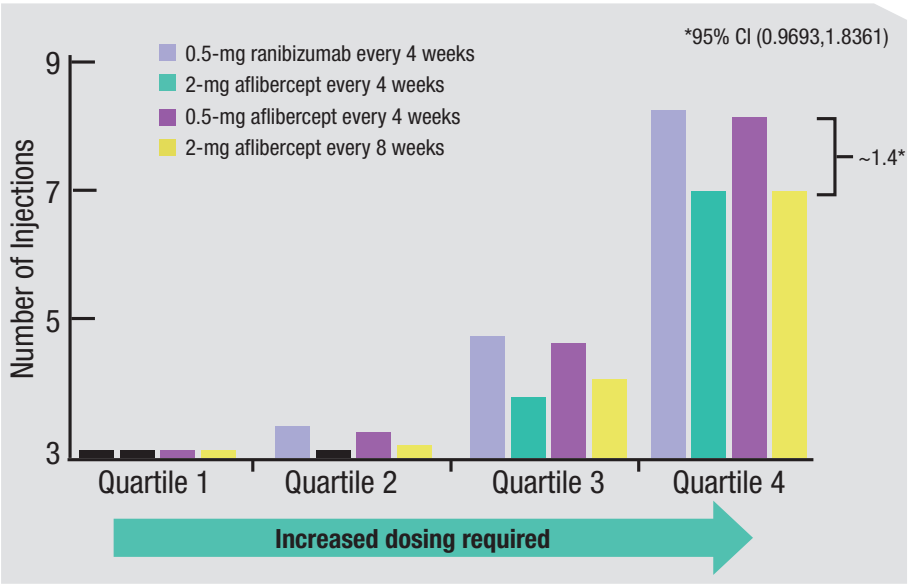
As far as clinical validation of the treat-and-extend protocol, Dr. Wykoff notes that evidence is limited. "We do have a few trials," he says. "The largest treat-and-extend trial was the Lucentis compared to Avastin study,

or LUCAS, a Norwegian-based study in which both arms were treat-and-extend; there was no monthly comparison arm. The only treat-and-extend trial that directly compared treat-and-extend to monthly dosing was TREX-AMD. This was a small trial—only 60 patients—but it appeared to show comparable outcomes between monthly and treat-and-extend dosing of ranibizumab. *[See chart, p.25]* Hopefully, in the future there will be a larger treat-and-extend trial that directly compares treat-and-extend to monthly dosing.

"One challenge is that we don't have data on what to do with patients who are at a 12- to 16-week interval," he notes. "Do they need to continue to receiving dosing indefinitely? Some of those patients stop getting injections and remain dry, but others will have a recurrence. Fortunately, some prospective trials are currently looking at this question."

W. Lloyd Clark, MD, who practices at the Palmetto Retina Center in West Columbia, S.C., and is assistant clinical professor of ophthalmology at the University of South Carolina School of Medicine, believes most patients will probably need to stay on a treat-and-extend protocol long-term. "Given how difficult severe recurrences are to manage," he says, "I think we're looking at a need for chronic therapy in a large percentage of patients."

Number of Injections: Aflibercept vs. Ranibizumab



Between weeks 52 and 96 in the two VIEW trials that compared intravitreal ranizumab to intravitreal aflibercept, among the eyes that had the greatest need for frequent injections (quartile 4), eyes receiving aflibercept required fewer injections than eyes receiving ranibizumab.[6]

The Issues Surrounding PRN

Dr. Wykoff notes that there are exceptions to his use of treat-and-extend. "If the eye dries out very quickly after one or two shots, and it was a small lesion to begin with, sometimes I will use PRN dosing," he says. "In that situation I'll observe the patient, usually at monthly intervals for many months, to see if exudative disease activity will recur. A small percentage of patients don't need long-term anti-VEGF injections. We've learned this from all of the PRN trials—originally from PrONTO, but also from CATT and HARBOR. In my hands, fewer than 10 percent of patients require no additional injections once the fluid has dried out the first time."

"The PRN approach is, I think, acceptable if used one time," says Dr. Brown. "In other words, if you think you may have dried the patient out, and everyone thinks that this is going to be the rare home run, letting the patient go without an injection is reasonable—once. But to require disease activity at every visit, to make an eye demonstrate fluid or hemorrhage each time before you treat, gives PRN a different meaning: 'Progressive Retinal Neglect.' When using PRN treatment, by definition, the patient has to get recurrent edema before you retreat. Using PRN repeatedly is very likely to lead to decreased visual acuity over time, and it gives you the highest risk of losing the visual gains the patient achieved with the initial loading doses. The other problem with PRN treatment is that it makes no sense unless your patient lives or works in your building, because you're making him come in all the time looking for recurrences. If you stretch those observational visits out and you miss early recurrences, you have an even greater risk of trouble."

Studies have found that after the initial monthly dosing, many doctors fall back upon PRN treatment and fewer injections. Dr. Brown says he understands why doctors would tend to shift in this direction. "I think both the doctor and the patient get fatigued by the protocol," he says. "Doctors are certainly aware that patients would prefer to come in less often. On the other hand, most patients don't want to go blind. So I don't think you can make a good argument for any paradigm that leads to undertreatment.

"As with anything in medicine, you can look at it in terms of the risks and benefits of the therapy," he adds. "The risk associated with an extra injection

is the risk of endophthalmitis, which is about 1 in every 3,000 injections. The risk of a recurrence of the disease is 80 or 90 percent. So it seems to me that the pendulum should always swing in favor of a fixed dosing schedule determined by treat-and-extend."

Which Drug to Use?

"All three anti-VEGF drugs can work very well," notes Dr. Wykoff. "We have very good comparative data from CATT and IVAN and other trials comparing Avastin and Lucentis, showing similar outcomes, although there are some signals from those trials that Lucentis may be a better drying agent than Avastin and may lead to a lower treatment burden over time. The only major head-to-head comparison data that we have for Lucentis and Eylea comes from the VIEW1 and VIEW2 trials, which were the registration trials that led to FDA approval of Eylea for wet AMD in the United States. Those trials compared monthly Lucentis and monthly Eylea, but there was also an arm that received Eylea every other month after three monthly doses. All the protocols turned out to have very similar efficacy in terms of visual acuity at the end of one and two years." Dr. Wykoff adds that his preference is to start treatment with an on-label medication—i.e., Lucentis or Eylea. "However, in many cases we're encouraged or mandated by insurance providers to start with the least-expensive option, which is Avastin," he says.

"The general consensus is that most patients with new-onset macular degeneration will respond pretty well to all three agents," says Dr. Clark. "Furthermore, it's difficult to predict which patients might have a better response to any one of them. With that being said, my view is that there are patients who respond better to Lucentis and Eylea than to Avastin. Those are the eyes that have more aggressive disease, recalcitrant eyes that require more therapy. There is some anecdotal evidence about patients that have been on chronic therapy with Avastin or Lucentis switching to Eylea and improving, and there is some evidence from clinical trials that patients with the most severe, treatment-resistant wet AMD may respond best to Eylea. However, those recalcitrant, chronic cases probably only represent about 5 percent of eyes.

"Probably the best clinical data relating to treatment-resistant eyes is from the VIEW1 and VIEW2 trials," he notes. "If you look at year two in the Eylea registration trials, a higher percentage of eyes in the Lucentis arm required numerous PRN injections compared to the Eylea arm. So eyes that needed a lot of treatment in year two were more likely to have been treated with Lucentis than Eylea. *[See chart, facing page].* Of course, this was a small sample; there weren't a lot of patients that needed a lot of treatment in year two. But if you add that to the anecdotal experience that many doctors have had, suggesting that the worst eyes tend to respond best to Eylea, I think it starts to tell a story for this small subset of patients."

Dr. Wykoff believes the anti-VEGF drug a patient is treated with it less important than the treatment regimen. "No matter which drug is being used, the goal should be to achieve and maintain a dry retina," he says. "Patients need to be treated on an individual basis. If they have fluid, they need to be treated aggressively. A study by Glenn Jaffe, MD, et al, that has been accepted by the journal *Ophthalmology*, looks at visual acuity outcomes in VIEW1 and VIEW2 with a focus on those patients who were consistently wet at the first four visits.[1] Those patients gained significantly more visual acuity over the remainder of the trial if they continued with monthly Eylea instead of switching to every-other-month Eylea dosing. In fact, the FDA label for Eylea was recently clarified to

specifically include that some patients do benefit from continued monthly dosing after the first three monthly loading doses of Eylea."

Nevertheless, Dr. Wykoff says he isn't convinced that one drug should be used exclusively in all cases. "In my clinic, regardless of which drug I'm using, I have a low threshold for switching drugs if I don't feel that I'm getting a maximum response."

When Anti-VEGF Doesn't Work

Dr. Wykoff notes that it's rare to find an individual who has no response to anti-VEGF therapy. "A significant number of wet AMD patients are recalcitrant," he says. "We inject them repeatedly, but they continue to show fluid. However, that's not the same as being a 'nonresponder.'

"If the patient is a true nonresponder, then I have a low threshold for switching to a different anti-VEGF agent early on and/or looking for an alternative diagnosis," he says. "Other processes can cause fluid in the macula, and it's critical to rule those out in a nonresponder; I want to make sure I'm not looking at central serous retinopathy or IPCV. If the problem truly is wet AMD, I think almost all eyes will respond at least partially to anti-VEGF therapy. If the patient is responding partially, consider switching the patient to an alternate anti-VEGF agent and see if you obtain a better effect."

Dr. Clark agrees that the first thing to do in this situation is exhaust all of the available approved anti-VEGF agents. "Whatever your initial drug of choice is, if you have a sub-maximal response after several months of monthly injections, move on to the next agent," he says. "If that agent isn't sufficient, try the third agent. You may have preconceived notions about which agent works better, but sometimes you'll be surprised, so keep an open mind. Ultimately, you'll find an anti-VEGF agent that's effective with monthly therapy for more than 90 percent of patients."

Dr. Wykoff notes another alternative: treating this type of patient more frequently. "In most cases I feel confident treating with anti-VEGF monthly, even in the presence of some persistent fluid," he says. "The ones that I do treat more frequently are those that develop, for example, new intraretinal or subretinal hemorrhages while on monthly dosing, or those that show progressive macular edema despite monthly dosing—usually after having tried all three agents. As a result, I have a small number of patients who receive injections more often than monthly, a clinical approach that has been reported previously.[2] Less than 1 percent of my wet AMD eyes need more than monthly dosing. Of course, care must be taken from an insurance-coverage perspective if us-

Anti-VEGF and Geographic Atrophy

One of the concerns some surgeons have about the long-term use of anti-VEGF agents is the possibility that their use contributes to the development of geographic atrophy. "Whether anti-VEGF drugs influence the development or progression of macular atrophy is still unclear," says Charles Wykoff, MD, PhD, co-director of the Greater Houston Retina Research Foundation. "Data from the CATT and HARBOR trials suggests that monthly dosing seems to increase the rate of growth of macular atrophy, with no consistent difference between the anti-VEGF drugs. However, it's important to remember that undertreatment of active wet AMD leads to sub-optimal visual outcomes, as we first learned through the PIER trial, where patients were transitioned to quarterly dosing after three monthly doses. On average, patients lost all of their visual gains. A sub-analysis revealed that patients who maintained a dry retina during quarterly dosing also maintained their visual gains; those who had a recurrence of exudative disease on OCT lost their visual gains. So we have very good prospective data showing that the presence of fluid on OCT should be taken seriously and treated aggressively with ongoing anti-VEGF injections, even if we ultimately find out that the anti-VEGFs do play a role in accelerating macular atrophy."

David M. Brown, MD, FACS, who is clinical professor of ophthalmology at Baylor College of Medicine and runs the Greater Houston Retina Research Center, says he doesn't find the evidence of a connection between the use of anti-VEGF and geographic atrophy convincing. "Geographic atrophy happens in a lot of these patients with or without treatment, and it happens in fellow eyes," he points out.

W. Lloyd Clark, MD, who practices at the Palmetto Retina Center in West Columbia, S.C., believes the action of anti-VEGF drugs and the processes leading to geographic atrophy are independent. "I see geographic atrophy as part of the spectrum of dry macular degeneration disease," he says. "Wet macular degeneration is a complication of the underlying dry macular degeneration, reflecting damage to the Bruch's membrane/choriocapillaris complex, leading to neovascularization underneath the retina. I suspect these patients would be getting geographic atrophy whether or not they developed wet macular degeneration.

"I can't defend the idea of limiting anti-VEGF therapy in a patient with active wet macular degeneration because of concerns about geographic atrophy," he continues. "If the patient has progression of the wet macular degeneration, or a subretinal hemorrhage or a retinal pigment epithelial tear, that's clearly a worse clinical outcome than the slow progression of geographic atrophy. I don't believe they're related, and I don't see the benefits of maximizing anti-VEGF therapy being outweighed by the potential progression of geographic atrophy."

—CK

ing anti-VEGF injections more frequently than monthly."

Dr. Clark notes that for the small percentage of patients that have an unacceptable amount of disease activity even with monthly therapy, treatment options are very limited. "Currently, we have no approved adjunctive agent to anti-VEGF," he says. "There are a few new agents under investigation targeting other pathogenic proteins, most notably the anti-platelet derived growth factor, or PDGF agents, as well as some co-formulated investigational compounds."

Dr. Clark says he believes there's still a role for photodynamic therapy in a small number of patients who don't respond to anti-VEGF drugs. "PDT is a good option for a patient who's already had significant vision loss either due to chronic disease or other comorbid conditions, especially if treatment burden has become overwhelming," he says. "PDT can inactivate the lesion, decreasing the treatment burden and maintaining the patient at a level of moderate vision loss, maybe between 20/80 and 20/200. On the other hand, if you're managing a patient with very good vision who has persistent disease activity, it's not clear to me that there's a better choice today than continued anti-VEGF therapy."

Dr. Brown believes that when a patient fails to dry completely with any of the available agents, the best option is to keep treating. "You really don't have any other option, except ones that might interfere with macular visual acuity," he says.

Issues Surrounding Avastin

As the least expensive anti-VEGF treatment option, many doctors start with Avastin (and insurers often insist on it). However, a couple of issues have arisen concerning the use of this drug in the clinic.

"One risk with Avastin is the need to use compounding pharmacies, which may introduce a small risk of endophthalmitis," says Dr. Brown. "The bigger risk is variability in the availability of the drug itself. Anti-VEGF proteins in the drug aggregate to the walls of plastic syringes, and the proteins also denature with heat. In many cases, we don't know how long the drug has been in the plastic vial."

"Unfortunately, the Avastin that was used in CATT, as well as in the DRCR.Net Protocol T trial that compared Avastin to the other anti-VEGFs, is not the same Avastin that retina specialists have access to in community practice," notes Dr. Wykoff. "The Avastin used in the trials was delivered in individual glass vials, whereas the Avastin used by most retina specialists is provided in plastic syringes. The process of compounding and storing bevacizumab in plastic syringes can result in high variability in its integrity and potency.[3] That very likely has a significant impact on the biological activity of the drug inside of the eye. In fact, we don't have any clinical data confirming that the Avastin that retina specialists use in plastic syringes has the same efficacy as the Avastin used in the head-to-head trials.

"Because of that," he says, "if I don't see a robust response anatomically when treating with Avastin, I have a low threshold to ask patients' insurance carriers if I can switch to a more expensive on-label medication."

Dr. Brown adds that a fair number of patients don't dry out with Avastin. "In the CATT study, after very carefully searching for evidence of fluid, Avastin dried out 30 or 40 percent of the patients," he says. "That means about 60 percent of patients would be switched to a branded drug, if it was possible for them."

Managing Patients Long-term

"Long-term follow-up data from the CATT and MARINA/ANCHOR

trials, at five and seven years after initiation of anti-VEGF therapy, respectively, are fairly sobering," says Dr. Wykoff. "The visual gains achieved at the end of one or two years of intensive therapy were not maintained over three to five additional years of follow-up." He notes that the reasons for this are not clear. "Were the eyes in both of these follow-up studies undertreated, meaning that wet AMD was the main cause of vision loss," he wonders, "or was it that these eyes were developing concurrent macular atrophy? The incidence of that in the SEVENUP cohort was very high; 98 percent of patients had macular atrophy. In the CATT five-year follow-up analysis, the percentage was lower, 41.4 percent, but a substantial portion of the patients developed macular atrophy and that probably contributed to some of those visual declines."

"At least two clinical trials have demonstrated that once we get away from protocol-based, criteria-driven treatment, trouble ensues," agrees Dr. Clark. "In the CATT trial, we treated people on a criteria-driven, protocol-based schedule for two years. The patients did pretty well with all three agents, but after the two-year period they were left to the treatment of their own physicians. These patients were recalled at year five, at which point we obtained EDTRS visual acuity and collected OCT data. It turned out that all of the visual gains seen in year two were gone, and 80 percent of the OCTs showed fluid. In fact, the cohort lost, on average, eight letters by year five. Investigators were asked to count the number of injections they'd given from years three through five. They averaged five injections per year. So when you have significantly reduced treatments—in the neighborhood of one treatment every 10 weeks or so—all the visual gains are lost."

Dr. Clark notes that the same thing happened in the Lucentis clinical trials. "The patients were initially enrolled into a variety of monthly treatment protocols," he explains. "Then they were followed in a long-term study called HORIZON. In HORIZON, they were treated according to investigator discretion. Again, at the end of several years, all the visual gains were lost."

Dr. Clark says that there is some good news, however. "Right now, I'm the principal investigator for a multicenter long-range follow-up to VIEW1 called the RANGE study," he says. "We're looking at protocol-based treatment of the patients who were initially in VIEW1 who went on to be part of the VIEW extension trial; they're now in RANGE. We have five-year data based on criteria-driven therapy, meaning that we saw these patients frequently and treated them for any disease activity, rather than allowing treatment to become less-frequent. Our data shows that this approach has maintained the patients' visual gains. It's a very small cohort—only 35 patients—but it's the first long-term protocol with anti-VEGF therapy to show maintenance of the gains.

"The take-home message is that if you maintain aggressive, long-term, disease-activity-based therapy, we believe you can maintain visual gains," he concludes. "It's clear that consistent dosing, even chronically, appears to be important."

Strategies for Success

To help ensure the best results with the fewest difficulties, surgeons suggest following this advice:

• ***Make sure to get patients onboard at the outset.*** "The initial discussion with patients is critical, because with current technology you're looking at a long-term treatment for most patients," says Dr. Wykoff. "I often make the analogy to treating blood pressure. I point out that blood pressure medications work very well, but they're not a cure for high blood pressure; if you stop taking them, the high blood pressure will likely return again. Similarly, we have really good treatments for wet macular degeneration today, but one of their shortcomings is that they don't cure the disease. This helps my patients understand the need for ongoing injections."

• ***Remember that treat-and-extend helps with patient throughput.*** "Aside from the fact that the evidence doesn't support the use of PRN therapy, adopting a treat-and-extend approach adds efficiency to the process of managing these patients," says Dr. Clark. "I've found that if you treat these patients PRN, they're confused a lot of the time; they come in not knowing what's going to happen. As a result, you often spend more time talking and relitigating the decision. If you use a fairly strict treat-and-extend approach with patients, they get into a rhythm and they understand what's happening. When your patients come in, you know they're getting an injection and they know they're getting an injection. As a result, the workflow is relatively consistent, and the patients' and doctor's expectations visit-to-visit are consistent. Following this protocol also means most of these patients will come in less frequently than once a month, making it easier to manage more patients."

• ***Don't do a dilated exam every time an injection patient comes in.*** "If a patient needs more than six injections a year, I don't think you necessarily have to examine the patient every time you see him," says Dr. Brown. "I look at the OCT of the eye—and the fellow eye—because I want to catch fluid if it's there. But I don't perform a clinical exam (or bill for one) in some of the visits when patients are coming in routinely. I think it's reasonable to examine this type of patient at least every two to three months, or if they have any new symptoms such as flashes, floaters, decreased vision or blurred vision, because sometimes

you'll find things you wouldn't detect on an OCT. But from a patient-flow perspective and a patient convenience standpoint, it makes sense to skip the dilated exam at some visits.

"In our clinic we have what's we call a 'fast track' or 'über track' for visits where I've examined a patient the time before and given her an injection," he continues. "After an undilated OCT, we check the pressure and vision; then we prep the eye and do the injection and the patient is out the door. That allows me to get three or four quick patients an hour added to my regular schedule, and that really helps with the volume."

Dr. Brown adds that these patients get express access to the OCT machine. "They basically go straight from the waiting room to the OCT, and then to a dedicated injection room. Many of these patients are in and out of the office in 30 or 40 minutes in one-third to two-thirds of their visits."

• ***If you think a patient is not responding, check the patient before a month has elapsed.*** "The patient may have responded at one week after the injection, but the response wore off substantially by the time you saw her again," notes Dr. Wykoff. "So if you think you have a nonresponder, it's important to see the patient at a short interval after an injection."

• ***Make sure your staff is well-versed in managing a large number of injection patients.*** "A well-trained, experienced staff can help to extend your efforts, in terms of education and patient management," says Dr. Clark.

Relief May Be In Sight

With the baby boomers aging, the potential explosion in the number of patients with wet AMD has many surgeons concerned about the impact on their practices. Dr. Wykoff, however, believes this may be less of an issue than some fear, thanks to new technology still in the pipeline. "There are a lot of very exciting new therapeutic approaches currently in Phase II and Phase III trials," he points out. "I believe these are going to significantly alter our treatment landscape and approach to treating these diseases.

"I see four major avenues under investigation," he continues. "The first is novel anti-VEGF agents. Abicipar (Allergan) and RTH258 (Alcon) are both currently in Phase III trials ; the hope is that these new agents will prove more potent and/or have longer durability than the current anti-VEGF agents.

"The second avenue is agents that target complementary signaling pathways," he says. "Blocking VEGF only impacts one growth factor. Other promising drugs under investigation block platelet-derived growth factor or angiopoietin-2, both being tested in combination with anti-VEGF drugs in human clinical trials being conducted by Genentech, Ophthotech and Regeneron. We've already seen positive clinical trial data from testing a simultaneous PDGF and VEGF blockade.[4] Other medications under investigation as standalone approaches compared to VEGF blockade include ICON-1 (Iconic Therapeutics), an inhibitor of tissue factor. I suspect that some of these will be clinically available within the next two to five years."

Dr. Wykoff says the third avenue under investigation is reservoir devices. "For example, Genentech's ongoing Phase II LADDER study uses a reservoir placed through the sclera that slowly releases ranibizumab over time," he says. "It might be possible to refill that reservoir a couple of times a year in the clinic.

"The fourth avenue is gene therapy and stem cells, and all of the associated derivatives," he adds. "These are fascinating approaches with great promise, with limited data to date, that continue to be pursued."

Dr. Wykoff also points out another development that could alleviate some of the in-office patient crunch: home monitoring. "Improving our home-monitoring systems so we can get photographs and OCT imaging of patients at home, to see if and when a patient converts to wet AMD or needs a treatment, could allow us to decrease clinic volumes across the country," he notes.

Dr. Brown points out that we've come a long way when it comes to treating macular degeneration. "In 2004, if you weren't in a clinical trial, you went blind," he says. "Today, there are a lot of ongoing pharmaceutical trials and a lot of research and development taking place. Hopefully, we can continue the momentum we now have in fighting blindness." REVIEW

Dr. Brown is a consultant for Regeneron/Bayer, Genentech/Roche, Allergan, Alimera, Alcon, Novartis and Thrombogenics. He has contracted research with Regeneron, Genentech, Allergan, Alimera, Novartis, GSK and Thrombogenics. Dr. Wykoff consults for and receives research support from Genentech and Regeneron, as well as numerous companies with related products still under development. Dr. Clark is a consultant for Genentech/Roche, Regeneron, Bayer and Santen and has received grant support from Allergan.

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Treatment That Fits DME Patients to a 'T'

Walter Bethke, Editor in Chief

Physicians use the results of Protocol T to inform their own treatment protocols.

Occasionally, a clinical trial will come along that's so well-designed and comprehensive, physicians feel compelled to work its findings into their daily practice, in whole or in part. One such trial was the DRCR.net Protocol T, which looked at the efficacy of Eylea (aflibercept), Lucentis (ranibizumab) and Avastin (bevacizumab) in the treatment of diabetic macular edema.[1] Though the Protocol T findings were solid, they still leave room for ophthalmologists to interpret them for their particular patients. Here, retinal specialists share their treatment protocols for DME, and discuss how clinical trial data influences them.

Protocol T's Algorithm

Though physicians will develop their own algorithm for treating DME, the process used in Protocol T can serve as a well-studied starting point.

Jack Wells, MD, a retinal specialist in Columbia, S.C., and lead author on the Protocol T study, says the study's algorithm is sometimes unfortunately viewed as overly complicated. "Many physicians—with some justification—claim it's complicated," he says. "It's really not that complicated. Basically, you start injecting with intravitreal anti-VEGF and keep injecting for six months until you get resolution. After six months, if there's persistent edema, you perform laser, but you don't keep giving injections after six months if it's not improving. If, however, there's been gradual improvement at six months, you don't do the laser but instead keep giving the injections. I think the algorithm is hard for people in clinical practice to follow because they can get impatient. After two, three or four injections, if the patient doesn't show dramatic improvement, some might say the treatment isn't working and switch to another anti-VEGF drug or to steroids. But this algorithm demands patience, that you keep plugging away until, ultimately, you get to a good place. It's a gradual, continuous improvement over a span of months. It does require a lot of treatment."

The First Line

Physicians reference the results of Protocol T when describing their first-line options, since the drugs seemed to perform differently for different patient presentations.

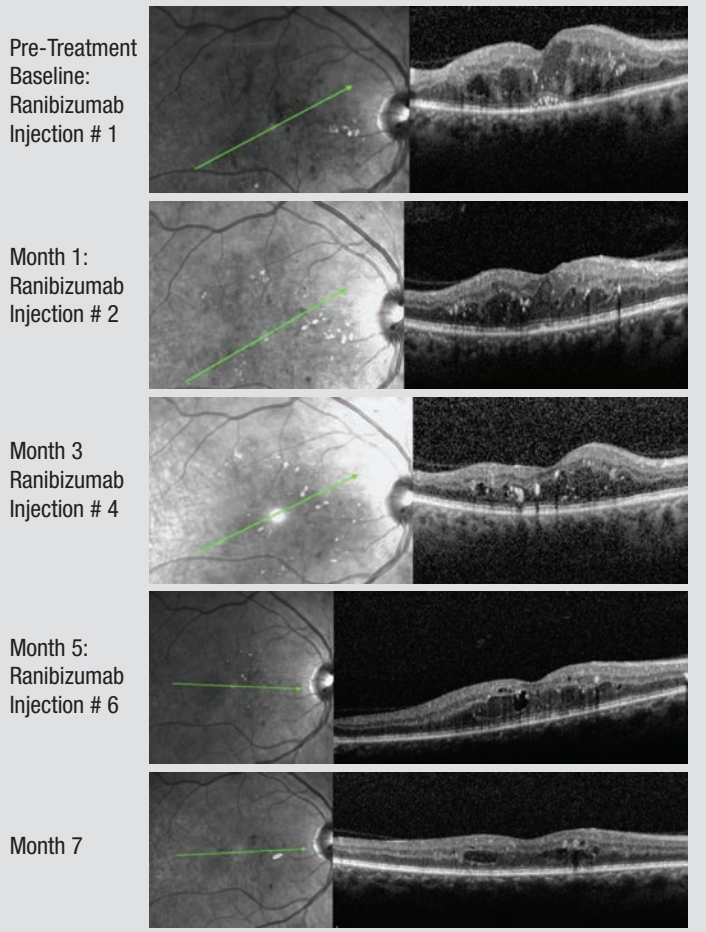
Dr. Wells says the Protocol T investigators prespecified an analysis based on baseline vision, hypothesizing that eyes with worse vision might have

thicker maculas because they had higher vascular endothelial growth factor levels. "A drug that has a higher VEGF binding capacity might give a better outcome," explains Dr. Wells. "So, we drew the acuity line at 20/50, because that was the median visual acuity in all the previous DRCR studies of DME. In the first year, we found that in eyes with better than 20/50 vision at baseline there was no difference in visual improvement between the three drugs; all three gained a mean of about eight letters. However, in eyes with vision worse than 20/50, aflibercept was better than the other two at one year: Eylea eyes gained 19 letters; Lucentis eyes gained 14; and Avastin subjects gained 12, differences that were highly statistically significant. The other thing we found at the first year follow-up was that eyes treated with Avastin didn't show as much of a reduction in edema as eyes treated with the other two drugs, regardless of baseline vision. So, Avastin didn't give the same drying effect. This didn't seem to matter in terms of vision in the better baseline vision group, but it did seem to matter in the group with worse baseline vision.

In the second year, we found that the vision gains and OCT improvement that were seen at one year were sustained," Dr. Wells adds. "So, you still had a very good improvement in vision and a reduction in DME, and that was maintained with a little more than half as many injections and with much less laser than was given in the first year: In the first year, eyes got nine or 10 injections, and in the second year they got five or six. Statistically, the difference between Eylea and Lucentis that was seen in year one diminished. By year two, the Eylea group had gained a mean of 19 letters, and Lucentis had gained a mean of 16, a difference that was no longer statistically significant. The difference between Eylea and Avastin was still statistically significant, however. A lot of people look at these results, then, and say, 'It doesn't matter which drug you start with.' There's some truth to that, because eventually you're going to get to the same place, but in that first year Eylea is so much better that I wouldn't want to deny patients that rapid improvement over that first year. Also, there were half as many laser treatments administered in the second year as in the first."

Following the results of the study, Charlotte, N.C., retinal specialist Andrew Antoszyk alters his approach based on the patient's baseline vision. "Based on the results of Protocol T, if the patient has good visual acuity (20/32 to 20/40), I'll begin treatment using Lucentis because of its better drying effects than Avastin and the availability of pharmaceutical-funded co-pay assistance," he says. "If they have worse VA (20/50 or less), then I'll start with Eylea because of the better visual acuity results in the first year of therapy. In situations where there are insurance issues for coverage of the injections, I'd use Avastin. The availability of drug makers' assistance programs makes the patient's out-of-

Figure 1. A Successful Course of Ranibizumab for DME



Case courtesy of Carl Regillo, MD

This 58-year-old diabetic macular edema patient was treated with monthly injections of ranibizumab (Lucentis) for seven months (not all follow-up visits are shown). The patient shows improvement each month, and his vision improved from 20/100 to 20/30.

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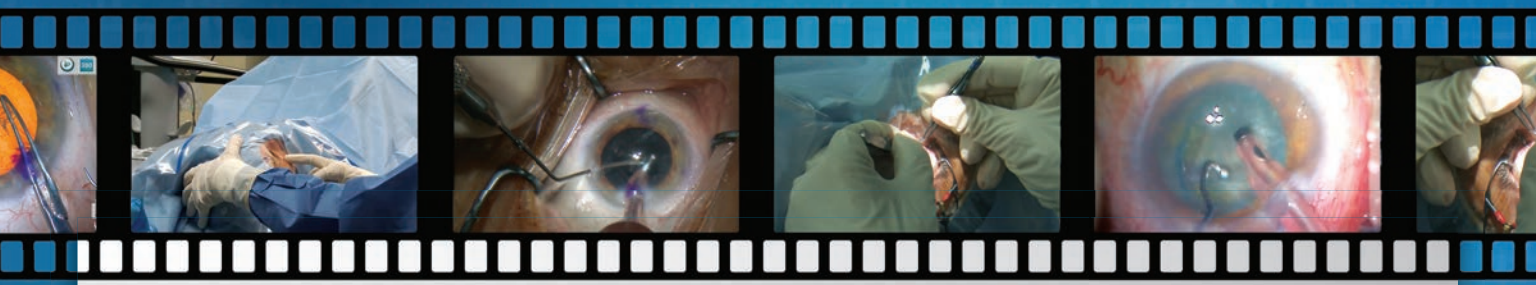

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2. To demonstrate methods to protect the posterior capsule from accidental aspiration during removal of both the nucleus and lens cortex.

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pocket cost for these injections less."

Some clinicians wonder if the presence of macular non-perfusion will alter therapy. "If the macula is still swollen, I'll still try to treat it," says Carl Regillo, MD, director of the retina service at Wills Eye Hospital. "I've had scenarios where there's obvious non-perfusion and you wouldn't think there'd be a visual acuity improvement—but there still can be if there's also edema. There are also scenarios where non-perfusion can improve on anti-VEGF therapy. So, if there's edema, perfused or even non-perfused, I'll start treatment and try to make the edema, and the vision, as good as possible. The presence of macular non-perfusion doesn't influence things at first—it explains things. It could influence whether I stop treatment earlier, and the intensity of the treatment may vary in the patient with non-perfusion."

Gauging Improvement

Just as they use Protocol T as a jumping-off point for choosing their initial therapy, physicians also use its protocol as a guide for determining the need for re-injection.

Dr. Wells says the study used as parameters a five-letter change in vision, better or worse; and a 10-percent change on OCT, for better or worse. "Basically, after you started treatment, if the patient came back for his next visit and the vision was five letters better or worse and/or the OCT was 10 percent better or worse, you retreated," he explains. "It was only if there was no change for two consecutive visits per these definitions that treatment was withheld. Injections then only resumed if the patient got worse. Then, at six months, if there was improvement compared to the previous visits, you didn't do laser, but instead kept injecting. So, after six months, you would only add laser if there was no improvement or the patient was getting worse."

Dr. Antoszyk modifies Protocol T's algorithm slightly. "If the patient has had a five-letter decline from his last visit or an increase in the central subfield thickness of 10 percent on OCT, then I'll retreat," he says. "Part of this decision is determined by symptoms. If the patient isn't bothered by this 10-percent change on OCT or the change in vision, I'll discuss the possibility of waiting a month to see what the disease does at that point. During the discussion, I'll show him the images and discuss the potential result of having edema over an extended period of time that can lead to moderate vision loss.

"If, after the treatments, the individual returns with excellent vision—which I'd define as 20/20, and the OCT is in the normal range—somewhere less than 300 µm—then I'd hold treatment and have him come back in a month," Dr. Antoszyk adds. "If the condition is the same then, I'd hold and have the patient come back in two months. If, after two months, he is still stable, in other words there's no change in visual acuity or recurrent fluid formation, then I'd go to four months. The visits would then be every four months for the first year. If there's no recurrence of macular edema, then follow-up would be dictated by the severity of the retinopathy. In other words, if it's mild, then follow-up could be yearly. If it's moderate, the follow-up could be every six months, and if it's severe, every four months."

Dr. Regillo says he tends to take more of a traditional PRN approach, which he describes as a little bit of a modified treat-and-extend. "Because many patients with DME can come off treatment at some point in their course—maybe six to 12 months into it—and because most need frequent, regular injections to get to their best point, which could be six to 12 months of therapy, for me treatment is essentially monthly until the macula is dry for all significant, center-involving DME, regardless of the drug used," he explains. "And the term 'significant' means, for a given patient, enough edema to start to cause some decreased acuity. Obviously, this doesn't mean treating every little bit of edema. Some patients will do well on their own with just small amounts of edema, even center-involving edema, and have good vision. I've always favored the on-label drugs, and the more edema there is, the more likely I am to use Eylea. Nothing's hard and fast though—we have to take all the information and put it together for any one patient.

"I'll treat until the macula gets to be as good as I think it's going to get," Dr. Regillo continues. "That may mean it's not completely dry, but I'll keep pushing until the macula looks like it's not getting any better. If it's dry, then great; that might be 60 or 70 percent of patients. And if it's not quite dry but there's good vision, I might be happy with that."

When to Switch

Unfortunately, not every patient will respond to the initial anti-VEGF therapy, and surgeons say there are no good, well-controlled studies looking at the various effects of switching to an alternative anti-VEGF drug or to a steroid—physicians just have to rely on their clinical experience and what they know about different drugs' mechanisms.

Dr. Antoszyk likes to give the anti-VEGF therapy some time before he'll contemplate a switch. "Usually, I'll treat a patient with an anti-VEGF drug for six months before I consider switching to an alternate therapy," he says. "So, if I start with Lucentis or Avastin and, after six months, the patient has come to a standstill in response, I'd consider switching to Eylea to see if there might be an additional benefit. This is a good way to see

if you'll get additional benefit without the side-effects of intraocular steroids, which include ocular hypertension and cataract formation. However, if the patient doesn't get a response after six Eylea injections, I'll switch to an Ozurdex implant. If they get a good response from Ozurdex, but require it on a repeated basis, they would be a good candidate for an Iluvien implant."

Dr. Wells, however, thinks some patience is in order when it comes to treating DME, and that it can take some time for the drugs to get the eye to an optimal condition. "Since I was in the study, I understand that it requires a lot of treatment to get to a good place, so I keep plugging away," he says. "We at the DRCR.net have even polled physicians about how many anti-VEGF injections they'll give before switching to a steroid, and they usually reply that it's between three and six. However, if you look at the study, nine to 10 injections were given in the first year, so most got an injection almost every time they came in. If you keep plugging away with the DRCR algorithm, you eventually get there. I'll start with Lucentis in eyes with good vision because I like to see the edema go away, and I don't think I'm going to see that as much with Avastin. However, if there's an insurance coverage issue for the patient, I'll start with Avastin. If I don't get the response I want from Lucentis treatment, I'll consider switching the patient to Eylea, which dries the edema a little bit better, especially in the worse-vision eyes.

"I stick to anti-VEGF therapy for a year or even more as long as there's improvement. It's really only after a year that I'll think about doing something else," Dr. Wells continues. "In my clinic, I add laser treatment if they're not getting better. In some cases, though, you perform an angiogram and observe this massive cystoid edema. I view that more like an inflammatory situation, and will therefore think of using a steroid at an earlier stage, such as six months, if they haven't gotten better."

As Dr. Wells alluded to, physicians still use laser in select cases as an adjunctive therapy. "It's still an effective technique," Dr. Regillo avers. "However, I treat with laser much less often now, and do so less aggressively. I'll use laser for non-center involving edema, especially with angiographically identifiable leaking microaneurysms that I can target with focal laser. I'll occasionally introduce it later in the course of anti-VEGF therapy if I've been able to dry things up but I get some recurrences of the edema, especially if it's non-center involving. When administering the treatment, I don't tend to push it quite as close to the center of the macula as we would have done in the old days when laser was all we had. Now it's careful and cautious use of laser, introduced for very specific, non-center-involving scenarios."

Safety Signals

Over the years, some physicians have wondered about the systemic impact of frequent injections of an anti-VEGF drug, especially in patients who already have health problems, as diabetic patients often do. Though retinal specialists say there's been nothing overtly negative reported on the topic of safety of anti-VEGF drugs, you can adjust your approach in certain patients.

Dr. Antoszyk says the timing of a patient's health events might change therapy. "None of the currently published studies have been powered adequately enough to do an overall clinical safety assessment," he says. "However, with the anti-VEGF drugs, there have been signals that there may be an increased rate of [Anti-platelet Trialists' Collaboration] events. In my practice, if a patient has had a stroke or heart attack within the past month, I might defer treatment—especially in DME—and may consider switching to a steroid within the first three months of an event. One of the issues in these patients is, once they've had an APTC event, they're at an increased risk for another, so is it the anti-VEGF that's causing the next event or their natural history due to multiple risk factors? It is possible that future meta-analyses may provide the answer to this question."

Dr. Regillo will also keep systemic risks in the back of his mind when initiating treatment. "Diabetics in general, at a given age, tend to be sicker from a cardiovascular standpoint, and probably are at an increased risk across the board for cardiovascular or cerebrovascular events," he says. "So, theoretically, these drugs might increase the risk, though there's no proof to this day that they do. It doesn't alter what I do. I might speak to someone with a history of stroke about this theoretical risk, but it's unlikely to alter what I do.

"If someone had a recent stroke and has a lot of other medical issues, I might offer a steroid," Dr. Regillo continues. "Theoretically, we might think of one anti-VEGF agent as being safer than another—the pharmacokinetics seem to suggest that Lucentis would be the safest from a systemic standpoint, or have the least exposure to risk. But studies really haven't borne out any differences between the drugs. If anything, they've been conflicting. It's hard to say if there really are any safety differences at this time." REVIEW

Dr. Regillo has consulted for Genentech and Regeneron. Dr. Wells has received grant support from Genentech, Regeneron and Allergan. Dr. Antoszyk has no financial interest in the products discussed.

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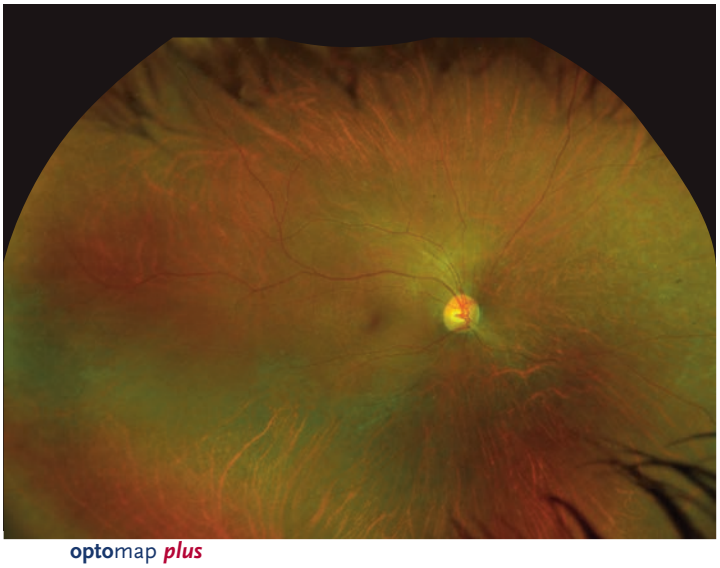

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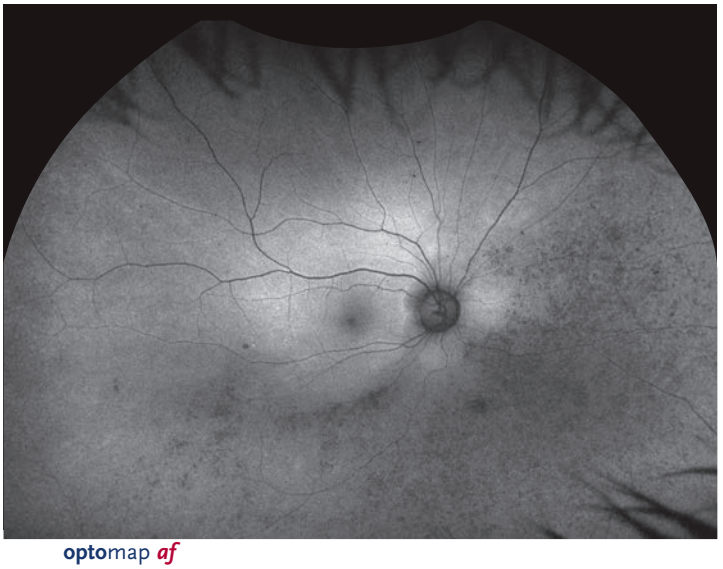

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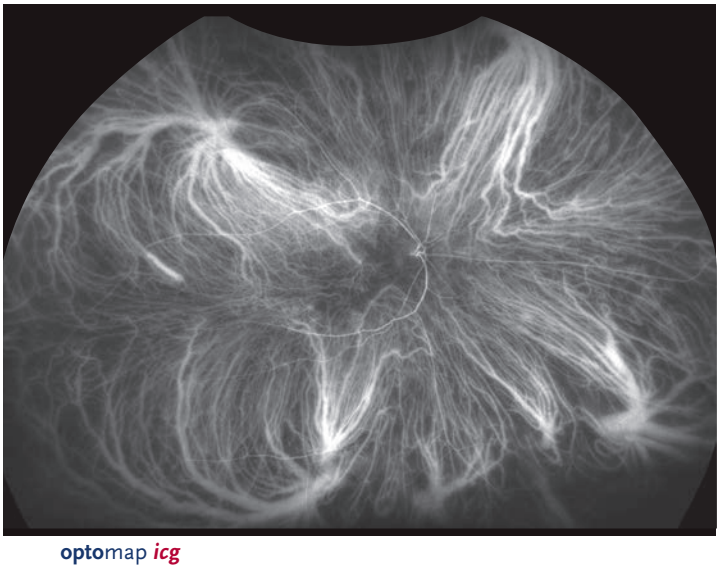

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The Evolution of Vein Occlusion Therapy

Michelle Stephenson, Contributing Editor

Investigators are experimenting with combination therapies that may enhance outcomes.

As the old saying goes, when you're vexed by a problem, sometimes two heads are better than one. However, in the case of vein occlusion treatment, it might be two drugs, and researchers are looking into the possible enhanced efficacy that may result from employing combination therapy for branch and central retinal vein occlusions. Here's a look at the current therapies, and what lies on the horizon.

Anti-VEGF Therapy

When treating branch or central retinal vein occlusion, anti-VEGF medications remain the gold standard. "The first line of treatment is still anti-VEGF medications. Avastin (bevacizumab), Lucentis (ranibizumab) and Eylea (aflibercept intravitreal injection) have all been used to successfully treat retinal vein occlusions. Corticosteroids are also effective. We have used triamcinolone and, more recently and more effectively, Ozurdex (dexamethasone intravitreal implant)," says Michael Singer, MD, who is in practice in San Antonio.

To determine the efficacy of anti-VEGF injection, a recent retrospective study included 81 patients with retinal vein occlusion and macular edema who were naïve to anti-VEGF therapy.[1] The researchers treated 26 eyes with ranibizumab and 33 eyes with bevacizumab. They also treated 22 eyes with bevacizumab and then switched them to ranibizumab. The main outcome measure was the change in acuity at three months, six months and at the final visit.

In the ranibizumab and bevacizumab groups, the mean visual acuity improved from 20/80 to 20/40 and from 20/125 to 20/60, respectively. The mean change in central subfield thickness was -186 µm for ranibizumab and -212 µm for bevacizumab. The mean time between injections was 94 ±21.1 days in the ranibizumab group and 103.8 ±10.5 days in the bevacizumab group. In the group that switched from bevacizumab to ranibizumab, mean initial visual acuity was 20/125. Visual acuity reached 20/60 at crossover and remained at 20/60 through the remainder of the study.

"However, the longer we have been treating retinal vein occlusion patients with anti-VEGF, the more we have realized that many of these patients can't get off treatment and require injections anywhere from every four to six weeks to every three months," says David Boyer, MD, who is in practice in Los Angeles. It appears that a true unmet need exists with anti-VEGF monotherapy.

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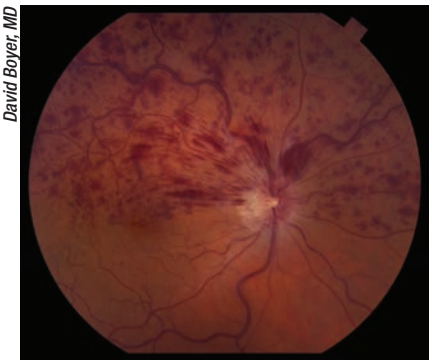
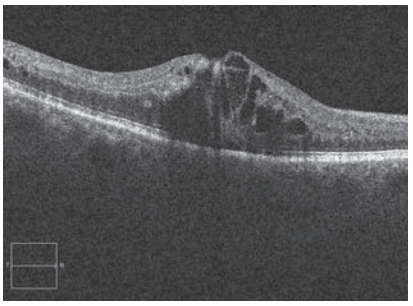
Steroids Step In

Studies have shown that corticosteroids are also a safe and effective treatment option. The Standard of Care vs. Corticosteroid for Retinal Vein Occlusion Study showed that intravitreal triamcinolone acetonide effectively reduces macular edema and improves visual acuity in patients with RVO.[2] Investigators conducted a secondary analysis of the incidence, risk factors and timing of IOP elevation occurring after IVTA, which can provide guidance for clinical decision-making and management of patients treated with IVTA. The study included 682 patients with macular edema secondary to retinal vein occlusion. Study participants were randomized to standard of care, 1 mg of IVTA, or 4 mg of IVTA therapy and were followed for a mean of 24.7 months. Kaplan-Meier incidences of IOP elevation greater than 10 mmHg from baseline at 36 months were 0.02, 0.09 and 0.45 in the standard of care, 1-mg IVTA and 4-mg IVTA groups, respectively. The 4-mg IVTA group also experienced higher rates of IOP-related events compared with the other groups. In patients treated with 1 mg and 4 mg of IVTA, the median number of days from time of first injection to IOP elevation greater than 10 mmHg from baseline was 34 and 52.5 days, respectively. The investigators concluded that the risk factors for an IOP-related event include a higher treatment dose, younger age and higher baseline IOP. The researchers added that IOP-related events may occur several months after the first IVTA injection, and physicians should consider these risk factors when assessing the risks and benefits of IVTA therapy and the need for long-term follow-up of patients who are at risk for this complication.

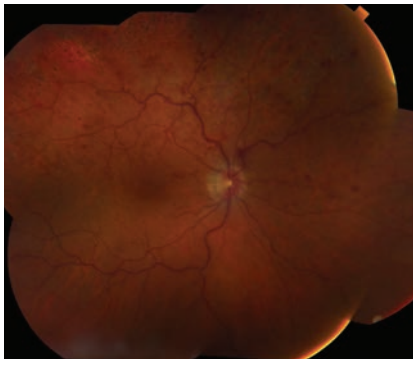
The dexamethasone implant (Ozurdex 0.7 mg, Allergan) has also been shown to effectively treat vein occlusion. A recent study evaluated the safety and efficacy of one or two treatments using dexamethasone intravitreal implants over 12 months in eyes with macular edema related to BRVO or CRVO.[3]

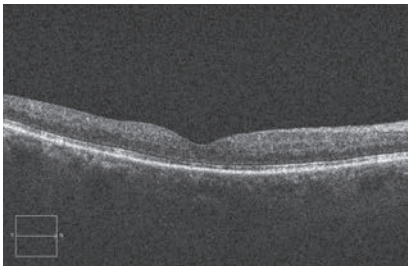


David Boyer, MD



This patient presented with the hallmark signs of branch retinal vein occlusion.





After a treatment with anti-VEGF and eventually Ozurdex, the edema was greatly reduced and vision had improved.

This study included 1,256 patients with vision loss caused by macular edema associated with retinal vein occlusion. At baseline, 421 patients received a dexamethasone 0.7-mg implant, 412 received a dexamethasone 0.35-mg implant, and 423 received a sham implant. At day 180, patients could receive a dexamethasone 0.7-mg implant if their best-corrected visual acuity was less than 84 letters or if their retinal thickness was greater than 250 µm, and this implant was received by 997 patients. Except for cataract, the incidence of ocular adverse events was similar in patients who received their first or second dexamethasone implant. Over 12 months, cataract progression occurred in 90 of 302 phakic eyes (29.8 percent) that received two dexamethasone 0.7-mg implant injections, compared with five of 88 sham-treated phakic eyes (5.7 percent). Cataract surgery was performed in four of the 302 (1.3 percent) phakic eyes that received two implants and one of 88 (1.1 percent) eyes that received the sham.

In terms of IOP effects, in the group receiving two 0.7-mg DEX implants, researchers reported an increase in IOP of 10 mmHg or greater from baseline in 12.6 percent of patients after the first treatment, and 15.4 percent after the second. The investigators found that the IOP increases were usually transient and controlled with medication or observation. After the second treatment, an additional 10.3 percent of patients initiated IOP-lowering medications.

An improvement in best-corrected visual acuity of 15 letters or more from baseline was achieved by 30 percent and 32 percent of patients 60 days after the first and second dexamethasone implant, respectively.

"Ozurdex works remarkably well in some patients. It is able to stabilize vision for longer periods of time, and in some cases, it can reduce the number of treatments that are necessary," Dr. Boyer adds.

A Combination Approach

While anti-VEGF and corticosteroid treatments work well alone, there's evidence that they work even better in combination, and according to Chicago-based vitreoretinal surgeon Seenu Hariprasad, MD, the treatment paradigm is headed toward combination therapy. "There is really good evidence in the literature that vein occlusion is a multifactorial disease. Of all the retinal diseases that we treat, branch retinal vein occlusion and central retinal vein occlusion cause the highest level of VEGF in the eye. There is also very good evidence that there is an inflammatory component that anti-VEGF monotherapy does not address. This may contribute to the high treatment burden with anti-VEGF therapy, so I am a big believer in incorporating other modalities of treatment, such as Ozurdex. I think a combination of an anti-VEGF and Ozurdex can be very powerful," adds Dr. Hariprasad.

A 2014 study found that bevacizumab combined with dexamethasone implants produced greater improvements in macular thickness than bevacizumab therapy alone and required fewer bevacizumab injections in both BRVO and CRVO.[4]

The study included 30 eyes that were randomly assigned to receive either combination therapy or monotherapy with bevacizumab. All patients received intravitreal bevacizumab at baseline, followed a week later by dexamethasone implants or sham injections. Monthly bevacizumab injections were given if the central subfield thickness was less than 250 µm, and the combined group received a second implant after four or five months if the central subfield thickness was less than 250 µm.

At six months, patients receiving combined therapy required fewer bevacizumab re-injections compared to those receiving monotherapy (two compared to three). They also experienced greater mean reductions in central subfield thickness (-56 µm compared to +45 µm) and were more likely to have resolved all edema, which was considered to be a central subfield thickness less than 250 µm (seven of 11 eyes compared to two of 14 eyes). Mean visual acuity changes from baseline were similar between groups.

Dr. Hariprasad notes that imaging is critical in this disease. "Using OCT is one of the best ways to track treatment response," he says. "We get a baseline OCT, and then we can determine whether the pharmacologic agent is working or not. So, it is a great way to track and quantify treatment. We also use fluorescein angiography to determine the amount of macular and peripheral ischemia and address both accordingly. I would recommend ultra-wide-field fluorescein angiography and OCT testing."

According to Dr. Hariprasad, a potentially important advance in the treatment of retinal vein occlusion is CLS-1003 (Clearside Biomedical), which consists of a microneedle injection of the company's Zuprata (triamcinolone acetonide) into the suprachoroidal space in combination with an intravitreal injection of Eylea. The therapy was developed for the treatment of macular edema associated with retinal vein occlusion.

In April, Clearside completed a small Phase II trial of 46 patients.[5] In this study, patients who received concomitant administration of Zuprata and Eylea qualified for approximately 60 percent fewer intravitreal Eylea treatments than those patients who received Eylea alone. This is the first controlled, masked, randomized trial conducted in patients with retinal vein occlusion where the drug was administered through the suprachoroidal space. No serious adverse events were reported during the trial, and treatment was generally well-tolerated. "In the past, we just used an anti-VEGF," Dr. Hariprasad says, commenting on the results. "Then, the corticosteroids came along and enhanced the way we treat the disease."

According to Daniel H. White, CEO and president of Clearside, "Based on these results, Clearside intends to follow a 505(b)(2) NDA regulatory approval pathway and expedite the preparations for a Zuprata Phase III registration program for the treatment of macular edema associated with RVO." REVIEW

Dr. Singer is a consultant for Allergan, Genentech and Regeneron. Dr. Boyer is a consultant for Allergan, Genentech, Roche, Bayer, Novartis and Regeneron. Dr. Hariprasad is a consultant for Alcon, Allergan, Bayer, Alimera Sciences, Clearside Biomedical, Janssen, Ocular Therapeutix, OD-OS, Optos, Regeneron and Spark.

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Anti-VEGF Everywhere, But Not a Drop to Use

Richard T. Atallah, Manuela Von Sneidern, Alan T. Sheyman, MD, Ben Z. Cohen, MD
New York City

Reusing Lucentis and Eylea vials might be feasible the authors say.

Intravitreal anti-vascular endothelial growth factor therapies have become an important treatment for patients with neovascular age related macular degeneration, diabetic macular edema, proliferative diabetic retinopathy and many other retinal conditions. When you draw a dose of an anti-VEGF drug, however, current regulations prohibit you from using any more from that vial, even though there may be several doses left.[1] Judging by the cost of injecting certain drugs such as Lucentis (ranibizumab) and Eylea (aflibercept), leaving these vials unused leads to hundreds of thousands of dollars in wasted drug each year. In this article, we take a look at the pros and cons of a compounded drug such as Avastin (bevacizumab), and the feasibility of reusing the vials of ostensibly safer, non-compounded drugs such as Lucentis for more than just one injection.

The Cost of Compounding

Though ophthalmologists want to do what's best for their patients, as in most areas of life, cost is a major factor; and there is a significant cost difference between the anti-VEGF medications.

In 2015, the American Society of Retina Specialists asked its members, "If Avastin, Lucentis and Eylea were the same cost for each patient, which drug would you use primarily for the treatment of new-onset exudative AMD?"[2] Less than 10 percent indicated that they would use Avastin first, even though, in the real world, it's actually the preferred first-line drug for 64 percent of ophthalmologists. Findings such as this show just how important cost is when choosing anti-VEGF medications.[3]

However, even though Avastin is cost-effective, it has a potential drawback, too: It needs to be compounded in order for it to be usable in the eye. This drawback looms large due to an outbreak of fungal meningitis from three lots of preservative-free methylprednisolone acetate compounded at the New England Compounding Center in September 2012. Further, in an article in *JAMA Ophthalmology* in 2013 by one of this article's co-authors, Alan Sheyman, MD, he and his colleagues described a series of eight patients who received an intravitreal injection of compounded combined bevacizumab-triamcinolone from the same lot—who were later diagnosed with fungal endophthalmitis.[4] This outbreak occurred despite the current practice of compounding pharmacies and outsourcing facilities performing microbiological testing on their com-

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pounded bevacizumab.

In addition to the obvious risk to patients in terms of complications and morbidity from using medications from compounding pharmacies and outsourcing facilities, prescribing a compounded drug may expose an ophthalmologist to liability if a patient has a negative outcome, especially if a suitable FDA-approved product is available.[5] What's more, ophthalmologists should be aware that if a claim arises, medical malpractice insurance companies may refuse coverage if a physician used non-FDA approved drugs.[6] Despite the risks, some may still feel that the cost difference between bevacizumab and the FDA-approved medications is significant enough to justify compounding. However, even the Pharmacy Compounding Accreditation Board's Principles of Compounding states, "Price differences are not a 'significant' difference to justify compounding."[7]

In response to the fungal meningitis outbreak, the Food and Drug Administration imposed stricter regulations on compounding pharmacies, including the mandated use of patient-specific prescriptions, which requires the pharmacy to only make one compounded drug for one specific patient rather than a large lot of it. However, a recent study of one retina practice showed that these PSP's reduced the use of Avastin by 32.7 percent. The study authors state, "Although PSP's of compounded medications improve patient safety, a burdensome effect on the practice of medicine occurs, leading to a shift to more expensive but more convenient alternatives, namely on-label medications."[8]

In some of the authors' own practice, we have a collection of Eylea and Lucentis vials that had been used a single time on a single patient, and still contain a lot of residual medication: Each vial contains 0.2 ml of drug, while the required dosage of medication is only 0.05 ml.

After being used for a single injection in one patient, vials of Food and Drug Administration-approved anti-VEGF drugs start to pile up, physicians say.

Against this backdrop of the questionable safety of Avastin and its production in compounding facilities, coupled with the apparent availability of non-compounded medication remaining in these vials, we got to wondering if we could safely use those vials again. We performed the following study to find an answer.

Our Study

For our study, we collected 60 Lucentis and 40 Eylea vials (a total of 100 vials) over the course of three years (2012 to 2015) after single dose/single patient use by a retina specialist (Dr. Cohen). All these vials had been stored over the course of those three years at room temperature in a bag on the shelf. Lucentis expiration dates ranged from 3/2014 to 9/2017, and Eylea dates ranged from 1/2015 to 3/2016. A third of the vials were used in 2013; a third were used in 2014 and a third were used in 2015. To administer the injections, Dr. Cohen retrieved the medicine by first removing the metal cap, wiping the rubber stopper with alcohol, removing the medicine with the 19-ga. filter needle and finally switching to a 30-ga. needle before intravitreal injection. Only the patient wore a facial mask.

We took the medication to a microbiology lab at New York University where the residual drug was removed from each vial. Under a sterile hood, we first cleaned each vial with alcohol for 10 seconds and then with Betadine for another 10 seconds. A sterile syringe with a 25-ga. needle was used to extract 0.05 ml of medication from each vial. We then plated the medication equally among blood agar and Sabouraud agar plates in an attempt to grow bacterial and fungal colonies. Then, we placed the 100 blood agar plates in an incubator at 98.6 degrees Fahrenheit for four days; we incubated the 100 Sabouraud agar plates at room temperature for three weeks. After incubation, we photographed each plate and examined it for bacterial and/or fungal growth. What we found was extremely intriguing: All 100 blood agar plates and 100 Sabouraud plates were negative—there

was no bacterial or fungal growth.

In our view, even though this was a small-scale study, the lack of contamination of 100 vials of Lucentis and Eylea calls into question the FDA's and Medicare's policies on the use of residual medication in such vials. Drawing more medication from a single vial isn't unprecedented: It may be surprising to know that in a survey by the Joint Commission, 6 percent of health-care practitioners admitted to sometimes or always using single dose vials for multiple patients. Also, according to a *JAMA* study in 2010, 28 percent of all ambulatory surgery centers admitted to using single-dose vials for multiple patients.[9] Nonetheless, governmental guidelines are intended to protect patients from infections where vials become contaminated from unsafe injection practices, and we completely support the spirit of the law. The fact remains, however, that our study showed no bacterial or fungal growth in the residual medication in these 100 vials over the course of three years of storage, a strong testament to the fact that these vials can most likely be reused safely. In the coming years, we hope to see a larger-scale evaluation of the stability of these drugs over time to reinforce our findings and possibly convince the powers-that-be to eliminate risk—and waste—from the system. REVIEW

Mr. Atallah and Ms. Von Sneidern are in the pre-med program at New York University. Dr. Sheyman is a retinal specialist at Northwestern University in Chicago. Dr. Cohen is a retinal specialist at Mt. Sinai Medical Center in New York City. *The authors would like to acknowledge Joel S. Mindel, MD, PhD, director of neuro-ophthalmology at Mt. Sinai School of Medicine in New York City, for his editorial review. None of the authors have a financial interest in the products discussed.*

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Targeting VEGF's Silent Partners in DME

A look at what's going on behind the scenes in patients for whom anti-VEGF therapy has little or no effect.

Rehan M. Hussain, MD, Thomas A. Ciulla, MD, MBA, Indianapolis

Vascular endothelial growth factor is the primary treatment target in many cases of diabetic macular edema, and the disease process often responds to intravitreal anti-VEGF injections. But what happens if you lock down VEGF with your injections but the patient doesn't respond and continues to lose vision? It turns out there are other mediators lurking behind the scenes, influencing the pathophysiology of DME. Ophthalmic research is dragging more of these mediators into the light every day, however. This review will cover the various contributors to vision loss in DME and how emerging drugs are targeting them. (It should be noted that many of these drugs affect several of these pathways; consequently, listing a particular drug under one pathway represents a simplification to enhance readability.)

Permeability

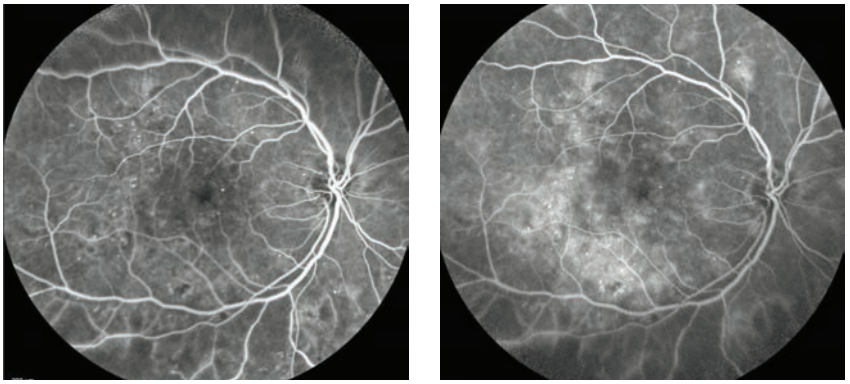
Vascular permeability, leading to macular edema, causes vision loss through mechanical distortion of the orderly retinal architecture as well as the secondary signal interference. In diabetes, chronic hyperglycemia contributes to alterations in the structural and cellular components of retinal microvasculature. Early on, there is damage to the pericytes responsible for regulating capillary perfusion, which results in microaneurysm formation and impaired regulation of retinal blood flow.[1] Damage to endothelial cells responsible for maintaining the blood-retinal barrier allows accumulation of extracellular fluid in the macula. There's also thickening of the capillary basement membrane and increased deposition of extracellular matrix components.[1,2,3] Over time, continued retinal microvasculature damage causes capillary nonperfusion and retinal ischemia, resulting in activation of hypoxia-inducible factor-1 alpha (HIF-1a) via signaling through phosphoinositide 3-kinase and its downstream target, mammalian target of rapamycin (mTOR).[4] HIF-1a causes upregulation of VEGF, which mediates vascular permeability.[5] Though there are several different VEGF isoforms in the body due to alternative splicing, VEGF-A and placental growth factor mediate vascular permeability and pathologic angiogenesis in the eye. Current agents, ranibizumab (Lucentis, Genentech/Roche), aflibercept (Eylea, Regeneron) and off-label bevacizumab (Avastin, Genentech/Roche), bind VEGF to prevent activation of VEGF receptors, thereby decreasing angiogenesis and vascular permeability, causing regression of diabetic neovascularization and reduction in DME, respectively.[2,6]

Another target of interest is the Tie-2 receptor tyrosine kinase, which is expressed by endothelial cells. When stimulated, it produces reinforcement of junctional proteins, more interaction with surrounding cells and matrix, and stabilization of the vasculature. Tie-2 is activated by Angiopoietin-1, which results in reduced permeability, whereas Angiopoietin-2 serves as a competitive antagonist that diminishes Tie-2 activity. Ischemic retina results in elevated Ang-2, which is also elevated in patients with DME.[7] Following are two investigational agents that target permeability.

- ***Nesvacumab.*** Ang-2 antibody Nesvacumab (Regeneron) binds Ang-2, allowing more Ang-1 to activate Tie-2, so that permeability can be di-

minished. Trials comparing aflibercept alone to aflibercept with Ang-2 antibodies in DME patients are on the horizon.

• ***AKB-9778.*** Also affecting the same pathway, AKB-9778 inactivates vascular endothelial-protein tyrosine phosphatase. VE-PTP dephosphorylates Tie-2, causing it to shift to an inactive state. Therefore, AKB-9778 helps keep Tie-2 active by inactivating VE-PTP. This drug is administered by subcutaneous injection, and may serve as an alternative option for patients averse to intravitreal injections. A Phase Ib trial showed that AKB-9778 was well-tolerated, caused significant reductions in retinal thickness and significantly improved visual acuity.[8]



Early (left) and late phase (right) fluorescein angiograms show the typical appearance of an eye with diabetic macular edema.

The Vitreoretinal Interface

For refractory cases of DME, it's important to assess the vitreoretinal interface carefully, as vitreomacular traction and epiretinal membrane can contribute to macular edema and associated visual loss via tractional forces that exacerbate hyperpermeability. Here's a look at two approaches addressing interface issues.

• ***Jetrea (ocriplasmin).*** The vitreoretinal interface is anchored by extracellular matrix proteins such as laminin, integrins, fibronectin and collagen types VI, VII and XVIII.[9] Ocriplasmin, a key ingredient in ThromboGenics' drug Jetrea, is a recombinant truncated form of human plasmin that has proteolytic activity against these proteins. However, it's not active against type IV collagen, a component of the internal limiting membrane, thus limiting its toxicity to the retina. When injected into the eye, ocriplasmin can cause pharmacologic vitreolysis and posterior vitreous detachment, offering an alternative to surgery. In one study, ocriplasmin caused resolution of VMT in 26.5 percent of eyes compared to 10.1 percent of placebo eyes within 28 days.[10] Ocriplasmin could be used in cases involving VMT with narrow vitreomacular adhesions.

Surgical intervention may be required in cases not amenable to ocriplasmin injection, however, such as those with broad vitreomacular adhesions or epiretinal membrane. In such cases, pars plana vitrectomy with or without membrane peel can serve to release the anteroposterior and tangential tractional forces of the vitreous on the ILM. Gradual restoration of the retinal architecture may result in reduction of edema and improvement in visual acuity. Diabetic eyes may have diffuse residual vitreous cortex after surgical creation of a PVD, which can lead to continued traction and development of ERM.[11] Surgical removal of the ILM eliminates the vitreous cortex and any potential proliferative scaffold that could contribute to ERM formation. In eyes with diffuse DME, the ILM becomes thickened and a variety of cells, including myofibroblasts and inflammatory cells, adhere to the inner surface of the ILM, with the potential to further exacerbate edema.[11]

• ***Luminate.*** Another potential treatment targets integrins, which are cell adhesion and cell signaling receptors. The integrin peptide antagonist Luminate (Allegro Ophthalmics) targets receptors involved in both angiogenesis and vitreolysis.

Integrins mediate cell functions, interactions among cells and the extracellular matrix, and activate intracellular pathways that promote angiogenesis. In the body, there are many different types of integrin receptors, but the $\alpha_v\beta_3$, $\alpha5\beta1$, and $\alpha_v\beta_5$ subtypes are expressed more in diabetic retinopathy.[12] Inhibiting $\alpha5\beta1$ has been shown to inhibit endothelial cell proliferation and produce regression of choroidal neovascular membranes.[13,14] Integrin $\alpha_3\beta_1$ mediates attachment of the vitreous to the retinal surface. Inhibiting $\alpha_3\beta_1$ results in vitreolysis and PVD, which can help patients with VMT, and may serve as an alternative treatment to ocriplasmin. Luminate is currently in Phase II trials for treatment of DME, VMT and AMD.

Inflammation

Inflammation plays an important role in diabetic retinopathy and DME, as leukostasis, prostaglandin upregulation and retinal accumulation of macrophages all occur in diabetes. Diabetics may have abnormally large and rigid leukocytes that adhere to the vascular endothelium, which can contribute to vascular occlusion and ischemia; these leukocytes generate toxic superoxide radicals and proteolytic enzymes.[15] The end result is endothelial dysfunction, vascular per-

meability, retinal nonperfusion and, potentially, angiogenesis, all of which lead to vision loss.

VEGF possesses inflammatory properties through its capacity to mediate microvascular permeability and increase adhesion of leukocytes. VEGF was found to stimulate expression of intracellular adhesion molecule-1 and vascular cell adhesion molecule-1,[6] therefore involving the inflammatory cascade, initiating early diabetic retinal leukocyte adhesion and contributing to the development of diabetic vasculopathy. Thus, anti-VEGF agents may also have a therapeutic mechanism that involves limitation of inflammation. Other inflammatory mediators such as tumor necrosis factor-alpha, interleukin-6, interleukin-8, cyclo-oxygenase-2 and monocyte chemotactic protein-1 may also be upregulated in DME.[17]

• ***Ozurdex and Iluvien.*** Recently, there's been interest in sustained-release corticosteroids, such as the dexamethasone intravitreal implant (Ozurdex, Allergan)[18] and the fluocinolone acetonide implant (Iluvien, Alimera),[19,20] both of which were approved for the treatment of DME in 2014. Research has suggested that inflammatory cytokines play a larger role in chronic DME than non-chronic DME.[18] For this reason, anti-VEGF therapy may not be effective in all patients, because targeting VEGF does not suppress all the inflammatory cytokines involved in chronic DME. Corticosteroids can address this aspect of the pathophysiology by inhibiting the arachidonic acid pathway, resulting in downregulation of prostaglandins, prostacyclin, thromboxanes and leukotrienes. In addition to this anti-inflammatory mechanism, corticosteroids can alter the composition of the endothelial basement membrane by changing the local ratio of two laminin isoforms, suppressing basement membrane dissolution and strengthening tight junctions to limit leakage that can cause macular edema.[22,23] In the future, the combination of anti-VEGF therapy and sustained-release corticosteroids is an area of research that may hold promise for treating refractory DME and decreasing the treatment burden of repeated injections.

There are also a couple of new therapies being explored to target the inflammatory component of DME that might serve as alternatives to corticosteroids:

• ***Infliximab.*** The drug infliximab inhibits the pro-inflammatory cytokine TNF-alpha, which has been implicated in breakdown of the blood-retinal barrier in diabetic animal models.[24] Small studies have yielded inconsistent results in regards to its efficacy in treating refractory DME, however. [25,26] IL-6 is another pro-inflammatory cytokine that may induce expression of VEGF or may directly increase vascular permeability.[27,28] IL-6 levels were found to be elevated in patients with DME without PVD, and correlated significantly with severity of disease.[29] An IL-6 antibody is currently in development for trials.

• ***KKS inhibitors.*** The kallikrein-kinin system is activated in response to vascular injury and leads to a local increase in bradykinin, which further results in pro-inflammatory effects such as vascular permeability, vasodilation and immune cell activation.[30] Rodent model studies have shown that diabetes and hypertension increase KKS components in the retina, and inhibition of plasma kallikrein was found to reduce vascular permeability.[31] VEGF also leads to increased kallikrein levels in the retina. A KKS inhibitor is being explored for therapeutic efficacy in Phase II trials.

Fibrosis

Retinal fibrosis, which severely distorts and destroys retinal tissue, can result from chronic DME, especially when hard exudates occupy the fovea. Consequently, limiting DME via any of the pathways noted above can minimize fibrosis. As previously mentioned, hypoxia-inducible factor-1a accumulates under hypoxic conditions and serves as a stimulator of VEGF. Hence, there is benefit to inhibiting this pathway that is regulated by the mTOR kinase.[4]

• ***Sirolimus.*** Also known as rapamycin, Pfizer's Sirolimus is an mTOR inhibitor with the ability to inhibit angiogenesis, permeability, inflammation and fibrosis, making it potentially useful for variety of retinal vascular diseases. It also inhibits protein kinase C and pro-inflammatory mediators such IL-8, endothelial-monocyte activating peptide-II, COX-1 and COX-2.[32,33] Rapamycin's ability to inhibit fibrosis,[34] an important contributor to irreversible photoreceptor death and severe visual loss, may fill a void in the currently available DME treatments.

Ischemia

In diabetic retinopathy, enlargement of the foveal avascular zone is detected by fluorescein angiography; it is considered an indication of ischemia and may contribute to macular edema.[35] Foveal ischemia in DME causes photoreceptor outer segment shortening and inner segment-outer segment disruption, resulting in outer retinal atrophic changes that correlate with visual loss.[36] Unfortunately, there are no treatments available to reverse the atrophic photoreceptor changes associated with macular ischemia.

The pathophysiology of DME is complex and allows for many potential therapeutic targets. While currently laser photocoagulation, anti-VEGF injections and corticosteroids are the most commonly used treatments, there are many intriguing options being explored to address other

(continued on page 60)

How Do You Quantify The Qualitative?

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Playwright and critic George Bernard Shaw once wrote, "The only man I know who behaves sensibly is my tailor; he takes my measurements anew each time he sees me. The rest go on with their old measurements and expect me to fit them." Measurement scales are so much a part of our daily routines we almost never give them a second thought. Yet, just as the tailor knows to adjust and re-measure every time, as ophthalmologists we should, from time to time, mentally recalibrate the scales we use to assess signs and symptoms, subject as they are to drift and bias. This is particularly true in the case of the subjective scales we use to measure qualitative data: our use of these metrics reflects our inherent knowledge and clinical experience, and their application should bear the scrutiny of comparisons with the broader scientific community. When it comes to scales, we should be asking the question: are we all on the same page? Is your 2+ redness the same as mine?

This month we'll consider the elements of these metrics and discuss the scales we use for grading the signs of ocular disease. In a future column, we'll explore symptom scales, questionnaires and patient-reported outcomes, all necessary tools of the trade that also need occasional sharpening. Understanding the statistical parameters and tests commonly used for assessing grading systems is an essential first step towards critically thinking about these grading scales and the responses and symptoms they measure.

The Measure of A Measure

The purpose of any scale is to provide a means to measure a trait, a physical change or any parameter not readily amenable to direct quantitation. Ultimately, we use the scores generated for comparison, as a function of age, health status or treatment regimen. All scales are not the same however, and when developing a new scale it's necessary to test for precision, for repeatability *(see the glossary on p. 51)* and for agreement between graders, as well as to test for agreement with existing disease metrics.

There are a number of statistical tests that measure agreement, such as the intra-class correlation coefficient. The ICC is a ratio derived from the analysis of measurement variance. The closer the ratio is to 1.0, the greater the agreement between tests.[2] One statistics text suggests that an ICC of 0.4 indicates poor agreement, 0.4 to 0.75 as fair to good agreement, and greater than 0.75 as excellent agreement.[3]

Agreement is also presented by Bland Altman plots,[4] which elegantly illustrate the difference in paired observations on the y-axis versus the mean of the observations on the x-axis, including horizontal lines for the mean difference ± two standard deviations. Bland Altman plots are a very useful snapshot of agreement between two devices, systems or graders. They originated the concept of limits of agreement between two methods. A correlation coefficient (r) is commonly and incorrectly used to measure agreement, when r actually measures the strength of relation between two variables, not the agreement between them.

There can be high concordance in using a scale because the categories are simply too broad. We could all throw a tennis ball through the width of a barn door, but what about through a window? In the case of wide confidence limits, the grading system won't be sensitive enough to

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measure change, regardless of the fact that we all agreed as to each step in the scale. Thus, we want a system that is not so coarse that sensitivity is lost, and not so fine that there is no agreement among users and, consequently, no ability to have comparable data.

A fine example of this was laid out in a fascinating 1991 paper on the use of scales.[5] Using the example of a lens opacity grading system, the authors had two graders score 87 lenses. Instead of using the 0 to 4 scale, they broke down the scale into finer granularity, with each integer divided into nine decimals, such as 2.1, 2.2,…, 2.9, etc. With the integer scale, the concordance was 74 percent, with variance equal to ±1 grading units. To fall out of the confidence limits, there had to be a difference of two grading units between the paired observations. When the decimalized scale was used, the concordance was only 9 percent between graders, but the confidence limits were at 0.8 grading units. Thus, the decimalized scale gave confidence limits 2.5 times finer than those given by the integer scale. While practicality drives us to continue to use integer scales, incorporating 0.5 increments increases granularity and improves the sensitivity of our grading.

Ideally, we want our measurement scales to be able to identify clinical change in our patients. In practice, we need to know if a keratitis or flare reaction is worse this week than last, and we use scales to measure the progression of disease.

Change can also be associated with treatment, either in practice or in research. In a clinical trial, treatment can be either positive (comparator) or negative (vehicle, placebo). It's particularly critical to have a sensitive measurement when dealing with a bioequivalence clinical trial of one active to a test compound. When both agents being studied in the trial have the same therapeutic effect—we must be sure differences in effect are measured sensitively and accurately to establish bioequivalence.[6]

The opposite can also be true, however. For the drug approval process using the conjunctival challenge model of ocular allergy, the data are highly reproducible, with tight standard deviations. This provides a level of sensitivity that is well above what occurs in seasonal allergic conjunctivitis studies. Because of this sensitivity level, the U.S. Food and Drug Administration mandates that not only statistical significance be provided by the dataset, but also that a one-unit change in integer increments demonstrates clinical significance, or an effect that would be perceptible to both the patient and the physician. In the case of dry-eye disease, one symptom and one sign are required to demonstrate efficacy by showing statistical significance in drug approval studies.[7]

Figure 1. Fluorescein Staining Scale

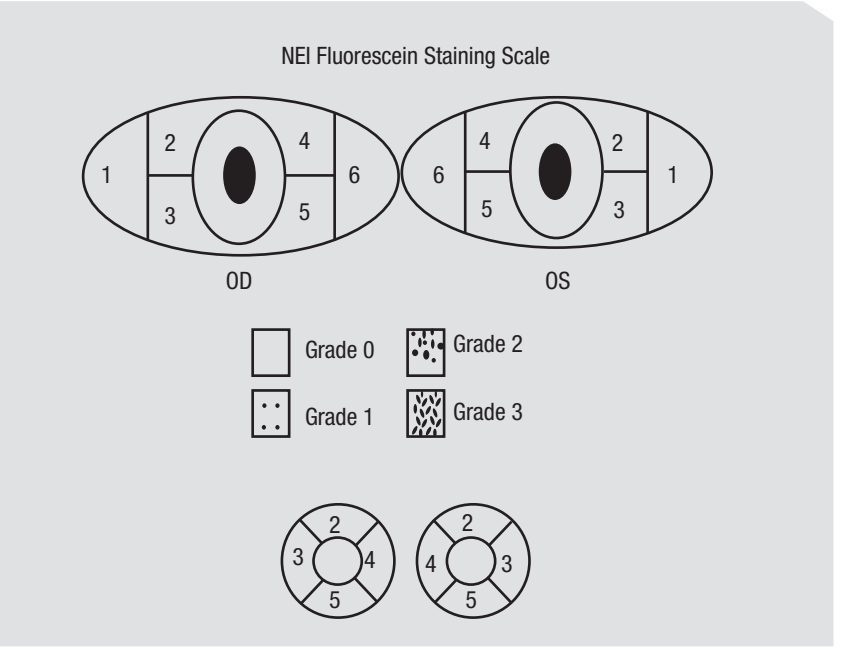

Figure 1. The NEI scale for grading fluorescein staining divides the corneal and conjunctival surfaces to help measure fluorescein uptake.[9] A standardized grading system of 0 to 3 is used for each of the five areas on each cornea. Grade 0 is specified when no staining is present, and the maximum score is 15.

Staining Scales

Some of scales the more commonly used to assess staining are the Baylor scale,[8] the National Eye Institute grading system,[9] the Oxford scale[10] and the van Bijsterfeld scale.[11]

The NEI scale for grading of fluorescein and lissamine staining is probably the most widely used by clinicians *(See Figure 1)*.[9] While this 0 to 3 grading system is fairly simple and easy to use, it divides the cornea into regions that, with the exception of the center, do not readily reflect physiologically-relevant anatomy. The NEI scale does not consider the importance of the limbus, which contains Langerhans cells essential for active participation in a corneal inflammatory response, as well as a depository of stem cells to enrich the cornea when new cells are needed. Also, the NEI scale rates all regions of the cornea as equivalent, while

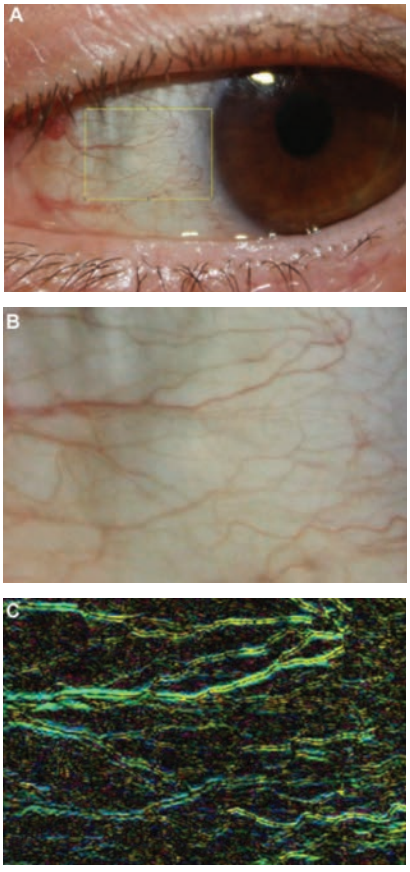

Figure 2. This automated dry-eye redness software system measures hue and horizontality.

our experience tells us that some areas convey more information about the underlying disease activity than others. In fact, the scales we use for grading fluorescein and lissamine green staining in clinical trials[12-14] home in on these specific regions and provide a more reproducible measure of the corneal responses that appear to be the most modifiable and responsive to treatments and exacerbation with exposure.[15]

While we all agree that counting keratitic dots would be an inefficient way to spend our day in the clinic, we've developed an automated method of counting the dots in slit lamp photos using computer software, and thus have an improved, continuous, numerical scale for grading fluorescein staining. While presently this software is used only in research, it's not unthinkable that one day a slit lamp photo will be scanned into the computer to yield an exact count while the patient waits.[16]

Rating Redness

Redness scales abound in the ophthalmic literature. These ideally are specific to disease, as we all know that many diseases respond with a characteristic hyperemia (a topic we have explored at length in past columns). The Ephron illustrated scales are often used, although these were developed for the grading of redness associated with contact lens wear. Interpretation is provided for the Efron scales as clinical action not required (0, normal), clinical action rarely required (1, trace), clinical action may be required (2, mild), clinical action usually required (3, moderate) and clinical action certainly required (4, severe).[17, 18]

We have developed redness scales specific to allergy, dry eye *(See Figure 2, left)*,[19] meibomian gland dysfunction and blepharitis (See the April and May 2016 Therapeutic Topics columns). These have been calibrated with thousands of patients in clinical trials among investigators all over the United States. Again, allowing for half increments improves the granularity and sensitivity of the scale. Image analysis techniques for redness assessment have been the focus of research by us and others,[19,20] and have been found to be six to 35 times more repeatable than subjective grading.[21] We've also developed automated software designed specifically to grade dry-eye redness, which has a unique horizontal component and which is best predicted by the combined characteristics of hue intensity and vessel geometry.[19] Our work confirms an earlier demonstration that edge detection and vessel area are as important as color intensity, using comparisons with the Annuziato, Efron, Brian Holden Vision Institute (formerly CCLRU) and Vistakon redness scales, all of which are based on photographic or illustrated reference images for each increment.[21] Both the Brian Holden scales, published in 1993, and the Efron scales, first published in 1997,[17,18] were developed with contact lens wear complications in mind. Johnson & Johnson (The Vision Care Institute) has also published photographic and pictorial scales of redness, staining and MGD, as well as pinguecula, pterygium and cortical cataract severity to aid in the management of chronic UV exposure.[22] Of course, redness scales are also useful in diagnosis of bacterial conjunctivitis and glaucoma. There are even apps for iPhones that give the clinician a sliding photographic scale with 0.1 increments to use during patient visits.

Scleritis and Uveitis

Other complex clinical presentations such as scleritis also need to be managed over time. Uveitis specialists have developed standardized photographs to consistently grade the severity of scleral inflammation.[23] Automating these types of scales through imaging is becoming more common, as OCT-derived measurements have been shown to have good agreement with clinical vitreous haze scores, and may be incorporated into the monitoring and retreatment regimens of patients with uveitis.[24]

It's inevitable that, in the not-too-distant future, imaging techniques and new technologies will ultimately replace the qualitative grading of signs that we currently use. However, the clinician will always be needed to assess and corroborate the results of these new approaches. Until then, we must bridge these techniques with accurate and comparable grading systems that function over time and over different graders, using statistical tools to assess how well the new or old method measures up to the gold stan-

A Grading System Lexicon

We hear these words bandied about all the time: precision; accuracy; reliability; agreement; concordance; reproducibility; correlation. Understanding their contextual meaning is key to understanding the value of data derived from them, so a brief terminology primer puts us all on the same page.[1,2]

Precision of a test measures its reproducibility; the degree to which repetitive measurements are given the same grade. A perfectly precise scale will always rate a 2+ red eye a 2+ red eye, just as a precise balance measures a standard weight the same every time.

Repeatability refers to the ability of an operator to consistently repeat the same measurement of the same part, using the same gauge, under the same conditions. Repeatability is, then, the variation between measurements that occurs when one person measures the same item several times, using the same measuring equipment. Repeatability of a system is used in the market approval process for all the medical devices we use on a daily basis. This repeatability is synonymous with **concordance**, or the frequency of perfect agreement over time and repeated measurements, or among graders scoring the same outcome.

Repeatability is different from precision, or **reproducibility**, which is the ability of a gauge, used by multiple operators, to consistently reproduce the same measurement of the same part, under the same conditions. Reproducibility is, then, the variation in average measurements of different appraisers who measure the same items using the same measuring equipment. It may also be used to compare different measuring devices at different locations.

Accuracy is bit more abstract, defined by the degree of closeness of measurements to the true value, or reference value. A grading system can of course be accurate but not precise, and vice versa. For example, a balance that measures a 1-gram weight standard at 2 grams every time is precise, but not accurate. If that same balance always measures that same standard somewhere between 0.8 and 1.2 grams, no matter who does the measuring, it would be considered accurate but not precise.

The example above also allows us to distinguish between **bias** and **error**. An example of a non-random bias could be the readings of two tonometers. If one was found to regularly add 2 mmHg to intraocular pressure, this bias can be accounted for in the outcome by recalibration of the instrument. However, you only know which tonometer is off by having a known standard. Without this, identifying which machine is off is impossible. Error, conversely, is random variability not accountable by any identified bias. In practice, identifying a true reference value is not a simple task when assessing qualitative data such as that used in non-continuous grading systems.

Confidence interval is a range that defines whether a measure is different from the expected result. For confidence intervals to be valuable there must be reproducibility in assigning grades to clinical signs. Grading systems that provide narrow confidence limits provide measures sensitive enough to detect clinical change. Confidence limits are often placed at 95 percent, which is to say that observations occurring outside of the confidence limits would occur under the reference value with only a 5 percent, or 1 in 20, chance.

A term that is used more of late is **granularity**, a measure of how sensitive a scale is to change. The degree or need for granularity is dependent upon the metric in question: Vitality works with a low granularity scale (dead or alive), while a complex metric such as pain often employs scales of 10 points or more.

dards. Recalibrating your thinking on a periodic basis about the scales you use in ophthalmic practice will improve the quality of your observations in the clinic and help you tailor the long-term care you provide to each of your patients. REVIEW

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MIGS & Meds: Refining Trabecular Bypass

Implanting a MIGS device and adding one drop may be a much better option for many glaucoma patients than a trab or tube.

E. Randy Craven, MD, Baltimore

Given that most of the aqueous leaves the eye by passing through the trabecular meshwork and the canal of Schlemm into collector channels—at least in a healthy eye—treating reduced outflow by finding ways to bypass the trabecular meshwork is a familiar idea. However, until recently this has been easier said than done.

Now, thanks to advances in technology such as dyes and imaging, that include optical coherence tomography, we're beginning to sort out how best to make this approach work. Hopefully, we'll soon be able to determine which eyes are good or poor candidates for trabecular bypass. As we learn more about how the outflow system works and how to repair it when it malfunctions, we're beginning to get a sense of the place trabecular bypass should hold in glaucoma treatment, and how we can best use it to care for our patients.

Here, I'd like to talk about some of what we've learned in this area and where it might lead us. In particular, I'd like to challenge some key popular ideas about what constitutes "successfully" treating glaucoma—ideas that may be preventing many of us from offering patients effective treatment options that are far more patient-friendly than a trabeculectomy or tube shunt.

Placing Stents Effectively

Many of the so-called micro-invasive glaucoma surgeries, or MIGS, offer minimally invasive ways to bypass the trabecular meshwork. I was involved in the first study of the iStent (Glaukos), which was also the first study ever to test so small a device. We wanted to find out how much pressure reduction we could achieve by using a device to get into the canal of Schlemm and bypass the trabecular meshwork. Unfortunately, there was a lot we didn't know about the device and how to use it most effectively. Also, we were focused on meeting the requirements and expectations of the U.S. Food and Drug Administration, and we were restricted to implanting the device during cataract surgery. When designing the trial we had not refined some important things, such as washout periods, control groups, adding medications during the trial and other factors.

The result was that the data from the iStent trial was kind of messy. Overall, the data seemed to indicate that there wasn't a big difference between phaco alone and the iStent combined with phaco. At the time, I told the company that those results didn't make sense to me because I had some patients who got terrific results—as much as a 35-percent reduction in IOP. Of course, these were the early days; there was no agreement about technique, or where to put the stent, or how to determine if it was even in the canal.

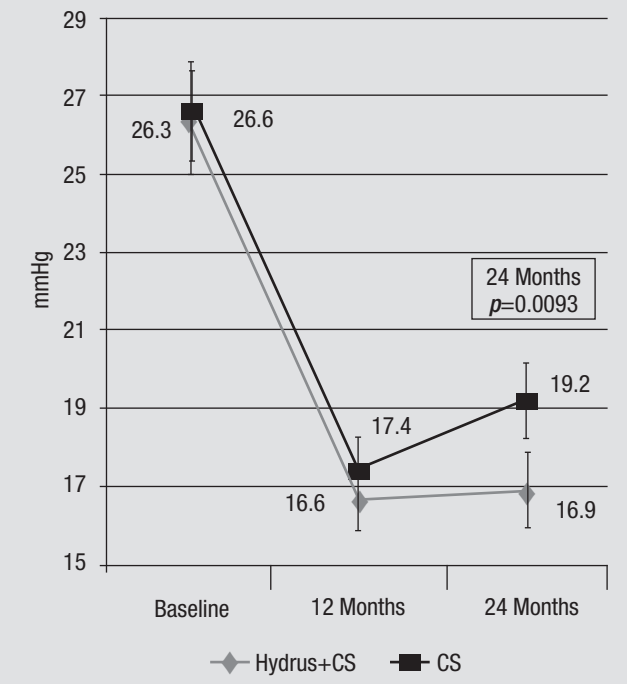
I was pretty obsessive about making sure the stent was actually in the canal. I would look for aqueous veins, and we knew from histopathological studies that there is a larger abundance of collector channels inferonasally, so I tried to target the inferonasal area. After I inserted the stent I would look at it under high magnification and check for blood reflux. Perhaps not surprisingly, a subset of patients in the trial looked really good. During the trial I did get to observe a few other surgeons who were participating, and I saw one surgeon who failed to get the stent into the canal at all. That

This article has no commercial sponsorship.

data is part of the study as well.

Today, we've learned a lot more about the trabecular meshwork, the canal and the collector channels, and the mixed results from that trial are beginning to make sense. For one thing, because outflow is segmental, we now know that it's beneficial to implant the device close to a patent collector channel. Recently, other studies have confirmed this. Reay Brown, MD, and his colleagues published a paper last year involving 47 eyes, in which they validated that the stents were placed effectively;[1] they reported a mean IOP reduction of 3.2 mmHg, which was statistically significant and much better pressure control than we achieved in the first iStent study. So it's clear that targeted placement makes a big difference in the outcome.

Washed-out Mean Diurnal IOP Post-cataract



In this 2015 study, 100 eyes with open-angle glaucoma and cataract and a washed-out diurnal intraocular pressure between 21 and 36 mmHg underwent cataract surgery, with or without implanting a Hydrus Microstent. At 24 months, washed-out mean diurnal IOP was significantly lower in the group that received the Hydrus implant. There were no differences in follow-up visual acuity between the groups.[3]

Their study's findings highlight the importance of correctly identifying the canal (to ensure that the device is actually in the canal) and then either being able to identify the collector channels and their condition, so the correctly implanted device has a chance to work, or using multiple stents and hoping that one (or both) are close to a functioning collector channel. Technology like OCT is beginning to make targeted placement possible, thanks to improved visualization of these structures.

Because placing the stent close to a functioning collector channel can be challenging, another way to increase the odds of effective pressure lowering is to implant more than one stent. That's the idea behind the iStent Inject Trabecular Micro-Bypass Stent, which comes preloaded with two stents. Results from a clinical trial of that device are indeed showing better pressure reduction than is seen in patients who receive a single iStent. A 17.5-percent between-group treatment difference in favor of the iStent Inject group was statistically significant (p=0.02) at the >50 percent level of IOP reduction.[2] It seems that implanting more stents does a better job of tapping into Schlemm's canal and gets us closer to the areas where outflow is functioning. In my experience, using two iStents—or a single well-placed iStent—gives us pressures somewhere in the mid to upper teens.

The importance of access to patent collector channels is also supported by the work being done with the Hydrus Microstent (Ivantis), which dilates and scaffolds a section of the canal. Trials are showing pretty good pressure reduction with the Hydrus, similar to what we're seeing with two iStents.[3] *(See chart, left.)*

"MIGS and Meds"

That brings us to the issue of what constitutes a "successful" glaucoma treatment. Many ophthalmologists believe that ideally we should get our patients completely off of medications. Given that the target pressure for many patients with significant glaucoma is 10 to 14 mmHg, the trabecular bypass approach is seen as a failure because it can't get most patients to that level by itself.

I believe that thinking needs to change, because the alternatives we have to offer these patients are problematic. The issues accompanying trabeculectomy and tube shunts are well-known. At the same time, implanting one or two well-placed iStents or a Hydrus, and adding a single medication, can easily get most patients into the 10- to 14-mmHg range. The end result is that you've done a minimally invasive surgery and the patient has to use one drop a day, and you've achieved a result equal to what you would have achieved with a trabeculectomy.

Make no mistake: Patients are happier with an iStent than they are after a trabeculectomy or tube shunt. I often have newer patients

ask for the iStent because they've spoken to others who have had a trabeculectomy or tube shunt and they didn't like what they heard. In addition to being an associate professor at Johns Hopkins University in Baltimore, I'm chief of glaucoma at King Khaled Eye Specialist Hospital in Riyadh, Saudi Arabia, and I've found that globally, the acceptance of the iStent is much higher than trabeculectomy. Combining a MIGS surgery like the iStent or Hydrus with a single medication may achieve the same level of pressure reduction with far less irritation for the patient.

This is why I came up with the phrase "MIGS and meds." It reflects the idea that this combination has some appeal. In the past, MIGS has been unfairly cast as an inferior option for patients, simply because they have to continue using one drop a day. (In reality, quite a few patients still end up using a drop every day after a trabeculectomy or tube shunt, too.) Reaching the target pressure with a minimally invasive surgery and one drop a day is a better success, in my opinion, than a trabeculectomy. At the least, it's reasonable to start with this and move to the more aggressive surgeries if this method fails. Patients are much more comfortable, and complications are much less likely.

Seeing the Unseen

Of course, there are patients for whom trabecular bypass isn't a good option. If the patient has raised episcleral venous pressure or atrophied collector systems, then repairing or improving the trabecular bypass system probably won't lower intraocular pressure much, if at all (and of course, certain types of glaucoma, such as neovascular glaucoma, wouldn't be helped by this approach.) The problem is, we don't have any tools right now that can do a good job of measuring either one of those things. So for now when a patient needs surgery I first opt to try implanting an iStent—or two of them—and see if it works. If it doesn't, then I move on to other options, because the failure suggests that the episcleral venous pressure is high and/or the collector system is not functioning.

Meanwhile, with the steady improvement in technologies like OCT and dyes, we may soon be able to look at the canal and identify which patients will be good or poor candidates for trabecular bypass. At this point, the latest OCT technology can reveal which areas of the canal are more dilated and more collapsed, and we can sometimes see collector channels. What this means is still unclear; however, thanks to the work of Murray Johnstone, MD, we know that the canal of Schlemm is a dynamic entity that functions as a biomechanical pump. In a healthy eye, blinking or moving the eye causes the trabecular meshwork to move and push aqueous out. Since the current OCT images we have are snapshots, it's possible that the collapsed areas of the canal are actually the sections that are functioning; the image may have caught the canal as it has pushed some aqueous into the collector channels. As time goes on, we'll find out. (Note: The OCT we've been using for this purpose is not yet FDA-approved.)

We're in the infancy of being able to do this, but it seems clear that as our ability to see these details and our understanding of what they are telling us improves, we're going to start getting answers about who would be a good trabecular bypass candidate.

The Cataract Factor

Another factor that has impacted how surgeons see MIGS options like the iStent is another legacy of the original trial of the iStent: the idea that this surgery makes the most sense when it's combined with cataract surgery. (The FDA approval for that circumstance alone, of course, has limited reimbursement as well.)

I've been doing a lot of Hydrus and iStent implantations in the Middle East as standalone procedures—no cataract surgery involved—and I can testify that it works in either pseudophakic or phakic eyes. Unfortunately, we have limited clinical data on the iStent as a standalone procedure outside of cataract surgery, although some studies do support this premise. There is currently a clinical trial evaluating the effectiveness of the Hydrus without cataract surgery. Also, a study conducted in Armenia, where patients received two iStents and a single medication, showed that all 39 patients achieved an IOP reduction of at least 20 percent and had an IOP of 14 mmHg or less at 18 months.[4] So, I believe cataract surgery is a secondary issue. If our perception of MIGS as not being "successful" for many patients were to shift, this might be more obvious.

Finding the Best Option

I think the biggest hurdle with the idea of trabecular bypass and devices like the iStent is that so many surgeons accept the idea that it doesn't work. They may look at the first paper and take that data as evidence that this conclusion is justified. But in reality, trabecular bypass with the iStent works very well in many patients. If some of those patients need to use one drop a day to reach our target, that's a pretty small burden to bear compared to the side effects of a trabeculectomy or tube shunt. My patients who have had an implant are much happier than my patients who have had trabeculectomies and tubes.

As our ability to judge which patients are most likely to benefit from trabecular bypass improves, success rates should increase. Nevertheless,

the ultimate popularity of this approach may depend on another factor: other MIGS devices in the pipeline. Some of these are aiming to lower pressure by siphoning aqueous into the suprachoroidal space. Early data does indicate that this approach can work well; data from the trial of the CyPass device (Alcon) is significantly better than the data from the first iStent trial (article in press). The safety data has also been very strong for the suprachoroidal devices that are in the pipeline; they seem to be well-tolerated without any significant issues beyond a little bit of bleeding, which is usually transient. There's been almost no hypotony. So these will probably be good options as well.

Which approach ends up being more popular may depend on timing; if it's still unclear which patients are good candidates for trabecular bypass when a suprachoroidal device is approved, surgeons may be inclined to move in that direction. On the other hand, my personal belief is that taking advantage of the physiological outflow pathway through the trabecular meshwork makes the most sense. With the possible addition of a single medication, I think it's a great first-line surgical procedure, at least in patients for whom I think it will work.

In order for "MIGS and meds" to work in the long run, we will definitely need to become better at visualizing the canal and collector channels so we can readily identify patients who are the best candidates. In the meantime, using more than one stent, or a new device like the Hydrus, will help surgeons ensure that bypassing the trabecular meshwork provides as much pressure relief as possible. With the addition of a single medication, even challenging patients should be able to reach our target pressures.

In my experience, patients who have gone down this path are far happier than those with trabeculectomies or tube shunts—and that's not a bad definition of success. REVIEW

Dr. Craven is an associate professor at Johns Hopkins University and chief of glaucoma at King Khaled Eye Specialist Hospital in Riyadh, Saudi Arabia. He is a consultant to Allergan, Alcon, Aerie, Transcend and Ivantis.

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Tips for Pre-LASIK Resurfacing

Doing your prep work ahead of time will make things smoother in the long run, surgeons say.

Walter Bethke, Editor in Chief

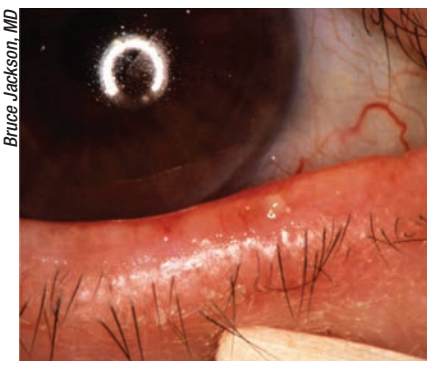
As any contractor or weekend do-it-yourselfer will tell you, prepping a surface before you start working on it is half the battle. The same goes for pre-LASIK preparation of the ocular surface. Surgeons say that dry eye due to causes such as aqueous deficiency, meibomian gland dysfunction or other disease entities can turn an otherwise successful case into a hard slog for patients and their surgeons as they deal with healing issues and exacerbated signs and symptoms postop. To avoid postop ocular surface issues, follow these refractive surgeons' tips.

Diagnostic Steps

By asking the right questions, surgeons say you can catch a lot of potential problems preop during your exam:

• ***History.*** Refractive surgeons say listening to patients' experiences with contact lenses can give a lot of clues. "We'll ask patients if they can wear contact lenses comfortably or if they have a history of wearing them but then having to stop because of irritation," says Edward Manche, MD, director of cornea and refractive surgery at Stanford University's Eye Laser Center. "We also get a handle on symptoms they're having that might be related to dryness."

Julie Schallhorn, MD, assistant professor of clinical ophthalmology at USC's Keck School of Medicine, says you can drill down deeper into the contact lens complaints. "A lot of contact lens wearers have irritation after wearing their lenses for a while," she says. "However, some may say that when they wake up in the morning their eyes are really irritated; that clues me in to the possibility that they may have a nocturnal exposure problem. A lot of young people, in particular, have some nocturnal exposure in which they open their lids a little at night. If you ask them about it, they'll say their eyeballs feel as if they're 'Velcroed' to their lids in the morning. Others may say that their eyes feel terrible when they're not wearing contact lenses, but as soon as they put in their lenses they feel great. This is a sign that there may be another ocular surface issue going on that the contact lens is masking, such as really bad meibomian gland dysfunction with a rapid tear-film breakup time. For them, the lens acts like a bandage and keeps tears on the cornea. But, when they remove it, they have a rapid TFBUT and sense the dryness." Dr. Schallhorn also says to be sure to check about systemic diseases like secondary Sjögren's, rheumatoid arthritis and scleroderma, all of which can be related to dry eye.



Bruce Jackson, MD

Patients with meibomian gland issues and rosacea will need special attention preop.

• ***Exam.*** Dr. Manche says a thorough anterior segment exam should turn up any issues. "We do vital dye staining with lissamine green and fluorescein," he says. "We'll do Schirmer's tests to make sure we don't have someone with Sjögren's. We then do a good external ocular exam looking for meibomian gland dysfunction." Surgeons

will press a little on the lid margin to try to express some meibum. "See if it runs clear or if she has meibomian glands that are backed-up and not working," says Dr. Schallhorn. "I'm also looking at the conjunctiva. Is there chalasis? If there is, it can be a sign of chronic dry-eye irritation and a cause of that irritation. I also evert all the lids of contact lens wearers to look for giant papillary conjunctivitis. On the cornea, note if they have any punctate epitheliopathy, and the exposure pattern. Is the pattern inferior or is it diffuse, as in toxic keratopathy?"

Bakersfield, Calif., surgeon Daniel Chang, MD, also says your corneal topographer can clue you in to surface issues. "Corneal topographers that do not employ a smoothing algorithm, such as the Zeiss Humphrey Atlas 900 that I use, can give a sense of the regularity of the ocular surface," he says. "If the surface is irregular, the topography will be bumpy and granular.

"After the initial consultation, about a week or so before surgery, my patients come back for preoperative measurements," Dr. Chang continues. "At that visit, we will have stressed the ocular surface—performed refractions, multiple diagnostic tests and dilation—and if their ocular surface can hold up to that, they'll probably do OK with LASIK. If it doesn't hold up, that's a red flag."

Treatment

Though ocular surface disease is often a mix of MGD and aqueous deficiency, physicians note that different treatments are more effective on one form or the other.

• ***MGD.*** "For meibomian gland disease, I'll recommend lid hygiene and lid washes," Dr. Schallhorn says. "There are many products out there that you can use. I also tend to supplement these patients with omega-3 fatty acids and flaxseed oil, at least leading up to the refractive surgery. And, depending on how bad it is, I at least get them to do some warm compresses. Then, depending on the severity of the disease, you can do oral tetracyclines. I like doxycycline or azithromycin, or a course of a steroid/antibiotic combination, depending on how bad the disease is. For most patients with MGD, however, lid hygiene, warm compresses and dietary supplementation will resolve the problem."

• ***Aqueous deficiency.*** Dr. Manche discusses the possibility of Restasis with these patients. "A lot like to start on Restasis initially," he says. "I give that a six- to eight-week trial and see how they respond. If they respond well and the surface looks good, then I'd consider performing refractive surgery. If they have a poor or half-way response, then I'd consider moving to punctal occlusion. If they do well with that approach, with clearing of any signs or symptoms, then they're reasonable candidates for surgery."

Dr. Schallhorn takes more time with aqueous-deficiency patients. "If someone is totally aqueous-deficient or has tear production problems prior to surgery, I'd take more time to observe them to see if they actually do or not, because that's something that will get worse after surgery," she says. "And, it's more concerning than a tear-film insufficiency/MGD-type picture. I'd consider putting them on topical cyclosporin and monitoring them to see if they start making more tears or if on the first day they saw me they were aberrantly low and they're actually fine after that. I'd want to see them again to look at their tear film and supply over a few visits before deciding to do refractive surgery."

• ***The red flags.*** Despite all this attention and therapy, there will be patients who simply aren't candidates for refractive surgery. "If they're truly aqueous-deficient—they're not making tears at baseline and they have the classic epitheliopathy and exposure pattern—I don't do refractive surgery on them," Dr. Schallhorn says. "If they have severe, unremitting MGD, with an incredibly unstable tear film that doesn't get better with treatment, I'd also consider not operating on them."

• ***Postop therapy.*** Though preop screening and treatment will help most patients, some will need ocular surface assistance for a short while postop. "For transient dry eyes following LASIK, my approach is primarily tear supplementation," says Dr. Chang. "If symptoms are still significant, I'll start Restasis, reminding them that it does take some time to have an effect. In some cases, I'll offer punctal plugs for a more immediate improvement. Patients often improve in a few weeks. With good preoperative screening, postoperative ocular surface issues are rarely severe." Dr. Manche says if the cornea becomes inflamed, he can extend the patient's topical steroids for several weeks to help quiet it. "Generally, though, if the eyes are well-controlled before surgery, they tend to recover quickly," he says. REVIEW

Dr. Chang has received consulting fees from Allergan and Zeiss. Drs. Manche and Schallhorn have no interest in the products discussed.

Refractive News

For surgeons hoping to get more functionality from Avedro's suite of cross-linking products, their hopes were answered in late July when the U.S. Food and Drug Administration approved the company's Photrexa, Photrexa Viscous and KXL system for use on patients with post-refractive surgery corneal ectasia. This approval comes hot on the heels of the system's initial approval for use in keratoconus.

Avedro notes that ectasia, which can occur within a week of a corneal refractive procedure and can decrease best-corrected and uncorrected vision and induce visual aberrations, affects about 160,000 individuals in the United States.

The Photrexa photoenhancers and the KXL system will be available by the end of the year, Avedro says.

LUNAR Glaucoma Study Results

Researchers at Bausch + Lomb recently conducted a prospective, randomized, double-masked, parallel-group, noninferiority clinical trial to compare the intraocular pressure-lowering effect of latanoprostene bunod 0.024% with timolol maleate 0.5% in subjects with open-angle glaucoma or ocular hypertension. The study's findings demonstrate that LBN 0.024% once daily in the evening is noninferior to timolol 0.5% administered twice daily and results in significantly greater IOP lowering over three months of treatment in subjects with OAG or OHT.

The researchers looked at adults with OAG or OHT from 46 clinical sites and randomized them 2:1 to LBN instilled once daily in the evening or timolol instilled twice a day for three months. The researchers then recorded IOP at weeks two and six, and at month three. A total of 387 subjects completed the study.

The analysis of covariance showed that average IOP reduction with LBN was not only noninferior to timolol but also significantly greater than timolol at all but the first time point in this study ($p \leq 0.025$). Regarding LBN- and timolol-treated subjects, respectively, 31 percent and 18.5 percent ($p=0.007$) had their IOP reduced ≥25 percent from baseline, and 17.7 percent and 11.1 percent, respectively, ($p=0.084$) had their IOP reduced to ≤18 mm Hg over all time points/visits in this study. Ocular emergent adverse events, while uncommon, appeared more frequently in the LBN group, all of which were mild to moderate except one case of severe hyperemia.

Am J Ophthalmol 2016;168:250-259.

Medeiros F, Martin K, Peace J, Sforzolini BS, Vittitow JL, Weinreb RN.

Diagnostic Accuracy for Identifying Glaucoma in Myopes

Ruling out glaucoma in myopic eyes often poses a diagnostic challenge because of atypical optic disc morphology and visual field defects that can mimic glaucoma. This case-control, cross-sectional study determined that Bruch's membrane opening minimum rim width is more sensitive than disc margin rim area and similar to retinal nerve fiber layer thickness for the identification of glaucoma in myopic eyes, and offers a valuable tool for diagnosing glaucoma patients with myopic optic discs.

The study looked at 56 myopic patients with glaucoma, with 74 non-glaucoma patients with myopia used as controls. Researchers recruited myopic subjects with refractive errors greater than -2 D and typical myopic optic disc morphology, with and without glaucoma, from a glaucoma clinic and a local optometry practice. The final classification of myopic glaucoma or myopic control was based on a consensus assessment by three clinicians using visual fields and optic disc photographs. The participants underwent imaging with confocal scanning laser tomography for measurement of DM rim area and with spectral domain optical coherence tomography for quantification of a BMO-based neuroretinal rim parameter, minimum rim width and RNFL thickness.

The researchers measured the sensitivity of DM-RA, BMO-MRW and RNFL thickness at a fixed specificity of 90 percent and partial area under the curves for global and sectoral parameters for specificities ≥90 percent.

The sensitivities at 90-percent specificity were 30 percent for DM-RA and 71 percent for both BMO-MRW and RNFL thickness. The pAUC was higher for the BMO-MRW compared with DM-RA ($p<0.001$), but similar to RNFL thickness ($p>0.5$). The sectoral values of BMO-MRW tended to have a higher, but not significantly higher, pAUC across all sectors compared

with RNFL thickness.

The researchers claim that further studies are necessary to better evaluate the utility of sectoral analysis in myopic eyes, but that these results suggest that it might provide useful diagnostic information.

Ophthalmology 2016;123:1181-1189.
Malik R, Belliveau AC, Sharpe GP, Shuba LM.

The Degradation of Mitomycin-C Under Various Storage Methods

Because pharmacies store MMC under various conditions before ophthalmic surgical use, researchers decided to study the storage conditions' effects on the drug. This study found similar high stabilities (96 to 98 percent) for all storage methods when MMC solutions were analyzed immediately after warming to room temperature. For MMC that had been refrigerated for two weeks or shipped on ice, sitting at room temperature for 24 hours resulted in negative slopes suggesting degradation; however, all MMC samples maintained greater than 90-percent retention.

The researchers used c18 reversed-phase high-performance liquid chromatography to determine the stability of 0.4 mg/mL MMC solutions, and liquid chromatography-electrospray ionization-mass spectrometry to identify degradation products. The conditions that this study compared were as follows: compounding and storage by refrigeration (one and two weeks); freezing (23 days); shipment on ice (one month frozen followed by one-week refrigeration); and immediately compounding dry powder. The researchers evaluated three samples for each storage method when samples reached room temperature, as well as one, four and 24 hours later, using MMC peak area as a percentage of total area detected with high-performance liquid chromatography as a measure of stability.

This study found similar high stabilities for all storage methods when MMC solutions were analyzed after warming to room temperature.

At time 0, there were similar stabilities for MMC (p=0.599) among all storage methods: one-week refrigerated (97.9 ±0.2 percent); dry powder (97.5 ±0.3 percent); two-week refrigerated (96.9 ±0.2 percent); 23-day frozen (96.7 ±3.1 percent); and shipment on ice (96 ±1.2 percent). However, MMC demonstrated significant degradation over a 24-hour period with two-week refrigeration (95.7 ±0.3 percent, B=-0.1 percent/h, p<0.001) and shipment on ice (93.1 ±1.8 percent, B=-0.1 percent/h, p=0.013). There were small amounts (<3.2 percent) of two degradants, cis-hydroxymitosene and trans-hydroxymitosene, across all samples.

The clinical significance of small amounts of MMC degradants is unclear.

J Glaucoma 2016;25:477-481.
Kinast RM, Akula KK, DeBarber AE, Barker GT.

Combined Trabectome and PPV for Treatment of Glaucoma and Vitreoretinal Pathology

Researchers at the Cincinnati Eye Institute studied patients who underwent combined Trabectome and pars plana vitrectomy for uncontrolled glaucoma and visually significant retinal pathology. The postoperative study looked at four patients during a one-year follow-up period. Optical coherence tomography outcomes at one year showed improvement in macular anatomy and foveal contour without cystoid macular edema.

Although the visual results and intraocular pressure reduction after the procedures didn't reach statistical significance, the researchers say there was a trend toward improvement in both macular anatomy and glaucoma control, suggesting that further study of combined vitrectomy and Trabectome surgery may be warranted. Another possible advantage of the procedure is that a combined approach that simultaneously addresses both conditions would be advantageous to patients in terms of reduced costs and potentially faster visual recovery.

Surgeons performed the combined Trabectome MIGS procedure and 25-gauge PPV on three eyes of four patients for primary open-angle glaucoma. There were two male and two female patients with their ages ranging from 63 to 80 years.

The mean preoperative LogMAR visual acuity was 0.39 (20/49) and 12-month LogMAR visual acuity was 0.21 (20/32) (p=0.06). The average maximum preoperative IOP was 27 mmHg, and the mean preoperative IOP was 17 mmHg, measured over a period of six to 12 months before the combined surgery. The 12-month average IOP was 12.8 mmHg (p=0.07). One postop patient developed a hyphema requiring anterior chamber washout at one week. No other complications occurred. Researchers note that the limitations of this study include its small sample size and case selection bias.

Retina 2016;36:1076-1080.
Toussaint B, Petersen MR, Sisk RA, Riemann CD.

REVIEW Advertising Index

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REVIEW Retinal Insider

(continued from page 47)

aspects of DME pathophysiology, including relief of vitreous traction, inflammation and fibrosis. Unfortunately, treatment strategies specifically targeting macular ischemia are lacking, and chronic macular edema can severely limit functional outcomes even if we're able to reduce macular thickness.[37] REVIEW

Dr. Hussain is an ophthalmology resident at the Indiana University School of Medicine. Dr. Ciulla is a volunteer Clinical Professor of Ophthalmology at Indiana University School of Medicine and has an employment relationship with Ophthotech Corporation. He also has been an investigator for Genentech/Roche, Regeneron, Thrombogenics, Allegro, Allergan, Alimera and Pfizer.

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Equipment and Supplies

Career Opportunities

OPHTHALMOLOGY

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For confidential consideration, please contact:
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Practice For Sale

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A patient with cancer and various sequelae also seeks treatment for three months of blurred vision.

Thomas L. Jenkins, MD, and Carol L. Shields, MD

Presentation

A 59-year-old male was referred to Wills Eye Hospital for evaluation of three months of bilateral blurred vision. Recent medical history revealed fatigue and weight loss necessitating inpatient admission, with an evaluation revealing a diagnosis of acute myeloblastic leukemia. At that time, his white blood cell count was 46,000 cells/mcL (normal: 4,500 to 10,000 cells/mcL); it peaked at 92,000 cells/mcL during his hospitalization. His course was complicated by admission to the intensive care unit for findings of leukostasis, acute respiratory distress syndrome and distributive shock that resolved with emergent leukophoresis. He was managed with induction chemotherapy using cytarabine and daunorubicin. He did not receive radiotherapy or surgery.

Medical History

Past medical history was significant for a 10-year history of type II diabetes mellitus, hypertension and hyperlipidemia. Prior to hospitalization, a local optometrist had diagnosed the patient with non-proliferative diabetic retinopathy.

Social history was unremarkable, but family history was significant for diabetes mellitus, renal cell carcinoma (sister) and colon carcinoma (brother). The patient's medications included metoprolol, metformin and insulin. He had no known drug allergies.

Examination

On examination, uncorrected visual acuity was 20/150 with pinhole improvement to 20/50 in the right eye and 20/70 in the left eye. External examination was unrevealing. Intraocular pressure was 11 mmHg OD and 13 mmHg OS. The anterior segment was normal in each eye except for mild nuclear sclerotic lens opacity in both eyes.

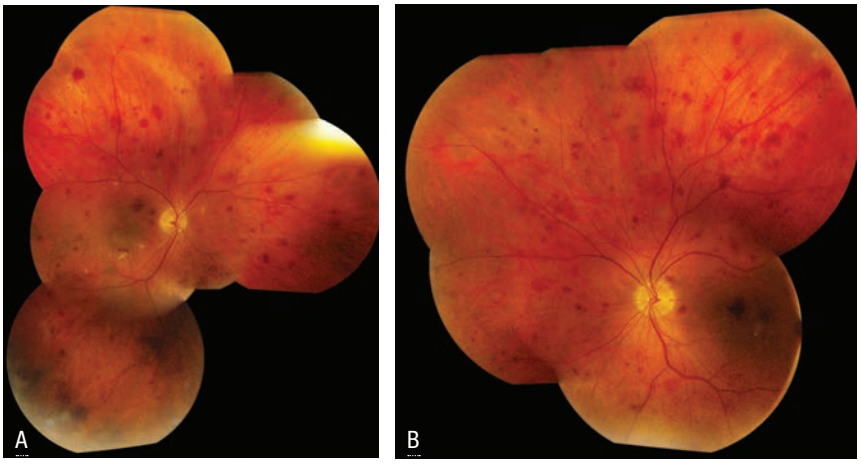

Figure 1. Montage fundus photography of the right (A) and left (B) eyes demonstrating scattered dot and blot retinal hemorrhages in both eyes and circumpapillary and macular nerve fiber layer infarctions, predominantly in the right eye.

Funduscopically, both eyes showed similar features of scattered dot and blot intraretinal hemorrhages involving the entire fundus *(See Figures 1A, 1B)*. There was no evidence of leukemic infiltration in the retina, choroid, vitreous or optic disc. Occasional white-centered hemorrhages were noted in the macular region. In the circumpapillary region, there were several nerve fiber layer infarctions. A coincidental flat choroidal nevus was noted along the inferotemporal vascular arcade, measuring only 0.5 mm in diameter.

What is your differential diagnosis? What further workup would you pursue? Please turn to p. 64.

Diagnosis, Workup and Treatment

Given this patient's clinical history and examination, leukemic retinopathy was the leading diagnosis. Leukemic retinopathy can manifest with a spectrum of features ranging from multifocal retinal hemorrhages secondary to underlying blood dycrasias to frank leukemic infiltration of the ocular tissues. Other diagnostic considerations included predominantly retinovascular disorders such as diabetic retinopathy, hypertensive retinopathy, ocular ischemic syndrome and retinal venous occlusive disease.

Given the funduscopic findings, a detailed history was completed revealing fevers, night sweats, weight loss and shortness of breath. Vital signs were obtained and found to be within normal limits: blood pressure of 110/70 mmHg; a heart rate of 73 beats per minute and a respiratory rate of 16 breaths per minute.

Laboratory evaluation included a recent complete blood count with differential indicating the leukemic profile, normal blood glucose and elevated hemoglobin A1C of 7.4 percent (normal: 4 to 5.6 percent).

Further ophthalmic evaluation of our patient included spectral-domain optical coherence tomography to investigate the macular anatomy. In both eyes, OCT revealed intraretinal optically dense thickening in the nerve fiber layer, representing nerve fiber layer infarction and swelling. Additionally, there were multilayer focal densities consistent with intraretinal hemorrhage. The fovea OD revealed slight opacification, edema and minor cystoid changes, whereas the fovea OS showed blunted contour and mild edema from deep retinal density suggestive of blood *(See Figure 2)*. There was no subretinal fluid. Fluorescein angiography demonstrated intact vascular filling with numerous areas of hypofluorescence corresponding to hemorrhage and nerve fiber layer infarction. There were extensive pinpoint areas of hyperfluorescence in all quadrants of both eyes. Mild retinal vascular staining was noted in the late frames *(See Figure 3)*.

These findings were suggestive of leukemic retinopathy. The patient was followed while on chemotherapy to document the resolution of fundus features.

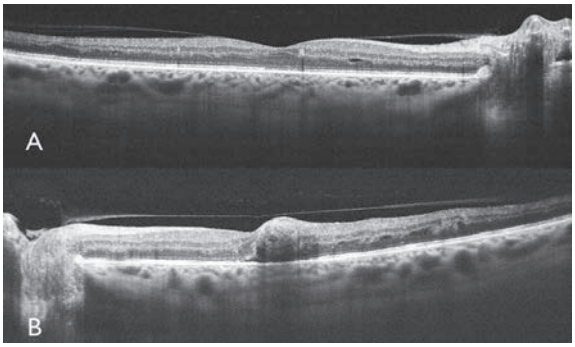

Figure 2. Optical coherence tomography of the right (A) and left (B) eyes revealing focal retinal opacification and trace edema in the right eye, and retinal distortion with foveal blunting from deep retinal hemorrhage in the left eye. There was no evidence of choroidal infiltration at this time.

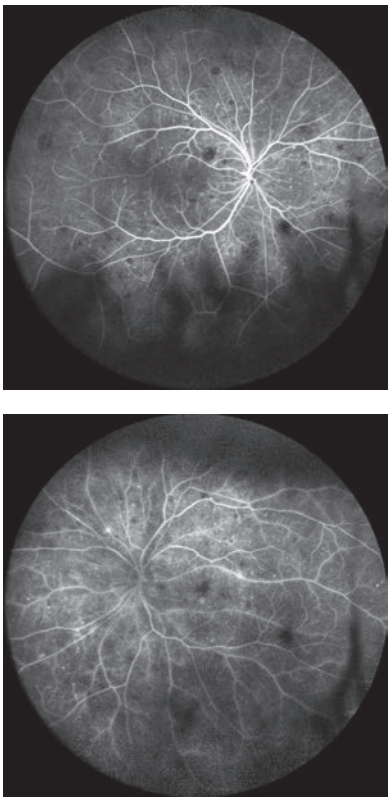

Figure 3. Fluorescein angiography of the right (top) and left (bottom) eyes showing scattered hypofluorescence from retinal hemorrhages and nerve fiber layer infarctions, hyperfluorescence from pinpoint leaks in the retina and mild vascular staining.

Discussion

Leukemia is a malignancy characterized by a proliferation of hematopoietic stem cells in the bone marrow. This malignancy is classified as either acute or chronic based on whether the tumor cells are predominantly immature blast cells or well-differentiated mature leukocytes. Leukemia can affect any structure in the eye through primary infiltration or, more commonly, through secondary changes. The retina is the most commonly involved tissue of the eye in patients with leukemia.[1]

Secondary retinal vascular changes can result from systemic abnormalities in the setting of leukemia, including anemia, thrombocytopenia, hy-

perviscocity and immunosuppression. In these cases, there can be evidence of vascular dilation and tortuosity, hemorrhage, ischemia or a combination of these features.[2] Common clinically recognizable retinal signs of leukemia include:

- retinal or vitreous hemorrhage;
- microaneurysms;
- nerve fiber layer infarctions;
- peripheral neovascularization;
- vascular occlusion;
- venous tortuosity;
- perivascular infiltration;
- macular edema;
- retinal detachment; and
- retinitis secondary to infection.[2,3]

As these findings are largely non-specific, in the absence of a documented clinical history of malignancy, it's possible to mistake ophthalmic signs of leukemia for other common disease entities, especially in patients with diabetes mellitus or other vascular diseases.[4,5] This was the case for our patient, whose funduscopic picture was initially mischaracterized as diabetic retinopathy by the primary caregiver before the retinal findings progressed in severity and before leukemia was documented.

While improvements in chemotherapy and radiotherapy treatment techniques for leukemia have made primary retina and choroid involvement quite rare, patients with acute leukemia may still manifest infiltration through the retinal arteries and veins, as well as in the choroidal vasculature. In fact, in autopsy specimens, the choroid is the most common ocular structure infiltrated with leukemic cells.[6]

A number of studies have evaluated the prevalence of ophthalmic signs in patients with leukemia at the time of diagnosis. In a study by Prof. Nicholas Jackson and colleagues, 63 newly diagnosed patients with acute leukemia were examined funduscopically and 33 (52 percent) were found to have at least one of the following findings: intra-retinal hemorrhage; white-centered hemorrhage; nerve fiber layer infarction; or macular hemorrhage. There was no association of the retinal findings with the severity of leukemic diagnosis, although there was an association with a higher white blood cell count.[7] In a prospective evaluation of 120 patients with newly diagnosed adult and pediatric leukemia, Andrew P. Schachat, MD, and colleagues found similar secondary findings of leukemia in 47 patients (39 percent) and primary leukemic infiltrates in four patients (3 percent).[1] James Karesh, MD, and colleagues conducted a two-year prospective study of 53 patients with acute myeloid leukemia wherein 34 patients (64 percent) were found to have retinal hemorrhages or nerve fiber layer infarctions. In their study, there was no association with age, sex or severity of disease, although there was a correlation with thrombocytopenia. During the follow-up period, no association was found between fundoscopic changes and treatment response. Interestingly, all patients who survived the induction phase of chemotherapy experienced complete resolution of all ocular findings.[8]

In our patient, the development of white-centered hemorrhages, frequently termed "Roth spots," is strongly suggestive of a systemic disorder. Once thought to be hemorrhages associated with septic emboli, WCH are now thought to be non-specific intraretinal hemorrhages with a white center of various compositions, most frequently fibrin deposition at a site of acute retinal capillary rupture.[3] They can be seen in numerous other conditions including connective tissue disorders, vasculitis, hypertension, anemia, trauma, disseminated fungal or bacterial infection, environmental toxicity and leukemia.[9] WCH can be rarely found with diabetic mellitus, but this would be unusual and might be expected only with a dramatic increase in glucose rather than the typical indolent progressive process of diabetic vascular change.[10]

In conclusion, leukemia can affect any segment of the eye either through primary or secondary involvement. Leukemic retinopathy is the most common ophthalmic manifestation of the disease and is frequently seen in patients with active leukemia. In numerous publications, retinal hemorrhage from thrombocytopenia and nerve fiber layer infarction from anemia and leukostasis can be identified, although the presence of retinal changes does not appear to correlate with prognosis or disease severity. Due to the non-specific retinovascular manifestations in this disorder, in the absence of an established diagnosis of leukemia, the findings can be mistaken for signs of more common processes like hypertensive or diabetic retinopathy. If you notice a sudden change in the severity of funduscopic appearance, or findings out of proportion to the severity of the patient's other systemic processes, this should prompt a detailed review of systems and appropriate laboratory evaluation. REVIEW

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Xiidra™ (lifitegrast ophthalmic solution) 5%

Rx Only

BRIEF SUMMARY:
Consult the Full Prescribing Information for complete product information.

INDICATIONS AND USAGE
Xiidra™ (lifitegrast ophthalmic solution) 5% is indicated for the treatment of the signs and symptoms of dry eye disease (DED).

DOSAGE AND ADMINISTRATION
Instill one drop of Xiidra twice daily (approximately 12 hours apart) into each eye using a single use container. Discard the single use container immediately after using in each eye. Contact lenses should be removed prior to the administration of Xiidra and may be reinserted 15 minutes following administration.

ADVERSE REACTIONS
Clinical Trials Experience
Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in clinical studies 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. In five clinical studies of dry eye disease conducted with lifitegrast ophthalmic solution, 1401 patients received at least 1 dose of lifitegrast (1287 of which received lifitegrast 5%). The majority of patients (84%) had ≤3 months of treatment exposure. 170 patients were exposed to lifitegrast for approximately 12 months. The majority of the treated patients were female (77%). The most common adverse reactions reported in 5-25 % of patients were instillation site irritation, dysgeusia and reduced visual acuity. Other adverse reactions reported in 1% to 5% of the patients were blurred vision, conjunctival hyperemia, eye irritation, headache, increased lacrimation, eye discharge, eye discomfort, eye pruritus and sinusitis.

USE IN SPECIFIC POPULATIONS
Pregnancy
There are no available data on Xiidra use in pregnant women to inform any drug associated risks. Intravenous (IV) administration of lifitegrast to pregnant rats, from pre-mating through gestation day 17, did not produce teratogenicity at clinically relevant systemic exposures. Intravenous administration of lifitegrast to pregnant rabbits during organogenesis produced an increased incidence of omphalocele at the lowest dose tested, 3 mg/kg/day (400-fold the human plasma exposure at the recommended human ophthalmic dose [RHOD], based on the area under the curve [AUC] level). Since human systemic exposure to lifitegrast following ocular administration of Xiidra at the RHOD is low, the applicability of animal findings to the risk of Xiidra use in humans during pregnancy is unclear.

Animal Data
Lifitegrast administered daily by intravenous (IV) injection to rats, from pre-mating through gestation day 17, caused an increase in mean preimplantation loss and an increased incidence of several minor skeletal anomalies at 30 mg /kg /day, representing 5,400-fold the human plasma exposure at the RHOD of Xiidra, based on AUC. No teratogenicity was observed in the rat at 10 mg /kg /day (460-fold the human plasma exposure at the RHOD, based on AUC). In the rabbit, an increased incidence of omphalocele was observed at the lowest dose tested, 3 mg /kg /day (400-fold the human plasma exposure at the RHOD, based on AUC), when administered by IV injection daily from gestation days 7 through 19. A fetal No Observed Adverse Effect Level (NOAEL) was not identified in the rabbit.

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

Pediatric Use
Safety and efficacy in pediatric patients below the age of 17 years have not been established.

Geriatric Use
No overall differences in safety or effectiveness have been observed between elderly and younger adult patients.

NONCLINICAL TOXICOLOGY
Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenesis: Animal studies have not been conducted to determine the carcinogenic potential of lifitegrast.
Mutagenesis: Lifitegrast was not mutagenic in the *in vitro* Ames assay. Lifitegrast was not clastogenic in the *in vivo* mouse micronucleus assay. In an *in vitro* chromosomal aberration assay using mammalian cells (Chinese hamster ovary cells), lifitegrast was positive at the highest concentration tested, without metabolic activation.
Impairment of fertility: Lifitegrast administered at intravenous (IV) doses of up to 30 mg/kg/day (5400-fold the human plasma exposure at the recommended human ophthalmic dose (RHOD) of lifitegrast ophthalmic solution, 5%) had no effect on fertility and reproductive performance in male and female treated rats.

Shire

Manufactured for: Shire US Inc., 300 Shire Way, Lexington, MA 02421.

For more information, go to www.Xiidra.com or call 1-800-828-2088.

US Patents: 8367701; 9353088; 7314938; 7745460; 7790743; 7928122; 9216174; 8168655; 8084047; 8592450; 9085553 and pending patent applications.
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Four randomized, double-masked, 12-week trials evaluated the efficacy and safety of Xiidra versus vehicle as assessed by improvement in the signs (measured by Inferior Corneal Staining Score) and/or symptoms (measured by Eye Dryness Score) of Dry Eye Disease (N=2133).

The safety of lifitegrast was evaluated in 5 clinical studies. 1401 patients received at least one dose of lifitegrast (1287 of which received Xiidra). The most common adverse reactions (5-25%) were instillation site irritation, dysgeusia, and reduced visual acuity.

Indication

Xiidra™ (lifitegrast ophthalmic solution) 5% is indicated for the treatment of signs and symptoms of dry eye disease (DED).

Important Safety Information

In clinical trials, the most common adverse reactions reported in 5-25% of patients were instillation site irritation, dysgeusia and reduced visual acuity. Other adverse reactions reported in 1% to 5% of the patients were blurred vision, conjunctival hyperemia, eye irritation, headache, increased lacrimation, eye discharge, eye discomfort, eye pruritus and sinusitis.

To avoid the potential for eye injury or contamination of the solution, patients should not touch the tip of the single-use container to their eye or to any surface.

Contact lenses should be removed prior to the administration of Xiidra and may be reinserted 15 minutes following administration.

Safety and efficacy in pediatric patients below the age of 17 years have not been established.

For additional safety information, see accompanying Brief Summary of Safety Information on the following page and Full Prescribing Information on Xiidra-ECP.com.

Shire