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REVIEW® of Ophthalmology

September 2016

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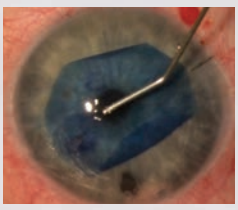
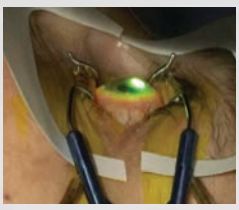
ANNUAL CORNEA ISSUE

Surmounting Challenges In Cornea

Approvals of new technologies and the evolution of surgical techniques make it easier for you to achieve excellent outcomes.



Perfecting Posterior Corneal Grafts P. 24



Making the Most of Cross-linking P. 32

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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REVIEW NEWS
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New MIGS on the Radar: CyPass Micro-Stent Approved

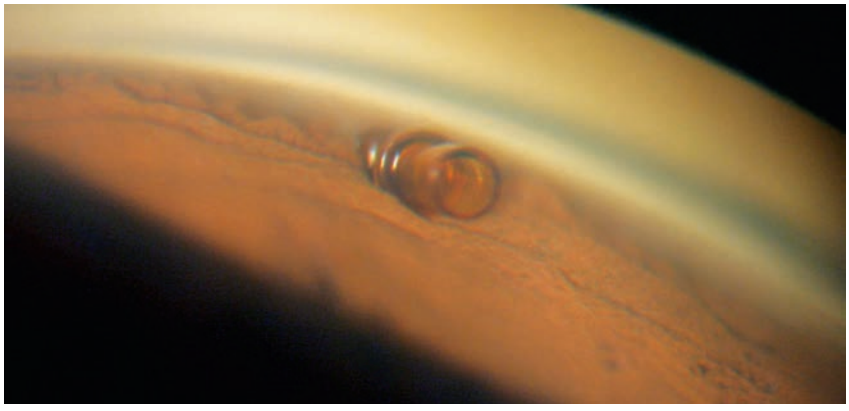
On August 2, 2016, Alcon announced that the CyPass Micro-Stent, (originally developed by Transcend Medical) had received clearance from the U.S. Food and Drug Administration. The CyPass shunt is a minimally invasive *ab interno* device designed to reduce IOP in adults with mild-to-moderate glaucoma. It's inserted through the angle between the scleral spur and the ciliary body into the supraciliary space in conjunction with cataract surgery; it takes advantage of the negative pressure gradient between the suprachoroidal space and the anterior chamber, causing aqueous to move into the suprachoroidal space. The device is 6.35 mm long, with an external diameter of 510 µm.

The approval was granted based on data from the COMPASS trial, a prospective, randomized, multicenter study that compared the pressure lowering in 505 patients who either underwent cataract surgery alone or cataract surgery plus implantation of the CyPass stent. Both the primary and secondary effectiveness endpoints were met; at 24 months, 73 percent in the CyPass group achieved a statistically significant decrease in IOP of more than 20 percent; 61 percent of the CyPass patients also achieved an IOP in the target range, between 6 and 18 mmHg—without medications—which was also statistically significant.

Adverse events included: BCVA loss of 10 or more letters at three months postop (8.8 percent for CyPass vs. 15.3 percent for cataract surgery only); anterior chamber cell and flare requiring steroid treatment 30 or more days after surgery (8.6 percent vs. 3.8 percent); worsening of visual field mean deviation by 2.5 dB or more (6.7 percent vs. 9.9 percent); an IOP increase of 10 or more mmHg 30 or more days after surgery (4.3 percent vs. 2.3 percent); and corneal edema 30 or more days after surgery, or severe in nature (3.5 percent vs. 1.5 percent).

"The FDA study for CyPass was performed in combination with phacoemulsification, and thus, this is where it will initially be used in clinical practice," says Ike K. Ahmed, MD, FRCSC, assistant professor at the University of Toronto in Ontario, Canada, who participated in the clinical trial. "Many of us have also had experience using the CyPass as a standalone option, and we hope to see further data on that soon."

Dr. Ahmed points out that this is another entry in the category of minimally invasive glaucoma surgery devices, or MIGS. "The suprachoroidal space is a natural drainage outflow tract that provides another MIGS alternative," he says. "It's exciting to see more options available for our patients. Further studies will help to elucidate differences between the growing MIGS options that are being approved."



The CyPass Micro-Stent does its work in a novel location: It's placed through the angle between the scleral spur and the ciliary body into the supraciliary space.

ASCRS/ASRS HORV Alert

Though the incidence is low after intraocular procedures, the American Society of Cataract and Refractive Surgery and the American Society of Retina Specialists joined forces to warn surgeons of the possible risk factors for and clinical signs of hemorrhagic occlusive retinal vasculitis. They also note that there seems to be an association between

(continued on page 9)

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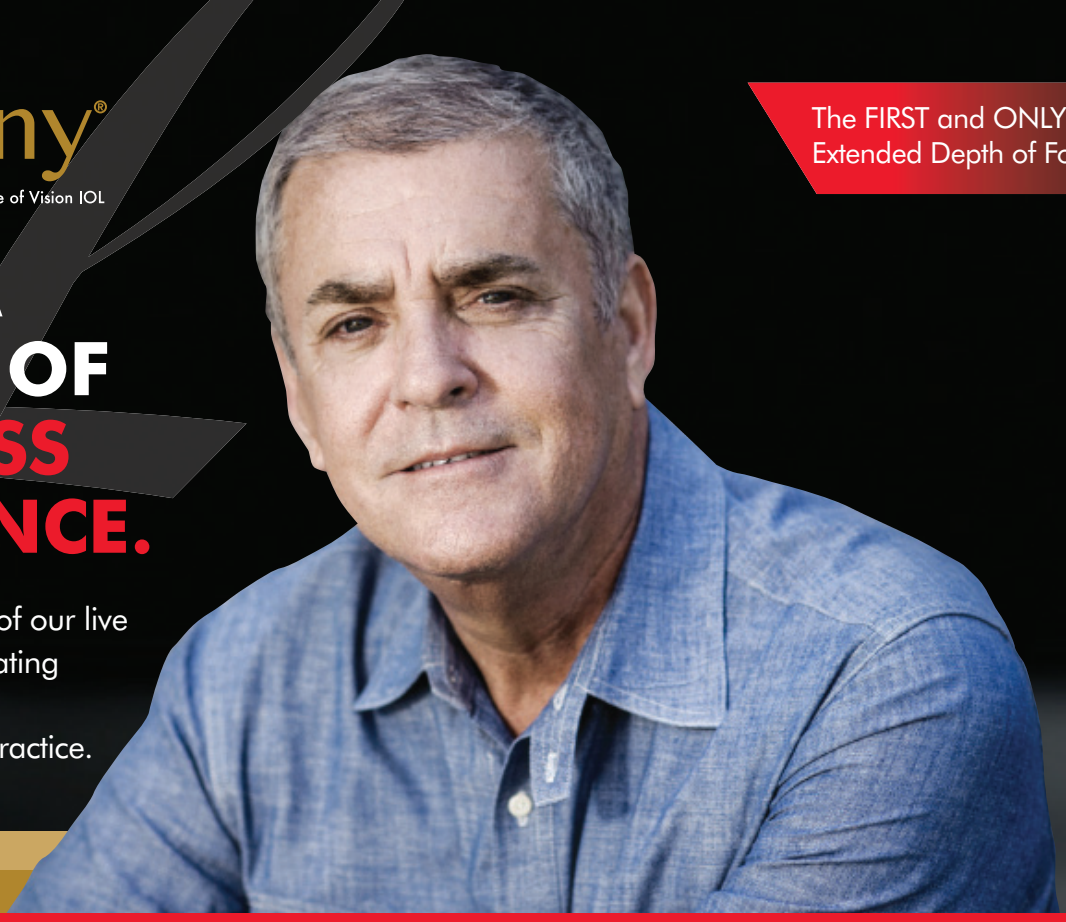

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INDICATIONS and IMPORTANT SAFETY INFORMATION for TECNIS SYMFONY and TECNIS SYMFONY TORIC IOLs

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INDICATIONS FOR USE: The TECNIS Symfony Extended Range of Vision IOL, Model ZXR00, is indicated for primary implantation for the visual correction of aphakia, in adult patients with less than 1 diopter of pre-existing corneal astigmatism, in whom a cataractous lens has been removed. The lens mitigates the effects of presbyopia by providing an extended depth of focus. Compared to an aspheric monofocal IOL, the lens provides improved intermediate and near visual acuity, while maintaining comparable distance visual acuity. The Model ZXR00 IOL is intended for capsular bag placement only. The TECNIS Symfony Toric Extended Range of Vision IOLs, Models ZXT150, ZXT225, ZXT300, and ZXT375, are indicated for primary implantation for the visual correction of aphakia and for reduction of residual refractive astigmatism in adult patients with greater than or equal to 1 diopter of preoperative corneal astigmatism, in whom a cataractous lens has been removed. The lens mitigates the effects of presbyopia by providing an extended depth of focus. Compared to an aspheric monofocal IOL, the lens provides improved intermediate and near visual acuity, while maintaining comparable distance visual acuity. The Model Series ZXT IOLs are intended for capsular bag placement only. **WARNINGS**: May cause a reduction in contrast sensitivity under certain conditions, compared to an aspheric monofocal IOL. Inform patients to exercise special caution when driving at night or in poor visibility conditions. Some visual effects may be expected due to the lens design, including: perception of halos, glare, or starbursts around lights under nighttime conditions. These will be bothersome or very bothersome in some people, particularly in low-illumination conditions, and on rare occasions, may be significant enough that the patient may request removal of the IOL. Rotation of the Tecnis Symfony Toric IOLs away from their intended axis can reduce their astigmatic correction, and misalignment >30° may increase postoperative refractive cylinder. If necessary, lens repositioning should occur as early as possible prior to lens encapsulation. **ATTENTION:** Reference the Directions for Use for a complete listing of Indications and Important Safety Information.

PP2016CT1089

(continued from page 7)

the use of intraocular vancomycin and the complication.

According to the alert, 22 cases of HORV have been identified, 14 of which were bilateral. In terms of timing, 12 of the cases occurred in 2015-2016, five in 2013-2014 and five before 2013.

"The difficult part about this complication is that it has occurred bilaterally in about half of the patients that were reported," says Nick Mamalis, MD, professor of ophthalmology at the University of Utah's Moran Eye Center and member of the HORV task force. "The sobering aspect is that it can have a delayed onset, meaning you can complete your first surgery, administer the antibiotic at the end of the case and the patient seems to do well initially. Then, a week to two weeks later, you do the second eye. After that eye's surgery is complete, the HORV reaction manifests itself in the first eye. The time before onset shows a very wide range: Some have reported it as soon as a day postop, but in other cases that have been reported it went out as far as 26 days. So, in many cases, you may not know the patient will have this reaction until you've already done his second eye."

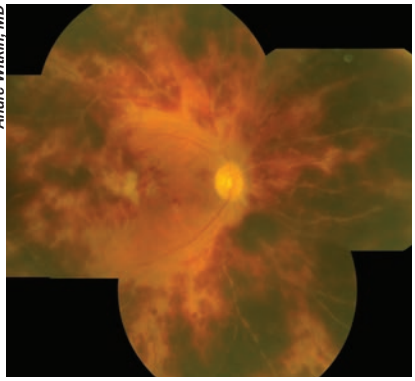
The one thing all the cases had in common was the intraocular use of vancomycin, a connection that researchers are trying to parse out. "We really hadn't seen anything like this before," Dr. Mamalis recalls. "It was different from some of the other retinal issues that we've seen after intraocular surgery. For instance, in the past, there have been instances of patients getting some retinal toxicity from an injection of the incorrect dose of gentamycin, or surgeons who use a very high dose of cefuroxime that was improperly diluted and end up getting a retinal complication. This, however, was unique. HORV gave this pattern of vasculitis that truly behaved as a vasculitis. And,

these cases were appearing up to two weeks after surgery without a toxic dose having been used. That aspect of it raised the suspicion that it had to be some sort of autoimmune reaction. The task force communicated with immunologists about it, and they have said that it's consistent with what's known as a Type III reaction, or what they call a leukocytoclastic vasculitis. That's the pattern that it fits. HORV seems most consistent with that type of reaction.

"We were careful when issuing this alert, however," Dr. Mamalis adds. "We don't want to put out a blanket recommendation of, 'Don't use intracameral vancomycin,' because there have probably been hundreds of thousands of cases of routine cataract surgeries performed with intracameral vancomycin that never had HORV. We're careful not to condemn vancomycin. However, we want to alert physicians that this entity can occur and, though it's exceedingly rare, when it does occur it can have very poor visual outcomes." Twenty-two of the 36 eyes with HORV (61 percent), ended up 20/200 or worse, and eight (22 percent) were NLP. The task force notes that seven of the eyes (19 percent), received an additional bolus of intravitreal vancomycin for the treatment of presumed bacterial endophthalmitis postop. These eyes had especially bad outcomes, with 5/7 being NLP. This highlights the importance of spreading the word about HORV and avoiding treating it as an infection.

To help catch HORV, the task force highlights these characteristics:

- occurrence after an intraocular procedure with normal undilated exam on postop day one;
- delayed onset of sudden painless decreased vision (range: one to 26 days postop; mean: eight days);
- visual acuity is often poor on presentation, but may be normal in mild cases of the complication;
- mild to moderate anterior chamber and vitreous inflammation, with no hypopyon;
- sectoral intraretinal hemorrhage in areas of nonperfusion;
- peripheral retinal involvement in all cases, with macular ischemia and whitening in advanced disease;
- sectoral retinal vasculitis and retinal vascular occlusion on FA, corresponding to areas of hemorrhage; and
- rapid progression to neovascular glaucoma.[1]



Andre Witkin, MD

A HORV eye, 18 days after cataract surgery, displays diffuse microvascular occlusion and extensive intraretinal hemorrhages.

The alert notes that HORV might be misdiagnosed as a central retinal vein occlusion, but says that an ischemic CRVO is unilateral, usually presents on the first postop day when associated with cataract surgery, and is associated with diffuse, small intraretinal hemorrhages. In contrast, HORV is often bilateral, has a delayed onset, and often presents with large areas of intraretinal hemorrhage only in the sectors of retinal vascular occlusion. Cystoid macular edema and severe vascular dilation and tortuosity are features of CRVO but not of HORV.[1]

"Surgeons should continue to weigh the relative merits of prophylactic intraocular antibiotic use in preventing endophthalmitis against the additional knowledge that intraocular vancomycin is associated with HORV, a rare but potentially devastating disease," Dr. Mamalis says. "In addition, surgeons using vancomycin prophylaxis with sequential cataract surgery should be aware that in addition to delayed onset of one to three weeks, HORV may be asymptomatic in the first eye and a dilated fundus exam may be the only way to detect it. The risk of bilateral HORV is therefore higher if close—or immediate sequential, same-day bilateral—surgery is performed. As alternatives to vancomycin, surgeons can use moxifloxacin or cefuroxime. Surgeons should have the issue of HORV enter into the consideration of how to approach antibiotic prophylaxis following routine cataract surgery."

If a surgeon suspects or encounters HORV, once again, reconsider vancomycin. "The first thing to consider is avoiding intravitreal vancomycin if you're considering HORV in a case that's been diagnosed as endophthalmitis," Dr. Mamalis says. "If you really aren't sure that it's endophthalmitis and suspect it may be HORV, pick another antibiotic. Also, look for other systemic syndromes if you're searching for a potential viral cause. However, once you've determined that it's HORV, you've got to be aggressive in terms of topical and systemic corticosteroids. Try to calm the inflammation. And, because these patients most likely will get significant glaucoma afterward—especially neovascular glaucoma—you want to consider using anti-VEGF treatments early, as well as consider doing panretinal photocoagulation early to take away the factors that can cause that secondary glaucoma."

The ASRS has established a HORV registry to help track the complication that can be accessed at asrs.org. REVIEW

1. ASCRS/ASRS HORV Clinical Alert. http://www.ascrs.org/node/26101. Accessed 18 August 2016.

Correction

In *Review*'s August retinal article on DME treatment, it states Eylea treated eyes in Protocol T had gained 19 letters from baseline at year two. They actually gained 18 letters. *Review* regrets the error.

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Systemic exposure of phenylephrine may cause elevations in blood pressure.

Use OMIDRIA with caution in individuals who have previously exhibited sensitivities to acetylsalicylic acid, phenylacetic acid derivatives, and other nonsteroidal anti-inflammatory drugs (NSAIDs), or have a past medical history of asthma.

The most commonly reported adverse reactions at 2-24% are eye irritation, posterior capsule opacification, increased intraocular pressure, and anterior chamber inflammation.

Use of OMIDRIA in children has not been established.

INDICATIONS AND USAGE

OMIDRIA is added to ophthalmic irrigation solution used during cataract surgery or intraocular lens replacement and is indicated for maintaining pupil size by preventing intraoperative miosis and reducing postoperative ocular pain.

Reference: 1. OMIDRIA [package insert]. Seattle, WA: Omeros Corporation; 2015.

Please see the Full Prescribing Information at www.omidria.com/prescribinginformation.

*Individual insurance coverage and policies may vary, and Omeros does not guarantee insurance coverage or payment. Omeros offers payments under the OMIDRIAssure "We Pay the Difference" program on behalf of qualifying patients. OMIDRIAssure is subject to change without notice.

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INDICATIONS AND USAGE

PROLENSA® (bromfenac ophthalmic solution) 0.07% is a nonsteroidal anti-inflammatory drug (NSAID) indicated for the treatment of postoperative inflammation and reduction of ocular pain in patients who have undergone cataract surgery.

IMPORTANT SAFETY INFORMATION ABOUT PROLENSA®

- PROLENSA® contains sodium sulfite, a sulfite that may cause allergic type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in non-asthmatic people.
- All topical nonsteroidal anti-inflammatory drugs (NSAIDs), including bromfenac, may slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.
- There is the potential for cross-sensitivity to acetylsalicylic acid, phenylacetic acid derivatives, and other NSAIDs, including bromfenac. Use with caution in patients who have previously exhibited sensitivities to these drugs.
- There have been reports that ocularly applied NSAIDs may cause increased bleeding of ocular tissues (including hyphemas) in conjunction with ocular surgery. Use with caution in patients with known bleeding tendencies or who are receiving other medications which may prolong bleeding time.
- Use of topical NSAIDs may result in keratitis. Patients with evidence of corneal epithelial breakdown should immediately discontinue use of topical NSAIDs, including bromfenac, and should be closely monitored for corneal health. Patients with complicated ocular surgeries, corneal denervation, corneal epithelial defects, diabetes mellitus, ocular surface diseases (e.g., dry eye syndrome), rheumatoid arthritis, or repeat ocular surgeries within a short period of time may be at increased risk for corneal adverse events which may become sight threatening. Topical NSAIDs should be used with caution in these patients. Post-marketing experience with topical NSAIDs suggests that use more than 24 hours prior to surgery or use beyond 14 days post-surgery may increase patient risk for the occurrence and severity of corneal adverse events.
- PROLENSA® should not be instilled while wearing contact lenses. The preservative in PROLENSA®, benzalkonium chloride, may be absorbed by soft contact lenses. Lenses may be reinserted after 10 minutes following administration of PROLENSA®.
- The most commonly reported adverse reactions in 3%-8% of patients were anterior chamber inflammation, foreign body sensation, eye pain, photophobia, and blurred vision.

Please see brief summary of full Prescribing Information for PROLENSA® on adjacent page.

References: 1. PROLENSA Prescribing Information, April 2013. **2.** Data on file, Bausch & Lomb Incorporated. **3.** Baklayan GA, Patterson HM, Song CK, Gow JA, McNamara TR. 24-hour evaluation of the ocular distribution of (14)C-labeled bromfenac following topical instillation into the eyes of New Zealand white rabbits. *J Ocul Pharmacol Ther.* 2008;24(4):392-398.

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PROLENSA® (bromfenac ophthalmic solution) 0.07%

Brief Summary

INDICATIONS AND USAGE

PROLENSA® (bromfenac ophthalmic solution) 0.07% is indicated for the treatment of postoperative inflammation and reduction of ocular pain in patients who have undergone cataract surgery.

DOSAGE AND ADMINISTRATION

Recommended Dosing

One drop of PROLENSA® ophthalmic solution should be applied to the affected eye once daily beginning 1 day prior to cataract surgery, continued on the day of surgery, and through the first 14 days of the postoperative period.

Use with Other Topical Ophthalmic Medications

PROLENSA ophthalmic solution may be administered in conjunction with other topical ophthalmic medications such as alpha-agonists, beta-blockers, carbonic anhydrase inhibitors, cycloplegics, and mydriatics. Drops should be administered at least 5 minutes apart.

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

Sulfite Allergic Reactions

Contains sodium sulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in non-asthmatic people.

Slow or Delayed Healing

All topical nonsteroidal anti-inflammatory drugs (NSAIDs), including bromfenac, may slow or delay healing. Topical corticosteroids are also known to slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.

Potential for Cross-Sensitivity

There is the potential for cross-sensitivity to acetylsalicylic acid, phenylacetic acid derivatives, and other NSAIDs, including bromfenac. Therefore, caution should be used when treating individuals who have previously exhibited sensitivities to these drugs.

Increased Bleeding Time

With some NSAIDs, including bromfenac, there exists the potential for increased bleeding time due to interference with platelet aggregation. There have been reports that ocularly applied NSAIDs may cause increased bleeding of ocular tissues (including hyphemas) in conjunction with ocular surgery.

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

Keratitis and Corneal Reactions

Use of topical NSAIDs may result in keratitis. In some susceptible patients, continued use of topical NSAIDs may result in epithelial breakdown, corneal thinning, corneal erosion, corneal ulceration or corneal perforation. These events may be sight threatening. Patients with evidence of corneal epithelial breakdown should immediately discontinue use of topical NSAIDs, including bromfenac, and should be closely monitored for corneal health.

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

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

Contact Lens Wear

PROLENSA should not be instilled while wearing contact lenses. Remove contact lenses prior to instillation of PROLENSA. The preservative in PROLENSA, benzalkonium chloride may be absorbed by soft contact lenses. Lenses may be reinserted after 10 minutes following administration of PROLENSA.

ADVERSE REACTIONS

Clinical Trial Experience

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

The most commonly reported adverse reactions following use of PROLENSA® ophthalmic solution following cataract surgery include: anterior chamber inflammation, foreign body sensation, eye pain, photophobia and vision blurred. These reactions were reported in 3 to 8% of patients.

USE IN SPECIFIC POPULATIONS

Pregnancy

Treatment of rats at oral doses up to 0.9 mg/kg/day (systemic exposure 90 times the systemic exposure predicted from the recommended human ophthalmic dose [RHOD] assuming the human systemic concentration is at the limit of quantification) and rabbits at oral doses up to 7.5 mg/kg/day (150 times the predicted human systemic exposure) produced no treatment-related malformations in reproduction studies. However, embryo-fetal lethality and maternal toxicity were produced in rats and rabbits at 0.9 mg/kg/day and 7.5 mg/kg/day, respectively. In rats, bromfenac treatment caused delayed parturition at 0.3 mg/kg/day (30 times the predicted human exposure), and caused dystocia, increased neonatal mortality and reduced postnatal growth at 0.9 mg/kg/day.

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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

Nursing Mothers

Caution should be exercised when PROLENSA is administered to a nursing woman.

Pediatric Use

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

Geriatric Use

There is no evidence that the efficacy or safety profiles for PROLENSA differ in patients 70 years of age and older compared to younger adult patients.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis and Impairment of Fertility

Long-term carcinogenicity studies in rats and mice given oral doses of bromfenac up to 0.6 mg/kg/day (systemic exposure 30 times the systemic exposure predicted from the recommended human ophthalmic dose [RHOD] assuming the human systemic concentration is at the limit of quantification) and 5 mg/kg/day (340 times the predicted human systemic exposure), respectively, revealed no significant increases in tumor incidence.

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

Bromfenac did not impair fertility when administered orally to male and female rats at doses up to 0.9 mg/kg/day and 0.3 mg/kg/day, respectively (systemic exposure 90 and 30 times the predicted human exposure, respectively).

PATIENT COUNSELING INFORMATION

Slowed or Delayed Healing

Advise patients of the possibility that slow or delayed healing may occur while using NSAIDs.

Sterility of Dropper Tip

Advise patients to replace bottle cap after using and to not touch dropper tip to any surface, as this may contaminate the contents. Advise patients that a single bottle of PROLENSA® ophthalmic solution, be used to treat only one eye.

Concomitant Use of Contact Lenses

Advise patients to remove contact lenses prior to instillation of PROLENSA. The preservative in PROLENSA, benzalkonium chloride, may be absorbed by soft contact lenses. Lenses may be reinserted after 10 minutes following administration of PROLENSA.

Concomitant Topical Ocular Therapy

If more than one topical ophthalmic medication is being used, the medicines should be administered at least 5 minutes apart.

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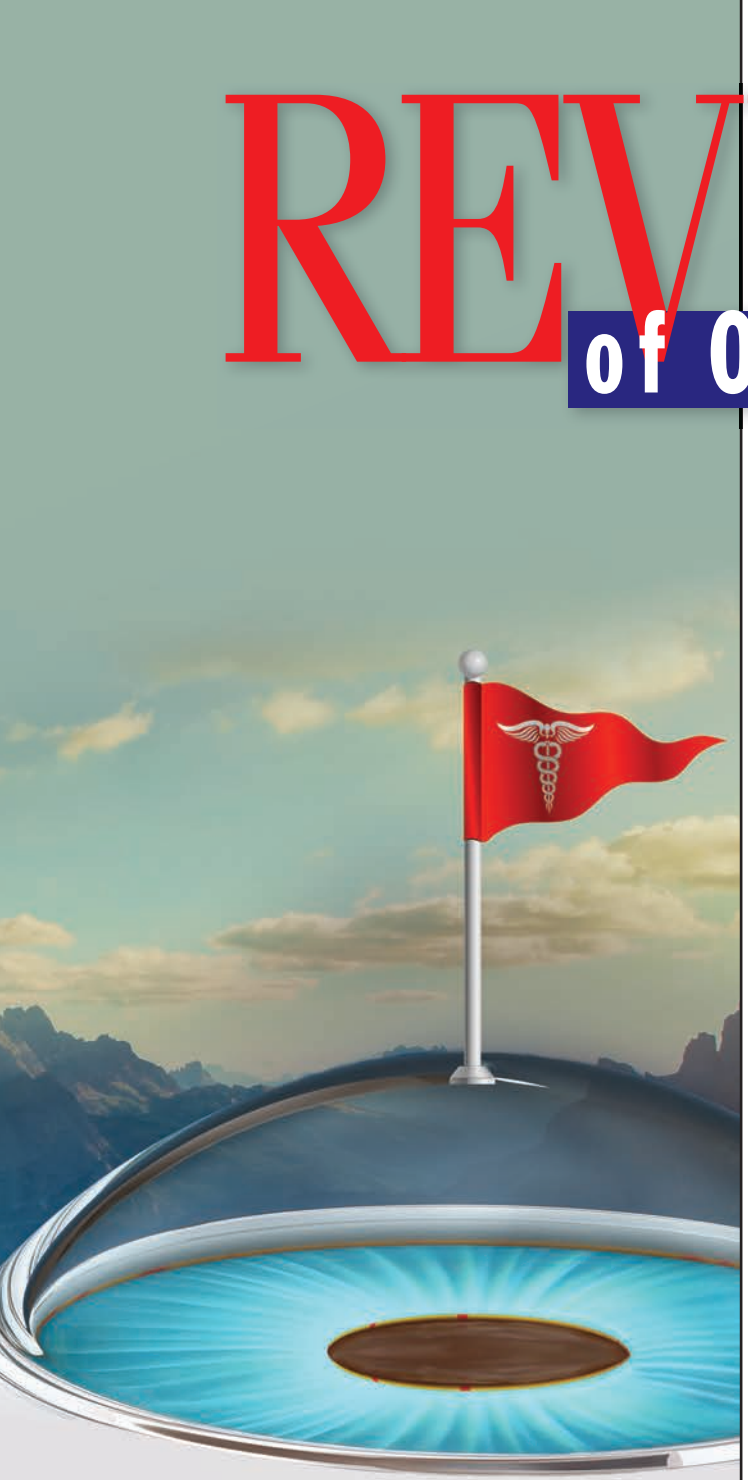

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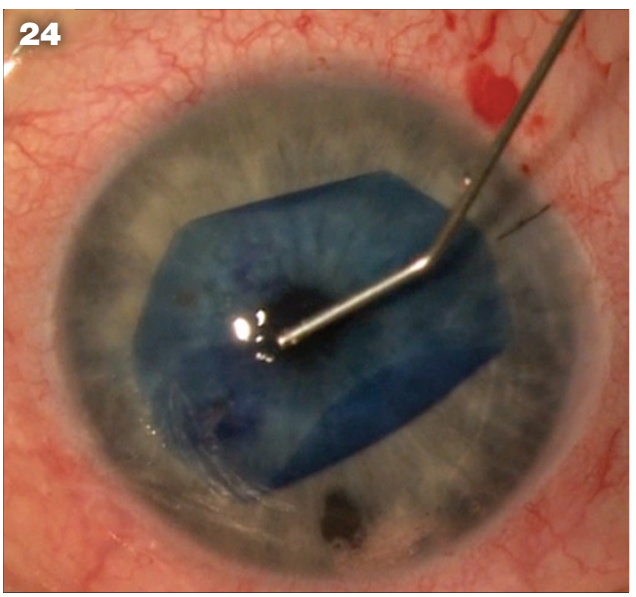

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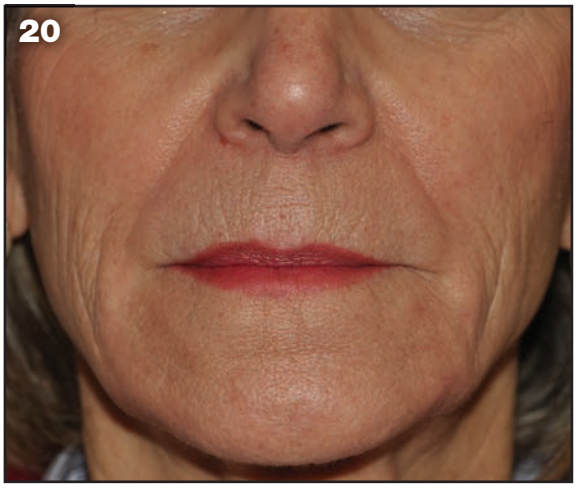
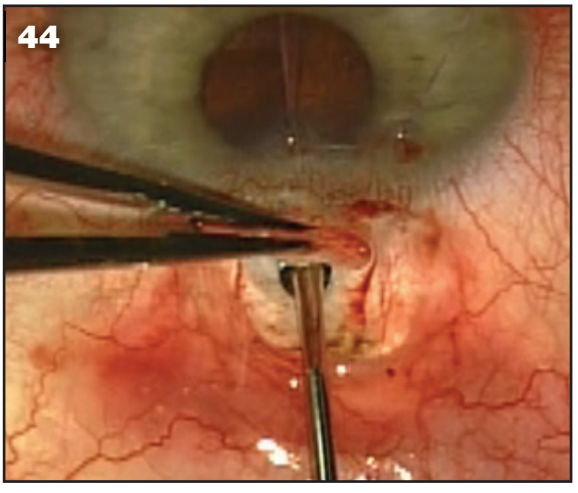
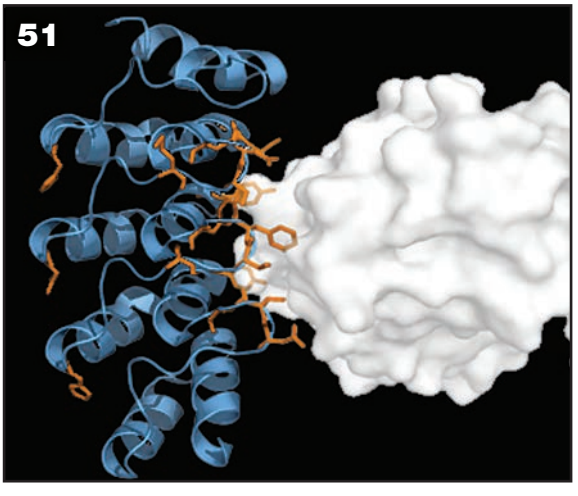
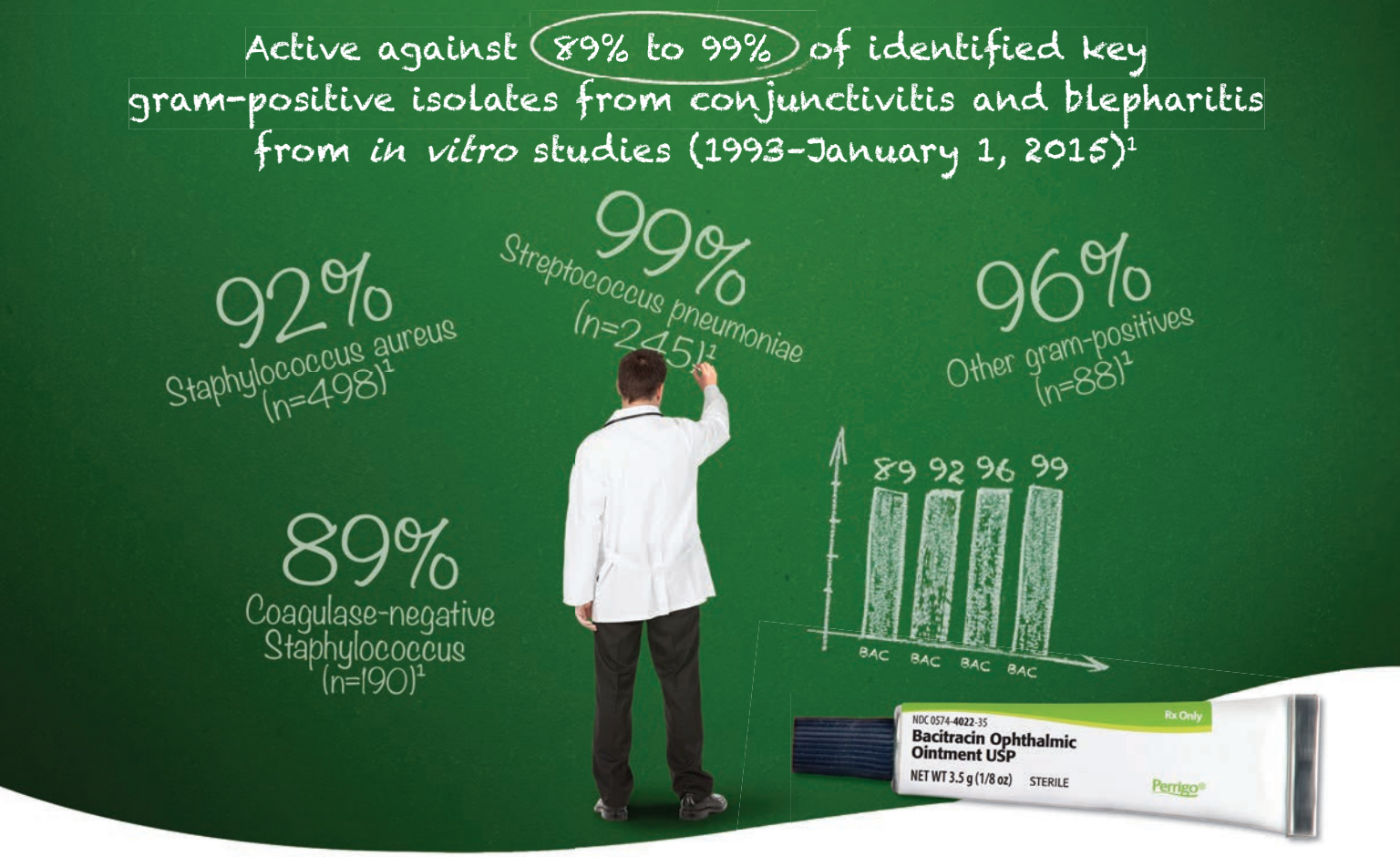






BACITRACIN OPHTHALMIC OINTMENT USP



***In Vitro* Susceptibility Data Provided Through the University of Pittsburgh Medical Center. *In Vitro* Data Should Not Be Considered Representative of Clinical Efficacy**[1]

Established therapeutic utility in blepharitis, conjunctivitis, and other superficial ocular infections caused by Bacitracin-susceptible organisms

- **Excellent safety profile**—low incidence of adverse events[2]
- Ointment provides **long-lasting ocular surface contact time** and **greater bioavailability**[3]
- **Anti-infective efficacy** in a lubricating base[2]
- **Flexible dosing**—1 to 3 times daily[2]
- **Tier 1 pharmacy benefit status**—on most insurance plans[4]

Indication

Bacitracin Ophthalmic Ointment is indicated for the treatment of superficial ocular infections involving the conjunctiva and/or cornea caused by Bacitracin susceptible organisms.

Important Safety Information

This product should not be used in patients with a history of hypersensitivity to Bacitracin.

Bacitracin Ophthalmic Ointment should not be used in deep-seated ocular infections or in those that are likely to become systemic.

There is a low incidence of allergenicity exhibited by Bacitracin. If such reactions do occur, therapy should be discontinued.

Please see adjacent page for full prescribing information.

For a closer look, visit www.perrigobacitracin.com

BACITRACIN OPHTHALMIC OINTMENT USP

Perrigo® Specialty Pharmaceuticals

Bacitracin Ophthalmic Ointment USP

STERILE **Rx Only**

DESCRIPTION: Each gram of ointment contains 500 units of Bacitracin in a low melting special base containing White Petrolatum and Mineral Oil.

CLINICAL PHARMACOLOGY: The antibiotic, Bacitracin, exerts a profound action against many gram-positive pathogens, including the common Streptococci and Staphylococci. It is also destructive for certain gram-negative organisms. It is ineffective against fungi.

INDICATIONS AND USAGE: For the treatment of superficial ocular infections involving the conjunctiva and/or cornea caused by Bacitracin susceptible organisms.

CONTRAINDICATIONS: This product should not be used in patients with a history of hypersensitivity to Bacitracin.

PRECAUTIONS: Bacitracin ophthalmic ointment should not be used in deep-seated ocular infections or in those that are likely to become systemic. The prolonged use of antibiotic containing preparations may result in overgrowth of nonsusceptible organisms particularly fungi. If new infections develop during treatment appropriate antibiotic or chemotherapy should be instituted.

ADVERSE REACTIONS: Bacitracin has such a low incidence of allergenicity that for all practical purposes side reactions are practically non-existent. However, if such reaction should occur, therapy should be discontinued.

To report SUSPECTED ADVERSE REACTIONS, contact Perrigo at 1-866-634-9120 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DOSAGE AND ADMINISTRATION: The ointment should be applied directly into the conjunctival sac 1 to 3 times daily. In blepharitis all scales and crusts should be carefully removed and the ointment then spread uniformly over the lid margins. Patients should be instructed to take appropriate measures to avoid gross contamination of the ointment when applying the ointment directly to the infected eye.

HOW SUPPLIED:

NDC 0574-**4022**-13 3 - 1 g sterile tamper evident tubes with ophthalmic tip.

NDC 0574-**4022**-35 3.5 g (1/8 oz.) sterile tamper evident tubes with ophthalmic tip.

Store at 20°-25°C (68°-77°F)
[see USP Controlled Room Temperature].

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References: 1. Antibiotic susceptibility: conjunctivitis and blepharitis. University of Pittsburgh Medical Center, Charles T. Campbell Eye Microbiology Lab Web site. http://eyemicrobiology.upmc.com/AntibioticSusceptibilities/Conjunctivitis.htm. Accessed March 21, 2016. **2.** Bacitracin Ophthalmic Ointment [package insert]. Minneapolis, MN: Perrigo Company; August 2013. **3.** Hecht G. Ophthalmic preparations. In: Gennaro AR, ed. *Remington: the Science and Practice of Pharmacy*. 20th ed. Baltimore, MD: Lippincott Williams & Wilkins; 2000. **4.** Data on file. Perrigo Company.

REVIEW® of Ophthalmology

21st Century Cure-all?

The recent approval of corneal collagen cross-linking in the United States was a milestone moment for ophthalmologists: They can now worry about how to do it better rather than when it will get approved.

This approval got me thinking about the recent flurry of approvals—in July alone there were several significant approvals in ophthalmology, opening up new treatment options. All this comes hot on the heels of 2015, which was a banner year for the FDA: 45 new drugs were approved in 2015, outpacing the annual average of 28 in the period of 2006 through 2014.[1] Some physicians are wondering whether this means change is in the air for the FDA and its approval process.

Their musings could well be correct, with one major example being the passing of the 21st Century Cures Act in the House of Representatives last summer. The act's main objective is to accelerate the process of FDA approval for drugs and devices, with a major benefit being an annual payment of $1.86 billion to the National Institutes of Health from 2016 through 2020. It also contains provisions to accelerate the approval of treatments for rare diseases. Such initiatives are welcomed by companies developing treatments, physicians eager to begin using them and patients desperate for therapies.

Some observers, however, urge caution. An article in the *New England Journal of Medicine* expressed concern that the bill might undermine the current drug approval process by allowing the use of such measures as "observational studies, registries and therapeutic use" rather than clinical trials.[2] It also took issue with the bill's plan to allow the use of biomarkers or other "surrogate" measurements to stand in for primary outcomes.[2] In addition to some pushback from physicians, Americans in general have some reservations about the bill: In a STAT-Harvard poll of around 1,000 consumers, 58 percent oppose altering standards to make the process for approving prescription drugs faster.[3] Half of the respondents oppose similar measures to quicken the approval of devices.[3] Supporters of the bill counter that it wouldn't lessen the FDA's standards, just give the agency more data to use. And the debate continues.

Now, I don't think anyone would call the FDA the paragon of speed but, by the same token, no one would want to think any corners were being cut on the review of a drug or device that could potentially be used by his or her family, either. If the agency is indeed streamlining its process, either by itself or with the help of a new law, I hope that it does so in a way that preserves the high standards that all of us potential patients deserve. It's important to be quick—but it's just as important not to rush.

—Walt Bethke, Editor in Chief

1. FDA Novel Drugs Summary. http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/ucm474696.htm. Accessed 22 August 2016.
2. Avorn J, Kesselheim A. The 21st century cures act: Will it take us back in time? N Engl J Med 2015;372:2473.
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Offering Your Patients An In-office "Face Lift"

If you're looking for an extra service to provide, some of the latest noninvasive skin-tightening treatments might fit the bill.

Christopher Kent, Senior Editor

In the search for ways to draw more patients into the office and offer more services to existing patients, ophthalmologists often consider offering procedures that would fall outside standard ophthalmic treatment. One service that can be performed in-office and will appeal to many ophthalmic patients is tightening of the skin on the face and neck. Dozens of devices that can accomplish this are available; all of them cause skin tightening by generating heat through or under the skin, causing damage at the cellular level. The healing that follows tightens the epidermis and underlying layers—sometimes including muscle, if used for something like a brow lift—and also causes the remodeling of collagen and elastin, further tightening the skin.

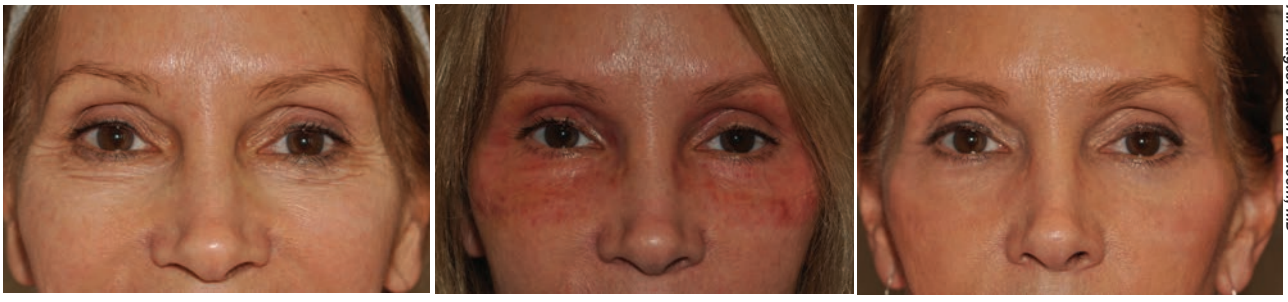
Jason D. Bloom, MD, is director of facial plastic and reconstructive surgery at the Main Line Center for Laser Surgery, which offers many nonsurgical skin-tightening procedures; the Center has participated in clinical trials of many of the devices currently used in the industry. Here, Dr. Bloom explains the basic options that are currently available and offers advice to any ophthalmologists considering offering one or more of these services.

Five Approaches

Dr. Bloom says he finds it helpful to divide today's nonsurgical skin-tightening technologies into five categories:

• ***Fractionated laser.*** "The first gold-standard technology used for facial skin tightening was the CO_2 laser, using unfractionated laser energy," Dr. Bloom says. "Very few people use that now. It produces a significant amount of skin tightening, but it comes with a very high risk of scarring and hypopigmentation; patients have two weeks of downtime and three to six months of being red like a tomato.

"Since then, the laser energy has been modified for fractionated delivery," he continues. "Unfractionated delivery creates something akin to scorched earth, while fractionated delivery creates a tiny checkerboard



All images: Jason D. Bloom, MD

Fractionated CO_2 laser treatment around the eyes, before (left), immediately afterwards (center) and at five days postop (right). The thermal damage caused by the laser results in remodeling of collagen and elastin, tightening the skin.

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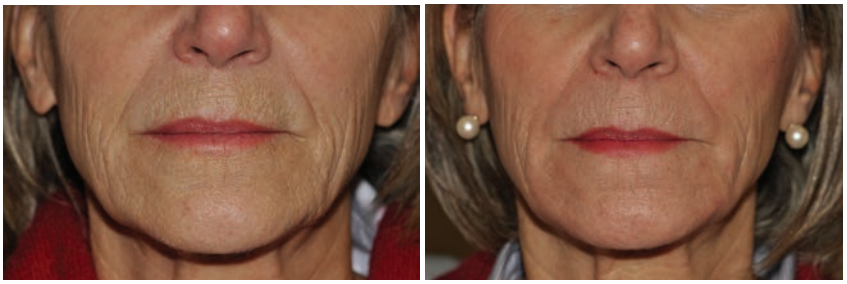


Fractionated laser around the mouth, before (left) and after treatment (right).

pattern of injury. Thus, lasered skin is next to unlasered; the undamaged tissue grows over the damaged tissue, and the area heals in about one-third of the time. Patients put on ointments for a couple of days, but by day five women are able to wear makeup again; then they're a little pink for another week. Systems designed for this purpose include the ResurFX module of Lumenis's M22 system, the Fraxel Repair and the Pixel CO_2 System. Other fractional ablative lasers use different light sources; some, such as erbium-based lasers, cause less thermal damage and leave the patient less red. The tradeoff is usually that they require a greater number of treatments to achieve the desired effect."

• ***Radio frequency energy.*** Devices in this category use radio frequency energy to generate heat transcutaneously. "Radio waves penetrate deep into the subcutaneous tissues," Dr. Bloom explains. "The heat stimulates production of collagen and elastin, which tightens down tissue over time. However, these devices tend to use lower energy levels and require multiple passes to create the desired effect. Devices in this category include Thermage CPT (Valeant), Exilis Protégé Elite (BTL), ThermiSmooth (Thermi) and Pelleve (Cynosure)."

• ***Microfocused ultrasound.*** Dr. Bloom says this third category is still noninvasive, but reaches a deeper tissue layer. "Ultrasound normally is nonspecific; it penetrates deeply but causes no lesions," says Dr. Bloom. "This technology focuses the energy, like a child using a magnifying glass to focus sunlight on an ant. You lay down lines of these subsurface microinjuries, causing contraction and remodeling of collagen and elastin. Using this technology, it can take three to six months to see the results. Ulthera is the only company with a product in this category; it's approved for brow-lifting and treating the lower face, neck and décolletage area. It does produce a fair amount of skin and soft-tissue tightening."

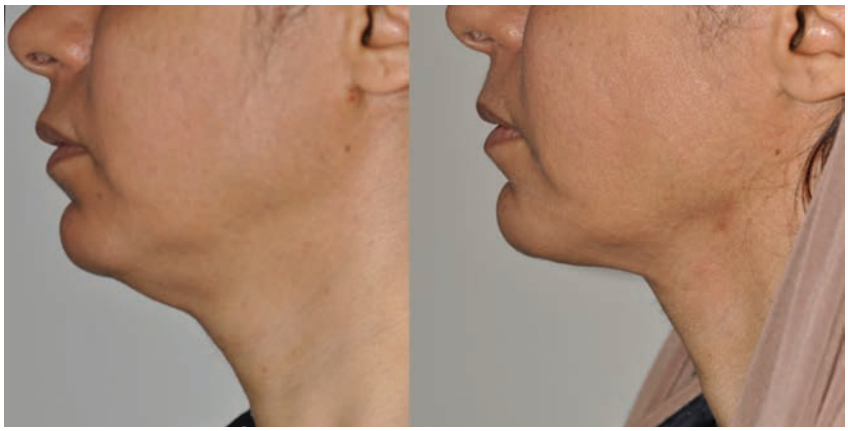
• ***Radio frequency microneedling.*** Dr. Bloom explains that these devices deliver the energy through the epidermis via tiny needles that pierce the skin. "Some of these devices have 150 needles; some have 24; some have 60; some use paired needle sets," he says. "Some use needles that are coated with insulation so the energy comes out only at the tip, while others are not insulated, so the energy causes damage along the entire needle track. More damage means more effect, but also more downtime; the latter patients can ooze a little bit because you're causing an injury all the way up through the epidermis. I only use the coated needles. Devices in this category include Infini (Lutronic), Profound (Syneron Candela), Fractora (InMode) and Intensif RF Microneedle (EndyMed)."

• ***Cannulated delivery under the skin.*** Dr. Bloom says the newest frontier involves using a stiff, insulated 18-ga. cannula that's inserted through a tiny hole in the skin and moved around by the surgeon. The cannula may deliver radio frequency or laser energy, depending on the system. "This approach is great for tightening the neck, but it's sometimes used in the face as well," he explains. "To treat the jowls and neck, I make three small openings with 16-ga. needles following tumescent anesthesia—one opening under the chin and one under each earlobe. I run the cannula back and forth under the surface of the skin in a fan pattern, above the muscle, just underneath the subcutaneous fat. I still consider this nonsurgical, because there's no trip to the OR and no sedation or general anesthesia; I tell the patients that I don't use any scalpels or sutures. This procedure takes about an hour and a half, with results that resemble a surgical facelift. *(See photos, facing page.)* It involves a little more surgical downtime, but most patients have it done on Wednesday or Thursday and are back at work on Monday. Devices in this category include ThermiTight (Thermi), PrecisionTx (Cynosure) and FaceTite/NeckTite (InMode).

Dr. Bloom says most of these procedures have a very short learning curve. "The one exception might be the last category of devices, which use a cannula," he says. "To use those you have to be familiar with tumescent anesthesia, and they take a couple of cases to get used to. But most of these procedures can be learned by almost anyone. In fact, that's a problem, because laws regulating these procedures differ from state to state. In some states, anyone can operate the equipment and perform procedures. As a tertiary site, we sometimes see patients who have been badly burned or disfigured by non-surgeon procedures. Meanwhile, in other states, only a doctor is allowed to perform these procedures."

Tips for Success

Dr. Bloom—who notes that he



Cannulated delivery of energy through tiny holes in the skin—done in-office using tumescent anesthesia—can produce results resembling a surgical face or neck lift.

has learned a lot about lasers from working with Eric Bernstein, MD, a dermatologic laser surgeon—offers these tips to any ophthalmologist considering adding one of these devices/procedures to your practice offerings:

• ***Check the regulations affecting use of these devices in your state before purchasing one—especially if you won't be the person operating the device.*** As noted, laws vary widely from state to state. "Make sure you're clear about the legal ramifications of offering these services before you begin," says Dr. Bloom.

• ***Never take advice on settings from the manufacturer's rep.*** "The rep will often tell you to turn the energy level up very high to get quick results," notes Dr. Bloom. "That's usually bad advice. Before I operate a new device I talk to colleagues who are familiar with it to get their advice on settings, patient selection and so forth."

• ***Consider taking a course on the procedure.*** "The American Society for Laser Medicine & Surgery provides excellent courses on the use of these technologies," says Dr. Bloom. "They have an annual meeting in April and offer regional courses as well. I lead a course on periorbital therapies using these devices. You can find information at ASLMS.org."

• ***When a rep brings in a new device, try it out on the rep.*** "This can be a good way to make sure the device is safe," Dr. Bloom notes.

• ***It might be worth offering more than one option.*** "One size does not fit all," says Dr. Bloom. "Patients want different results, have different tolerance for downtime, different financial situations, different tolerance for invasiveness, different pain tolerance and different ideas about how long they're willing to wait before seeing results. If you can offer more than one option, you'll get more patients interested."

• ***Don't try to use one device to do everything.*** "You can't use one device to do everything, or use the same device on every patient," says Dr. Bloom. "For example, some lasers work better on light or dark skin. These devices aren't cheap; they range from $45,000 to $100,000 or more. On the other hand, some of these devices, such as a CO_2 laser, can be used for multiple purposes. If you're going to invest in a single device, think carefully about what your patients are likely to be interested in, and do your homework before purchasing." REVIEW

Dr. Bloom serves as a trainer, consultant or speaker for many of the companies mentioned, as well as many others across the laser and aesthetics industry.

Perfecting Posterior Corneal Grafts

Sadeer B. Hannush, MD
Philadelphia

A look at the options waiting behind DSAEK, especially its closest rival, DMEK.

Ophthalmologists in general, and corneal specialists specifically, are always striving to get their posterior corneal transplant patients the best anatomic and visual outcomes possible. In recent years, this drive has led to the development of alternatives to penetrating keratoplasty, such as Descemet's stripping automated endothelial keratoplasty, Descemet's membrane endothelial keratoplasty and even newer techniques. With increasingly better outcomes, however, come increasingly difficult procedures, and not everyone has embraced techniques such as DMEK. In this article, I'll review the cutting-edge transplant techniques, with an emphasis on DMEK, since it is the closest to achieving the kind of acceptance that DSAEK now enjoys.

Why DMEK?

DSAEK currently sits in the sweet spot in which it can provide good outcomes for patients with Fuchs' and other posterior corneal dystrophies, as well as aphakic and pseudophakic bullous keratopathy, while, at the same time, not putting a lot of technical demands on the surgeon.

There are reasons to consider DMEK, however, as it can potentially offer even more benefits, such as:

- true anatomic replacement of Descemet's membrane and endothelium, a 15 to 20-µm thick structure;
- pachymetric uniformity across the entire graft, which DSAEK can't always achieve;
- lower antigenic stimulus—and therefore lower incidence of allograft rejection—by virtue of less tissue being transplanted;
- the need for less steroids to prevent immune rejection;
- a lower incidence of steroid-induced intraocular pressure elevation and glaucoma; and
- if done correctly, the possibility of quicker visual rehabilitation.[1]

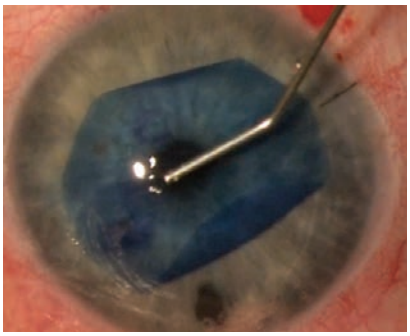
DMEK, for all its advantages, isn't for every patient, however. The ideal patient is a pseudophake with a posterior chamber lens implant, ideally one that's situated in the capsular bag, with or without a posterior capsulotomy. For patients with serious co-morbidities, I still prefer to perform DSAEK. With this in mind, patient presentations in which to avoid DMEK—at least for the novice DMEK surgeon—are patients with:

- anterior chamber intraocular lens implants;
- unicameral eyes;
- vitreous prolapse into the anterior chamber;
- a history of trabeculectomy;

This article has no commercial sponsorship.

• a history of tube shunt implantation;[2]
• failed penetrating grafts; and
• failed previous DSAEK grafts.

The common themes among these relative contraindications include the possibility of losing the graft into the vitreous cavity, the difficulty you'll have in unscrolling the graft in the eye and the potential increased challenge of attaching the graft.



Tapping technique to unscroll a DMEK graft.

The Four Challenges of DMEK

For surgeons experienced with DMEK, as well as surgeons just starting out, there are four areas that will test their skills. It's these areas that currently hold DMEK back in terms of being a widely accepted technique. You can clear these hurdles, however. Here's a look at why these stages are particularly challenging, and ways you can make them more manageable.

• ***Preparation of the donor tissue.*** This challenge is not so much the actual pre-stripping of the tissue—the vast majority of us have trained an eye-bank technician to strip the tissue for us, and most of them have become better than us at this task. Instead, it's more about an awareness of the donor's age and diabetic status, and how both will affect the tissue's behavior.

Corneal specialists have unofficially agreed that the tissue donor shouldn't be younger than 50 years of age, diabetic or have had previous cataract surgery. Why is this? Because the younger the tissue, the harder it is to strip the Descemet's membrane/endothelial complex off the donor cornea, and the tighter its subsequent scroll is when you try to unscroll it in the recipient's anterior chamber. I won't hesitate to accept a donor that's 70 to 72 years of age, however, because the Cornea Donor Study showed there wasn't much of a difference in risk of graft failure in grafts from donors up to age 75;[3] I know I'll be able to handle an older donor's tissue inside the eye more easily. Secondly, diabetic patients' tissue has been shown to be more difficult to strip and more likely to develop tears.

Finally, if the donor has had previous intraocular surgery, particularly cataract surgery, and especially if the cataract surgeon made a long phaco incision tunnel, you or the eye-bank tech may encounter the internal lumen of the old cataract incision while stripping the tissue. If this occurs, that's a likely location for a tear.

Also, preparing the donor graft from perfectly pre-stripped tissue can be challenging, as punching, isolating and placing the graft into the delivery device is not without potential complications.

• ***Insertion of tissue into the anterior chamber.*** DMEK surgeons usually use one of two ways to insert the tissue: 1) a push-through technique by way of a glass tube or a modified intraocular lens inserter; or 2) a pull-through technique after placing the donor graft on a Busin glide, contact lens or similar platform. Most DMEK surgeons are currently using a push-through method. With this being the case, it's important to note that the glass tube and modified IOL inserter have advantages and limitations.

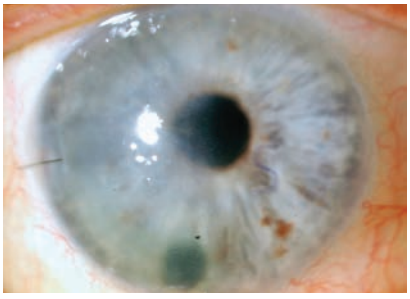
The glass tube is actually a modified version of the Jones tube we've used for years for dacryocystorhinostomy procedures. The tube's shape has been slightly modified by Michael Straiko, MD, of the Devers Eye Institute in Portland, Ore., creating what's known

as the Straiko-modified Jones tube. It can be inserted through a 3.2- to 3.5-mm incision. Proponents of these tubes believe that they do less endothelial cell damage if the graft tissue touches the glass wall of the tube, compared to the plastic interior of a modified IOL cartridge.

One of the pearls for working with a glass tube is that it's important to get a feel for how to aspirate the tissue into the tube. This is because you're aspirating the tissue from a petri dish rather than placing it into the back of the tube. To get a feel for this, use peripheral fragments of Descemet's membrane from the donor tissue after the punch, not the graft itself, to see how much to pull on the plunger to aspirate the tissue up into the tube.

Surgeons who use plastic, modified IOL injection cartridges argue that one of the main benefits of their approach is that the tissue can be inserted through a 2.4- to 2.8-mm incision. The main challenge with IOL inserters is that they're not meant to push such thin tissue—about 20 µm thick—into the eye. This can cause issues as you work with the inserter (indeed, not all inserters are created equal for this purpose). This is because in the course of its normal operation, the inserter's plunger doesn't completely seal the channel that it goes into, and it doesn't need to for the purpose of injecting an IOL. Because of this, though, saline solution can occasionally leak from the back of the cartridge—taking the thin DMEK graft with it and incarcerating it between the plunger and the wall of the cartridge. Note that this is more likely to occur if you use a chamber maintainer with fluid infusion during the insertion.

If you use either of these methods, glass tube or modified inserter, the number-one technique tip is to size the wound in such a way that you can insert the tube or cartridge into the incision tightly but without difficulty. You don't want to encounter a problem with going through the wound after you've floated the graft into the glass tube or cartridge. Also, choose an inserter that allows for a tight seal between the plunger and the wall of the cartridge.



Temporal corneal edema after DMEK secondary to a DMEK detachment. Note the letter S nasally in its correct orientation.

As mentioned above, there are ways to introduce the graft into the eye other than as a scroll, such as a method that involves placing the graft on a Busin glide or other platform, similar to the way in which the surgeon inserts a DSAEK graft, using a two-handed, pull-through technique. However, since most surgeons insert the DMEK graft into the eye as a scroll, that is what this article focuses on.

This brings us to the challenge of getting the graft oriented correctly when it unscrolls.

• ***Unscrolling the tissue and achieving successful tamponade.*** Getting the thin DMEK graft to unscroll can be a challenge, especially when the tissue is tightly scrolled.[4] Several techniques have been developed to help you unscroll it, however.

First off, one way to achieve the correct orientation of the tissue as it transitions from a scroll to an unscrolled sheet is the marking method. The method involves the eye bank, or whoever prepares the tissue, marking the stromal side with a letter S to aid in the subsequent placement in the eye. An ideal way to make this mark is by using a stamper colored with a gentian violet surgical pen and allowing the alcohol to evaporate.[5]

Alternatively, you can intraoperatively discern the graft orientation once it's in the eye using either a slit lamp attached to your operating microscope, or a tiny handheld slit lamp. As the graft unscrolls it will begin to take on the shape of the letter C, with the endothelium on the outside of the C. So, if by using the slit beam you can tell the orientation of the C, you'll always know which side is up; you want the inside of the C to be facing up, so it looks like a cup under the dome of the cornea.

Aside from these popular approaches, there are other published techniques to aid in determining the orientation of the graft, too. Of course, an operating microscope with built-in OCT will accomplish that goal … at a significantly higher cost.

In terms of getting the graft to unscroll, one method used by many surgeons is the tapping technique, developed by Efdal Yoeruek, MD, of Eberhard-Karls University in Tübingen, Germany. The technique involves bouncing an instrument, usually a BSS or 27- or 30-ga cannula, on the cornea over the location of the scroll together with a simultaneously shallowing of the anterior chamber. This tapping sends fluid waves through the anterior chamber that unscroll the tissue. This technique usually works best if the chamber is shallow enough so that, when you start unscrolling the graft, it doesn't just scroll right back again. A good rule of thumb for this chamber shallowing is to make it less than one corneal thickness deep. For example, if the average cornea is 500 to 600 µm thick, the anterior chamber should be roughly 0.5 mm or less in depth after the graft is unscrolled, as opposed to its usual 2.5 to 3.5 mm depth, in order to successfully tap and unscroll the tissue and keep it unscrolled until the air/gas bubble is injected.

Selective irrigation is another method that can help unscroll the tissue. To understand this, it helps to know that

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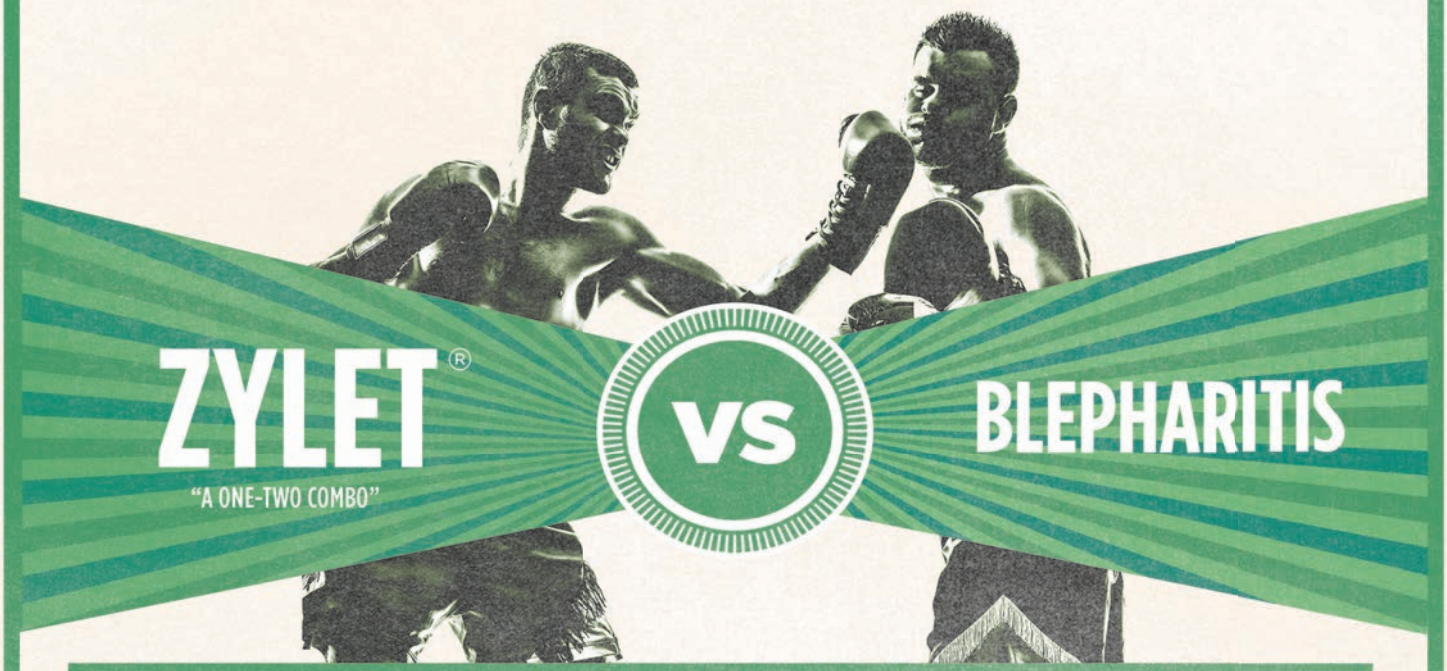

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INDICATIONS AND USAGE

ZYLET® (loteprednol etabonate 0.5% and tobramycin 0.3% ophthalmic suspension) is a topical anti-infective and corticosteroid combination for steroid-responsive inflammatory ocular conditions for which a corticosteroid is indicated and where superficial bacterial ocular infection or a risk of bacterial ocular infection exists.

Ocular steroids are indicated in inflammatory conditions of the palpebral and bulbar conjunctiva, cornea and anterior segment of the globe such as allergic conjunctivitis, acne rosacea, superficial punctate keratitis, herpes zoster keratitis, iritis, cyclitis, and where the inherent risk of steroid use in certain infective conjunctivitides is accepted to obtain a diminution in edema and inflammation. They are also indicated in chronic anterior uveitis and corneal injury from chemical, radiation or thermal burns, or penetration of foreign bodies.

The use of a combination drug with an anti-infective component is indicated where the risk of superficial ocular infection is high or where there is an expectation that potentially dangerous numbers of bacteria will be present in the eye.

The particular anti-infective drug in this product (tobramycin) is active against the following common bacterial eye pathogens: Staphylococci, including S. *aureus* and S. *epidermidis* (coagulase-positive and coagulase-negative), including penicillin-resistant strains. Streptococci, including some of the Group A-beta-hemolytic species, some nonhemolytic species, and some *Streptococcus pneumoniae, Pseudomonas aeruginosa, Escherichia coli, Klebsiella pneumoniae, Enterobacter aerogenes, Proteus mirabilis, Morganella morganii,* most *Proteus vulgaris strains, Haemophilus influenzae,* and *H. aegyptius, Moraxella lacunata, Acinetobacter calcoaceticus* and some *Neisseria species.*

IMPORTANT SAFETY INFORMATION

- ZYLET® is contraindicated in most viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal diseases of ocular structures.

IMPORTANT SAFETY INFORMATION (continued)

- Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision. Steroids should be used with caution in the presence of glaucoma. If this product is used for 10 days or longer, intraocular pressure should be monitored.
- Use of corticosteroids may result in posterior subcapsular cataract formation.
- The use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation. In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical steroids. The initial prescription and renewal of the medication order should be made by a physician only after examination of the patient with the aid of magnification such as a slit lamp biomicroscopy and, where appropriate, fluorescein staining.
- Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. In acute purulent conditions, steroids may mask infection or enhance existing infections. If signs and symptoms fail to improve after 2 days, the patient should be re-evaluated.
- Employment of corticosteroid medication in the treatment of patients with a history of herpes simplex requires great caution. Use of ocular steroids may prolong the course and exacerbate the severity of many viral infections of the eye (including herpes simplex).
- Fungal infections of the cornea are particularly prone to develop coincidentally with long-term local steroid application. Fungus invasion must be considered in any persistent corneal ulceration where a steroid has been used or is in use.
- Most common adverse reactions reported in patients were injection and superficial punctate keratitis, increased intraocular pressure, burning and stinging upon instillation.

Please see Brief Summary of Prescribing Information for ZYLET® on adjacent page.

BAUSCH+LOMB

Zylet®
loteprednol etabonate
0.5% and tobramycin 0.3%
ophthalmic suspension

BRIEF SUMMARY OF PRESCRIBING INFORMATION

This Brief Summary does not include all the information needed to use Zylet safely and effectively. See full prescribing information for Zylet.

Zylet® (loteprednol etabonate 0.5% and tobramycin 0.3% ophthalmic suspension)

Initial U.S. Approval: 2004

DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

Apply one or two drops of Zylet into the conjunctival sac of the affected eye every four to six hours. During the initial 24 to 48 hours, the dosing may be increased, to every one to two hours. Frequency should be decreased gradually as warranted by improvement in clinical signs. Care should be taken not to discontinue therapy prematurely.

2.2 Prescription Guideline

Not more than 20 mL should be prescribed initially and the prescription should not be refilled without further evaluation [*see Warnings and Precautions (5.3)*].

CONTRAINDICATIONS

4.1 Nonbacterial Etiology

Zylet, as with other steroid anti-infective ophthalmic combination drugs, is contraindicated in most viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal diseases of ocular structures.

WARNINGS AND PRECAUTIONS

5.1 Intraocular Pressure (IOP) Increase

Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision. Steroids should be used with caution in the presence of glaucoma.

If this product is used for 10 days or longer, intraocular pressure should be monitored.

5.2 Cataracts

Use of corticosteroids may result in posterior subcapsular cataract formation.

5.3 Delayed Healing

The use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation. In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical steroids. The initial prescription and renewal of the medication order should be made by a physician only after examination of the patient with the aid of magnification such as a slit lamp biomicroscopy and, where appropriate, fluorescein staining.

5.4 Bacterial Infections

Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. In acute purulent conditions of the eye, steroids may mask infection or enhance existing infection. If signs and symptoms fail to improve after 2 days, the patient should be re-evaluated.

5.5 Viral Infections

Employment of a corticosteroid medication in the treatment of patients with a history of herpes simplex requires great caution. Use of ocular steroids may prolong the course and may exacerbate the severity of many viral infections of the eye (including herpes simplex).

5.6 Fungal Infections

Fungal infections of the cornea are particularly prone to develop coincidentally with long-term local steroid application. Fungus invasion must be considered in any persistent corneal ulceration where a steroid has been used or is in use. Fungal cultures should be taken when appropriate.

5.7 Aminoglycoside Hypersensitivity

Sensitivity to topically applied aminoglycosides may occur in some patients. If hypersensitivity develops with this product, discontinue use and institute appropriate therapy.

ADVERSE REACTIONS

Adverse reactions have occurred with steroid/anti-infective combination drugs which can be attributed to the steroid component, the anti-infective component, or the combination.

Zylet:

In a 42 day safety study comparing Zylet to placebo, ocular adverse reactions included injection (approximately 20%) and superficial punctate keratitis (approximately 15%). Increased intraocular pressure was reported in 10% (Zylet) and 4% (placebo) of subjects. Nine percent (9%) of Zylet subjects reported burning and stinging upon instillation.

Ocular reactions reported with an incidence less than 4% include vision disorders, discharge, itching, lacrimation disorder, photophobia, corneal deposits, ocular discomfort, eyelid disorder, and other unspecified eye disorders.

The incidence of non-ocular reactions reported in approximately 14% of subjects was headache; all other non-ocular reactions had an incidence of less than 5%.

Loteprednol etabonate ophthalmic suspension 0.2% - 0.5%:

Reactions associated with ophthalmic steroids include elevated intraocular pressure, which may be associated with infrequent optic nerve damage, visual acuity and field defects, posterior subcapsular cataract formation, delayed wound healing and secondary ocular infection from pathogens including herpes simplex, and perforation of the globe where there is thinning of the cornea or sclera.

In a summation of controlled, randomized studies of individuals treated for 28 days or longer with loteprednol etabonate, the incidence of significant elevation of intraocular pressure (≥10 mm Hg) was 2% (15/901) among patients receiving loteprednol etabonate, 7% (11/164) among patients receiving 1% prednisolone acetate and 0.5% (3/583) among patients receiving placebo.

Tobramycin ophthalmic solution 0.3%:

The most frequent adverse reactions to topical tobramycin are hypersensitivity and localized ocular toxicity, including lid itching and swelling and conjunctival erythema. These reactions occur in less than 4% of patients. Similar reactions may occur with the topical use of other aminoglycoside antibiotics.

Secondary Infection:

The development of secondary infection has occurred after use of combinations containing steroids and antimicrobials. Fungal infections of the cornea are particularly prone to develop coincidentally with long-term applications of steroids.

The possibility of fungal invasion must be considered in any persistent corneal ulceration where steroid treatment has been used.

Secondary bacterial ocular infection following suppression of host responses also occurs.

USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic effects: Pregnancy Category C. Loteprednol etabonate has been shown to be embryotoxic (delayed ossification) and teratogenic (increased incidence of meningocele, abnormal left common carotid artery, and limb fixtures) when administered orally to rabbits during organogenesis at a dose of 3 mg/kg/day (35 times the maximum daily clinical dose), a dose which caused no maternal toxicity. The no-observed-effect-level (NOEL) for these effects was 0.5 mg/kg/day (6 times the maximum daily clinical dose). Oral treatment of rats during organogenesis resulted in teratogenicity (absent innominate artery at ≥5 mg/kg/day doses, and cleft palate and umbilical hernia at ≥50 mg/kg/day) and embryotoxicity (increased post-implantation losses at 100 mg/kg/day and decreased fetal body weight and skeletal ossification with ≥50 mg/kg/day). Treatment of rats at 0.5 mg/kg/day (6 times the maximum daily clinical dose) during organogenesis did not result in any reproductive toxicity. Loteprednol etabonate was maternally toxic (significantly reduced body weight gain during treatment) when administered to pregnant rats during organogenesis at doses of ≥5 mg/kg/day.

Oral exposure of female rats to 50 mg/kg/day of loteprednol etabonate from the start of the fetal period through the end of lactation, a maternally toxic treatment regimen (significantly decreased body weight gain), gave rise to decreased growth and survival and retarded development in the offspring during lactation; the NOEL for these effects was 5 mg/kg/day. Loteprednol etabonate had no effect on the duration of gestation or parturition when administered orally to pregnant rats at doses up to 50 mg/kg/day during the fetal period.

Reproductive studies have been performed in rats and rabbits with tobramycin at doses up to 100 mg/kg/day parenterally and have revealed no evidence of impaired fertility or harm to the fetus. There are no adequate and well controlled studies in pregnant women. Zylet should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.3 Nursing Mothers

It is not known whether topical ophthalmic administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. Systemic steroids that appear in human milk could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. Caution should be exercised when Zylet is administered to a nursing woman.

8.4 Pediatric Use

Two trials were conducted to evaluate the safety and efficacy of Zylet® (loteprednol etabonate and tobramycin ophthalmic suspension) in pediatric subjects age zero to six years; one was in subjects with lid inflammation and the other was in subjects with blepharoconjunctivitis.

In the lid inflammation trial, Zylet with warm compresses did not demonstrate efficacy compared to vehicle with warm compresses. Patients received warm compress lid treatment plus Zylet or vehicle for 14 days. The majority of patients in both treatment groups showed reduced lid inflammation.

In the blepharoconjunctivitis trial, Zylet did not demonstrate efficacy compared to vehicle, loteprednol etabonate ophthalmic suspension, or tobramycin ophthalmic solution. There was no difference between treatment groups in mean change from baseline blepharoconjunctivitis score at Day 15.

There were no differences in safety assessments between the treatment groups in either trial.

8.5 Geriatric Use

No overall differences in safety and effectiveness have been observed between elderly and younger patients.

NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been conducted to evaluate the carcinogenic potential of loteprednol etabonate or tobramycin.

Loteprednol etabonate was not genotoxic *in vitro* in the Ames test, the mouse lymphoma TK assay, a chromosome aberration test in human lymphocytes, or in an *in vivo* mouse micronucleus assay.

Oral treatment of male and female rats at 50 mg/kg/day and 25 mg/kg/day of loteprednol etabonate, respectively, (500 and 250 times the maximum clinical dose, respectively) prior to and during mating did not impair fertility in either gender. No impairment of fertility was noted in studies of subcutaneous tobramycin in rats at 100 mg/kg/day (1700 times the maximum daily clinical dose).

PATIENT COUNSELING INFORMATION

This product is sterile when packaged. Patients should be advised not to allow the dropper tip to touch any surface, as this may contaminate the suspension. If pain develops, redness, itching or inflammation becomes aggravated, the patient should be advised to consult a physician. As with all ophthalmic preparations containing benzalkonium chloride, patients should be advised not to wear soft contact lenses when using Zylet.

MANUFACTURER INFORMATION

BAUSCH & LOMB INCORPORATED

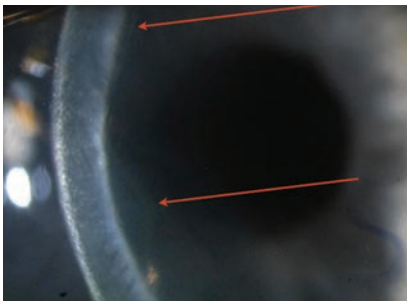
TAMPA, FLORIDA 33637 USA

Based on 9007705-9004405 Revised 08/2013 US/ZYL/15/0014

most DMEK surgeons will make two to four paracenteses that are used for many functions during the procedure: One use for the paracenteses is to deepen the chamber when necessary. For example, if, after you unscroll the tissue you find that it's upside down—i.e., you notice the letter S marking is inverted—you need to deepen the anterior chamber to release the tissue and scroll it again so you can flip it over. Another use for the paracenteses is to use the irrigation to move the tissue toward the center of the chamber. A third use of irrigation is if the tissue is in a double-scroll configuration, or even a three-corner folded graft (think Napoleon's hat), the fluid pulses can be used to open up the tissue. My colleague in India, Rajesh Fogla, MD, has developed a cannula with multiple irrigation holes dubbed the Fogla DMEK Cannula (Storz Ophthalmics) that is situated inside the scroll. Once the Fogla cannula is inside the scroll, the surgeon injects the fluid and the scroll opens.

Another method that some may consider dexterity-intensive, but which is exciting to watch, is called the bubble roll, developed by Friedrich Kruse, MD, of Erlangen, Germany.[6] With this technique, when the graft is inside the injector cartridge, the surgeon places a small bubble inside the scroll. Then, when the graft enters the eye, he can place pressure on the dome of the cornea to move the bubble around inside the scroll to unscroll it.

For my own part, I've teamed with Phillipsburg, N.J., ophthalmologist, William B. Neusidl to develop an instrument for unscrolling the DMEK graft. We've dubbed it the Neusidl-Hannush Loop, or NHL. The NHL's operation involves a polypropylene thread inside a metal lumen that's pulled taut and inserted into the anterior chamber and inside



Slit view of the detached DMEK graft from p. 26, highlighted by the arrows.

the DMEK scroll. An actuator then opens the loop to unscroll the graft. The instrument has been tested successfully in the wet lab, and is currently in the manufacturing process.

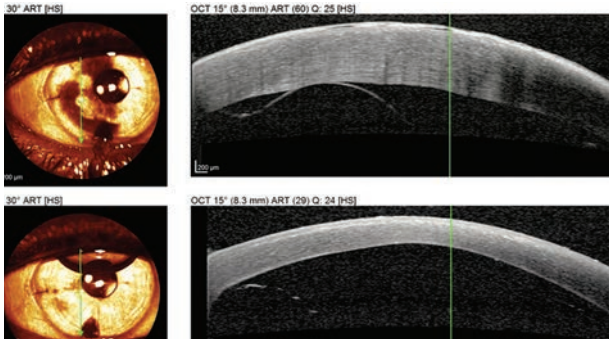
Once the graft is unscrolled, the surgeon has to tamponade it to the host cornea. For this, the options are to use a bubble composed of either air or 20% SF6. The main advantage of the latter is that it lasts longer, which may be helpful in achieving full apposition of the DMEK graft to the host cornea. With DSAEK you mainly need to tamponade the graft for 10 minutes with a pressure above 30 mmHG and the graft will usually stay in place, as long as there's no fluid between the graft and the host. With DMEK things are different. For DMEK, many surgeons feel that it's important to have a longer-lasting bubble and to make sure the patient lies on his/her back postop for at least the first 24 hours, then at least a few hours a day for the next several days. So for DMEK a longer-lasting SF6 bubble can make a difference; e.g., an 80-percent air bubble may last three to four days, while an 80-percent SF6 bubble can last twice as long, and might help increase your chance of success with DMEK graft attachment. Also, remember all DMEK patients should receive an inferior iridotomy. I should also mention here that a plethora of online videos can be of great help to the novice DMEK surgeon, both in facilitating the successful completion of the procedure and in avoiding and managing complications.

• ***Postop management.*** When DMEK surgeons discuss postop management, we're usually referring to decreasing the incidence of and managing graft detachment. To decrease this risk, it's important that the patient lie on his back, take the drops, refrain from rubbing the eye and keep up with the follow-up visits.

In terms of how long the patient must remain on his back, if we've used SF6, which can last about a week, we ask the patient to be on his back continuously for the first day, and then for two hours in the morning and two hours in the afternoon for the next five days postop. Since I frequently remove the central epithelium at the time of surgery, a bandage contact lens is used for the first week. It must be noted, however, that not every surgeon performs the keratectomy/contact lens step.

In addition to a postop steroid and antibiotic, my postop medical regimen usually includes Muro 128 hypertonic solution to promote deturgescence of the host stroma. I usually start the Muro the second week after the surface has healed and the antibiotic has been discontinued.

The main concern during the postop course is how to respond if the graft doesn't adhere completely. In my practice, the incidence of partial graft non-attachment requir-

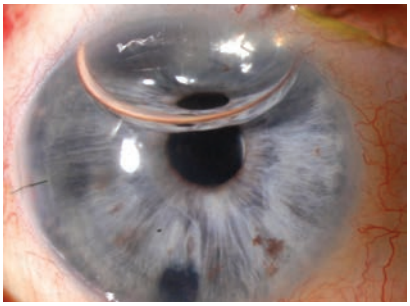


The OCT appearance of the detached graft in the slit image above (top) and the OCT of the eye following reattachment with a rebubbling procedure (bottom).

ing rebubbling (complete detachment is very rare) is 20 percent, vs. less than 5 percent for DSAEK. Studies have also found a higher rebubbling rate with DMEK.[7] Netherlands surgeon and DMEK originator Gerritt Melles, MD, has argued that if less than one-third of the graft isn't adhered, especially if the area of non-attachment is not visually significant, the surgeon may observe the patient, since grafts that are 60- to 70-percent attached will almost always completely attach and stay in place in time. That's also been my experience for the most part. However, I also think that the longer you leave the graft unattached, the worse the visual prognosis becomes, due to chronic edema. Therefore, if the area of detachment extends over the undilated pupillary aperture, I prefer to rebubble—create a new bubble for tamponade—usually between 10 and 20 days postop, a strategy I've learned from Dr. Kruse and that has served my patients well. If I find it challenging to discern the existence or extent of the detachment, especially if it's very shallow and in the setting of corneal edema, anterior segment OCT has been very helpful in determining the presence of a graft detachment and its extent.

In practice, if I see a DMEK patient a week postop and notice that the cornea is a little edematous, and I can't see the graft well—and then perform an OCT and find a shallow detachment—I'll inform the patient that I'll most likely want to put another bubble in the eye the following week. In preparation for this appointment, I advise the patient to bring someone along for assistance, and to be prepared to spend a couple of hours at my office, which is where I perform almost all rebubbling procedures. Some surgeons prefer to do it in the OR, and still others do it in a minor procedure room.

At that rebubbling visit, I sit the patient at the slit lamp and use one of the existing paracenteses to inject air



The eye from pg. 29, with the graft attached after a rebubbling procedure.

for the creation of the new bubble. A note for rebubbling: With DSAEK, you only need to insert the air cannula a little bit into the anterior chamber and, as long as you're behind the graft, you can inject the air. With DMEK, however, if you're too peripheral when the bubble starts to form, you can push the graft aside like an accordion and detach it completely. Therefore, make sure the cannula is in the center of the anterior chamber behind the graft before you start injecting the air.

Though rebubbling is an effective response to graft non-attachment, it's important to note that graft failure can still occur for a multitude of reasons. Graft failure may occur due to poor attachment, an upside-down graft or rejection. In my hands, and I believe those of many colleagues, graft failure may be a function of marked manipulation of the graft. This manipulation usually occurs intraoperatively during the unscrolling step, in what is referred to as "the dance," and leads to a significant loss of endothelium. In the literature, the rate of primary graft failure with DMEK varies from 2.5 to 10 percent.[8-10]

Techniques in Development

Though DSAEK may be entrenched as the less-invasive alternative to penetrating keratoplasty for the indication of endothelial dysfunction, as well as the one associated with better visual results than PK (mainly because of reduced astigmatism), and DMEK is the more technically challenging—but potentially better—aspirant to the throne, there are other approaches to endothelial keratoplasty that are worth noting.

• ***Ultra-thin DSAEK.*** In an effort to achieve some of the benefits of DMEK but perhaps with an easier time working with the graft, Italy's Massimo Busin, MD, and co-workers developed UT-DSAEK.[11] In practice, UT-DSAEK involves preparing a DSAEK graft thinner than 100 µm by a combination of several methods: removing the epithelium before making the microkeratome pass; making a double-pass with the microkeratome; using a 300, 350, or even 400 µm microkeratome head; increasing the pressure in the anterior chamber to about 90 mmHG as you make the pass; and/or making a slower microkeratome pass.

Working with a thinner DSAEK graft is technically less challenging than a DMEK graft. Theoretically, it may offer better visual results than conventional DSAEK, mostly due to the increased uniformity and thickness of the donor tissue. There have been no formal studies showing the benefit of UT-DSAEK over DSAEK or DMEK, so the jury is currently still out on this. Anecdotally, however, many surgeons, myself included, seem to think patients do get better vision from a thinner graft. Therefore, I aim for that type of graft whenever possible.

• ***Redistributed endothelial cells.*** In the past several years, some ophthalmologists have questioned whether we need to perform a keratoplasty of any sort in cases of Fuchs' endothelial dystrophy. Instead, they say, there may be a way to just coax the endothelium to return to its normal level of function, or to redistribute healthy endothelium to a central location where it may perform its function better.

The Netherlands' Dr. Melles reported on an 80-year-old patient who underwent DMEK for Fuchs', but had

(continued on page 68)

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DRY EYE THERAPY

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***These statements have not been evaluated by the FDA. This product is not intended to diagnose, treat, cure, or prevent any disease.**

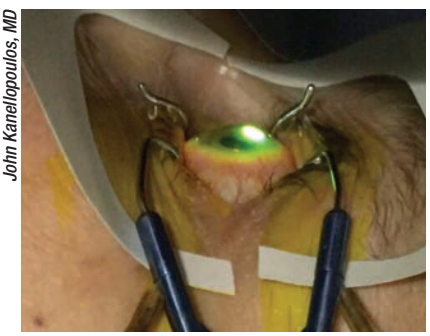
Reference: 1. Srinivasan S, Ngo W, Jones L. The relief of dry eye signs and symptoms using a combination of lubricants, lid hygiene, and ocular nutraceuticals. Poster presented at: ARVO annual meeting; April 2015; Denver, CO.

AKORN Consumer Health

Making the Most of Corneal Cross-linking

Christopher Kent, Senior Editor

Surgeons offer advice to first-time users for getting great results and staying out of trouble.



John Kanellopoulos, MD

Corneal collagen cross-linking is the only treatment that's been shown to strengthen the cornea and stop the progression of keratoconus or ectasia.

With the recent approvals of Avedro's KXL cross-linking system to treat progressive keratoconus and ectasia, American surgeons can finally begin to use cross-linking to help their patients. However, like any new technology, cross-linking comes with a learning curve and potential complications. Here, four surgeons experienced in using this technology share their thoughts on how to use the Avedro system; what pitfalls to avoid; and where this technology may be headed next.

The Power of Cross-linking

"Cross-linking is a major advance," notes Roy S. Rubinfeld, MD, MS, in private practice and a clinical associate professor at Georgetown University Medical Center. "It's the first and only treatment demonstrated to effectively strengthen the cornea and stop the progression of keratoconus or ectasia. Furthermore, it's been well-tested since it was originally introduced in the late 1990s by Michael Mrochen, PhD, and Theo Seiler, MD, PhD, in Dresden. It's expected to markedly reduce the number of corneal transplants performed in the United States, which is very good news.

"At the same time, it's important for surgeons to realize that the currently approved version of cross-linking [with removal of the epithelium] is not to be taken lightly," he says. "It's crucial to pay attention to patient selection and ocular surface assessment and treatment, both preoperatively and postoperatively. In my experience, healing after cross-linking is even slower and more critical than it is following PRK. Patients with ocular surface disease, as well as patients with very steep corneas, are at higher risk for delayed epithelial healing and potential complications, so surgeons should monitor their patients frequently until the epithelium regrows."

Peter S. Hersh, MD, FACS, clinical professor and director of cornea and refractive surgery at the Institute of Ophthalmology and Visual Science, Rutgers-New Jersey Medical School, was medical monitor for the trial that led to Avedro's FDA approval. "The first of the two FDA approvals to date was for collagen cross-linking for the treatment of progressive keratoconus," he explains. "Although cross-linking may improve the corneal topography modestly in some cases, the primary goal of crosslinking is stabilization of the disease process, so you want to be sure that you're dealing with progressive keratoconus. Also, for this indication, the patient should be age 14 or older."

This article has no commercial sponsorship.

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(lifitegrast
ophthalmic solution)5%

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Check it out at Xiidra-ECP.com

Reference: 1. FDA approves new medication for dry eye disease. FDA News Release. July 2016. *http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm510720.htm*. Accessed July 12, 2016.

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

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

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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.
Last Modified: 07/2016 S13681

The second indication, which received FDA approval this July, is as a treatment for corneal ectasia after refractive surgery. "In our own studies we've found this procedure to be as effective in stabilizing ectasia as it is keratoconus," notes Dr. Hersh. "However, ectasia patients tend to have less of a change in topography than keratoconus patients. This may be because the topographic irregularities in ectasia are less severe than in keratoconus, or because the topographic elevations tend to be more eccentric."

Avedro's KXL cross-linking system, currently approved to treat progressive keratoconus and ectasia.

Using the System

Dr. Hersh notes that the approved procedure is a standard epi-off protocol. "The Avedro system produces 365 µm ultraviolet light at 3 mW/cm^2, which is what we used in the clinical trial," he says. "It comes with two kinds of riboflavin. Photrexa Viscous is the standard riboflavin solution we use in cross-linking; it's used for initial riboflavin loading and during UV exposure. The other formulation is Photrexa, which is a hypotonic riboflavin without dextran, used to induce corneal swelling. Before starting the UV light, you want the pachymetry measurement to be 400 µm or more, because if the cornea is too thin, the riboflavin-UV interaction could potentially have a toxic effect on the endothelium. If the cornea isn't thick enough, you use the Photrexa to swell it before UV exposure.

"The first step is a 9-mm-diameter removal of the epithelium, done according to the surgeon's preference," he continues. "I delineate a 9-mm area with an optical zone marker and then use either a bird bath or a pledget of 20-percent ethyl alcohol to loosen the epithelium; then I remove it with a cellulose sponge and spatula. At that point you apply Photrexa Viscous every two minutes for a total of 30 minutes. Obviously, you have to have the speculum in for epithelium removal, but I like to take the speculum out while putting in the drops so the cornea doesn't dehydrate and become thinner. Then I measure the thickness using ultrasound pachymetry. If the cornea is over 400 µm, I proceed; if not, I apply the hypotonic Photrexa riboflavin every 10 seconds for two minutes, with the eye closed between drops. If the cornea has still not reached 400 µm, I again apply the hypotonic Photrexa riboflavin for further counts of two minutes.

"Typically, most patients who are under 400 µm will swell to 400 µm within one or two sessions of Photrexa, although you can continue beyond that," he notes. "I have not had any patients who were unable to swell adequately. The most important thing is to avoid selecting patients whose corneas are very thin at the outset. If a patient initially has a 280-µm cornea with the epithelium intact, he's not a candidate for cross-linking."

Dr. Hersh says you will almost always have good riboflavin uptake. "However, you want to confirm that you have stromal saturation at the slit lamp, especially when you're just starting to perform this procedure," he says. "Using the cobalt blue filter, you should see green spread homogeneously throughout the cornea. Also, you should see anterior chamber flare from the riboflavin. That's riboflavin that has made it into the anterior chamber, which denotes that you have full-thickness saturation.

"Once the cornea is at least 400 µm thick and is saturated with riboflavin, you have the patient look up at the KXL system's UV light unit and you center it on the x,y and z planes," he says. "The patient gazes at the fixation light for the next half hour. During that time you continue to give the riboflavin dextran solution every two minutes. Once that's completed, the procedure is done. Then we apply antibiotic, corticosteroid and a bandage contact lens. We check the patient on day one to make sure everything is OK, and on day four or five to make sure the epithelium has healed; then we remove the contact lens. We continue antibiotic drops for a week and taper the corticosteroid drops over the course of two or three weeks. This is essentially the same as the Dresden protocol, on which the clinical trial was based."

Who Gets Better Outcomes?

"In my practice we've done studies looking at which patients are better candidates," says Dr. Hersh. "We looked at three concerns. First, is stability the same for every patient? Second, who gets a better topographic result and who tends to fail the treatment and continue progressing? Third, which patients have a better chance of losing or gaining vision?

"The FDA clinical trial, which was placebo-controlled, showed that there was a significant difference in the change in the maximum keratometry as measured by topography—i.e., the height of the cone—between treated and untreated eyes," he continues. "At one year, patients who had progressive keratoconus by the criteria of the study improved their topography by 1.6 D, while as expected, untreated patients continued to worsen.

"We also found that there was a modest overall improvement in BCVA and UCVA in the treated eyes, about one Snellen line or so," he says. "In our own studies, unrelated to the FDA approval, we found that about 25 percent of corneas flattened by 2 D or more, and that patients who had keratometry of 55 D or more at the cone peak had a greater chance of being in this improvement group. However, both groups had an equivalent chance of remaining stable over time.

"With regard to correctable vision, most patients remained stable," he says. "However, about 20 percent—the patients with worse topography, i.e., 55 D or more—improved their correctable vision by two or more Snellen lines and were five times more likely to improve their topography. In terms of acuity, patients who were 20/40 or worse before treatment were about five times more likely to improve their vision by two or more lines than patients who were better than 20/40."

Managing Patient Expectations

Roy S. Rubinfeld, MD, MS, in private practice and a clinical associate professor at Georgetown University Medical Center, notes that surgeons need to set patient expectations regarding what cross-linking does and does not do and the timeline for the expected results. "Patients often think that any eye surgery is similar to either cataract surgery or LASIK, in which patients see markedly better the next day and have just one evening of scratchiness and irritation," he says. "Standard epi-off cross-linking is nothing like that. There is significant discomfort that generally lasts for up to a week or more, with markedly reduced vision during the first few weeks or even months.

"Patients also need to understand that cross-linking is not a cure-all for keratoconus," he continues. "The major objective of cross-linking is to stop the progression of a disease that is causing them to lose vision and potentially need corneal transplantation. Furthermore, the timeline for all of this is months and years."

Dr. Rubinfeld also points out that the course of recovery may not be smooth. "In several studies of standard epithelium-off cross-linking, vision has been seen to actually drop off for months postoperatively, and then start to return to where it was before," he says. "That makes it very easy for patients to become anxious, or to believe that it's not working or was a mistake. With epi-off cross-linking, patients need a great deal of handholding, discussion about expectations and reassurance."

Peter S. Hersh, MD, FACS, clinical professor and director of cornea and refractive surgery at the Institute of Ophthalmology and Visual Science, Rutgers-New Jersey Medical School, notes that this is especially important when the patient has very good vision before treatment. "If a patient is starting with 20/20 or 20/25 vision," he says, "the loss of a line because of epithelialization or corneal haze might be more noticeable to him."

—CK

Potential Complications

"This is a relatively straightforward procedure; there aren't many mistakes doctors can make," notes Doyle Stulting, MD, PhD, director of the Stulting Research Center at Woolfson Eye Institute in Atlanta, professor of ophthalmology, emeritus, at Emory University and adjunct professor of ophthalmology at the Moran Eye Center. "The risks involved with this procedure are not zero, but they're relatively small and the benefits are significant. Most of the complications that can occur are related to epithelial removal."

"Theo Seiler published a paper that lists many of the problems you could potentially run across," says Dr. Rubinfeld.[1] (That study, involving 117 eyes of 99 patients, reported that 2.9 percent of eyes had lost two or more Snellen lines at 12 months. No patients had a severe complication, although the authors acknowledge that such complications have been reported at meetings.) "Regrowth and healing are generally compromised in steeper corneas and corneas with ocular surface disease," he notes. "Scars, infections, haze and other problems can also occur. For that reason it's important to look for signs of dry eye, blepharitis and other conditions that can compromise the ocular surface.

"Dr. Seiler's paper also shows that the steeper the cornea, the more likely the patient is to have either a poor response to the treatment or an adverse event," he continues. "His study found that a preoperative maximum K-reading less than 58 D may reduce your failure rate, so if your patient has a very steep cone, that's a reason to be particularly attentive to any ocular surface issues and postoperative epithelial healing. He also found that restricting patient age to younger than 35 years may substantially reduce the complication rates, so older patients may also require extra postoperative follow-up. But ultimately it's important to remember that the safety profile of epi-off corneal cross-linking is markedly better than the safety profile of corneal transplantation."

Off-label Uses for CXL

Many uses for cross-linking that go far beyond the uses approved by the FDA are being explored outside the United States. In the meantime, some less-dramatic off-label uses may be of interest to U.S. surgeons:

• ***Non-progressing patients.*** "At first we reserved this procedure for patients who had progressive keratoconus, which is what the current approval is for," says Dr. Stulting. "We thought that people who were not going to progress wouldn't get any benefit. But we've sometimes seen a significant benefit in terms of improved vision in patients we thought wouldn't

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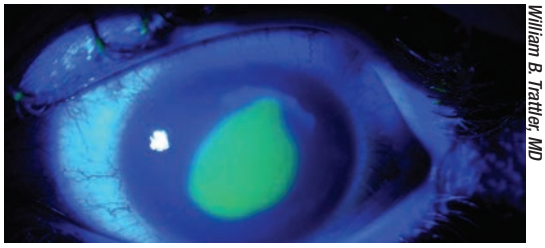
benefit from it. For example, doctors often assume that older patients with keratoconus are not likely to progress. However, we've seen 66-year-olds with significant progression over six months, and we've seen patients in their 50s whose uncorrected and corrected vision improved significantly after cross-linking."



William B. Trattler, MD

Cross-linking with epithelial removal can lead to complications such as delayed epithelial healing and an infiltrate (pictured above, postop day two).

Dr. Rubinfeld acknowledges that the risk/benefit ratio may be different if the patient's keratoconus isn't progressing. "The reality, however, is that keratoconus is an unpredictable disease," he points out. "Not treating is a bit like saying, 'Well, you have glaucoma and your pressure is high, but we think you might have a couple of years before you start really losing your sight so we're not going to treat you.' That wouldn't hold up in court, and when you put your head on the pillow at night, you wouldn't feel great about it.

"If the surgeon believes that this off-label use is in the patient's interest, he'll need to have a discussion with the patient under scope of practice," he adds. "The surgeon, of course, will be responsible for those choices."

• ***Younger patients.*** "Some of the people who need this the most are fairly young," says Dr. Rubinfeld. "It's understandable to want to treat them before they start losing their sight. We've treated patients as young as 8 years old in our study with excellent results."

"You want to do this procedure early on to decrease progression as soon as possible," adds Dr. Hersh. "And, just as in the treatment of macular degeneration and other diseases, probably the earlier, the better."

• ***Treating infectious keratitis.*** Dr. Rubinfeld notes that there have been some published studies on the use of cross-linking to treat infectious keratitis. "My personal experience with that, as well as our study group's experience, has not been very compelling," he says. "I would urge caution in considering the use of cross-linking in the setting of infectious keratitis."

Dr. Stulting agrees. "We don't have good evidence that it is superior to standard, routine treatment for infectious keratitis," he says.

• ***Improving vision.*** "Ultimately, a bigger and more satisfying objective is to improve vision in keratoconus patients, not just stop the progression of the disease," says Dr. Rubinfeld. "That's why outside the United States it's become common to perform cross-linking and topography-guided laser ablations together. Under institutional review board approval, we've done some of these cases. However, my personal experience, as well as that of some of my colleagues, is that this is a field in evolution. It seems to be more of an art than a science with currently available technologies. Also, adding PRK to cross-linking may cause the epithelial healing to be even slower and more critical."

Dr. Rubinfeld says that there's another, less invasive way to move in the same direction. "Since 2012, our group has been combining two non-invasive procedures on an investigational basis," he says. "We use conductive keratoplasty to reshape the cornea and then use our proprietary trans-epithelial cross-linking technique to lock in the effect. We now have two-year data demonstrating that this approach not only stops the progression but markedly improves both UCVA and BCVA. It's been extremely gratifying for the patients and surgeons."

• ***Leaving the epithelium on.*** Dr. Rubinfeld is one of a number of surgeons working on versions of the protocol that do not require removing the epithelium. "The effective epi-on version of cross-linking has been in development since 2010," he says. "Dr. Stulting, in the prestigious Binkhorst Lecture at the 2016 American Society of Cataract and Refractive Surgery annual meeting, described the first long-term data. It showed that this proprietary, patent-pending treatment is as good as or better than the Dresden protocol, while markedly reducing the risk, discomfort and recovery time that would otherwise be related to removing the epithelium. This is clearly the next generation of cross-linking."

A. John Kanellopoulos, MD, medical director of the Laservision.gr Clinical and Research Eye Institute in Athens, Greece, and clinical professor of ophthalmology at NYU Medical School in New York, has been a pioneer in investigating alternative protocols and uses for corneal cross-linking. "Over the past 15 years we've introduced and practiced—internationally—fluences of 6, 10 and 30 mW/cm^2," he says. "We've also used techniques such as combining cross-linking with a partial topography-guided PRK, known as the Athens Protocol; we've used 10 mW/cm^2 for 10 minutes with *in-situ* placement of the riboflavin in a femtosecond-laser-created corneal pocket; and we've used 30 mW/cm^2 for 90 minutes as an adjunct to routine LASIK in high-risk myopic and all hyperopic cases. The latter approach was recently reported to increase biomechanical strength in the underlying LASIK stroma by 120 percent, *ex-vivo*."

Despite all the promising uses for cross-linking that go beyond the FDA approval, Dr. Kanellopoulos believes it's prudent for American physicians to initially adhere to the approved pro-

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[1] Epitropoulos, Alice T, Donnenfeld, Eric D., et al., Effect of Oral Re-esterified Omega-3 Nutritional Supplementation on Dry Eyes. Cornea 2016;0:1-7

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tocol. "The epi-off procedure is not without potential complications such as infection, melts, inflammation and potential scarring," he says. "I think clinicians should become proficient with the standard technique before attempting to engage in off-label applications. All of those techniques will probably receive FDA approval at some point. It would probably be wise to wait until then to use them in the United States."

Strategies for Success

Surgeons offer these pearls to help cross-linking novices get good results and avoid complications:

• ***Make sure that referring doctors don't think this is a refractive procedure.*** "Referring doctors who are not well-acquainted with the procedure may contribute to patients' incorrect expectations," notes Dr. Hersh. "A few cross-linking patients may see better, but the purpose of cross-linking is stabilization of the progression of keratoconus, not giving the patient better vision."

• ***If you diagnose a patient with keratoconus, refer the patient for cross-linking right away.*** Dr. Stulting says new patients with keratoconus are referred to him every week, but many doctors wait until the patient is on the verge of needing a transplant before making the referral. "Even after educating our referring doctors that referral is appropriate when someone is first diagnosed, I still get patients sent to me as a last resort when they can no longer wear a contact lens," he says. "The referring doctors seem to think that corneal collagen cross-linking will somehow keep the patient from needing a graft, but that's not the case for advanced disease.

"I see many keratoconus patients who are in their teens," he continues. "I tell the parents about cross-linking and they say, 'You mean you have a treatment that will keep our child's vision from getting worse? Why didn't my doctor tell us about this three years ago when my child's vision was much better?' More and more, I'm having trouble answering that question. Now that the technology is approved, it's going to be impossible to explain a late referral. I think it's just a matter of time before litigation and established standard of care forces the adoption of topography as a part of normal childhood eye examinations. It certainly should be done for patients who are myopic, astigmatic or have corrected visual acuity less than 20/20."

• ***When starting out, choose corneas that are at least 350 µm thick before treatment.*** "You don't want the cornea to be overly thin, because you won't be able to swell it to 400 µm," says Dr. Hersh. "In the clinical trials, we included patients down to 300 µm and used the swelling technique to get them to 400 µm. But in my own practice, I've found that it becomes difficult to reach 400 µm when the cornea starts below 350 µm."

• ***Evaluate postoperative epithelial healing at the slit lamp early on.*** "Epithelial irregularity can diminish vision," Dr. Hersh points out. "If you see an indication that the healing is irregular, be sure to address conditions such as dry eye and blepharitis aggressively."

• ***If you see delayed epithelial closure postoperatively, consider removing the bandage contact lens.*** "Once treated with cross-linking, patients need to be followed fairly closely until the epithelial defect closes, which typically occurs during the first week," says Dr. Stulting. "We learned early on that if we see delayed epithelial closure in these patients, particularly with persistent epithelial defects over the apex of the cone, we need to remove the contact lens, even though the epithelium hasn't closed yet. The contact lens itself can interfere with epithelial closure."

• ***Don't let the patient resume contact lens wear until the ocular surface is completely healed.*** "The key to resuming contacts after cross-linking is ensuring that the ocular surface is completely healed," says Dr. Hersh. "It should have regained its preoperative smoothness and integrity to avoid renewed injury or infection. We typically resume contact lens wear at the one-month follow-up."

• ***Expect to see some corneal haze at the slit lamp for the first few months in some patients.*** "In our own clinical trial most cross-linking patients had a course of corneal haze that dissipated back to baseline by 12 months," notes Dr. Hersh. "It typically doesn't trouble the patient, but you can see it at the slit lamp. It begins as a generalized haze, like a dusting of the cornea, and evolves to the demarcation line, which we believe indicates the depth of the cross-linking, typically 250 to 300 µm deep. Nothing needs to be done to address the haze, unless it's unusual; just provide general care for the ocular surface."

What's Next?

Although American surgeons are excited about finally having access to cross-linking, there are mixed feelings about still being behind the rest of the world, given the limitations of the approval.

"The procedure that's been approved in this country is almost a decade and a half old," notes Dr. Stulting. "Many improvements to the procedure have been proposed, and some have been found to be effective, but because of the delay in FDA approval we aren't able to take advantage of them in this country. I'm afraid that alternate versions of the procedure will not be approved any time soon. Cross-linking has orphan designation, so Avedro is protected from competition for seven years, and there's little motivation for them to invest millions of dollars in obtaining approval for an

advanced technique before the approved one becomes widely utilized."

"The FDA-approved system from Avedro is a great device," says Dr. Kanellopoulos. "We've used it in Europe since 2010. However, it's unfortunate that higher fluences of 6, 9, 18 and 30 mW/cm^2 are not yet available; that would widen the possible techniques and indications. The worst thing, in my opinion, is the obligatory use of adjunct dextran-diluted riboflavin, because it causes significant dehydration and thinning of the tissue during soaking. Most available solutions internationally are now saline-based. We switched to saline back in 2004."

Despite its limitations, Dr. Stulting says he still believes the approved procedure is an important tool for American surgeons to have. "There's good data from Oslo, Norway, showing the value of the procedure," he says. "At Oslo University Hospital, cross-linking was implemented almost a decade ago. They saw a 53-percent decrease in their incidence of corneal transplantation for keratoconus over a seven-year period. In the United States, the rate of corneal transplantation increased 19 percent over the same time period. The approved procedure may not be the best procedure, but it's certainly better than nothing."

"Research is going on that will make this procedure safer, better, more comfortable, less invasive and more predictable," adds Dr. Rubinfeld. "There's plenty of reason for optimism." REVIEW

Dr. Hersh is a consultant for Avedro. Dr. Rubinfeld has ownership equity in CXL Ophthalmics and is managing member and president of CXLUSA. Dr. Kanellopoulos is a consultant for Avedro and Alcon. Dr. Stulting has no financial interest in any product mentioned.

1. Koller T, Mrochen M, Seiler T. Complication and failure rates after corneal crosslinking. J Cataract Refract Surg 2009;35:1358–1362.

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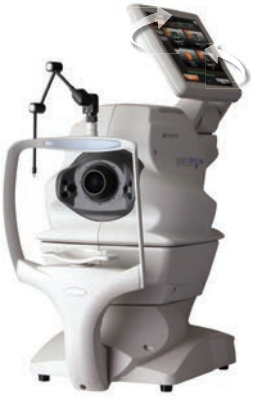

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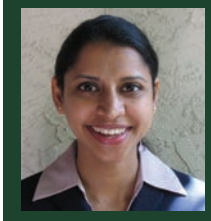
Filtering Surgery: Optimizing Outcomes




Sunita Radhakrishnan, MD, and Andrew G. Iwach, MD
San Francisco

Expert tips for this time-tested glaucoma procedure.

As much as glaucoma surgeons love to hate filtering surgery, trabeculectomy continues to be an important component of our surgical armamentarium, especially for patients with advanced optic nerve damage. Trabeculectomy creates a pathway for aqueous to drain from the anterior chamber to the subconjunctival space where bleb formation occurs. Short-term success of trabeculectomy surgery is mainly dependent on intraoperative technique and postoperative care, whereas longer-term success depends on the patient's healing response, which varies widely between individuals. In this article, we present some of our considerations in filtering surgery that can help you increase your chances of success.

PREOPERATIVE CONSIDERATIONS

As with any surgery, patient selection and timing is key. It's important to be mindful that we're treating the patient, not just the eye. Factors to consider beyond intraocular pressure and optic nerve status include patient age, general health, life expectancy, lifestyle and family history. A filtering procedure that's successful from the surgeon's perspective may, in fact, diminish a patient's quality of life due to long-term bleb-related complications. Therefore, it's important to consider other IOP-lowering procedures before making the decision to proceed with filtering surgery.

Trabeculectomy requires frequent postoperative visits and the patient must be able and willing to keep these appointments. It's also important to assess the risk of bleb infection in the context of the patient's lifestyle. For example, a person who often travels to remote areas without access to medical care, or one who engages in water-based sports as a hobby or for a living, isn't a good candidate for filtering surgery.

Carefully assess the ocular history, paying special attention to factors that may increase the risk for scarring, such as multiple prior surgeries and uncontrolled uveitis. You should also evaluate the factors that could increase the risk of complications. For example, patients with high myopia and pigment dispersion are at higher risk for hypotony maculopathy, whereas patients with angle closure disease and high hyperopia are at risk for malignant glaucoma after filtering surgery. Contact lens wearers may not

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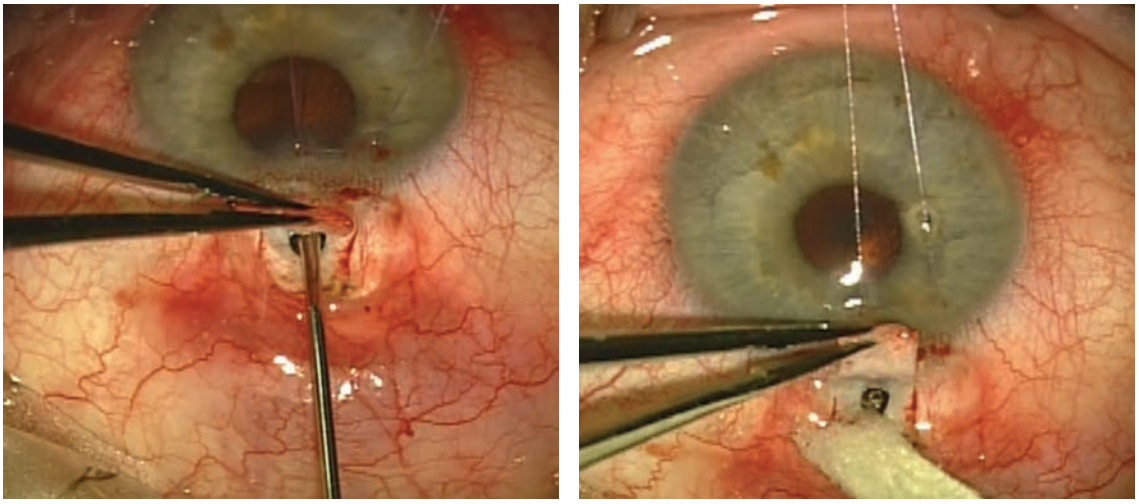

Insertion of the Ex-PRESS shunt under a partial thickness scleral flap.

be able to continue wearing lenses after filtering surgery and you should discuss this possibility with them beforehand. Finally, a history of a bad outcome after filtration surgery in the fellow eye should be taken seriously.

A careful preoperative slit lamp examination is a must. Specifically, assess the superior conjunctiva for mobility—this can be easily done by having the patient look down and then moving the eyelid over the superior conjunctiva. It's also helpful to locate vascular landmarks in the superior conjunctiva that you can use later to identify the scleral flap site intraoperatively.

INTRAOPERATIVE CONSIDERATIONS

We typically perform modified trabeculectomy with an Ex-PRESS shunt (the P50 model) because the visual recovery is quicker compared to standard trabeculectomy.[1] This is important for these patients because they don't have visual symptoms before surgery, but the surgery ends up inducing some temporary visual distortion. So, the quicker they can recover their vision, the more acceptable the surgery is to them. Also, using the shunt obviates the need for a sclerectomy and an iridectomy.

Important aspects of surgery include:

• ***Adequate exposure.*** We use a Lieberman eyelid speculum and a superior corneal traction suture to provide adequate exposure of the superior quadrant. While passing the traction suture, take care to avoid corneal perforation, which will result in aqueous leak and low IOP, a situation that's not ideal for scleral flap dissection. If inadvertent corneal perforation does occur, place viscoelastic in the AC, which will allow the case to proceed in the usual fashion.

• ***Conjunctival flap and closure.*** The conjunctival flap can be limbus- or fornix-based, with the latter being our preferred approach. Maintaining conjunctival integrity is critical for the success of filtration surgery, and therefore this tissue should be handled with great care, especially in eyes with thin or scarred conjunctiva in which buttonholes can easily form. Conjunctival manipulation should be gentle and minimal; when possible, grasp subconjunctival Tenon's tissue rather than the conjunctival edge. A watertight conjunctival closure is critical for the formation of an elevated bleb, and you can ensure this by inflating the anterior chamber with balanced salt solution and confirming that there is no aqueous leak at the end of surgery.

• ***Scleral flap and closure.*** We use a 3x3-mm square, partial thickness scleral flap, typically closed with two 10-0 nylon sutures. During scleral flap dissection, care should be taken to maintain adequate flap thickness in order to cover the Ex-PRESS shunt, as well as an adequate scleral bed on which the device can rest.

• ***Mitomycin-C application.*** There are many ways to apply mitomycin-C during filtering surgery, but the main goal is a diffuse distribution as posteriorly as possible in order to minimize the formation of localized, cystic and avascular blebs. We perform a conjunctival snip incision at the limbus as the first step after placement of the corneal stay suture. We then use a cannula to instill 0.1 ml of 0.2 mg/ml mitomycin-C in the subconjunctival space and then

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use a Weck-Cel sponge to distribute the mitomycin-C diffusely. We create the conjunctival flap at the end of this step, and use BSS to irrigate the subconjunctival space.

POSTOPERATIVE CONSIDERATIONS

We often tell patients that half the work in filtering surgery is in the operating room performing the procedure and the other half is in the clinic with postoperative care. The goals during the postoperative follow-up period are monitoring for complications and identifying factors that may jeopardize long-term bleb function and then intervening appropriately. For example, if the IOP is high two weeks after surgery due to tight flap sutures, then the appropriate intervention is not to restart IOP-lowering medications but to lyse (or remove) one or more flap sutures so that a bleb can form (or enlarge).

Although postoperative care for filtering surgery is more intense than for other surgeries, most early complications are transient, and serious complications such as choroidal hemorrhage are fortunately rare. Following are some common postop situations and our response to them:

• ***Low IOP.*** If the IOP is too low after surgery, the first step is to identify the cause of the hypotony. The most common causes are overfiltration and wound leak. A careful slit lamp examination after instillation of fluorescein drops can identify most wound leaks; however, sometimes a fluorescein strip may be required to pinpoint the exact site of aqueous leak. Hypotony after filtering surgery is usually transient and most cases can be managed conservatively. The decision to intervene depends on several factors, such as the presence and extent of wound leak, bleb height, AC depth, presence and extent of choroidals, and the status of the macula. For example, a patient with a small wound leak in the presence of an elevated bleb and peripheral iridocorneal touch can be managed conservatively, whereas a patient with hypotony and a flat AC usually requires urgent intervention in order to prevent endothelial damage.

In many cases, the bleb can be revived with the use of interventions such as aggressive steroids, 5-FU injections, timely suturelysis, digital massage and needling.

• ***High IOP.*** If the IOP is too high after filtering surgery, the first step, again, is to identify the cause. The most common causes are tight scleral flap sutures and retained viscoelastic. Other possibilities include ciliary block, suprachoroidal hemorrhage, early bleb encapsulation, and sclerostomy or Ex-PRESS lumen plugged by blood, iris or vitreous. The decision to intervene depends on factors such as the level of IOP elevation, the optic nerve status and the risk of hypotony. Tight flap sutures are effectively addressed by laser suturelysis, but this is best avoided in the first few days after surgery, if possible. Digital massage to separate the scleral flap edges allows aqueous outflow and usually lowers IOP until sutures can be lysed.

• ***IOP is acceptable.*** If the IOP is on target, a watchful eye must still be maintained on the bleb and surrounding conjunctiva to detect signs of early bleb scarring. Interventions in this situation have a better chance of succeeding when performed as early as possible, while the bleb is scarring, as opposed to when it has completely scarred. In many cases, the bleb can be revived with the use of interventions such as aggressive topical steroids, 5-fluorouracil injections, timely suturelysis, digital massage and bleb needling.

While the recent development of blebless surgeries is welcome and exciting, in some of our patients there's just no substitute for filtering surgery. Therefore, it's important for a glaucoma surgeon to be able to perform this procedure well and expertly manage the postoperative course and potential complications in order to minimize risk and maximize outcomes. REVIEW

Dr. Radhakrishnan is an associate at the Glaucoma Center of San Francisco and research director of the Glaucoma Research and Education Group in San Francisco. She has no financial interest in the products discussed. Dr. Iwach is the executive director of the Glaucoma Center of San Francisco, an associate clinical professor of ophthalmology at the University of California, San Francisco and a faculty instructor at the California Pacific Medical Center Department of Ophthalmology. He is a consultant to Bausch + Lomb, Alcon, Allergan and AcuMEMS.

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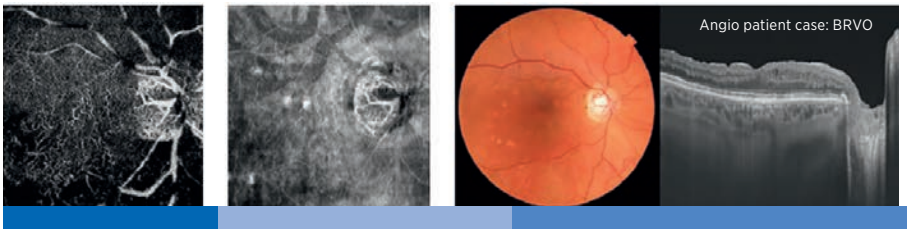

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In Search of the Best AMD Therapy

A look at the ways researchers and clinicians are trying to overcome the shortcomings of current therapies.

Ashleigh L. Levison, MD, Mark R. Barakat, MD, and Pravin U. Dugel, MD, Phoenix

An old adage that goes, "Good, better, best—never let it rest—until your good is better and your better is best," could very well apply to ophthalmologists' battle with exudative age-related macular degeneration. A little over a decade ago, the treatment for this disease underwent a revolutionary change with the development and use of anti-vascular endothelial growth factor medications. This certainly made our treatments better; prior to anti-VEGF therapy, patients with exudative AMD typically experienced significant, irreversible vision loss over time. Thanks to these new drugs, we no longer had to simply attempt to slow inevitable vision loss, but instead could maintain vision or even improve it in many patients. However, clinicians and researchers don't want to settle for treatments that are just better, because current therapies still pose significant obstacles in the treatment of exudative AMD, including the treatment burden and progressive vision loss in some patients. Instead, we want the best.

In this article, we chronicle ophthalmology's efforts to overcome these problems and find even better treatments for exudative AMD.

Current Treatment

Bevacizumab, ranibizumab and aflibercept have provided invaluable visual benefit for patients with exudative AMD. In 2006, the ANCHOR and MARINA trials showed that treatment with these agents could provide visual benefit in such patients[1,2] and drastically changed physicians' and patients' expectations regarding outcomes.

Unfortunately we still have the issue of a costly, ongoing treatment that puts a significant burden on both the patient and the physician. Trials have looked at monthly, PRN, quarterly and, more recently, treat-and-extend protocols for wet AMD, and found that monthly treatment appears to optimize visual outcomes. A study published in 2014, however, reported that patients with exudative AMD receive significantly fewer injections than clinical trials recommend.[3] Unfortunately, less-frequent treatment can lead to poorer visual acuity outcomes. The SEVEN-UP study showed us that, seven years after ranibizumab therapy, in the ANCHOR and MARINA trials, one-third of patients had poor visual results. It's apparent that despite years of therapy, patients are still at significant risk of visual decline and require continued treatment.[4]

Several approaches are being taken to address the issues of continued vision loss in some patients and the treatment burden of frequent injections. These include finding better anti-VEGF agents, improving anti-VEGF delivery and developing drugs with targets other than VEGF.

Novel Anti-VEGF Agents

One approach to improving treatment of exudative AMD includes development of new anti-VEGF agents. Some of these agents may be able to extend treatment duration, lessening the burden of frequent injections.

• ***Brolucizumab.*** Formerly known as RTH-258 and ESBA-1008, brolucizumab is being developed by Alcon and Novartis. It is a humanized, single-chain antibody fragment that inhibits VEGF, and is able to bind to all isoforms of VEGF-A. Brolucizumab is significantly smaller than bevacizumab, ranibizumab and aflibercept, which may allow for better tissue penetration, more active drug reaching

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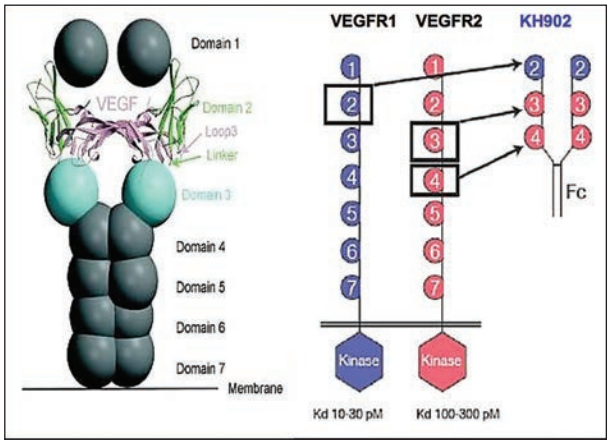
the target tissue and possibly less systemic exposure. Animal studies of brolucizumab and ranibizumab have shown more of the former entering the retina, as well as less systemic drug exposure.[5,6]

Early human trials suggested that a single injection of brolucizumab may have more potent and longer-lasting effects than a single dose of ranibizumab. The drug showed a reduction in central subfield thickness on OCT comparable to ranibizumab, and there was also a greater mean gain in best-corrected visual acuity compared to ranibizumab, with a trend towards a longer duration of effect.[5,6] A subsequent trial showed results similar to aflibercept.[7] A Phase III trial is currently ongoing.

• ***Abicipar.*** Formerly known as AGN-150998A, abicipar is a DARPin (Designed Ankyrin Repeat Proteins) agent being developed by Allergan. A DARPin is a new class of binding molecule that has a smaller molecular weight and higher target binding affinity than antibodies or antibody fragments.[8] Because this agent has a small molecular size and repeat structure, its affinity for VEGF is high.

The Phase II REACH study was designed to analyze abicipar in wet AMD.[9,10] In the Phase IIb study, abicipar provided equal or greater vision gains, with the potential for fewer injections, compared to ranibizumab. Phase IIb data suggest that abicipar may be injected every 12 weeks after loading doses. Since the initial results were promising, the Phase III clinical trial started enrollment in July 2015.[11]

• ***Conbercept.*** This is a fusion protein of key domains from human VEGF receptors 1 and 2 with human IgG Fc that's approved in China for the treatment of AMD.[12] It has a high affinity for all VEGF-A/B isoforms as well as placental growth factor. A trial comparing two doses of conbercept showed positive visual acuity outcomes for exudative AMD.[13]



Conbercept, approved in China for AMD treatment, is a fusion molecule combining IgG Fc and VEGF receptors.

• ***OPT-302.*** Opthea's OPT-302 is a vascular endothelial growth factor receptor 3 (VEGFR-3), or "Trap," molecule. This is the first anti-VEGF agent targeted towards VEGF-C and -D. OPT-302 is currently in Phase I dose-escalation trials both by itself and as an agent used in combination with ranibizumab. Enrollment is complete.[14]

Gene Therapy to Impact VEGF

Another method to improve drug therapy for patients with neovascular AMD is to develop a better anti-VEGF delivery system. One such avenue is gene therapy.

Gene therapy involves introducing genetic material into cells in order to compensate for abnormal or absent genes. The goal of gene therapy is to allow for the production of a beneficial protein in cells that otherwise lack that protein. In gene therapy, the gene carrier, called a vector, is genetically engineered to deliver the gene into cells. Currently, the most popular vector is the adeno-associated virus, as viruses, by their very nature, are able to deliver genetic material into another genome. Researchers hope that gene therapy could be used to provide long-term delivery of anti-VEGF therapy to an eye with exudative AMD.

Drugmakers Genzyme and Avalanche are attempting to utilize adenovirus's innate transfection capabilities to provide long-lasting gene therapy via intravitreal or subretinal administration, respectively. In Genzyme's approach, it adds the genetic sequence for sFLT01, a tyrosine kinase inhibitor, to the genetic sequence of the adenovirus producing AAV2-sFLT01. AAV2-sFLT01 is injected intravitreally. As an anti-VEGF agent, sFLT01 blocks the VEGF cascade more distal to where the current anti-VEGF agents block it.[15]

In animal studies, the intravitreal injection of AAV2-sFLT01 led to sFLT01 expression in the anterior chamber fluid of the animals. In addition it was also associated with decreased growth of laser-induced choroidal neovascularization.[16] A Phase I, open-label, multicenter, dose-escalating safety and tolerability study of a single intravitreal injection of AAV2-sFLT01 in patients with neovascular AMD is still ongoing, and has completed enrollment.[17]

Besides injecting the adenovirus intravitreally, the same modified virus is also being administered subretinally in the form of Avalanche Biotechnologies' AVA-101, a route of administration that some feel may be more effective than an intravitreal injection and lead to fewer side effects. After a vitrectomy, a small needle is used to inject the virus vector subretinally, and animal studies have shown this therapy to be without safety issues or an increase in geographic atrophy.[18,19] The first human trials did show a reduction in central retinal thickness similar to that seen with intravitreal anti-VEGF agents. In addition, a significant number of patients didn't need continued anti-VEGF therapy for a year follow-

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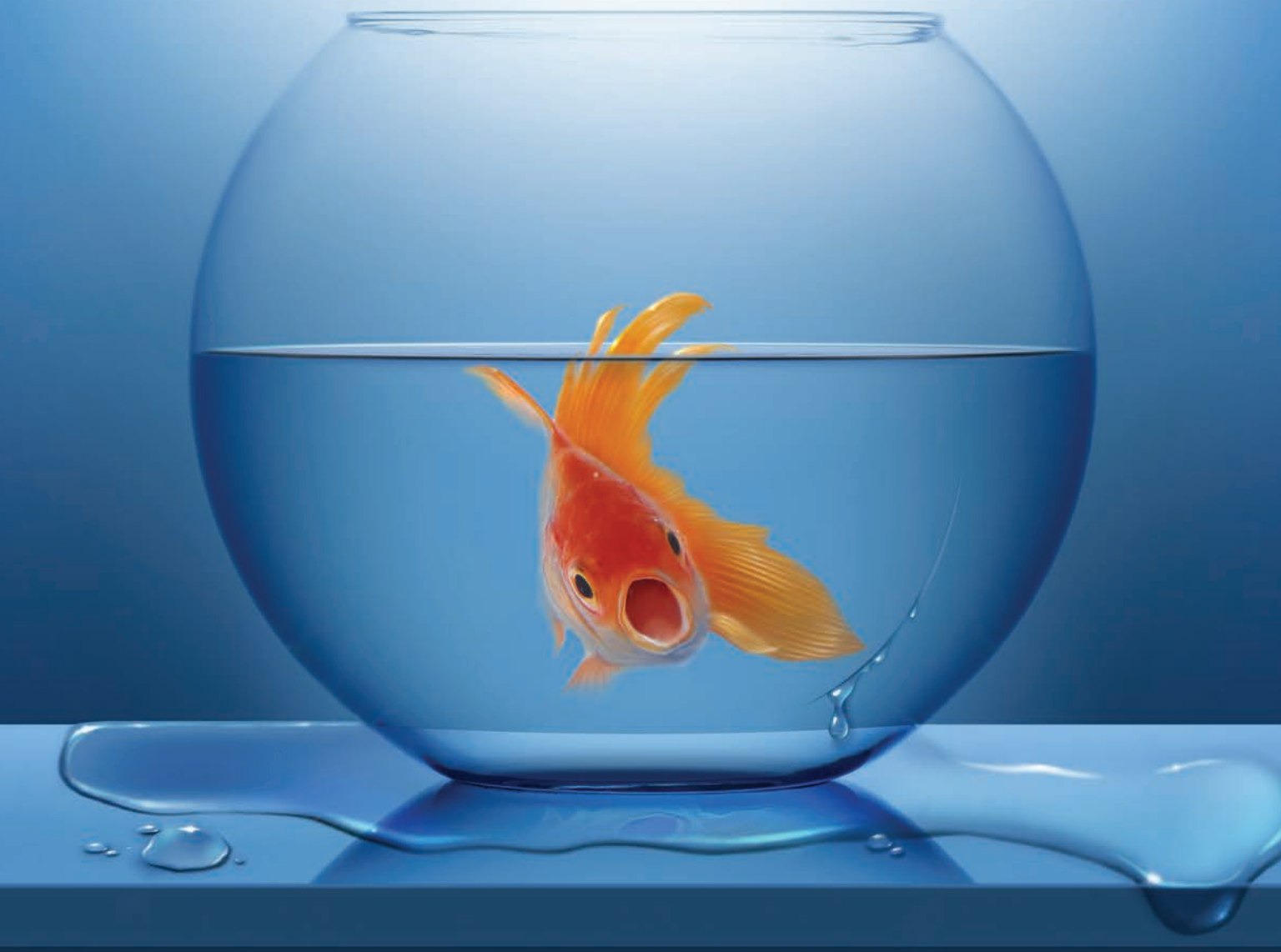

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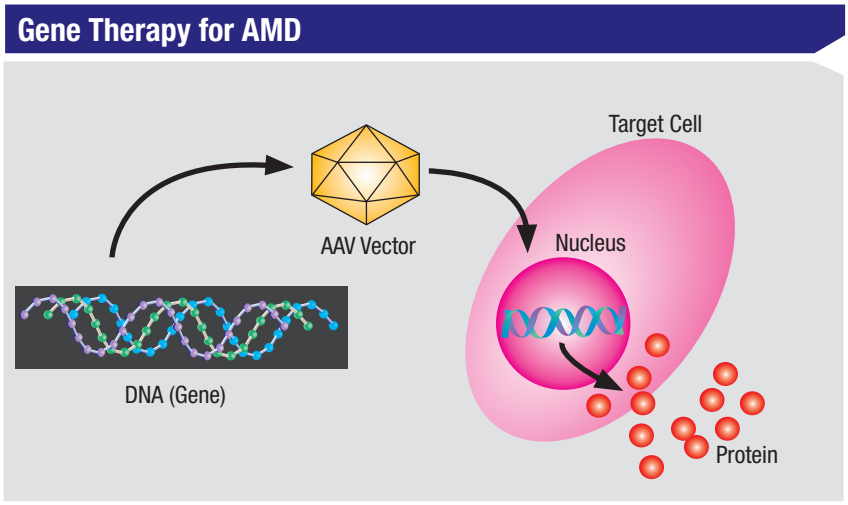

In gene therapy approaches to AMD treatment, adeno-associated virus can be programmed to introduce therapeutic DNA sequences into target cells.

ing injection.[20] A 12-month, Phase IIa trial had a +11.5-letter difference between treatment and control, however the control had a loss of -9.3 letters. The treatment group had a higher likelihood of stability of vision with two or fewer rescue treatments in the gene therapy group (42.9 percent) versus the control group (9.1 percent).[21]

Other Forms of Delivery

Another method of providing longer duration of drug delivery with the goal of decreasing treatment burden would be to implant a reservoir in the eye that releases medication over an extended period of time. One study, the LADDER trial sponsored by Genentech, is designed to compare a refillable ranibizumab drug port delivery system to monthly ranibizumab injections.[22] It's currently recruiting patients.

Identifying Additional Targets

Developing drugs aimed at therapeutic targets other than VEGF offers another opportunity for improving treatment of exudative AMD. Fortunately, in addition to VEGF, there are many other compounds involved in angiogenesis. Targeting these other compounds may improve treatment of choroidal neovascularization by attacking CNV from different angles.

• ***Platelet-derived growth factor.*** This is a growth factor whose production is induced by hypoxia, and it's also been implicated in angiogenesis. Overproduction of PDGF by endothelial cells increases pericyte content of vessels, leading to the formation of mature vascular networks.[23] Disruption of the VEGF pathways with anti-VEGF agents can induce upregulation of PDGF, which in turn allows pericytes to make vascular networks more mature and, therefore, more resistant to further anti-VEGF treatment.[24-26] Additionally, overactivity of PDGF has been associated with the development of fibrosis.[27] In oncology literature, anti-PDGF agents disrupt pericyte-endothelial communication, sensitizing the neovascular tissue to anti-VEGF agents.[28] Theoretically then, an anti-PDGF therapeutic agent could remove the pericyte protective network from the neovascular lesion, exposing the underlying endothelial cells to the anti-VEGF agent. This approach may allow for neovascular regression instead of the current method of disease maintenance. Multiple companies are developing anti-PDGF agents, including Ophthotech, Santen, Allergan and Regeneron.

Fovista is a pegylated aptamer developed by Ophthotech.[29,30] Phase IIb data has shown that Fovista, when combined with ranibizumab, improves visual outcomes compared to ranibizumab monotherapy. When comparing 0.3 mg to 1.5 mg of Fovista combined with ranibizumab versus ranibizumab alone, at the higher Fovista dose, the combination therapy improved visual acuity by 62 percent over baseline. Patients were 71 percent (0.3-mg dose) and 190 percent (1.5-mg dose) more likely to experience greater than four and five lines of visual improvement with Fovista. Fovista combined with ranibizumab resulted in a 119 percent relative benefit towards achieving a visual acuity of 20/25 or better. In addition to improvement in intraretinal, subretinal and sub-RPE fluid, there was reduction in subretinal hyperreflective material with combination therapy. Researchers are hoping that the antifibrotic nature of Fovista will lead to reduced fibrosis and vision loss in patients treated with combination therapy vs. monotherapy.[31-33]

The phase III studies are currently in progress for Fovista in combination with ranibizumab for the treatment of exudative AMD. The hope is that the inhibition of both VEGF and PDGF may result in a reduction of exudation from CNV as well a reduction of the neovascular complex itself. The antifibrotic effect of anti-PDGF agents may also result in less scarring in patients and therefore may have a significant positive impact on visual acuity.

• ***DE-120.*** Santen's DE-120 is a molecule that acts as a dual-kinase receptor inhibitor and is able to block both VEGF and PDGF.[34] The Phase I/II study is an open-label, dose-escalating, sequential-cohort study of DE-120 injectable solution administered in patients with late-stage exudative AMD. The study is ongoing but is no longer recruiting new patients.[34]

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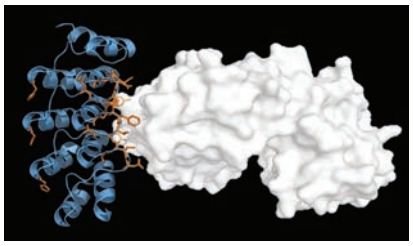

Designed ankyrin repeat proteins (DARPins) like those used in abicipar have a small molecular size with a repeat structure that can be created for a specific duration.

• ***OHR-102 (squalamine).*** What makes this agent from Ohr Pharmaceutical unique is that it's topically administered, which would offer a less-invasive way to treat exudative AMD.

Squalamine is an amino sterol developed from dogfish shark cartilage. It's taken up by endothelial cells and is a potent anti-angiogenic molecule that binds calmodulin intracellularly, preventing receptor activation and causing broad inhibition of multiple factors including VEGF, PDGF and basic fibroblast growth factor.[10] Phase II trials of topical squalamine combined with intravitreal ranibizumab vs. intravitreal ranibizumab alone showed visual acuity improvements and reductions in retinal thickness on OCT.[10] Patients in the phase II IMPACT study of squalamine who had classic-CNV-containing lesions experienced an acuity improvement of +11 letters with squalamine in combination with ranibizumab versus +5 letters with ranibizumab alone. Three-line gains in visual acuity were present in 44 percent of these patients in the combination treatment arm compared to 29 percent in the ranibizumab monotherapy arm.[35] A Phase III trial is planned.

• ***Pazopanib, Regorafenib and PAN-90806.*** Pazopanib is another medication administered topically, and is being developed by GlaxoSmith-Kline. It's a tyrosine kinase inhibitor that inhibits VEGF receptors and the PDGF pathway.

Regorafenib (Bayer AG) is another tyrosine kinase inhibitor that inhibits VEGF receptors, TIE2 and other tyrosine kinase receptors. Finally, PAN-90806 (PanOptica) is a topical drop that acts as a selective VEGF inhibitor.

While our current approach to treating AMD has had a positive impact on visual acuity, it has limitations that must be addressed: Patients still can experience vision loss and there remains a significant treatment burden. Help appears to be on the way, however. Longer-acting drugs, new methods of sustained delivery and novel compounds that target other agents involved in angiogenesis besides VEGF will help improve outcomes. REVIEW

Drs. Levison and Barakat practice with Retinal Consultants of Arizona in Phoenix. Dr. Dugel is managing partner of Retinal Consultants of Arizona, clinical professor at USC Roski Eye Institute, and executive director of the Phoenix Eye Institute.

Dr. Levison has no pertinent financial interests. Dr. Barakat reports financial interest in Ohr as a minor investor. Dr. Dugel reports financial interests as a consultant to Alcon, Allergan, Acucela, Avalanche, Genentech, Novartis and Regeneron, as well as an investor/consultant in Ophthotech. Contact Dr. Levison at 1101 E Missouri Ave, Phoenix, AZ 85014 or ALevison@retinalconsultantsaz.com.

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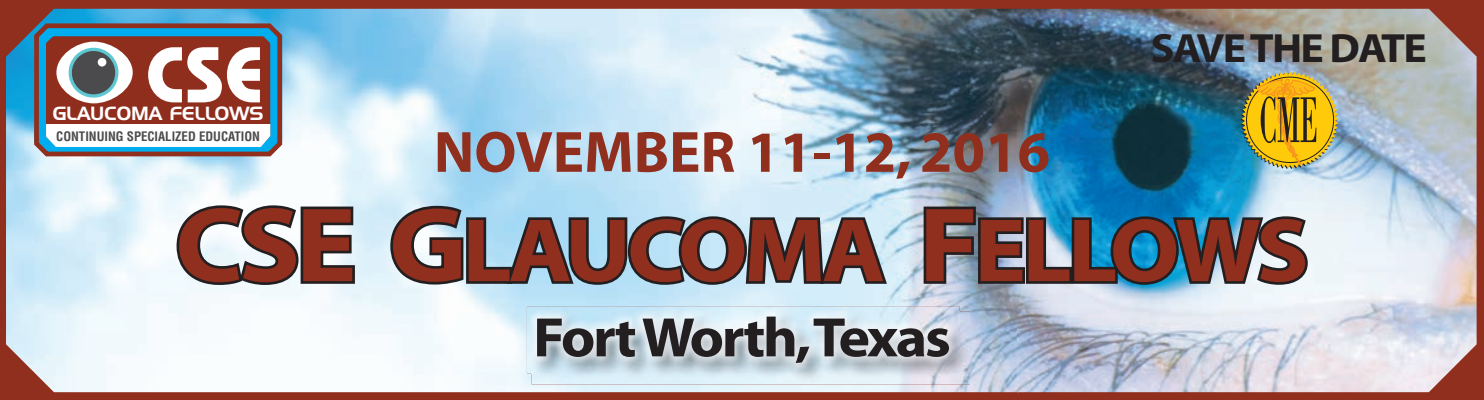

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Objective: Symptomatic Assessment Strategies

Symptom scores can be helpful when treating dry eye, but constructing good questionnaires can be a challenge.

Mark B. Abelson, MD, CM, FRCSC, FARVO, David A. Hollander, MD, MBA, and James McLaughlin, PhD
Andover, Mass.

Last month we explored the application and interpretation of various measures for the signs of ocular disease: the scales we use to rate redness, lid swelling or corneal staining. An analogous methodology is also applied to quantify symptoms of ocular disease such as pain, itch or other forms of discomfort. Because we rely on our patients to report the intensity, character and progression of disease symptoms, it's crucial that we take great care in how we pose that deceptively simple question, "How are you feeling?"

This month, we delve into the nuances of symptomatic assessment. We'll discuss both the importance of establishing an approach that allows us to best employ the information our patients provide for diagnosis and treatment assessment, and the role this information plays in developing new therapies. Issues surrounding the optimization of symptom evaluation are critical in developing dry-eye treatments, and they're also of interest in therapies for allergy, ocular inflammation and postoperative ocular pain.

Ask Better Questions

Dry-eye disease is an ocular condition defined by patients' symptoms: The name of the condition is itself a symptomatic description. We're aware that the central confounder in DED is that symptoms and signs are often discordant, and patients often report significant symptomatic disease with little or no ocular surface staining or tear-film dysfunction.[1-2] This has led to a focus on clinical refinement of the tools we use to quantify symptomatic DED. There are dozens of variations of the questionnaires used to provide an objective measure of dry-eye symptoms, and the particular value of each is a function of its specific use; some are designed for epidemiologic studies[3-7] while others are constructed for use as clinical diagnostic tools. Often the diagnostic questionnaires are also employed in therapeutic trials, but these can leave room for improvement in that specific role.

Dry-eye questionnaires such as the National Eye Institute visual function questionnaire, the Women's Health Study questionnaire and the Dry Eye Epidemiology Project's questionnaire are tools designed to assess the scope of ocular disease, that were later used to evaluate symptoms. In general, these were limited by either having too many questions or too few dry-eye related queries. Another group of these symptomatic measures, including the Ocular Surface Disease Index, the McMonnies Dry Eye Index and the Dry Eye Questionnaire, focused more on the key issues of DED symptom characteristics, symptom severity and disease impact. The McMonnies and the OSDI were characterized in greater detail and validated for use in clinical trials.

What makes a good questionnaire? The goal is to allow the patient to provide accurate information about his symptoms in a way that precisely and reproducibly reflects the disease state. Most questions are formatted so that the patient responds with a scalar numeric; for example, a question from the OSDI asks:

"Have you experienced the following in the last week: painful or sore eyes (4) all of the time (3) most of the time (2) half of the time (1) some of the time (0) none of the time."

Structuring questions in this way, where higher numerical scores are

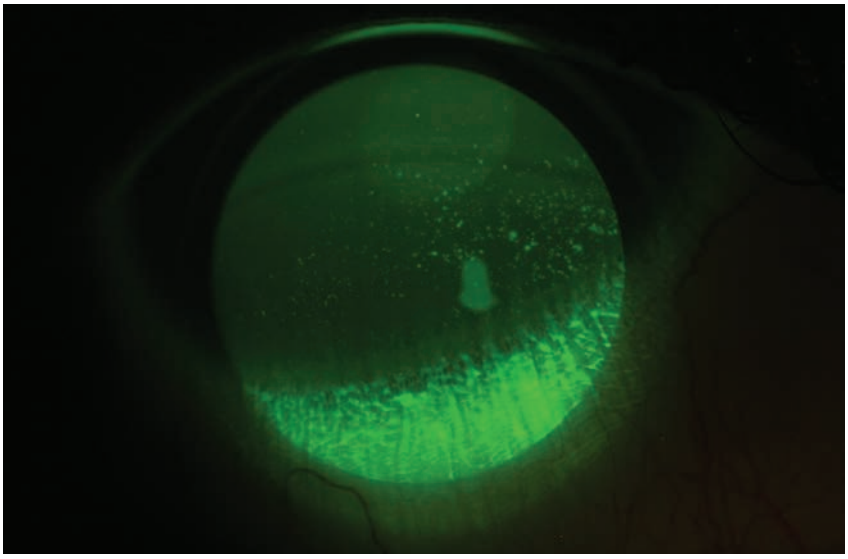
associated with increased disease severity, allows questionnaires with 10 to 15 questions like the OSDI to generate a summated score in which ranges of total scores are designated as mild, moderate or severe symptomatic disease.

Several other factors are critical to a reliable, reproducible questionnaire that can provide an accurate DED evaluation. First, the number of questions should be kept to a minimum, allowing patients to maintain a consistent degree of focus in answering each question. Our experience tells us that questionnaires should be no longer than the 12 to 15 questions of the McMonnies or the OSDI; and it may be that four or five well-structured questions are sufficient, or even superior, in terms of the goals stated above. This is particularly true in a clinical trial setting, where a greater number of questions provides more—but not necessarily better—data, and the resulting greater variability in the dataset often confounds the outcome.

Simplifying Symptom Scoring

Greater numbers of questions in the setting of a clinical trial also provides a greater potential for the Hawthorne Effect, where subjects interject their perceptions regarding right or wrong/better or worse answers in response to a perceived need on the part of those administering the test. This subjective influence can ultimately blur distinctions between treatment and control groups.

A second factor that can have a big impact on symptom questionnaires is the degree to which questions rely on recollection. Questions that ask, "How often in the last week…"or "How many days in the past month …" are dependent upon a subject's recall and therefore have an inherent potential for inaccuracy. As with longer surveys, those with questions that focus on a historical perspective from the patient's view will allow for an interpretive response with an increased subjective impact. Recent studies suggest that recall bias is a particularly significant issue in older patient populations, and that recall issues may introduce systematic biases into the responses and, therefore, the symptomatic assessments.[8] In the context of a clinical trial, however, it's also important to remember that if the survey is used to assess primary or secondary endpoints, then it needs to specify the time frame and optimize this based on the predicted temporal characteristics of the intervention being tested.[9] Questions ideally need to strike a balance between contemporaneous and retrospective reporting of a patient's experience.



One of the confounding aspects of treating dry-eye disease is that a patient with an objective sign, such as staining, may not have corresponding symptoms, and vice versa.

In an ideal world, our symptom questionnaire would have a single question and a correlation with disease severity of 1. As we live in the real world, we strive for a few simple questions and a correlation of 0.7 or better. Further complicating the refinement of symptomatic assessments are the contrasting aspirations of questionnaires designed for the clinic and those optimized for a clinical trial: While an inclusion error is good in the practice of medicine, an exclusion error is better in a drug-development setting.

Several approaches have been used to address the pitfalls of current questionnaires by combining old and new questionnaires or focusing on specific questions with a symptom survey. One study employed the OSDI questionnaire in combination with a simpler, four-question survey of subjects' current dry-eye symptomatology (Ora Calibra Four-Symptom Scale).[10] Another trial used the OSDI, but then defined a secondary symptomatic endpoint based upon the mean change from baseline in the visual-related function subscale score of the OSDI.[11] In this case, several OSDI questions that focus on visual function were plucked from the survey, predefined as a unique endpoint and scored separately. This approach may be the best of both worlds: inclusion of more extensive, validated methods such as OSDI allows for an assessment comparable to other trials, while simplified scales such as the Four-Symptom Scale are key to a more objective and tighter dataset able to rigorously describe the efficacy of an intervention.

Beyond Dry Eye

When we talk about disease symptoms, we refer in almost every case to some type of pain or discomfort: dryness; grittiness; burning; itching; and even photophobia. Many of these are associated with conditions other than dry eye, and so should be part of the diagnosis for those conditions as well. Eye pain and photophobia, for example, are two hallmark symptoms of migraine headache.[12] There are many different pain-assessment instruments available that range from extensive questionnaires to simple cartoon graphics, but, as with the dry-eye surveys, the goal here is to provide a reliable assessment of patient symptoms as a means to guide treatment or therapy development.

Pain is often a key sequela to procedures such as cataract or refractive surgery, and in these cases the most reliable measure is obtained with a visual analog scale. Comparisons of numerical scales without verbal descriptors and those with graded descriptors such as mild, moderate or severe show that it is primarily the anchoring descriptors that impact the reliability of the scale.[13]

Use of symptomatic data in clinical trials is always more difficult than endpoints with clearly defined, objective metrics. Despite this, they're often the most clinically meaningful measures, and so their inclusion is often essential from a regulatory perspective. An approach that is seen with increasing frequency to address this and other trial design issues is the composite endpoint, in which specific treatment goals are combined into one amalgamated efficacy measure.[14,15] For example, use of a composite endpoint including a structural endpoint (such as retinal optical coherence tomography) combined with some measure of visual function has been suggested for glaucoma trials, where limitations of each measure could be mitigated by their combination.[15] In this case, where disease progression is slow and often not tightly correlated with anatomical changes, the combination allows for an amplification of potential therapeutic effects.

Often, composite endpoints function to increase the statistical power of a study without increasing the number of subjects required; an example of this is the total nasal symptom score used in trials of allergy therapies. The TNSS combines symptomatic scores for rhinorrhea, nasal congestion, nasal itching and sneezing, and has become the metric for therapeutic assessment of anti-allergics.[16] Of course, combining measures of multiple symptoms implies that all are equal contributors to patient symptomatology. Because this may not always be the case, there is a risk that treatments with specific effects are approved for more extensive indications. In the case of the TNSS score, for example, a drug with strong anticholinergic action may potently abolish rhinorrhea but have little effect on other components of the composite score. With an overwhelming effect on one component, such a drug could generate statistically significant reductions in TNSS and thus potentially receive an indication for relief of all the symptoms included in the composite. In this way, use of composite endpoints can lead to artifacts in the regulatory process and an artificial broadening of the therapeutic indication. This reminds us to look carefully at each component of a composite score with the goal of selecting those that equally reflect the symptomatology of the target condition.

Despite these caveats, composite endpoints do have a potential utility, whether for enhancement of our ability to address symptomatic diseases or as a tool in the broader context of clinical therapeutic development. Key to the process of symptom assessment, regardless of the specific measure or metric selected, is the fact that it must be based on a clear and honest conversation between patient and physician. REVIEW

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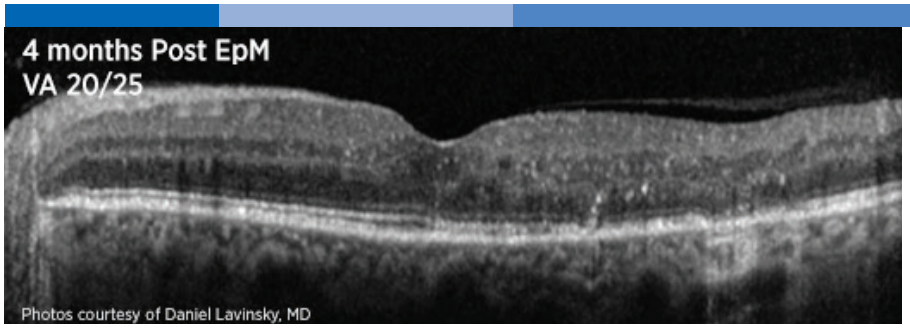

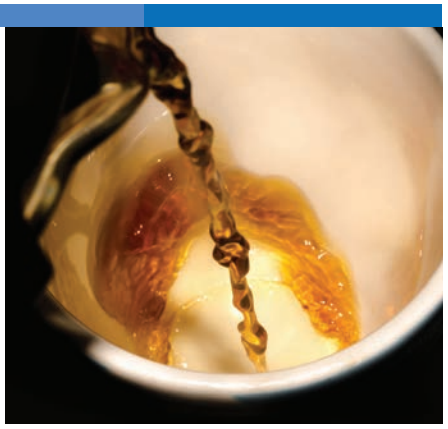

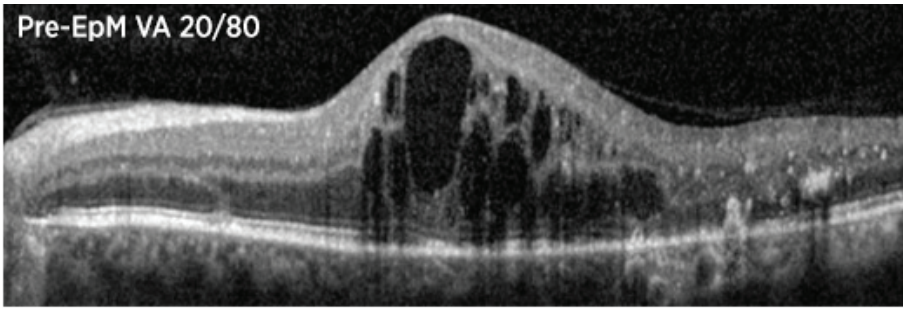

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ECP & Cataract Surgery: Perfect Together?

Evidence suggests that endoscopic cyclophotocoagulation can be a safe and effective adjunct to cataract surgery.

Carla J. Siegfried, MD, St. Louis

As a general rule, we think of glaucoma as an optic neuropathy associated with disease of the outflow pathway of aqueous humor. Perhaps for that reason, many surgeons are reluctant to use a procedure that ablates part of the ciliary processes to limit aqueous inflow, except as a last resort—e.g., for patients who have refractory glaucoma with very high pressure and very poor vision, or patients who have had so many surgeries that you're not excited about doing another incisional procedure. It's true that in this situation a cycloablative procedure is an option, but restricting such a procedure to this type of situation may be unnecessary.

Ironically, many topical drops we prescribe to treat glaucoma work by reducing inflow; often, aqueous suppressants are used as initial or additive therapy. One might argue that this is not equivalent to ciliary ablation because medication effects are reversible. However, it's worth remembering that while cyclophotocoagulation is not reversible, it is titratable; we only ablate a portion of the ciliary processes. (Besides, even treating 360 degrees won't completely stop aqueous production.)

Recently, endoscopic cyclophotocoagulation has come to the forefront because it's currently often done in combination with cataract surgery, making it an adjunctive procedure in the early stages of glaucoma. Because it is a minimally invasive glaucoma surgery, one could also put it into the category of MIGS.

I should make it clear that I don't perform a great deal of ciliary ablation. However, endoscopic cyclophotocoagulation (and transscleral cyclophotocoagulation) are part of our armamentarium, and I think we should have as many tools as possible at our disposal. There are times when one of these procedures may be the right procedure to help your patient.

A Brief History

In the past, surgeons have tried to limit ciliary production of aqueous using surgical excision, penetrating diathermy (i.e., cautery), cryotherapy, ultrasound and lasers of different kinds. Transscleral cyclophotocoagulation is now most commonly performed using a semiconductor diode G-probe that contacts the eye. The laser energy is absorbed by the pigmented ciliary epithelial tissues, resulting in destruction of the cells.

It was Martin Uram, MD, who first designed and developed the endoscopic laser in Little Silver, N.J. (current home of Endo Optiks, manufacturer of the instrument). It uses an 810-µm diode continuous-wave laser that allows you to "paint" the ciliary processes. The reusable probes, available in curved or straight versions and in different sizes, contain a light source, video camera and the laser, with an aiming beam that allows you to see the area you're treating. The optics of the system provide enough depth of focus—from 1 to 30 mm—to let you pull back and get a wider field of view when necessary. As a retina specialist, Dr. Uram used the instrument through the pars plana to treat the ciliary processes when he was doing vitrectomies. Later it was converted for use through the limbus or through a corneal wound during cataract surgery. Today, ECP is usually done through a clear cornea cataract surgery incision. (ECP can also be done as a stand-alone procedure in

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pseudophakic patients.)

Today, because ECP is relatively efficient as an adjunct to cataract surgery, it's become more commonly used in patients who have good visual potential and mild glaucomatous damage. The transscleral approaches are still primarily reserved for end-stage, more refractory glaucoma. However, I believe even transscleral procedures are being used earlier in the disease, perhaps because of what we've learned from ECP—that cyclophotocoagulation can be done earlier, and it can be very safe. I now use TCP for elderly patients, and even patients with good central vision that I don't want to take to the OR. I can do this in the treatment room under local anesthetic, without sedation.

Performing the Procedure

When I perform ECP in the OR in conjunction with cataract surgery, I use topical lidocaine gel and then inject a small amount of lidocaine intracamerally at the time of the procedure. (As a general rule, I don't do retrobulbar injections for any surgical procedures.) When I do TCP in the treatment room (i.e., not in conjunction with cataract surgery), I always use a sub-Tenon's injection of lidocaine 2%/marcaine 0.375% for anesthesia.

When done in conjunction with cataract surgery, ECP is performed after the lens implant is in place. I work through the cataract wound (usually a clear-cornea, limbal, 2.5-mm incision); I place viscoelastic into the sulcus, which elevates the iris and lowers the IOL, providing a direct line of sight to the ciliary process. A pars plana approach may be undertaken by vitreoretinal surgeons following a pars plana vitrectomy.

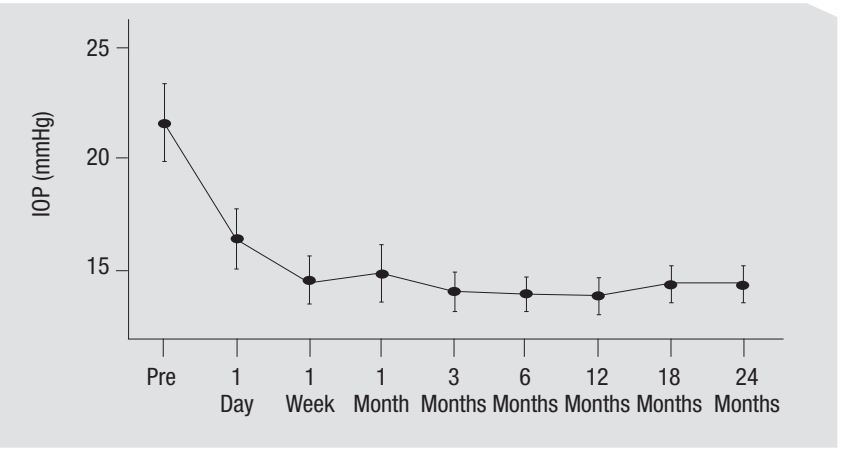
It's important to learn to watch the monitor and occasionally glance at the eye during the procedure, to make sure the anterior chamber is acceptable, without significant torque of the eye. During the treatment, as you "paint" the ciliary process, you're looking for blanching and shrinking of the process; you don't want to see popping or explosions. This is one of the differences between ECP and TCP; I once filmed a transscleral treatment using the endoscope, and you could see some of the ciliary processes exploding as they absorbed the laser energy.

Histology of eyes that have undergone TCP shows widespread tissue disruption, signs of a prolonged reduction in blood flow and coagulative necrosis of the ciliary stroma. In contrast, during ECP you see blanching and shrinking but no exploding tissue. Histopathology after ECP demonstrates localized contraction of the ciliary processes, signs of a temporary reduction in iris root/ciliary process perfusion, less architectural disorganization and sparing of the ciliary muscle. (The impact of the last factor may be muted by the fact that the accommodation is no longer an issue after standard cataract surgery.) It's not clear whether one approach or the other leads to a greater reduction in pressure.

As noted, this treatment is titratable. (Malik Kahook, MD, at the University of Colorado, Denver, did a retrospective, consecutive case review of 40 patients who underwent combined ECP and phaco, and found greater reduction in IOP at both three and six months when 360 degrees were treated, compared to when less than 300 degrees were treated.[1]) Using the curved probe, I'm able to treat 270 degrees through one incision; if you want to treat 360 degrees, you'll need to make a second incision. Once you're finished, it's important to remove the viscoelastic, because viscoelastic that's left behind is a significant cause of pressure spikes after the procedure.

Postoperatively, I inject a miotic such as acetylcholine or carbachol, along with topical steroids and antibiotics, just as I would following any cataract surgery. I keep the patient on pressure-lowering medications until the pressure comes down, but I continue steroids a bit longer than I would after standard cataract surgery. (After cataract surgery I start to taper the steroid drops after a week. Following cataract surgery

Reduction in IOP Following Phaco with ECP



A retrospective review of 56 phaco-ECP patients found that IOP was reduced from a mean of 21.5 mmHg at baseline to 14.4 mmHg at 18 and 24 months ($p<0.01$). Medications were reduced from a mean of 2.1 at baseline to 2.0 at 24 months ($p>0.05$).[3]

with ECP, I may keep the patient on the steroids for three or four weeks, tapering the patient off by six weeks.) Non-steroidal topical agents may also be used in some patients.

"ECP plus" is another variation of the procedure, done through the pars plana incision, a variation most likely to be performed by a retina specialist. The "plus" refers to additionally treating part of the pars plana. The ciliary epithelium not only covers the ciliary process—the structure that comes out from the wall of the eye—but also the pars plana, which can be thought of as a very anterior part of the retina. Since that area does have ciliary epithelial cells, you can treat the anterior 1 to 2 mm of the pars plana to generate additional reduction in aqueous. Usually, this would be done as part of a standard pars plana vitrectomy, with the probe inserted through the sclerostomy.

Indications

Today, the most common use for ECP is as primary therapy combined with phaco. However, it is also used in a number of other situations:

- combined with other MIGS procedures (as in the ICE procedure, consisting of iStent, cataract extraction and ECP);
- to treat refractory glaucoma;
- if TCP fails to lower pressure (direct visualization via ECP may yield an improved outcome);
- as concomitant therapy with pars plana vitrectomy;
- to treat aphakic and pseudophakic pediatric glaucoma;
- in patients with a history of scleral disease. For example, some patients have a very thin sclera, (e.g., osteogenesis imperfecta). In these cases, you don't want to do an invasive incisional procedure such as a trabeculectomy or a tube shunt.
- to address plateau-iris syndrome, in which the eye has an anterior rotation of the ciliary process, by performing endocycloplasty. Cycloablation causes shrinkage of the ciliary process, rotating it backwards, which helps to open up the peripheral angle.
- for endoscopic visualization. Using the probe can be very helpful if you have a displaced or improperly placed implant; you can see precisely where the IOL haptics are and whether they're in the wrong position. Similarly, the endoscopic system is helpful when patients have corneal disorders that obstruct the surgeon's view inside the eye; surgical procedures can still be done, using the endoscopic probe to see what's going on behind the corneal or lenticular opacity. (The endoscope can also be used as a diagnostic tool in these circumstances.)

Caveats and Complications

Several things should be considered relative contraindications for ECP:

- ***Pseudoexfoliation glaucoma.*** Because this disease leaves a white, fibrillar material on the ciliary processes, they may not absorb the laser energy as well.
- ***Weakened zonules.*** It's important to be especially careful if you perform ECP in patients with weakened zonules. The probe is very close to the lens during the procedure, and over the course of the procedure the viscoelastic that's maintaining the space between the lens implant and the iris gradually diffuses into the anterior chamber, causing the opening in which you're working to become shallower. As that happens, it becomes possible for the probe to touch the lens implant. That's not a problem, as long as you don't put any pressure on the lens; but if for some reason you do—I've seen trainees make this mistake—you may stretch or break some of the zonules.
- ***A history of inflammatory eye disease or cystoid macular edema.*** ECP patients will have more postoperative inflammation than patients who undergo standard cata-ract surgery. CME is a possible complication, making patients with this kind of history more likely to have trouble postoperatively.

Although ECP is generally a safe procedure, complications can occur. These include:

- ***Inflammation.***
- ***Hyphema.*** (This has been reported, although I've never seen it during any of my procedures.)
- ***Cystoid macular edema.*** As noted above, this can occur, especially in those who have a history of CME.
- ***Zonular damage.*** This can occur if the surgeon accidentally pushes on the lens during the procedure.
- ***Hypotony or phthisis.*** In theory, this could happen after the procedure, but I'm not sure it's ever been reported.
- ***Postoperative change in refractive error.*** This could theoretically happen as a consequence of a change in effective lens position caused by inadvertent pressure placed on the lens implant. One study looked at postoperative refractive error changes following ECP; the data revealed some slight differences, but they were not significant.[2]

What the Data Show

How effective is treatment with ECP when combined with cataract surgery? Here are the data from a number of studies:

- A retrospective review of 56 phaco-ECP patients found that IOP was reduced from a mean of 21.5 mmHg at baseline to 14.4 mmHg at 18 and 24 months ($p<0.01$). Medications were reduced from a mean of 2.1 at baseline to 2.0 at 24 months ($p>0.05$).[3]
- A retrospective review of 63 phaco-ECP eyes that received 270 to 360 degrees of treatment looked at the 12-month follow-up.[4] Mean IOP

Allergan Displays ForSight

In August, Allergan announced its intent to purchase eye-care company ForSight Vision5, which has a sustained-release drug device in development. Per the agreement, Allergan will acquire ForSight Vision5 for an initial $95 million payment and a launch milestone payment related to the company's lead product, the sustained-release device.

ForSight's device is a periy-ocular ring that's preservative-free and rests on the surface of the eye beneath the lid. In its current iteration, it releases the glaucoma drug bimatoprost over a period of months to help lower intraocular pressure while avoiding issues with patients' adherence to glaucoma drop schedules.

"We know if we're going to take care of thousands of patients, we need a lot of tools in our bag," says Jay Parekh, MD, vice president for medical affairs and global lead for eye care at Allergan. "And, when you have a disease therapy that could run a 20- or 30-year course, compliance is a key aspect of it."

—The Editors

dropped from 21.1 ±6.2 at baseline to 16.1 ±5.27 mmHg ($p<0.01$). Medications dropped from 2.7 ±1.1 to 1.47 ±1.3 ($p<0.01$). (How much pressure lowering can be attributed to the phaco alone is difficult to say, because there was no control group.) Of note, the outcomes were best in older patients and those with a higher baseline IOP. Whether this reflects a difference in the vascularity of the ciliary cells, or a different response to a change in inflow due to age or high pressure, is impossible to determine.

Notably, all medications in this group were discontinued after surgery and re-introduced as needed. I suspect this may be the reason they found more of a decrease in the number of medications than many studies find. In general, we discontinue all medications after a full-fledged glaucoma surgery, but many times with MIGS procedures, especially if the patient has moderate disease, we're more hesitant to do so. As a result, we may be not seeing the full effect of these treatments, at least in terms of their ability to decrease medication use.

This study also looked at complications. The data showed a small amount of induced astigmatism (possibly related to movement of the lens); posterior vitreous detachment, a few cases of increased IOP, and an unusually high 11 percent of cases having fibrinous uveitis, an event I've rarely seen following ECP. Overall, the study authors concluded that the procedure was safe and effective, with a success rate—defined as a greater-than-20-percent reduction in IOP—of 55.5 percent.

• A prospective, nonrandomized, matched-control study compared phaco with ECP to phaco alone in 160 patients (80 per group) matched for age and baseline IOP.[5] In the study group, mean IOP decreased from 18.1 ±3 mmHg to 16.0 ±3.3 at two years, with medication use dropping from 1.5 ±0.8 to 0.4 ±0.7. The phaco-only group decreased from 18.1 ±3 mmHg to 17.3 ±3.2 at two years, with medications decreasing from 2.4 ±1.0 to 2.0 ±1.0. The difference in pressure and medication reduction between the groups was statistically significant at all time points.

• Another retrospective chart review with a 36-month follow-up compared phaco with ECP to phaco alone; 261 eyes underwent combined surgery, while 52 eyes underwent only cataract surgery.[6] The difference between the IOP-lowering in the two groups wasn't significant at 16 weeks (14.6 mmHg vs. 15.5 mmHg, $p=0.34$). However, the percentage of patients meeting the definition of full success (a greater-than-20-percent reduction in IOP and a decrease of one medication) was significantly different between the two groups: 61.4 percent vs. 23.3 percent ($p<0.001$). Likewise, comparing the percentage in each group that achieved qualified success (IOP lower than baseline with a decrease of one medication), the difference between the groups was also significant: 72.6 percent vs. 23.3 percent ($p<0.001$). Put another way, those who underwent cataract surgery alone had a one-in-four chance of getting a significant pressure reduction and a decrease in medications. Those who underwent the combination surgery had three times better odds of this result.

• Finally, one retrospective chart review looked at the combined procedure in 104 eyes of 104 patients with advanced glaucoma at the time of surgery.[7] Follow-up was 17.3 ±1.8 months. Among these patients, mean IOP decreased from 17 ±1.4 mmHg to 14.7 ±1.3 mmHg. Only 11.9 percent achieved absolute success, defined as an IOP ≤15 mmHg on no medications; however, 72.3 percent achieved qualified success, defined as an IOP ≤15 mmHg with medications.

Because ECP—often combined with phaco—can be considered a MIGS procedure, it would be helpful to have some prospective, randomized studies comparing it to the other MIGS procedures. So far, I'm not aware of any studies fitting that description. However, we presented a poster last year at both the American Academy of Ophthalmology and American Glaucoma Society annual meetings showing data from a retrospective study of 150 patients at the Barnes-Jewish Hospital/Washington University School of Medicine; 41 underwent phaco alone; 52 underwent phaco with ECP; and 57 underwent phaco with Trabectome. As expected, higher IOPs, more medications and worse disease had influenced the surgeons to choose a combined procedure.

Among the results:

• There was significant pressure lowering with both phaco-Trabectome and phaco-ECP, as well as higher rates of success (defined as a reduction in IOP of at least 20 percent, or a reduction of at least one medication) compared to phaco alone.

• Success rates of the two combined procedures weren't significantly different at 24 months, although there was a trend toward better pressure reduction with phaco-Trabectome.

• In terms of complications, there was more hyphema with phaco-Trabectome and more CME with phaco-ECP.

It's worth noting that because the study was retrospective, patients were not matched for preoperative IOP, medications or disease severity.

Increasing Popularity

There's no question that the use of ECP has expanded significantly over the past 10 years. Starting in 2005, the single billing code for ciliary ablation was separated into transscleral procedures and endoscopic procedures. By 2012, use of transscleral procedures dropped from 5,978 to 3,268, a 45-percent decrease. During the same period, ECP procedures grew from 5,383 to 10,728, a 99-percent increase. Of note, reimbursement for ECP is significantly greater than for transscleral procedures—$635.84 vs. $434.57; ECP is a more involved procedure performed in the OR.

Given that ECP has a good track record for safety, and may produce significant IOP lowering following cataract surgery—with minimal risk—it's an adjunctive treatment worth considering. REVIEW

Dr. Siegfried is the Jacquelyn E. and Allan E. Kolker, MD, Distinguished Professor of Ophthalmology at Washington University School of Medicine in St. Louis. She has no financial interest in any product discussed.

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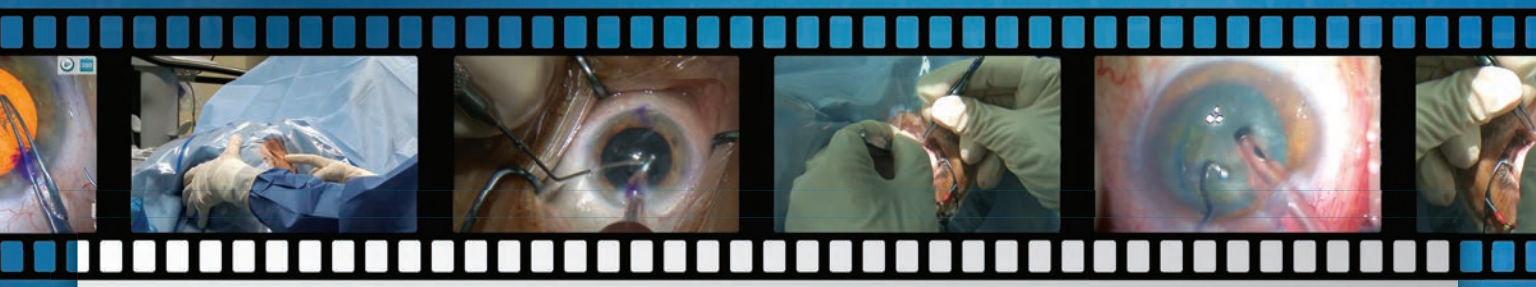

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"The Deformed Cornea"

Surgical Video by:
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Video Overview:

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This educational activity aims to present a series of Dr. Mackool's surgical videos, carefully selected to address the specific learning objectives of this activity, with the goal of making surgical training available as needed online for surgeons motivated to improve or expand their surgical repertoire.

Learning Objectives:

After viewing the video, participants should be able to:

1. Present refractive considerations when performing cataract-implant surgery on patients with keratoconus.
2. Present, discuss and ameliorate corneal-induced visualization problems during cataract surgery.

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This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of the Institute for the Advancement of Human Behavior (IAHB) and Postgraduate Healthcare Education, LLC (PHE). IAHB is accredited by the ACCME to provide continuing medical education for physicians.

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(continued from page 30)

a detached graft hours after the procedure.[12] The patient elected to wait and observe the situation because the eye had low visual potential. One month postoperatively, the cornea began to clear. At six months, only minor edema remained in the superior far periphery. The corneal pachymetry returned to normal and the endothelial cell density was 830 cells/mm^2. After this result, Dr. Melles saw a potential therapy and tentatively called the practice of a descemetorhexis followed by the deposition of a free-floating Descemet's scroll in the anterior chamber "Descemet's membrane endothelial transfer,"or DMET. Dr. Melles found a similar result in a small group of Fuchs' patients undergoing DMET, but not a group with bullous keratopathy.[13]

The question, of course, is whether the source of new endothelium centrally was the donor graft or the relatively healthy peripheral host endothelium in Fuchs'. The University of Chicago's Kathryn Colby, MD, PhD, has also been working with a less-invasive way to treat some Fuchs' patients. In her retrospective study, she stripped the central Descemet's membrane in 13 eyes of 11 patients at the time of their cataract surgery. At a follow-up of six months and later (range: six to 24 months), 10 of the patients had corneal clearing, with a visible central endothelial cell mosaic, and saw between 20/20 and 20/15 (preop: 20/25 to 20/400).[14]

Though this approach seems to confirm what many of us suspected—that stripping the central 5 mm of endothelium in Fuchs' dystrophy might allow the cornea to redistribute the remaining healthy endothelial cells from the periphery—we're not sure if this approach works enough of the time to justify its widespread use. We'll observe developments in this area with interest.

• ***Pre-Descemet's Endothelial Keratoplasty.*** With PDEK, a procedure developed by India's Amar Agarwal, MD, and Great Britain's Harminder Dua, MD, the idea is to include the newly discovered (though disputed by some) Dua's layer of the cornea in the posterior graft of endothelium and Descemet's membrane.[15] This makes the graft 30 to 40 µm thick, which is only slightly thicker than a DMEK graft but much easier to work with in several ways: 1) Since you're not stripping Descemet's from stroma, the risk of damaging Descemet's membrane is eliminated. 2) You're not restricted to using donors older than 50 because you don't need to worry about tearing Descemet's membrane during stripping as can occur in DMEK. 3) A PDEK scroll is 30 to 40 µm thick, not 15 or 20 µm as in DMEK, so it's easier to unscroll in the anterior chamber.

The challenge, however, is in harvesting the tissue for PDEK, which is the main reason the technique hasn't caught on yet. To harvest the donor graft, you can't strip it through a posterior approach. Instead you have to create a "big bubble" similar to that used in deep anterior lamellar keratoplasty. The eye-bank technician or the surgeon has to create this bubble so that, when it expands and separates the tissue, it yields a posterior layer that has all three layers needed for PDEK before trephining the graft. The challenge is that we don't always achieve a big bubble, and, if we don't achieve it, the corneal tissue is potentially permanently damaged and unusable.

• ***Rho-associated kinase inhibitor drops.*** Japan's Shigeru Kinoshita, MD, has been developing a technique for the treatment of endothelial dysfunction that involves instilling ROCK inhibitor eye drops to promote endothelial healing. After finding accelerated healing due to the drops in animal models, he instilled them in eight patients with endothelial dysfunction and reported a positive effect.[16] The next step in this research is *ex-vivo* expansion of healthy host endothelial cells.[17]

Though it's true that DMEK is more challenging to perform than DSAEK, not many things in life or in ophthalmology that are worth doing are ever easy. If you can stay with DMEK through the learning curve and put to use some of these principles, you and your patients will often be rewarded with excellent outcomes. REVIEW

Dr. Hannush is an attending surgeon in the Cornea Service at Wills Eye Hospital, Department of Ophthalmology, Sidney Kimmel Medical College of Thomas Jefferson University. He is also the medical director of the Lions Eye Bank of Delaware Valley.

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A recent immigrant to the United States complains of redness, swelling and pain in the lids of his left eye.

Jeffrey F. McMahon, MD

Presentation

A 25-year-old Hispanic male complained of redness and swelling of the left eyelids for two weeks. The patient had initially presented to an outside ophthalmologist five days prior, and was prescribed oral cephalexin 500 mg four times daily for treatment of presumed preseptal cellulitis, without progression or improvement in his symptoms. He reported ongoing pain in the left eye with movement, most notably in up-gaze, but denied concurrent diplopia, photophobia, recent illness or trauma. Systemic review was only significant for left nasal congestion over the preceding few weeks.

Medical History

Past medical, surgical and ocular history were noncontributory. The patient's social history was notable for recent immigration to the United States from El Salvador eight weeks prior to presentation. The patient denied tobacco or illicit drug use and drank alcohol socially. He had no known drug allergies.

Examination

On examination, axillary temperature was 101.7 degrees Fahrenheit; the remaining vital signs were within normal limits. Ocular examination showed uncorrected visual acuity of 20/25 in both eyes. Pupils were equal and briskly reactive, without an afferent pupillary defect. Confrontation visual fields and Ishihara color plates were full bilaterally. External examination disclosed displacement of the nasal bridge to the right with moderate left upper and lower eyelid erythema and mild edema *(Figure 1)*. Extraocular motility was full OD but limited OS, most notably in up-gaze *(Figure 2)*.

Slit lamp examination of both eyes was unremarkable. Intraocular pressure by Goldmann tonometry was 14 mmHg OD and 17 mmHg OS. Hertel exophthalmometry disclosed 3 mm of relative left-sided proptosis. Dilated fundus exam in both eyes was unremarkable.

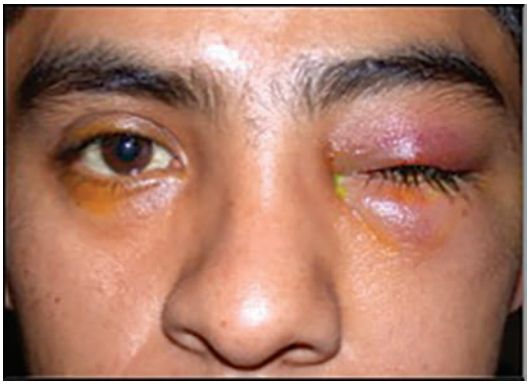

Figure 1: External photograph of nasal displacement with soft tissue swelling, left upper and lower eyelid erythema and edema.

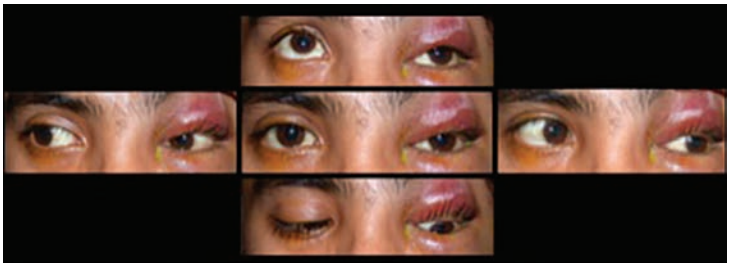

Figure 2: Extraocular motility montage disclosing limited up-gaze with mild hypoglobus of the left eye.

What is your differential diagnosis? What further workup would you pursue? Please turn to p. 72.

Diagnosis, Workup and Treatment

Given the concern for an evolving orbital process, computed tomography of the midface and orbits was obtained with and without contrast. Imaging disclosed complete opacification of the left nasal cavity, left frontal sinus, left maxillary sinus, left ethmoid sinuses and left sphenoid sinus, with partial opacification of the right frontal sinus and mucosal thickening of the right maxillary sinus. Preseptal soft tissue swelling was noted, as was an opacified collection within the left orbit adjacent to the lamina papyracea, concerning for a subperiosteal abscess *(Figure 3)*. Possible bone erosion of the left medial orbit and skull base was evident. Clinical management for orbital cellulitis with subperiosteal abscess formation was initiated.

Based on the available information, the differential diagnosis was concerning for infectious etiologies including sino-orbital aspergillosis, mucorymycosis and tuberculosis. Inflammatory causes were also considered, such as granulomatosis with polyangitis (GPA, Wegener granulomatosis), as well as neoplasms including primary sinonasal carcinoma, rhabdomyosarcoma and lymphoproliferative disorders. Trauma and cocaine abuse with secondary infection were also considered. Given the concern for infection, our patient was started on intravenous ampicillin/sulbactam for presumed bacterial orbital cellulitis. Serologies were obtained, including complete blood cell count, human immunodeficiency virus antibody, anti-neutrophil cytoplasmic antibodies, hemoglobin-A1c, urinalysis and urine drug screen, and found to be within normal limits. The presence of bony erosion on CT was concerning for aspergillosis or a neoplastic process with secondary sinusitis, prompting urgent left transnasal endoscopic sinus surgery by the Otolaryngology department to explore the sinuses and drain any purulent collections. During surgery, necrotic tissue was noted to fill the nasal cavity. Multiple nasal and sinus biopsies were obtained.

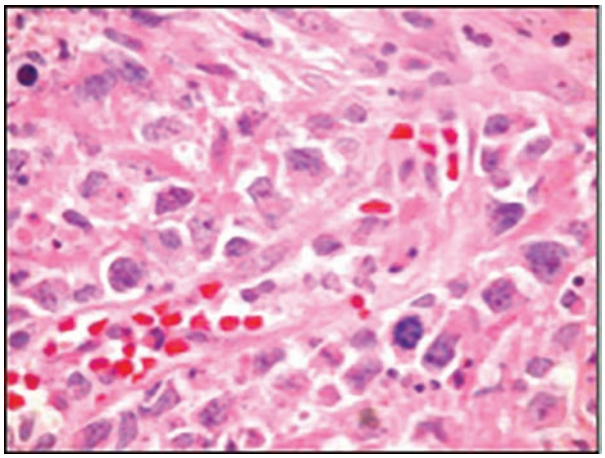

Figure 4: Hematoxylin and eosin staining demonstrating a large cell neoplasm with a high mitotic index in tumor cells with prominent nucleoli.

Cytology revealed a large cell neoplasm demonstrating a high mitotic index in tumor cells with prominent nucleoli *(Figure 4)*. Immunohistochemical staining was positive for CD2, cytoplasmic CD3, CD30, CD45 and CD56, and negative for CD4, CD5, CD20, S100 and AE1/AE3. The clinical presentation and immunohistochemical profiling strongly favored a diagnosis of extranodal natural killer/T-cell lymphoma (NKTL) of nasal type.

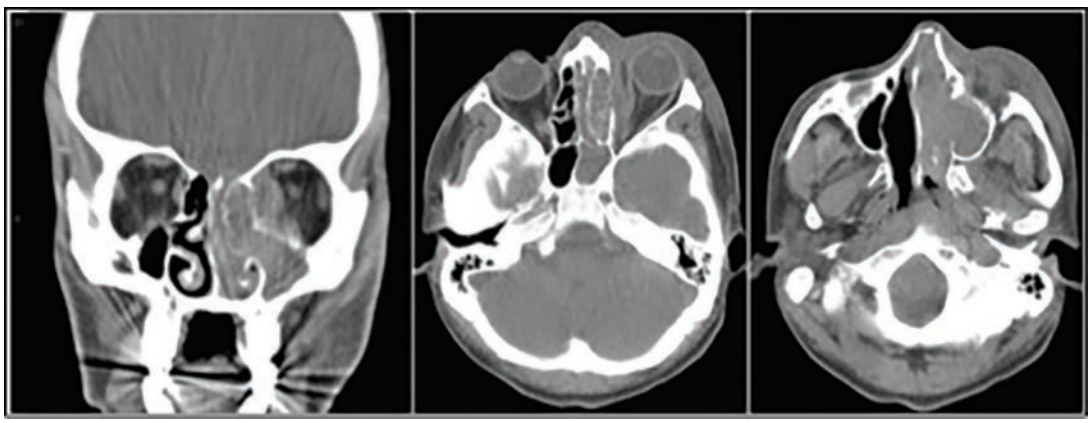

Figure 3: Maxillofacial CT without contrast (soft tissue windows). One coronal and two axial sections demonstrate extensive nasal/sinus cavity disease with complete opacification of left ethmoid, sphenoid and maxillary sinuses, as well as subperiosteal opacification abutting the medial rectus, concerning for left orbital subperiosteal abscess. Note the possible bone erosion on the left.

The patient underwent systemic staging, including bone marrow biopsy, which was negative; he was diagnosed with Stage IE disease. Under the care of medical oncology and radiation oncology the patient was started on concurrent cyclo-

phosphamide, hydroxydaunorubicin, vincristine and prednisone chemotherapy as well as external beam radiation therapy to both orbits, the sinonasal cavities and the skull base. He has undergone annual medical oncology follow-up with positron emission tomography scans yearly for surveillance. He was noted to be disease free at his 11-year follow up.

Discussion

Extranodal NK/T-cell lymphoma, nasal type, is a non-Hodgkin lymphoma composed of malignant natural killer cells in a majority of cases; however, a cytotoxic T-cell phenotype is also observed, leading the World Health Organization to reclassify the terminology in 2008.[1] These malignancies typically involve the nasal cavity and or paranasal sinuses, with intraorbital involvement being less common and invariably secondary spread from adjacent sinonasal disease.[1,2] Synonymous terms appearing in the literature include lethal midline granuloma, angiocentric T-cell lymphoma, malignant midline reticulosis, polymorphic reticulosis and angiocentric immunoproliferative lesion.[1,3] The latter terms describe the characteristic vascular damage and prominent necrosis typically observed with histological analysis, with a resemblance to that seen in GPA. NKTL is more prevalent in Asians, as well as the Native American populations of Mexico, Central America and South America, and is more common in males than females.[1,2,4] While little is known about its etiology, there is a strong association with the Epstein-Barr Virus, almost always subtype A, regardless of ethnic origin, suggesting a probable pathogenic role of the virus.[5,6] In nearly all cases, neoplastic cells harbor clonal episomal EBV, and disease activity and prognosis have been shown to correlate with circulating EBV DNA titers.[1,6,7]

Clinically, patients may present with nasal obstruction or congestion, as in this case, or with extensive midfacial destruction. NKTL may spread to adjacent structures, including the orbit, and the rapid growth and necrosis result in an inflammatory response in surrounding tissue, often making clinical distinction from orbital cellulitis challenging.[3,4,8] The mainstays of treatment have relied heavily on high-dose EBRT and chemotherapeutic regimens, with further studies needed to confirm the efficacy of various combinations.[5] Of note, in contrast to other lymphomas, at present no monoclonal antibody (biologic) therapy is available for NKTL. Prognosis was generally extremely poor in the past (hence the term lethal midline granuloma). However, prognosis is now variable, largely depending on initial stage at presentation, with five-year overall survival ranging from 42 percent to 64 percent in four recent studies.[7] It is likely that our patient's successful long-term survival was due to the combination of Stage IE disease and aggressive clinical management. REVIEW

The author would like to acknowledge Jurij Bilyk, MD, for his contributions and editing of this case report.

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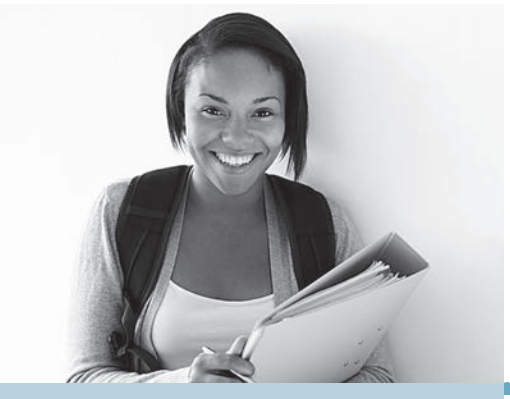

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