A PUBLICATION BY REVIEW of Ophthalmology

RETINA SPECIALIST

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LATEST in AI For MANAGING DR

Ongoing investigations are validating its sensitivity and specificity for monitoring diabetic retinopathy.

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Pipeline Report

Online Video

Also Inside

For your appropriate patients with severe acute or chronic uveitis, keratitis, or scleritis

Envision another way
to treat ocular inflammatory disease

Acthar® GEL
(repository corticotropin injection) 80 U/mL

For more information, visit **actharophthalmology.com**

Indication
Acthar® Gel (repository corticotropin injection) is indicated for severe acute and chronic allergic and inflammatory processes involving the eye and its adnexa such as: keratitis, iritis, iridocyclitis, diffuse posterior uveitis and choroiditis, optic neuritis, chorioretinitis, anterior segment inflammation.

Important Safety Information
Contraindications
- Acthar should never be administered intravenously
- Administration of live or live attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of Acthar
- Acthar is contraindicated where congenital infections are suspected in infants
- Acthar is contraindicated in patients with scleroderma, osteoporosis, systemic fungal infections, ocular herpes simplex, recent surgery, history of or the presence of a peptic ulcer, congestive heart failure, uncontrolled hypertension, primary adrenocortical insufficiency, adrenocortical hyperfunction or sensitivity to proteins of porcine origins

Warnings and Precautions
- The adverse effects of Acthar are related primarily to its steroidogenic effects
- Acthar may increase susceptibility to new infection or reactivation of latent infections
- Suppression of the hypothalamic-pituitary-axis (HPA) may occur following prolonged therapy with the potential for adrenal insufficiency after withdrawal of the medication. Adrenal insufficiency may be minimized by tapering of the dose when discontinuing treatment. During recovery of the adrenal gland patients should be protected from the stress (e.g. trauma or surgery) by the use of corticosteroids. Monitor patients for effects of HPA suppression after stopping treatment
- Cushing's syndrome may occur during therapy but generally resolves after therapy is stopped. Monitor patients for signs and symptoms
- Acthar can cause elevation of blood pressure, salt and water retention, and hypokalemia. Blood pressure, sodium and potassium levels may need to be monitored
- Acthar often acts by masking symptoms of other diseases/disorders. Monitor patients carefully during and for a period following discontinuation of therapy
- Acthar can cause GI bleeding and gastric ulcer. There is also an increased risk for perforation in patients with certain gastrointestinal disorders. Monitor for signs of bleeding
- Acthar may be associated with central nervous system effects ranging from euphoria, insomnia, irritability, mood swings, personality changes, and severe depression, and psychosis. Existing conditions may be aggravated
- Patients with comorbid disease may have that disease worsened. Caution should be used when prescribing Acthar in patients with diabetes and myasthenia gravis
- Prolonged use of Acthar may produce cataracts, glaucoma and secondary ocular infections. Monitor for signs and symptoms
- Acthar is immunogenic and prolonged administration of Acthar may increase the risk of hypersensitivity reactions. Neutralizing antibodies with chronic administration may lead to loss of endogenous ACTH activity
- There is an enhanced effect in patients with hypothyroidism and in those with cirrhosis of the liver
- Long-term use may have negative effects on growth and physical development in children. Monitor pediatric patients
- Decrease in bone density may occur. Bone density should be monitored for patients on long-term therapy
- Pregnancy Class C: Acthar has been shown to have an embryocidal effect and should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus

Adverse Reactions
- Common adverse reactions for Acthar are similar to those of corticosteroids and include fluid retention, alteration in glucose tolerance, elevation in blood pressure, behavioral and mood changes, increased appetite and weight gain
- Specific adverse reactions reported in IS clinical trials in infants and children under 2 years of age included: infection, hypertension, irritability, Cushingoid symptoms, constipation, diarrhea, vomiting, pyrexia, weight gain, increased appetite, decreased appetite, nasal congestion, acne, rash, and cardiac hypertrophy. Convulsions were also reported, but these may actually be occurring because some IS patients progress to other forms of seizures and IS sometimes mask other seizures, which become visible once the clinical spasms from IS resolve

Other adverse events reported are included in the full Prescribing Information. Please see Brief Summary of full Prescribing Information on the adjacent page.

Mallinckrodt Pharmaceuticals

BRIEF SUMMARY - Consult full prescribing information before use.

Acthar® Gel (repository corticotropin injection) INJECTION, GEL for INTRAMUSCULAR I SUBCUTANEOUS use
Initial U.S. Approval: 1952

INDICATIONS AND USAGE

Infantile spasms:
Acthar Gel (repository corticotropin injection) is indicated as monotherapy for the treatment of infantile spasms in infants and children under 2 years of age.

Multiple Sclerosis:
Acthar Gel (repository corticotropin injection) is indicated for the treatment of acute exacerbations of multiple sclerosis in adults. Controlled clinical trials have shown Acthar Gel to be effective in speeding the resolution of acute exacerbations of multiple sclerosis. However, there is no evidence that it affects the ultimate outcome or natural history of the disease.

Rheumatic Disorders:
As adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in: Psoriatic arthritis; Rheumatoid arthritis, including juvenile rheumatoid arthritis (selected cases may require low-dose maintenance therapy), Ankylosing spondylitis.

Collagen Diseases:
During an exacerbation or as maintenance therapy in selected cases of: systemic lupus erythematosus, systemic dermatomyositis (polymyositis).

Dermatologic Diseases:
Severe erythema multiforme, Stevens-Johnson syndrome.

Allergic States:
Serum sickness.

Ophthalmic Diseases:
Severe acute and chronic allergic and inflammatory processes involving the eye and its adnexa such as: keratitis; iritis, iridocyclitis, diffuse posterior uveitis and choroiditis, optic neuritis, chorioretinitis; anterior segment inflammation.

Respiratory Diseases:
Symptomatic sarcoidosis.

Edematous State:
To induce a diuresis or a remission of proteinuria in the nephrotic syndrome without uremia of the idiopathic type or that due to lupus erythematosus.

CONTRAINDICATIONS

Acthar Gel is contraindicated for intravenous administration.

Acthar Gel is contraindicated where congenital infections are suspected in infants.

Administration of live or live attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of Acthar Gel.

Acthar Gel is contraindicated in patients with scleroderma, osteoporosis, systemic fungal infections, ocular herpes simplex, recent surgery, history of or the presence of a peptic ulcer, congestive heart failure, uncontrolled hypertension, primary adrenocortical insufficiency, adrenocortical hyperfunction or sensitivity to proteins of porcine origin.

WARNINGS AND PRECAUTIONS

The adverse effects of Acthar Gel are related primarily to its steroidogenic effects. Not all of the adverse events described below have been seen after treatment with Acthar Gel, but might be expected to occur. *[see Adverse Reactions (6.3)]*

Infections
Acthar Gel may increase the risks related to infections with any pathogen, including viral, bacterial, fungal, protozoan or helminthic infections. Patients with latent tuberculosis or tuberculin reactivity should be observed closely, and if therapy is prolonged, chemoprophylaxis should be instituted.

Cushing's Syndrome and Adrenal Insufficiency Upon Withdrawal
Treatment with Acthar Gel can cause hypothalamic-pituitary-axis (HPA) suppression and Cushing's syndrome. These conditions should be monitored especially with chronic use.

Suppression of the HPA may occur following prolonged therapy with the potential for adrenal insufficiency after withdrawal of the medication. Patients should be monitored for signs of insufficiency such as weakness, hyperpigmentation, weight loss, hypotension and abdominal pain.

The symptoms of adrenal insufficiency in infants treated for infantile spasms can be difficult to identify. The symptoms are non-specific and may include anorexia, fatigue, lethargy, weakness, excessive weight loss, hypotension and abdominal pain. It is critical that parents and caregivers be made aware of the possibility of adrenal insufficiency when discontinuing Acthar Gel and should be instructed to observe for, and be able to recognize, these symptoms. *[see Patient Counseling Information (17)]*

The recovery of the adrenal gland may take from days to months so patients should be protected from the stress (e.g. trauma or surgery) by the use of corticosteroids during the period of stress.

The adrenal insufficiency may be minimized in adults and infants by tapering of the dose when discontinuing treatment.

Signs or symptoms of Cushing's syndrome may occur during therapy but generally resolve after therapy is stopped. Patients should be monitored for these signs and symptoms such as deposition of adipose tissue in characteristics sites (e.g., moon face, truncal obesity), cutaneous striae, easy bruisability, decreased bone mineralization, weight gain, muscle weakness, hyperglycemia, and hypertension.

Elevated Blood Pressure, Salt and Water Retention and Hypokalemia
Acthar Gel can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium and calcium. Dietary salt restriction and potassium supplementation may be necessary. Caution should be used in the treatment of patients with hypertension, congestive heart failure, or renal insufficiency.

Vaccination
Administration of live or live attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of Acthar Gel. Killed or inactivated vaccines may be administered; however, the response to such vaccines can not be predicted. Other immunization procedures should be undertaken with caution in patients who are receiving Acthar Gel, especially when high doses are administered, because of the possible hazards of neurological complications and lack of antibody response.

Masking Symptoms of Other Diseases
Acthar Gel often acts by masking symptoms of other diseases/disorders without altering the course of the other disease/disorder. Patients should be monitored carefully during and for a period following discontinuation of therapy for signs of infection, abnormal cardiac function, hypertension, hyperglycemia, change in body weight and fecal blood loss.

Gastrointestinal Perforation and Bleeding
Acthar Gel can cause GI bleeding and gastric ulcer. There is also an increased risk for perforation in patients with certain gastrointestinal disorders. Signs of gastrointestinal perforation, such as peritoneal irritation, may be masked by the therapy. Use caution where there is the possibility of impending perforation, abscess or other pyogenic infections, diverticulitis, fresh intestinal anastomoses, and active or latent peptic ulcer.

Behavioral and Mood Disturbances
Use of Acthar Gel may be associated with central nervous system effects ranging from euphoria, insomnia, irritability (especially in infants), mood swings, personality changes, and severe depression, to frank psychotic manifestations. Also, existing emotional instability or psychotic tendencies may be aggravated.

Comorbid Diseases
Patients with a comorbid disease may have that disease worsened. Caution should be used when prescribing Acthar Gel in patients with diabetes and myasthenia gravis.

Ophthalmic Effects
Prolonged use of Acthar Gel may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves and may enhance the establishment of secondary ocular infections due to fungi and viruses.

Immunogenicity Potential
Acthar Gel is immunogenic. Limited available data suggest that a patient may develop antibodies to Acthar Gel after chronic administration and loss of endogenous ACTH and Acthar Gel activity. Prolonged administration of Acthar Gel may increase the risk of hypersensitivity reactions. Sensitivity to porcine protein should be considered before starting therapy and during the course of treatment should symptoms arise.

Use in Patients with Hypothyroidism or Liver Cirrhosis
There is an enhanced effect in patients with hypothyroidism and in those with cirrhosis of the liver.

Negative Effects on Growth and Physical Development
Long-term use of Acthar Gel may have negative effects on growth and physical development in children. Changes in appetite are seen with Acthar Gel therapy, with the effects becoming more frequent as the dose or treatment period increases. These effects are reversible once Acthar Gel therapy is stopped. Growth and physical development of pediatric patients on prolonged therapy should be carefully monitored.

Decrease in Bone Density
Decrease in bone formation and an increase in bone resorption both through an effect on calcium regulation (i.e. decreasing absorption and increasing excretion) and inhibition of osteoblast function may occur. These, together with a decrease in the protein matrix of the bone (secondary to an increase in protein catabolism) and reduced sex hormone production, may lead to inhibition of bone growth in children and adolescents and to the development of osteoporosis at any age. Special consideration should be given to patients at increased risk of osteoporosis (i.e., postmenopausal women) before initiating therapy, and bone density should be monitored in patients on long term therapy.

Use in Pregnancy
Acthar Gel has been shown to have an embryocidal effect. Apprise women of potential harm to the fetus. *[see Use in Specific Populations (8.1)]*

ADVERSE REACTIONS

Please refer to *Adverse Reactions in Infants and Children Under 2 Years of Age (Section 6.1.1)* for consideration when treating patients with Infantile Spasms. The adverse reactions presented in Section 6.2 are primarily provided for consideration in use in adults and in children over 2 years of age, but these adverse reactions should also be considered when treating infants and children under 2 years of age.

Acthar Gel causes the release of endogenous cortisol from the adrenal gland. Therefore all the adverse effects known to occur with elevated cortisol may occur with Acthar Gel administration as well. Common adverse reactions include fluid retention, alteration in glucose tolerance, elevation in blood pressure, behavioral and mood changes, increased appetite and weight gain.

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

Adverse Reactions in Infants and Children Under 2 Years of Age
While the types of adverse reactions seen in infants and children under age 2 treated for infantile spasms are similar to those seen in older patients, their frequency and severity may be different due to the very young age of the infant, the underlying disorder, the duration of therapy and the dosage regimen. Below is a summary of adverse reactions specifically tabulated from source data derived from retrospective chart reviews and clinical trials in children under 2 years of age treated for infantile spasms. The number of patients in controlled trials at the recommended dose was too few to provide meaningful incidence rates or to permit a meaningful comparison to the control groups.

TABLE: Incidence (%) of Treatment Emergent Adverse Events Occurring in ≥ 2% of Acthar Gel (repository corticotropin injection) Infants and Children under 2 years of Age

System Organ Class	Recommended 75 U/m² bid n=122, (%)	150 U/m² qd n=37 (%)
Cardiac disorders		
Cardiac Hypertrophy	3	0
Endocrine disorders		
Cushingoid	3	22
Gastrointestinal disorders		
Constipation	0	5
Diarrhea	3	14
Vomiting	3	5
General disorders and administration site conditions		
Irritability	7	19
Pyrexia	5	8
Infections and infestations		
Infection*	20	46
Investigations		
Weight gain	1	3
Metabolism and nutrition disorders		
Increased appetite	0	5
Decreased appetite	3	3
Nervous system disorders		
Convulsion†	12	3
Respiratory, thoracic and mediastinal disorders		
Nasal Congestion	1	5
Skin and subcutaneous tissue disorders		
Acne	0	14
Rash	0	8
Vascular disorders		
Hypertension	11	19

*Specific infections that occurred at ≥2% were candidiasis, otitis media, pneumonia and upper respiratory tract infections. †In the treatment of Infantile Spasms, other types of seizures/convulsions may occur because some patients with infantile spasms progress to other forms of seizures (for example, Lennox-Gastaut Syndrome). Additionally the spasms sometimes mask other seizures and once the spasms resolve after treatment, the other seizures may become visible.

These adverse reactions may also be seen in adults and children over 2 years of age when treated for other purposes and with different doses and regimens.

Postmarketing Experience
The following adverse reactions associated with the use of Acthar Gel have been identified from postmarketing experience with Acthar Gel. Only adverse events that are not listed above as adverse events reported from retrospective chart reviews and non-sponsor conducted clinical trials and those not discussed elsewhere in labeling, are listed in this section. Because the adverse reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate their frequency or establish a causal relationship to use with Acthar Gel. Events are categorized by system organ class. Unless otherwise noted these adverse events have been reported in infants, children and adults.

Allergic Reactions
Allergic responses have presented as dizziness, nausea and shock (adults only).

Cardiovascular
Necrotizing angitis (adults only) and congestive heart failure.

Dermatologic
Skin thinning (adults only), facial erythema and increased sweating (adults only).

Endocrine
Decreased carbohydrate tolerance (infants only) and hirsutism.

Gastrointestinal
Pancreatitis (adults only), abdominal distention and ulcerative esophagitis.

General Disorders and Administration Site Conditions
Injection site reactions.

Metabolic
Hypokalemic alkalosis (infants only).

Musculoskeletal
Muscle weakness and vertebral compression fractures (infants only).

Neurological
Headache (adults only), vertigo (adults only), subdural hematoma, intracranial hemorrhage (adults only), and reversible brain shrinkage (usually secondary to hypertension) (infants only).

Possible Additional Steroidogenic Effects
Based on steroidogenic effects of Acthar Gel certain adverse events may be expected due to the pharmacological effects of corticosteroids. The adverse events that may occur but have not been reported for Acthar Gel are:

Dermatologic
Impaired wound healing, abscess, petechiae and ecchymoses, and suppression of skin test reactions.

Endocrine
Menstrual irregularities.

Metabolic
Negative nitrogen balance due to protein catabolism.

Musculoskeletal
Loss of muscle mass and aseptic necrosis of femoral and humeral heads.

Neurological
Increased intracranial pressure with papilledema, (pseudo-tumor cerebri) usually after treatment, and subdural effusion.

Ophthalmic
Exophthalmos.

DRUG INTERACTIONS

Formal drug-drug interaction studies have not been performed.

Acthar Gel may accentuate the electrolyte loss associated with diuretic therapy.

USE IN SPECIFIC POPULATIONS

Pregnancy
Pregnancy Class C: Acthar Gel has been shown to have an embryocidal effect. There are no adequate and well-controlled studies in pregnant women. Acthar Gel should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers
It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Acthar Gel, when treating a nursing mother, a decision should be made whether to discontinue nursing or to discontinue the drug, considering the risk and benefit to the mother.

Pediatric Use
Acthar Gel is indicated as monotherapy for the treatment of infantile spasms in infants and children less than 2 years of age. Both serious and other adverse reactions in this population are discussed in Warnings and Adverse Reactions in Infants and Children Under 2 Years of Age *[see Sections 5 and 6.1.1]*.

The efficacy of Acthar Gel for the treatment of infantile spasms in infants and children less than 2 years of age was evaluated in a randomized, single blinded (video EEG interpreter blinded) clinical trial and an additional active control supportive trial *[see Clinical Studies (14)]*. A responding patient was defined as having both complete cessation of spasms and elimination of hypsarrhythmia.

Safety in the pediatric population for infantile spasms was evaluated by retrospective chart reviews and data from non-sponsor conducted clinical trials *[see Adverse Reactions (6.1.1)]*. While the types of adverse reactions seen in infants and children under 2 years of age treated for infantile spasms are similar to those seen in older patients, their frequency and severity may be different due to the very young age of the infant, the underlying disorder, the duration of therapy and the dosage regimen. Effects on growth are of particular concern *[see Warnings and Precautions (5.12)]*. Serious adverse reactions observed in adults may also occur in children *[see Warnings and Precautions (5)]*.

OVERDOSAGE

While chronic exposure to Acthar Gel at high doses can be associated with a variety of potential serious adverse effects, it is not expected that a single high dose, or even several large doses, has the potential for serious adverse effects compared to a standard dose. There have been no reports of death or acute overdose symptoms from Acthar Gel in clinical studies or in the published literature.

The intramuscular route of administration makes it unlikely that an inadvertent acute overdose will occur. The typical daily dose of Acthar Gel to treat an infant that has a BSA of 0.4 m^2 would be 60 U/day. Using the 1-cc syringe supplied with Acthar Gel, the maximum amount that can be injected is 80 U/injection, which is a well-tolerated single dose.

HOW SUPPLIED / STORAGE AND HANDLING

Acthar Gel (repository corticotropin injection) is supplied as 5 mL multi-dose vial (63004-8710-1) containing 80 USP Units per mL. Acthar Gel (repository corticotropin injection) should be warmed to room temperature before using. Do not over pressurize the vial prior to withdrawing the product.

Store Acthar Gel (repository corticotropin injection) under refrigeration between 2° to 8°C (36° to 46°F). Product is stable for the period indicated on the label when stored under the conditions described.

PATIENT COUNSELING INFORMATION

Caretakers of patients with infantile spasms should be informed of the availability of a Medication Guide, and they should be instructed to read the Medication Guide prior to administering Acthar Gel. Patients should be instructed to take Acthar Gel only as prescribed. They should not stop treatment suddenly unless instructed by their physician to do so.

Patients, their caregivers and families should be advised as to the importance of the need for careful monitoring while on and during titration from Acthar Gel treatment and the importance of not missing scheduled doctor's appointments.

Patients, their caregivers and families should be advised that if the patient develops an infection or fever they should contact their physician. They should be educated that a fever may not necessarily be present during infection. The patient should also try to limit contact with other people with infections to minimize the risk of infection while taking Acthar Gel. *[see Warnings and Precautions (5.1) and Adverse Reactions (6.1.1)]*

Patients, their caregivers and families should be advised that if the patient experiences an increase in blood pressure they should contact their physician. *[see Warnings and Precautions (5.3) and Adverse Reactions (6.1.1)]*

Patients, their caregivers and families should be advised that if the patient or the caregiver notices blood or a change in color of the patient's stool they should contact their physician. *[see Warnings and Precautions (5.6)]*

Caregivers and families of infants and children treated with Acthar Gel should be informed that the patient may show signs of irritability and sleep disturbances. These effects are reversible once Acthar Gel therapy is stopped. *[see Warnings and Precautions (5.7) and Adverse Reactions (6.1.1)]*

Patients, their caregivers and families should be advised that changes in appetite, most often leading to weight gain, are seen with Acthar Gel therapy, becoming more frequent as the dose or treatment period increases. These effects are reversible once Acthar Gel therapy is stopped. *[see Warnings and Precautions (5.12) and Adverse Reactions (6.1.1)]*

Patients, their caregivers and families should be advised that the patient may be monitored for signs of adrenal insufficiency such as weakness, fatigue, lethargy, anorexia, weight loss, hypotension, abdominal pain or hyperpigmentation (adults only) after treatment has stopped. Since the recovery of the adrenal gland varies from days to months, patients may need to be protected from the stress of trauma or surgery by the use of corticosteroids during the period of stress. *[see Warnings and Precautions (5.2)]*

Patients should be advised not to be vaccinated with live or live attenuated vaccines during treatment with Acthar Gel. Additionally, other immunization procedures in patients or in family members who will be in contact with the patient should be undertaken with caution while the patient is taking Acthar Gel. *[see Warnings and Precautions (5.4)]*

Patients, their caregivers and families should be advised that prolonged use of Acthar Gel in children may result in Cushing's syndrome and associated adverse reactions, may inhibit skeletal growth, and may cause osteoporosis and decreased bone density. If prolonged use is necessary, Acthar Gel should be given intermittently along with careful observation. *[see Warnings and Precautions (5.2), (5.12), and (5.13) and Adverse Reactions (6.1.1)]*

Patients, their caregivers and families should be informed that Acthar Gel may mask symptoms of other diseases/disorders without altering the course of the other disease/disorder. The patient will need to be monitored carefully during and for a period following discontinuation of therapy for signs of infection, abnormal cardiac function, hypertension, hyperglycemia, change in body weight, and fecal blood loss. *[see Warnings and Precautions (5.5)]*

In the treatment of Infantile Spasms, other types of seizures may occur because some patients with infantile spasms progress to other forms of seizures (for example, Lennox-Gastaut Syndrome). Additionally the spasms sometimes mask other seizures and once the spasms resolve after treatment with Acthar Gel, the other seizures may become visible. Parents and caregivers should inform their physician of any new onset of seizures so that appropriate management can then be instituted. *[see Adverse Reactions (6.1.1)]*

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EDITORIAL

By Charles C. Wykoff, MD, PhD

Too many meetings? Sign me up

A colleague and friend recently approached me about starting a new retina meeting. The idea was good, but nevertheless the conversation made my stomach turn and led me to audibly groan. Really, do we need another?

Why are there so many retina meetings? We are inundated with meetings. There are, according to my rough calculations and Google searches, at least an average of about one meeting involving retina every 5.7 days, probably many more. Many of us spend far more time at meetings than we do in the operating room or out to dinner with our partner/spouse/kids!

It's a veritable alphabet soup of meetings: ASRS, IOIS, ARDS, ACRC, VBS, AAO, FAVS, ARVO, WOC, EVRS, WRC, etc. And, these are just some of the national and international CME meetings. The host of local society meetings, dinner symposia, advisory boards, steering committee meetings and planning sessions round out a truly overwhelming schedule for many in our beloved space.

Nevertheless, the more meetings I've attended, the more I've appreciated the value of each. Each embodies a unique character. Some are didactic while others are oriented to discussion; some are surgical; some emphasize new data while others are case-based. Many aim to incorporate all of these themes to differing degrees. They range from relaxed-anything-goes to erudite-choose-your-words-carefully. Something for everyone.

If your go-to meetings are the big ones, I encourage you to seek out some of the smaller meetings. The big meetings are fantastic, and hectic. The smaller meetings can provide unique opportunities for genuine debate, discussion and multi-directional exchange. Plus, they're often much more family friendly with smaller crowds that foster closer connections with colleagues. Amidst the winter-season of ski meetings, this year I'm attending the Squaw Valley Retinal Symposium in Tahoe for the first time, and look forward to hitting the slopes with my son.

In the end, I agreed to move ahead with the new meeting, this one aiming to provide a forum for debate and discussion related to optimizing clinical trial endpoints and designs. We are fortunate to be retina specialists, a group defined by productivity, willingness to engage new technologies and approaches, and a deep-seated drive to advance the boundaries of knowledge.

As far as I can tell, our plethora of meetings is unique across medicine, and something to cherish. See you at the meetings!

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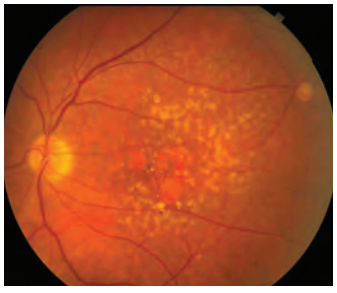
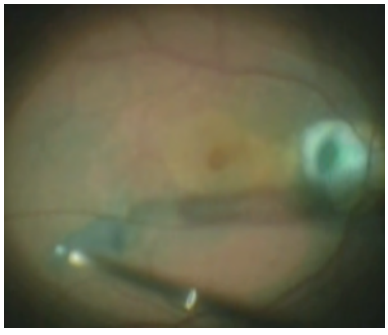
FEATURES

Pipeline Report



courtesy Sunir Garg, MD

DEPARTMENTS



CANTREAT: High-level evidence to support treat-and-extend out to two years

Retina specialists have long trusted that treat-and-extend is a medically valid approach for administering anti-VEGF agents in neovascular age-related macular degeneration, but with the publication of two-year results of the CANTREAT trial they now have Level 1 randomized clinical trial evidence that validates the treatment approach long term.[1]

"This gives us good long-term evidence to support what we do in practice," lead author Peter J. Kertes, MD, CM, of the Sunnybrook Health Sciences Centre and University of Toronto tells *Retina Specialist*. "It should give us a little bit more comfort in doing what we think is best for patients."

CANTREAT stands for the Canadian Treat-and-Extend Analysis Trial with Ranibizumab in Patients with Neovascular Age-Related Macular Degeneration. The trial randomized 580 patients to ranibizumab (Lucentis, Roche/Genentech) either monthly or T&E. At two years, 466 patients had completed the study. Patients in the T&E arm received an average of 17.6 injections compared with 23.5 in the monthly arm ($p<0.001$). The study also found that about 40 percent of patients could be extended out to 12 weeks maximum.

The following visual acuity outcomes were similar in both arms:

- a mean improvement of 6.8 and 6 letters in the T&E and monthly dosing arms ($p=0.21$);
- a gain of 15 or more letters in 25.5 and 23.1 percent of the respective arms ($p=0.59$); and
- a loss of 15 or more letters in 6.5 and 5.8 percent ($p=085$).

Dr. Kertes notes that the TREND2 study in Europe also provides convincing evidence of the effectiveness and safety of T&E, but that trial was stopped after one year. TREND, with 650 patients, and CANTREAT are similarly powered.

Two important elements of CANTREAT's design validate its findings, Dr. Kertes says: The randomization eliminated a bias in treatment allocation; and it took into account the nature of dropouts in an elderly population over two years. "I feel confident it was an adequately powered study."

He emphasizes that the CANTREAT findings don't invalidate monthly dosing with ranibizumab. "There are retina specialists who routinely treat every month, and that's not an unreasonable way to manage patients," he says. "The registry trials used monthly treatment."

Patients who require monthly treatment shouldn't be considered failures, Dr. Kertes says. "Different patients will have different intervals at which their disease remains quiescent. The goal is to never let that disease get ahead of you; hopefully it's less than every month, but if monthly dosing is necessary, that's acceptable."

Going forward, Dr. Kertes says the CANTREAT investigators expect to publish data on a cohort that has been followed out to three years. Other parameters they expect to explore are geographic atrophy, long-term intraocular pressure and predictive patient characteristics.

While the maximum extension in CANTREAT was 12 weeks, some patients may be extended out even longer, Dr. Kertes says. "As new agents come online and we're looking for more durable therapies, we have to think about those in the context of what we can achieve in many patients with a treat-and-extend regimen with ranibizumab," he says.

REFERENCES

1. Kertes PJ, Galic IJ, Greve M, et al. Efficacy of a treat-and-extend regimen with ranibizumab in patients with neovascular age-related macular disease: A randomized clinical trial. JAMA Ophthalmol. 2020 Jan 9. doi: 10.1001/jamaophthalmol.2019.5540. [Epub ahead of print]
2. Silva R, Berta A, Larsen M, Macfadden W, Feller C, Monés J; TREND Study Group. Treat-and-extend versus monthly regimen in neovascular age-related macular degeneration: results with ranibizumab from the TREND Study. Ophthalmology. 2018;125:57-65.

IN BRIEF

Retina specialists can now order the **Eylea prefilled syringe (Regeneron),** a 2-mg, single-dose prefilled syringe of aflibercept. The Food and Drug Administration approved the Eylea prefilled syringe in August.

Bausch + Lomb has initiated a clinical trial evaluating the safety and efficacy of a new cohesive ophthalmic viscosurgical device intended to provide surgeons with an additional option. This is the second new OVD that the company is developing.

The FDA has approved an orphan new drug application for **DORC's TissueBlue** (Brilliant Blue G Ophthalmic Solution) 0.025%. It's the first FDA-approved dye for use as an aid in ophthalmic surgery by selectively staining the internal limiting membrane.

Atherosclerosis study hints at link between bad diet and late-stage AMD

For generations researchers have worked to better understand the role of diet in age-related macular degeneration. Recently published results of a large study of people with atherosclerosis has potentially identified a link between unhealthy diets and late-stage AMD.[1]

A cohort study of the Atherosclerosis Risk in Communities (ARIC) study has reported that patients with characteristics of an unhealthy diet, labeled "Western" diet in the study, had a threefold higher odds of incident late AMD than people who leaned toward a healthy, or "prudent," diet in the study.

Lead author Amy Millen, MD, an epidemiologist at the State University of New York at Buffalo, describes how the two dietary patterns differ. "In our study, the Western pattern consisted of a high intake of processed and red meat, fried food, dessert, eggs, refined grains, high-fat dairy and sugar-sweetened beverages, and low intake of yogurt, low-fat dairy, fresh fruit, cruciferous vegetables, whole grains and carotene vegetables," she tells *Retina Specialist*. "The prudent pattern was defined by high consumption of all vegetables, including dark leafy vegetables, legumes, poultry, fish and seafood and by low intake of sugar sweetened beverages, fried food, coffee, processed meat, sweets and candy, eggs, ice cream and desserts."

The study focused on the link between dietary patterns and the 18-year incidence of AMD. It included ARIC patients who showed changes in AMD lesions on retinal photographs taken at two separate visits 18 years apart (117 patients had early AMD and 27 had late AMD). Patients were also asked to answer a 66-line item food questionnaire.

Quotable

"We should study how to motivate dietary change among those at high risk for AMD incidence or progression to help maintain vision over time."

— Amy Millen, MD

The study also found that the prudent diet was associated with a lower risk of developing AMD, but it was not statistically significant. However, the overall risk was 0.51 (p=0.954). Other work in Europe has generated supportive evidence that healthy diets are associated with decreased incident late AMD. This study points to a need for more cohort studies to better understand the risk between diet ant late AMD, Dr. Millen says.

"If we continue to see protective associations against the development or progression of disease in those consuming prudent-type diets and increased incidence of early or late AMD among those consuming Western-type diets, our next steps should focus on dietary modification trials to reduce vision loss," she says. "We should study how to motivate dietary change among those at high risk for AMD incidence or progression to help maintain vision over time." RS

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Multimodal imaging and diagnosing ARN

Retinal whitening plus vitreous inflammation mean raised suspicion for acute retinal necrosis.
By Matthew R. Starr, MD, and Jason Hsu, MD

Matthew R. Starr, MD

Jason Hsu, MD

A 42-year-old Caucasian male presented with a one-week history of blurry vision, foreign body sensation, eye injection and mild ocular pain in his left eye. His medical history was unremarkable. He wasn't taking any medications and denied any additional symptoms on a review of systems.

Workup and imaging findings

The patient appeared generally healthy, and his vital signs were within normal limits. On ocular examination, Snellen visual acuity with correction was 20/20 OD and 20/25 OS. Intraocular pressures were 17 mmHg OU. Pupil examination revealed a relative afferent pupillary defect OS. Anterior segment examination was unremarkable OD, but notable OS for moderate conjunctival injection, 2+ anterior chamber cell without keratic precipitates or iris transillumination deficits.

Posterior segment examination of the right eye was unremarkable. Posterior evaluation of the left eye showed 2+ vitreous cell with a large area of retinal whitening in the temporal peripheral retina with scattered patches of retinal whitening extending toward the posterior pole.

Perivascular hemorrhages with vascular sheathing were visible in the temporal retina (*Figure 1*). Fluorescein angiography of the left eye (*Figure 2*) revealed extensive hypofluorescence of the temporal retina likely associated with blocking from the areas of retinal whitening seen on the fundoscopic exam. There were additional areas of hypofluorescence associated with arteriovascular occlusion as well as areas of perivascular hyperfluorescence consistent with leakage.

Optical coherence tomography of the left eye revealed subretinal fluid emanating from the optic nerve as well as vitreous cells overlying the macula (*Figure 3*). The differential diagnosis of this patient with unilateral acute anterior chamber and vitreous inflammation with retinal whitening included infectious and potentially inflammatory etiologies. Infectious

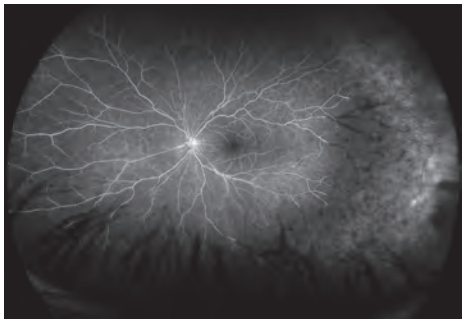

Figure 2. Fluorescein angiography of the left eye at 1:53 shows noticeable hypofluorescence temporally and inferiorly due to vascular occlusion as well as blockage from the retinal whitening and hemorrhages seen in Figure 1. Faint hyperfluorescence along some veins and arteries throughout the posterior pole is evident.

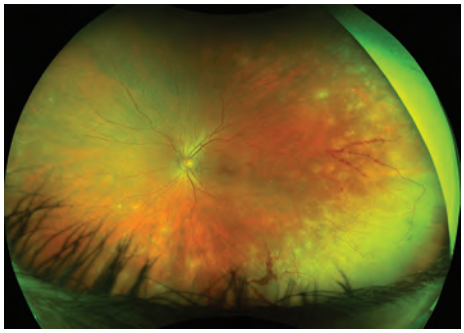

Figure 1. Fundus photograph of the left eye with clear media shows trace disc edema but with preservation of the disc margins, and a hemorrhagic vasculitis with sheathing affecting both arteries and veins mainly temporal and inferior. Discrete, granular areas of retinal whitening focused temporally with satellite lesions appear throughout the retinal periphery and even into the inferonasal retina, but most confluent in the inferotemporal retina.

Bios

Drs. Starr and Hsu are with Mid Atlantic Retina, Wills Eye Hospital, Thomas Jefferson University, Philadelphia.

DISCLOSURES: Drs. Starr and Hsu have no relevant financial relationships to disclose.

causes included bacterial (e.g., tuberculosis, syphilis, Lyme disease), viral (e.g., herpetic necrotizing retinitis, cytomegalovirus retinitis), or parasitic (toxoplasmosis). Inflammatory diseases such as sarcoidosis, lupus and antineutrophil cytoplasmic antibody-associated vasculitis were considered but thought to be less likely.

Early diagnosis is critical

Multimodal imaging played a valuable role in making the diagnosis of acute retinal necrosis (ARN) in this healthy middle-aged male. Early diagnosis of ARN is paramount because any delay in therapy can result in permanent vision loss.

Workup, diagnosis and treatment

Given the significant retinal whitening and evidence of obliterative vasculopathy on fluorescein angiography in the left eye, we emergently treated the patient with a single intravitreal injection of foscarnet 2.4 mg/0.1 mL and initiated oral valacyclovir 2 g t.i.d. We treated the patient's anterior uveitis with prednisolone acetate 1% q2h and atropine b.i.d. in the left eye.

We performed an anterior chamber paracentesis at the time of the intravitreal injection and sent the sample for polymerase chain reaction (PCR) testing for varicella zoster virus (VZV), herpes simplex virus (HSV)-1 and -2, cytomegalovirus and toxoplasmosis.

Blood work including syphilis serologies, quantiFERON-tuberculosis gold, anti-double-stranded-DNA antibody, lupus anticoagulant, angiotensin converting enzyme, a complete blood count, and a complete metabolic panel was normal.

Two days after presentation, the anterior chamber PCR returned positive for VZV. Two days after that we started the patient on oral prednisone 40 mg per day and slowly tapered over three weeks. We also slowly tapered his topical drops as the clinical course improved. Two months after presentation his visual acuity was 20/20 with early atrophy and scarring forming in the periphery. The retina remained attached without the use of prophylactic laser barricade (*Figure 4, page 10*).

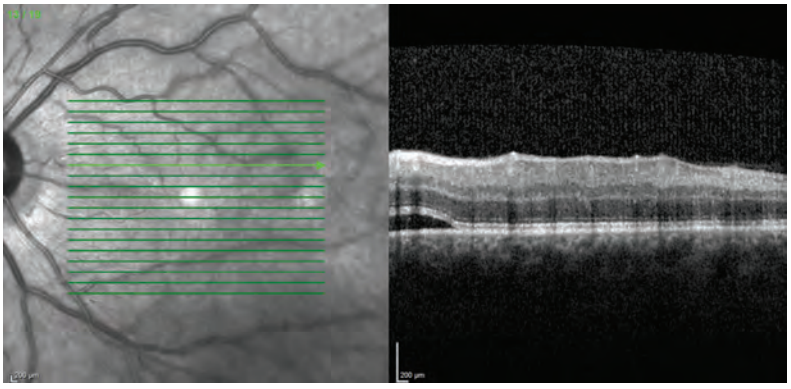

Figure 3. Optical coherence tomography of the left eye from Figure 1 with moderate subretinal fluid emanating from the optic nerve head as well as vitreous cells overlying the macula.

Disease presentation

Acute retinal necrosis typically presents with patches of peripheral retinal whitening that coalesce to form confluent areas of necrotic retina. The spread of the whitening typically occurs centripetally before spreading posteriorly towards the macula.[1] New areas of retinal whitening spread rapidly in the absence of antiviral medication, and an obliterative vasculopathy with retinal hemorrhages in the areas of retinal whitening can also occur. Interestingly, the disease routinely spares the macula.

The most common isolated viridin is VZV, found in up to two-thirds of patients with ARN,[2] while herpes simplex types 1 and 2 are the other common causes. Epstein-Barr virus (EBV) has been a reported cause of ARN; however, definitive proof is scant and most cases believed to be related to EBV were likely due to varicella.[2] The retinitis lasts four to six weeks, leaving scarred pigmented lesions in the place of previous retinal whitening.[3]

The border between the necrotic and perfused retina is a frequent site for the development of retinal tears, with up to 75 percent of untreated eyes developing rhegmatogenous retinal detachments

Early diagnosis of ARN is paramount because any delay in therapy can result in permanent vision loss.

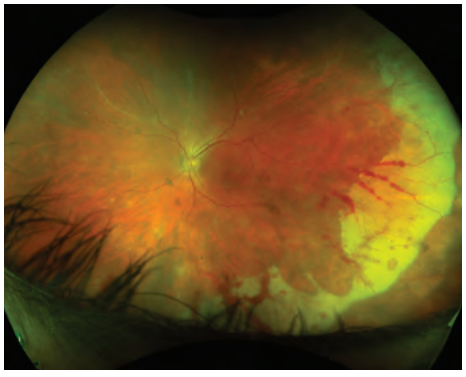

Figure 4. Fundus photograph of the left eye from Figure 1 three weeks after intravitreal foscarnet and high-dose systemic valacyclovir therapy and two weeks after oral prednisone were started shows improvement of the retinal whitening and hemorrhagic vasculitis temporally. New nasal vasculature sheathing is now apparent.

within one to two months after the onset of disease.[3] Bilateral involvement has been noted in roughly one-third of untreated cases and usually occurs within six weeks. However, very late involvement, even years after the initial diagnosis, has been reported.[4]

A high degree of suspicion for ARN is critical when encountering retinal whitening with vitreous inflammation on exam. The diagnosis is purely clinical.

Making the diagnosis

A high degree of suspicion for ARN is critical when encountering retinal whitening with vitreous inflammation on exam. The diagnosis of ARN is purely clinical. The American Uveitis Society lists the following required criteria when diagnosing ARN:[1]

- a focus of retinal necrosis with discrete borders;
- rapid progression of the disease in the absence of anti-viral therapy;
- circumferential spread of the disease;
- an occlusive vasculopathy with involvement of the arteries; and
- a significant anterior chamber and vitreous inflammatory response.

The most sensitive and specific means for diagnosis are PCR assays, which are able to detect a single virion from the biopsy.[5] Reports have indicated a sensitivity of 100 percent and specificity of 97 percent from vitreous biopsy PCR analyses,[6] while anterior chamber analysis can identify the specific viridin in approximately 86 percent of cases.[7]

If clinical suspicion remains high even after negative PCR testing, an endoretinal biopsy may be undertaken, making a note to take a sample in the zone between the normal and necrotic retina as this greatly increases the diagnostic yield.[8] Lastly, assessing immune status is crucial; a recent report found that as many as 16 percent of patients presenting with ARN have some form of impaired cellular immunity.[9]

Bottom line

The American Academy of Ophthalmology's position paper on the management of ARN stated that no differences were found between oral or intravenous antiviral therapies from treatment initiation to initial and complete remission of the necrosis.[10] High-dose oral valacyclovir (2 g q.i.d.) can achieve plasma levels similar to that of intravenous acyclovir; however, patients can still achieve favorable outcomes with a dosing of 2 g t.i.d. It's thus reasonable to treat viral necrosis with initial oral antivirals at the time of presentation.

Additionally, intravitreal antiviral injections such as foscarnet 2.4 mg/0.1 mL or ganciclovir 2 mg/0.1 mL are available as adjunctive therapy to systemic treatment and may further aid in controlling the spread of necrosis.[11] No consensus exists on the number of required injections or when to re-dose, but clinicians agree that more aggressive posterior disease may require repeated intravitreal injections.[10] Intravitreal injections offer an opportunity for vitreous or anterior chamber sampling, which can aid in identifying the causative virus.

Lastly, the use of prophylactic laser barricade in preventing retinal detachment is highly debatable. No prospective clinical trials have proven the effectiveness of laser

(Continued on page 15)

Department Editor *Akshay S. Thomas, MD, MS*

When to consider systemic treatments

Scenarios for systemic immunosuppression, and where conventional immunosuppressants and biologics fit in. By Laura J. Kopplin, MD, PhD

Laura J. Kopplin, MD, PhD

Akshay S. Thomas, MD, MS

The uveitides, particularly of the posterior segment, are a collection of diseases with the potential for permanent vision loss without careful control of intraocular inflammation. The systemic treatments available continue to expand, particularly with the ongoing development of biologic and small molecule inhibitor therapies. Here, we review the indications for pursuing systemic therapy, conventional immunosuppressants and biologic agents, along with future treatments under investigation.

When to consider systemic therapy

Systemic immunosuppression is frequently managed in conjunction with a rheumatologist. The patient and the treating ophthalmologist and rheumatologist must collaborate on a decision to proceed with a systemic agent. In cases with an active systemic autoimmune disease in which uveitis is one of several manifestations, the underlying condition will frequently direct the choice of therapeutic agent.

Consider systemic corticosteroids for uveitis in the following three scenarios:

- when other treatments fail to control the uveitis;
- in cases that require frequent or ongoing short-acting periocular or intravitreal steroid injections (to avoid "sawtooth decline"); and
- in pediatric patients who need frequent topical steroids.

A systemic approach may also be preferred in patients with known intraocular pressure steroid responses or those with bilateral disease.

Follow-up data from the Multicenter Uveitis Steroid Treatment (MUST) trial found systemic corticosteroids and immunosuppression yielded better visual acuity at seven years than a long-acting local corticosteroid implant (fluocinolone acetonide 0.59 mg).[1] Systemic adverse outcomes were similar between the treatment groups except when more frequent infections required treatment in the immunosuppression arm.[1] The goal of steroid-sparing therapy is to control ocular inflammation while allowing for taper of systemic corticosteroids to <7.5 mg daily, with complete taper off systemic corticosteroids being ideal.

Conventional immunosuppressants

Conventional immunosuppressants consist of three classes (*Table, page 12*): antimetabolites (methotrexate, mycophenolate, azathioprine); calcineurin inhibitors (cyclosporine, tacrolimus); and alkylating agents (cyclophosphamide and chlorambucil). Many physicians prefer methotrexate and mycophenolate as initial steroid-

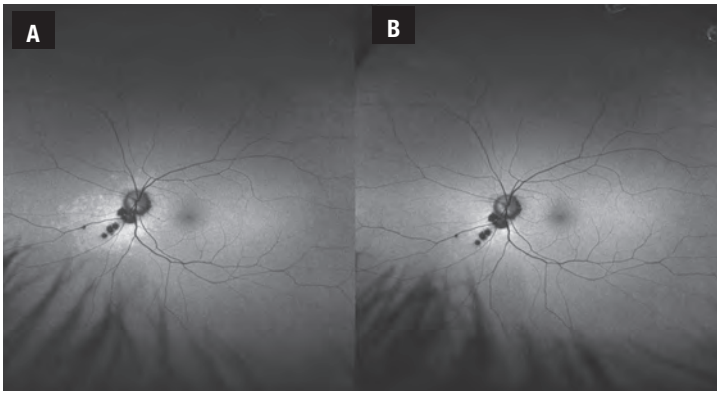

Figure 1. Fundus autofluorescence of multifocal choroiditis during a flare (A) and after starting azathioprine and a prednisone taper (B). Hyperautofluorescence improved following immunosuppressive therapy.

Bios

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DISCLOSURE: Drs. Koppin and Thomas have no relevant financial relationships to disclose.

sparing therapies because they have fewer side effects than azathioprine.

However, azathioprine is often used in women with plans for childbearing due to the teratogenic potential of methotrexate and mycophenolate. In the Systemic Immunosuppressive Therapy for Eye Diseases (SITE) cohort, methotrexate, mycophenolate and azathioprine therapy resulted in control of uveitis with a corticosteroid sparing effect in 58, 55 and 47 percent of subjects, respectively, within a year of therapy (*Figure 1, page 11*).[2-4]

The First-line Antimetabolites as Steroid-sparing Treatment (FAST) trial recently compared oral methotrexate 25 mg weekly with mycophenolate mofetil 3 g daily in a randomized fashion for noninfectious intermediate, posterior and panuveitis. The study found methotrexate to be noninferior to mycophenolate in controlling uveitis with a corticosteroid-sparing effect by six months of treatment.[5] Either methotrexate or mycophenolate is a reasonable first-line agent in patients requiring a steroid-sparing treatment. The individual patient's social and medical history and personal preferences should play a role in the agent selected.

Calcineurin inhibitors are most commonly used in conjunction with an antimetabolite in cases where antimetabolite monotherapy is inadequate to control uveitis. Now many physicians will escalate therapy to a biologic agent, most commonly a tumor necrosis factor (TNF) inhibitor, rather than adding a calcineurin inhibitor.

Due to the associated risk for malignancies, alkylating agents are typically reserved for severe, recalcitrant cases of uveitis, although they have the potential to induce remission.[6] All conventional immunosuppressants carry an increased risk for infection and require routine monitoring of blood counts and hepatic and renal function for toxicity.

Biologic treatments

Biologic therapies, engineered proteins that target specific immune molecules, are

Common immunosuppressants for treatment of uveitis

Medication (brand name, manufacturer)	Mechanism of action	Dosage/route	Potential side effects/complications
Methotrexate	Antimetabolite	10 to 25 mg weekly oral or subcutaneous injection	Infection, hepatotoxicity, renal toxicity, bone marrow suppression, nausea, fatigue, oral ulcers, hair thinning
Mycophenolate (CellCept, Genentech; Myfortic, Novartis)	Antimetabolite	1,000 to 1,500 mg b.i.d. oral	Infection, hepatotoxicity, renal toxicity, bone marrow suppression, nausea, diarrhea
Azathioprine (Azasan; Imuran)	Antimetabolite	2 to 3 mg/kg day oral	Infection, hepatotoxicity, renal toxicity, bone marrow suppression, nausea, flu-like allergic reaction
Cyclosporine	Calcineurin inhibitor	2.5 to 5 mg/kg day oral	Infection, renal toxicity, hypertension, hirsutism, gingival hyperplasia
Adalimumab (Humira, AbbVie)	Tumor necrosis factor (TNF) inhibitor	40 mg subcutaneous injection q2w after loading doses	Infection, reactivation of tuberculosis or hepatitis, injection site reaction, demyelinating disease, heart failure, drug induced autoimmune disease
Infliximab (Remicade, Janssen)	TNF inhibitor	3 to 10 mg/kg IV infusion every q4-8w after loading doses	Infection, reactivation of tuberculosis or hepatitis, infusion reaction, demyelinating disease, heart failure, drug induced autoimmune disease
Tocilizumab (Actemra, Roche/Genentech)	Anti-interleukin 6 receptor	4 to 8 mg/kg intravenous q4w	Infection, infusion reaction, gastrointestinal perforation, dyslipidemia, elevated liver enzymes, cytopenia, hypertension

becoming increasingly important in treating severe uveitis. The most used class, TNF inhibitors, consists of five agents:

- adalimumab (Humira, AbbVie);
- infliximab (Remicade, Janssen);
- certolizumab (Cimzia, UCB);
- golimumab (Simponi, Janssen); and
- etanercept (Enbrel, Amgen).

TNF inhibitors require baseline screening for tuberculosis and hepatitis, and should be avoided in patients with known demyelinating disorders (*Table*).

The Food and Drug Administration approved adalimumab, administered subcutaneously, in 2016 for treatment of noninfectious intermediate, posterior and panuveitis. Clinical trials demonstrated adalimumab increased time to treatment failure in both active and corticosteroid-dependent inactive uveitis after systemic corticosteroid taper (*Figure 2*).[7,8] A trial also found adalimumab effective for juvenile idiopathic arthritis uveitis incompletely controlled with methotrexate.[9]

Infliximab, another TNF inhibitor administered intravenously, also shows significant evidence for efficacy in treating uveitis. Golimumab and certolizumab have been used successfully in some cases of uveitis refractory to other TNF inhibitors. Etanercept is less effective in controlling ocular inflammation and isn't recommended for management of uveitis.

Anti-IL6 receptor

Inhibition of the interleukin-6 signaling pathway has shown efficacy in treating intermediate, posterior and panuveitis in two small clinical trials of tocilizumab[10] and sarilumab.[11] A retrospective case series of tocilizumab (Actemra, Roche/Genentech) demonstrated efficacy in treating refractory uveitic macular edema in patients with a history of failing TNF inhibitor therapy.[12] As with other biologic therapies, anti-IL6 therapy carries an increased risk for infection; the use of this class of drug requires monitoring for cytopenias and transaminitis (*Table*).

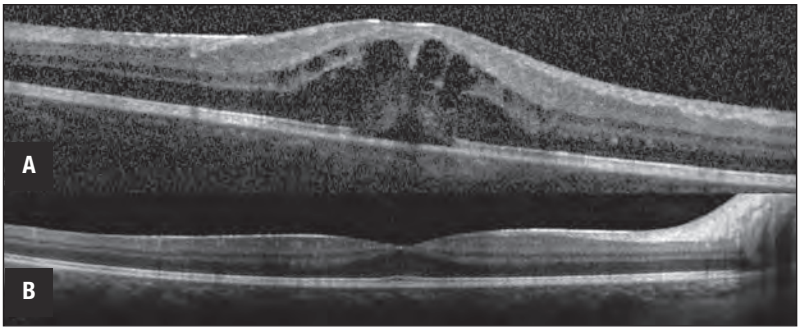


Figure 2. Optical coherence tomography before (A) and after (B) treatment of intermediate uveitis with adalimumab (Humira, AbbVie). The patient required ongoing adalimumab therapy to maintain quiescence and resolution of the edema.

Future therapies

New systemic therapeutics continue to be investigated for use in uveitis. Randomized clinical trials to assess the efficacy of Janus kinase inhibitors are being conducted in intermediate, posterior and panuveitis (NCT03207815) and in juvenile ideopathic arthritis-associated uveitis (NCT04088409). Continued efforts are also being made to compare the effectiveness of agents already available, including a randomized controlled trial comparing the effectiveness of adalimumab vs. conventional agents in corticosteroid sparing inflammation control of noninfectious intermediate, posterior and panuveitis (NCT03828019).[13]

Bottom line

Systemic immunosuppression remains a mainstay in the management of uveitis, particularly to avoid patient exposure to long-term corticosteroids. Many patients will require therapy with more than one agent to control their disease. Collaboration and close communication with rheumatology colleagues are key in selecting an appropriate therapeutic regimen, in determining how patients respond to and tolerate the medications, and in ensuring treatment advances in persistent cases. RS

(References continued on page 15)

Systemic immunosuppression remains a mainstay in managing uveitis, particularly to avoid patient exposure to long-term corticosteroids.

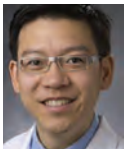
Department Editor ***Paul Hahn, MD, PhD***

Refractory optic pit maculopathy surgery

This approach for this challenging operation uses an internal limiting membrane flap as a 'plug.' By Mark P. Breazzano, MD, and Royce W.S. Chen, MD

Mark P. Breazzano, MD

Royce W.S. Chen, MD



Paul Hahn, MD, PhD

Bios

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Dr. Hahn is a partner at New Jersey Retina in Teaneck.

DISCLOSURES: Dr. Hahn is a consultant to Alcon.

Optic pit maculopathy can be surgically challenging and has variable outcomes. While many cases may resolve spontaneously, others persist and may be amenable to a variety of approaches. Here, we describe our approach after failed initial vitrectomy with internal limiting membrane peeling to improve the macular fluid associated with the optic pit.

Specifically, we use a flap of internal limiting membrane to "plug" the pit,[1] using perfluorocarbon liquid to displace macular fluid while making a small retinotomy for draining submacular fluid. We also apply endolaser to barricade the subretinal space between the pit and outer macula.

Surgical technique

We prefer smaller-gauge vitrectomy (25- or even 27-ga) in these cases. We inject indocyanine green dye to stain the remaining ILM, which we then peel toward both arcades (*Figure A*). Carefully and gently, we place the subsequent ILM flap into the optic pit (*Figure B*). Any vitreous plug or remnants within the optic pit should first be removed, which can often be observed with preoperative optical coherence tomographic imaging.[2]

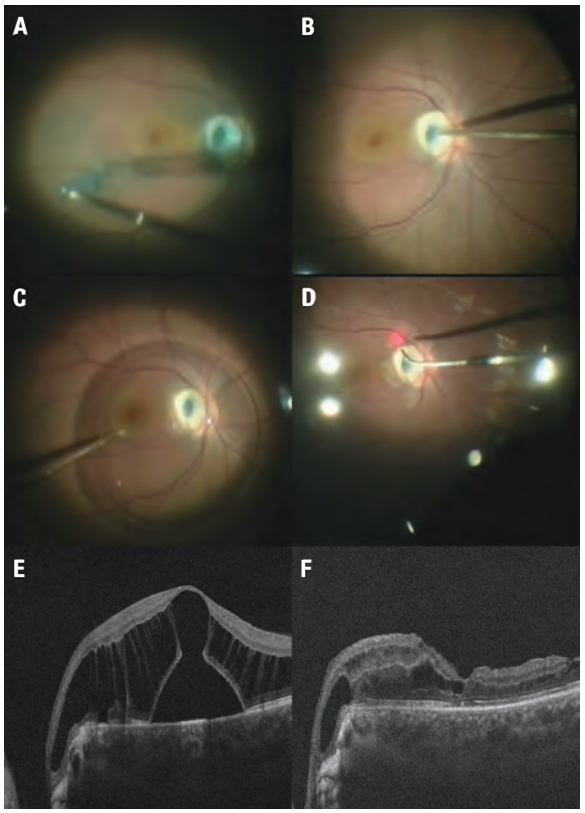
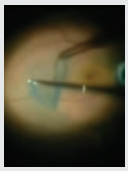


Figure. Surgery for reoperation of optic pit maculopathy involves the following steps: A) indocyanine green stains the previously peeled internal limiting membrane to enable an additional, broader peel toward both arcades; B) the flap of peeled internal limiting membrane is then carefully placed into the optic pit: C) diathermy is then focally administered at the edge of the macular fluid, as far from the fovea as possible and the resulting retinotomy is then used for drainage with a back-flush cannula; and D) endolaser is applied with a single row just temporal to the optic disc. Preoperative optical coherence tomography (E) shows marked intraretinal and subretinal fluid communicating with the optic pit with 20/400 visual acuity, and the last postoperative visit (F) demonstrates 20/50 visual acuity and improvement in fluid on OCT.

An injection of PFCL near the optic nerve displaces the macular fluid. A side-flow cannula avoids sudden pressure fluctuations, and the tip of the cannula should always stay within the bubble. PFCL is injected until it reaches the anterior-most fluid in the macula.

A small retinotomy on the edge of the macular fluid collection is created with diathermy (*Figure C*). A backflush cannula drains the subretinal fluid through the

View the Video



Watch as Drs. Breazzano and Chen perform surgical repair of refractory optic pit maculopathy. Available at: http://bit.ly/VideoPearl_015

retinotomy, first with active and then passive aspiration. A partial air-fluid exchange removes infusion fluid but maintains the PFCL bubble for ongoing displacement of residual papillomacular fluid.

Application of endolaser creates a retinopexy 180 degrees temporally around the optic nerve in a single row (*Figure D*), as well as around the retinotomy. The residual PFCL is removed with additional and complete air-fluid exchange. Finally, 15% C3F8 gas is then exchanged.

We instructed this patient to remain face-down for one week. By six months, vision improved from 20/400 preoperatively (*Figure E*) to 20/50 with a marked decrease in macular fluid at the last postoperative exam (*Figure F*).

Bottom line

Optic pit maculopathy is poorly understood and the best surgical approach isn't well-defined. In cases of optic pit maculopathy refractory to initial vitrectomy, a combination of various approaches, including plugging the pit, draining subretinal fluid, temporal peripapillary endolaser, long-acting gas and face-down positioning, may increase the chances of success.

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Multimodal imaging and diagnosing ARN

(Continued from page 10)

demarcation, while the studies advocating for it likely had a component of sampling bias as many of the eyes that didn't receive laser were more likely to have media opacities limiting its use.[12]

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When to consider systemic treatments

(Continued from page 13)

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The latest in AI for managing DR

In ongoing investigations, artificial intelligence platforms have shown strong sensitivity and specificity in monitoring diabetic retinopathy.

Jennifer I. Lim, MD

Jennifer I. Lim, MD

Take-home points

- Existing deep-learning algorithms have demonstrated high sensitivity and specificity as point-of-care tools for screening diabetic retinopathy.
- Artificial intelligence systems that perform automated assessment of images of patients with diabetes have been shown to be more cost-effective, efficient and possibly more accurate than human graders.
- Telemedicine still has hurdles to overcome, evidenced by a study that showed only 40 to 55 percent of patients in primary-care clinics underwent screening although it was made available to all.
- AI systems used to screen DR require a high sensitivity for detection of sight-threatening retinopathy to be safe and a high specificity to distinguish DR from other conditions.

The International Diabetes Federation estimated in 2017 that 8.5 percent of the world's population is affected by diabetes mellitus.[1] This translates to about 415 million people afflicted with DM currently and a projected 642 million people by 2040. All of them require screening examinations for the detection of diabetic retinopathy.

DR screening with timely treatment can prevent blindness. The American Academy of Ophthalmology recommends that patients with type 1 DM should first be screened within five years of onset and then yearly after 10 years duration.[2] For type 2 DM patients, the AAO recommends DR screening at the time of diagnosis and then annually. Numerous studies support the association of earlier treatment with better outcomes.[3,4] Yet, only a fraction of diabetes patients have DR screening. Several factors contribute to this low rate: lack of transportation; lack of insurance; noncompliance with recommendations and follow-up; and poor access to health care. Some of these are related to health-care disparities.[5]

This article looks at the latest research into artificial intelligence for DR and provides updates on the systems either available commercially or in the advanced stages of development.

Challenge of more DR screenings

Possible solutions to increase the proportion of patients getting DR screening include mobile screening units, remote telescreening using fundus photography[6] and point-of-care screening using automated analysis of fundus photos with artificial intelligence networks.[7] Mobile screening units are expensive and their access is limited to the geographical location of the mobile clinic. Tele-ophthalmology screening using fundus photography requires trained personnel to take photos and ophthalmologists to read the images. Since remote and

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DISCLOSURES: Dr. Lim has no relevant relationships to disclose.

multiple locations feed fundus photographs to the ophthalmologist, telemedicine has greater reach.

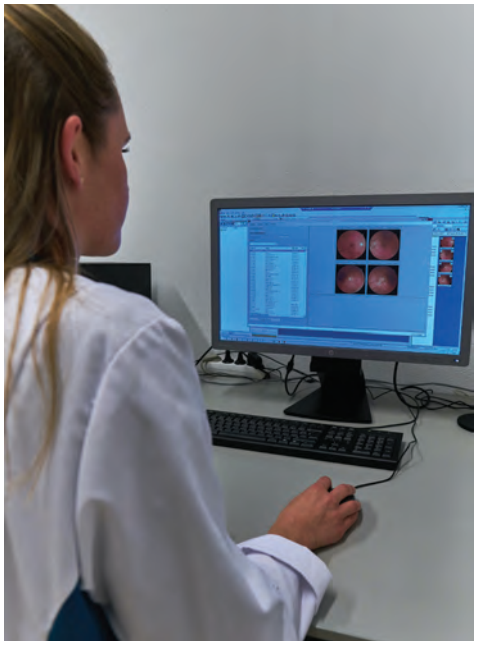
Use of retinal images in traditional telescreening results in a lag in relaying the results to the patient. In contrast, AI systems can "read" the fundus image within seconds and inform the patient quickly whether she needs further evaluation or if he or she can return for a screening visit in a year. Within minutes, these systems evaluate thousands of images to efficiently triage patients for referable diabetic retinopathy. AI systems that perform automated assessment of images would be more cost-effective, efficient and may also have improved accuracy compared to human grading.

In a systematic review of 18 studies, Francisco Pasquel, MD, and colleagues at Emory University evaluated the cost-effectiveness of various DR screening approaches.[8] They concluded "the ideal screening technology must be portable, noninvasive, reliable and easy to use by relatively unskilled persons." A Veterans Health Administration study also validated the cost-effectiveness of telescreening for DR.[9] Although telemedicine was available to all patients in the primary-care clinics, only 40 to 55 percent had annual screenings, suggesting that there are still hurdles to overcome.[10]

Ease and efficiency of fundus images

Research has validated the use of fundus photos for DR screening. Initially 30-degree Early Treatment Diabetic Retinopathy (ETDRS) photos were shown to be comparable to retina specialists for the detection of DR.[11] As early as 2011, automatic detection of DR was possible.[12] More recently, 45-degree photos have been shown to be equivalent to seven-field ETDRS images.[13] This simplifies the number of fundus photographs required for DR screening. Alternatives to 45-degree fundus photos are spectral-domain optical coherence tomography or OCT angiography images. However, these are significantly more expensive and studies have not yet validated these methods for detection of DR.

Several AI systems designed to screen for DR utilize fundus photos. When evaluating these AI systems, sensitivity is indicative of safety and specificity of effectiveness. That is, a high sensitivity for detection of sight-threatening retinopathy is needed for the system to be safe. A high specificity is also needed so that the system can distinguish DR from other conditions and thus be an effective screening tool. Several AI systems are capable of detecting DR.



The IDx-DR system demonstrated a sensitivity of 87.2 percent and a specificity of 90.7 percent for detection of more-than-mild diabetic retinopathy in a pivotal trial of 900 patients in primary-care offices. (*Photo courtesy IDx-DR*)

IDx-DR paves the way

The IDx-DR system is the first commercially available AI diabetic screening system.[14] Earlier versions of IDx-DR were evaluated as part of the Iowa Detection Program (IDP). With modifications to the IDP algorithms, improved sensitivity with maintained specificity resulted. The IDx-DR uses two 45-degree fundus images, which trained staff captures with a Topcon non-mydriatic fundus camera.

The IDx-DR algorithm determines the presence of more-than-mild DR (mtmDR), defined as ETDRS level 35 or higher and/or diabetic macular edema in at least one eye. Presence of mtmDR triggers a recommendation for ophthalmic evaluation.

A pivotal trial of 900 patients in primary-care offices found a sensitivity for detection of mtmDR of 87.2 percent and a specificity of 90.7 percent.[15] Study patients underwent IDx-DR imaging and four-widefield stereoscopic fundus photographs (equivalent to the area of the retina covered by the modified seven-field stereo film ETDRS protocol) and macular OCT. The study compared the detection rate of

The current deep-learning algorithms have shown both high sensitivity (safety) and high specificity (effectiveness) and thus show that they can enable point-of-care diabetic retinopathy screening.

mtmDR with the IDx-DR system to the Wisconsin Fundus Photograph Reading Center (FRCP) certified retinal photographers' readings of the reference standards (photos and OCT).

The Food and Drug Administration approved this first fully autonomous AI diagnostic system in 2018.[16] IDX-DR systems have since been deployed to several locations and studies are ongoing to further evaluate its effectiveness. By collaborating with locations using the IDx-DR, investigators currently seek to find out whether patients who were advised to see an eye-care provider are doing so and being treated for DR.

Google Deep Mind

Google Deep Mind is a convolutional neural network-based DR-detection algorithm first published in 2016.[17] Deep Mind showed a high sensitivity and specificity for detection of DR. This DR deep-learning (DL) algorithm was used on the Messidor-2 dataset as well as a retrospective dataset of 9,963 images taken as part of routine DR screening in the United States and India. The algorithm performed well compared to human graders (seven for the Messidor-2 and eight for the other set), using a majority decision as a reference standard for referable retinopathy.

When evaluated on the Messidor-2 images, the DL algorithm, when tuned for high sensitivity, resulted in 96.1 percent sensitivity and 93.9 percent specificity. When tuned for high specificity, the sensitivity was 87 percent and specificity 98.5 percent. When used on the retrospective data set and tuned for high sensitivity, sensitivity was 97.5 percent and specificity 93.4 percent. When tuned for high specificity, sensitivity was 90.3 percent and specificity 98.1 percent. These results are quite good and suggest both safety in detecting referable DR and efficacy in that false positives were low (1-specificity).

A nationwide DR screening program in Thailand validated the Google DL algorithm in a community setting.[18] A total of 25,326 gradable retinal images from 7,517 patients with diabetes were analyzed for different DR severity levels and macular edema. The algorithm was improved from detection of referable and non-referable DR into detection of the five severity levels of DR. This study performed grading adjudication among an international group of retinal specialists with a majority consensus serving as the reference standard.

Compared with human graders, the algorithm had higher sensitivity across all severity levels of DR and DME ($p < 0.001$). For detecting different severity levels for referrals (moderate nonproliferative DR, severe NPDR, proliferative DR and DME), the algorithm also had significantly higher sensitivity (0.97 vs. 0.74, $p<0.001$) and slightly lower specificity (0.96 vs. 0.98, $p<0.001$). False negatives were reduced by 23 percent at the cost of a 2 percent increase in false positives.

EyeArt System

Another DL-based system is the EyeArt system (Eyenuk). This system of multiple deep-neural networks for specific classification tasks on images was trained on 375,000 images and validated on 250,000. EyeArt uses cloud-based software and has an application that can interface with existing imaging and telescreening software.

The system analyzes 45-degree fundus photos to determine the presence of referable DR within 60 seconds. It uses the International Classification of Diabetic Retinopathy (ICDR) definition of greater than or equal to moderate NPDR and or clinically significant DME to define referable DR. It also generates a recommendation report regarding patient disposition, referral or return for future screening.

The EyeArt system was studied on smartphone app-based fundus images. The study analyzed retinal images of 296 patients taken with a Remidio Fundus on Phone device. Even though the EyeArt algorithms were not trained on smartphone-based fundus

photography, EyeArt achieved a sensitivity of 95.8 percent for any DR, 99.3 percent for referable DR and 99.1 percent for sight-threatening DR, with specificities of 80.2, 68.8 and 80.4 percent, respectively.[19]

A point-of-care prospective study at 15 sites (primary care, endocrinology, ophthalmology and retina offices) recently evaluated EyeArt to screen for referable DR. Adult patients were included if they had a diagnosis of DM and excluded if they had known other retinal vascular disease, documented DME, prior retinal laser or prior eye surgery other than cataract extraction. In this study, non-mydriatic (or mydriatic images, mydriasis allowed if needed), 45-degree, two-field fundus photos were uploaded to the cloud for determination of referable DR. The system's determination of referable DR was compared to four 45-degree, widefield stereoscopic mydriatic photos read by the Wisconsin FPRC.

Of the 1,830 images, 1,674 were gradable by both the EyeArt System and the reading center. Of 1,364 eyes negative for referable DR, EyeArt correctly identified 1,180 with 184 false positives, which were composed mostly of mild NPDR. Of 310 eyes positive for referable DR, EyeArt correctly identified 296 of them. False negatives were all composed of level 35 moderate NPDR. Sensitivity was 96 percent, specificity 86 percent and gradability 87.5 percent, increasing to 97.4 percent with dilation as needed.

SERI-NUS System

The Singapore Eye Research Institute (SERI) has developed and validated the SERI-NUS DL system on more than 500,000 fundus images.[20,21] This system has shown a sensitivity of 90.5 percent and specificity of 91.3 percent for detection of referable DR compared to 91.6 percent sensitivity and 99.3 percent specificity by professional graders.[22] For detection of sight-threatening DR, sensitivity was 100 percent and specificity 91.1 percent compared to 88.6 percent sensitivity and 99.6 percent specificity of human graders.

Unlike other systems, SERI-NUS also has algorithms for detecting glaucoma suspects (cup-to-disc ratio $\geq$0.8 or presence of optic disc hemorrhage or notching), or intermediate or higher AMD. Sensitivity and specificity were 96.4 and 87.2 percent, respectively, for the glaucoma algorithm, and 93.2 and 88.7 percent, respectively, for the AMD algorithm. Area under the curve was high for both (0.942 for glaucoma and 0.931 for AMD)—important as these patients after a certain age need yearly check-ups.

Bottom line

The current DL algorithms have demonstrated both high sensitivity (safety) and high

(Continued on page 38)

Machine learning training neural networks

Aside from deep-learning systems, machine-learning systems use specified features of a disease to train the neural networks. These systems don't require the huge number of inputs that a DL system requires in order to "learn" to identify a disease.

RetmarkerDR by Retmarker in Portugal is a system that uses feature-based machine learning algorithms. It can sort images into disease presence or absence based upon the feature. In addition, it's capable of comparing current images to images from a prior screening, thus establishing whether disease progression occurred. RetmarkerDR can detect the "microaneurysm turnover rate"—the rate that new microaneurysms form and old microaneurysms disappear.[23] Some studies have shown this feature is useful for determining progression to clinically significant diabetic macular edema.

Sensitivities for RetmarkerDR were 73 percent for any retinopathy, 85 percent for referable retinopathy and 97.9 percent for proliferative diabetic retinopathy. The system's false-positive rate was 47 percent. A recent study found RetmarkerDR and the EyeArt artificial intelligence systems to be cost-effective for detection of referable retinopathy compared to human graders.[24]

A system at the University of Illinois at Chicago has been developed based upon machine learning and the optical coherence tomography angiography features of DR. This system classifies DR based upon six key features:

- blood vessel tortuosity;
- blood vascular caliber;
- vessel perimeter index;
- blood vessel density;
- foveal avascular zone (FAZ) area; and
- FAZ contour irregularity.

These features have been validated for objective classification and staging of DR.[25,26] The Support Vector Machine algorithm uses these features to classify an image as DR vs. control (no DR) and also to classify the DR as mild, moderate or severe. It needs further work to identify PDR and DME.

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LEARNING OBJECTIVES
After participating in this educational activity, attendees should be able to:

- Describe how new research pertains to emerging issues in glaucoma, including risk assessment, imaging, management and progression analysis.
- Consider how the latest research can impact selection of medical and surgical treatments for glaucoma patients.
- Understand how specific procedures and devices, including MIGS, address outflow and assist in glaucoma management.
- Develop customized treatment plans for cataract patients based on both clinical findings and lifestyle needs.
- Discuss the mechanism of action of various short- and long- term therapies for dry eye and select appropriate treatment.
- Outline the rationale for current and investigational treatments for posterior segment diseases, including age-related macular degeneration and diabetic macular edema.
- Recognize how inflammation fits into the pathophysiology of retinal disease and consider the consequences of inflammation when it is left untreated.
- Discuss how various imaging technologies, such as OCT and angiography, can assist in diagnosing and monitoring ocular conditions.
- Consider new approaches to ophthalmic drug delivery.
- Describe options for cosmetic facial procedures, including neurotoxins and fillers.
- Recognize the vision and life threatening conditions in neuro-ophthalmology.

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How SD-OCT is enhancing our management of DR

The high speed of spectral-domain optical coherence tomography enables imaging of the retinal layers and vasculature all at once.

Emily S. Levine, MTM

Nadia K. Waheed, MD, MPH

Jay S. Duker, MD

By Emily S. Levine, MTM, Nadia K. Waheed, MD, MPH, and Jay S. Duker, MD

Take-home points

- Optical coherence tomography has been a vast improvement over the limitations of fundus photography and fluorescein angiography for the diagnosis and management of diabetic macular edema.
- OCT has been shown to be more objective and accurate for evaluating macular thickness than the standard assessment imaging outlined in the Early Treatment Diabetic Retinopathy Study.
- After initial anti-VEGF treatment for non-center-involving diabetic macular edema, qualitative evaluation and thickness measurements between baseline and follow-up OCT scans allow physicians to follow the patient's progress and determine management.
- Other indications for OCT in managing DR include evaluating unexplained visual acuity loss and detecting other forms of macular disease.

Laser therapy was a major breakthrough in diabetic retinopathy treatment, with its efficacy validated by a number of clinical studies in the last three decades of the 20th century. However, it relied on fundus photography and fluorescein angiography to diagnose clinically significant macular edema. Since then, optical coherence tomography has revolutionized the clinical management of diabetic macular edema because of its widespread availability, ease of use, and ability to quantify DME noninvasively. This tool has become even more powerful coupled with the emergence of pharmacotherapies to treat the disease.

Here, we review how OCT has changed the way retina specialists manage DR and explore the latest research into spectral-domain OCT and OCT angiography.

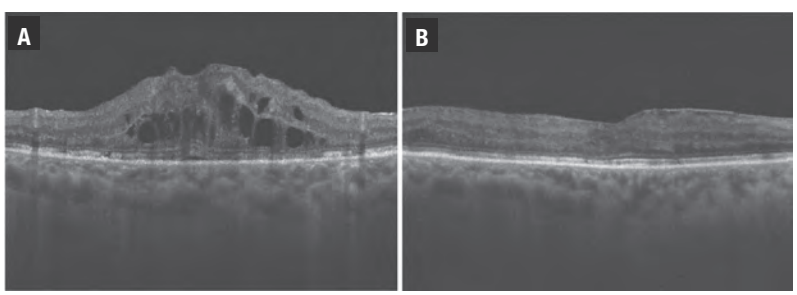

Figure 1. Spectral-domain optical coherence tomography of the right eye of a 73-year-old patient with type 1 diabetes showing (A) moderate nonproliferative diabetic retinopathy with clinically significant cystoid macular edema and (B) resolution of edema one month after intravitreal injection of aflibercept (Eylea, Regeneron Phrmaceuticals).

Lasers relied on subjective judgment

Prevention of DR with tight control of blood glucose levels and hypertension would be ideal, but progression of the disease to DME typically warrants medical or procedural intervention. Until the development of pharmacotherapy, laser therapy remained the standard of care for both DME

and proliferative diabetic retinopathy. Its clinical efficacy as a tool to treat DR was first established in 1971 with the multicenter, randomized Diabetic Retinopathy Study (DRS), which showed that laser panretinal photocoagulation (PRP) significantly decreased the risk of severe vision loss in patients with PDR.[1]

The Early Treatment Diabetic Retinopathy Study (ETDRS) was designed to evaluate argon laser photocoagulation in the management of patients with non-proliferative DR and early PDR, as well as DME. In 1985, the first report from the ETDRS recommended macular laser to treat clinically significant macular edema (CSME).[2]

The ETDRS defined CSME as retinal thickening or hard exudates associated with adjacent retinal thickening involving the center 500 µm of the macula or threatening to involve it. This clinical definition set the standard for assessing DME for many years. Importantly, at the time of these studies, the diagnosis of CSME was subjectively based on stereo fundus photography and fluorescein angiography.

OCT changed course of diagnosis

The advent of OCT changed the course of DR management. OCT uses the reflectivity of ocular structures to portray *in vivo* cross-sectional images of the retina. It does so using interferometry to measure the interference pattern between the light backscattered from the sample (e.g., the retina) and a reference.[3]

Before OCT's clinical debut in the mid-1990s, the *en face*, two-dimensional nature of imaging made the quantification of macular thickness difficult. Even the standard of care, stereoscopic imaging, did not sufficiently detect subtle macular edema. The novelty of OCT lay in its ability to generate cross-sectional images of the retina that paralleled histology, such that the retinal layers and pathologic features could be assessed and measured *in vivo*.[3,4]

Burgeoning clinical data on OCT in the late 1990s and into the 2000s produced novel insights into the characterization of DME. A variety of DME classification schemes were developed to account for newly visualized morphological changes, including patterns of fluid accumulation (*Figure 1*) and the presence of vitreomacular traction.[5,6] Critically, OCT could also quantify the degree and location of macular thickness. OCT was consequently found to be more objective and accurate for the evaluation of macular thickness than the standard assessment imaging outlined by the ETDRS.[7-9]

OCT and pharmacotherapies

Serendipitously, the maturation of standard OCT assessment coincided with the arrival of pharmacological agents such as anti-VEGF drugs and corticosteroids, and the need to assess their efficacy for treating DME. Large multicenter clinical trials, from industry-sponsored trials such as RISE and RIDE to the Diabetic Retinopathy Clinical Research Network (DRCR.net) collaboration, adopted OCT as an objective tool to measure retinal thickness in their patients.[10,11]

Specifically, OCT was used in early clinical trials to subdivide CSME based on the presence or absence of central macular involvement with a central subfield thickness (CST) of ≥250 to 275 µm as enrollment criteria.[11,12] CST is a mean of thickness values obtained in the circular 1-mm diameter area centered at the fovea, which was found to be highly reproducible and therefore valued as a standard OCT measure across studies.[13,14]

OCT for measuring central thickness led to the bisection of the term CSME into definitions now commonly used today: center-involving and non-center-involving edema. This distinction was made because foveal center involvement is associated with a higher risk of vision loss and greater need for treatment. However, while it's clinically useful to measure central macular thickness to follow and manage DME, a change in CST does not by itself correlate with visual acuity, so it can't be used to predict outcomes.[15]

The original OCT technology was based

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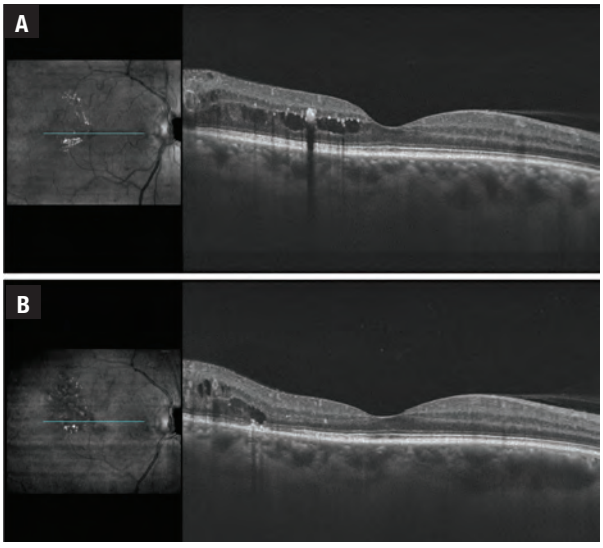

Figure 2. Spectral-domain optical coherence tomography of the right eye of a 47-year-old patient with type 2 diabetes showing (A) mild to moderate non-proliferative diabetic retinopathy with non-center-involving diabetic macular edema and hard exudates, and (B) improvement of the edema three months after modified grid laser treatment. En face images on the left-hand side show the location in the macula where the cross-section was generated.

on time-domain detection and was used in clinical trials on DME management until 2011. The majority of commercial OCT devices today are spectral-domain systems, which refers to the way the device receives and processes the returning light signal. This technology entered the market in 2006 and enabled imaging speeds 25 to 100 times faster than time-domain instruments, which led to improved image quality, the ability to register images from visit to visit, and a reduction in skip areas when doing macular mapping.[16,17]

Imaging the outer retinal layers

The enhanced sensitivity of SD-OCT imaging made it possible to visualize the boundaries between retinal layers more accurately, with novel clarity of the outer retinal layers where the photoreceptors reside. Several studies found a correlation between disruption of two outer retinal layers—the external limiting membrane and ellipsoid zone—and visual acuity, showing that photoreceptor integrity prior to treatment can predict visual recovery in DME.[18,19] Recent work has shown that ischemia of the inner retina leading to disorganization of the inner layers retinal also correlates with visual acuity outcomes in DME.[20]

In clinical practice today, the diagnosis and treatment of DME are largely based on OCT findings. Clinical trials have shown that anti-VEGF treatments improve visual acuity and reduce macular edema in patients with center-involving DME compared to laser therapy alone. In non-center-involving DME, clinical guidelines still recommend consideration of laser therapy (*Figure 2*).

After initial treatment, qualitative evaluation and thickness measurements between baseline and follow-up OCT scans allow us to follow progress and determine management. For example, the degree of change in macular thickness measured on OCT can help us decide whether to repeat anti-VEGF injections or change therapeutic agents. OCT can also identify areas of vitreomacular traction that need treatment with vitrectomy surgery. Other indications for OCT in managing DR include evaluating unexplained visual acuity loss and detecting other forms of macular disease. (OCT is currently not indicated for screening of patients with diabetes having no or minimal retinopathy beyond obtaining a baseline image.[10])

Imaging the vessels

Because DR is inherently a disease of blood vessels, imaging the microvasculature affected by DR has always been of great interest to clinicians and researchers. FA has been used in DR assessment for decades to help identify retinal neovascularization, retinal vascular incompetence, particularly leaking microaneurysms (MA); and areas of ischemia. However, as focal laser surgery has decreased with the advent of anti-VEGF therapy, the need to localize such findings has also decreased, and thus, so has the utility of FA.

OCT angiography technology has emerged to visualize the retinal and

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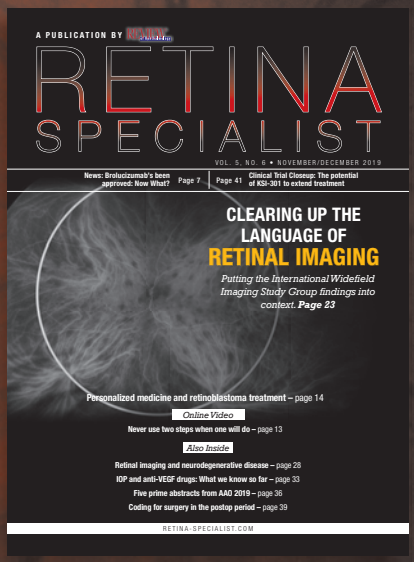

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choroidal vasculature in precise detail. The approach generates a volumetric image of the blood vessels by using motion contrast between erythrocytes in sequential scans relative to the rest of the static retina, negating the need for invasive dye. The high speed of SD-OCT compared to TD-OCT made it possible to image the retinal layers and vasculature all at once when the angiography algorithm was developed.

Unlike two-dimensional FA images, OCTA can delineate the different layers of retinal vasculature, which has allowed for novel insights into the characteristics of vascular change in DR. OCTA can depict many, but not all, of the MAs visible on FA, and it doesn't visualize leakage because it doesn't utilize dye.[21]

However, OCTA is clinically useful for identifying and quantifying features of macular ischemic change such as areas of capillary loss or dropout, retinal nonperfusion and enlargement of the foveal avascular zone.[22] Recent work has even been able to detect and quantify vascular changes in patients with diabetes before classic signs of DR are clinically visible.[23,24]

Although the features described here are still investigational, this research suggests measuring vascular features with OCTA may one day be a tool for screening diabetes patients and directing management.

Bottom line

Current research is investigating ways to harness these OCTA measurements to predict the development and progression of retinopathy so that treatment choices can become more efficient and effective. One of the major limitations of most current commercial OCTA technology is that imaging is restricted to between a 3 x 3- and 12 x 12-mm view of the central macula, although significant ischemic burden is concentrated in the periphery.

However, innovations in OCTA are allowing for deeper and wider imaging capabilities. Although the features described here are still investigational, this research suggests that measuring vascular features using OCTA may one day be a powerful tool for screening diabetes patients and directing management. RS

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Pipeline Report

The path to GA treatment: What's hot, what's not

A review of past trials that disappointed and current trials that are showing promise as potential treatments.

By Joon-Bom (Albert) Kim, MD, and Eleonora M. Lad, MD, PhD

Joon-Bom (Albert) Kim, MD

Eleonora M. Lad, MD, PhD

Take-home points

- Despite numerous clinical studies targeting geographic atrophy pathophysiology and the excitement surrounding early clinical trials of emerging agents, no approved treatments for GA exist.
- The most promising investigational drug in parallel Phase III trials is the C3 complement inhibitor APL-2 (Apellis).
- Elamipretide, an antioxidative agent targeting the mitochondria, and the brimonidine implant have been subjects of positive Phase II trials.
- Improved understanding of GA pathophysiology will be necessary to help broaden the therapeutic targets for GA.

The advent of anti-VEGF agents has been a remarkable success for the treatment of neovascular age-related macular degeneration, but despite significant research and investigation, no approved treatment exists for the much more common dry form of AMD that affects approximately 85 percent of patients[1] and manifests as geographic atrophy in the late stage.[2]

GA can enlarge and may coalesce, resulting in irreversible paracentral or central scotoma, depending on the size and location of atrophy. Even parafoveal GA can cause substantial vision impairment with dark adaptation, reading and driving, and can affect quality of life.[3] Here, we review past early phase GA trials that failed to show efficacy and current clinical trials that have shown promising results as potential treatments of GA.

Neuroprotective agents

Brimonidine is a selective alpha2 adrenergic receptor agonist that has long been used for the treatment of glaucoma. Animal studies have demonstrated that brimonidine is also neuroprotective for photoreceptors, bipolar cells and retinal ganglion cells against retinal phototoxicty and retinal ischemia through the release of brain-derived neurotrophic factor from retinal ganglion cells and by upregulation of the cell survival pathway. Thus, brimonidine has been investigated as a potential therapy for GA.[4]

The multicenter, randomized, double-masked, controlled Phase IIb BEACON study of 310 patients evaluated a second-generation Brimo DDS (Allergan) in a tartrate form, administered every three months compared with sham procedure in patients with GA (DDS stands for drug-delivery system).[5] The implant showed a 7-percent reduction in GA area growth from baseline at month 24 and a statistically significant 11-percent reduction at month 30. Two definitive Phase III randomized, prospective multicenter studies of Brimo DDS at 200 µg and 400 µg doses are planned.[5]

Another investigative treatment, ciliary

Bios

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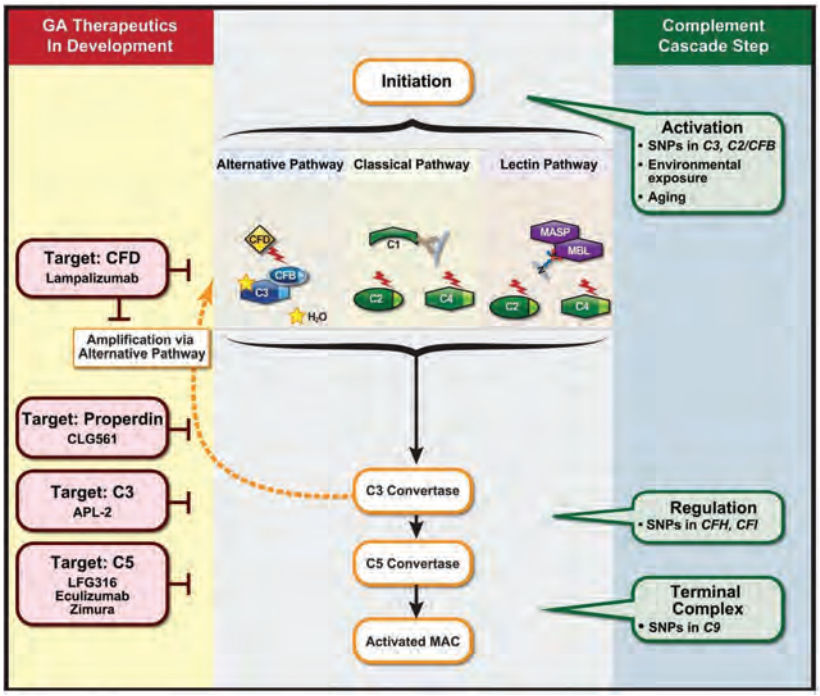

Figure. Several therapeutics (left) targeting different components of the complement cascade (center) are in Phase II or Phase III clinical trials. This diagram also shows factors, such as the identified genetic variations (SNPs) that can affect complement cascade activity (right). Key: CF: complement factor; MAC: membrane attack complex. (*Used with permission of Retina. 2017;37:819-836*)

neurotrophic factor (CNTF), is a member of the interleukin-6 family of cytokines that is also a neurotrophic factor shown to slow the photoreceptor loss in animal models of retinal degeneration.[6] In a pilot Phase II double-masked, sham-controlled dose-ranging trial, 51 patients with GA were randomized to CNTF delivered via intraocular encapsulated implant or sham surgery. The primary endpoint was change in best-corrected visual acuity at 12 months. While the CNTF group showed a statistically significant macular volume compared to controls, the treatment group showed no improvement in visual acuity or difference in GA area.[7]

Mitochondrial enhancer

Elamipretide (Stealth Biotherapeutics) is a tetrapeptide believed to target cardiolipin in mitochondria, reduce reactive oxygen species production and increase adenosine triphosphate production in cells. ReCLAIM was a Phase I open-label, single-site study that evaluated subcutaneous elamipretide for 24 weeks in patients with dry AMD with non-central GA or high-risk drusen. The initial study enrolled 40 patients and showed a significant improvement in low-luminance visual acuity and best-corrected visual acuity in the treatment arm. A randomized, double-masked, sham-controlled Phase IIb trial is under way and estimated to be completed by the end of 2020.[8]

Subthreshold nanosecond laser

Subthreshold nanosecond laser (SNL) initially showed promising results *in vitro* and in preclinical studies, as a single application of SNL resulted in reduction of drusen load without damage to overlying photoreceptors.[9] The Laser Intervention in Early Stages of Age-Related Macular Degeneration (LEAD) study was a 36-month, randomized, sham-controlled trial of 292 patients with bilateral large drusen without any sign of atrophy on optical coherence tomography. The primary outcome was time to development of late AMD defined by multimodal imaging.

The study found that SNL treatment wasn't effective in slowing the progression from intermediate to late AMD. A post hoc analysis showed patients with reticular pseudodrusen (RPD) are at particularly increased risk of progression with SNL treatment. Further studies are warranted to elucidate the benefit of SNL in patients without RPD.[10]

Complement inhibitors

This class of drugs includes the following investigational therapies:

• ***Lampalizumab (Roche/Genentech)*** is an antigen-binding fragment (Fab) of a humanized monoclonal antibody directed against complement factor D (CFD). It selectively inhibits the alternative complement pathway that has been implicated in the pathogenesis of GA. The initial MAHALO

Phase II study showed promising results, as the treatment arm receiving monthly and every-other-month intravitreal lampalizumab had a 20-percent reduction in GA area progression compared to sham control.[11]

However, two Phase III, double-masked, randomized, sham-controlled clinical trials—Chroma and Spectri—failed to show reduction of GA growth compared to sham after 48 weeks and both studies were terminated.[12] The trials randomized patients 2:1:2:1 to intravitreal lampalizumab every four weeks, sham procedure every four weeks, intravitreal lampalizumab every six weeks, and sham procedure every six weeks.

• ***Eculizumab (Soliris, Alexion Pharmaceuticals)*** is an inhibitor of complement component C5 but administered via intravenous infusion. In the Phase II COMPLETE study, 30 patients with GA were randomized to intravenous eculizumab or placebo over six months. The systemic medication was well-tolerated but didn't significantly decrease the growth rate of GA.[13]

• ***Avacincaptad pegol (Zimura, Iveric bio)*** is a polyethylene glycol, single-strand nucleic acid aptamer that targets and inhibits complement factor C5. Recruitment of a double-masked, randomized, sham-controlled Phase IIb clinical trial was completed with 286 patients with dry AMD with GA. Patients that received 2 mg or 4 mg of the drug experienced a mean reduction in GA growth of approximately 27 percent at 12 months compared to the sham group.[14] Patients will continue to be treated with the study drug and followed through month 18 for additional data collection.

Multiple complement inhibitors

Pegcetacoplan is a pegylated peptide that binds specifically to C3 and blocks all three complement pathways (classical, lectin and alternative). APL-2 (Apellis) is a modified version of the peptide designed to have a longer half-life. In the prospective, multicenter, randomized, sham-controlled Phase II FILLY study, 256 patients with GA were randomized to APL-2 or sham intravitreal injections for 12 months and followed for an additional six months. The primary efficacy endpoint was mean change in square root GA lesion from baseline to month 12.

The FILLY study met its primary endpoint, and patients receiving APL-2 monthly or every other month experienced a 29- and 20-percent reduction, respectively, in GA growth rate compared to the sham treatment group. A post-hoc analysis of 176 subjects that completed the 12-month visit with no missing data revealed that the FILLY trial population was a typical GA population, and that the benefit of APL-2 compared to sham remained statistically significant when the population was controlled for all key risk factors of GA progression.

However, pegcetacoplan eyes also had an increased incidence of exudative AMD; 21 and 9 percent in monthly and every-other-month groups compared to 1.2 percent in sham-treated eyes.[15] Despite failures of previous complement inhibitors, there is cautious optimism for APL-2. Two Phase III trials (OAKS and DERBY) of 600 patients each, are under way; they're expected to be completed in 2022.

Bottom line

Improved understanding of GA pathophysiology will be necessary to help broaden the realm of potential therapeutic targets for the treatment of GA. In addition, more sophisticated methods for patient classification, through the use of machine or deep learning, and earlier identification of GA lesions by spectral-domain OCT will be of benefit, allowing detection of the subjects most likely to respond to promising GA therapies in the future. These breakthroughs could help structure successful clinical trials in GA. RS

(References continued on page 38)

Despite failures of previous complement inhibitors, there is cautious optimism for APL-2. Two Phase III trials are under way with completion expected in 2022.

Pipeline Report

Despite major approvals, the queue gets longer

Treatments for exudative disease were notable for four significant exits from our listing and seven new entries this year.

By Richard Mark Kirkner, Editor

Take-home Points

- Another potential blockbuster is pending approval by midyear.
- Conbercept joins the list as global trials move forward.
- Listing includes two treatments using light-activated therapy.

Expert commentary

"2020 promises to be a great year for the exudative retinal disease-development pipeline. In particular, I'm looking forward to continued efficacy and safety outcomes of the two major anti-VEGF gene therapy programs in development; REGENXBIO and Adverum both have programs in Phase I with possible entry into Phase II; and Phase III results from the Port Delivery System with ranibizumab and faricimab programs."

—Charles C. Wykoff, MD, PhD, Chief Medical Editor

The year ahead promises another robust round of trial readouts and at least one major approval in the arena of biologic and chemical agents to treat exudative disease (and two light-activated therapies). Most notable is the anticipated approval of abicipar pegol, the DARPin therapy for neovascular age-related macular degeneration that Allergan and Molecular Partners are developing. Human trials of no less than 20 other agents (and the aforementioned light-activated therapies) are ongoing, with many expected to provide readouts in 2020.

This year's list consists of 23 entries, three more than last year. The past year was notable for three major approvals that resulted in exits from our list: Novartis' Beovu (brolicizumab) for nAMD; and two for Regeneron Pharmaceuticals' Eylea (aflibercept)—an indication for all stages of diabetic retinopathy and the prefilled syringe.

Another notable exit is THR-317, a placental growth factor antibody. Oxurion pulled investment in the program last year, choosing to focus instead on two other DME agents, both new to this year's list. Also new this year are high-dose aflibercept; the AR-1105 biodegradable dexamethasone implant (Aerie Pharmaceuticals); conbercept anti-VEGF (Chengdu Kanghong Biotechnology); the light-activated therapy Retilux (PhotoOpTx); and Xiflam (Ocunexus) oral agent.

This listing only includes therapies in human trials or soon to be in the clinic. The narrative omits agents discussed in the previous article on geographic atrophy treatments, although the listing includes them.

Abicipar pegol

Last fall the FDA accepted the Biologics License Application for abicipar pegol. This is usually a precursor to approval, and that could come well before the midyear time frame Allergan and Molecular Partners say they expect.

Encouraging two-year results of the Phase III CEDAR and SEQUOIA trials have shown noninferiority of eight- and 12-week regimens of abicipar 2 mg compared with four-week treatment with Lucentis (ranibizumab, Roche/Genentech).[1] Outcomes for changes in best-corrected visual acuity and central retinal thickness were also similar between the three treatment groups.

Reformulation of the drug aimed to ad-

dress the high rates of intraocular inflammation reported in the first-year CEDAR and SEQUOIA results—over 15 percent in the abicipar arms vs. 0.6 percent in the Lucentis arm. Recent two-year results showed the pooled rate of new cases of intraocular inflammation was 1.9 percent in both abicipar arms vs. 1 percent in the Lucentis arm.

Aflibercept high-dose (Regeneron Pharmaceuticals)

A Phase II trial of in treatment-naïve nAMD started enrolling patients last November. The trial is designed to randomize 100 patients to Eylea (aflibercept 2 mg) or higher-dose and higher-frequency treatments. An earlier previous trial of 33 eyes resistant to other anti-VEGF agents switched them to Eylea every eight weeks, escalated to every four weeks, and then switched to aflibercept 4 mg every four weeks.[2] Nine percent of eyes developed geographic atrophy during follow-up, but none had adverse events after the higher-dose therapy.

AKB-9778 (Aerpio Pharmaceuticals)

This first-in-class Tie2 activator binds to and inhibits vascular endothelial protein tyrosine phosphatase (VE-PTP). Patients self-administer the drug subcutaneously. Last year, Aerpio completed the Phase IIb TIME-2b clinical trial in patients with nonproliferative DR. Those results extended out to 48 weeks the reduction in intraocular pressure and improved kidney function in patients with early DR reported in TIME-2.

Three-month TIME-2 results showed that AKB-9778 in combination with Lucentis achieved a 50 percent greater reduction in central subfield thickness and a 58-percent improvement in retinal drying than ranibizumab alone.[3] Aerpio is also conducting preclinical studies of ARP-1536, an anti-VE-PTP Tie2 activator that might be a useful adjunct to anti-VEGF therapy in DME.

AKST4290 (Alkahest)

AKST4290 is an oral small-molecule CCR3 inhibitor that targets choroidal blood flow in AMD. Alkahest initiated an open-label Phase II trial, called AKST4290-206 (STEEL), in patients with nAMD in one eye. The Phase IIa trial, known as AKST4290-202, evaluated the agent in nAMD patients no longer responding to anti-VEGF injections.[4] Twenty-six patients took AKST4290 400 mg b.i.d. for six weeks; 72 percent showed improvement or maintenance of BCVA.

AR-1105

Aerie is best-known for its glaucoma franchise, having received FDA approval for Rhopressa (netarsudil) and Rocklatan (netarsudil and latanoprost) for lowering IOP. AR-1105 is a sustained release bio-erodible intravitreal dexamethasone implant for macular edema associated with retinal vein occlusion. Last October the company completed enrollment in a Phase II trial for this indication (n=45). The company expects to report interim results on the first 20 patients this year. Aerie has also entered the clinic with AR-13503, a sustained-release implant containing the active metabolite of netarsudil, for nAMD and DME.

Conbercept

Conbercept is an anti-VEGF recombinant fusion protein that was approved in China in 2013. Like Eylea, conbercept targets VEGF-A and -B and PLGF (placental growth factor). Preclinical studies have shown it has a greater affinity for binding to vascular endothelial growth factor than Lucentis.[5]

Two global Phase III trials in nAMD started recruiting in the past year: PANDA-1 and PANDA-2. Each trial is evaluating 1,140 patients randomized to conbercept, 0.5 or 1 mg, or Eylea 2 mg, with primary efficacy analysis at 36 weeks. PANDA-1 patients will receive three loading doses through week eight, then continue with dosing every eight weeks through week 92. PANDA-2 is a trial of *pro re nata* dosing after week 40, with the 0.5-mg conbercept and Eylea groups on the same regimen as PANDA-1 up until that

Expert commentary

"There will be a number of Phase III trials worth watching this year and next: the Archway study results of the Port Delivery System with ranibizumab, the first true sustained-release platform that could be accesible at the pivotal trial level; topline Phase III data of faricimab in diabetic macular edema this year and age-related macular degeneration in 2021; and the conbercept Phase III PANDA trial, which has completed enrollment. Those results should come to fruition this year and next. Also stay tuned for additional durability outcomes of KSI-301 in an open-label study for treating AMD, DME and vein occlusion."

—Carl Regillo, MD

How the list was compiled

This listing was compiled from company press releases and regulatory filings, published reports in the literature, and presentations at the American Academy of Ophthalmology Retina Subspecialty Day, American Society of Retina Specialists 2019, and the Ophthalmology Innovation Summits at both the AAO and ASRS. It doesn't include investigational stem cell and gene therapies for exudative disease. That listing will appear later in the year.

point, after which the conbercept 1-mg arm shifts to 12-week dosing after eight weeks and moves onto PRN at week 40. PANDA-1 is due for completion next January and PANDA-2 in March 2022.

DE-122 (carotuximab, Santen Pharmaceutical/Tracon)

The Phase II AVANTE trial in nAMD aims to enroll 76 patients to evaluate DE-122 in combination with ranibizumab vs. ranibi-

Table. Exudative disease pipeline

Drug name (manufacturer)	Description/active agent	Indication	Status
Abicipar pegol (Allergan/Molecular Partners)	DARPin therapy	neovascular age-related macular degeneration	Biologics License Application accepted September 2019; action expected midyear 2020; positive two-year CEDAR and SEQUOIA results fall 2019.
NEW: Aflibercept high-dose (Regeneron Pharmaceuticals)	anti-VEGF-A and placental growth factor (PLGF)	nAMD	Phase II trial started enrolling treatment-naive patients November 2019.
AKB-9778 (Aerpio Therapeutics)	Small-molecule VE-PTP inhibitor/Tie-2 activator	moderate/severe nonproliferative diabetic retinopathy	TIME-2b Phase IIb trial completed reproducing reduction in intraocular pressure and improvement in kidney function shown in TIME-2 trial.
AKST4290 (formerly ALK4290) (Alkahest Inc.)	Oral small-molecule CCR3 inhibitor	nAMD	Open-label Phase II trial initiated December 2019; positive Phase IIa results reported July 2019.
APL-2 (Apellis)	Complement C3 inhibitor	Dry AMD/geographic atrophy	Enrollment in Phase III trials resumed March 2019; positive 12-month Phase II results published September 2019
NEW: AR-1105 (Aerie Pharmaceuticals)	Biodegradable dexamethasone implant	Macular edema associated with retinal vein occlusion	Enrollment in Phase II trial completed October 2019; interim data readout due 2020
NEW: Conbercept (Chengdu Kanghong Biotechnology)	Recombinant fusion protein targeting VEGF-A and -B and PLGF	nAMD	Phase III PANDA-1 (q8w dosing) and PANDA-2 (PRN) trials recruiting, completion due 2022.
DE-122 (Santen/TRACON Pharmaceuticals)	Carotuximab endoglin antibody	nAMD	Completion of Phase II AVANTE trial in combination with ranibizumab estimated for January 2020.
Elamipretide (Stealth BioTherapeutics)	Daily subcutaneous injections	Dry AMD with GA	Phase IIb ReCLAIM to complete enrollment early this year; positive Phase I results reported July 2019.
Faricimab (Roche/Genentech)	Anti-VEGF + anti-Ang-2 bispecific antibody	nAMD, diabetic macular edema	Positive Phase II STAIRWAY (nAMD) data reported July 2019; Phase III YOSEMITE, RHINE (DME) ongoing.
GB-102 (Graybug Vision)	Sunitinib (pan VEGFR antagonist)	nAMD, DME	Phase IIIA data reported 2019; Phase IIb ALTISSIMO trial (nAMD) initiated fall 2019; readout due 2021; Phase II trial in DME, RVO enrolling; readout due Q2 2019.
ICON-1 (Iconic Therapeutics)	Anti-tissue factor fusion protein	CNV secondary to AMD	Second Phase II trial ongoing.
KSI-301 (Kodiak Sciences)	Antibody bipolymer conjugate	nAMD, DME, retinal vein occlusion	Positive Phase Ib study results reported October 2019; Phase II DAZZLE trial recruiting with completion expected November 2022.
OPT-302 (Ophthea)	"Trap" mechanism targeting VEGF-C and VEGF-D	nAMD, DME	Positive Phase IIb results in combination with ranibizumab (nAMD); topline Phase IIa data (DME) due Q2.
PAN-90806 (PanOptica)	Topical agent targeting VEGFR-2	nAMD, DME, RVO	Positive Phase I/II trials demonstrated acceptable safety and tolerability and reduction in anti-VEGF injection burden.
Port Delivery System (PDS) with ranibizumab (Roche/Genentech)	Refillable eye implant of ranibizumab 0.5%	nAMD, DME	Data collection of Phase III Archway trial (nAMD) due in March; Phase III Pagoda trial (DME) initiated January.
NEW: Retilux (PhotoOpTx)	Worn laser therapy device using photobiomodulation	DME	Pilot study (DRCR Retina Network Protocol AE) launched April 2019; completion due in August.
Risuteganib (Allegro Ophthalmics)	Luminate broad-spectrum anti-integrin peptide	DME, dry AMD	Positive top-line Phase IIa (dry AMD) trial reported mid-2019;Phase IIb/III (dry AMD) and Phase III (DME) trials to start in 2020.
NEW: THR-149 (Oxurion)	Plasma kallikrein inhibitor	DME	Positive Phase I results reported in 2019; Phase II trial expected in 2020.
NEW: THR-687 (Oxurion)	Pan-RGD integrin antagonist	DME	Positive Phase I results reported; Phase II trial expected in 2H 2020.
Valeda Light Delivery System (LumiThera)	Light-delivery system using photobiomodulation	dry AMD	Positive LIGHTSITE I results published ß2019; LIGHTSITE III recruiting.
NEW: Xiflam (Ocunexus)	Oral small-molecule connexin43 hemichannel blocker	DME, GA secondary to dry AMD	Phase IIb trial to begin Q3 2020.
Zimura (iVERIC bio)	Avacincaptad pegol complement factor C5 inhibitor	GA secondary to dry AMD	Phase III trial to begin enrollment soon; positive IIb results reported fall 2019.

zumab alone. The study completion date posted in ClnicalTrials.gov is January 2020.

Faricimab (Roche/Genentech)

This bispecific antibody binds and neutralizes both angiopoietin-2 (Ang-2) and VEGF-A. Twenty-four week Phase II BOULEVARD results showed that treatment-naïve patients receiving faricimab 6 mg for nAMD gained on average 3.6 letters more than patients on Lucentis (p=0.03).[6] Other positive faricimab outcomes were a higher percentage of macular leakage resolution in both treatment-naïve and previously treated patients, and a potential for longer time to retreatment compared to Lucentis. The Phase III YOSEMITE and RHINE trials are evaluating extended interval dosing in DME.

GB-102 (sunitinib, Graybug Vision)

This pan-VEGF inhibitor is dosed twice yearly for choroidal neovascularization. Once injected, GB-102 forms a depot of pegylated PLGA microparticles containing sunitinib that biodegrades and releases over time. Six-month Phase I/IIa ADAGIO trial results in nAMD reported that between 50 and 88 percent of patients treated with one dose of GB-102 (either 0.25, 0.5, 1 or 2 mg) were rescue-free after three loading doses of anti-VEGF.[7] Last fall the Phase IIb ALTISSIMO trial in nAMD started enrollment, with a readout due next year. A Phase II trial in DME and RVO is also ongoing with a readout due in the second quarter.

ICON-1 (Iconic Therapeutics)

This fusion protein binds to tissue factor overexpressed in the retina and choroid of patients with AMD. A second Phase II study is evaluating intravitreal ICON-1 in combination with Eylea for CNV in AMD. The first Phase II trial, EMERGE, demonstrated biological activity and the ability to target important clinical endpoints. Iconic is also evaluating ICON-4, an anti-tissue factor monoclonal antibody for AMD, with the aim of starting clinical trials this year. Last year Iconic signed an agreement giving Novartis an option on its ophthalmology portfolio.

KS-301 (Kodiak Sciences)

The Phase Ib study of KS-301 demonstrated that about 80 percent of nAMD and DME treated eyes were extended to four months or longer without treatment.[8] Treated patients also demonstrated an average 9-letter gain in BCVA and a 121-µm reduction in CST at 90 days. The Phase II DAZZLE study is recruiting about 400 patients with treatment-naïve nAMD. It will compare KS-301 and Eylea.

OPT-302 (Opthea)

Australia-based Opthea describes this drug as a potent inhibitor of VEGF-C and D which binds to VEGF receptors 2 and 3—important distinctions from the other anti-VEGF drugs with which it has been paired in studies. Last fall, Opthea reported topline data from the Phase IIb trial of 366 patients with treatment-naïve nAMD treated with both OPT-302 and VEGF-A inhibitor Lucentis or Lucentis alone. The combination group gained 14.2 letters from baseline, on average, vs. 10.8 letters for the Lucentis-only group. Topline data from the Phase IIa trial in DME of OPT-302 in combination with Eylea, which inhibits both VEGF-A and B, are due in the second quarter.

PAN-90806 (PanOptica)

This once-daily topical drop targets VEGF receptor 2 (VEGFR2). Phase I/II trials in nAMD confirmed safety and tolerability of three doses: 2 mg/mL; 6 mg/mL; or 10 mg/mL. Six percent of patients (n=51) discontinued the drop, but none of the reported adverse events was serious. The trial evaluated PAN-90806 monotherapy in nAMD and proliferative DR without DME over eight weeks as well as maintenance therapy in nAMD following Lucentis injection over 12 weeks. Patients averaged three fewer injections than they would have had on monthly dosing.

Expert commentary

"Given the unmet need surrounding durability and efficacy in the treatment of neovascular age-related macular degeneration, data from Kodiak Sciences, Graybug Vision and REGENXBIO should be very interesting. The Phase III data from the Genentech Port Delivery System with ranibizumab is potentially paradigm shifting, and I look forward to scrutinizing this information. I'm also excited to examine my evolving experience with brolucizumab more formally to try and gauge how the asset performs in a real-world environment."

—Jonathan L. Prenner, MD

Expert commentary

"For neovascular age-related macular degeneration, longer durability to extend treatment intervals in more patients will continue to be the goal in 2020. I am looking forward to the Food and Drug Administration decision on abicipar pegol, the primary outcome data for the Port Delivery System with ranibizumab, and seeing how the launch of brolucizumab changes our treatment paradigm. Research in gene therapy will continue to gain momentum. For diabetic macular edema, I am eager for the results of the pilot trial with photobiomodulation for center-involved diabetic macular edema with good vision (Protocol AE) from the DRCR Retina Network."

—Judy E. Kim, MD

Port Delivery System with ranibizumab (Roche/Genentech)

Genentech initiated the Phase III Pagoda study of the PDS in DME of this refillable, surgically implanted mini-reservoir filled with 100 mg/mL of ranibizumab, releasing the drug for up to six months. The Phase III Archway trial of the PDS in nAMD is evaluating 418 patients. Data collection is due to finish in March, with completion next year.

Retilux

This device is worn like an eye patch to deliver laser therapy directly to the effected eye. A DRCR Retina Network Protocol AE trial aims to randomize 134 patients to Retilux or a sham device. Study participants wear the device over the affected eye twice a day for 90 seconds. Enrollment started last spring.

Risuteganib (Luminate, Allegro Ophthalmics)

This synthetic arginyl-glycyl-aspartic acid-class broad-spectrum peptide regulates the functions of several integrin isoforms. Topline results of the first Phase IIa intermediate dry AMD clinical trial showed 48 percent of patients in the risuteganib arm at week 28 gained 8 letters or more from baseline, compared to 7 percent of patients in the sham group at week 12 (p=0.013). The study also confirmed the drug's safety. Allegro anticipates starting a larger Phase IIb/III U.S. trial in the first half of the year. A Phase III study for DME is also on the drawing board.

THR-149, THR-687 (Oxurion)

Oxurion's two new VEGF-independent treatments for DME are the plasma kallikrein inhibitor THR-149 and the pan-RGD integrin antagonist THR-687. The Phase I study of THR-149 showed an average improvement of 6.4 letters in BCVA at three months. The Phase I trial of THR-687 showed a BCVA improvement of 8.3 letters at three months. The company expects to move into Phase II for both this year.

Valeda Light Delivery System (LumiThera)

Valeda uses a process called photobiomodulation. The LIGHTSITE III trial last fall enrolled its first patients in a U.S. multicenter study for dry AMD, with the goal to enroll 96 patients. Already approved in Europe, results of the pilot LIGHTSITE I trial reported that about half of treated patients (n=30, 46 eyes) gained at least 5 letters in BCVA vs. 13.6 percent in the sham group (p<0.01) after two series of treatments.[9]

Xiflam

This oral small-molecule agent targets connexin43 hemichannels that are overexpressed in exudative retinal disease. Xiflam aims to block the opening of these hemichannels at the cell membranes, preventing release of inflammatory mediators. The company expects to start its clinical trial in the third quarter.

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Downsides of doctors on social media

How retina specialists can avoid the risks and pitfalls of putting their professional reputation out there.

As we have mentioned before, patients' use of social media for health-related purposes continues to rise, with approximately 26 percent of surveyed patients reporting such use.[1] Similarly, a survey of more than 4,000 physicians found that more than 90 percent use some form of social media for personal activities and 65 percent use these sites for professional reasons.[2,3] Physicians use social media as a means to share information, promote disease education, engage health-care debate and interact with patients and colleagues.

Previously, we focused on strategies to best employ social media to benefit practice promotion and brand development. However, as more physicians use social media, keep in mind that, for physicians, social media pose potential risks for the distribution of poor-quality information, damage to professional image, violation of personal-professional boundaries, breaches of patient privacy, licensing infringements and legal misgivings.[4] Although discussion of all of the latter issues is beyond the scope of this column, we can focus on two overlapping themes: patient-physician boundaries and privacy.

Patient-physician boundaries

Physicians who interact with patients on social media may be violating the patient-physician boundary even if patients initiate the online communication.[5] The most effective, and simplest, strategy to mitigate this danger is to keep separate professional and personal profiles and to not accept any online "friend" requests.

Additionally, post only content of medical value on your professional profile and don't overlap with any personal posts or comments. You can think of this "division of profiles" analogous to the boundaries in a patient-physician relationship. What you wouldn't share with a patient in the clinic should be the same standard you apply to online communication.

Privacy is paramount

We've emphasized this point before. Providing specific patient information online would violate patient privacy and has serious legal consequences. Always be cognizant of the Health Insurance Portability and Accountability Act (HIPAA). If you're posting any patient clinical information or images, it has to have all identifying information removed. You can go one step further and have patients consent to you posting anonymized clinical details for educational purposes on your professional profile to safeguard potential HIPAA privacy breaches.

And don't use an online platform to communicate directly with a patient about a specific medical problem. If a patient posts or comments with a question that's directly related to a specific medical condition or procedure, have the office contact her or him to discuss further or to schedule an office visit.

By following these guidelines, you can prudently grow your online presence without the risk of violating elements of the physician-patient relationship, which can have serious ramifications.

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Details of billing new patient exams

The devil is in them and knowing the multiple rules can avoid costly claim denials and audits.

By Ellen R. Adams, MBA

All physicians use evaluation and management odes for clinical encounters. Ophthalmologists also have specific "eye codes" at their disposal. Though it may seem that adding more choice will just create confusion, both E/M and eye codes are useful tools for billing retinal exams. Here, I'll focus on new patient exams as the E/M code system has slightly different rules for new vs. established patients.

Is that patient really 'new'?

First, be sure the patient meets the "new" criteria. A new patient is one who hasn't been seen by any ophthalmologist in the practice in the past three years. Once you know the patient truly is "new," a properly documented retinal exam will often meet the requirements of three codes:[1]

- 92004—Comprehensive eye, new patient (2020 national Medicare payment rate $152.66).
- 99204—Level 4 E/M, new patient (2020 Medicare payment rate $167.09).
- 99205—Level 5 E/M, new patient (2020 Medicare payment rate $211.12).

Details of documentation

The most commonly used new patient code is 92004; 52 percent of new patient eye exams are billed with this code, 31.8 percent with 99204 and 1.8 percent with 99205.[2] A vitreoretinal subspecialist may see more complex patients needing immediate major surgery and have a higher percentage of level 4 and 5 E/M codes. A specialist who sees a mix of new diabetes, early dry age-related macular degeneration and posterior vitreous detachments that don't need surgery may have a utilization rate closer to the national average.

Code 92004 is typically easy to document; the requirements fit the usual retinal exam. The rules are straightforward: Document a chief complaint, a relevant review of systems and a relevant medical history review.

Other musts for documentation

The comprehensive exam must include general medical observations (i.e., *alert & oriented X3*), gross visual fields (typically by confrontation), extraocular motility, external eye and adnexa, ophthalmoscopy and other elements relevant to the chief complaint. Payers expect documentation of vision, intraocular pressure, conjunctiva, cornea, pupil/iris and lens, and that the fundus exam is dilated (unless dilation is contraindicated).

Both a diagnostic and treatment plan are also required. Diagnostic examples are refraction, optical coherence tomography, fundus/disc photos or angiography, and even non-billable same-day diagnostic tests that aren't part of an exam (i.e., Amsler grid). Treatment may include major or minor surgery, over-the-counter or prescribed medications, or counseling (blood sugar monitoring or follow-up with another provider). The physical exam requirements match what most ophthalmologists consider a complete eye exam.

E/M codes have arcane rules and more detailed documentation requirements, especially for the history. I encourage you to learn and adhere to these requirements to avoid costly claim denials on audit. This article isn't a deep dive into the rules, but a summary. If you plan to bill level 4 or 5 E/M codes, hit all the documentation targets. Otherwise, a lesser code will be supported., even with serious retinal disease requiring treatment.

Three sections of requirements

Documentation requirements for E/M codes are divided into three sections: history; exam; and medical decision-making. You must attest that you obtained the history of the present illness. If a technician obtains

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an initial chief complaint, the provider must review, enhance and/or edit the information for the history of present illness to count toward the documentation requirements. A comprehensive history includes:[3,4]

- ***History of present illness (HPI):*** four or more factors (e.g., timing, duration, location, modifying factors).
- ***Review of systems (ROS):*** 10 or more systems reviewed for symptomatology (e.g., cardiovascular, ear, nose and throat, respiratory).
- ***Past/family/social history (PFSH):*** documentation of two of these three areas—current medications and allergies, social and family histories, relevant surgeries or tobacco/alcohol/drug use.

The exam component must include all the elements of a comprehensive exam. A systemic evaluation of the patient's mental status (e.g., alert and oriented, mood and affect) is also required.

If all work-up requirements are documented, you may then code the exam based on medical decision-making. If the patient is at moderate risk for loss of vision or function, a level 4 (99204) may be appropriate. A high risk may qualify for a level 5 exam (99205).

Examples of codes in practice

How does this look in practice? New patient retinal exams generally fall into three categories, meshing with the codes described here.

- ***92004, New patient low-risk disease:*** treatment consisting of counseling and/or home care, such as diabetic with minimal retinopathy; low-risk dry AMD; or posterior vitreous detachment with no complicating retinal pathology.
- ***99204, New patient serious, non-urgent disease:*** scheduled procedures, such as anti-VEGF injections for diabetic macular edema or wet AMD; laser retinopexy for posterior vitreous detachment with concurrent low-risk atrophic hole; or posterior vitreous detachment with concurrent low-risk atrophic hole requiring laser retinopexy.
- ***99205, New patient serious disease***: urgent or emergent surgery, such as urgent pars plana vitrectomy and endolaser for proliferative diabetic retinopathy with high IOP and vitreous hemorrhage; urgent PPV with air/fluid exchange and silicone oil or gas for macula-on retinal hole or tear with retinal detachment; or choroidal hemorrhage with intractable high IOP requiring PPV and choroidal drainage.

Don't overstate risk

When considering the new patient code, avoid overstating the risk. If a procedure is offered the same day for patient convenience but could otherwise wait a few days, don't up-code the exam. If the outcome would be the same had the procedure been scheduled a week or two later, it would be a level 4 E/M, not a level 5.

Other new patient codes are available. The new patient intermediate eye (92002) and E/M levels 2 and 3 (99202, 99203) often don't reflect the work for a dilated, comprehensive eye exam. However, emergencies occur, and you may see a new patient with an anterior segment diagnosis. If no retinal exam is required for a corneal abrasion patient, for instance, bill the more appropriate 92002 exam level.

We strongly recommend comprehensive training in appropriate documentation and coding to avoid any missteps when coding low-risk patient exams, as well as to be able to code appropriately and confidently when facing a patient with imminent vision loss.

When considering the new patient code, it's important to avoid overstating the risk. For instance, if a procedure offered the same day for patient convenience could otherwise wait a few days, don't up-code the exam.

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The path to GA treatment

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Latest in AI for managing DR

(Continued from page 19)

specificity (effectiveness) and thus show that they can enable point-of-care DR screening. This will be invaluable in the future for triage and identification of DR patients.

Refinements in these algorithms and perhaps additional programming to screen for other conditions will make the programs even more powerful in screening for DR and associated ocular conditions.

AI will transform the management of patients. It will lead to more efficient use of our health-care workers and resources while also achieving increased detection of DR in patients. Properly deployed, it can reduce disparities in health care in terms of disease detection. Ultimately the true test of AI's effectiveness will be whether or not more patients with referable DR are indeed seen and cared for by ophthalmologists. Compared to telescreening, AI has been shown to be cost-effective. Perhaps the saved health-care dollars from its use can then be applied toward the cost of ophthalmic procedures to treat DR and prevent blindness.

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LUCENTIS®
RANIBIZUMAB INJECTION

Brief summary–please see the LUCENTIS® package insert for full prescribing information.

1 INDICATIONS AND USAGE
LUCENTIS is indicated for the treatment of patients with:

1.1 Neovascular (Wet) Age-Related Macular Degeneration (AMD)

1.2 Macular Edema Following Retinal Vein Occlusion (RVO)

1.3 Diabetic Macular Edema (DME)

1.4 Diabetic Retinopathy (DR)

1.5 Myopic Choroidal Neovascularization (mCNV)

4 CONTRAINDICATIONS

4.1 Ocular or Periocular Infections
LUCENTIS is contraindicated in patients with ocular or periocular infections.

4.2 Hypersensitivity
LUCENTIS is contraindicated in patients with known hypersensitivity to ranibizumab or any of the excipients in LUCENTIS. Hypersensitivity reactions may manifest as severe intraocular inflammation.

5 WARNINGS AND PRECAUTIONS

5.1 Endophthalmitis and Retinal Detachments
Intravitreal injections, including those with LUCENTIS, have been associated with endophthalmitis and retinal detachments. Proper aseptic injection technique should always be used when administering LUCENTIS. In addition, patients should be monitored following the injection to permit early treatment should an infection occur *[see Dosage and Administration (2.6, 2.7) in the full prescribing information and Patient Counseling Information (17)]*.

5.2 Increases in Intraocular Pressure
Increases in intraocular pressure have been noted both pre-injection and post-injection (at 60 minutes) while being treated with LUCENTIS. Monitor intraocular pressure prior to and following intravitreal injection with LUCENTIS and manage appropriately *[see Dosage and Administration (2.7 in the full prescribing information)]*.

5.3 Thromboembolic Events
Although there was a low rate of arterial thromboembolic events (ATEs) observed in the LUCENTIS clinical trials, there is a potential risk of ATEs following intravitreal use of VEGF inhibitors. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause).

Neovascular (Wet) Age-Related Macular Degeneration
The ATE rate in the three controlled neovascular AMD studies (AMD-1, AMD-2, AMD-3) during the first year was 1.9% (17 of 874) in the combined group of patients treated with 0.3 mg or 0.5 mg LUCENTIS compared with 1.1% (5 of 441) in patients from the control arms *[see Clinical Studies (14.1 in the full prescribing information)]*. In the second year of Studies AMD-1 and AMD-2, the ATE rate was 2.6% (19 of 721) in the combined group of LUCENTIS-treated patients compared with 2.9% (10 of 344) in patients from the control arms. In Study AMD-4, the ATE rates observed in the 0.5 mg arms during the first and second year were similar to rates observed in Studies AMD-1, AMD-2, and AMD-3.

In a pooled analysis of 2-year controlled studies (AMD-1, AMD-2, and a study of LUCENTIS used adjunctively with verteporfin photodynamic therapy), the stroke rate (including both ischemic and hemorrhagic stroke) was 2.7% (13 of 484) in patients treated with 0.5 mg LUCENTIS compared to 1.1% (5 of 435) in patients in the control arms (odds ratio 2.2 (95% confidence interval (0.8-7.1))).

Macular Edema Following Retinal Vein Occlusion
The ATE rate in the two controlled RVO studies during the first 6 months was 0.8% in both the LUCENTIS and control arms of the studies (4 of 525 in the combined group of patients treated with 0.3 mg or 0.5 mg LUCENTIS and 2 of 260 in the control arms) *[see Clinical Studies (14.2 in the full prescribing information)]*. The stroke rate was 0.2% (1 of 525) in the combined group of LUCENTIS-treated patients compared to 0.4% (1 of 260) in the control arms.

Diabetic Macular Edema and Diabetic Retinopathy
Safety data are derived from studies D-1 and D-2. All enrolled patients had DME and DR at baseline *[see Clinical Studies (14.3, 14.4 in the full prescribing information)]*.

In a pooled analysis of Studies D-1 and D-2 *[see Clinical Studies (14.3 in the full prescribing information)]*, the ATE rate at 2 years was 7.2% (18 of 250) with 0.5 mg LUCENTIS, 5.6% (14 of 250) with 0.3 mg LUCENTIS, and 5.2% (13 of 250) with control. The stroke rate at 2 years was 3.2% (8 of 250) with 0.5 mg LUCENTIS, 1.2% (3 of 250) with 0.3 mg LUCENTIS, and 1.6% (4 of 250) with control. At 3 years, the ATE rate was 10.4% (26 of 249) with 0.5 mg LUCENTIS and 10.8% (27 of 250) with 0.3 mg LUCENTIS; the stroke rate was 4.8% (12 of 249) with 0.5 mg LUCENTIS and 2.0% (5 of 250) with 0.3 mg LUCENTIS.

5.4 Fatal Events in Patients with DME and DR at baseline
Diabetic Macular Edema and Diabetic Retinopathy
Safety data are derived from studies D-1 and D-2. All enrolled patients had DME and DR at baseline *[see Clinical Studies (14.3, 14.4 in the full prescribing information)]*.

A pooled analysis of Studies D-1 and D-2 *[see Clinical Studies (14.3 in the full prescribing information)]*, showed that fatalities in the first 2 years occurred in 4.4% (11 of 250) of patients treated with 0.5 mg LUCENTIS, in 2.8% (7 of 250) of patients treated with 0.3 mg LUCENTIS, and in 1.2% (3 of 250) of control patients. Over 3 years, fatalities occurred in 6.4% (16 of 249) of patients treated with 0.5 mg LUCENTIS and in 4.4% (11 of 250) of patients treated with 0.3 mg LUCENTIS. Although the rate of fatal events was low and included causes of death typical of patients with advanced diabetic complications, a potential relationship between these events and intravitreal use of VEGF inhibitors cannot be excluded.

6 ADVERSE REACTIONS
The following adverse reactions are discussed in greater detail in other sections of the label:

- Endophthalmitis and Retinal Detachments *[see Warnings and Precautions (5.1)]*
- Increases in Intraocular Pressure *[see Warnings and Precautions (5.2)]*
- Thromboembolic Events *[see Warnings and Precautions (5.3)]*
- Fatal Events in patients with DME and DR at baseline *[see Warnings and Precautions (5.4)]*

6.1 Injection Procedure
Serious adverse reactions related to the injection procedure have occurred in < 0.1% of intravitreal injections, including endophthalmitis *[see Warnings and Precautions (5.1)]*, rhegmatogenous retinal detachment, and iatrogenic traumatic cataract.

6.2 Clinical Studies Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in one clinical trial of a drug cannot be directly compared with rates in the clinical trials of the same or another drug and may not reflect the rates observed in practice.

The data below reflect exposure to 0.5 mg LUCENTIS in 440 patients with neovascular AMD in Studies AMD-1, AMD-2, and AMD-3; in 259 patients with macular edema following RVO. The data also reflect exposure to 0.3 mg LUCENTIS in 250 patients with DME and DR at baseline *[see Clinical Studies (14 in the full prescribing information)]*.

Safety data observed in Study AMD-4, D-3, and in 224 patients with mCNV were consistent with these results. On average, the rates and types of adverse reactions in patients were not significantly affected by dosing regimen.

Ocular Reactions
Table 1 shows frequently reported ocular adverse reactions in LUCENTIS-treated patients compared with the control group.

Table 1 Ocular Reactions in the DME and DR, AMD, and RVO Studies

	DME and DR 2-year		AMD 2-year		AMD 1-year		RVO 6-month	
	LUCENTIS 0.3 mg	Control	LUCENTIS 0.5 mg	Control	LUCENTIS 0.5 mg	Control	LUCENTIS 0.5 mg	Control
Adverse Reaction	n=250	n=250	n=379	n=379	n=440	n=441	n=259	n=260
Conjunctival hemorrhage	47%	32%	74%	60%	64%	50%	48%	37%
Eye pain	17%	13%	35%	30%	26%	20%	17%	12%
Vitreous floaters	10%	4%	27%	8%	19%	5%	7%	2%
Intraocular pressure increased	18%	7%	24%	7%	17%	5%	7%	2%
Vitreous detachment	11%	15%	21%	19%	15%	15%	4%	2%
Intraocular inflammation	4%	3%	18%	8%	13%	7%	1%	3%
Cataract	28%	32%	17%	14%	11%	9%	2%	2%
Foreign body sensation in eyes	10%	5%	16%	14%	13%	10%	7%	5%
Eye irritation	8%	5%	15%	15%	13%	12%	7%	6%
Lacrimation increased	5%	4%	14%	12%	8%	8%	2%	3%
Blepharitis	3%	2%	12%	8%	8%	5%	0%	1%
Dry eye	5%	3%	12%	7%	7%	7%	3%	3%
Visual disturbance or vision blurred	8%	4%	18%	15%	13%	10%	5%	3%
Eye pruritus	4%	4%	12%	11%	9%	7%	1%	2%
Ocular hyperemia	9%	9%	11%	8%	7%	4%	5%	3%
Retinal disorder	2%	2%	10%	7%	8%	4%	2%	1%
Maculopathy	5%	7%	9%	9%	6%	6%	11%	7%
Retinal degeneration	1%	0%	8%	6%	5%	3%	1%	0%
Ocular discomfort	2%	1%	7%	4%	5%	2%	2%	2%
Conjunctival hyperemia	1%	2%	7%	6%	5%	4%	0%	0%
Posterior capsule opacification	4%	3%	7%	4%	2%	2%	0%	1%
Injection site hemorrhage	1%	0%	5%	2%	3%	1%	0%	0%

Non-Ocular Reactions
Non-ocular adverse reactions with an incidence of ≥ 5% in patients receiving LUCENTIS for DR, DME, AMD, and/or RVO and which occurred at a ≥ 1% higher frequency in patients treated with LUCENTIS compared to control are shown in Table 2. Though less common, wound healing complications were also observed in some studies.

Table 2 Non-Ocular Reactions in the DME and DR, AMD, and RVO Studies

	DME and DR 2-year		AMD 2-year		AMD 1-year		RVO 6-month	
	LUCENTIS 0.3 mg	Control	LUCENTIS 0.5 mg	Control	LUCENTIS 0.5 mg	Control	LUCENTIS 0.5 mg	Control
Adverse Reaction	n=250	n=250	n=379	n=379	n=440	n=441	n=259	n=260
Nasopharyngitis	12%	6%	16%	13%	8%	9%	5%	4%
Anemia	11%	10%	8%	7%	4%	3%	1%	1%
Nausea	10%	9%	9%	6%	5%	5%	1%	2%
Cough	9%	4%	9%	8%	5%	4%	1%	2%
Constipation	8%	4%	5%	7%	3%	4%	0%	1%
Seasonal allergy	8%	4%	4%	4%	2%	2%	0%	2%
Hypercholesterolemia	7%	5%	5%	5%	3%	2%	1%	1%
Influenza	7%	3%	7%	5%	3%	2%	3%	2%
Renal failure	7%	6%	1%	1%	0%	0%	0%	0%
Upper respiratory tract infection	7%	7%	9%	8%	5%	5%	2%	2%
Gastroesophageal reflux disease	6%	4%	4%	6%	3%	4%	1%	0%
Headache	6%	8%	12%	9%	6%	5%	3%	3%
Edema peripheral	6%	4%	3%	5%	2%	3%	0%	1%
Renal failure chronic	6%	2%	0%	1%	0%	0%	0%	0%
Neuropathy peripheral	5%	3%	1%	1%	1%	0%	0%	0%
Sinusitis	5%	8%	8%	7%	5%	5%	3%	2%
Bronchitis	4%	4%	11%	9%	6%	5%	0%	2%
Atrial fibrillation	3%	3%	5%	4%	2%	2%	1%	0%
Arthralgia	3%	3%	11%	9%	5%	5%	2%	1%
Chronic obstructive pulmonary disease	1%	1%	6%	3%	3%	1%	0%	0%
Wound healing complications	1%	0%	1%	1%	1%	0%	0%	0%

6.3 Immunogenicity
As with all therapeutic proteins, there is the potential for an immune response in patients treated with LUCENTIS. The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to LUCENTIS in immunoassays and are highly dependent on the sensitivity and specificity of the assays.

The pre-treatment incidence of immunoreactivity to LUCENTIS was 0%-5% across treatment groups. After monthly dosing with LUCENTIS for 6 to 24 months, antibodies to LUCENTIS were detected in approximately 1%-9% of patients.

The clinical significance of immunoreactivity to LUCENTIS is unclear at this time. Among neovascular AMD patients with the highest levels of immunoreactivity, some were noted to have iritis or vitritis. Intraocular inflammation was not observed in patients with DME and DR at baseline, or RVO patients with the highest levels of immunoreactivity.

6.4 Postmarketing Experience
The following adverse reaction has been identified during post-approval use of LUCENTIS. Because this reaction was reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate the frequency or establish a causal relationship to drug exposure.

- Ocular: Tear of retinal pigment epithelium among patients with neovascular AMD

7 DRUG INTERACTIONS
Drug interaction studies have not been conducted with LUCENTIS.

LUCENTIS intravitreal injection has been used adjunctively with verteporfin photodynamic therapy (PDT). Twelve (12) of 105 (11%) patients with neovascular AMD developed serious intraocular inflammation; in 10 of the 12 patients, this occurred when LUCENTIS was administered 7 days (± 2 days) after verteporfin PDT.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Risk Summary
There are no adequate and well-controlled studies of LUCENTIS administration in pregnant women.

Administration of ranibizumab to pregnant monkeys throughout the period of organogenesis resulted in a low incidence of skeletal abnormalities at intravitreal doses 13-times the predicted human exposure (based on maximal serum trough levels [C_{ave}]) after a single eye treatment at the recommended clinical dose. No skeletal abnormalities were observed at serum trough levels equivalent to the predicted human exposure after a single eye treatment at the recommended clinical dose *[see Animal Data]*.

Animal reproduction studies are not always predictive of human response, and it is not known whether ranibizumab can cause fetal harm when administered to a pregnant woman. Based on the anti-VEGF mechanism of action for ranibizumab *[see Clinical Pharmacology (12.1 in the full prescribing information)]*, treatment with LUCENTIS may pose a risk to human embryofetal development.

LUCENTIS should be given to a pregnant woman only if clearly needed.

Data
Animal Data
An embryo-fetal developmental toxicity study was performed on pregnant cynomolgus monkeys. Pregnant animals received intravitreal injections of ranibizumab every 14 days starting on Day 20 of gestation, until Day 62 at doses of 0, 0.125, and 1 mg/eye. Skeletal abnormalities including incomplete and/or irregular ossification of bones in the skull, vertebral column, and hindlimbs and shortened supernumerary ribs were seen at a low incidence in fetuses from animals treated with 1 mg/eye of ranibizumab. The 1 mg/eye dose resulted in trough serum ranibizumab levels up to 13 times higher than predicted C_{ave} levels with single eye treatment in humans. No skeletal abnormalities were seen at the lower dose of 0.125 mg/eye, a dose which resulted in trough exposures equivalent to single eye treatment in humans. No effect on the weight or structure of the placenta, maternal toxicity, or embryotoxicity was observed.

8.2 Lactation
Risk Summary
There are no data available on the presence of ranibizumab in human milk, the effects of ranibizumab on the breastfed infant or the effects of ranibizumab on milk production/excretion.

Because many drugs are excreted in human milk, and because the potential for absorption and harm to infant growth and development exists, caution should be exercised when LUCENTIS is administered to a nursing woman.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for LUCENTIS and any potential adverse effects on the breastfed child from ranibizumab.

8.3 Females and Males of Reproductive Potential
Infertility
No studies on the effects of ranibizumab on fertility have been conducted. and it is not known whether ranibizumab can affect reproduction capacity. Based on the anti-VEGF mechanism of action for ranibizumab, treatment with LUCENTIS may pose a risk to reproductive capacity.

8.4 Pediatric Use
The safety and effectiveness of LUCENTIS in pediatric patients have not been established.

8.5 Geriatric Use
In the clinical studies, approximately 76% (2449 of 3227) of patients randomized to treatment with LUCENTIS were ≥ 65 years of age and approximately 51% (1644 of 3227) were ≥ 75 years of age *[see Clinical Studies (14 in the full prescribing information)]*. No notable differences in efficacy or safety were seen with increasing age in these studies. Age did not have a significant effect on systemic exposure.

10 OVERDOSAGE
More concentrated doses as high as 2 mg ranibizumab in 0.05 mL have been administered to patients. No additional unexpected adverse reactions were seen.

17 PATIENT COUNSELING INFORMATION
Advise patients that in the days following LUCENTIS administration, patients are at risk of developing endophthalmitis. If the eye becomes red, sensitive to light, painful, or develops a change in vision, advise the patient to seek immediate care from an ophthalmologist *[see Warnings and Precautions (5.1)]*.

LUCENTIS®
[ranibizumab injection]
Manufactured by:
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A Member of the Roche Group
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94080-4990

Initial US Approval: June 2006
Revision Date: LUC/021815/0050(4) 2017

LUCENTIS 0.5 MG PREFILLED SYRINGE

EFFICACY DELIVERED

The efficacy and safety of LUCENTIS 0.5 mg studied in 7 pivotal trials,* available in a prefilled syringe.[1]

LUCENTIS®
RANIBIZUMAB INJECTION

INDICATIONS

LUCENTIS® (ranibizumab injection) 0.5 mg is indicated for the treatment of patients with:

- Neovascular (wet) age-related macular degeneration (wAMD)
- Macular edema following retinal vein occlusion (RVO)
- Myopic choroidal neovascularization (mCNV)

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

- LUCENTIS is contraindicated in patients with ocular or periocular infections or known hypersensitivity to ranibizumab or any of the excipients in LUCENTIS. Hypersensitivity reactions may manifest as severe intraocular inflammation

WARNINGS AND PRECAUTIONS

- Intravitreal injections, including those with LUCENTIS, have been associated with endophthalmitis, retinal detachment, and iatrogenic traumatic cataract. Proper aseptic injection technique should always be utilized when administering LUCENTIS. Patients should be monitored following the injection to permit early treatment, should an infection occur
- Increases in intraocular pressure (IOP) have been noted both pre-injection and post-injection (at 60 minutes) with LUCENTIS. Monitor intraocular pressure prior to and following intravitreal injection with LUCENTIS and manage appropriately
- Although there was a low rate of arterial thromboembolic events (ATEs) observed in the LUCENTIS clinical trials, there is a potential risk of ATEs following intravitreal use of VEGF inhibitors. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause)

ADVERSE EVENTS

- Serious adverse events related to the injection procedure that occurred in <0.1% of intravitreal injections included endophthalmitis, rhegmatogenous retinal detachment, and iatrogenic traumatic cataract
- In the LUCENTIS Phase III clinical trials, the most common ocular side effects included conjunctival hemorrhage, eye pain, vitreous floaters, and increased intraocular pressure. The most common non-ocular side effects included nasopharyngitis, anemia, nausea, and cough

Please see Brief Summary of LUCENTIS full Prescribing Information on next page.

*The following randomized, double-masked pivotal trials were conducted for the wet AMD, macular edema following RVO, and mCNV LUCENTIS indications: **wAMD:** ***MARINA***—Phase III, multicenter, 2-year, sham injection–controlled study; primary end point at 1 year. ***ANCHOR***—Phase III, multicenter, 2-year, active treatment–controlled study; primary end point at 1 year. ***PIER***—Phase IIIb, 2-year, sham injection–controlled study; primary end point at 1 year. ***HARBOR***—Phase III, multicenter, 2-year, active treatment–controlled dose-response study; primary end point at 1 year. **RVO:** ***BRAVO***—Phase III, multicenter, 1-year, sham injection–controlled study; primary end point at 6 months. ***CRUISE***—Phase III, multicenter, 1-year, sham injection–controlled study; primary end point at 6 months. **mCNV:** ***RADIANCE***—Phase III, multicenter, 1-year, active-controlled study; key clinical outcomes at month 3.[2-8]

VEGF, vascular endothelial growth factor.

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