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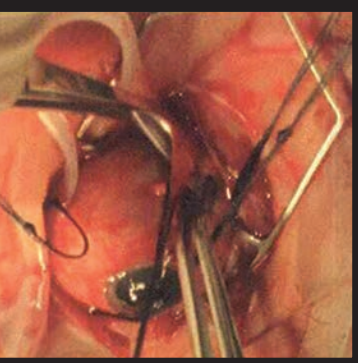
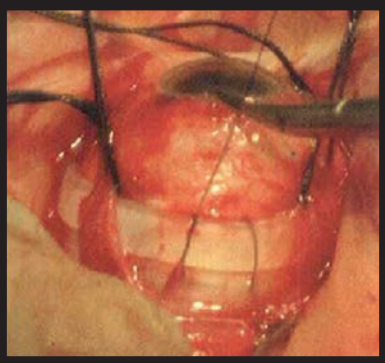
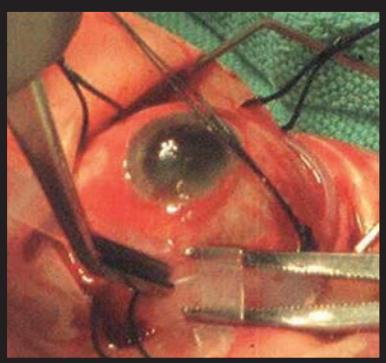
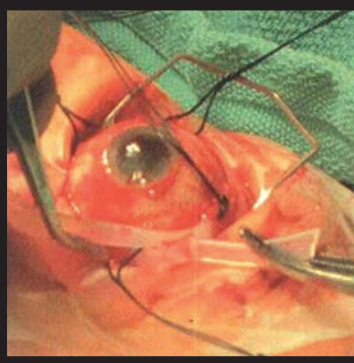





SCLERAL BUCKLING SURGERY: AS VITAL AS EVER

A review of modern techniques and indications for repair of rhegmatogenous retinal detachments.

Online Video

Also Inside

Now Approved *for an expanded indication in* ***Diabetic Retinopathy (DR)***[1]

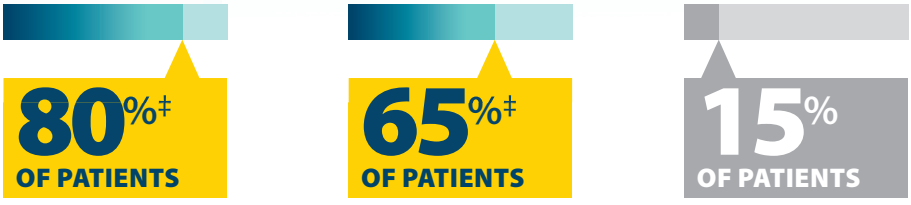
EYLEA® (aflibercept) Injection For Intravitreal Injection

POWER AGAINST

In PANORAMA, EYLEA significantly improved DR severity scores at week 52[1]

Proportion of patients achieving a ≥2-step improvement in ETDRS-DRSS* score from baseline (primary endpoint)[1,†]

‡*P*<0.01 vs sham.



EYLEA 2 mg every 8 weeks[§] (n=134)

EYLEA 2 mg every 16 weeks[‖] (n=135)

sham (n=133)

The recommended dose for EYLEA in DR is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (approximately every 25 days, monthly), additional efficacy was not demonstrated in most patients when EYLEA was dosed every 4 weeks compared to every 8 weeks. Some patients may need every-4-week (monthly) dosing after the first 20 weeks (5 months).[1]

Efficacy and safety data of EYLEA in DR are also derived from VISTA and VIVID.[1] The percentage of patients with a ≥2-step improvement on the ETDRS-DRSS from baseline at 100 weeks was 38%, 38%, and 16% in VISTA and 32%, 28%, and 7% in VIVID with EYLEA 2 mg every 8 weeks after 5 initial monthly doses, EYLEA 2 mg every 4 weeks, and control, respectively (secondary endpoint).[1]

PANORAMA study design: Multicenter, double-masked, controlled study in which patients with moderately severe to severe NPDR (ETDRS-DRSS: 47 or 53) without central-involved DME (CI-DME) (N=402; age range: 25-85 years, with a mean of 56 years) were randomized to receive 1) 3 initial monthly EYLEA 2 mg injections, followed by 1 injection after 8 weeks and then 1 injection every 16 weeks; 2) 5 initial monthly EYLEA 2 mg injections, followed by 1 injection every 8 weeks; or 3) sham treatment. Protocol-specified visits occurred every 28±7 days for the first 5 visits, then every 8 weeks (56±7 days). The primary efficacy endpoint was the proportion of patients who improved by ≥2 steps on the ETDRS-DRSS from baseline to week 24 in the combined EYLEA groups vs sham and at week 52 in the EYLEA 2 mg every-16-week and EYLEA 2 mg every-8-week groups individually vs sham. A secondary endpoint was the proportion of patients developing the composite endpoint of proliferative DR (PDR) or anterior segment neovascularization.

VISTA and VIVID study designs: Two randomized, multicenter, double-masked, controlled studies in which patients with DME (N=862; age range: 23-87 years, with a mean of 63 years) were randomized and received 1) EYLEA 2 mg administered every 8 weeks following 5 initial monthly doses; 2) EYLEA 2 mg administered every 4 weeks; or 3) macular laser photocoagulation (control), at baseline and then as needed. Protocol-specified visits occurred every 28 (±7) days. In both studies, efficacy endpoints included the mean change from baseline in best-corrected visual acuity (BCVA), as measured by ETDRS letters, at 52 weeks (primary endpoint) and 100 weeks (secondary endpoint).

INDICATIONS AND IMPORTANT SAFETY INFORMATION

INDICATIONS

EYLEA is indicated for the treatment of patients with Neovascular (Wet) Age-related Macular Degeneration (AMD), Macular Edema following Retinal Vein Occlusion (RVO), Diabetic Macular Edema (DME), and Diabetic Retinopathy (DR).

CONTRAINDICATIONS

- EYLEA is contraindicated in patients with ocular or periocular infections, active intraocular inflammation, or known hypersensitivity to aflibercept or to any of the excipients in EYLEA.

*Early Treatment Diabetic Retinopathy Study–Diabetic Retinopathy Severity Scale: An established grading scale for measuring the severity of DR.
†Full analysis set.
§3 initial monthly injections, followed by 1 injection after 8 weeks and then 1 injection every 16 weeks.
‖5 initial monthly injections, followed by 1 injection every 8 weeks.

EYLEA is a registered trademark of Regeneron Pharmaceuticals, Inc.

REGENERON

777 Old Saw Mill River Road, Tarrytown, NY 10591

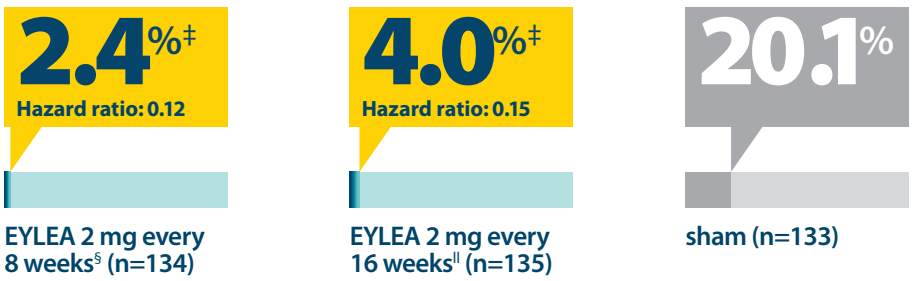
Start with EYLEA to help stop progression to PDR[1]
Visit STARTEYLEA.COM to learn more

DISEASE PROGRESSION[1]

EYLEA can help prevent DR vision-threatening complications that can lead to blindness[1]

Significantly fewer patients developed PDR or ASNV with EYLEA at week 52[1]

Composite endpoint of patients who developed PDR or ASNV at week 52 (event rates) (secondary endpoint)[1,†]



EYLEA 2 mg every 8 weeks[§] (n=134)

EYLEA 2 mg every 16 weeks[‖] (n=135)

sham (n=133)

‡*P*<0.01 vs sham.

All patients were treatment-naïve to focal or grid laser photocoagulation, panretinal photocoagulation, and any anti–vascular endothelial growth factor (anti-VEGF) treatment.[2] Composite endpoint of developing PDR or anterior segment neovascularization (ASNV) was diagnosed by either the reading center or investigator through week 52. Event rate was estimated using the Kaplan-Meier method.[1]

WARNINGS AND PRECAUTIONS

- Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments. Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately. Intraocular inflammation has been reported with the use of EYLEA.
- Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with VEGF inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately.
- There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including EYLEA. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of reported thromboembolic events in wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA compared with 1.5% (9 out of 595) in patients treated with ranibizumab; through 96 weeks, the incidence was 3.3% (60 out of 1824) in the EYLEA group compared with 3.2% (19 out of 595) in the ranibizumab group. The incidence in the DME studies from baseline to week 52 was 3.3% (19 out of 578) in the combined group of patients treated with EYLEA compared with 2.8% (8 out of 287) in the control group; from baseline to week 100, the incidence was 6.4% (37 out of 578) in the combined group of patients treated with EYLEA compared with 4.2% (12 out of 287) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the RVO studies

ADVERSE REACTIONS

- Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment.
- The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and intraocular pressure increased.

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

References: 1. EYLEA® (aflibercept) Injection full Prescribing Information. Regeneron Pharmaceuticals, Inc. May 2019. **2.** Data on file. Regeneron Pharmaceuticals, Inc.

05/2019
US-LEA-14375

EYLEA®
(aflibercept) Injection
For Intravitreal Injection

BRIEF SUMMARY—Please see the EYLEA full Prescribing Information available on HCP.EYLEA.US for additional product information.

1 INDICATIONS AND USAGE
EYLEA is a vascular endothelial growth factor (VEGF) inhibitor indicated for the treatment of:

Neovascular (Wet) Age-Related Macular Degeneration (AMD); Macular Edema Following Retinal Vein Occlusion (RVO); Diabetic Macular Edema (DME); Diabetic Retinopathy (DR).

4 CONTRAINDICATIONS

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

4.2 Active Intraocular Inflammation
EYLEA is contraindicated in patients with active intraocular inflammation.

4.3 Hypersensitivity
EYLEA is contraindicated in patients with known hypersensitivity to aflibercept or any of the excipients in EYLEA. Hypersensitivity reactions may manifest as rash, pruritus, urticaria, severe anaphylactic/anaphylactoid reactions, or severe intraocular inflammation.

5 WARNINGS AND PRECAUTIONS

5.1 Endophthalmitis and Retinal Detachments.
Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments [*see Adverse Reactions (6.1)*]. Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately [*see Patient Counseling Information (17)*].

5.2 Increase in Intraocular Pressure.
Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA [*see Adverse Reactions (6.1)*]. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with vascular endothelial growth factor (VEGF) inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately.

5.3 Thromboembolic Events.
There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including EYLEA. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of reported thromboembolic events in wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA compared with 1.5% (9 out of 595) in patients treated with ranibizumab; through 96 weeks, the incidence was 3.3% (60 out of 1824) in the EYLEA group compared with 3.2% (19 out of 595) in the ranibizumab group. The incidence in the DME studies from baseline to week 52 was 3.3% (19 out of 578) in the combined group of patients treated with EYLEA compared with 2.8% (8 out of 287) in the control group; from baseline to week 100, the incidence was 6.4% (37 out of 578) in the combined group of patients treated with EYLEA compared with 4.2% (12 out of 287) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the RVO studies.

6 ADVERSE REACTIONS
The following potentially serious adverse reactions are described elsewhere in the labeling:
- Hypersensitivity [*see Contraindications (4.3)*]
- Endophthalmitis and retinal detachments [*see Warnings and Precautions (5.1)*]
- Increase in intraocular pressure [*see Warnings and Precautions (5.2)*]
- Thromboembolic events [*see Warnings and Precautions (5.3)*]

6.1 Clinical Trials Experience.
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in other clinical trials of the same or another drug and may not reflect the rates observed in practice.
A total of 2980 patients treated with EYLEA constituted the safety population in eight phase 3 studies. Among those, 2379 patients were treated with the recommended dose of 2 mg. Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment. The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and intraocular pressure increased.

Neovascular (Wet) Age-Related Macular Degeneration (AMD). The data described below reflect exposure to EYLEA in 1824 patients with wet AMD, including 1223 patients treated with the 2-mg dose, in 2 double-masked, controlled clinical studies (VIEW1 and VIEW2) for 24 months (with active control in year 1).
Safety data observed in the EYLEA group in a 52-week, double-masked, Phase 2 study were consistent with these results.

Table 1: Most Common Adverse Reactions (≥1%) in Wet AMD Studies

	Baseline to Week 52		Baseline to Week 96	
Adverse Reactions	**EYLEA (N=1824)**	**Active Control (ranibizumab) (N=595)**	**EYLEA (N=1824)**	**Control (ranibizumab) (N=595)**
Conjunctival hemorrhage	25%	28%	27%	30%
Eye pain	9%	9%	10%	10%
Cataract	7%	7%	13%	10%
Vitreous detachment	6%	6%	8%	8%
Vitreous floaters	6%	7%	8%	10%
Intraocular pressure increased	5%	7%	7%	11%
Ocular hyperemia	4%	8%	5%	10%
Corneal epithelium defect	4%	5%	5%	6%
Detachment of the retinal pigment epithelium	3%	3%	5%	5%
Injection site pain	3%	3%	3%	4%
Foreign body sensation in eyes	3%	4%	4%	4%
Lacrimation increased	3%	1%	4%	2%
Vision blurred	2%	2%	4%	3%
Intraocular inflammation	2%	3%	3%	4%
Retinal pigment epithelium tear	2%	1%	2%	2%
Injection site hemorrhage	1%	2%	2%	2%
Eyelid edema	1%	2%	2%	3%
Corneal edema	1%	1%	1%	1%
Retinal detachment	<1%	<1%	1%	1%

Less common serious adverse reactions reported in <1% of the patients treated with EYLEA were hypersensitivity, retinal tear, and endophthalmitis.

Macular Edema Following Retinal Vein Occlusion (RVO). The data described below reflect 6 months exposure to EYLEA with a monthly 2 mg dose in 218 patients following CRVO in 2 clinical studies (COPERNICUS and GALILEO) and 91 patients following BRVO in one clinical study (VIBRANT).

Table 2: Most Common Adverse Reactions (≥1%) in RVO Studies

	CRVO		BRVO	
Adverse Reactions	**EYLEA (N=218)**	**Control (N=142)**	**EYLEA (N=91)**	**Control (N=92)**
Eye pain	13%	5%	4%	5%
Conjunctival hemorrhage	12%	11%	20%	4%
Intraocular pressure increased	8%	6%	2%	0%
Corneal epithelium defect	5%	4%	2%	0%
Vitreous floaters	5%	1%	1%	0%
Ocular hyperemia	5%	3%	2%	2%
Foreign body sensation in eyes	3%	5%	3%	0%
Vitreous detachment	3%	4%	2%	0%
Lacrimation increased	3%	4%	3%	0%
Injection site pain	3%	1%	1%	0%
Vision blurred	1%	<1%	1%	1%
Intraocular inflammation	1%	1%	0%	0%
Cataract	<1%	1%	5%	0%
Eyelid edema	<1%	1%	1%	0%

Less common adverse reactions reported in <1% of the patients treated with EYLEA in the CRVO studies were corneal edema, retinal tear, hypersensitivity, and endophthalmitis.

Diabetic Macular Edema (DME) and Diabetic Retinopathy (DR). The data described below reflect exposure to EYLEA in 578 patients with DME treated with the 2-mg dose in 2 double-masked, controlled clinical studies (VIVID and VISTA) from baseline to week 52 and from baseline to week 100.

Table 3: Most Common Adverse Reactions (≥1%) in DME Studies

	Baseline to Week 52		Baseline to Week 100	
Adverse Reactions	**EYLEA (N=578)**	**Control (N=287)**	**EYLEA (N=578)**	**Control (N=287)**
Conjunctival hemorrhage	28%	17%	31%	21%
Eye pain	9%	6%	11%	9%
Cataract	8%	9%	19%	17%
Vitreous floaters	6%	3%	8%	6%
Corneal epithelium defect	5%	3%	7%	5%
Intraocular pressure increased	5%	3%	9%	5%
Ocular hyperemia	5%	6%	5%	6%
Vitreous detachment	3%	3%	8%	6%
Foreign body sensation in eyes	3%	3%	3%	3%
Lacrimation increased	3%	2%	4%	2%
Vision blurred	2%	2%	3%	4%
Intraocular inflammation	2%	<1%	3%	1%
Injection site pain	2%	<1%	2%	<1%
Eyelid edema	<1%	1%	2%	1%

Less common adverse reactions reported in <1% of the patients treated with EYLEA were hypersensitivity, retinal detachment, retinal tear, corneal edema, and injection site hemorrhage.
Safety data observed in 269 patients with nonproliferative diabetic retinopathy (NPDR) through week 52 in the PANORAMA trial were consistent with those seen in the phase 3 VIVID and VISTA trials (see Table 3 above).

6.2 Immunogenicity.
As with all therapeutic proteins, there is a potential for an immune response in patients treated with EYLEA. The immunogenicity of EYLEA was evaluated in serum samples. The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to EYLEA in immunoassays. The detection of an immune response is highly dependent on the sensitivity and specificity of the assays used, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to EYLEA with the incidence of antibodies to other products may be misleading.
In the wet AMD, RVO, and DME studies, the pre-treatment incidence of immunoreactivity to EYLEA was approximately 1% to 3% across treatment groups. After dosing with EYLEA for 24-100 weeks, antibodies to EYLEA were detected in a similar percentage range of patients. There were no differences in efficacy or safety between patients with or without immunoreactivity.

8 USE IN SPECIFIC POPULATIONS.

8.1 Pregnancy
Risk Summary
Adequate and well-controlled studies with EYLEA have not been conducted in pregnant women. Aflibercept produced adverse embryofetal effects in rabbits, including external, visceral, and skeletal malformations. A fetal No Observed Adverse Effect Level (NOAEL) was not identified. At the lowest dose shown to produce adverse embryofetal effects, systemic exposures (based on AUC for free aflibercept) were approximately 6 times higher than AUC values observed in humans after a single intravitreal 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 EYLEA can cause fetal harm when administered to a pregnant woman. Based on the anti-VEGF mechanism of action for aflibercept, treatment with EYLEA may pose a risk to human embryofetal development. EYLEA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data
Animal Data
In two embryofetal development studies, aflibercept produced adverse embryofetal effects when administered every three days during organogenesis to pregnant rabbits at intravenous doses ≥3 mg per kg, or every six days during organogenesis at subcutaneous doses ≥0.1 mg per kg.
Adverse embryofetal effects included increased incidences of postimplantation loss and fetal malformations, including anasarca, umbilical hernia, diaphragmatic hernia, gastroschisis, cleft palate, ectrodactyly, intestinal atresia, spina bifida, encephalomeningocele, heart and major vessel defects, and skeletal malformations (fused vertebrae, sternebrae, and ribs; supernumerary vertebral arches and ribs; and incomplete ossification). The maternal No Observed Adverse Effect Level (NOAEL) in these studies was 3 mg per kg. Aflibercept produced fetal malformations at all doses assessed in rabbits and the fetal NOAEL was not identified. At the lowest dose shown to produce adverse embryofetal effects in rabbits (0.1 mg per kg), systemic exposure (AUC) of free aflibercept was approximately 6 times higher than systemic exposure (AUC) observed in humans after a single intravitreal dose of 2 mg.

8.2 Lactation
Risk Summary
There is no information regarding the presence of aflibercept in human milk, the effects of the drug on the breastfed infant, or the effects of the drug 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, EYLEA is not recommended during breastfeeding.
The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for EYLEA and any potential adverse effects on the breastfed child from EYLEA.

8.3 Females and Males of Reproductive Potential
Contraception
Females of reproductive potential are advised to use effective contraception prior to the initial dose, during treatment, and for at least 3 months after the last intravitreal injection of EYLEA.

Infertility
There are no data regarding the effects of EYLEA on human fertility. Aflibercept adversely affected female and male reproductive systems in cynomolgus monkeys when administered by intravenous injection at a dose approximately 1500 times higher than the systemic level observed humans with an intravitreal dose of 2 mg. A No Observed Adverse Effect Level (NOAEL) was not identified. These findings were reversible within 20 weeks after cessation of treatment.

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

8.5 Geriatric Use.
In the clinical studies, approximately 76% (2049/2701) of patients randomized to treatment with EYLEA were ≥65 years of age and approximately 46% (1250/2701) were ≥75 years of age. No significant differences in efficacy or safety were seen with increasing age in these studies.

17 PATIENT COUNSELING INFORMATION
In the days following EYLEA administration, patients are at risk of developing endophthalmitis or retinal detachment. If the eye becomes red, sensitive to light, painful, or develops a change in vision, advise patients to seek immediate care from an ophthalmologist [*see Warnings and Precautions (5.1)*].
Patients may experience temporary visual disturbances after an intravitreal injection with EYLEA and the associated eye examinations [*see Adverse Reactions (6)*]. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

REGENERON

Manufactured by:
Regeneron Pharmaceuticals, Inc.
777 Old Saw Mill River Road
Tarrytown, NY 10591

Issue Date: 05/2019
Initial U.S. Approval: 2011

Based on the May 2019
EYLEA® (aflibercept) Injection full Prescribing Information.

US-LEA-13708(2)a(2)

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RETINA SPECIALIST

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EDITORIAL

By Charles C. Wykoff, MD, PhD

Clinically relevant

What makes a trial outcome clinically relevant?

When no treatment exists for a blinding disease, any improvement compared to natural history may be clinically relevant. For example, while the role of photodynamic therapy in the widespread management of neovascular age-related macular degeneration was short lived, it did modify the natural trajectory of visual acuity decline, at least in some populations. Similarly, a first-in-class therapy that slows the progression of geographic atrophy, even slightly, will likely be highly clinically relevant.

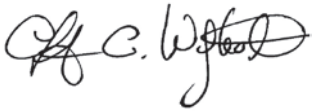
When a validated therapy already exists, noninferiority trials can help define the clinical relevance of a new treatment beyond visual acuity; e.g., by decreasing treatment burden or offering an alternative, potentially surgical, approach to management.

Sometimes clinically relevant outcomes only become apparent with long-term follow-up. Despite monthly dosing, nearly 18 percent of patients in RIDE/RISE developed proliferative diabetic retinopathy within three years, a finding both clinically relevant and valuable in highlighting the shortcomings of pulsatile anti-VEGF monotherapy.

Traditionally, Food and Drug Administration approval of a pharmaceutical for a new retinal indication hinged directly on vision. More recently, the FDA has accepted anatomic biomarkers that have a valid correlation with vision to serve as the primary endpoint. Examples include optical coherence tomography-based vitreomacular traction, autofluorescence-based GA area and, most recently, fundus photography-based changes on the Diabetic Retinopathy Severity Scale. The association of improvements in DRSS scores with the clinically relevant outcomes of PDR and development of diabetic macular edema within PANORAMA are currently being debated.

Two-year results of the Diabetic Retinopathy Clinical Research Network Protocol V give us the opportunity to reconsider what is clinically relevant for DME patients with good vision. On page 38, John Pitcher, MD, and Namrata Saroj, OD, explore these outcomes. At baseline, mean central subfield thickness was 311 µm, arguably very mild DME. Between 25 and 34 percent of laser and observation eyes lost VA and received aflibercept rescue. Ultimately at two years, 16 to 19 percent of each arm experienced a ≥5-letter VA loss.

Based on this data, if we agree that many patients with very early DME don't warrant pulsatile treatment with current-generation anti-VEGF agents, we must also keep in mind that early DME continues to represent a non-optimal, pathologic state. In the context of DME being a major cause of global visual impairment, then we must consider that mild DME is not acceptable and remains highly clinically relevant. For the next generation, ideally more durable and less invasive treatments may be needed to shift the threshold for initiating treatment. RS



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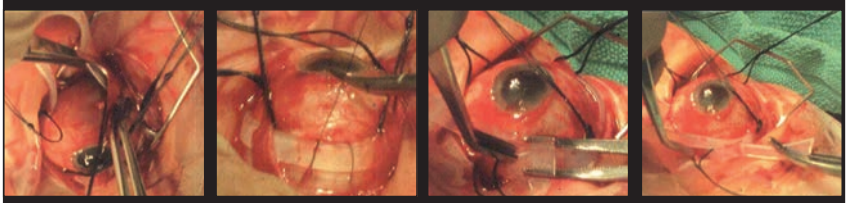
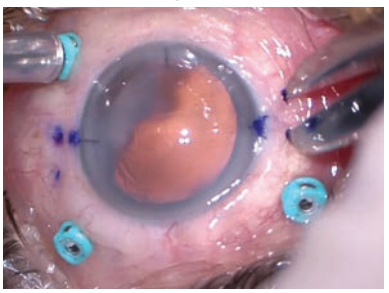
FEATURES



DEPARTMENTS

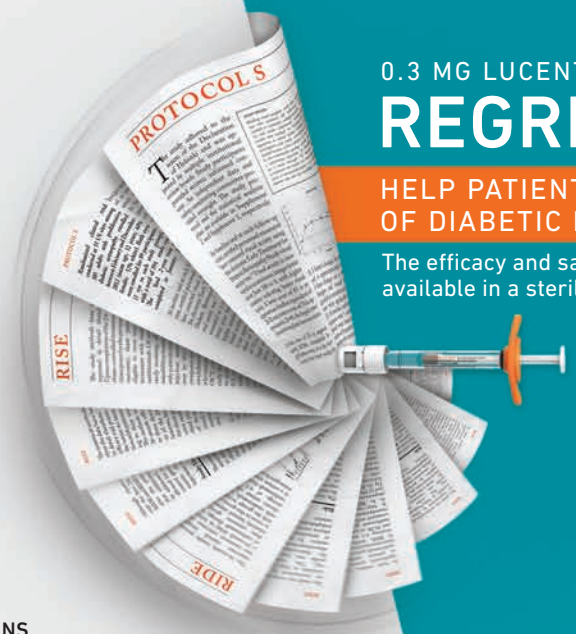


0.3 MG LUCENTIS PREFILLED SYRINGE

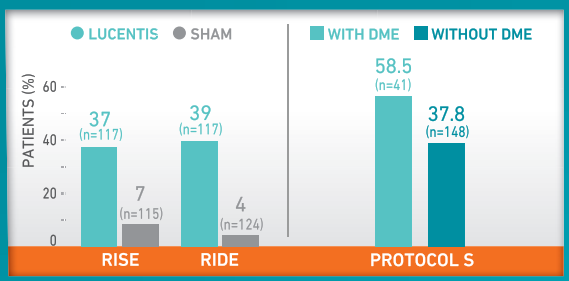
REGRESSION DELIVERED[1]

HELP PATIENTS TURN BACK TO AN EARLIER STAGE OF DIABETIC RETINOPATHY (DR)[1]

The efficacy and safety of LUCENTIS in DR, studied in 3 clinical trials, available in a sterile glass prefilled syringe.[1]



≥2-STEP IMPROVEMENTS AT 2 YEARS[1]*



≥3-STEP IMPROVEMENTS AT 2 YEARS[1]:

RISE AND RIDE
- LUCENTIS 0.3 mg: 9% (n=117) and 17% (n=117), respectively
- Sham arms: 0% (n=115) and 2% (n=124), respectively

PROTOCOL S
- Patients without DME: 28.4% (n=148)
- Patients with DME: 31.7% (n=41)

Confidence intervals (95%): ≥2-step—RISE: 31% (21%, 40%); RIDE: 35% (26%, 44%). Protocol S (DR with DME): 58.5% (43.5%, 73.6%); (DR without DME): 37.8% (30%, 45.7%). ≥3-step—RISE: 9% (4%, 14%); RIDE: 15% (7%, 22%). Protocol S (DR with DME): 31.7% (17.5%, 46%); (DR without DME): 28.4% (21.1%, 35.6%).[1]

INDICATIONS

LUCENTIS® (ranibizumab injection) is indicated for the treatment of patients with:
- Diabetic retinopathy (DR)
- Diabetic macular edema (DME)

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)
- In a pooled analysis of Studies DME-1 and DME-2, 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
- Fatal events occurred more frequently in patients with DME and DR at baseline treated monthly with LUCENTIS compared with control. A pooled analysis of Studies D-1 and D-2, 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

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
- As with all therapeutic proteins, there is the potential for an immune response in patients treated with LUCENTIS. The clinical significance of immunoreactivity to LUCENTIS is unclear at this time

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

*The following clinical trials were conducted for the **DR & DME** indications: ***RISE & RIDE***—Two methodologically identical, randomized, double-masked, sham injection–controlled, Phase III pivotal trials (N=759) that studied the efficacy and safety of LUCENTIS 0.3 mg and 0.5 mg administered monthly to patients with DR and DME at baseline. The primary outcome was the proportion of patients gaining ≥15 letters at 2 years. ***Protocol S***—A randomized, active-controlled study that evaluated LUCENTIS 0.5 mg vs panretinal photocoagulation in DR patients with and without DME. All eyes in the LUCENTIS group (n=191) received a baseline 0.5 mg intravitreal injection followed by 3 monthly injections. Further treatments were guided by prespecified retreatment criteria. FDA approval was based on an analysis of the LUCENTIS arm of Protocol S. The primary outcome was mean change in visual acuity from baseline to 2 years.[2-3]

LUCENTIS 0.3 mg is recommended to be administered by intravitreal injection once a month (approximately 28 days).[1]

DME, diabetic macular edema.

REFERENCES: 1. LUCENTIS [package insert]. South San Francisco, CA: Genentech, Inc; 2018. **2.** Brown DM, et al; RISE and RIDE Research Group. *Ophthalmology*. 2013;120:2013-2022. **3.** Gross JG, et al; Writing Committee for the Diabetic Retinopathy Clinical Research Network. *JAMA*. 2015;314:2137-2146.

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LUCENTIS®
RANIBIZUMAB INJECTION

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	
Adverse Reaction	LUCENTIS 0.3 mg n=250	Control n=250	LUCENTIS 0.5 mg n=379	Control n=379	LUCENTIS 0.5 mg n=440	Control n=441	LUCENTIS 0.5 mg n=259	Control 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	
Adverse Reaction	LUCENTIS 0.3 mg n=250	Control n=250	LUCENTIS 0.5 mg n=379	Control n=379	LUCENTIS 0.5 mg n=440	Control n=441	LUCENTIS 0.5 mg n=259	Control 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_{max}]) 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_{max} 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:
Genentech, Inc.
A Member of the Roche Group
1 DNA Way
South San Francisco, CA
94080-4990

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

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Court orders halt at Florida stem cell clinic that blinded three patients after treatments

The Food and Drug Administration has succeeded in its efforts to stop a company that operates two Florida-based stem-cell clinics, including one where three patients went blind after receiving treatments to cure their age-related macular degeneration, from peddling its adipose-tissue-derived stem-cell products. Last month, a federal district court granted the agency's request for a permanent injunction against the company.

Judge Ursula Ungaro's order stops U.S. Stem Cell Clinic locations in Weston and Sunrise, along with the company's chief scientific officer Kristin Comella, PhD, from manufacturing or distributing any stromal vascular fraction products until they come into compliance with the law, the FDA said.

Three patients went blind after they received intravitreal injections of autologous adipose tissue-derived stem cells at the Sunrise clinic, as documented in a March 2017 *New England Journal of Medicine* article by Ajay E. Kuriyan, MD, Thomas Albini, MD, and colleagues.[1] They reported the patients' vision loss was associated with ocular hypertension, hemorrhagic retinopathy, vitreous hemorrhage, combined traction and rhegmatogenous retinal detachment

The entrance to the U.S. Stem Cell clinic in Sunrise, Fla., where three patients went blind after intravitreal stem-cell injections. (Jim Rassol / South Florida Sun Sentinel /Polaris).

or lens dislocation, and that their visual acuity ranged from 20/200 to no light perception one year after receiving treatment. (Drs. Kuriyan and Albini reported on their findings about cell therapy clinics in the January/February 2019 issue of *Retina Specialist*.)

In 2018, the FDA issued the company a warning letter and filed for the permanent injunction. During the court proceedings, *The New York Times* reported Dr. Comella had argued that the stem-cell extracts injected into the patients' eyes contained the patients' own cells and so were not a drug and, hence, were exempt from FDA regulation.

The FDA hopes this action sends a warning to other stem-cell clinics that have been operating outside the agency's purview. "Today's action by Judge Ungaro is significant and sends a strong message to others manufacturing violative stem-cell products," acting FDA Commissioner Norman E. Sharpless, MD, and director of the center for biologics evaluation and research Peter Marks, MD, PhD, said in a joint statement. They said the agency is going to continue to issue warning letters and bring court cases against unauthorized stem-cell clinics. Over the past year, the FDA has issued 46 "regulatory correspondences," which include warning letters. One court case is ongoing.

In the meantime, the FDA says it will continue to work with legitimate stem-cell providers through its expedited review programs and engagement with manufacturers to provide informal and non-binding evaluations of cell- and tissue-based products.

REFERENCE

1. Kuriyan AE, Albini TA, Townsend JH, et al. Vision loss after Intravitreal injection autologous "stem cells" for AMD. N Engl J Med. 2017;376:1047-1053.

IN BRIEF

Glaukos Corp., maker of microinvasive inserts for the treatment of glaucoma, has agreed to acquire **DOSE Medical Corporation**, developer of multiple microinvasive, bioerodable, sustained-release drug-delivery platforms for retinal diseases. Glaukos agreed to pay $2.5 million cash and make a series of performance-based milestone payments later on.

Zeiss Medical Technology has received Food and Drug Administration 510(K) clearance for the CLARUS 700 high-definition, ultra-widefield imaging system that provides what Zeiss describes as a complete range of fundus imaging modalities, including fluorescein angiography.

DORC has received notification that the FDA has accepted its new drug application for Brilliant Blue G ophthalmic solution. The proposed indication is to selectively stain the internal limiting membrane.

More evidence of lipid-lowering drugs' benefits in diabetic retinal disease

A large U.S. population study has provided further evidence that patients with diabetes taking statins have lower rates of both nonproliferative and proliferative diabetic retinopathy as well as diabetic macular edema, according to an article in press in the *American Journal of Ophthalmology*.[1]

The study authors, led by Darius M. Moshfeghi, MD, at the Byers Eye Institute at Stanford University, analyzed 269,782 patients in the Truven MarketScan Commercial Claims and Encounters database, 37 percent (99,233) of whom were on lipid-lowering therapy. The rates of diabetic retinal disease diagnosis or related treatment were approximately 10 percent lower in the treated population, 6 percent vs. 6.5 percent ($p<0.01$). The study considered patients with a diagnosis of NPDR, PDR or DME, or a history of treatment for retinal disease—either intravitreal injection, pars plana vitrectomy or laser—following a diagnosis of diabetes as the affected population.

Digging deeper, the researchers found that patients who were taking lipid-lowering drugs before they were diagnosed with type 2 diabetes had statistically significant lower risk of progressing on to any retinopathy diagnosis or receiving any treatment for retinopathy—lower by 40 and 19 percent, respectively.

The study acknowledged earlier evidence of the association between hyperlipidemia and high triglyceride levels and retinopathy, as well as the beneficial effects of lipid-lower drugs on retinal disease and related treatment, most notably recent studies from Japan and Taiwan.[2,3] The aim of the most recent study was to perform a real-world analysis of a large database in a diverse population.

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Rates of diagnosis or treatment for diabetic retinal disease among study population[1]

Outcome	No lipid-lowering medication (n=166,520) N (%)	Lipid-lowering medication (n=99,233) N (%)
Any retinopathy diagnosis	2,629 (1.6)	922 (0.9)
Nonproliferative diabetic retinopathy	1,833 (1.1)	680 (0.7)
Proliferative DR	675 (0.4)	151 (0.2)
Diabetic macular edema	1,026 (0.6)	223 (0.2)
Any retinopathy treatment	8,344 (5.0)	4,849 (4.9)
Intravitreal injection of anti-VEGF medication	8,040 (4.8)	4,651 (4.7)
Focal or panretinal laser photocoagulation	207 (0.1)	85 (0.1)
Vitrectomy	406 (0.2)	200 (0.2)

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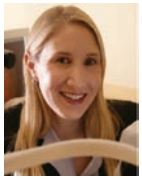
What's causing this patient's blind spot?

How OCT angiography may enhance our understanding of this fascinating maculopathy.

By Karine D. Bojikian, MD, PhD and Steven S. Saraf, MD



Department Editor
Lisa C. Olmos de Koo, MD, MBA

An 18-year-old Caucasian woman presented with the complaint of a fixed blind spot in her right eye of three months duration. The onset of her visual symptoms was preceded by two episodes of bilateral visual disturbances associated with neurologic complaints. One month before the onset of the blind spot, she described having seen dark spots in both eyes accompanied by numbness in her left arm that lasted about one hour. She went to an emergency department for evaluation, where a brain MRI was performed. Her symptoms were attributed to visual aura associated with classic migraine without headache.

One week later she had another episode of similar bilateral vision changes, but this time her symptoms were accompanied by facial numbness. Evaluation in the emergency department was again unremarkable. Two weeks later she noted the blind spot in her right eye upon awakening, which has remained constant since. She describes that sometimes the missing spot appears as a spinning light and sometimes as a dark void; however, the spot does not change position.

Medical and ocular history

Her ocular and medical histories were unremarkable. She took oral contraceptives, but no other medications. After the onset of her symptoms, she stopped the OCPs. She had undergone an extensive workup, but those results were unavailable for review at the time of her visit.

Laboratory testing was suggestive of scleroderma, but she didn't have consistent systemic complaints or findings. She denied prior episodes of blood clots, miscarriages or familial blood dyscrasias. She denied the use of tobacco, alcohol or illegal drugs, including alkyl nitrites.

What the exam found

Visual acuity was 20/20 in each eye. Intraocular pressures were normal, and pupils equal, round and reactive with no relative afferent pupillary defect. Extraocular motility was full, as were color plates in each eye. Amsler grid showed a superotemporal scotoma in the right eye. Slit lamp examination was within normal limits in both eyes. The dilated fundus exam in the right eye was notable for a faded ring-shaped pigmented area of ~1/8 disc diameters in the inferonasal macula (*Figure 1A*).

Workup

Fluorescein angiography revealed adequate perfusion to the macula with no vasculitis or ischemic changes. Fundus photography of the right eye was within normal limits. The infrared reflectance image revealed a ring-shaped lesion in the inferonasal macula (*Figure 1B*). Spectral domain optical coherence tomography of the right macula revealed a focal signal reduction of the ellipsoid zone in the corresponding area (*Figure 2*). OCT angiography using a swept-source platform (Plex Elite 9000, Carl Zeiss Meditec) was obtained, and the segmented image of the

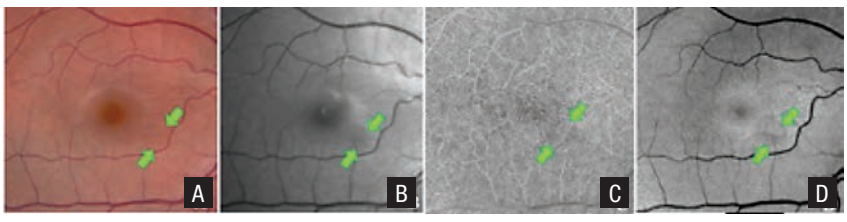


Figure 1. Color fundus (A) and red-free fundus photographs (B) reveal a ring-shaped lesion in the inferonasal macula (arrows). Optical coherence tomography angiography (C) and en face image (D) of the outer retina reveal a hyporeflective ring in the inferonasal macula.

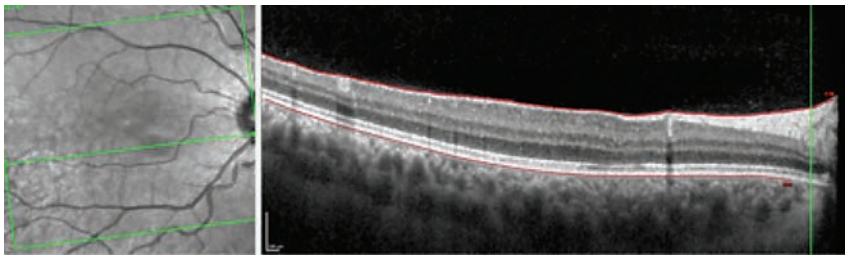


Figure 2. Spectral domain optical coherence tomography shows focal signal reduction of the inner segment/outer segment (IS/OS) junction in the inferonasal macula.

outer retina to choriocapillaris (ORCC) layer (*Figure 1C*) and en face (*Figure 1D*) image revealed a hyporeflective ring in the inferonasal macula.

Diagnosis and management

The patient was diagnosed with acute macular neuroretinopathy (AMN) given the sudden onset of a typical paracentral scotoma, persisting for three months. Focal signal reduction in the ellipsoid zone and infrared reflectance supported the diagnosis. The patient was advised that oral contraceptive use has been associated with this condition. She continues to follow up in the clinic and doesn't plan to resume OCPs.

Pathology of AMN

Pierre J.M. Bos, MD, and August F. Deutman, MD, originally described AMN in four patients with paracentral scotomata, slightly decreased visual acuity and reddish, wedge-shaped intraretinal lesions directed toward the fovea.[1] Amani Fawzi, MD, and colleagues further characterized the disease as presenting at onset with hyperreflective changes in the outer plexiform layer (OPL) and outer nuclear layer (ONL) on SD-OCT.[2] Over time, ONL reflectivity recovers, but the lesion progresses to disruption of the ellipsoid zone and OS/retinal pigment epithelium junctions with chronic thinning of the ONL.

The disease preferentially affects young, non-Latino white women. Several associations or risk factors have been identified, with the most common being nonspecific flu-like illness or fever (47.5 percent), use of oral contraceptives (35.6 percent) and exposure to either epinephrine or ephedrine (7.9 percent).[3] The disease is bilateral in about half of cases and visual acuity at presentation is usually good.[3] Some authors have proposed ischemic vascular occlusion in the macula as a pathogenic mechanism.[4]

Diagnosing AMN

Currently, AMN diagnosis is based on the patient's history and symptoms, infrared reflectance images and outer retinal changes on SD-OCT. Fluorescein angiography, indocyanine green angiography and fundus autofluorescence are normal in the vast majority of cases.[4] However, these imaging techniques are still helpful in excluding other causes of acute vision loss, including white dot syndromes that occur in a similar demographic, and may produce other angiographic and FAF findings.

OCTA studies have previously shown that AMN lesions are associated with capillary vascular occlusions. However, the primary capillary plexus affected in these entities remains an area of great controversy. Recent studies implicated ischemia of the deep capillary plexus (DCP)[5,6] and choriocapillaris,[7,8] but these reports weren't conclusive due to the limitations of OCTA in which signal attenuation can be confused with a flow deficit.

Sally Chu, MD, and colleagues at Northwestern University reported use of projection-resolved (PR)-OCTA in five patients diagnosed with AMN and described reduced DCP flow signal, along with normal superficial, middle capillary plexuses (MCP) and choriocapillaris flow signal in the area of the lesion.[9] In our case, we report the use of swept-source OCTA,

(Continued on page 26)

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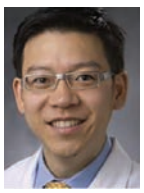
Dr. Olmos de Koo is an associate professor of ophthalmology and director of the retina fellowship program at the University of Washington in Seattle, where Dr. Bojikian is a second-year ophthalmology resident and Dr. Saraf is a retina fellow.

The Yamane technique optimized

A modification of the highly regarded approach to intraocular lens scleral fixation.

By Mansoor Mughal, MD, and Sumit P. Shah, MD, FACS



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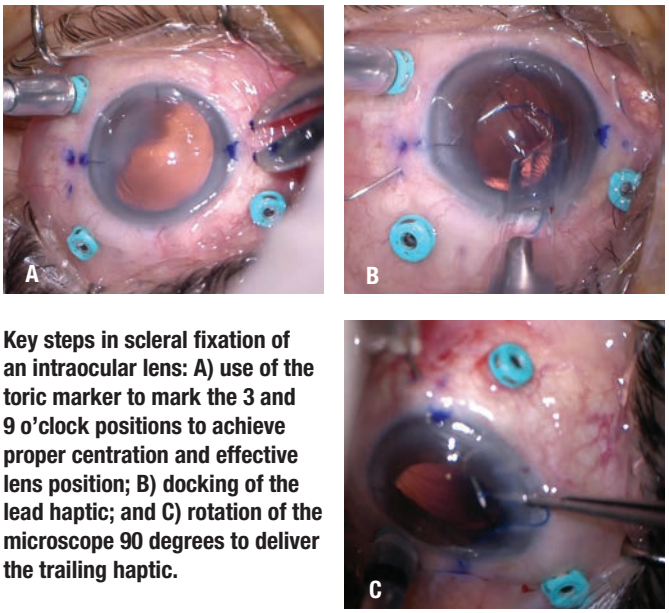
DISCLOSURES: Dr. Hahn is a consultant to Alcon.

Drs. Mughal and Shah have no relevant relationships to disclose.

Techniques to place intraocular lenses in the absence of adequate capsular support continue to be an important part of the vitreoretinal surgeon's armamentarium. Shin Yamane, MD, pioneered a modification of sutureless intrascleral IOL fixation using needles to dock and externalize the haptics.[1] Here, we describe our approach to optimize the procedure.



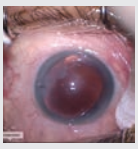
Key steps in scleral fixation of an intraocular lens: A) use of the toric marker to mark the 3 and 9 o'clock positions to achieve proper centration and effective lens position; B) docking of the lead haptic; and C) rotation of the microscope 90 degrees to deliver the trailing haptic.

Key steps

• ***The setup.*** A toric marker is important to mark the 3 and 9 o'clock positions (*Figure A*). Calipers are used to mark the conjunctiva 2 mm from the limbus, with another mark placed 2 mm superior (at 3) and 2 mm inferior (at 9). As needed, a standard pars plana vitrectomy and/or lensectomy is performed with cannulas placed away from the above marked locations. A dispersive viscoelastic is placed in the anterior chamber. A keratome fashions a triplanar 3.2-mm clear corneal incision at the superior limbus.

• ***Lens and injector.*** The Zeiss CT Lucia 602 three-piece IOL is well suited for intrascleral fixation because of the strength of its haptics. The IOL is loaded in a 3.2-mm Alcon Type A cartridge, delivered through the corneal wound using a Monarch II handpiece (Alcon).

View the Video



Drs. Mughal and Shah scleral fixate an intraocular lens with a modified Yamane technique. Available at: http://bit.ly/VideoPearl_012

• ***Delivery.*** A 0.5-inch long, 30-ga. thin-walled TSK needle is placed on a TB syringe and bent about 75 degrees with the bevel facing inward (docking needle). A standard-bore 30-ga. needle, often found in the operating room, won't accept most haptics.

The docking needle is inserted with the left hand at 3 o'clock via a tunnel using the previously placed marks. The loaded lens cartridge is inserted into the clear corneal wound with the right hand. The assistant advances the Monarch II injector. The IOL is advanced until the lead haptic emerges (*Figure B*) and is simultaneously docked into the lumen of the TSK needle before advancing the remainder of the IOL.

Alternatively, the IOL can be delivered partially in the anterior chamber with the trailing haptic outside of the eye and the lead haptic docked into the lumen of the TSK needle using microforceps. The TSK needle is withdrawn and the lead haptic externalized. The haptic is grasped with microforceps and low-temperature cautery

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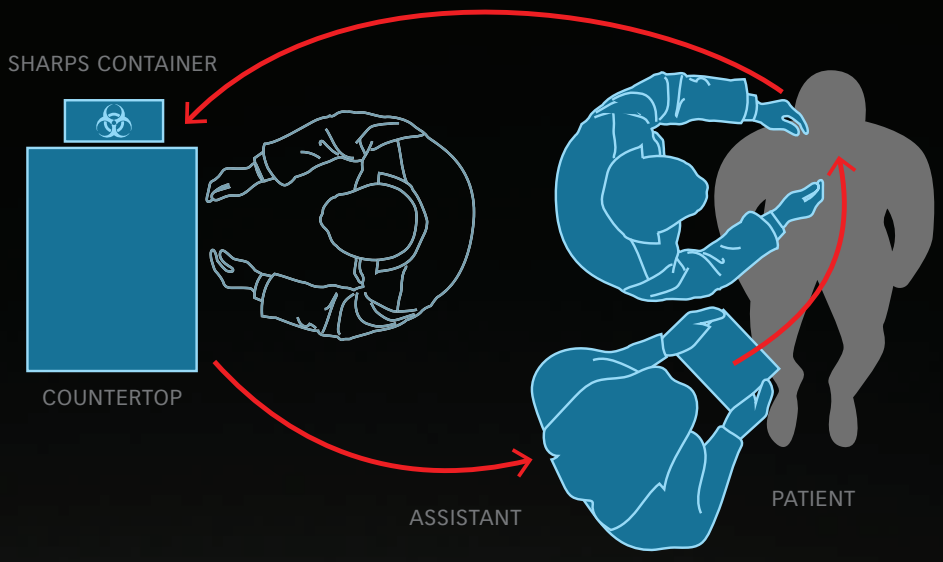

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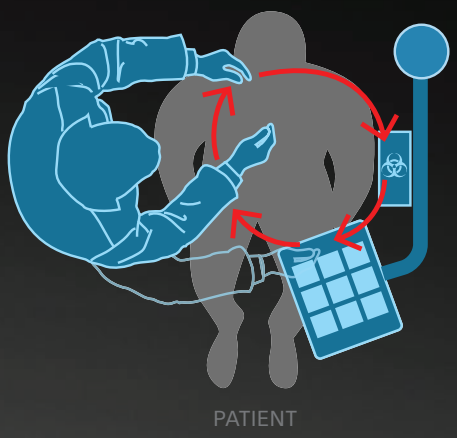

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Scleral buckling surgery: As vital as ever

A review of modern techniques and indications for the repair of rhegmatogenous retinal detachments.

By William H. Ross, MD, FRCSC, and Nakhoul Nakhoul, MD

William H. Ross, MD, FRCSC

Nakhoul Nakhoul, MD

Take-home points

- Scleral buckling surgery remains an essential procedure for the management of rhegmatogenous retinal detachments.
- SB surgery should be the initial procedure to repair RRD in phakic patients up to age 55.
- A SB that covers 5 to 7 mm of peripheral retina will close most retinal tears.
- Planning SB surgery involves selecting the appropriate explant.

The development of small-gauge vitrectomy units with high-speed cutters, wide-angle systems and perfluorocarbon liquid has revolutionized the repair of rhegmatogenous retinal detachments and has led to the misconception that scleral buckling surgery is no longer needed in the management of RRD. However, the use of SB surgery remains an essential procedure in RRD management.

One of us (WHR) has operated on 8,903 retinal detachments between 1973 and 2010, 6,216 managed with a scleral buckle alone and 2,687 with a combined pars plana vitrectomy and SB procedure. We make the argument that SB surgery should be the initial procedure performed in phakic patients under 55 years of age who present with RRD.

The vast majority of retinal tears are 1 to 3 mm in size and occur at the posterior margin of the insertion of the vitreous base, 3 to 4 mm from the ora serrata. Therefore, a SB that covers 5 to 7 mm of peripheral retina will close most retinal tears (*Figure 1*).

Here, we review the repair of retinal detachments in phakic younger patients without the presence of proliferative vitreoretinopathy (PVR)—i.e., there are no fixed folds in the detached retina and the retinal tears do not have any rolled edges. Detachments with vitreous hemorrhage that obscure a complete view of the peripheral retina are excluded from this article. The technique

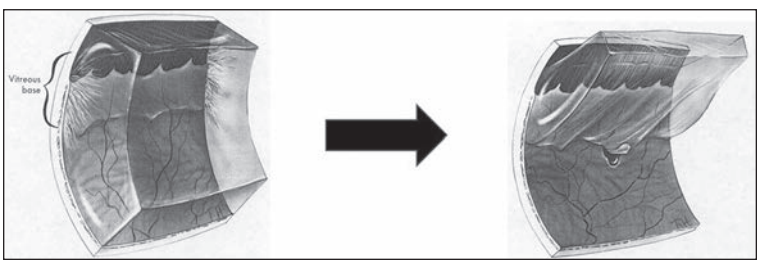

Figure 1. View of a retinal break at the posterior margin of the insertion of the vitreous base.

Bios

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Dr. Nakhoul was the vitreoretinal fellow at UBC from July 1, 2018, to June 30, 2019.

DISCLOSURES: Drs. Ross and Nakhoul have no relevant financial relationships to disclose.

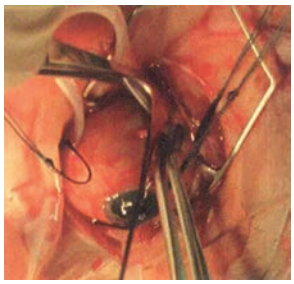

Figure 2. Place the thin explant underneath the extraocular muscle.

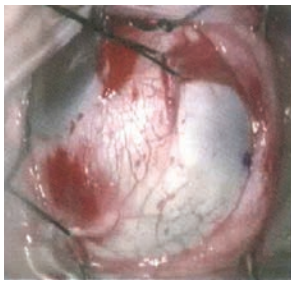

Figure 3. Mark the retinal tear that had been identified with indirect ophthalmoscopy.

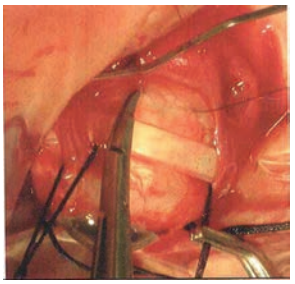

Figure 4. Make a long suture bite with 5-0 nylon suture.

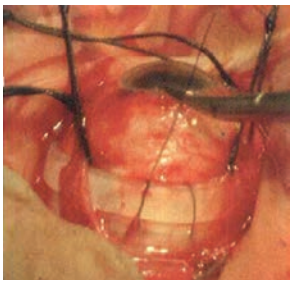

Figure 5. Tie the single-mattress suture over the 5-mm band in the inferior quadrant. Sutures are placed 7 mm apart.

we describe does not require drainage of the subretinal fluid.

Surgical planning

Surgical planning begins with a preoperative, peripheral retinal examination with 360-degree scleral depression to find all retinal tears. We perform a retinal drawing to identify all retinal tears and confirm that PVR is not present.

Planning the operation involves selecting the appropriate explant. Explants to repair the detachments have to be wide enough to close the retinal breaks. Explants 3.5 mm (#41), 4 mm (#42) or 5 mm (#5040) in width can be used. The height of the explant would be 0.75 mm (#41), 1 mm (#5040) or 1.25 mm (#42). This thin explant makes it possible to easily pass the explant beneath the extraocular muscles (*Figure 2*), and will not disturb the function of the muscles by producing diplopia postoperatively. The explant is placed around the eye for 360 degrees to close the original retinal tear and to relieve vitreoretinal traction, to prevent the formation of new retinal tears which would lead to redetachment.

Surgical technique

Modern SB surgery is an external, noninvasive procedure with an operating room time of approximately 30 minutes. It involves the following 15 steps:

1. Administer local retrobulbar anesthesia.
2. Perform conjunctival peritomy for 360 degrees.
3. Hook rectus muscles with 3-0 silk sutures.
4. Perform indirect ophthalmoscopy to identify and mark all retinal tears (*Figure 3*).
5. Perform cryopexy of retinal breaks (postoperative laser).
6. Place the band beneath the recti muscles around the globe for 360 degrees.
7. Place 5-0 nylon mattress suture(s) in two inferior quadrants (*Figure 4*) spaced accordingly:
   - 5 mm apart (3.5-mm explant);
   - 6.5 mm apart (4-mm explant); or
   - 7 mm apart (5-mm explant).
8. Tie 5-1 nylon mattress sutures in the two inferior quadrants (*Figure 5*).
9. Perform the first anterior chamber tap.
10. Place and tie a 5-0 nylon mattress sutures in the two superior quadrants.
11. Place the silicone sleeve to enclose, not tighten, 5-mm band to avoid myopia (*Figure 6*).
12. Perform the second anterior chamber tap if needed (*Figure 7, page 24*).
13. Remove the 3-0 silk sutures.
14. Close Tenon's capsule and conjunctiva with 7-0 vicryl or 6-0 plain gut.
15. Perform indirect ophthalmoscopy to check for central retinal artery pulsations.

Instead of drainage of the subretinal fluid, we use the following steps that allow for tightening of the scleral mattress sutures around the band without increasing intraocular pressure:

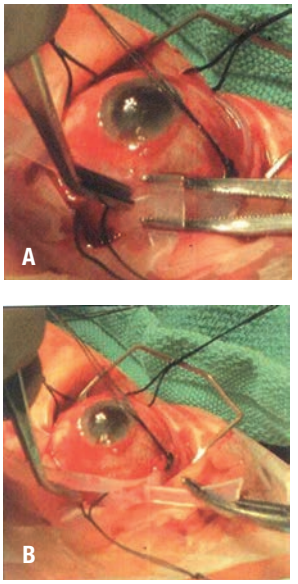

Figure 6. Place the silicone sleeve over the encircling bands (A) and then enclose the silicone explant with a silicone sleeve (B). The sleeve encloses but does not tighten the band to avoid myopia.

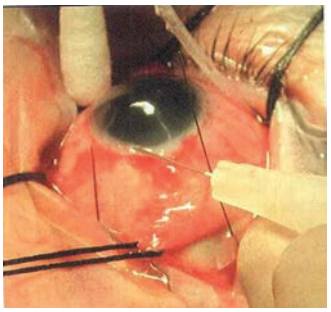

Figure 7. Perform a second anterior chamber tap if necessary.

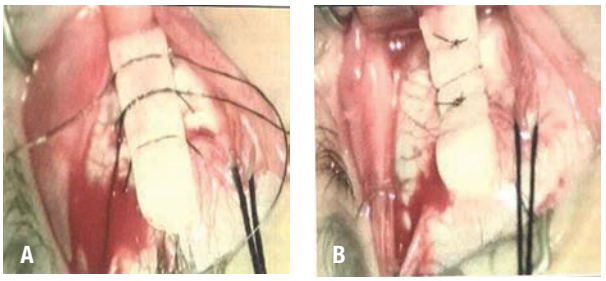

Figure 8. Place two vertical mattress sutures 7 mm apart to secure the one-half-thickness 5-mm radial sponge (A), then tie the 5-0 nylon mattress sutures over the radial sponge before trimming the ends.

- hooking of the recti muscles with 3-0 silk suture;
- cryopexy of the retinal breaks; and
- anterior chamber paracentesis (one or two taps, as needed).

Radial sponges can be extremely useful in the management of retinal detachment secondary to inferior mid-equatorial tears (*Figure 8*).[1]

Radial sponges can be extremely useful in the management of retinal detachments secondary to inferior mid-equatorial tears.

The Value of SB Surgery

This presentation focuses on the management of phakic retinal detachments in younger patients without evidence of PVR. These cases can be successfully managed with an encircling element and without drainage of subretinal fluid, as outlined earlier. These cases represent approximately 50 percent of retinal detachments referred to our clinic for management.

In the remaining 50 percent of patients who present with phakic detachments and associated grade 1 to grade 2 PVR (i.e., fixed folds in one or two quadrants), SB surgery is also indicated. In these cases, a biconvex, segmental buckle 6 or 7 mm wide can be used in one or two quadrants.

Two mattress sutures 7 to 8 mm apart are placed over the solid silicone explant in each quadrant. An encircling 2-mm band is also placed around the globe. Drainage of subretinal fluid beneath the scleral explant can be carried out, followed by injection of SF-6 gas or BSS to restore the volume of the globe and to prevent postoperative myopia. The encircling 2-mm band is simply enclosed in a sleeve without tightening the ends of the 2-mm band to prevent myopia.

The Preference and Trends (PAT) survey of the American Society of Retina Specialists revealed surprising insights into how retina specialists approach phakic RDs.[2] When asked how they would manage a hypothetical 45-year-old -3 D myope with a phakic RD, with a one-half clock-hour size flap tear at 6 o'clock anterior to the equator with the macula on and poorer visual acuity in the fellow eye, the survey reported that:

- 58.3 percent would use a primary buckle;
- 21 percent would perform vitrectomy without a buckle; and
- 19.6 percent would perform a vitrectomy with a SB.

What's alarming is that this type of detachment could easily be managed successfully with a SB procedure without the need of a vitrectomy and its subsequent complications.

Why PnR and SB are still relevant

Many vitreoretinal fellowships no longer emphasize the pneumatic retinopexy (PnR) procedure and SB surgery for RD repair. Virtually all cases undergo PPV. Meanwhile, the majority of patients who present with RD are phakic. The Netherlands study of 2,998 cases revealed that 66.5 percent of patients who presented with RD were phakic.[3] It also demonstrated that the age of patients with the detachments ranged from 55 to 59 years.

The advantages of SB surgery vs. PPV in

Gallery of slam-dunk indications for scleral buckling surgery in phakic patients age <55 years without PVR

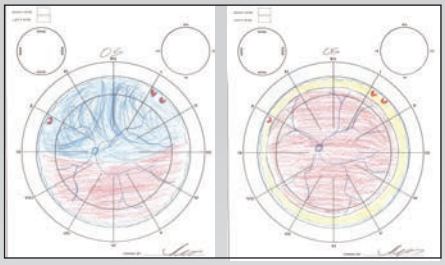

Figure 9. Retinal detachment secondary to superior tear(s) not suitable for pneumatic retinopexy.

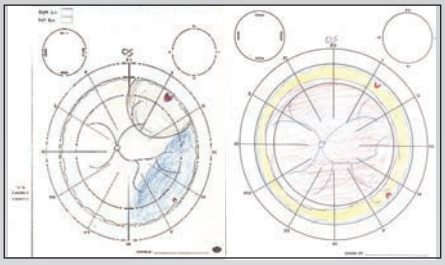

Figure 10. RD secondary to failed pneumatic retinopexy.

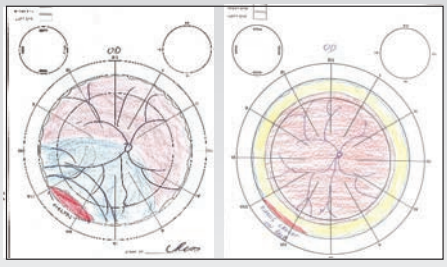

Figure 11. Retinal detachment secondary to traumatic retinal dialysis.[11,12]

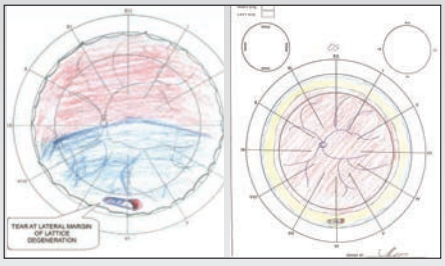

Figure 12. Retinal detachment secondary to tears at the border of lattice degeneration.

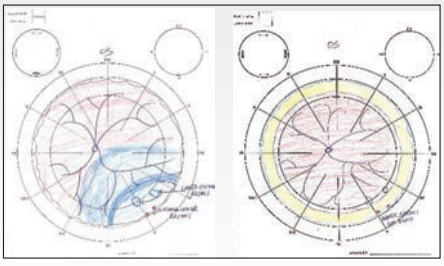

Figure 13. Retinal detachment secondary to retinoschisis detachment.

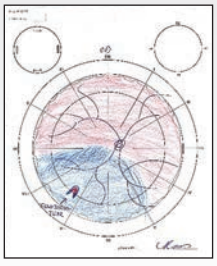

Figure 14. RD secondary to inferior equatorial tear.

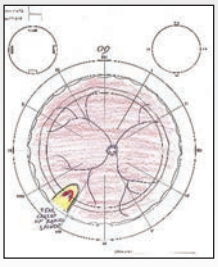

Figure 15. Tear caught on radial sponge.

managing these detachments include:

- No progression of lens opacities that require cataract surgery in one to two years.
- No loss of accommodation in phakic patients following cataract surgery.
- In myopic patients, who represent 35 percent of retinal detachments,[4] PPV would result in anisometropia following cataract surgery, requiring the patient to wear a contact lens or undergo a clear lens extraction in the fellow eye.
- No invasion of the vitreous with an increased stimulus for postoperative PVR.
- No restriction on air travel due to gas expansion and elevated IOP following PPV surgery.
- A reattachment rate of 92 to 94 percent, which is comparable to PPV surgery.
- Faster postoperative rehabilitation.

In the 6 to 8 percent of patients for whom buckling surgery is not initially successful, a secondary PPV with the buckle in place would result in a higher reattachment rate.

Has fellowship training forsaken scleral buckling surgery?

At our institution, each vitreoretinal fellow performs between 120 and 200 PnR

In the 6 to 8 percent of patients for whom buckling surgery is not initially successful, a secondary PPV with the buckle in place would result in a higher reattachment rate.

Two cases in which PPV was used instead of SB surgery, with severe complications

These two cases illustrate how a simple scleral buckle procedure could have reattached the retina in young patients and avoided the poor outcomes that resulted after pars plana vitrectomy.

Case 1

A 21-year-old man with -11 D of myopia presented with an inferior detachment at the 6 o'clock position secondary to lattice degeneration.

First procedure: PPV, air-fluid exchange (AFX) with drainage through the retinal tear, endolaser and SF-6 air exchange.

Postoperative course: Four weeks later the patient presents with a total retinal detachment with fixed folds in all quadrants.

Second procedure: Repeat PPV, peeling of preretinal membranes, AFX with drainage of fluid through a peripheral break and silicone oil infusion.

Postoperative course: Six weeks later the patient develops a recurrent retinal detachment beneath the silicone oil.

Third procedure: Repeat PPV, peeling of preretinal membranes, AFX and reinjection of silicone oil. Retina remains detached.

Outcome: Six months postoperatively, the eye becomes soft due to phthisis bulbi.

Case 2

A 24-year-old professional basketball player presented with a traumatic inferior retinal detachment secondary to a retinal dialysis at the 7 o'clock position in his right eye after he was struck in the eye by an elbow from a player on the opposing team.

First procedure: PPV, perfluoro-n-octane (PFO), laser to dialysis, and air-PFO and air-SF-6 exchange.

Postoperative course: Two weeks later, he has a total retinal detachment with PVR and fixed folds in all quadrants.

Second procedure: Repeat PPV, peeling of epiretinal membranes, PFO, drainage through peripheral retinotomy, 360-degree laser, air-PFO exchange and silicone oil.

Third procedure: Repeat PPV with removal of silicone oil three months later.

Postoperative course: Two weeks later the retina redetaches.

Fourth procedure: PPV, inferior retinectomy between 3 o'clock and 9 o'clock, AFX, endolaser, silicone oil.

Fifth procedure: Three months later, the silicone oil is removed.

Outcome: The retina remained flat. The patient maintained inferior visual field and vision was reduced to count fingers. Because of his loss of depth perception, he can no longer perform at the level of a professional basketball player and had to terminate his career.

Virtually all patients who present with RDs are managed with PPV, despite evidence that PnR and scleral buckling surgery produce comparable anatomic and visual results.

procedures and 35 and 70 SB operations during the one-year program. We've trained 57 VR fellows since 1986, including 11 from Canada and 29 from the United States. However, we've noted that the majority of vitreoretinal fellowships in the United States and abroad don't adequately teach the value of PnR procedures and SB surgery in the management of phakic RDs. Virtually all patients who present with RDs are managed with PPV, despite evidence that PnR and scleral buckling surgery produce comparable anatomic and visual results.

A recent prospective study by Roxane J. Hillier, MBChB,[5] compared pneumatic retinopexies with PPV in the management of phakic RDs. The primary anatomic success at 12 months was achieved in 80.8 percent of patients undergoing PnR vs. 93.2 percent undergoing PPV (p=0.045), with 98.7 and 98.6 percent, respectively, achieving secondary anatomic success. Most importantly, 65 percent of phakic patients in the PPV arm underwent cataract surgery in the study eye within 12 months vs. 16 percent in the PnR group (p<0.001).

A prospective, randomized multicenter clinical study[8] reported an equal single-operation success of 63.6 and 63.8 percent for SB and PPV, respectively, in phakic detachments. In North America, we anticipate a single-operation success rate of approxi-

Busting myths about scleral buckle surgery

Among the commonly held myths vitreoretinal surgeons offer to justify not performing scleral buckle surgery are that it:

- Takes more operating time.
- Requires general anesthesia.
- Produces postoperative pain.
- Produces significant myopia.
- Causes diplopia.
- Leads to a high incidence of extrusion and infection of the buckle.

Here's the truth about modern SB surgery:

- Average operative time is 30 minutes.
- It's done under local anesthesia.
- Postoperative pain is minimal or nonexistent.
- It induces minimal myopia because the sleeve encloses but does not tighten the encircling band.
- Thin scleral explants don't disturb extraocular muscle function and, hence, don't produce diplopia.
- Extrusion or infection are unlikely because the band is enclosed in a silicone sleeve and is covered with Tenon's capsule and conjunctiva.

mately 90 percent for both scleral buckling and pars plana vitrectomies

It's interesting to speculate why SB surgery is no longer used universally in the management of phakic detachments.[7,8] The reason may be that many vitreoretinal fellowships no longer teach SB surgery. It requires properly marking the retinal breaks, placing the scleral sutures and draining the subretinal fluid, if necessary. We strongly believe that teaching the technique of SB surgery in the management of the types of detachments we've outlined should be an integral part of any vitreoretinal fellowship.

Treatment plan for phakic RRD

If the RD involves the superior retina between 8 and 4 o'clock, and if the break or group of breaks are no larger than one clock hour (i.e., 30 degrees of detached retina), a PnR procedure should be performed first. We anticipate a success rate of between 70 and 80 percent with a pneumatic procedure.[9,10]

If the PnR fails, then a scleral buckling procedure should be carried out. This would increase the reattachment rate to between 92 and 94 percent. PPV would be reserved for patients who remained detached following scleral buckling surgery, with a final reattachment rate of 98 to 99 percent.

Bottom line

For inferior retinal detachments, SB surgery is the treatment of choice. It will result in a success rate of 92 to 94 percent. For the 6 to 8 percent of patients in whom SB surgery is unsuccessful, a PPV would then be carried out. PPV will result in a final reattachment rate of 98 to 99 percent. RS

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We strongly believe that teaching the technique of SB surgery in the management of the types of detachments we've outlined should be an integral part of any vitreoretinal fellowship.

The promise and pitfalls of suprachoroidal dosing

Investigational suprachoroidal delivery platforms have leveraged excellent bioavailability with favorable safety signals.


David Levine, MD


Steven Yeh, MD

By David Levine, MD, and Steven Yeh, MD

Take-home points

- High bioavailability with increased drug concentration and compartmentalization make the suprachoroidal space an attractive site for drug delivery.
- Among the investigational platforms for dosing via the suprachoroidal space are the ab interno approach, microneedle injection and sclerotomy with micro-cannulation for noninfectious uveitis.
- Suprachoroidal microneedle injection is being investigated through clinical trials involving macular edema associated with infectious uveitis and diabetic macular edema.

Intravitreal injection remains an efficacious and safe method for drug delivery to the posterior segment for myriad diseases. However, patient and physician treatment burden, as well as the low risk of injection-related adverse effects—e.g., endophthalmitis, retinal tears/detachment and elevated intraocular pressure—remain concerns that may make alternative drug-delivery platforms advantageous.

Phase I/II and III trials have demonstrated that using the suprachoroidal space as a site for drug delivery when treating macular edema due to non-infectious uveitis holds promise. With characteristics such as high bioavailability with lower drug doses and compartmentalization of the drug with a potentially favorable side-effect profile (i.e., reduction of IOP-related adverse events), the suprachoroidal space is an attractive site for drug delivery.[1,2] Studies have been developed to help optimize this drug delivery platform and evaluate its clinical efficacy.

Although multiple approaches to access the suprachoroidal space exist, including the *ab interno* approach (Cypass, iStent, etc.) and standard hypodermic needle injection, only a few have demonstrated reliable access to the suprachoroidal space for drug delivery to the posterior segment. Two of these methods are suprachoroidal microneedle injection (Xipere, Clearside Biomedical) and sclerotomy with micro-cannulation (iTrack, Ellex).

Sclerotomy and micro-cannulation

Investigational work has been performed, fashioning a sclerotomy using a specialized microcatheter with a flashing diode to access the suprachoroidal space. One benefit of this platform is that the drug delivery site can be accurately visualized. It has demonstrated promise in animal models as well as in humans as a treatment modality.[3-5] Thus far, this technique has been used in humans for treatment of severe subfoveal hard exudates and exudative age-related macular degeneration.[3,5]

Bios

Drs. Levine and Yeh are with the Emory Eye Center, Emory University School of Medicine, Atlanta.

DISCLOSURES: Dr. Yeh disclosed acting as a consultant to Clearside Biomedical.

Dr. Levine has no relevant relationships to disclose.

Timothy Olsen, MD, and colleagues have demonstrated that with this approach, medications could be introduced into the suprachoroidal space safely and effectively in porcine and primate subjects.[4,7] One shortcoming they described was that suprachoroidal bevacizumab (Avastin, Roche/Genentech) was no longer detected after one week, whereas intravitreal bevacizumab was present 30 to 60 days after injection. Another potential disadvantage of this drug-delivery method is the need for surgery, which may not be convenient for the routine treatment of AMD, uveitis or other conditions where office-based intravitreal injections are the standard-of-care.

The treatment of intraocular tumors has also been considered as a potential application of this microcatheterization technology. Further studies will be needed before it's widely adopted, but its viability as a surgical procedure has been validated and warrants investigation.

The hollow microneedle

Another promising therapeutic option for suprachoroidal drug delivery is the hollow microneedle. Microneedles consist of a 30-ga. syringe <1 mm in length (usually 900 or 1,000 µm), and are injected posterior to or within the pars plana.[6,7] The microneedle is injected in a fashion similar to that of intravitreal injections, and therefore can be utilized in the outpatient setting. Potential drug reflux is generally managed by maintaining the needle within the suprachoroidal space briefly prior to removal.[8]

Five active clinical trials have been evaluating microneedles for suprachoroidal drug delivery for treatment of noninfectious uveitis and associated macular edema. One of them is the PEACHTREE study, which is investigating the use of Xipere. This trial has shown promising efficacy and safety results.[10]

Findings from PEACHTREE

In PEACHTREE, a randomized, masked, sham-controlled Phase III trial, 160 patients were enrolled and randomized in a 3:2 ratio to suprachoroid- administered proprietary, preservative-free formulation of triamcinolone acetonide or sham control at baseline and 12 weeks, with primary efficacy and safety endpoints assessed at 24 weeks.

The primary efficacy endpoint of PEACHTREE was a ≥15-letter gain in best-corrected visual acuity, which 47 percent of patients receiving suprachoroidal corticosteroid achieved vs. only 16 percent of controls ($p<0.001$).

Patients receiving suprachoroidal corticosteroid injection also experienced an approximately 150-µm reduction of central subfield thickness, compared to 18 µm in controls. IOP elevation rates and cataract progression or development rates were favorable as well compared to controls: IOP-related adverse events were reported in 12 percent of treated patients and 16 percent of controls; and cataract-related adverse events in 7 and 6 percent, respectively.

The Phase II TYBEE trial is investigating Xipere for the treatment of diabetic macular edema. This trial has randomized 71 patients to aflibercept (Eylea, Regeneron) alone or suprachoroidal triamcinolone acetonide with aflibercept. Both arms have shown VA gains (13.5 letters in the aflibercept arm vs. 12.3 letters in the combination arm). Notably, the combination arm required fewer aflibercept treatments (2.8 injections) than the aflibercept-only arm (4.7 injections).

Additional considerations

Lately, there has been research into microneedle injection into the suprachoroidal space with subsequent iontophoresis to drive drug particles to the posterior pole. One study showed a 30 percent increase in drug concentration at the posterior pole after suprachoroidal injection and iontophoresis in an animal model.[9] These results may help in the development of supra-

(Continued on page 26)

Further studies of microcatheterization technology are needed before it's widely adopted, but its viability as a surgical procedure has been validated and warrants investigation.

YUTIQ™ (fluocinolone acetonide intravitreal implant) 0.18 mg, for intravitreal injection
Initial U.S. Approval: 1963

BRIEF SUMMARY: Please see package insert for full prescribing information.

1. INDICATIONS AND USAGE. YUTIQ™ (fluocinolone acetonide intravitreal implant) 0.18 mg is indicated for the treatment of chronic non-infectious uveitis affecting the posterior segment of the eye.

4. CONTRAINDICATIONS. 4.1. Ocular or Periocular Infections. YUTIQ is contraindicated in patients with active or suspected ocular or periocular infections including most viral disease of the cornea and conjunctiva including active epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, mycobacterial infections and fungal diseases. **4.2. Hypersensitivity.** YUTIQ is contraindicated in patients with known hypersensitivity to any components of this product.

5. WARNINGS AND PRECAUTIONS. 5.1. Intravitreal Injection-related Effects. Intravitreal injections, including those with YUTIQ, have been associated with endophthalmitis, eye inflammation, increased or decreased intraocular pressure, and choroidal or retinal detachments. Hypotony has been observed within 24 hours of injection and has resolved within 2 weeks. Patients should be monitored following the intravitreal injection *[see Patient Counseling Information (17) in the full prescribing information]*. **5.2. Steroid-related Effects.** Use of corticosteroids including YUTIQ may produce posterior subcapsular cataracts, increased intraocular pressure and glaucoma. Use of corticosteroids may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses. Corticosteroids are not recommended to be used in patients with a history of ocular herpes simplex because of the potential for reactivation of the viral infection. **5.3. Risk of Implant Migration.** Patients in whom the posterior capsule of the lens is absent or has a tear are at risk of implant migration into the anterior chamber.

6. ADVERSE REACTIONS. 6.1. 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 associated with ophthalmic steroids including YUTIQ include cataract formation and subsequent cataract surgery, elevated intraocular pressure, which may be associated with optic nerve damage, visual acuity and field defects, secondary ocular infection from pathogens including herpes simplex, and perforation of the globe where there is thinning of the cornea or sclera. Studies 1 and 2 were multicenter, randomized, sham injection-controlled, masked trials in which patients with non-infectious uveitis affecting the posterior segment of the eye were treated once with either YUTIQ or sham injection, and then received standard care for the duration of the study. Study 3 was a multicenter, randomized, masked trial in which patients with non-infectious uveitis affecting the posterior segment of the eye were all treated once with YUTIQ, administered by one of two different applicators, and then received standard care for the duration of the study. Table 1 summarizes data available from studies 1, 2 and 3 through 12 months for study eyes treated with YUTIQ (n=226) or sham injection (n=94). The most common ocular (study eye) and non-ocular adverse reactions are shown in Table 1 and Table 2.

Table 1: Ocular Adverse Reactions Reported in ≥ 1% of Subject Eyes and Non-Ocular Adverse Reactions Reported in ≥ 2% of Patients

Ocular		
ADVERSE REACTIONS	**YUTIQ (N=226 Eyes) n (%)**	**Sham Injection (N=94 Eyes) n (%)**
Cataract[1]	63/113 (56%)	13/56 (23%)
Visual Acuity Reduced	33 (15%)	11 (12%)
Macular Edema	25 (11%)	33 (35%)
Uveitis	22 (10%)	33 (35%)
Conjunctival Hemorrhage	17 (8%)	5 (5%)
Eye Pain	17 (8%)	12 (13%)
Hypotony Of Eye	16 (7%)	1 (1%)
Anterior Chamber Inflammation	12 (5%)	6 (6%)
Dry Eye	10 (4%)	3 (3%)
Vitreous Opacities	9 (4%)	8 (9%)
Conjunctivitis	9 (4%)	5 (5%)
Posterior Capsule Opacification	8 (4%)	3 (3%)
Ocular Hyperemia	8 (4%)	7 (7%)
Vitreous Haze	7 (3%)	4 (4%)
Foreign Body Sensation In Eyes	7 (3%)	2 (2%)
Vitritis	6 (3%)	8 (9%)
Vitreous Floaters	6 (3%)	5 (5%)
Eye Pruritus	6 (3%)	5 (5%)
Conjunctival Hyperemia	5 (2%)	2 (2%)
Ocular Discomfort	5 (2%)	1 (1%)
Macular Fibrosis	5 (2%)	2 (2%)
Glaucoma	4 (2%)	1 (1%)
Photopsia	4 (2%)	2 (2%)

(continued)

Table 1: Ocular Adverse Reactions Reported in ≥ 1% of Subject Eyes and Non-Ocular Adverse Reactions Reported in ≥ 2% of Patients

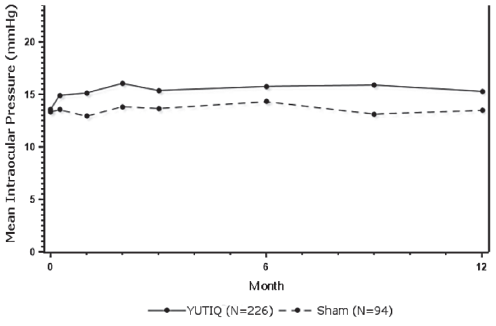
Ocular		
ADVERSE REACTIONS	**YUTIQ (N=226 Eyes) n (%)**	**Sham Injection (N=94 Eyes) n (%)**
Vitreous Hemorrhage	4 (2%)	0
Iridocyclitis	3 (1%)	7 (7%)
Eye Inflammation	3 (1%)	2 (2%)
Choroiditis	3 (1%)	1 (1%)
Eye Irritation	3 (1%)	1 (1%)
Visual Field Defect	3 (1%)	0
Lacrimation Increased	3 (1%)	0
Non-ocular		
ADVERSE REACTIONS	**YUTIQ (N=214 Patients) n (%)**	**Sham Injection (N=94 Patients) n (%)**
Nasopharyngitis	10 (5%)	5 (5%)
Hypertension	6 (3%)	1 (1%)
Arthralgia	5 (2%)	1 (1%)

1. Includes cataract, cataract subcapsular and lenticular opacities in study eyes that were phakic at baseline. 113 of the 226 YUTIQ study eyes were phakic at baseline; 56 of 94 sham-controlled study eyes were phakic at baseline.

Table 2: Summary of Elevated IOP Related Adverse Reactions

ADVERSE REACTIONS	YUTIQ (N=226 Eyes) n (%)	Sham (N=94 Eyes) n (%)
IOP elevation ≥ 10 mmHg from Baseline	50 (22%)	11 (12%)
IOP elevation > 30 mmHg	28 (12%)	3 (3%)
Any IOP-lowering medication	98 (43%)	39 (41%)
Any surgical intervention for elevated IOP	5 (2%)	2 (2%)

Figure 1: Mean IOP During the Studies



8. USE IN SPECIFIC POPULATIONS. 8.1 Pregnancy. Risk Summary. Adequate and well-controlled studies with YUTIQ have not been conducted in pregnant women to inform drug associated risk. Animal reproduction studies have not been conducted with YUTIQ. It is not known whether YUTIQ can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. YUTIQ should be given to a pregnant woman only if the potential benefit justifies the potential risk to the fetus. All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the United States general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. **8.2 Lactation.** Risk Summary. Systemically administered corticosteroids are present in human milk and can suppress growth, interfere with endogenous corticosteroid production. Clinical or nonclinical lactation studies have not been conducted with YUTIQ. It is not known whether intravitreal treatment with YUTIQ could result in sufficient systemic absorption to produce detectable quantities of fluocinolone acetonide in human milk, or affect breastfed infants or milk production. The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for YUTIQ and any potential adverse effects on the breastfed child from YUTIQ. **8.4 Pediatric Use.** Safety and effectiveness of YUTIQ in pediatric patients have not been established. **8.5 Geriatric Use.** No overall differences in safety or effectiveness have been observed between elderly and younger patients.

Manufactured by:
EyePoint Pharmaceuticals US, Inc., 480 Pleasant Street, Watertown, MA 02472 USA
Patented.

YUTIQ™
(fluocinolone acetonide intravitreal implant) 0.18 mg

Discover continuous calm in uveitis

YUTIQ™ (fluocinolone acetonide intravitreal implant) 0.18 mg

Designed to deliver a sustained release of fluocinolone for up to 36 months for patients with chronic noninfectious uveitis affecting the posterior segment of the eye[1]

- Proven to reduce uveitis recurrence at 6 and 12 months[1]*
  [At 6 months–18% for YUTIQ and 79% for sham for study 1 and 22% for YUTIQ and 54% for sham for study 2 (*P*<.01). At 12 months–28% for YUTIQ and 86% for sham for study 1 and 33% for YUTIQ and 60% for sham for study 2.]
- Extended median time to first recurrence of uveitis[1,2]
  [At 12 months–NE† for YUTIQ/92 days for sham in study 1; NE for YUTIQ/187 days for sham in study 2.]
- Mean intraocular pressure (IOP) increase was comparable to sham[1,2]
  Study was not sized to detect statistically significant differences in mean IOP.

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

*Study design: The efficacy of YUTIQ was assessed in 2 randomized, multicenter, sham-controlled, double-masked, Phase 3 studies in adult patients (N=282) with noninfectious uveitis affecting the posterior segment of the eye. The primary endpoint in both studies was the proportion of patients who experienced recurrence of uveitis in the study eye within 6 months of follow-up; recurrence was also assessed at 12 months. Recurrence was defined as either deterioration in visual acuity, vitreous haze attributable to noninfectious uveitis, or the need for rescue medications.

†NE=non-evaluable due to the low number of recurrences in the YUTIQ group.

INDICATIONS AND USAGE

YUTIQ™ (fluocinolone acetonide intravitreal implant) 0.18 mg is indicated for the treatment of chronic noninfectious uveitis affecting the posterior segment of the eye.

IMPORTANT SAFETY INFORMATION

Contraindications

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Steroid-related Effects: Use of corticosteroids including YUTIQ may produce posterior subcapsular cataracts, increased intraocular pressure and glaucoma. Use of corticosteroids may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses. Corticosteroids are not recommended to be used in patients with a history of ocular herpes simplex because of the potential for reactivation of the viral infection.

Risk of Implant Migration: Patients in whom the posterior capsule of the lens is absent or has a tear are at risk of implant migration into the anterior chamber.

Adverse Reactions

In controlled studies, the most common adverse reactions reported were cataract development and increases in intraocular pressure.

References: 1. YUTIQ™ (fluocinolone acetonide intravitreal implant) 0.18 mg full U.S. Prescribing Information. EyePoint Pharmaceuticals, Inc. October 2018. **2.** Data on file.

Please see next page for Brief Summary of full Prescribing Information.

EyePoint™ PHARMACEUTICALS

480 Pleasant Street, Suite B300, Watertown, MA 02472

5/2019
US-YUT-1900057

Suprachoroidal dosing

(Continued from page 23)

choroidal drug-delivery modalities.

Bottom line

Given its unique tissue distribution, the suprachoroidal space has demonstrated promise as a unique drug-delivery pathway with the potential to treat inflammatory and vascular diseases of the posterior segment. While both surgical and non-surgical options for accessing the suprachoirdal space have been studied for commonly encountered posterior segment conditions, recent trials have shown the potential of suprachoroidal dosing in the clinic.

Given the favorable drug distribution profile that suprachoroidal drug delivery may offer, its use could offer a multitude of potential benefits, such as a reduction of treatment burden, improved efficacy and safety, and new indications for treatment of posterior segment disease. RS

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What's causing blind spot?

(Continued from page 13)

which provides fully automated segmentation to obtain 11 structural en face images, including the ORCC en face image (*Figure 1D, page 12*), which was obtained with a slab extended from the outer boundary of the OPL to 8 µm beneath Bruch's membrane. The ORCC en face image enabled the identification of possible signal loss in the area corresponding to the patient's scotoma.

Bottom line

Our case highlights that the pathophysiology of AMN appears to be related to ischemic vascular changes in the macula, and those changes appear to be limited to the DCP. OCTA is a new imaging modality that offers the ability to segment each of the retinal capillary networks, and it further characterizes the retinal microvasculature and has great potential to enhance our understanding of AMN. RS

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Yamane technique optimized

(Continued from page 14)

thermally deforms the end of the haptic into a nailhead.

Overcoming the challenge

Placing the trailing haptic can be challenging due to awkward hand positions from a standard superior vitreoretinal surgery approach. It becomes ergonomically easier to rotate the seating position and microscope 90 degrees to a nasal approach for right eyes and a temporal approach for left eyes (*Figure C, page 14*). Again, a 0.5-inch, 30-ga. TSK needle is mounted on a TB syringe and bent almost 90 degrees bevel up. This is inserted along the previous markings at 9 o'clock parallel to the limbus. The needle is brought up to the anterior chamber near the clear corneal wound or even externalized through the clear corneal wound. The second haptic is grasped with microforceps and introduced into the bore of the needle. Once the haptic is docked, the TB syringe is withdrawn, and the externalized trailing haptic is grasped with microforceps and thermally deformed. Both haptics are placed flush with the sclera in the subconjunctival space to center the IOL. RS

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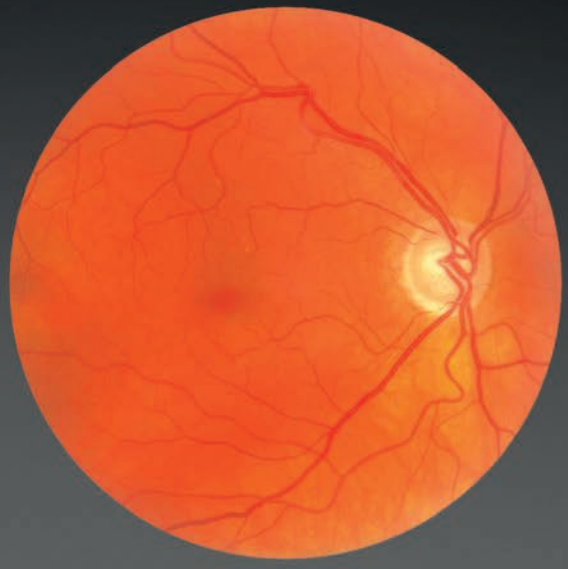

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Regression following IVT Anti-VEGF in ROP

A review of disease progression patterns and the role for laser ablative therapy and intravitreal bevacizumab therapy.

Edward H. Wood, MD

Darius M. Moshfeghi, MD

By Edward H. Wood, MD, and Darius M. Moshfeghi, MD

Take-home points

- Dysregulated angiogenesis in retinopathy of prematurity occurs in two phases: at post-menstrual age 22 to 30 weeks; and at PMA 31 to 44 weeks.
- Understanding the patterns of ROP regression is important to determine intervention with early retreatment opportunities.
- Eyes treated with intravitreal bevacizumab have several unique regression features, including frequent vascular arrest, and must be followed closely after treatment.
- Before screening is completed, these eyes should undergo fluorescein angiography with possible adjunctive ablative laser therapy.

Bios

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Retinopathy of prematurity delays physiologic retinal vascular development, resulting in avascularity and ischemia of the peripheral retina. This may elaborate growth factors, including vascular endothelial growth factor, leading to vasoproliferation at the junction between avascular and vascular retina (Stage 3 ROP).

The dysregulated angiogenesis in ROP occurs in two well-defined phases. In phase 1, occurring during postmenstrual age (PMA) 22 to 30 weeks, relative hyperoxia results in oxygen-induced arrest of normal vascular development and obliteration of immature retinal vascular elements.[1] In phase 2, at PMA 31 to 44 weeks, the retina becomes more mature and metabolically active, resulting in relative retinal ischemia that drives pathologic vasoproliferation.[2]

Outcomes when ROP left untreated

Ninety-nine percent of infants who will develop ROP do so by 46.3 weeks.[3] Left untreated, dysregulated angiogenesis may proliferate and potentially progress toward fibrosis, contraction and ultimately effusive and tractional retinal detachment (stage 4 or 5 ROP).[4]

While it's critical to understand ROP classification[5] and treatment guidelines,[6,7] it's equally important to understand patterns of disease regression so that we don't miss early retreatment opportunities.

In this article, we'll review patterns of disease regression following observation (type 2 ROP or lower), laser ablative therapy and intravitreal bevacizumab (Avastin, Roche/Genentech) therapy, highlighting patterns unique to bevacizumab therapy.

Spontaneous ROP regression

Initially, the Cryotherapy for Retinopathy of Prematurity (CRYO-ROP) study[8,9] defined treatment guidelines, later modified by the Early Treatment for Diabetic Retinopathy (ETROP) study.[10] ETROP defined type 1 ROP accordingly:

Table 1. Pattern of retinopathy of prematurity regression

Regression flow	Spontaneous regression	Regression post-laser
Reversal of plus disease	First to occur (closure of AV shunt)	Typically first to resolve (may take weeks)
Reversal of disease stage	Lags behind plus disease	Lags behind plus disease (typically resolved in three weeks)
Growth of blood vessels past ridge	Straight and unbranched vessels of regression	May occur (within atrophic retina)
Full vascular maturation	Ideal but may not occur	Rarely occurs (within atrophic retina)
Disease persistence	Rare (consider familial exudative vitreoretinopathy [FEVR])	Very rare (consider FEVR)
Retinal detachment	Rare (likely from dedifferentiated hyaloidal endothelial cells)	Rare (majority occur >3 weeks after laser)

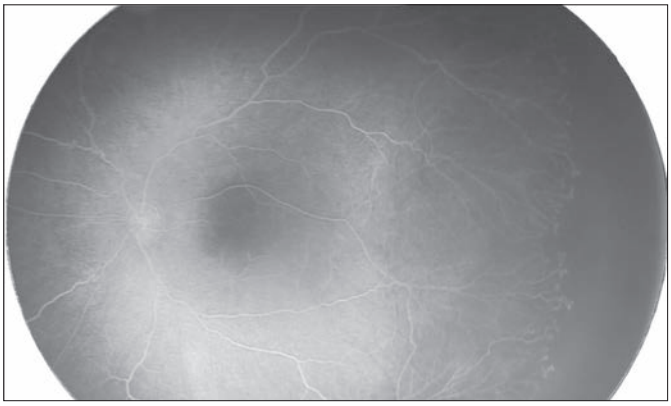

Figure 1. After intravitreal bevacizumab treatment, approximately 42 percent of treated patients manifest vascular arrest alone (VAA), characterized by resolution of plus disease and vascular tortuosity but with chronic vascular arrest.

- zone I, any stage ROP with plus disease;
- zone I, stage 3 ROP without plus disease; or
- zone II, stages 2 or 3 with plus disease.

Type 1 ROP currently requires acute treatment with either ablative laser therapy[1,11] or intravitreal anti-VEGF agents.[12,13]

Type 2 ROP is defined as:

- zone I, stages 1 and 2 without plus disease; or
- zone II, stage 3 without plus disease, or lower.

Close observation with serial examination with retinal photography is the preferred approach for type 2 ROP. Most type 2 ROP doesn't progress, although approximately 20 percent of type 2 did progress to type 1 in the ETROP study, with a mean time of progression of nine days after diagnosis.[14]

Regression without treatment

When treatment isn't indicated, spontaneous ROP regression follows a regular pattern: resolution of plus disease followed by reversal of stage of disease, subsequent growth of "vessels of regression" (straight and unbranched) past the ridge, and ideally full vascular maturation to the ora serrata (*Table 1*).

The duration and degree of spontaneous ROP regression depends on the presenting stage and zone of disease. While most ROP not requiring treatment does regress in the acute phase, roughly 2 percent of infants with type 2 ROP will not regress, exhibiting persistent ROP past 50 weeks.[3]

In the 98 percent of patients that do regress, degrees of persistent peripheral avascular retina will vary. When present, persistent peripheral avascularity creates a milieu for retinal tears and detachments

Disclosures

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Dr. Moshfeghi disclosed relationships with Akebia Therapeutics, Alcon, Allegro Ophthalmics, Apellis Pharmaceuticals, Congruence Medical Solutions, Iconic Therapeutics, Irenix Medical, Grand Legend Technology, Novartis, Pykus, Regeneron and Visunex Medical Systems. He is a founder and board member of dSentz Inc., Linc, Pr3vent and Promisight, and a founder of Versl.

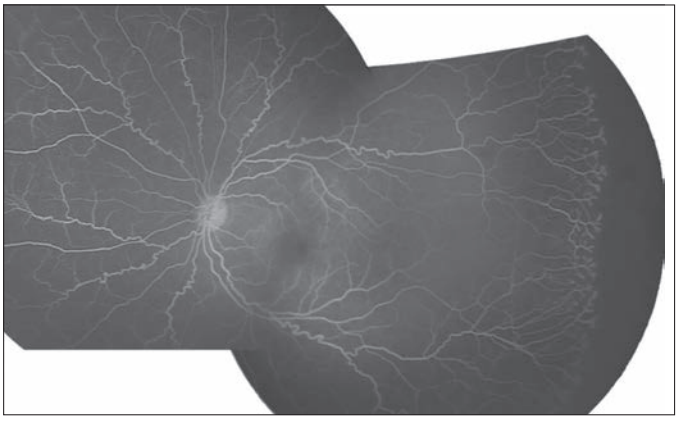

Figure 2. Approximately 38 percent of treated patients exhibited vascular arrest with tortuosity (VAT) after intravitreal bevacizumab, showing no signs of resolution of vascular tortuosity while also displaying chronic vascular arrest.

that can occur in teenage years and adulthood.[5,15]

ROP regression following ALT

When ROP is classified as type 1 or aggressive posterior ROP (APROP), one may choose to treat it with ablative laser therapy or intravitreal anti-VEGF therapy. Laser is performed at a mean peak incidence of 35 to 36 weeks PMA (depending on presenting stage and zone of disease), and is usually completed in a single procedure.[11] In ETROP, laser ablation was shown to reduce unfavorable structural outcomes from 15.6 to 9 percent at nine months.[10]

The pattern of ROP regression after laser therapy has been well documented[11] and follows that of spontaneous regression: reversal of plus disease, followed by downstaging of disease and subsequent vascular growth and maturation (*Table 2*). This is usually complete by 10 weeks after laser.[11] Reduction in the number of active stage 3 clock hours as well as separation of the neovascularization from the ridge are characteristics of disease involution.[11]

Plus disease and disease stage typically resolve in three weeks. Development of vitreous organization may accompany the reduction in neovascularization and should be noted. Regression following laser therapy is further characterized by the development of prominent retinal pigment epithelial changes in the previously avascular retina that had received ablative therapy.

Vascularization may develop at the ora serrata, but the blood vessels are often straight and unbranching with associated retinal thinning and atrophy. After laser, babies are regularly followed up to 50 weeks PMA, by which time they are very unlikely to develop a retinal detachment if they have not already done so.

The pattern of ROP regression after laser therapy follows that of spontaneous regression: reversal of plus disease, followed by downstaging and vascular growth.

Table 2. Outcomes after intravitreal bevacizumab for retinopathy of prematurity

Regression flow	Percentage (%)	Notes or appearance
Scalloped regression	~100	Fine vessel arborization at transition zone
Vascular arrest alone (VAA)	~42	Chronic vascular arrest without tortuosity
Vascular arrest with tortuosity (VAT)	~38	Chronic vascular arrest with tortuous vessels
Full vascular maturation	~3 (by ~60 weeks post-menstrual age [PMA])	Within 2 disc diameters of ora serrata
Disease reactivation	~17 percent (mean ~50 week PMA)	Variable presentation
Retinal detachment	Rare	Mean ~55 weeks PMA

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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.

BRIEF SUMMARY - Consult full prescribing information before use.

Acthar® Gel (repository corticotropin injection) INJECTION, GEL for INTRAMUSCULAR | 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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Mallinckrodt™ Pharmaceuticals

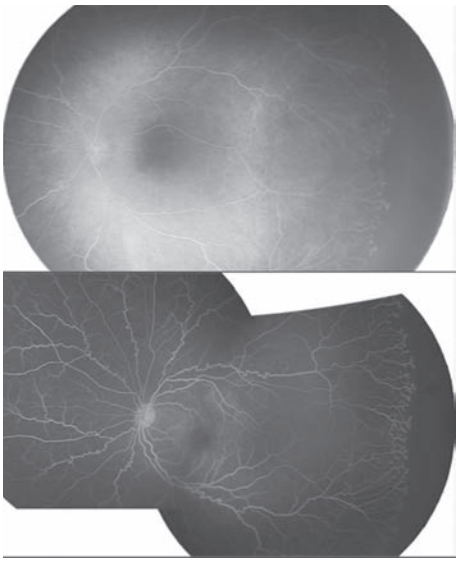

Figure 3. After treatment with intravitreal bevacizumab, 18 percent of eyes exhibited reactivation of retinopathy of prematurity, defined as recurrence of stage of disease, and received ablative laser therapy.

ROP regression post-bevacizumab

When ROP is classified as type 1, one may alternatively choose to treat with intravitreal anti-VEGF (VEGF-I) therapy. Intravitreal ranibizumab (IVR, Lucentis, Roche/Genentech),[12] aflibercept (Eylea, Regeneron),[16] bevacizumab (IVB)[6] and conbercept (Lumitin, Chengdu Kang Hong Biotech)[17] have been used in the treatment of type 1 ROP.

IVB is a humanized monoclonal antibody against VEGF-A and has been the most widely used agent to date for the treatment of type 1 ROP. While numerous studies have demonstrated the efficacy of IVB in inducing ROP regression,[18,19] concerns exist that a percentage of patients exhibit variable disease reactivation[20] and chronic vascular arrest beyond current screening guidelines.[6]

Domenico Lepore, MD, and colleagues have highlighted the inadequacy of clinical examination and photography, either alone or in combination, to follow the vascular maturation and even recurrence in post-VEGF-I-treated ROP patients. They have introduced fluorescein angiography as a more effective way to follow them.[21]

Regression following IVB therapy follows a unique pattern. A characteristic feature of ROP treated with anti-VEGF therapy is called "scalloped regression." This refers to fine vessel arborization at the junction of vascular and avascular retina reminiscent of the acute capillary budding phase of spontaneously regressing ROP. It persists for many weeks and appears without the retinal atrophy that typically accompanies involution with partial vascularization.[6] While the significance of scalloped regression is unknown, it is present in 100 percent of patients treated with anti-VEGF and isn't seen in other forms of regression described.

To further define regression patterns in eyes treated with IVB, Tiffany Chen, MD, and colleagues analyzed 92 eyes treated at a single center with IVB.[22] They found that only three eyes (3.3 percent) treated with IVB reached complete vascular maturity at the time of examination under anesthesia/fluorescein angiography (EUA/FA), typically performed at around 60 weeks PMA. They defined complete vascularization by vasculature reaching within 2 disc diameters of the ora serrata (as per International Committee for the Classification of Retinopathy of Prematurity[5]).

Of the eyes that did not completely vascularize (n=89), they found that 39 (43.8 percent) experienced resolution of plus disease and vascular tortuosity, but had chronic vascular arrest, termed "vascular arrest alone" (*VAA, Figure 1, page 29*). Thirty-four eyes (38.2 percent) didn't experience resolution of vascular tortuosity while also displaying chronic vascular arrest, termed "vascular arrest with tortuosity" (*VAT, Figure 2, page 30*). Sixteen eyes (18 percent) had reactivated ROP, defined as recurrence of stage of disease; these were acutely treated with ablative laser.

Therefore, when considering all IVB treated eyes (n=92), approximately 3

'Scalloped regression' refers to fine vessel arborization at the vascular-avascular retina junction reminiscent of acute capillary budding of spontaneously regressing ROP.

percent reached full vascular maturation, 42 percent exhibited VAA, 38 percent exhibited VAT and 17 percent exhibited disease reactivation (*Figure 3, page 33*). This series reported no retinal progressive detachments. All patients not reaching full vascular maturation (97 percent) underwent ablative laser therapy at the time of FA (typically at around 60 weeks PMA).

Eyes that reactivated were prone to be of Asian ethnicity and to have presented with zone I, stage 2-plus disease and APROP. Persistent tortuosity following treatment with IVB was found to correlate more strongly with younger gestational age than low birth weight. Based on observations of published data with ranibizumab[12] and conbercept,[17] this type of regression appears to be a VEGF-I class phenomenon (*Table 3*).

Persistent tortuosity following treatment with IVB was found to correlate more strongly with younger gestational age than low birth weight.

Bottom line

Knowledge of regression patterns following treatment of type 1 ROP is an important part of ROP care. IVB-treated eyes display several unique regression features including frequent vascular arrest (approximately 97 percent), with or without persistent vascular tortuosity, and the possibility for disease reactivation (approximately 17 percent) even after the completion of classic screening guidelines. Therefore, IVB eyes need to be followed closely after treatment. Before completing their screening, these eyes should undergo FA with possible adjunctive ablative laser therapy. RS

Table 3. Class effect of VEGF-I regression (from most to least debilitating)

- Disease persistence/reactivation
- Vascular arrest with tortuosity (VAT)
- Vascular arrest alone (VAA)
- Full vascular maturation

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Retina Standouts from ARVO 2019

Protocol V, ERM biomarker, AI and injection for GA

The case for observation in CI-DME, DRIL in ERM surgery, AI to predict HbA1c and screen for DR, and a subcutaneous mitochondrial agent.

Ashkan M. Abbey, MD

By Ashkan M. Abbey, MD

Take-home points

- Evidence now supports observation or focal laser for the management of patients with center-involved diabetic macular edema with good vision.
- Disorganization of the retinal inner layers shows promise as a biomarker for epiretinal membrane surgery.
- Artificial intelligence may transform how we measure HbA1c and screen for referable diabetic retinopathy.
- Subcutaneous injection of a mitochondrial agent showed vision gains in patients with geographic atrophy.

The annual meeting of the Association for Research in Vision and Ophthalmology in Vancouver brought together the best retina researchers to explore the latest in diagnostics, treatment and management strategies. Every year, ARVO distinguishes itself from other ophthalmology meetings by including a broad spectrum of research, from innovative basic science to the latest clinical trials.

Here, we present summaries of five compelling posters and presentations: results from Protocol V of the Diabetic Retinopathy Clinical Research Network; a report about the disorganization of retinal inner layers as a biomarker for epiretinal membrane surgery; use of artificial intelligence to predict hemoglobin A1c (HbA1c) and to screen for diabetic retinopathy; and a look at a promising subcutaneous injection for dry age-related macular degeneration.

Protocol V: observation, focal laser in center-involved DME with good VA

The DRCR.net has once again provided novel information that will be particularly useful in our clinical practices. In Protocol V, the authors sought to determine the best initial management for eyes with center-involved (CI) and good visual acuity.[1] This randomized, prospective, multicenter clinical study included 702 eyes with CI-DME and best-corrected visual acuity of 20/25 or better. The participants were randomized to one of three management groups:

- intravitreal injection of aflibercept (Eylea, Regeneron Pharmaceuticals) as frequently as every four weeks (n=226);
- focal/grid laser photocoagulation (n=240); and
- observation (n=236).

Eyes in the laser photocoagulation or observation groups that had ≥10-letter decrease in visual acuity from baseline at any visit, or a 5-to-9-letter loss at two consecutive visits were treated with aflibercept. At two years, the percentage of eyes with a ≥5-letter VA decrease was 16 percent (33/205), 17 percent (36/212) and 19 percent (39/208) in the aflibercept, laser photocoagulation and observation groups, respectively. There were no statistically

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DISCLOSRE: Dr. Abbey is a consultant for Allergan and Genentech

significant risk differences between any of the groups (p=0.79 for all comparisons). Twenty-five percent (60/240) of the laser group and 34 percent (80/236) of the observation group required aflibercept therapy during the study.

Prior this study, there had been significant debate among retina specialists regarding the best approach for treating eyes with CI-DME and good visual acuity. Some elected to treat these eyes with anti-VEGF medications due to the excellent results seen in a number of large clinical trials treating CI-DME patients with reduced vision. In eyes with CI-DME and good vision, Protocol V demonstrated no significant differences in rates of visual acuity loss of ≥5 letters with the initial use of aflibercept, focal laser or observation.

We now have evidence to support the management of these patients with observation (or focal laser) unless VA worsens, allowing us to mitigate the expense, risk and inconveniences associated with intravitreal injections. Patients given the option of observation must be made aware of the importance of close follow-up so that significant vision loss doesn't occur between visits.

We now have evidence to support the management of patients with CI-involved DME and good vision with observation or focal laser unless VA worsens.

Disorganization of retinal inner layers (DRIL) as biomarker for ERM surgery

DRIL is a well-described finding on optical coherence tomography that can be present in patients with DME and ERM, among others. In a multicenter retrospective case series,[2] the central 2,000 µm of the OCT were used to confirm the presence and grade the severity of DRIL in patients with ERM. The boundaries between the ganglion cell-inner plexiform layer complex (GCIPL) and inner nuclear layer (INL), and between the INL and outer plexiform layer (OPL), were evaluated to distinguish between each layer (distinguishable/indistinguishable) and for regularity of boundaries (regular/irregular). The authors summarized these characteristics to create a DRIL severity score: 0 = no DRIL; 1 to 3 = mild DRIL; 4 = severe DRIL.

The study included 90 eyes with idiopathic ERM that underwent vitrectomy and membrane peeling with 12-month follow-up. Patients without DRIL or with mild DRIL had a significantly better baseline BCVA compared to patients with severe DRIL. DRIL severity was statistically significantly associated with decreased BCVA, increased central foveal subfield thickness and increased maximum retinal thickness on OCT (p=0.003, p<0.001 and p<0.001, respectively). Mean improvement in BCVA was 3 lines of vision for the eyes without or with mild DRIL, but only 1 line for the eyes with severe DRIL.

This study demonstrated that DRIL can be used as an OCT biomarker in patients with ERM to predict outcomes after surgery. Patients without DRIL or with mild DRIL had much better postoperative visual and anatomic outcomes than those with severe DRIL. This highlights the need for an in-depth analysis of the preoperative OCT in patients with ERM. If severe DRIL is present, the patient should be counseled appropriately regarding the limited visual prognosis in order to make a sufficiently informed decision regarding surgery.

Estimation of HbA1c from retinal photographs using deep learning

Artificial intelligence is poised to revolutionize medicine in the coming years. Deep learning and neural networks are being actively investigated for screening and diagnosis in ophthalmology. The Singapore Eye Research Institute has now taken a major step forward in showcasing the early diagnostic utility of AI by demonstrating the ability of deep learning to determine a patient's HbA1c from an eye exam.

Their study used fundus photographs and serum samples of 17,422 participants from five population-based and clinical eye studies.[3] In all, 13,937 participants were used to train the deep-learning system, and 3,485 were used to validate it. The results were quite promising. The system was able to estimate HbA1c with a mean error of 0.87

percent. The system generated a slight underestimation of HbA1c for patients with diabetes and a slight overestimation for healthy individuals.

With further validation, this deep-learning system could transform the current paradigm for diabetic screening, potentially allowing for HbA1c measurement from a smartphone fundus photograph instead of requiring a blood test at the doctor's office. This promising development appears to be just the tip of the iceberg with respect to AI's involvement with ophthalmology and healthcare.

AI for diabetic retinopathy screening

The number of people globally with diabetes continues to increase at an alarming rate, bringing with it the challenge of screening for DR in millions of patients with a limited number of eye-care providers. By eliminating the need for human screeners, AI appears to be a promising solution to this problem. Eyenuk just completed a pivotal multicenter prospective clinical trial evaluating its AI system (EyeArt) for DR screening.[4]

The trial enrolled 1,674 eyes from 942 subjects. They underwent undilated two-field fundus photographs and dilated four-wide field stereoscopic fundus photography. The EyeArt system then determined the presence of referable DR (rDR), defined as moderate non-proliferative DR or higher or clinically significant DME. EyeArt was then compared to expert graders at the Wisconsin Fundus Photograph Reading Center.

Sensitivity of the EyeArt system using undilated images was 95.5 percent (95 percent CI: 92.4–98.5 percent), specificity was 86 percent (95 percent CI: 83.7–88.4) and gradeability rate was 87.5 percent (95 percent CI: 85.4–89.7 percent).

The EyeArt AI system was able to detect rDR with excellent sensitivity and specificity using undilated fundus photographs. This well-validated technology could revolutionize our current model of screening for DR and potentially result in better outcomes due to earlier interventions in these patients.

Mitochondria-targeting elamipretide for treatment of dry AMD

Elamipretide (Stealth Biotherapeutics) is an aromatic-cationic tetrapeptide that penetrates cell membranes and is transported to the inner mitochondrial membrane where it associates with cardiolipin. Through this mechanism of action, it can restore energy production, reduce production of reactive oxygen species and increase the energy supplied to diseased cells and organs.[5]

ReCLAIM was an open-label, Phase I trial of daily subcutaneous elamipretide (40 mg) for 24 weeks in individuals with dry AMD and non-central geographic atrophy or high-risk drusen (HRD).[6] Patients with non-central GA (n=15) showed a mean increase in low-luminance VA of 5.4 ±7.9 letters (baseline: 43.9 ±19.8 letters; p=0.025) and BCVA of 4.6 ±5.1 letters (baseline 73.7±9.5 letters; p=0.003). They also showed significant improvement in low-luminance, smallest-line-read-correctly of -0.52 ±0.75 (p<0.017). HRD patients (n=19) also showed statistically significant improvements in BCVA, low-luminance VA, reading acuity and patient-reported outcomes.

Elamipretide is a promising subcutaneous therapy for both GA and HRD in dry AMD. It avoids the burden and risks of intravitreal injections and also appears to improve vision (a rarity in the current research landscape for treatment of dry AMD). A Phase II clinical trial for dry AMD with GA is underway. RS

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Elamipretide is a promising subcutaneous therapy for both GA and HRD in dry AMD. It avoids the burden and risks of intravitreal injections and also appears to improve vision.

Case for consistent treatment of DR, DME

Data from clinical trials and real-world findings suggest early and regular treatment provides optimal outcomes.

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Namrata Saroj, OD

John D. Pitcher, III, MD and Namrata Saroj, OD

Take-home points

- Recent data suggest that early intervention in the treatment of diabetic retinal disease provides better outcomes than delayed intervention.
- To sustain the benefit, consistent and frequent treatments are important, especially in eyes with diabetic macular edema.
- Challenges exist in maintaining treatment schedules for these patients, raising the importance of research into sustained-delivery platforms.

Studies have estimated that one-third of patients with diabetes have diabetic retinopathy, a third of which is vision-threatening; that is, severe nonproliferative DR, proliferative DR or diabetic macular edema. Recent therapeutic advances have improved control, and in some cases prevented development, of DR-related ocular complications [1]

Leading that charge have been vascular endothelial growth factor inhibitors. They have revolutionized the management of DME, and multiple landmark studies have demonstrated benefit of treatment with anti-VEGFs.[2,3] While anti-VEGF agents have become the standard of care for treatment of DME, timing and frequency of treatments remain variable amongst treating physicians. Nonetheless, emerging data continue to support the importance of early and frequent treatment in eyes with DME.

Evidence from clinical trials

In the pivotal RISE and RIDE studies evaluating ranibizumab (Lucentis, Roche/Genentech) for DME, the sham group was switched to ranibizumab in the third year of follow-up. With this delayed anti-VEGF treatment, patients in the sham group still gained vision. However, the extent of the visual gains in the sham group (4.7 and 4.3 letters in RIDE and RISE, respectively) were lower than that of patients who had been originally randomized to ranibizumab (10.6 and 14.2 letters, respectively).[2]

Similarly, in the pivotal VISTA and VIVID trials evaluating aflibercept (Eylea, Regeneron Pharmaceuticals) for DME, patients in the laser group upon switching to aflibercept had significant visual gains. However, their final visual acuity gain from baseline was lower (2.2 and 3.8 letters in VISTA and VIVID, respectively) than the patients originally assigned to aflibercept (9.7 and 13.6 letters, respectively).[3]

It's worth noting that patients in the laser group who were switched to aflibercept had to have significant vision loss per protocol criteria. Further study has demon-

Bios

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Prevalence of diabetic retinopathy in adults[1]

Overall	Studies included (n)	Total subjects (n)	Cases (n)	Prevalence (95% CI)
Any DR	18	12,620	4,487	35.36
Proliferative DR	21	13,436	957	7.24
Diabetic macular edema	20	14,554	1,039	7.48
Vision-threatening DR	18	12,710	1,481	11.72

Data extracted from pooled analysis of 35 studies conducted from 1980 to 2008.

strated that delayed treatment may have greater negative consequences, with greater risk of subretinal fluid, severe edema, large cysts or renal disease.[4]

Recently, results from the Diabetic Retinopathy Clinical Research Network-led Protocol V study evaluated three treatment strategies—initial observation, laser or aflibercept therapy—for eyes with center-involved DME and good vision.[5] The study concluded that observation until vision worsens is a viable option. Approximately one-third of eyes managed with initial observation required treatment with aflibercept based on vision loss per protocol criteria. Further evaluation of the clinical course of eyes that needed rescue treatment will provide a better understanding of the appropriate timing of intervention.

Real-world findings

Pivotal trials such as RIDE/RISE and VISTA/VIVID required consistent and frequent dosing that resulted in excellent visual outcomes. Emerging real-world data suggest that patients are being undertreated in clinical practice resulting in sub-optimal outcomes.[6,7]

In our recent retrospective analysis of the Vestrum Health Database, which included patients from more than 250 retina specialists, more than 40 percent of the patients received fewer than six injections in the first year of treatment resulting in visual gains significantly inferior to those who received more frequent injections during the same period (+3.7 vs. +8 in terms of visual acuity score, respectively).[8]

Furthermore, for patients who received less frequent treatment in the first year, increasing treatment frequency in the second year didn't provide additional benefit. Thomas Ciulla, MD, and colleagues also reported a similar relationship of lower visual gains with less frequent treatment based on their analysis of the American Academy of Ophthalmology Intelligent Research in Sight (IRIS) database.[9] Interestingly, we also found that the annual trend on injection frequency for DME during the first year of treatment has not shifted in the last few years, highlighting the persistence of undertreatment in clinical practice.

Shift toward earlier intervention

The landmark Early Treatment Diabetic Retinopathy Study (ETDRS) demonstrated that if left untreated, DR progression rates increase based on severity.[10] In general, the AAO recommends that eyes with mild or moderate NPDR without clinically significant DME can be observed.[11] Panretinal photocoagulation or anti-VEGF therapy is suggested for severe NPDR and PDR. A shift toward earlier intervention for DR is beginning, with repeated evidence that it potentially prevents vision-threatening complications.

PRP has been the most common approach for treatment of DR. The adverse effects as a result of PDR are well-established and are associated with the intensity, area and number of PRP treatments.[12] High-risk PDR can require significant PRP. However, PRP administered at an earlier stage—e.g., for severe NPDR—is likely to reduce the amount of overall treatments and, hence, reduce the associated adverse effects.[13]

Recent data supports anti-VEGF as

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Dr. Saroj disclosed relationships with Aerie, Allegro, Apellis, Adverum, and Regeneron Pharmaceuticals, and equity interests in Allegro, Pr3vent and SamaCare.

an excellent alternative for treatment of DR with a better safety profile than PRP. DRCR.net-led Protocol S compared PRP with intravitreal ranibizumab as frequently as every four weeks in eyes with PDR.[14] Even though the injection group was non-inferior to PRP treatment at two years in terms of visual change, mean peripheral visual field sensitivity loss was worse and vitrectomy and DME formation were more frequent in the laser group. Similarly, in the CLARITY trial, aflibercept was found to be superior to PRP with regards to visual acuity at 52 weeks in a similar population.[15]

The possibility of achieving DR regression using anti-VEGF therapy offers the opportunity to prevent vision-threatening complications with early intervention. Two-step and three-step improvements in Diabetic Retinopathy Severity Score (DRSS) have been seen in multiple trials. Post-hoc analysis of the RISE and RIDE studies demonstrated greater benefit in patients with baseline moderately severe to severe NPDR with two-step or greater regression in DRSS in 78 percent of patients vs. 31 percent in those with baseline PDR.[16]

Most recently, the PANORAMA study evaluated aflibercept for the treatment of eyes with moderate to severe NPDR. At 52 weeks, 80 percent of patients achieved two-step regression in DRSS with eight-week dosing of aflibercept. Perhaps more importantly for clinical practice was the reduction in vision threatening complications. Compared with sham, the aflibercept arms had a 75 percent relative risk reduction in the development of proliferative disease or center-involved DME.[17]

In the PANORAMA study, the aflibercept arms had a 75 percent relative risk reduction in developing proliferative disease or center-involved DME vs. sham.

Bottom line

The totality of these data suggest that early intervention in the treatment of diabetic retinal disease is important to provide the best outcomes. Furthermore, consistent and frequent treatments are important, especially in eyes with DME, to sustain the benefit. We acknowledge that there are challenges in maintaining treatment schedules, and current research on long-term delivery applications hopefully will address this unmet need to provide the best treatment for our patients. RS

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AMD is gene therapy's emerging darling

Most programs in retinal disease still target inherited disorders, but both wet and dry forms of age-related macular degeneration are attracting interest.

The first gene therapies for retinal disease targeted inherited genetic disorders, such as Spark Therapeutics' Luxturna for treatment of biallelic *RPE65* mutation-associated retinal dystrophy, the first approved gene therapy for inherited disease. However, increasingly early phase gene therapy programs are targeting age-related macular degeneration, both the wet and dry forms, although inherited retinal diseases still remain the most desired target.

This report focuses on gene therapy programs in human clinical trials (*Table, page 42*). A few companies not mentioned here, including 4D Molecular Therapies and IVERIC bio, formerly known as Ophthotech, have ophthalmic programs in the preclinical stage. And in 2016 Allergan acquired RetroSense Therapeutics, which had been developing RST-001, an optogenetic platform for retinitis pigmentosa, but no progress has been reported since. The list we provide here is not all-inclusive, but reports on programs that have publicized readouts in the past year or have had active trials through that time.

Phase III trials

• ***GenSight Biologics.*** The REVERSE Phase III clinical trial of GS010 enrolled 37 subjects who had visual loss due to the *11778-ND4* form of Leber hereditary optic neuropathy (LHON) that occurred in the previous six to 12 months. At 96 weeks, GS010-treated eyes showed a mean improvement equivalent to 15.4 letters or 3 lines, sustaining improvements reported in 48- and 72-week readouts. GS010 isn't GenSight's only rodeo. It's also evaluating GS030 for retinitis pigmentosa (Phase I/II), and is doing preclinical work on a vector for the ND form of LHON and a treatment for dry AMD and geographic atrophy.

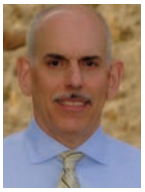
• ***Neurotech Pharmaceuticals.*** NT-501, also known as Renexus, is an encapsulated cell therapy for treatment of macular telangiectasia. Phase II results, published in the journal *Ophthalmology*,[1] reported NT-501 treatment slowed the progression of retinal degeneration compared to the sham group. The study also documented that treated patients stabilized their reading speeds. NT-501 is a novel cell-based drug-delivery system in which human-derived cells encapsulated in a semipermeable hollow fiber membrane device release ciliary neurotrophic factor (CNTF). Patients from Phase I/II studies are being followed to evaluate the long-term effects of CNTF on retinal degeneration.

Programs in AMD

• ***Adverum Biotechnologies.*** The program to develop AADVM-022 for treatment of nAMD took a step forward in May when the Food and Drug Administration lifted the clinical hold on dosing of the second cohort of the OPTIC Phase I trial. This cohort is to receive a dose three-times greater than that used in the first cohort (n=6), although the initial dose in the second cohort will actually be three times lower. ADVM-022 is a proprietary vector capsid, AAV.7m8, that carries an aflibercept coding sequence to provide sustained dosing. Adverum received fast-track designation for ADVM-022 last year. The company expects to present interim 24-week data from the OPTIC trial at the Retina Society meeting in September.

• ***REGENXBIO.*** RGX-314 is being developed as a potential one-time subretinal treatment for wet AMD and diabetic retinopathy. It uses the proprietary NAV technology with the AAV8 vector encoding an antibody fragment to inhibit vascular endothelial growth factor. The Phase I/IIa trial has completed dosing in all five cohorts. An interim readout reported that patients in one cohort had a durable treatment at one year after a single administration of RGX-314 after pretreatment. Top-line data from the trial, including the fourth and fifth cohorts, is due by year end.

• ***Hemera Biosciences.*** HMR59 is a sol-



Department Editor
Richard Mark Kirkner

Increasingly early phase gene therapy programs are targeting age-related macular degeneration, both the wet and dry forms, although inherited retinal diseases still remain the most desired target.

Gene therapies for retinal disease in human clinical trials

Agent name (manufacturer)	Description	Indication	Status
ADVM-022 (Adverum)	AAV.7m8 vector carrying encoded sequence of aflibercept	Neovascular age-related macular degeneration	Results from Phase I OPTIC trial due at Retina Society in September
rAAV2tYF-CB-hRS1 (Applied Genetic Technologies Corp. [AGTC])	Targets mutations in RS1 gene via subretinal injection.	X-linked retinoschisis	Six-month Phase I/II readout showed safety of agent but no clinical signal. Interim six-month results due later in year.
rAAV2tYF-PR1.7-hCNGB3 (AGTC)	Targets mutations in the CNGB3 gene via subretinal injection.	Achromatopsia	Top-line, interim six-month results of Phase I/II dose-escalation portion due fourth quarter 2019.
rAAV2tYF-PR1.7-hCNGA3 (AGTC)	Targets mutations in the CNGA3 gene via subretinal injection.	Achromatopsia	Top-line, interim six-month results of Phase I/II dose-escalation portion due fourth quarter 2019.
rAAV2tYF-GRK1-RPGR (AGTC)	Targets mutations in RPGR gene via subretinal injection.	X-linked retinitis pigmentosa	Top-line, interim six-month results of Phase I/II dose-escalation portion due third quarter 2019.
EYS606 (Eyevensys)	Electro-transfection procedure uses non-viral product to encodes potent TNFa inhibitor.	Noninfectious uveitis	Phase II trial ongoing.
GS010 (GenSight Biologics)	Proprietary mitochondrial targeting sequence AAV vector.	11778 Leber hereditary optic neuropathy	96-week Phase III results showed sustained gains in vision improvement.
GS030 (GenSight Biologics)	Gene encoding for light-sensitive protein in retinal ganglion cells.	Retinitis pigmentosa	First safety review of Phase I/II trial completed in May.
HMR59 (Hemera Biosciences)	AAV2 transgene product, soluble form of CD 59 blocks complement at MAC	Dry and nAMD, diabetic eye disease	Phase I trials in dry AMD/geographic atrophy (n=17) and new onset nAMD (n=15) ongoing.
IBI302 (Innovent Biotechnologies)	Recombinant human bi-specific fusion protein targeting VEGF and complement proteins	nAMD	Enrollment in Phase I open-label, single-center, dose escalation trial started in April.
AAV-RPE65 (MeiraGTx)	Second-generation AAV delivered intravitreally to modify RPE65 gene.	RPE65 deficiency	Phase I/II dose-escalation trial met safety and tolerability endpoint at six months.
NT-501 or Renexus (Neurotech Pharmaceuticals)	Encapsulated cell therapy releases ciliary neurotrophic factor	Macular telangiectasia	Fast-track designation granted in February. Phase III trial to complete enrollment mid-2019; clinical results expected mid-2021
RGX-314 (REGENXBIO)	NAV AAV8 vector encoding antibody fragment to inhibit VEGF	nAMD	Completed dosing in Phase I/IIa trial. Phase IIb trial to start end of 2019.
SPK-7001 (Spark Therapeutics)	Subretinal-delivered AAV platform.	Choroideremia	Open-label, dose-escalating Phase I/II trial ongoing.

AAV = adeno-associated viral vector

uble form of CD59, the protective protein normally found on the cellular plasma membrane. Intended to be a one-time intravitreal treatment for both wet and dry AMD, it's in Phase I trials for both indications. Eighteen-month data from the dry AMD study is expected at an upcoming meeting.

• ***Innovent Biologics.*** This Suzhou, China-based company initiated enrollment this spring in a Phase I trial of IBI302, a novel recombinant fully human bi-specific fusion protein targeting both VEGF and complement proteins in nAMD. Like Hemera's HMR59, the goal is to develop a one-time intravitreal treatment for the disease.

Other noteworthy programs

At least four other companies are pursuing gene therapies for other indications. Two worth mentioning are:

• ***Spark Therapeutics.*** An open-label, dose-escalating Phase I/II trial of investigational SPK-7001 for treatment of x-linked choroideremia (CHM) is ongoing.

• ***Applied Genetics Technologies Corp.*** AGTC may have the most robust pipeline, although it encountered a setback late last year when Biogen terminated a collaboration agreement. AGTC has four adeno-associated virus (AAV)-based gene therapies in human trials, including rAAV2tYF-CB-hRS1, an intravitreal injection for X-linked retinoschisis due to mutations in the RS1 gene. Results late last year showed that the agent is generally safe and well-tolerated, but showed no signs of clinical activity at six-months. AGTC is monitoring enrolled patients, with interim six-month data of dose-escalation and dose-expansion groups due in the third and fourth quarters, respectively.

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Modulating macrophages to target GA

Investigational candidate aims to change macrophage behavior in management of dry age-related macular degeneration.

By Richard Mark Kirkner, Editor

Department Editor
Emmett T. Cunningham Jr., MD, PhD

You don't have to read it here to know there's no approved treatment for the dry form of age-related macular degeneration, but that fact is pivotal in drug-development programs Translatum Medicus is pursuing. Instead of targeting the complement factor in macular degeneration, its lead candidate, TMi-018, aims to reduce and alter the activity of macrophages to reduce angiogenesis.

TMi-018 is a first-in-class transcriptional modulator. As a small synthetic molecule, it has been shown to be stable and suitable for both short- and long-term delivery. Focusing first on the short-acting formulation, Translatum (TMi) has demonstrated its efficacy in preclinical studies and is currently in preclinical safety studies, says Shelley Boyd, MD, FRCSC, TMi president and chief executive officer. She says that TMi is currently preparing its investigational new drug (IND) application with the Food and Drug Administration, approval of which will then enable Phase I/IIa studies.

It's worth noting that Dr. Boyd is also a practicing retina specialist. She's director of the High-Risk Dry AMD Clinic at St. Michael's Hospital, Toronto, and an assistant professor at the University of Toronto. She's also the former head of the global ocular angiogenesis research program at Novartis during the early in-licensing and development of ranibizumab (Lucentis) with Genentech.

But developing clinical trials for dry AMD can be a challenge. It involves enrolling patients late in the disease course and measuring their rate of geographic atrophy expansion. Reflecting on her Novartis experience, Dr Boyd notes that just as researchers developing anti-VEGF agents used angiogenesis as a paradigm for neovascular AMD in animal studies, the team developing TMi-018 is focusing on atrophy and developed a model that has demonstrated a reduction in both GA onset and expansion with the agent.

The work in TMi-018 is predicated on the activity of macrophages. For example, Dr. Boyd notes that drusen regression can predict late-stage AMD, and believes this reflects local activation of the macrophage population.

Macrophages and monocyte chemoattractant protein-1 (MCP1) have been found in eyes with both GA and neovascularization.[1,2] Previous studies have demonstrated the plasticity of macrophage polarization.[3] The goal of TMi-018 is to neutralize macrophage behavior at the mRNA level, altering the "transcriptome," the repertoire of genes expressed.

TMi is pursuing three programs for TMi-018: the short-acting formulation in dry AMD, which is the most advanced and is now in the preclinical safety phase; a slow-release formulation that is in preclinical research and development; and a program in diabetic retinopathy, which is also in the preclinical R&D phase.

Here, David S. Boyer, MD, a principal partner at Retina-Vitreous Associates Medical Group in Los Angeles, answers questions about TMi-018. Dr. Boyer is a scientific adviser to and an investor in TMi.

Q How does TMi-018 potentially target dry AMD?

A Evidence has shown that macrophages drive inflammation, tissue damage and even angiogenesis. Modulation of the macrophages may be able to downregulate inflammasomes and the complement system. We know that in the absence of macrophages, neovascular AMD doesn't occur. Also, levels of MCP1 are elevated in anterior chamber samples in eyes with dry AMD.

(Continued on page 46)

Instead of targeting the complement factor, TMi-018, aims to reduce and alter the activity of macrophages to reduce angiogenesis.

Arm yourself for payer negotiations

Uphill battle or slippery slope? These ideas can give you solid footing when seeking better reimbursement terms.

By Alison L. Ratliff, MBA

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Like "uphill battle" or "slippery slope," "negotiating payer contracts" is a phrase that you don't often connect with success and satisfaction. Negotiating with payers is challenging, defeating, frustrating and promising all at the same time. Yet, just as battles can be won and hills can be overcome, contracts can be successfully negotiated.

To provide insight into how involved physicians are in the contract and billing aspects of their practices, 50 retina specialists recently participated in a short survey. They were asked to answer various contract and reimbursement questions with the same level of certainty used in medical decision-making. An overwhelming percentage couldn't identify their best or worst contract, state what the reimbursement amount for a miscellaneous J-code would be, or indicate what contracts allowed more or less than Medicare rates. There is nothing wrong with a physician not knowing these answers, but it is absolutely necessarily that someone, preferably several staff members, does know them.

How much do you need or want it?

Just as we negotiate many things in daily life, such as the purchase of cars, homes and pharmaceuticals, we can negotiate payer contracts. In order to have a positive outcome to a negotiation, it is first important to evaluate three aspects:

• ***How much do you need a contract?*** In this situation, success will be measured by simply obtaining the contract, even if it's not the most desirable fee schedule. Perhaps a new office is empty most of the time with staff and physicians idle, and this contract will boost patient appointments and generate some, although not optimal, revenue.

• ***How much do you need this contract?*** Obtaining a certain contract may be vital to eliminating a threat of another physician coming into your geographic area. Often, practices will accept some contracts at sub-par rates to preserve the patient population of other existing agreements.

• ***How much do you want this contract?*** Will obtaining this contract allow you to enter a new market area and open a new facility? Perhaps it will allow your practice to begin operating at a new desirable ambulatory surgery center, or it may even allow you to hire an additional associate and expand your group.

The WHAT of evaluating contracts

Consider the WHAT acronym to properly evaluate new or existing contracts. It covers four main areas:

• ***Who.*** To whom is the contract offered, individuals or groups?

• ***Hospitals.*** What hospitals and ASCs are in the network? Do they align with your current block time allocations?

• ***Attachments.*** What are the exhibits—fee schedule, carve outs, J-code exceptions and authorization requirements?

• ***Term/termination.*** What is the initial term? What are options for renewal? What are the clauses for termination with and without cause?

Know your region and competitors

In my career, I have seen many consulting companies enter practices and guarantee their ability to negotiate better rates or criticize already accepted rates. Although there's always room for improvement, pushing too far in negotiating with some payers will result in the loss of the agreement.

Most commonly, when payers begin to explore opportunities with other practices, your competitors may accept the contract at your current or even lower rates. For example, in my current location, we

Medicare, Medi-Cal reimbursements selected CPT codes*

CPT code (description)	Medicare	Medi-Cal	Excess Medicare vs. Medi-Cal
92012 (Returning patient exam)	$100.58	$37.15	$63.43
92134 (Optical coherence tomography)	$46.73	$32.25	$14.48
67028 (Intravitreal injection of pharmacologic agent)	$113.87	$364.11	-$250.24
TOTAL	$261.18	$433.51	-$172.33

*J-codes purposely excluded to avoid any reimbursement discrepancy.

are surrounded by retina specialists, even having two other competitors in our same building.

Before you negotiate, it's vital to know how much revenue each contract generates and what percentage of the practice is dependent upon that payer. The results of this reporting structure will serve as a guide in determining how aggressive your negotiation strategy should be.

Evaluating the fee schedule

Often anything associated with Medicaid or a contract based on a percentage of Medicaid is immediately deemed to be a sub-par return on investment of clinic time. However, now in an environment where injections are so common, a further evaluation of rates is necessary. For example, in California, Medi-Cal reimburses at the rates noted in the table.

I selected these codes as common examples of typical office visits for a returning injection patient. Although the Medi-Cal rates are significantly lower for both the office visit and optical coherence tomography code, the very high injection code reimbursement more than compensates for the loss on the other two codes.

Therefore, if a clinic follows the above listed billing repetition, Medi-Cal contracts may be more lucrative than most commercial contracts following the Medicare fee schedule. This same logic can be applied to all contracts beyond just Medicaid. The profitability of each contract is dependent upon the rates for the codes that are most commonly used and not the entirety of the fee schedule.

Using this example, if your practice doesn't support the use of the 25-modifier and doesn't bill an office visit on the day of injection, the revenue increase of Medi-Cal over Medicare becomes even larger as the $63 Medicare office visit excess is removed from the equation.

How to follow the money

Most offices are extremely focused on inventory management software. We're constantly analyzing programs for increased use of radio-frequency identification tagging and reporting capabilities to remove aspects of human error. This leads to the question: Why don't we have the same concern for removing human error in our billing offices?

Billing staff can misread explanation of benefits (EOBs) that require inappropriate write-offs, resulting in thousands of dollars of lost revenue that have a small chance of ever being noticed. If offices are using an auto-post software (which most do), checking the reports after the computer automatically posts the EOB is crucial. The computer will do exactly what the EOB states and erroneous write-offs occur consistently. This, too, is part of the contract process.

Most practice management programs will allow you to enter the allowable amounts by payer for each code into the system and alert you if you receive less than the expect-

Billing staff can misread explanation of benefits that require inappropriate write-offs, resulting in thousands of dollars of lost revenue that have a small chance of ever being noticed.

Arm yourself for payer negotiations

than the expected amount from your carriers. Again, this leads us back to the importance of having each contract on hand and being able to reference the critical parts of the document easily. By running additional reports, you'll be able to identify if your payers are following the agreed-upon contract.

Accounts receivable reports run by carrier will show if payers are paying on time. Write-off reports (not payment reports) by carrier will show if the billing staff is allowing excessive write-offs. Payment reports will give drastically different numbers and won't lead to a solid analysis. Payment amounts won't reflect allowables, since copays, deductibles and coinsurance amounts will effect these numbers.

The more accurate way to detect appropriate payments by a particular carrier is to evaluate a write-off report by carrier. The contractual obligation write-off for each code for each patient should be the same within each carrier. If it's not, you will be able to easily identify posting errors made by the billing department.

Back to basics

The first step in negotiating with a payer is to find existing copies of your contracts. If you can't find these documents, request copies from your carriers. Then, once in hand, review the contracts for pertinent points, such as reimbursement rates, timely filing and payment parameters, and miscellaneous J-code billing procedures.

It's imperative to know the contract language regarding miscellaneous J-code billing. Common verbiage may read, "Services not listed in the Medicare RBRVS are not to exceed 50 percent of billed charges," or something similar. That means if you purchase a drug for $1,000 and charge $1,300, you will only receive $650 from the carrier, resulting in a significant loss each time you use a new drug with an unassigned J-code. After the fact, there is very little you can do fix that.

Bottom line

The success of negotiating contacts with payers is relative and can't be measured simply by what numbers end up in the agreement. Identify your ultimate goal before you negotiate by first analyzing all aspects of the contract and the impact adding or removing payers will have on the clinic. Highlighting the value your practice adds to the payer is just as important as the value the payer adds to your clinic. RS

Modulating macrophages to target GA

(Continued from page 43)

Q Please describe the mechanism of action in your own words.

A TMi-018 modulates the macrophage response, therefore avoiding activation of the inflammatory and potentially the angiogenic response. Macrophages are increased in geographic atrophy, drusen and neovascularization. This approach could reduce secretion of vascular endothelial growth factor and control angiogenesis.

Q What is the rationale for targeting dry AMD with TMi-018?

A Because dry macular degeneration is a chronic condition, short-term formulations aren't practical for the patient or the clinician. TMi has elected to work with synthetic molecules rather than biologics and has already demonstrated their long-term stability and suitability for extended release. Long-acting formulations may include nanoparticles or other long-acting solutions.

Q What have the preclinical studies shown about the efficacy of the short-acting formulation?

A Since there are no good animal models for dry macular degeneration, TMi has devised an *in vivo* model that mimics dry atrophic macular degeneration. The experiments performed on the patch used in the studies have shown a dose-dependent protection for the formation of geographic atrophy and for expansion.

Q What are the next steps in the development of TMi-018?

A The next steps are to take this technology into the clinic to prove its effectiveness. Once the effectiveness of the treatment is established, this technology can be used to prevent progression or development of GA. With CMC (chemistry, manufacturing and control) nearing completion, the next step will be IND regulatory approval, and a Phase I/IIa safety and dose-escalating study. Once the ideal dose has been identified, a Phase II study can be undertaken. RS

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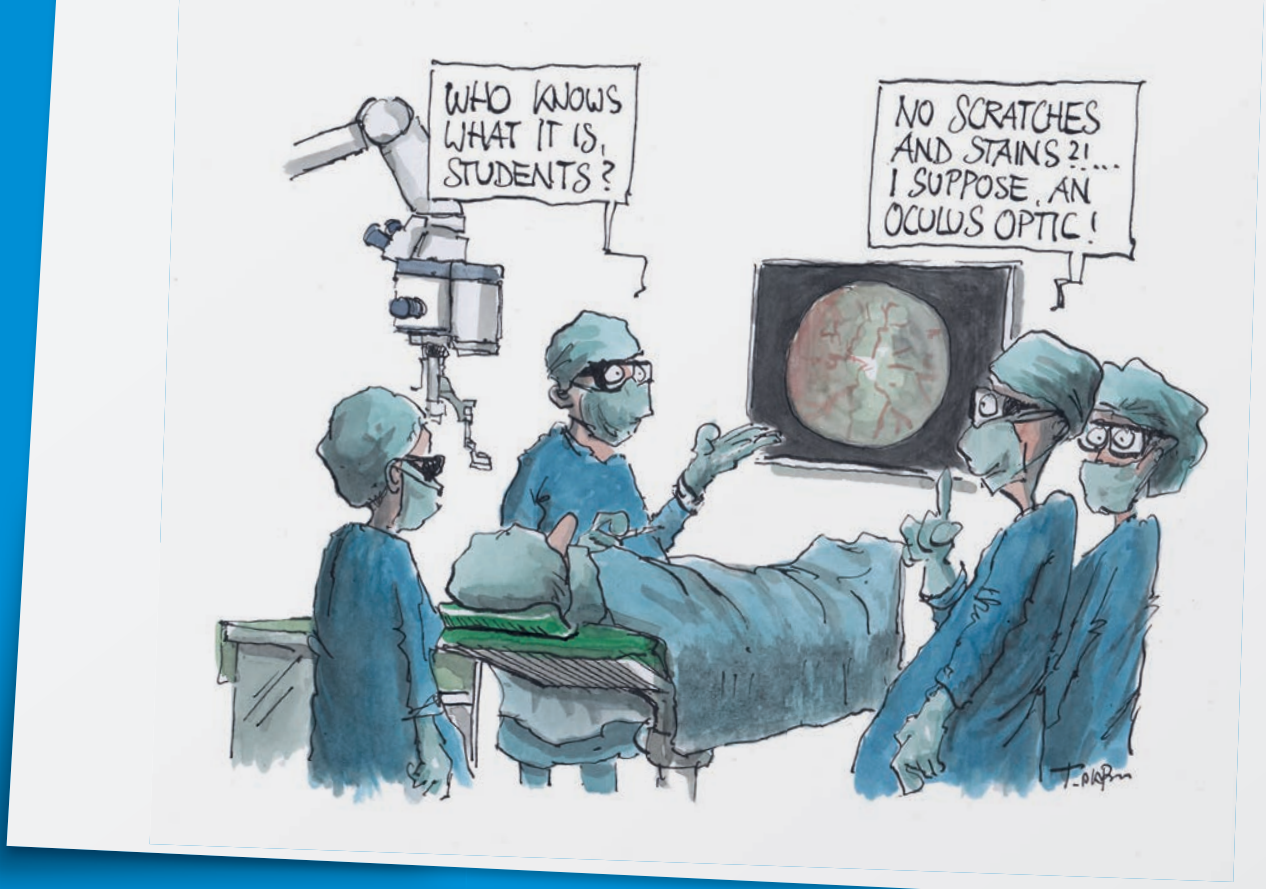

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Reference: 1. Chiang B, Jung JH, Prausnitz MR. The suprachoroidal space as a route of administration to the posterior segment of the eye. *Adv Drug Deliv Rev.* 2018;126:58-66.