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RETINA SPECIALIST

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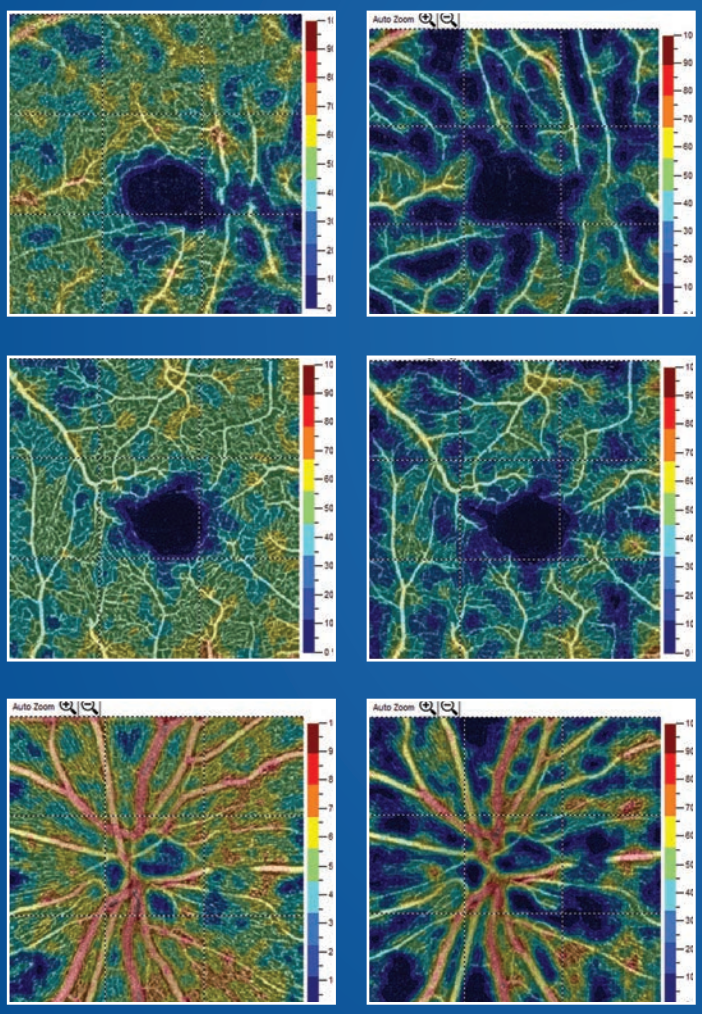

FOCUS ON IMAGING

What OCT-A Reveals about IVT Repetitive Stress Injuries

PAGE 22

Online Videos

Also Inside

IMPORTANT SAFETY INFORMATION

Warnings and Precautions

- **Endophthalmitis** may occur following any intraocular surgical procedure or injection. Use proper aseptic injection technique when administering LUXTURNA, and monitor for and advise patients to report any signs or symptoms of infection or inflammation to permit early treatment of any infection.
- **Permanent decline in visual acuity** may occur following subretinal injection of LUXTURNA. Monitor patients for visual disturbances.
- **Retinal abnormalities** may occur during or following the subretinal injection of LUXTURNA, including macular holes, foveal thinning, loss of foveal function, foveal dehiscence, and retinal hemorrhage. Monitor and manage these retinal abnormalities appropriately. Do not administer LUXTURNA in the immediate vicinity of the fovea. Retinal abnormalities may occur during or following vitrectomy, including retinal tears, epiretinal membrane, or retinal detachment. Monitor patients during and following the injection to permit early treatment of these retinal abnormalities. Advise patients to report any signs or symptoms of retinal tears and/or detachment without delay.
- **Increased intraocular pressure** may occur after subretinal injection of LUXTURNA. Monitor and manage intraocular pressure appropriately.
- **Expansion of intraocular air bubbles** Instruct patients to avoid air travel, travel to high elevations or scuba diving until the air bubble formed following administration of LUXTURNA has completely dissipated from the eye. It may take one week or more following injection for the air bubble to dissipate. A change in altitude while the air bubble is still present can result in irreversible vision loss. Verify the dissipation of the air bubble through ophthalmic examination.
- **Cataract** Subretinal injection of LUXTURNA, especially vitrectomy surgery, is associated with an increased incidence of cataract development and/or progression.

Adverse Reactions

- In clinical studies, ocular adverse reactions occurred in 66% of study participants (57% of injected eyes), and may have been related to LUXTURNA, the subretinal injection procedure, the concomitant use of corticosteroids, or a combination of these procedures and products.

A New Vision

for your patients with an inherited retinal disease (IRD)

LUXTURNA (voretigene neparvovec-rzyl) is a one-time gene therapy that improves functional vision in individuals with an IRD who have confirmed biallelic *RPE65* gene mutations and viable retinal cells.[1]

With LUXTURNA, patients experienced a clinically meaningful improvement in the ability to navigate at lower light levels.[1]

IMPORTANT SAFETY INFORMATION (CONT'D)

- The most common adverse reactions (incidence ≥ 5% of study participants) were conjunctival hyperemia (22%), cataract (20%), increased intraocular pressure (15%), retinal tear (10%), dellen (thinning of the corneal stroma) (7%), macular hole (7%), subretinal deposits (7%), eye inflammation (5%), eye irritation (5%), eye pain (5%), and maculopathy (wrinkling on the surface of the macula) (5%).

Immunogenicity
Immune reactions and extra-ocular exposure to LUXTURNA in clinical studies were mild. No clinically significant cytotoxic T-cell response to either AAV2 or RPE65 has been observed. In clinical studies, the interval between the subretinal injections into the two eyes ranged from 7 to 14 days and 1.7 to 4.6 years. Study participants received systemic corticosteroids before and after subretinal injection of LUXTURNA to each eye, which may have decreased the potential immune reaction to either AAV2 or RPE65.

Pediatric Use
Treatment with LUXTURNA is not recommended for patients younger than 12 months of age, because the retinal cells are still undergoing cell proliferation, and LUXTURNA would potentially be diluted or lost during the cell proliferation. The safety and efficacy of LUXTURNA have been established in pediatric patients. There were no significant differences in safety between the different age subgroups.

Please see a brief summary of the US Full Prescribing Information on the following pages.

Reference: 1. LUXTURNA [package insert]. Philadelphia, PA: Spark Therapeutics, Inc; 2017.

P-RPE65-US-360005 April 2018

IDENTIFYING APPROPRIATE PATIENTS FOR LUXTURNA STARTS WITH YOU

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LUXTURNA™
voretigene neparvovec-rzyl
for subretinal injection

Illuminating possibilities.

LUXTURNA™
voretigene neparvovec-rzyl
for subretinal injection

Brief Summary of US Full Prescribing Information for LUXTURNA (voretigene neparvovec-rzyl)

1 INDICATIONS AND USAGE
LUXTURNA (voretigene neparvovec-rzyl) is an adeno-associated virus vector-based gene therapy indicated for the treatment of patients with confirmed biallelic *RPE65* mutation-associated retinal dystrophy. Patients must have viable retinal cells as determined by the treating physicians.

4 CONTRAINDICATIONS
None.

5 WARNINGS AND PRECAUTIONS

5.1 Endophthalmitis
Endophthalmitis may occur following any intraocular surgical procedure or injection. Proper aseptic injection technique should be used when administering LUXTURNA. Following the injection, patients should be monitored to permit early treatment of any infection. Advise patients to report any signs or symptoms of infection or inflammation without delay.

5.2 Permanent decline in visual acuity
Permanent decline in visual acuity may occur following subretinal injection of LUXTURNA. Monitor patients for visual disturbances.

5.3 Retinal abnormalities
Retinal abnormalities may occur during or following the subretinal injection of LUXTURNA, including macular holes, foveal thinning, loss of foveal function, foveal dehiscence, and retinal hemorrhage. Monitor and manage these retinal abnormalities appropriately. LUXTURNA must not be administered in the immediate vicinity of the fovea. *[See Dosage and Administration (2.3) in full prescribing information]*

Retinal abnormalities may occur during or following vitrectomy, including retinal tears, epiretinal membrane, or retinal detachment. Monitor patients during and following the injection to permit early treatment of these retinal abnormalities. Advise patients to report any signs or symptoms of retinal tears and/or detachment without delay.

5.4 Increased intraocular pressure
Increased intraocular pressure may occur after subretinal injection of LUXTURNA. Monitor and manage intraocular pressure appropriately.

5.5 Expansion of intraocular air bubbles
Instruct patients to avoid air travel, travel to high elevations, or scuba diving until the air bubble formed following administration of LUXTURNA has completely dissipated from the eye. It may take one week or more following injection for the air bubble to dissipate. A change in altitude while the air bubble is still present can result in irreversible vision loss. Verify the dissipation of the air bubble through ophthalmic examination.

5.6 Cataract
Subretinal injection of LUXTURNA, especially vitrectomy surgery, is associated with an increased incidence of cataract development and/or progression.

6 ADVERSE REACTIONS
The most common adverse reactions (incidence ≥5%) were conjunctival hyperemia, cataract, increased intraocular pressure, retinal tear, dellen (thinning of the corneal stroma), macular hole, subretinal deposits, eye inflammation, eye irritation, eye pain, and maculopathy (wrinkling on the surface of the macula).

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 the clinical trials of other products and may not reflect the rates observed in practice.

The safety data described in this section reflect exposure to LUXTURNA in two clinical trials consisting of 41 subjects (81 eyes) with confirmed biallelic *RPE65* mutation-associated retinal dystrophy. Forty of the 41 subjects received sequential subretinal injections of LUXTURNA to each eye. One subject received LUXTURNA in only one eye. Seventy-two of the 81 eyes were exposed to the recommended dose of LUXTURNA at 1.5×10^{11} vg; 9 eyes were exposed to lower doses of LUXTURNA. Study 1 (n=12) was an open-label, dose-exploration safety study. Study 2 (n=29) was an open-label, randomized, controlled study for both efficacy and safety *[see Clinical Studies (14) in full prescribing information]*. The average age of the 41 subjects was 17 years, ranging from 4 to 44 years. Of the 41 subjects, 25 (61%) were pediatric subjects under 18 years of age, and 23 (56%) were females.

Twenty-seven (27/41, 66%) subjects had ocular adverse reactions that involved 46 injected eyes (46/81, 57%). Adverse reactions among all subjects in Studies 1 and 2 are described in Table 1. Adverse reactions may have been related to LUXTURNA, the subretinal injection procedure, the concomitant use of corticosteroids, or a combination of these procedures and products.

Table 1. Ocular Adverse Reactions Following Treatment with LUXTURNA (N=41)

Adverse Reactions	Subjects n=41	Treated Eyes n=81
Any ocular adverse reaction	27 (66%)	46 (57%)
Conjunctival hyperemia	9 (22%)	9 (11%)
Cataract	8 (20%)	15 (19%)
Increased intraocular pressure	6 (15%)	8 (10%)
Retinal tear	4 (10%)	4 (5%)
Dellen (thinning of the corneal stroma)	3 (7%)	3 (4%)
Macular hole	3 (7%)	3 (4%)
Subretinal deposits*	3 (7%)	3 (4%)
Eye inflammation	2 (5%)	4 (5%)
Eye irritation	2 (5%)	2 (2%)
Eye pain	2 (5%)	2 (2%)
Maculopathy (wrinkling on the surface of the macula)	2 (5%)	3 (4%)
Foveal thinning and loss of foveal function	1 (2%)	2 (2%)
Endophthalmitis	1 (2%)	1 (1%)
Foveal dehiscence (separation of the retinal layers in the center of the macula)	1 (2%)	1 (1%)
Retinal hemorrhage	1 (2%)	1 (1%)

*Transient appearance of asymptomatic subretinal precipitates inferior to the retinal injection site 1-6 days after injection.

Immunogenicity
At all doses of LUXTURNA evaluated in Studies 1 and 2, immune reactions and extra-ocular exposure were mild. In Study 1 (n=12), the interval between the subretinal injections into the two eyes ranged from 1.7 to 4.6 years. In Study 2, the interval between the subretinal injections into the two eyes ranged from 7 to 14 days. No subject had a clinically significant cytotoxic T-cell response to either AAV2 or RPE65.

Subjects received systemic corticosteroids before and after subretinal injection of LUXTURNA to each eye. The corticosteroids may have decreased the potential immune reaction to either vector capsid (adeno-associated virus serotype 2 [AAV2] vector) or transgene product (retinal pigment epithelial 65 kDa protein [RPE65]).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Risk Summary: Adequate and well-controlled studies with LUXTURNA have not been conducted in pregnant women. Animal reproductive studies have not been conducted with LUXTURNA. In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

8.2 Lactation
Risk Summary: There is no information regarding the presence of LUXTURNA in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for LUXTURNA and any potential adverse effects on the breastfed infant from LUXTURNA.

8.3 Females and Males of Reproductive Potential
No nonclinical or clinical studies were performed to evaluate the effect of LUXTURNA on fertility.

8.4 Pediatric Use
Treatment with LUXTURNA is not recommended for patients younger than 12 months of age because the retinal cells are still undergoing cell proliferation, and LUXTURNA would potentially be diluted or lost during cell proliferation.

The safety and efficacy of LUXTURNA have been established in pediatric patients. Use of LUXTURNA is supported by Study 1 and Study 2 *[see Clinical Studies (14) in full prescribing information]* that included 25 pediatric patients with biallelic *RPE65* mutation-associated retinal dystrophy in the following age groups: 21 children (age 4 years to less than 12 years) and 4 adolescents (age 12 years to less than 17 years). There were no significant differences in safety between the different age subgroups.

8.5 Geriatric Use
The safety and effectiveness of LUXTURNA have not been established in geriatric patients. Clinical studies of LUXTURNA for this indication did not include patients age 65 years and over.

17 PATIENT COUNSELING INFORMATION
Advise patients and/or their caregivers of the following risks:

Endophthalmitis and other eye infections: Serious infection can occur inside of the eye and may lead to blindness. In such cases, there is an urgent need for management without delay. Advise patients to call their healthcare provider if they experience new floaters, eye pain, or any change in vision.

Permanent decline in visual acuity: Permanent decline in visual acuity may occur following subretinal injection of LUXTURNA. Advise patients to contact their healthcare provider if they experience any change in vision.

Retinal abnormalities: Treatment with LUXTURNA may cause some defects in the retina such as a small tear or a hole in the area or vicinity of the injection. Treatment may cause thinning of the central retina or bleeding in the retina. Advise patients to follow up with their healthcare provider on a regular basis and report any symptoms, such as decreased vision, blurred vision, flashes of light, or floaters in their vision without delay.

Increased intraocular pressure: Treatment with LUXTURNA may cause transient or persistent increase in intraocular pressure. If untreated, such increases in intraocular pressure may cause blindness. Advise patients to follow up with their healthcare provider to detect and treat any increase in intraocular pressure.

Expansion of intraocular air bubbles: Advise patients to avoid air travel, travel to high elevations, or scuba diving until the air bubble formed following administration of LUXTURNA has completely dissipated from the eye. A change in altitude while the air bubble is still present may cause irreversible damage.

Cataract: Advise patients that following treatment with LUXTURNA, they may develop a new cataract, or any existing cataract may get worse.

Shedding of LUXTURNA: Transient and low-level shedding of LUXTURNA may occur in patient tears. Advise patients and/or their caregivers on proper handling of waste material generated from dressing, tears, and nasal secretion, which may include storage of waste material in sealed bags prior to disposal. These handling precautions should be followed for up to 7 days following LUXTURNA administration.

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EDITORIAL

By Charles C. Wykoff, MD, PhD

Weather forecasting

The Great Galveston Hurricane of 1900 was the deadliest natural disaster in U.S. history, killing up to 12,000 people. The morning the storm made Texas landfall, the sky was calm with scattered clouds, with no suggestion of the impending storm surge and destruction from which the island would never fully recover.

Since then, weather forecasting has improved tremendously with refinement of complex algorithms that incorporate millions of data points. These systems allow remarkably accurate hurricane tracking three to five days in advance, enabling local preparations and evacuations, saving tens of thousands of lives annually.

Severe nonproliferative diabetic retinopathy without diabetic macular edema provides a similar scenario. This population of about 3 million Americans are typically asymptomatic with excellent visual acuity. While we recognize the risk of these eyes developing proliferative DR or DME, the most common cause of blindness among American working-age adults, severe NPDR remains a major clinical hurdle to initiating intravitreal anti-VEGF injections. The skies are a bit cloudy, but there's no hurricane in sight, yet.

PANORAMA,[1] the first prospective trial involving high-risk NPDR eyes without central-involved DME since the Early Treatment Diabetic Retinopathy Study of the 1980s,[2] provides valuable data to inform decision making in the anti-VEGF era. In PANORAMA, about 40 percent of untreated eyes developed PDR or CI-DME at one year, a rate reduced by approximately 75 percent with fixed aflibercept dosing.

But, can we predict which eyes will progress? In the ETDRS, 12, 26 and 52 percent of eyes with DR Severity Scale (DRSS) levels of 43, 47 and 53, respectively, developed PDR within one year.[2] While we categorize level 53 eyes as highest risk, even one of eight individuals with level 43 are anticipated to develop PDR within one year. Description of the specific NPDR DRSS score may be irrelevant if we can predict disease progression at an individual level.

As emphasized in previous editorials, I am committed to the promise of artificial intelligence and deep learning. In these pages, two articles describe attempts to harness the power of retinal images and algorithms to predict DR progression.

In the 21st century, it's ridiculous to consider initiating a coastal hurricane evacuation only once the storm makes landfall. It is equally absurd to consider evacuating the entire Eastern seaboard every time a hurricane forms in the Atlantic. Accurate predictability is key. Similarly, it's logical to treat DR before the advanced stages of the disease are manifest and VA loss has occurred. Improved prognostic granularity is coming.

REFERENCES

1. Wykoff CC. Intravitreal aflibercept for moderately severe to severe nonproliferative diabetic retinopathy (NPDR): 1-year of the phase 3 PANORAMA study. On behalf of the PANORAMA investigators. Paper presented at Angiogenesis, Exudation, and Degeneration 2019; Miami, FL: February 9, 2019.
2. Fundus photographic risk factors for progression of diabetic retinopathy. ETDRS report number 12. Early Treatment Diabetic Retinopathy Study Research Group. Ophthalmology. 1991;98(5 Suppl):823-833.

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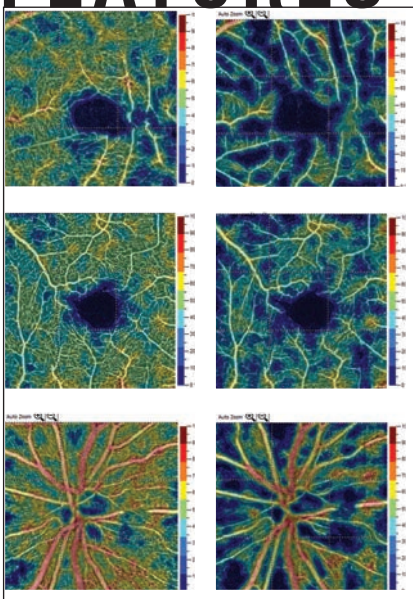
MARCH/APRIL 2019 • VOL. 5, NO. 2

FEATURES



Focus on Imaging

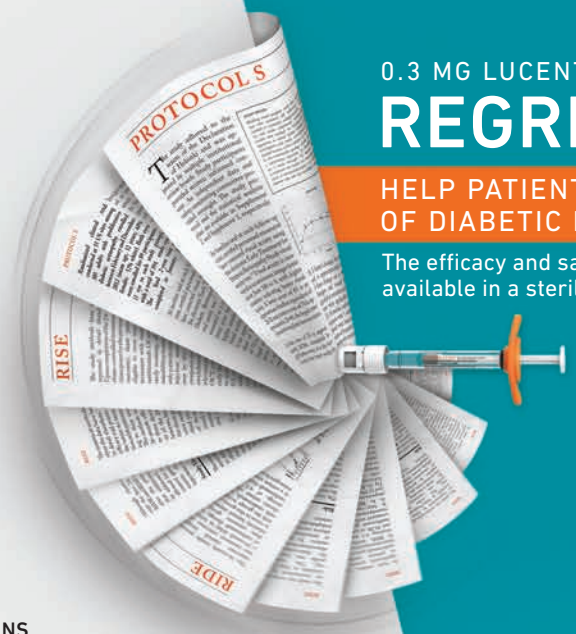
DEPARTMENTS

0.3 MG LUCENTIS PREFILLED SYRINGE

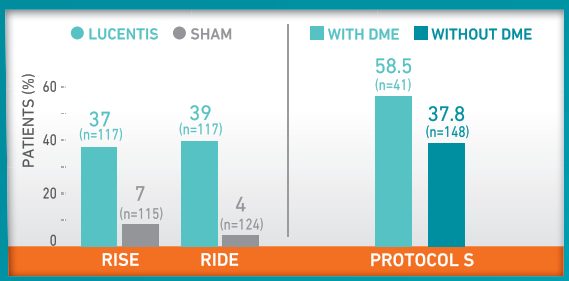
REGRESSION DELIVERED[1]

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

Deep-learning model uses photos to predict OCT changes in DME

More evidence has emerged that deep learning can play a role in predicting progression from diabetic retinopathy to diabetic macular edema, with publication of a study that found a model using color fundus photographs and a relatively smaller dataset could predict changes in macular thickness detectable with time-domain optical coherence tomography.

Researchers from Roche in Switzerland and its Genentech unit in San Francisco reported in the journal *Investigative Ophthalmology & Visual Science* on a deep-learning (DL) model that used fundus photographs to quantify central subfield thickness (CST) and central foveal thickness (CFT), which correlated with measurements on TD-OCT.[1]

CST models most promising

The study evaluated four DL models, finding that the models using CST seemed to perform better than those using CFT. "This is likely due to the fact that the performance of a DL regression is generally more sensitive to the stability of the endpoint and the CFT is a less reliable endpoint compared to CST," co-author Jeffrey R. Willis, MD, PhD, associate medical director of ophthalmology, at Genentech, tells *Retina Specialist*. "The binary classification models, upon further development with larger datasets, will be more likely to reach a performance high enough to become a diagnostic solution to be deployed in the real world."

The best DL model was able to predict CST ≥ 250 µm and CST ≥ 400 µm with an area under the curve (AUC) of 0.97 (87.5-percent sensitivity, 96.4-percent specificity) and of 0.94 (99-percent sensitivity, 94.4-percent specificity), respectively. To predict CFT ≥ 250 µm and CFT ≥ 400 µm, the best DL model had an AUC of 0.91 (80-percent sensitivity, 85-percent specificity) and of 0.97 (90-percent sensitivity, 94-percent specificity), respectively.

Quality fundus photos key

The study found the quality of fundus photography can be a key factor in building predictive DL models. "The study told us that the performance of DL algorithms improves as the quality of the color fundus photographs improves," says Dr. Willis.

"The idea here is that our proof-of-concept study showed that DL is able to quantify three-dimensional features (i.e., OCT measure of macular thickening [MT]) from a two-dimensional color fundus photograph," he says. That 3-D quantification of MT can provide clues about the severity of DME.

Potential for smaller datasets

The study also showed the promise of using a relatively small dataset to construct DL models, as it used 18,000 fundus photographs and associated OCT measurements from the RIDE and RISE trials. "The benefit of using RIDE/RISE clinical trial data is that it's likely more standardized and perhaps of better quality than data taken in the real-world setting," Dr. Willis says. "Our study also showed that a smaller dataset could be used to train DL algorithms if one takes a transfer-learning cascade approach"—that is, using learnings from other datasets before training the data on the final, smaller dataset.

The next step for the research team is to further train the model and validate it in real-world practice, Dr. Willis says.

REFERENCE

1. Arcadu F, Benmansour F, Maunz A, et al. Deep learning predicts OCT measures of diabetic macular thickening from color fundus photographs. Invest Ophthalmol Vis Sci. 2019;60:852-857

IN BRIEF

Apellis Pharmaceuticals resumed enrollment in two Phase III trials, DERBY and OAKS, of intravitreal APL-2 for geographic atrophy. The company voluntarily paused enrollment last year because of reports of ocular inflammation in patients dosed with one manufactured batch. Enrollment should be completed by the end of the first quarter of 2020.

Faricimab (**Roche/Genentech**) bispecific antibody is the subject of two large global Phase III clinical trials in wet age-related macular degeneration. The TENAYA and LUCERNE trials were initiated at the beginning of March.

Ocular Therapeutix dosed the first patient in a Phase I trial of OTX-TKI (tyrosine kinase inhibitor implant) for wet age-related macular degeneration at the Sydney Retina Clinic Australia.

The Food and Drug Administration granted orphan drug designation for OCU400 (**Ocugen**), a novel gene therapy for the treatment of NR2E3 mutation-associated retinal degenerative disease.

No is the latest word on anti-VEGF and CV events

The evidence linking intravitreal anti-VEGF therapy with a heightened risk of cardiovascular events has been split, but a population-based, retrospective cohort study in *JAMA Ophthalmology* has reported that intravitreal anti-VEGF treatment for neovascular, or exudative, age-related macular degeneration has come down on the side that these treatments do not raise CV event risk.[1]

"Our treatment cohort, who received anti-VEGF therapy for e-AMD according to real-world practice patterns, was compared to an age-matched, e-AMD group prior to the availability of anti-VEGF treatment," lead author Raymond Iezzi, MD, of Mayo Clinic in Rochester, Minn., tells *Retina Specialist*. Anti-VEGF drugs "introduced no statistically-significant increase in five-year risk of cardiovascular events in patients with e-AMD."

The study included 504 patients who had at least one anti-VEGF injection for e-AMD from 2004 through 2013 and matched to three cohorts from 13 previous years, when anti-VEGF treatments were not available: with e-AMD; with dry AMD; and controls with no history of AMD (*Table*). Most patients in the anti-VEGF group (n=377, 75 percent) received bevacizumab (Avastin, Roche/Genentech), and 292 patients received at least three IVT injections in the last year before having a CV event.

The anti-VEGF era cohorts had a five-year risk for stroke of 7.2 percent, for myocardial infarction (MI) of 6.1 percent and death of 30 percent. The study found, on multivariate analysis, a 63 percent increased risk of death compared with controls with e-AMD in pre-anti-VEGF era, but not the other control groups on multivariate analysis ($p < 0.001$).

"We found that while anti-VEGF-treated e-AMD patients had an increased five-year mortality risk compared to e-AMD patients who did not receive anti-VEGF therapy, no increased risk of mortality or cardiovascular events was noted when compared to the two other control groups," he says. "Our overall conclusion is that anti-VEGF treatment did not increase the five-year risk of stroke, myocardial infarction or death in our population."

The study called for additional research to evaluate CV risks in patients with dry AMD receiving anti-VEGF injections, as well as among different anti-VEGF agents.

REFERENCE

1. Dalvin LA, Starr MR, AbouChehade JE, et al. Association of intravitreal anti-vascular endothelial growth factor therapy with risk of stroke, myocardial infarction, and death in patients with exudative age-related macular degeneration. JAMA Ophtalmol. 2019 January 31. [epub before print]
2. Meyerhardt JA, Li L, Sanoff HK, Carpenter W 4th, Schrag D. Effectiveness of bevacizumab with first-line combination chemotherapy for Medicare patients with stage IV colorectal cancer. J Clin Oncol. 2012;30:608-615.

Table. Cardiovascular events with, without IVT anti-VEGF

Cohort	Stroke	Myocardial infarction	Death (all-cause mortality)
Injection (2004-2013)	7.2% (p=0.01)	6.1% (p=0.01)	30% (p=0.36)
Dry age-related macular degeneration (1990-2003)	3% (p=0.01)	6.2% (p=0.71)	27.7% (p=0.24)
Exudative AMD (1990-2003)	9% (p=0.23)	11.4% (p=0.01)	26.8% (p=0.36)
No AMD (1990-2003)	7% (p=0.99)	7.2% (p=0.96)	23% (p=0.03)

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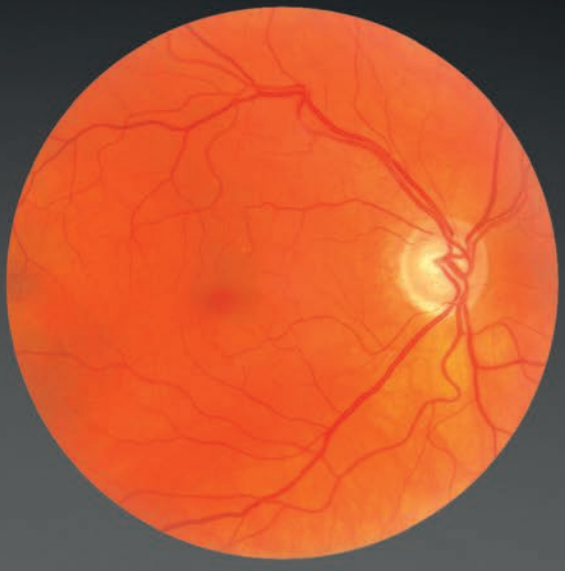

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INDICATION[1]

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

IMPORTANT SAFETY INFORMATION[1]

SERIOUS INFECTIONS

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

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

Reported infections include:

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

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

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

MALIGNANCY

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

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

HYPERSENSITIVITY

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

HEPATITIS B VIRUS REACTIVATION

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

NEUROLOGIC REACTIONS

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

HEMATOLOGIC REACTIONS

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

CONGESTIVE HEART FAILURE

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

AUTOIMMUNITY

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

IMMUNIZATIONS

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

ADVERSE REACTIONS

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

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

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

abbvie

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

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

Now approved

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

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

HUMIRA + MTX was proven to:

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

†HUMIRA is not indicated for anterior uveitis.

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

HUMIRA® adalimumab

HUMIRA® (adalimumab)

PROFESSIONAL BRIEF SUMMARY
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

WARNING: SERIOUS INFECTIONS AND MALIGNANCY

SERIOUS INFECTIONS

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

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

Reported infections include:

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

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

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

MALIGNANCY

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

INDICATIONS AND USAGE

Rheumatoid Arthritis

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

Juvenile Idiopathic Arthritis

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

Psoriatic Arthritis

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

Ankylosing Spondylitis

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

Adult Crohn's Disease

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

Pediatric Crohn's Disease

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

Ulcerative Colitis

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

Plaque Psoriasis

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

Hidradenitis Suppurativa

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

Uveitis

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

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Serious Infections

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

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

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

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

Tuberculosis

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

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

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

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

Monitoring

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

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

Invasive Fungal Infections

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

Malignancies

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

Malignancies in Adults

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

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

Non-Melanoma Skin Cancer

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

Lymphoma and Leukemia

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

Malignancies in Pediatric Patients and Young Adults

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

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

Hypersensitivity Reactions

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

Hepatitis B Virus Reactivation

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

Neurologic Reactions

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

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

Hematological Reactions

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

Use with Anakinra

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

Heart Failure

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

Autoimmunity

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

Immunizations

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

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

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

Use with Abatacept

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

ADVERSE REACTIONS

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

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

Clinical Trials Experience

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

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

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

Infections

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

Tuberculosis and Opportunistic Infections

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

Autoantibodies

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

Liver Enzyme Elevations

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

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

Immunogenicity

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

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

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

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

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

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

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

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

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

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

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

Other Adverse Reactions

Rheumatoid Arthritis Clinical Studies

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

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

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

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

* Laboratory test abnormalities were reported as adverse reactions in European trials

** Does not include injection site erythema, itching, hemorrhage, pain or swelling

Juvenile Idiopathic Arthritis Clinical Studies

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

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

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

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

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

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

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

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

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

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

Psoriatic Arthritis and Ankylosing Spondylitis Clinical Studies

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

Adult Crohn's Disease Clinical Studies

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

Pediatric Crohn's Disease Clinical Studies

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

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

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

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

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

Ulcerative Colitis Clinical Studies

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

Plaque Psoriasis Clinical Studies

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

Hidradenitis Suppurativa Clinical Studies

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

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

Uveitis Clinical Studies

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

Postmarketing Experience

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

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

General disorders and administration site conditions: Pyrexia

Hepato-biliary disorders: Liver failure, hepatitis

Immune system disorders: Sarcoidosis

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

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

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

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

Vascular disorders: Systemic vasculitis, deep vein thrombosis

DRUG INTERACTIONS

Methotrexate

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

Biological Products

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

Live Vaccines

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

Cytochrome P450 Substrates

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

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

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

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

Clinical Considerations

Disease-associated maternal and embryo/fetal risk

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

Fetal/Neonatal Adverse Reactions

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

Data

Human Data

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

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

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

Animal Data

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

Lactation

Risk Summary

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

Pediatric Use

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

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

Juvenile Idiopathic Arthritis

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

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

Pediatric Crohn's Disease

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

Pediatric Uveitis

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

Hidradenitis Suppurativa

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

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

Geriatric Use

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

OVERDOSAGE

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

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

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

PATIENT COUNSELING INFORMATION

Patient Counseling

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

Advise patients of the potential benefits and risks of HUMIRA.

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

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What PIVOT tells us about RRD repair

Trial authors comment on findings about the effectiveness of pneumatic retinopexy vs. pars plana vitrectomy for rhegmatogenous retinal detachment.

By Rajeev H. Muni, MD, MSc, FRCS, and Roxane J. Hillier, MB-ChB, FRCOphth, MSc

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Bios

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The management of primary rhegmatogenous retinal detachment is at the heart of surgical retina practice. Yet, retinal detachment repair remains the subject of significant controversy, with various eminent surgeons strongly advocating one approach over another.

The management of routine RRD can vary widely, from pneumatic retinopexy to combined vitrectomy plus scleral buckle as the standard of care from one academic institution to the next. Part of the reason for the lack of consensus has been the limited evidence base surrounding retinal detachment repair. Only a handful of randomized trials have demonstrated the benefits of one procedure over another for certain morphologies of RD.

Besides the intrinsic difficulties of performing a randomized controlled trial for an emergency surgical procedure, interpretation of the results can be challenging, because they are really only applicable to the specific inclusion and exclusion criteria of the study in question. For a randomized trial to be useful, the results must be generalizable to a significant proportion of patients with RD.

Purpose of PIVOT

With this in mind, we designed the PIVOT study, a randomized controlled trial that compared pneumatic retinopexy to pars plana vitrectomy, specifically for patients with retinal detachments with one or more breaks in detached retina within one clock hour, in the superior eight clock hours.[1] These inclusion criteria were intended to replicate the inclusion criteria of the Pneumatic Retinopexy Trial performed almost 30 years ago that demonstrated favorable visual acuity results for pneumatic retinopexy compared to scleral buckle.[2]

PIVOT inclusion and exclusion criteria

Inclusion criteria

- Single retinal break or group of breaks no longer than one clock hour (30 degrees) in detached retina
- All breaks in detached retina to lie above 8 and 4 o'clock meridian
- Breaks or lattice degeneration in attached retina at any location, even inferior aspect

Exclusion criteria

- Inferior breaks in detached retina
- Significant media opacity (e.g., vitreous hemorrhage or cataract preventing examination of retina)
- Proliferative vitreoretinopathy grade B or worse
- Previous retinal detachment (index eye)
- Age <18 years
- Mental incapacity
- Inability to read English
- Preexisting ocular diagnosis that would impact visual outcome
- Physical inability to posture postoperatively

However, to make the results more generalizable, we included patients with any number, location and size of breaks or lattice degeneration in attached retina. We estimate that inclusion of these features makes the results of the PIVOT trial applicable to approximately one-third of RD patients.

Another key aspect of the trial design was to minimize sources of bias. Specifically, we were careful to perform vitrectomies as fast as possible. Because pneumatic retinopexy is an in-office procedure, we sought to avoid comparing pneumatic retinopexy performed immediately vs. vitrectomy performed a week later. The protocol required macula-on cases to be done within 24 hours and macula-off patients within 72 hours.

It turned out that the mean time to

surgery was eight hours for macula-on patients and 22 hours for macula-off cases, which we believe exceeded current standard practice.

Managing cataract formation

Another major issue with any trial involving vitrectomy is the development of cataract. We went to great lengths to identify and treat visually significant cataracts as soon as they occurred. This led to 65 percent of phakic patients in the vitrectomy arm undergoing cataract surgery during the study. Of course, a minority of patients with lens opacity opted not to proceed with cataract surgery—a reality of everyday surgical retina practice.

In the end, we believe that our endeavors to remove clinically significant cataracts from the vitrectomized patients likely biased the visual outcomes in favor of the vitrectomy arm, as evidenced by the overall higher cataract grading scores in the pneumatic retinopexy arm at one year.

Pneumatic retinopexy superior

PIVOT demonstrated superior visual acuity results for pneumatic retinopexy compared to pars plana vitrectomy at every time point, and by 4.9 Early Treatment Diabetic Retinopathy Study letters at one year (p=0.024, Figure). The proportion of patients who had better than 70 ETDRS letters (20/40) visual acuity was 90.3 percent in the pneumatic retinopexy group vs. 75.3 percent in the vitrectomy group.

Scores for the 25-item National Eye Institute Visual Function Questionnaire were superior for pneumatic retinopexy compared to vitrectomy at three and six months, with no significant difference at one year. There were no significant differences in the proportion of patients who required additional vitrectomy for macular pucker, macular hole or vitreous debris.

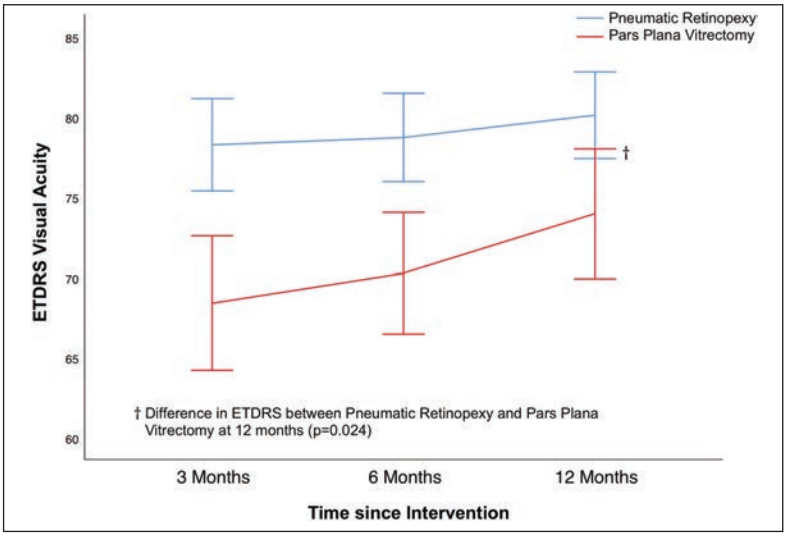


Figure. Graph shows pneumatic retinopexy was superior to pars plana vitrectomy in terms of Early Treatment Diabetic Retinopathy Study visual acuity in intention-to-treat groups at three, six and 12 months of follow-up. (Used with permission Elsevier Science and Technology Journals. Hillier RJ, Felfeli T, Berger AR, et al. Ophthalmology. 2018 Nov 22. Epub ahead of print.)

Primary anatomical reattachment rates were 80.8 percent for pneumatic retinopexy vs. 93.2 percent for vitrectomy (p<0.045). We anticipated this difference in reattachment rates. It was important to see that patients with a failed pneumatic retinopexy still had very good visual acuity outcomes following PPV (average 20/40 visual acuity). In other words a failed pneumatic retinopexy didn't jeopardize final visual acuity outcome. Specifically, secondary reattachment rates were 99 percent in both groups.

What was most interesting was that objectively measured vertical distortion was significantly less following pneumatic retinopexy compared to vitrectomy. The reduced vertical distortion with pneumatic retinopexy suggests differences in the mechanism and quality of the retinal reattachment.

At the American Society of Retina

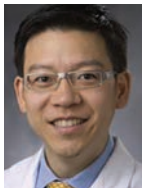
(Continued on page 21)

Disclosures
The authors have no relevant financial relationships to disclose.

Minimally invasive IOL deposit removal

This surgical approach to intraocular lens opacities utilizes a flex loop.

By Akshay Thomas, MD, MS



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DISCLOSURES: Dr. Hahn is a consultant to Alcon. Dr. Thomas has no relevant financial relationships to disclose.

Visually significant deposits on the surface of intraocular lenses frequently pose a challenge to retina specialists (*Figure 1*). Calcific deposits have been noted to develop on the posterior surface of silicone IOLs following YAG capsulotomy in eyes with asteroid hyalosis. Additionally, some hydrophilic acrylic lenses have been found to undergo opacification with deposition of calcium phosphate crystals with time.

Additional cases of visually significant pigment deposition on eyes with pigment dispersion and uveitis as well as deposition of pseudoexfoliative material in the visual axis have been reported. While the cause of IOL opacification is not always clear, intervention is usually needed to augment vision.

A minimally invasive option

The approach to such deposits has ranged from use of an Nd:YAG laser to IOL exchange and sometimes vitrectomy. However, the Nd:YAG laser may be ineffective and can cause IOL pitting. A vitreous cutter may be ineffective in removing the fine granular IOL deposits. Here, Akshay Thomas, MD, MS, of Tennessee Retina describes a minimally invasive technique using an Alcon Finesse flex loop (*Figure 2A, B*).

Preoperative evaluation

Key things to note are whether the posterior capsule is intact and where the IOL deposits are located. By the time we are evaluating a patient for IOL deposits, a YAG capsulotomy will often have already been performed.

For this technique, an intact posterior capsule will need to be opened. While it's most common for the deposits to be on the anterior or posterior surface of the IOL, some deposits may actually be within the substance of the IOL, which would necessitate an IOL exchange.

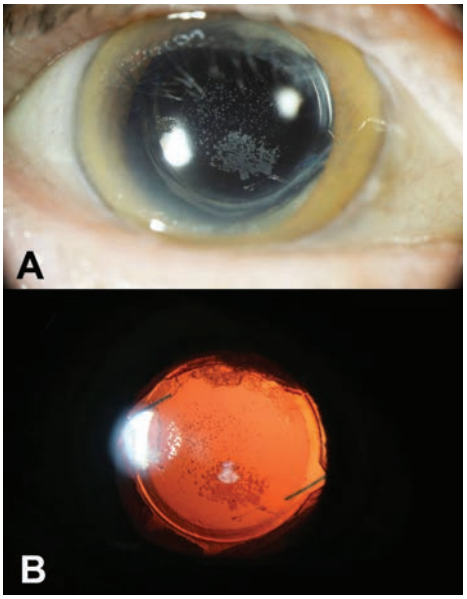


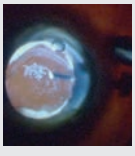
Figure 1. Slit lamp photography without (A) and with (B) retroillumination shows visually significant posterior intraocular lens deposits with an open posterior capsule.

Surgical technique

This approach to treating lenticular deposits involves the following eight steps:

1. Set up for standard three-port vitrectomy. Position the wrist rest lower than normal as most of the case will require anterior angulation of surgical instruments.
2. If the posterior capsule is still intact, perform a limited anterior vitrectomy and make a 3-mm cen-

View the Video



Dr. Thomas demonstrates his surgical technique for removing posterior lenticular deposits. Available at: http://bit.ly/VideoPearl_010

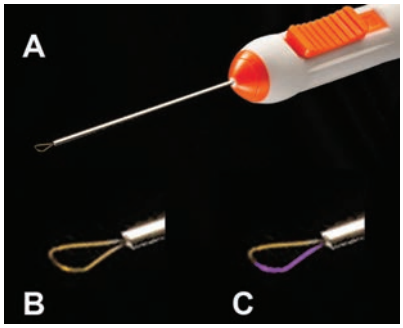


Figure 2. The Alcon Finesse flex loop (A) with the nitinol loop magnified (B). Position the loop (C) perpendicular to the intraocular lens so that only one edge (purple portion) is in contact with the lens.

tral opening with the vitreous cutter.

3. Larger IOL deposits may be amenable to removal with vitreous cutter suction.
4. Insert the flex loop and retract the shaft such that the entire loop is exposed.
5. Position the loop perpendicular to the posterior IOL surface such that only half of the loop is in contact with the lens (*Figure 2C*).
6. Next, use the loop to gently scrub the back of the IOL to remove the deposits. If the deposits aren't coming off easily, shorten to loop to increase its stiffness and then repeat.
7. Most deposits are usually trapped within the serrations of the loop and may be periodically washed off.
8. If a significant amount of deposits are released into the vitreous cavity, a limited vitrectomy can be performed. You may opt to start off with only one or two ports and place additional ports only if a vitrectomy is required. RS

What PIVOT tells us about RRD repair

(Continued from page 19)

Specialists and EURETINA meetings in 2018, we demonstrated that patients who underwent pneumatic retinopexy had significantly less disruption of the interdigitation zone, ellipsoid zone and the external limiting membrane on optical coherence tomography imaging compared to PPV.[3,4]

After carefully interpreting the results of the trial, we believe the superiority of pneumatic retinopexy over vitrectomy is likely multifactorial and related to more than the disparity in cataract formation.

Pneumatic retinopexy benefit

The ability to perform pneumatic retinopexy swiftly—potentially in the office, with the need for minimal specialist equipment—and thus reattach the macula within a couple of hours, quickly reestablishing the integrity of the retina-RPE interaction, is likely an advantage.

Furthermore, distortion and optical coherence tomography results suggest that pneumatic retinopexy is associated with a superior quality of retinal reattachment. We believe that the more natural reabsorption of the subretinal fluid by the RPE pump in pneumatic retinopexy likely provides an advantage over the forced drainage that occurs during vitrectomy. Multimodal imaging studies by our group are currently underway which will provide clarity on these differences in the near future.

PIVOT has helped fill a gap in our current knowledge regarding the differences between pneumatic retinopexy and PPV for routine primary RRD. The superior visual acuity and distortion results suggest a definite advantage for pneumatic retinopexy.

The bottom line

An often-cited drawback of pneumatic retinopexy is the lower primary anatomical reattachment rate. The difference for patients in this trial was 12 percent. This yields a number needed to treat of 8.33. In other words, proponents of a vitrectomy-first approach on the basis of reattachment rates would be advocating for approximately eight patients to undergo vitrectomy surgery rather than pneumatic retinopexy, to save one patient from incurring a failed pneumatic retinopexy, thereby subjecting the remaining seven patients to potentially avoidable cataract surgery and inferior functional outcomes. This despite the knowledge that a patient with a failed pneumatic retinopexy is likely to achieve a final visual acuity outcome similar to a patient having undergone vitrectomy from the outset.

As with everything in life, RD outcomes ought not to be only about the quantity, but quality. The majority of our patients value their final visual outcomes above anything, and that is what we should strive to optimize. RS

REFERENCES

1. Hillier RJ, Felfeli T, Berger AR, et al. The Pneumatic Retinopexy vs. Vitrectomy for the management of Primary Rhegmatogenous Retinal Detachment Outcomes Randomized Trial (PIVOT). Ophthalmology. 2018 Nov 22. Epub ahead of print.
2. Tornambe PE, Hilton GF. Pneumatic retinopexy. A multicenter randomized controlled clinical trial comparing pneumatic retinopexy with scleral buckling. The Retinal Detachment Study Group. Ophthalmology. 1989;96:772–783; discussion 784.
3. Muni R. Difference in metamorphopsia and OCT changes after retinal detachment repair: RCT comparing pneumatic retinopexy to vitrectomy at 1 year. Paper presented at American Society of Retina Specialists; Vancouver, BC: July 25, 2018.
4. Hillier R, Felfeli T, Juncal V, Lampert Monte Francisconi C, Mak M, Muni R. Metamorphopsia and OCT changes following retinal detachment repair: Pneumatic retinopexy versus vitrectomy ("PIVOT" 1-year data). Paper Presented at EURETINA: Vienna, Austria; September 21, 2018.

Focus on Imaging

What OCT-A reveals about MACULAR PERFUSION

It may provide clues of intraocular pressure-related repetitive stress injuries.

Alexander Barash, MD

Richard B. Rosen, MD

By Alexander Barash, MD, and Richard B. Rosen, MD

Take-home points

- Intravitreal injections induce acute changes in intraocular pressure and affect retinal angiographic perfusion density.
- A preliminary study of 40 eyes shows that the superficial layers of the macula are three times more affected than the deep layers.
- These alterations may explain the sudden loss of vision that patients have immediately postinjection, and correlate with changes in macular perfusion seen in glaucomatous eyes.
- Larger studies are needed to look deeper into the connection between intravitreal injections and glaucoma.

Intravitreal injections have become a therapeutic mainstay in the treatment of many retinal conditions, and the latest data show that the number of intravitreal injections in the United States was projected to reach more than 6 million in 2016.[1] Each injection acutely and temporarily increases intraocular pressure, but the long-term effects of these IOP changes are not known.[2]

Multiple studies have concluded that an increased number of injections given correlates with sustained, long-term, elevations in IOP.[3-7] Here, we review our own research, previously published in the journal *Retina*, of how IOP elevations from IVT injections affect ocular perfusion.[8]

What the data show

Studies have shown that IOP spikes to an average of 44 mmHg immediately after injection, decreases to 35 mmHg two to three minutes later, and then drifts back to a baseline of 15 mmHg within 30 minutes.[2] Some patients in our clinic had acute IOP elevations as high as 61 mmHg with 0.05-mL injections, and up to 71 mmHg with double-dose 0.1-mL injections.

The largest study of 23,776 patients that received 12 to 25 anti-VEGF injections showed that 2.6 percent of injected eyes had a significant IOP increase (>6 mmHg to <21 mmHg) compared with 1.5 percent of untreated fellow eyes.[4] While this study controlled for a diagnosis of glaucoma, it did not account for patients that received treatment in the form of a new glaucoma medication or glaucoma surgery between baseline and year one.

Furthermore, this study excluded patients with an IOP of 22 mmHg or more at baseline, a subset of patients that may be more prone to glaucoma. Thus, the study may have underestimated the effects of injections on IOP and glaucoma.

MARINA, ANCHOR subanalysis

These data are not new. A subanalysis of the MARINA and ANCHOR trials found that intravitreal injections increased the

Bios

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risk of clinically significant IOP elevation: 23.6 percent of those getting ranibizumab (Lucentis, Roche/Genentech) had clinically significant IOP increases, but only 13.6 percent of sham did.[9]

Additionally, not all patients respond the same way. Patients with preexisting glaucoma, or with a predisposition to glaucoma, are likely at higher risk. Elizabeth Atchison, MD, and colleagues reported that three times more patients who had a significant IOP rise after intravitreal injections had a preexisting diagnosis of glaucoma.[4]

Two mechanisms by which IVT injections may sustainably increase IOP are:

- damage to the trabecular meshwork[10] incites inflammation that alters the TM;[11] and
- blockage of TM outflow due to injected anti-VEGF agents,[12] proteins or contaminant particles in the solution, such as silicone oil.[13]

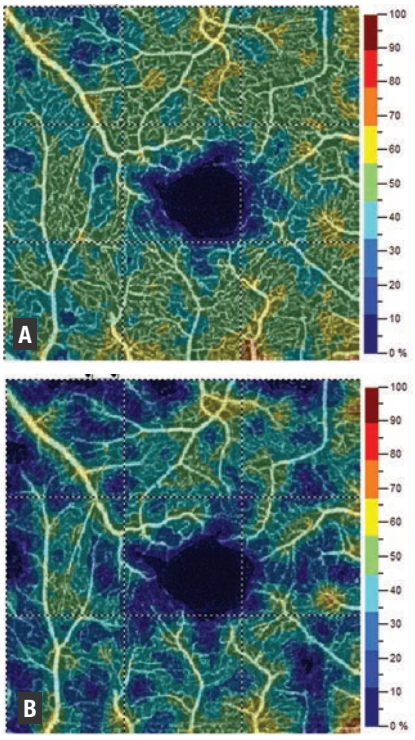


Figure 1. Optical coherence tomography angiography shows noted differences in macular perfusion before (A) and after (B) intravitreal injection.

Evidence of long-term IOP effects

Despite multiple studies that suggest IVT injections lead to sustained IOP elevations in a subset of patients, a meta-analysis reported mixed data on long-term IOP elevation.[7] Studies have shown 4 to 15 percent of patients have sustained IOP elevation at nine to 24 months, while 6 percent had no long-term change in IOP at one to 36 months in a review.[14]

While the early data on long-term IOP elevations are mixed, a growing body of evidence suggests that pressure spikes with intraocular injections can have long-term glaucomatous effects, even in eyes in which injections do not lead to sustained IOP elevations. Progressive retinal nerve fiber layer thinning occurs in IVT-treated eyes,[15] and a higher number of IVT injections is associated with the need for glaucoma surgery.[3]

How we designed our study

Based on the growing body of evidence that intravitreal injections can affect ocular perfusion and increase the risk of glaucomatous changes, we designed a study to assess the acute changes in macular and peripapillary perfusion density and macular thickness following IVT injections using optical coherence tomography imaging with and without angiography.[8] Our goal was to describe the retinal perfusion changes and thickness alterations associated with acute IOP elevations. Data about the pathophysiology of acute IOP elevations can be further extrapolated to other causes of acute IOP elevation, such as intraocular surgery and in acute angle closure.

We imaged 40 eyes of 39 adults without media opacities or other ocular changes that would preclud OCT-A (*table, page 26*). Eyes received intravitreal injections of: 0.05 mL bevacizumab (1.25 mg, Avastin, Roche/Genentech, n=32); 0.05 mL aflibercept (2 mg, Eylea, Regeneron, n=3); and 0.1 mL bevacizumab (2.50 mg, n=5) in

(Continued on page 26)

Disclosures

Dr. Rosen disclosed he is a consultant to OptoVue, Boehringer-Ingelheim, Astellas, Genentech-Roche, NanoRetina, OD-OS, Regeneron and Bayer; and he has personal financial interests in Optcology, Guardion Health.

Dr. Barash has no financial relationships to disclose

Their study was supported by the Marrus Family Foundation and the Geraldine Violett Foundation. The sponsors and funding organizations had no role in the design or conduct of this research. The research was performed at the New York Eye and Ear Infirmary.

The authors have published an article in the journal *Retina*[8] from the same study.

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

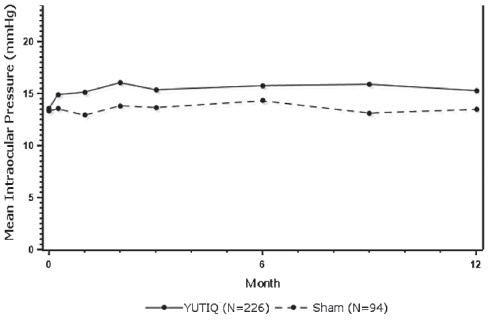
Ocular		
ADVERSE REACTIONS	**YUTIQ (N=226 Eyes) n (%)**	**Sham Injection (N=94 Eyes) n (%)**
Vitreous Hemorrhage	4 (2%)	0
Iridocyclitis	3 (1%)	7 (7%)
Eye Inflammation	3 (1%)	2 (2%)
Choroiditis	3 (1%)	1 (1%)
Eye Irritation	3 (1%)	1 (1%)
Visual Field Defect	3 (1%)	0
Lacrimation Increased	3 (1%)	0
Non-ocular		
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 patients with chronic noninfectious posterior uveitis for up to 36 months[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/154 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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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

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(Continued from page 23)
eyes that also received radiation retinopathy per our ocular oncologist's protocol. The injections were given for a diverse set of diseases including diabetic retinopathy, macular degeneration, choroidal neovascular membrane and retinal vein occlusion. Intraocular pressures were checked with a Tonopen (Reichert) before and 15 seconds after injection.

OCT-A imaging of the macular (3 x 3 mm) and peripapillary (4.5 x 4.5 mm) areas was obtained before and immediately after injections (within two to three minutes) using the RTVue XR 100 Avanti machine (Optovue). The limiting factor was how quickly each patient could be transferred from the injection procedure room to the imaging suite. AngioAnalytics software performed automatic segmentation of vessel layers into superficial and deep, as well as into the following subsections:

- macular OCT-A, subdivided into nine regions of interest—macula, fovea, parafovea, superior hemifield, inferior hemifield, temporal, superior, nasal and inferior; and
- peripapillary OCT-A, subdivided into eight regions of interest—optic nerve head, peripapillary, nasal, temporal, inferonasal, inferotemporal, superotemporal and superonasal.

Paired t-test analysis of each patient's pre- and postinjection OCT-A perfusion density and macular OCT thickness, and regression analysis regarding the confounding effects of the patient's age, baseline IOP and IOP change as independent variables, were performed in STATA (v14.2, StataCorp). *P* values less than 0.05 were considered statistically significant.

Injections caused significant decreases in macular perfusion density of 7.5 percent on average.

Table. Characteristics of our study population

Mean age	60.6 years
Intraocular pressure	33 to 84 mmHg
Gender	Female 17 (44%); male 22 (66%)
Disease process (n)	**Subset (n)**
Diabetes (14)	Proliferative diabetic retinopathy (9)
	Nonproliferative diabetic retinopathy with cystoid macular edema (5)
Retinal vein occlusion (9)	Hemiretinal/central retinal vein occlusion (6)
	Branch retinal vein occlusion (3)
Macular degeneration (8)	Age-related macular degeneration (6)
	Idiopathic polypoidal choroidal vasculopathy (2)
Other (3)	

How injections affect macular, optic nerve perfusion density

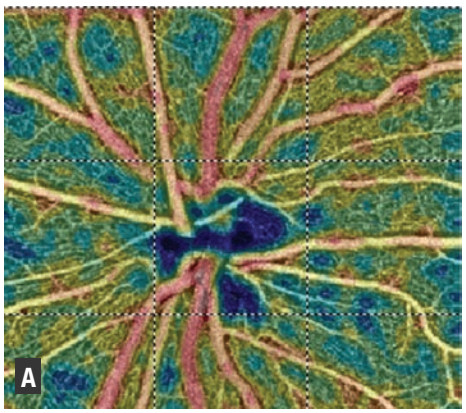
Injections caused significant acute decreases in macular perfusion density of 7.5 percent on average, but did not significantly affect perfusion of the fovea. The deep macula was also affected, with an average decrease of 2.4 percent, one-third that of the superficial perfusion.

Macular thickness was significantly decreased in the temporal and significantly increased in the nasal aspects, possibly a redistribution phenomenon. Overall OCT thickness was unchanged.

Injections also significantly decreased optic nerve perfusion density, with an average change of 3.3 percent in the optic nerve head. In the radial peripapillary capillary (RPC) layer, essentially the superficial perfusion in the peripapillary area, perfusion density decreased 2.9 percent on average. The temporal aspect of the disc was most affected.

Age was significantly related to overall superficial macular perfusion, suggesting that older patients may be at higher risk for perfusion changes with injections. IOP change was related to decreased overall superficial macular perfusion, suggesting that the extent of the pressure spike impacts the extent of decreased perfusion in the superficial macula.

Overall, our study showed that intravitreal injections produce acute IOP changes that are associated with reduced macular and peripapillary perfusion density. Therefore, it is possible that patients receiving regular intravitreal injections may



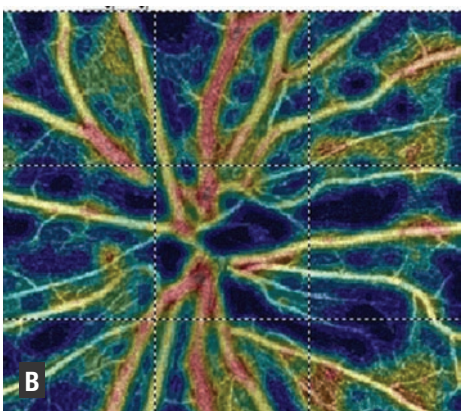


Figure 2. Optical coherence tomography angiography shows perfusion density significantly decreased in optic nerve scans when pre- and postinjection images (A, B) were compared.

be sustaining perfusion-related injury to ocular structures that may produce glaucomatous damage to the macula and optic nerve.

OCT-A and macular perfusion

OCT-A has been used to identify vascular changes in a variety of ophthalmic diseases,[16,17] including glaucoma. OCT-A measurements of peripapillary angiographic perfusion density can help diagnose and quantify glaucoma prior to RNFL thickness changes or visual field losses.[18,19]

Additionally, OCT-A perfused capillary density may have diagnostic accuracy comparable to RNFL thickness measurements for differentiating healthy and glaucomatous eyes.[18] These results suggest that OCT-A measurements identify early damage to tissues that may contribute to the pathophysiology of glaucoma.

In our study, we found that macular perfusion was decreased after intravitreal injections (*Figure 1, page 23*), with significantly more of an effect on superficial macular vessels (7.5 percent decrease in perfusion on average) than deep vessels (decrease of 2.4 percent).

This matches the findings of Hana Takusagawa, MD, and colleagues at Casey Eye Institute in Oregon—that glaucoma patients have significantly decreased macular perfusion on OCT-A, affecting the superficial plexus more than the deep.[20] Thus, it is possible that we are seeing the acute ischemic effects of increased IOP. This lends credence to the idea that intravitreal injections may stress the same structures that are damaged in glaucomatous eyes.

Our study found that OCT-A perfusion density was significantly decreased in both optic nerve scans (*Figure 2*), with an average change of approximately 3 percent. The temporal aspect of the nerve was most significantly affected. These results agree with several other studies,[21] including a study by Gabor Hollo in Hungary that reported peripapillary superficial capillary perfusion density increased significantly with an IOP reduction of 50 percent or more (over approximately one month).[22]

Researchers at UCLA found that retinal capillary perfusion density measured one month after injection of anti-VEGF was unchanged,[23] suggesting that our measurements are of short-term effects more likely to be related to IOP rather than medication. Our study also corroborates other reports that OCT thickness does not change significantly with acute IOP elevations due to intravitreal injections.[23]

Understanding effects in perfusion

We are likely underestimating the transient impact on perfusion. We measured IOP 15 seconds after injection, whereas the OCT-A was done at >2 minutes, when IOP was in the process of equilibration. If

Patients receiving regular intravitreal injections may be sustaining perfusion-related injury to ocular structures that may produce glaucomatous damage to the macula and optic nerve.

the OCT-A images had been taken closer to the time of injection, they might have shown even greater changes in perfusion density and possibly OCT thickness.

It is important to note that while IOP rises to such high pressures immediately upon injection, the pressures are generally not sustained. A major risk stems from the repetitive nature of such injections and the potential for cumulative trauma to the retina and optic nerve.[3]

As we previously mentioned, there is so far mixed data about the IOP effects of intravitreal injections. While in the short term most eyes may tolerate injections, the risk of damage likely increases over the longer term, on a cumulative basis. Diabetic Retinopathy Clinical Research Network studies support this, showing a 5.7 percent rate of sustained clinically significant IOP increase at one year, almost doubling to 9.5 percent after three years of injections.[24]

The temporal RNFL may be at highest risk for glaucomatous damage from repeated IOP spikes from IVT injections, because it has shown the largest postinjection perfusion change. It should be preferentially monitored for evidence of early RNFL thinning following IVT injections. Ganglion cells that rely on superficial macular plexus for perfusion may be especially vulnerable.

The temporal retinal nerve fiber layer may be at highest risk for glaucomatous damage from repeated IOP spikes from injections, because it has shown the largest postinjection perfusion change.

Is pretreatment an option?

Larger, long-term studies are needed to identify glaucomatous changes in patients who undergo repeated injections. A meta-analysis found the following were associated with lower IOP elevations after IVT injections:[14]

- pretreatment with topical glaucoma medications;
- anterior chamber paracentesis;
- vitreous reflux;
- longer intervals between injections; and
- longer axial lengths.

Perhaps we should consider pretreatment with IOP-lowering medications of all or a subset of patients most susceptible to injury. There is an ongoing study at the New York Eye and Ear Infirmary to test the effects of premedication with apraclonidine 0.5%.

In our clinic, we have begun to weigh the risks of injections in patients with mild macular edema if they have preexisting glaucoma or cupping. We now tend to wait to allow these patients' blood-pressure and blood-glucose levels to stabilize, when possible, to minimize their risk of glaucoma.

The impact of greater injection volumes such as those given with 0.1 mL triamcinolone or 0.1 mL bevacizumab for radiation retinopathy needs further investigation. Few patients in our study received 0.1 mL, and although mean IOP in these patients was higher after injection, it is difficult to draw any conclusions given the limited number of patients receiving this dose.

Our study population was very diverse; diagnosis, age, and other patient and disease characteristics differed significantly. The patient population may have included individuals with undiagnosed glaucoma or other changes that could skew the data. The effects of intravitreal injections in each disease state or patient may vary and may affect the outcomes we measured. Patients were used as their own controls, and the changes that occurred within each individual patient correlated well with our overall results. Future studies of larger patient populations will be helpful to confirm that these changes are real and reproducible.

The bottom line

Intravitreal injections induce acute changes in IOP and affect retinal angiographic capillary perfusion density. Our preliminary study of 40 eyes shows that the superficial layers of the macula are more affected than deep layers, by a factor of three. These alterations may explain the sudden loss of vision that patients have

immediately postinjection, and correlate with changes in macular perfusion seen in glaucomatous eyes.[20] The temporal aspect of the optic nerve has the most significant decreases in perfusion density, so it may be prudent to focus on this area with serial perfusion scans, RNFL measurements and visual fields to assess the long-term glaucomatous effects of intravitreal injections.

We need further research with larger sample sizes and longitudinal data about glaucoma progression to look deeper into the connection between intravitreal injections and glaucoma. These studies will also provide a window into the pathophysiology of perfusion changes that occur during other instances of acute IOP elevation, such as acute angle closure and malignant glaucoma and during intraocular surgery, and help point to more effective therapeutic interventions.

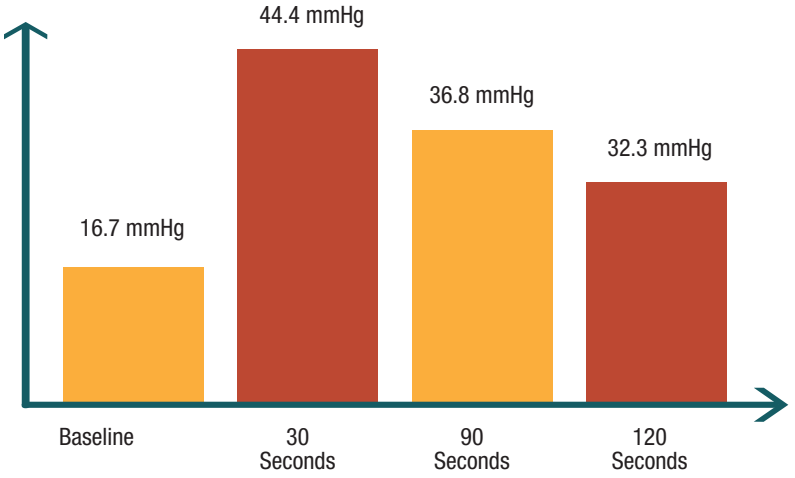


Figure 3. In the authors' pilot study of 10 patients, the average intraocular pressure measurements in study eyes rosed significantly from baseline at three different time intervals after intravitreal injections.

REFERENCES

1. Williams GA. IVT Injections: Health policy implications. Rev Ophthalmol. 2014;21:62-64.
2. Lee JW, Park H, Choi JH, et al. Short-term changes of intraocular pressure and ocular perfusion pressure after intravitreal injection of bevacizumab or ranibizumab. BMC Ophthalmol. 2016;16:69.
3. Eadie BD, Etminan M, Carleton BC, Maberley DA, Mikelberg FS. Association of repeated intravitreous bevacizumab injections with risk for glaucoma surgery. JAMA Ophthalmol. 2017;135:363-368.
4. Atchison EA, Wood KM, Mattox CG, Barry CN, Lum F, MacCumber MW. The real-world effect of intravitreous anti-vascular endothelial growth factor drugs on intraocular pressure: An analysis using the IRIS registry. Ophthalmology. 2018;125:676-682.
5. Hoang QV, Mendonca LS, Della Torre KE, Jung JJ, Tsuang AJ, Freund KB. Effect on intraocular pressure in patients receiving unilateral intravitreal anti-vascular endothelial growth factor injections. Ophthalmology. 2012;119:321-326.
6. Moraru A, Pinzaru G, Motoc A, Costin D, Branisteanu D. Incidence of ocular hypertension after intravitreal injection of anti-VEGF agents in the treatment of neovascular AMD. Rom J Ophthalmol. 2017;61:207-211.
7. Vo Kim S, Fajnkuchen F, Sarda V, Qu-Knafo L, Bodaghi B, Giocanti-Auregan A. Sustained intraocular pressure elevation in eyes treated with intravitreal injections of anti-vascular endothelial growth factor for diabetic macular edema in a real-life setting. Graefes Arch Clin Exp Ophthalmol. 2017;255:2165-2171.
8. Barash A, Chul TYP, Garcia P, Rosen RB. Acute macular and peripapillary angiographic changes with intravitreal injections. Retina. 2019 Feb 11. [Epub ahead of print]
9. Bakri SJ, Moshfeghi DM, Francom S, et al. Intraocular pressure in eyes receiving monthly ranibizumab in two pivotal age-related macular degeneration clinical trials. Ophthalmology. 2014;121:1102-1108.
10. Kim JE, Mantravadi AV, Hur EY, Covert DJ. Short-term intraocular pressure changes immediately after intravitreal injections of anti-vascular endothelial growth factor agents. Am J Ophthalmol. 2008;146:930-934 e931.
11. Menke MN, Salam A, Framme C, Wolf S. Long-term intraocular pressure changes in patients with neovascular age-related macular degeneration treated with ranibizumab. Ophthalmologica. 2013;229:168-172.
12. Kahook MY, Ammar DA. In vitro effects of antivascular endothelial growth factors on cultured human trabecular meshwork cells. J Glaucoma. 2010;19:437-441.
13. Kahook MY, Liu L, Ruzycki P, et al. High-molecular-weight aggregates in repackaged bevacizumab. Retina. 2010;30:887-892.
14. Hoguet A, Chen PP, Junk AK, et al. The effect of anti-vascular endothelial growth factor agents on intraocular pressure and glaucoma: A report by the American Academy of Ophthalmology. Ophthalmology. 2018 Nov 22. [Epub ahead of print]
15. Martinez-de-la-Casa JM, Ruiz-Calvo A, Saenz-Frances F, et al. Retinal nerve fiber layer thickness changes in patients with age-related macular degeneration treated with intravitreal ranibizumab. Invest Ophthalmol Vis Sci. 2012;53:6214-6218.
16. de Carlo TE, Romano A, Waheed NK, Duker JS. A review of optical coherence tomography angiography (OCTA). Int J Retina Vitreous. 2015;1:5.
17. Chen CL, Wang RK. Optical coherence tomography based angiography [Invited]. Biomed Opt Express. 2017;8:1056-1082.
18. Yarmohammadi A, Zangwill LM, Diniz-Filho A, et al. Optical coherence tomography angiography vessel density in healthy, glaucoma suspect, and glaucoma eyes. Invest Ophthalmol Vis Sci. 2016;57:OCT451-459.
19. Shin JW, Lee J, Kwon J, Choi J, Kook MS. Regional vascular density-visual field sensitivity relationship in glaucoma according to disease severity. Br J Ophthalmol. 2017;101:1666-1672.
20. Takusagawa HL, Liu L, Ma KN, et al. Projection-resolved optical coherence tomography angiography of macular retinal circulation in glaucoma. Ophthalmology. 2017;124:1589-1599.
21. Schmidl D, Boltz A, Kaya S, et al. Comparison of choroidal and optic nerve head blood flow regulation during changes in ocular perfusion pressure. Invest Ophthalmol Vis Sci. 2012;53:4337-4346.
22. Hollo G. Influence of large intraocular pressure reduction on peripapillary OCT vessel density in ocular hypertensive and glaucoma eyes. J Glaucoma. 2017;26:e7-e10.
23. Ghasemi Falavarjani K, Iafe NA, Hubschman JP, Tsui I, Sadda SR, Sarraf D. Optical coherence tomography angiography analysis of the foveal avascular zone and macular vessel density after anti-VEGF therapy in eyes with diabetic macular edema and retinal vein occlusion. Invest Ophthalmol Vis Sci. 2017;58:30-34.
24. Bressler SB, Almukhtar T, Bhorade A, et al. Repeated intravitreous ranibizumab injections for diabetic macular edema and the risk of sustained elevation of intraocular pressure or the need for ocular hypotensive treatment. JAMA Ophthalmol. 2015;133:589-597.

The temporal aspect of the optic nerve has the most significant decreases in perfusion density, so it may be prudent to focus on this area with serial perfusion scans, RNFL measurements and visual fields.

Focus on Imaging

Can RETINAL IMAGING predict progression to DME?

The role of optical coherence tomography, OCT angiography and ultra-widefield fluorescein angiography in identifying risk factors.


Lauren Mason, MBA


John Mason III, MD


Richard Feist Jr., MD

By Lauren Mason, MBA, Richard Feist Jr., MD, and John Mason III, MD

Take-home points

- The authors performed a small study that found optical coherence tomography hyperreflective foci and ultra-widefield angiography peripheral vessel leakage may help to predict progression from diabetic retinopathy to diabetic macular edema.
- Other studies have found a positive correlation between peripheral nonperfusion and DME.
- Larger studies would validate the utility of OCT, OCT angiography and ultra-widefield angiography to elucidate additional risk factors for development of DME.

All patients with diabetes are at risk of developing diabetic macular edema, which is painless and usually insidious. Diabetic retinopathy is increasingly prevalent with long-standing diabetes, higher incidence baseline A1C levels, hypertension, hyperlipidemia, diabetic nephropathy and diabetic neuropathy—all of which are significant predictors of progression to DME.[1,2]

DME is an accumulation of fluid resulting from an imbalance of multiple and intricate mechanisms involved in hydro-ionic homeostasis, their molecular and cellular basis, and inner and outer blood retinal barrier disruption driven by Starling's law.[3]

Although these risk factors are well known, an additional question is whether retinal imaging in its current state can provide risk factors for progression from DR to DME. Here, we examine the role optical coherence tomography, OCT angiography and ultra-widefield fluorescein angiography (UWFA) can play in identifying predictors of DME, and we report findings from our own small study of these imaging modalities.

Role of OCT angiography

OCT provides a topographical and structural analysis of DR microvascular abnormalities. It can help to identify and characterize complications such as neovascularization, DME, and quantitative and qualitative assessment of macular perfusion.[4]

Most studies agree that a relationship exists between macular perfusion and stage of DR. OCTA can also reveal alterations in density and morphology of the macular microvasculature in the deep (DCP) and superficial capillary plexus (SCP), as well as correlate the number of microaneurysms in the DCP to the presence of DME. However, OCT has not been able to provide definitive risk factors for progression to DME.[5,6]

Imaging of the peripheral retina

Imaging the peripheral retina is crucial

Bios

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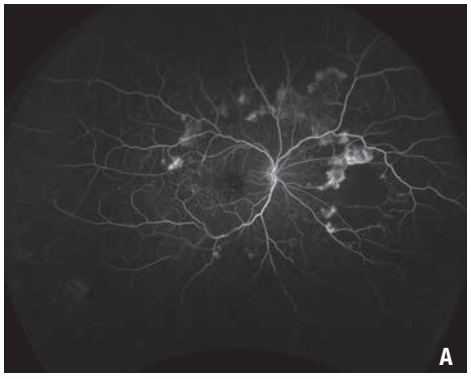

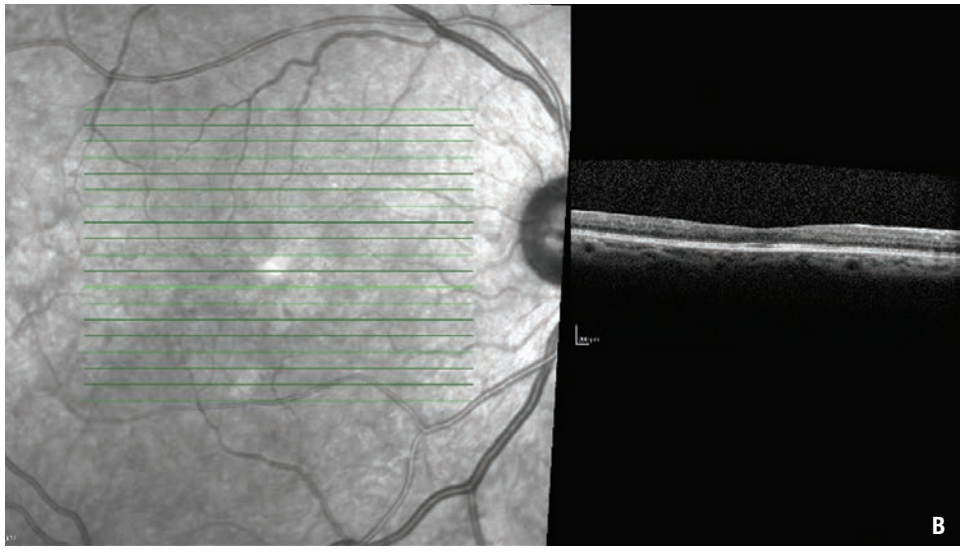

Figure 1. Ultra-widefield angiography (A) shows nonperfusion and neovascularization, while optical coherence tomography (B) of the same patient shows no diabetic macular edema.

in the effective diagnosis, management and prognosis of DR, and for quantifying and documenting retinal pathology more precisely than conventional FA. Patients with predominately peripheral lesions have been reported to have a fourfold risk of progressing to proliferative disease than those with more centrally located retinopathy.[7,8]

Furthermore, identification of the retinal nonperfusion area and calculation of the ischemic index evaluating peripheral nonperfusion using UWFA have been shown to correlate with the severity of DR, as well as defining the presence of peripheral lesions being a risk factor for progression of DR.

The data regarding the ability of UWFA in predicting progression to DME are conflicting. In a retrospective case series, Scott Oliver, MD, and Steven Schwartz, MD, at UCLA did not find a correlation between peripheral nonperfusion and DME, but did create a term, "peripheral vessel leakage" (PVL), to describe late leakage from retinal vessels extending beyond the vessel wall, and found a correlation with PVL and focal DME.[9]

In contrast, Szilard Kiss, MD, and colleagues at Weill Cornell Medical College found a positive correlation between peripheral nonperfusion (ischemic index) and DME. They reported that peripheral ischemia was an independent risk factor for DME development.[10]

Findings on OCT

Many biomarkers, including sub-

The data regarding the ability of ultra-widefield angiography in predicting progression to diabetic macular edema are conflicting.

Disclosures
Dr. Mason is a consultant to Castlebiosciences.

Ms. Mason and Dr. Feist have no financial relationships to disclose.

Table. Predictors of progression to diabetic macular edema

Risk Factor	*p*-value
Ultra-widefield angiography ischemic index (n=48)	0.62
UWFA peripheral vessel leakage (n=48)	0.01
Hyperreflective foci on optical coherence tomography (n=44)	0.03

retinal fluid (SRF), inner segment/outer segment (IS/OS) continuity, absence of hyperreflective foci, attached vitreoretinal interface, central subfield thickness (CST), cube average thickness, disruption of external limiting membrane (ELM) and ellipsoid zone (EZ) have been evaluated to identify early phases of DR and progression of DR.[11,12]

Although these biomarkers have been correlated to severity of DR and visual acuity changes, no strong evidence exists that they correlate to progression of DME. However, changes in these biomarkers are seen with DME and therefore are presumed to be indicators of worsening DR and DME.

Changes in these biomarkers are seen with diabetic macular edema and therefore are presumed to be indicators of worsening diabetic retinopathy and DME.

Hyperreflective foci correlate with lipoprotein extravasation after breakdown of the inner blood-retinal barrier in the initial stage of developing hard exudates. Researchers in South Korea determined that hyperreflective foci on spectral-domain OCT are markers of increased DME activity.[13] They proposed that hyperreflective foci were lipoprotein, migrated microglia or a combination of both.

Our study of UWFA and OCT

We retrospectively evaluated 48 eyes of 24 consecutive patients who underwent UWFA for very severe nonproliferative or proliferative DR, grading for DME, neovascularization, peripheral perfusion ischemic index and PVL. Grading was masked, and both ischemic index and PVL were grouped into mild, moderate and severe categories. OCT of each eye was then evaluated to confirm the presence or absence of DME. Ischemic index and PVL category were then correlated with the patients' OCT, and statistical analysis was performed

A higher ischemic index was not associated with DME (p=0.62), while higher PVL was correlated with DME (p=0.01) (*Table*). Our findings are similar to those Drs. Oliver and Schwartz reported.[9]

We retrospectively evaluated 44 eyes of 22 consecutive patients with severe NPDR without DME on initial OCT. Initial OCT was then correlated to OCT taken at a mean of 24 months later (range, 18 to 27 months), with respect to hyperreflective foci, SRF, IS/OS continuity, disruptions

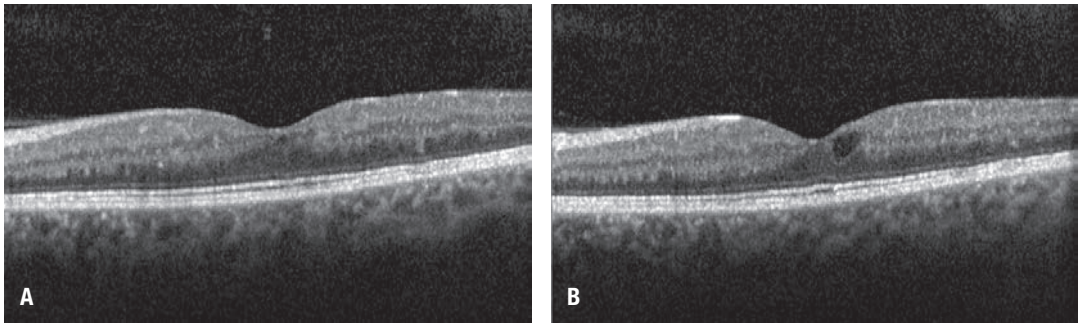

Figure 2. Baseline optical coherence tomography (A) shows hyperreflective foci. Eighteen months later, OCT (B) exhibits diabetic macular edema.

of ELM and EZ, CST, cube average thickness and the development of DME. The later OCT was graded in a masked fashion. DME was judged to be either present or absent on the later OCT.

Statistical analysis was used to compare the initial OCT to the later OCT using *chi* square testing. We found that only hyperreflective foci correlate with progression to DME (p=0.03) (*Table*). Our findings are consistent with the initial findings of the previously mentioned researchers in Korea.[13]

Bottom line

Findings on retinal imaging, including OCT hyperreflective foci and UWFA peripheral vessel leakage, may predict progression from DR to DME in our study. Other studies have found a positive correlation between peripheral nonperfusion and DME. Although development of DME is a multifactorial process that comprises systemic health, metabolic control, cytokines, growth factors and other mechanisms violating the blood retinal barrier, further studies with a larger number of patients would validate the utility for OCTA, OCT and UWFA to elucidate additional risk factors for development of DME.

REFERENCES

1. Klein R, Klein BE, Moss SE, Davis MD, DeMets DL. The Wisconsin epidemiologic study of diabetic retinopathy. III. Prevalence and risk of diabetic retinopathy when age at diagnosis is 30 or more years. Arch Ophthalmol. 1984;102:527-532.
2. Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group, Lachin JM, Genuth S, Cleary P, Davis MD, Nathan DM. Retinopathy and nephropathy in patients with type 1 diabetes four years after a trial of intensive therapy. N Engl J Med. 2000;342:381-389.
3. Daruich, A, Matet, A, Kowalczuk, L et al. Mechanisms of macular edema: Beyond the surface. Prog Retin Eye Res. 2018; 63:20-68.
4. Pedinielli A, Bonnin S, Sanharawi ME, et al. Three different optical coherence tomography angiography measurement methods for assessing capillary density changes in diabetic retinopathy. Ophthalmic Surg Lasers Imaging Retina. 48:378–384.
5. Onishi AC, Nesper PL, Roberts PK, et al. Importance of considering the middle capillary plexus on OCT angiography in diabetic retinopathy. Investi Opthalmol Vis Sci. 2018;59:2167-2176.
6. Hasegawa N, Nozaki M, Takase N, Yoshida M, Ogura Y. New insights into microaneurysms in the deep capillary plexus detected by optical coherence tomography angiography in diabetic macular edema. Invest Ophthalmol Vis Sci. 2016;57:OCT348-355.
7. Brown K, Sewell JM, Trempe C, Peto T, Travison TG. Comparison of image-assisted versus traditional fundus examination. Eye Brain. 2013;5:1-8.
8. Wessel MM, Aaker GD, Parlitsis G, Cho M, D'Amico DJ, Kiss S. Ultra-wide-field angiography improves the detection and classification of diabetic retinopathy. Retina. 2012;32:785-791.
9. Oliver SCN, Schwartz S. Peripheral vessel leakage (PVL): A new angiographic finding in diabetic retinopathy identified with ultra wide-field fluorescein angiography Sem Ophthalmol. 2010; 25:27–33.
10. Wessel MM, Nair N, Aaker GD, Ehrlich JR, D'Amico DJ, Kiss S. Peripheral retinal ischemia, as evaluated by ultra-widefield fluorescein angiography, is associated with diabetic macular edema. Br J Ophthalmol. 2012;96:694-698.
11. Srivastav K, Baskaran P. Re: Zur et al.: OCT biomarkers as functional outcome predictors in diabetic macular edema treated with dexamethasone implant. Ophthalmology. 2018;125:267-275.
12. Phadikar P, Saxena S, Ruia S, Lai TY, Meyer CH, Eliott D. The potential of spectral domain optical coherence tomography imaging based retinal biomarkers. Int J Retina Vitreous. 2017;3:1-10.
13. Kang JW, Chung H, Chan Kim H. Correlation of optical coherence tomographic hyperreflective foci with visual outcomes in different patterns of diabetic macular edema. Retina. 2016;36:1630–1639.

Focus on Imaging

The promise of PREDICTIVE ANALYTICS in DR

Vision-threatening diabetic retinopathy is one area where risk calculators can help build better predictive models.

Bobeck S. Modjtahedi, MD

Donald S. Fong, MD, MPH

By Bobeck S. Modjtahedi, MD, and Donald S. Fong, MD, MPH

Take-home points

- More accurate prediction models can improve our ability to detect vision-threatening forms of diabetic retinopathy earlier.
- Artificial intelligence/deep learning/neural networks may help to build better predictive models.
- A simplified points-based scoring system based on eight variables allowed for stratification of patients into low-, moderate- and high-risk groups for three-year year risk of diabetic macular edema

Whether it is the ancient Greek legend of Amphiaraus or the blockbuster film "Minority Report," people have always been fascinated by the idea of predicting the future—a fascination that has been deeply entrenched within medicine for generations.

Improvements in data collection and processing, including the utilization of large databases and the evolving field of machine learning/artificial intelligence, have refocused medicine's interest in predictive analytics. Developing prediction models that can rapidly and accurately assess patients' risk of future morbidity may help revolutionize patient care.

Diabetes is one area that could benefit tremendously from better prediction models. Early detection is the cornerstone of the management of the ocular manifestations of diabetes. Detecting vision-threatening forms of diabetic retinopathy (VTDR) is important because they can have catastrophic consequences to individual patients while also carrying a high societal cost.

This article reviews the state of the science of using predictive models in medicine and how "big data" has the potential to help physicians identify patients at greatest risk of progressing onto severe disease. We will also explore our institution's work in developing a predictive model for diabetic macular edema.

Risk calculators in medicine

Risk calculators have been a mainstay in medicine for decades, most notably in cardiology, where medical management decisions rely heavily on risk-stratification algorithms derived from robust clinical data. Clinical questions such as a patient's optimal blood pressure, cholesterol or anticoagulation status are based on one's 10-year risk of cardiovascular events, which can be readily calculated using several key variables.

Although Michael Klein, MD, and colleagues provided a popular tool for predicting the 10-year risk of advanced age-related macular degeneration,[1] ophthalmology has lagged behind

Bios

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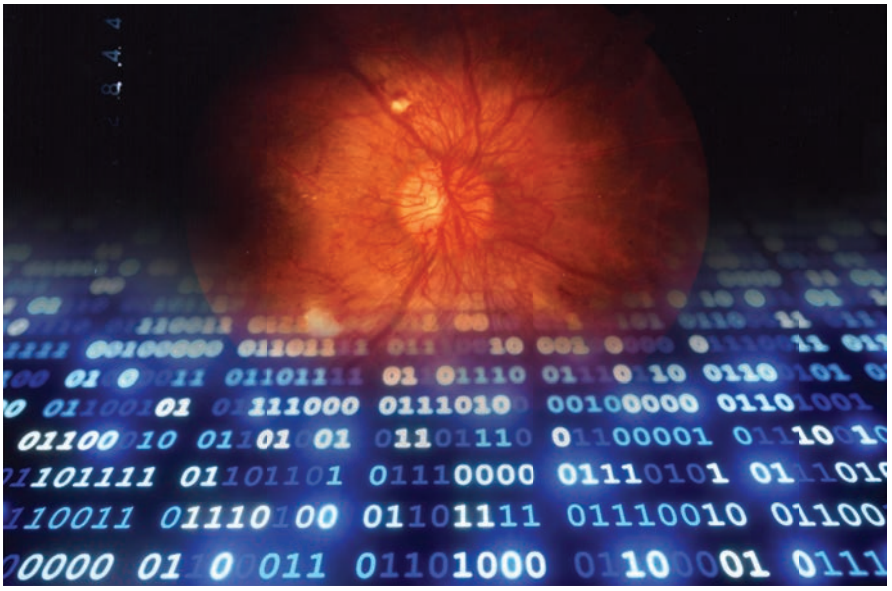
other specialties in developing risk-stratification tools and clinical prediction analysis. This is partly because of the complexity of assessing the risk of ophthalmic disease, which requires incorporating not only ophthalmic factors but also their interaction with systemic factors to create an overall risk estimate. Further compounding this difficulty is the abundance of possible data points; it remains unclear which ones are worthy of inclusion into any model.



Role of AI and neural networks

This is one area where artificial intelligence/deep learning/neural networks may help expand our capacity to build better predictive models. Whereas previous attempts to build models required the use of multiple regression analyses and user-defined inputs, AI could detect a number of variables that a user might not even realize need to be considered.

The ability to examine a database with AI may help solve some of our current limitations, because AI can analyze data "in bulk," allowing machine learning algorithms to work their way through multiple threads of data to isolate the factors that have the most value.

Similarly, our ability to incorporate features from fundus photography into prediction analysis is limited by current methods for manual interpretation and the finite number of macroscopic details that can be defined.

Role of neural networks

Neural networks, on the other hand, have the capacity to rapidly assess quantifiable metrics such as capillary density or vascular diameter, and they can search for yet undefined clues within fundus photographs to build a predictive model. That would be impractical for a human grader to do on a large scale.

Significant work remains on how to optimally utilize AI to build the best models. For example, an AI-based model may examine every piece of data in a patient's medical history—laboratory values, home address, family history and hospital bed, and conclude that patients admitted to the fifth floor of the hospital have higher risk of perioperative mortality.

That might seem like a fascinating insight at first, which would compel further investigation into whether there are breakdowns in clinical care on the fifth floor or if some previously unaccounted for factor (like bad fung shui) was responsible for this heightened mortality. However, upon further inspection, you might learn that the fifth floor is where the surgical intensive care unit is located, explaining why there is greater mortality there compared to non-intensive care unit floors.

Stratifying risk for VTDR

As retina specialists know too well, DME is an important cause of visual morbidity and the leading cause of new

Neural networks have the capacity to rapidly assess quantifiable metrics and search for yet undefined clues within fundus photographs to build a predictive model.

onset blindness among adults in the United States.

In addition to its direct visual consequences, DME is associated with a loss of work productivity and a high treatment burden with frequent clinic visits and costly interventions.[2] Broadly speaking, the care of diabetic patients constitutes 10 percent of U.S. health-care costs,[3] and caring for patients with DME is almost 30 percent more expensive than the treatment of their peers.[4]

Earlier detection and treatment of diabetic macular edema is associated with better visual outcomes and reduced injection burden, thus benefiting patients as well as reducing the cost to the health-care system.[5]

The challenge in diabetes care is that we spend a significant amount of time and effort screening all patients to identify the relatively few that require more intensive evaluation and management.

Few patients drive cost burden

Although the individual and societal costs of diabetic retinopathy are considerable, these costs are largely driven by a minority of patients. Most studies estimate that 10 percent of diabetes patients have VTDR, which is consistent with our experience within Kaiser Permanente.

The challenge in diabetes care is that we spend a significant amount of time and effort screening all patients to identify the relatively few that require more intensive evaluation and management. More accurately stratifying patient risk for VTDR would have substantial benefits.

We could initiate more aggressive systemic management of diabetes when the opportunity to prevent worsening retinopathy is greatest. We could screen patients more closely to detect and treat pathology earlier, allowing for a better prognosis. And we could use our resources more judiciously on the highest-risk patients while letting lower-risk patients "pass through" with less frequent screening.

Although the duration of diabetes and long-term glycemic control are well established as important risk factors for VTDR, investigations into secondary risk factors have produced mixed results.

Isolating individual risk factors

Further, most studies examine the role of individual risk factors in isolation and if they are independently associated with the risk of VTDR. It remains unclear how various risk factors interact to create a global risk for VTDR. It's not uncommon to see a patient with a remarkably elevated hemoglobin A1c but no significant morbidity, while other patients can have significant retinal pathology.

Intuitively, we can tell there is more to retinopathy risk than just the hemoglobin A1c and disease duration. Genetics appears to play a role in the risk of retinopathy,[6] although accounting for

(Continued on page 41)

Our own experience with a predictive model

We recently started to explore this possibility of bringing together both ocular and systemic variables to predict the risk of vision-threatening diabetic retinopathy and developed an initial model using a points-based risk calculator to predict the three-year risk of DME.[9] Baseline degree of retinopathy and 21 different systemic factors of 184,147 patients were analyzed using Cox regressions to develop a risk calculator.

We found that patients could be stratified into low-, medium-, and high-risk groups based on a scoring system that uses age, sex, race, duration of diabetes, A1c, chronic kidney disease stage, insulin use and baseline degree of retinopathy, with high-risk patients being about 415 percent more likely to develop DME than low-risk patients.[9]

Further work needs to be done to refine this model before it's ready for wide-scale implementation, including adding more variables and looking at more granular data.

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Thanos Papakostas, MD

Kunyong Xu, MD, and Thanos Papakostas, MD

Take-home points

- Perfluorocarbon liquid fluid can be used to unfold giant retinal tears.
- Incomplete removal of anterior vitreous around the GRT might lead to redetachment.
- Proliferative vitreoretinopathy may occur in cases of GRTs causing surgical failure or loss.
- Remove the fluid anterior to the PFCL to prevent slippage of the retina before removing the PFCL itself.
- Scleral buckle may counteract residual vitreous base traction that causes tangential tractional forces.

Giant retinal tear is defined as a full-thickness circumferential break in the retina extending more than three clock hours or 90 degrees.[1,2] GRTs arise from liquefaction of central vitreous and peripheral vitreous condensation with concomitant traction at the vitreous base. As a result, the retina tears circumferentially at the posterior vitreous base.[3]

For GRTs, the vitreous gel remains attached to the anterior flap of the retina, while the posterior retina moves freely and can fold upon itself.[3] An important distinguishing factor between GRTs and dialyses is the status of the vitreous. In a dialysis, the vitreous is attached; in GRTs, the posterior vitreous is detached.

The incidence of GRTs is about 0.05: 100,000 per year.[4] GRTs are mostly idiopathic; however, they can occur in the setting of trauma, cataract surgery, young age, high myopia, aphakia, pseudophakia or genetic mutations.[2,5–10] The incidence of GRTs is estimated at 1.5 percent of rhegmatogenous retinal detachments (RRD),[3] and proliferative vitreoretinopathy (PVR) may occur in cases of GRTs causing surgical failure or vision loss.

In 1962, Charles L. Schepens, MD, and colleagues were among the first to report on the difficulties of managing RD with GRT and the importance of performing timely surgery to minimize PVR.[11] Despite advancements of surgical instruments and techniques, the management of RD with GRT is still a surgical challenge because of the technical difficulties and associated complications. In this article, we describe our opinions related to surgical management for RD with GRT.

Surgical management

Currently, pars plana vitrectomy is considered to be the conventional and standard procedure to repair RD with GRT.[12] Unfolding GRTs can be achieved by using PPV followed by intraoperative perfluorocarbon liquid.

For pseudophakic eyes without PVR, PPV without scleral buckling is commonly used for RD with GRT. Without a scleral buckle, meticulous vitreous base trimming with scleral indentation and appropriate

Bios

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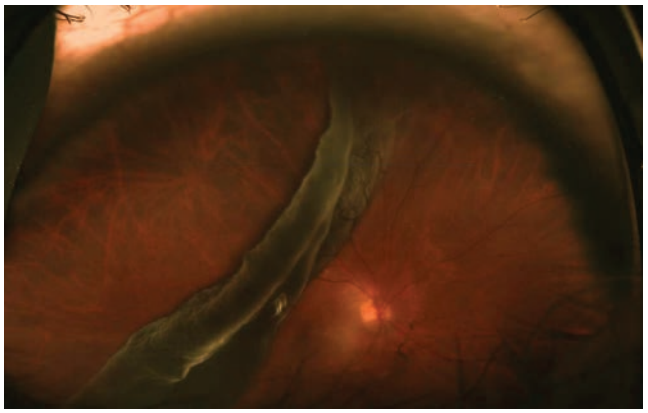


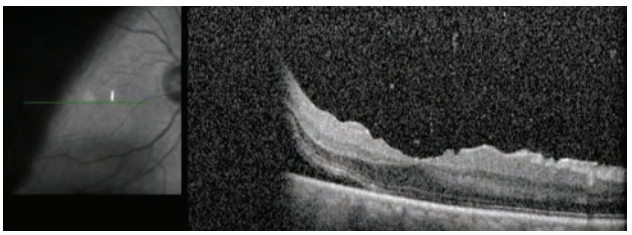


Figure 1. Preoperative wide-angle color photograph shows a retinal detachment with a giant retinal tear in a 66-year-old pseudophakic man. He experienced a shadow in the vision of his right eye for a week. Visual acuity was 20/30 OD, 20/25 OS. Optical coherence tomography preoperatively shows that the fovea is still attached.

tamponade are usually adequate for vitreous-base dissection and GRT reapposition in cases with no significant PVR.[6,13,14]

During PPV, a thorough vitrectomy is necessary. Pay attention to remove all the vitreous and traction to the retinal break. You can use PFCL to flatten the retina by using a dual-bore cannula. You can safely remove the anterior vitreous using the vitrectomy probe with the assistance of a scleral depressor when the posterior retina is stabilized. Incomplete removal of the anterior vitreous around the GRT might lead to redetachment and occurrence of PVR.

The fluid-air exchange is crucial in GRT vitrectomy. It's important to remove the fluid anterior to the PFCL to prevent the slippage of the retina before the removal of PFCL. At the conclusion of the surgery, the eye can be filled with either gas or oil.

To add a buckle or not

PPV with adjuvant scleral buckle can be used for pseudophakic eyes with PVR or phakic eyes with inferior GRT <180 degrees with or without PVR. The vitrectomy for those cases is performed with the same techniques described previously. Place a low-lying, encircling scleral buckle prior to the vitrectomy. A high buckle can increase the rate of slippage during fluid-air exchange. Adjuvant scleral buckle is used to support the vitreous base and the attached retina, especially at both ends of the GRT.[2] Also, the scleral buckle can counteract residual vitreous base traction that causes tangential tractional forces.[15]

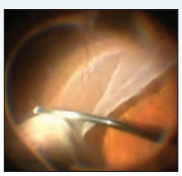
We don't recommend performing a lensectomy in a phakic GRT case because the modern small-gauge cutters can facilitate a thorough vitrectomy while respecting the crystalline lens.

Reports on adjuvant scleral buckle

The literature has shown a trend for higher anatomical success rates for patients who had adjuvant scleral buckle compared to those who had PPV only.[16–22] However, these studies haven't shown an advantage to using an encircling buckle in addition to PPV in terms of anatomical or visual acuity outcomes for RD with GRT.[2,20] In addition, the reoperation rates were higher in cases with encircling buckles[23,24] compared to those without encircling buckles.[24,25]

These studies generally had small sample sizes, and it's difficult to compare these results due to the difference in the clinical characteristics of the study subjects and surgical techniques or procedures. More recently, John D. Pitcher, MD, and col-

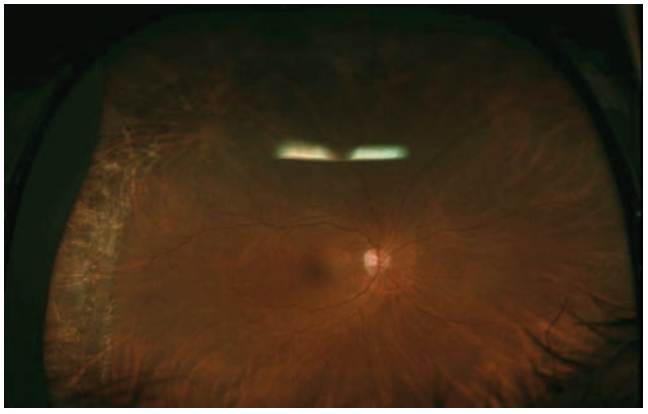
View the Video



Dr. Papakostas demonstrates the key steps in his technique for repairing a giant retinal tear.
Available at: : http://bit.ly/RetSpec_GRT_0319

Key steps during PPV for retinal detachment with giant retinal tear:

- Meticulous vitreous base dissection.
- Excision of anterior flap.
- Use of PFCL to flatten the retina.
- Slow fluid-air exchange along the edges to prevent slippage.



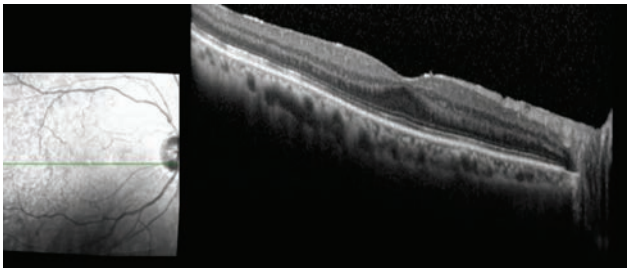


Figure 2. Six months postoperatively, photography and optical coherence tomography show the retina is attached. Visual acuity is 20/25.

Although adjuvant buckling is associated with good anatomical success rates, emerging research has shown high anatomical success rates using PPV alone.

leagues reported that adding a buckle did not significantly alter the success rates in GRT associated RDs.[26]

Gas or oil?

We usually use long-acting gas (14% C3F8) as a tamponade agent. Silicone oil can be used in cases of PVR or during a direct PFCL-SO exchange in cases of retinal slippage. David G. Charteris, MD, and his group at Moorfields Eye Hospital reported that eyes with gas as tamponade achieved better vision, had fewer postoperative complications and there was no difference in final attachment rates when compared to the eyes that received silicone oil.[27]

Role of prophylactic laser

The use of laser in these cases is controversial because of the lack of evidence. One study from Italy with long-term follow-up showed that the group that received prophylactic laser had a higher incidence of tears with localized pre-equatorial RD and lower incidence of macula-off GRT RDs compared to the observation group.[28] To get an unequivocal answer to this question would require a randomized trial consisting of 645 eyes in each group with a minimum follow-up of five years.

The bottom line

The prognosis of managing GRTs has improved over the recent years with better instrumentation and surgical visualization. Surgical advances include small-gauge PPV for managing RD with GRT.[29–31]

From our perspective, vitreoretinal surgeons should pay attention to the key steps of vitrectomy to increase the surgical success, including complete removal of the anterior vitreous and release of the traction on the retinal breaks, identifying and treating all breaks, and prevention of slippage of the retina. Although adjuvant buckling is associated with good anatomical success rates, emerging research has shown high anatomical success rates using PPV alone in managing RD with GRT.[6,14,16,26,32] RS

REFERENCES

1. Mathis A, Pagot V, Gazagne C, Malecaze F. Giant retinal tears: surgical techniques and results using perfluorodecalin and silicone oil tamponade. Retina. 1992; 12: S7–S10.
2. Kertes PJ, Wafapoor H, Peyman GA, Calixto Jr N, Thompson H. The management of giant retinal tears using perfluoroperhydrophenanthrene: a multicentre case series. Vitreon Collaborative Study Group. Ophthalmology. 1997:104:1159-1165.
3. Shunmugam M, Ang GS, Lois, N. Giant retinal tears. Surv Ophthalmol. 2014;59:192-216.
4. Berrocal MH, Chenworth ML, Acaba LA. Management of giant retinal tear detachments. J Ophthalmic Vis Res. 2017;12:93-7.
5. Scott IU, Murray TG, Flynn HW, Feuer WJ, Schiffman JC. Perfluoron Study Group. Outcomes and complications associated with giant retinal tear management usingperfluoro-n-octane. Ophthalmology. 2002; 109: 1828–1833.
6. Ambresin A, Wolfensberger TJ, Bovey EH. Management of giant retinal tears with vitrectomy, internal tamponade, and peripheral 360 degrees retinal photocoagulation. Retina. 2003; 23: 622e8.
7. Chang S, Lopez JM. Giant retinal tears and proliferative vitreoretinopathy. In: Ryan SJ, editor. Retina. 4th ed. St. Louis: Mosby; 2006. p. 2345-2351.
8. Ang GS, Townend J, Lois N. Interventions for prevention of giant retinal tear in the fellow eye. Cochrane Database Syst Rev. 2009;2:CD006909.
9. Aylward GW, Cooling RJ, Leaver PK. Trauma-induced retinal detachment associated with giant retinal tears. Retina. 1993;13:136-141.
10. Mehdizadeh M, Afarid M, Hagigi MS. Risk factors for giant retinal tears. J Ophthalmic Vis Res 2010;5:246-249.
11. Schepens CL, Dobble JG, Mc MJ. Retinal detachments with giant breaks: preliminary report. Trans Am Acad Ophthalmol Otolaryngol.

1962;66:471e9.
12. Gonzalez MA, Flynn HW, Smiddy WE, Albini TA, Tenzel P. Surgery for retinal detachment in patients with giant retinal tear: etiologies, management strategies, and outcomes. Ophthalmic Surg Lasers Imaging Retina. 2013; 44: 232–237.
13. Freeman HM, Castillejos ME. Current management of giant retinal breaks: results with vitrectomy and total air fluid exchange in 95 cases. Trans Am Ophthalmol Soc.1981;79:89e102.
14. Kreiger AE, Lewis H. Management of giant retinal tears without scleral buckling. Use of radical dissection of the vitreous base and perfluoro-octane and intraocular tamponade. Ophthalmology. 1992;99:491e7.
15. Ie D, Glaser BM, Sjaarda RN, et al. The use of perfluoro-octane in the management of giant retinal tears without proliferative vitreoretinopathy. Retina. 1994;14:323e8.
16. Chang S, Lincoff H, Zimmerman NJ, Fuchs W. Giant retinal tears. Surgical techniques and results using perfluorocarbon liquids. Arch Ophthalmol. 1989; 107:761–766.
17. Ghosh YK, Banerjee S, Savant V, Kotamarthi V, Benson MT, Scott RA et al. Surgical treatment and outcome of patients with giant retinal tears. Eye. 2004; 18: 996e1000.
18. Goezinne F, LAH EC, Berendschot TT, Gast ST, Liem AT, Lundqvist IL et al. Low redetachment rate due to encircling scleral buckle in giant retinal tears treated with vitrectomy and silicone oil. Retina. 2008; 28: 485–492.
19. Lee SY, Ong SG, Wong DWK, Ang CL. Giant retinal tear management: an Asian experience. Eye. 2009; 23: 601-605.
20. Al-Khairi AM, Al-Kahtani E, Kangave D, et al. Prognostic factors associated with outcomes after giant retinal tear management using perfluorocarbon liquids. Eur J Ophthalmol. 2008;18:270e7.
21. Unlu N, Kocaoglan H, Acar MA, et al. The management of giant retinal tears with silicone oil. Eur J Ophthalmol. 2003;13:192e5.
22. Verstraeten T, Williams GA, Chang S, et al. Lens-sparing vitrectomy with perfluorocarbon liquid for the primary treatment of giant retinal tears. Ophthalmology. 1995;102:17e20.
23. Bottoni F, Bailo G, Arpa P, et al. Management of giant retinal tears using perfluorodecalin as a postoperative short-term vitreoretinal tamponade: a long-term follow-up study. Ophthalmic Surg. 1994; 25:365e73.
24. Glaser BM, Carter JB, Kuppermann BD, et al. Perfluorooctane in the treatment of giant retinal tears with proliferative vitreoretinopathy. Ophthalmology. 1991;98:1613e21.
25. Rofail M, Lee LR. Perfluoro-n-octane as a postoperative vitreoretinal tamponade in the management of giant retinal tears. Retina. 2005;25:897e901.
26. Pitcher JD 3rd, Khan MA, Storey PP, et al. Contemporary management of rhegmatogenous retinal detachment due to giant retinal tears: A consecutive case series. Ophthalmic Surg Lasers Imaging Retina. 2015; 46: 566–570.
27. Banerjee PJ, Chandra A, Petrou P, Charteris DG. Silicone oil versus gas tamponade for giant retinal tear-associated fovea-sparing retinal detachment: A comparison of outcome. Eye. 2017;31:1302-1307.
28. Ripandelli G, Rossi T, Cacciamani A, Scarinci F, Piaggi P, Stirpe M. Laser prophylactic treatment of the fellow eye in giant retinal tears: Long-term follow-up. Retina. 2016;36:962-926.
29. Oliveira LB, Reis PA. Silicone oil tamponade in 23-gauge transconjunctival sutureless vitrectomy. Retina. 2007;27:1054e8.
30. Riemann CD, Miller DM, Foster RE, et al. Outcomes of transconjunctival sutureless 25-gauge vitrectomy with silicone oil infusion. Retina. 2007;27:296e303.
31. Tsang CW, Cheung BT, Lam RF, et al. Primary 23-gauge transconjunctival sutureless vitrectomy for rhegmatogenous retinal detachment. Retina. 2008;28:1075e81.
32. Batman C, Cekic O. Vitrectomy with silicone oil or long-acting gas in eyes with giant retinal tears: Long-term follow-up of a randomized clinical trial. Retina. 1999;19:188e92.

The promise of predictive analytics in DR

(Continued from page 36)

individual genetic variations on a wide-scale clinically is not presently practical. If we could determine how various ocular and systemic risk factors interact to create a global individualized risk for patients, we could provide improved and more personalized care.

Ideally, a model would predict the risk of DME several years in advance to allow for sufficient time for aggressive systemic treatment to modify the disease course to prevent worsening retinopathy. Such a model may also help identify the specific targets for various systemic risk factors. Perhaps a patient's A1c should be adjusted based on one's degree of retinopathy and other risk factors, such as renal status.

Efforts to predict progression

Marco Dutra Medeiros, MD, and colleagues in Portugal performed a longitudinal epidemiologic study that found that duration of diabetes, age at diagnosis, and insulin use were associated with an increased risk of incidence as well as progression of diabetic retinopathy.[7]

They suggested these findings could serve as the foundation for personalized screening schedule. However, the ability to generalize their results is unclear for non-Portuguese populations because race likely plays a role in the risk of DR progression.

Rajeev Pappuru, MD, and colleagues reported on an image-based approach to predict diabetic retinopathy progression using analyses of fundus photography.[8] They examined the outcomes of 205 patients over the course of two years and found that microaneurysm turnover was a good predictor of retinopathy worsening (based on Early Treatment Diabetic Retinopathy Study grading step changes and development of macular edema).[8]

Bottom line

Bringing together both ocular and systemic variables to predict the risk of VTDR would likely lead to superior prediction models since diabetes is fundamentally a systemic disease. We recently started doing our own work in this area (*sidebar, page 36*).

Although much work needs to be done before prediction models are ready for "prime time," we continue to inch closer to a reality once only envisioned by science fiction writers.

REFERENCES

1. Klein ML, Francis PJ, Ferris FL 3rd, Hamon SC, Clemons TE. Risk assessment model for development of advanced age-related macular degeneration. Arch Ophthalmol. 2011;129:1543-1550.
2. Pershing S, Enns EA, Matesic B, Owens DK, Goldhaber-Fiebert JD. Cost-effectiveness of treatment of diabetic macular edema. Ann Intern Med. 2014;160:18-29.
3. Centers for Disease Control and Prevention. National Diabetes Fact Sheet: National Estimates and General Information on Diabetes and Prediabetes in the United States, 2011. Centers for Disease Control and Prevention; Atlanta, GA: Dec 8, 2011. Accessed at www.cdc.gov/diabetes/pubs/pdf/ndfs_2011.pdf. 2011.
4. Shea AM, Curtis LH, Hammill BG, et al. Resource use and costs associated with diabetic macular edema in elderly persons. Arch Ophthalmol. 2008;126:1748-1754.
5. Wykoff CC, Elman MJ, Regillo CD, Ding B, Lu N, Stoilov I. Predictors of diabetic macular edema treatment frequency with ranibizumab during the open-label extension of the RIDE and RISE trials. Ophthalmology. 2016;123:1716-1721.
6. Graham PS, Kaidonis G, Abhary S, et al. Genome-wide association studies for diabetic macular edema and proliferative diabetic retinopathy. BMC Med Genet. 2018;19:71.
7. Dutra Medeiros M, Mesquita E, Gardete-Correia L, et al. First incidence and progression study for diabetic retinopathy in Portugal, the RETINODIAB study: evaluation of the screening program for Lisbon Region. Ophthalmology. 2015;122:2473-81.
8. Microaneurysm turnover is a predictor of diabetic retinopathy progression. Pappuru RKR, Ribeiro L, Lobo C, Alves D, Cunha-Vaz J. Br J Ophthalmol. 2019;103:222-226.
9. Modjtahedi BS, Wang Y, Luong TQ, Fong DS. Development of a points-based risk score to predict the three-year risk of DME. Paper presented at American Academy of Ophthalmology Annual Meeting; October 27, 2018: Chicago, IL.

PE: Coming soon to your neighborhood?

Private equity is here to stay, but here's how to tell if it's a fit, even if you've already jumped in.

By Paul Lucas

Department Editor
Kari Rasmussen

The private equity incursion in ophthalmology appears alive and well in 2019. Ophthalmology is a fragmented market, and the retina subspecialty in particular even more so. Given the ample number of practice groups, there's no reason to believe this phenomenon will be subsiding anytime soon.

Here's a close look at private equity in ophthalmology, and why some groups opt to maintain their independence while others jump in.

Why practices consider PE

The reasons to consider private equity are consistent across the country. They are:

- "De-risking" the physicians by removing them personally from the ever-changing Medicare and regulatory environments.
- Gaining capital to fund new and expanded clinic locations and patient-preferred surgical centers.
- Getting relief from the administrative pressures of operating an independent practice.
- Seeking an alternative to hospital affiliation and retaining some autonomy.

Geography may play a role in a practice's approach to private equity. Those in rural settings and regions with limited competition may want to stay the course. Practices in more urban markets with a lot of competition, particularly smaller to mid-size groups that may not be able recruit sophisticated administrative support or get the capital to grow and upgrade equipment, may find themselves attracted to the expertise and capital private equity can bring. Every market has its local nuances, and every retina group its unique circumstances.

Why PE likes health care

Who are these private-equity firms and why are they here? Private equity—non-publicly traded investment firms—have been around for decades. Industries that are widely diverse, profitable and oftentimes undergoing radical change and increased regulation have long attracted attention for opportunities to consolidate. Just look at energy, telecommunications and banking, to name a few.

Health care, and private medical practices in particular, pose some unique challenges, primarily that health care is local and specialty-specific. What plays in Peoria doesn't always apply in Albuquerque.

One factor that always prevails, however, is quality patient care. Patients demand it, and equity firms are attracted to it. Here, the physicians remain in full clinical control. Equity groups knowledgeable about health care encourage the development of clinical standards and organized physician advisory boards to direct the clinical initiatives within their management model.

The culture of potential partners

Whether you are considering a direct investment from a private equity firm or an affiliation with a private-equity backed management company, spend time understanding the culture and philosophies of these potential partners. Strategies, expertise and personalities among private-equity partners can be as diverse as practices.

These PE-backed models, when structured properly, have little if any impact on the daily lives of retina specialists and clinic functions. Equity firms know what they know, and perhaps more importantly from the affiliating doctor's perspective, know what they don't know. They leave clinical matters to the specialists.

The most common structure of private equity ownership is the management services organization (MSO). The MSO generally assumes administrative functions—

(Continued on page 45)

Bios

Ms. Rasmussen is chief operating officer of Rocky Mountain Retina Consultants, Salt Lake City. Mr. Lucas is president, posterior division of EyeSouth Partners and former administrator/chief financial officer of Georgia Retina in northern Georgia, which is now affiliated with private equity-backed EyeSouth Partners.

Can patients take OCT home with them?

Early work with home-based optical coherence tomography shows patients can use it, but how good are the images?

When the Food and Drug Administration established breakthrough device designation in 2016, the idea was to offer manufacturers an expedited review pathway for devices that "provide for more effective treatment or diagnosis of life-threatening or irreversibly debilitating diseases or conditions."

In December 2018, the FDA bestowed that designation on the Notal Vision Home OCT System, a cloud-based optical coherence tomography platform that patients diagnosed with wet age-related macular degeneration can use in their home. The artificial-intelligence-based device is designed for remote monitoring of retinal fluid changes in the central 10 degrees. Notal Vision says it hopes to bring the home-based OCT to market next year.

Potential advantages of in-home OCT

Among the retina specialists evaluating the home-based OCT in the clinic is Judy E. Kim, MD, a professor at the Medical College of Wisconsin in Milwaukee. (Dr. Kim is a paid adviser to Notal Vision on the product.)

"Much of our diagnosis and treatment of diseases such as age-related macular degeneration, diabetic macular edema, central serous chorioretinopathy, retinal vein occlusion and many other conditions are guided by the OCT findings," Dr. Kim says. "Currently these images can be obtained only in doctors' offices, requiring the patients to come in for a visit."

Moving that function from the doctor's office and into a more convenient place for patients offers a number of benefits, Dr. Kim notes. "Can you imagine what it would be like to have these OCTs at patients' homes?" she asks. "The advantages are obvious."

Finding the optimal interval

One of the challenges of treating patients with retinal diseases is learning the optimal treatment interval for each individual patient. "As a result, we have various dosing schedules, such as monthly, as needed, or treat-and-extend," Dr. Kim notes. "Instead of overtreating some patients with monthly dosing or risking recurrences with as-needed dosing or guessing how far to extend the interval between injections, we will now know exactly when the fluid recurs and patients can come in then."

In-home OCT monitoring can potentially address the second treatment challenge retina specialists have with these patients: minimizing the treatment burden while minimizing vision loss from undiagnosed fluid recurrence.

"Home OCT will allow us to gain better knowledge of a patient's response to one drug over another in a more dynamic and timely manner," Dr. Kim says. "We will be able to treat patients in a more timely and individualized manner with home OCT."

Individualizing treatment schedules

She notes both the HARBOR[1] and CATT[2] trials reported wide disparities in the frequency of injections among patients; some needed only three injections over 23 months while others needed monthly treatments. As every retina specialist knows, determining what treatment interval the patient would benefit most from is a trial-and-error process that requires multiple office visits.

"Home-based OCT may help in reducing the treatment burden and in adopting a more individualized treatment approach," Dr. Kim says. "This may result in increased compliance with needed injections."

She also points out that as more drugs are being investigated for longer durability, determining the optimal dosing interval will be critical. "We should also remember that every injection carries a small but known risks of endophthalmitis, intraocular

(Continued on page 46)

Department Editor
Richard Mark Kirkner

"Home OCT will allow us to gain better knowledge of a patient's response to one drug over another in a more dynamic and timely manner." —Judy Kim, MD

Wet AMD gene therapy shows promise

Phase I/IIa results of RGX-314 confirm protein uptake over months.

By Richard Mark Kirkner

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

The surgical procedure used to place the vector involves a three-port small gauge core vitrectomy to induce a posterior vitreous detachment, similar to the procedure used to place other gene therapies.

RGX-314 is one of a number of gene therapy candidates targeting retinal diseases, but where the bulk of these agents target inherited retinal disease, RGX-314 is unique in that it's one of the few gene therapies that targets wet age-related macular degeneration. REGENXBIO, the company developing RGX-314, says the goal is to have a one-time subretinal treatment for wet AMD.

RGX-314 includes a vector of adeno-associated virus serotype 8 (AAV8). Because this serotype shows a greater affinity for liver transduction than other serotypes, it is the preferred vector for hemophilia A and familial hypercholesterolemia.[1] More recent research in retinal diseases has implicated AAV8 in inducing immune responses in primate retinas[2] and, more specifically, in suppressing vascular endothelial growth factor.[3]

REGENXBIO has developed RGX-314 based on a proprietary platform called NAV. RGX-314 contains a gene that encodes for a monoclonal antibody fragment that binds to and neutralizes VEGF activity.

Phase I/IIa dose-escalation trial

A Phase I/IIa dose-escalation trial is currently evaluating four doses of RGX-314: 3E9 GC/eye; 1E10 GC/eye; 6E10 GC/eye; and 1.6E11 GC/eye. At last report, 30 subjects have been dosed in the trial. The trial is also now recruiting an additional cohort of 12 patients at a dose of 2.5E11 GC/eye.

These trial results will be used to help design the Phase IIb trial, which principal investigator Jeffrey S. Heier, MD, says is scheduled to begin by the end of the year.

Here, Dr. Heier, director of the vitreoretinal service at Ophthalmic Consultants of Boston, answers questions about the Phase I/IIa trial.

Q What can you tell us about the mechanism of action of RGX-314?

A RGX-314 utilizes an AAV8 viral vector that carries a gene encoding for an anti-VEGF protein. The vector is taken up preferentially by retinal cells. In essence, it uses the patient's cells to produce high levels of the therapeutic protein.

Q How is RGX-314 administered?

A It's administered subretinally. The procedure used to place the vector involves a conventional three-port, small-gauge core vitrectomy and, if not already present, a posterior vitreous detachment is induced. Then, using a small-gauge, subretinal cannula, the gene therapy product is introduced into the subretinal space. A bleb is created by injecting 250-µl of the gene therapy product adjacent to, but not in, the macula. This is similar to the procedure used for other retinal gene therapies, such as voretigene neparvovec-rzyl (Luxturna, Spark Therapeutics).

Q What are the potential advantages of subretinal delivery?

A The hypothesis is that subretinal delivery will provide broader retinal coverage, higher protein expression and reduced sensitivity to neutralizing antibodies than intravitreal delivery. This will potentially lead to higher and longer gene expression.

Q What have the Phase I/IIa results shown so far?

A The Phase I/IIa study is designed primarily to evaluate safety, but it is also designed to show long-term protein expression after administering RGX-314. In each cohort we have seen increasing levels of protein expression as measured by anterior chamber taps. Fifty percent of the patients in cohort 3 (6E10 GC/

eye) haven't received any rescue injections out to nine months. Patients in cohort 4 (1.6E11 GC/eye), which is still recruiting, had continued evidence of dose-dependent protein expression.

Q What are the safety findings at this point?

A The surgery is well tolerated. Very few complications have been reported. One patient developed a peripheral retinal detachment that was successfully repaired, and that patient continues to do well.

Q What are the functional and anatomical findings so far?

A Patients in cohort 3 continued to have stable to increasing visual acuity and stable to decreased retinal thickness despite few injections. Half of these patients (3 of 6) received no further treatment after RGX-314 delivery, and they continued to show stability in terms of retinal thickness.

Q What types of patients were included in the trial?

A The patients treated in this study are long-term patients, with an average disease duration of five years and a history of 30-plus injections each. They demonstrated a chronic and frequent need for anti-VEGF injections. The fact that they've demonstrated stability in vision up to this point is most encouraging.

Q Where would RGX-314 fit in real-world practice?

A The data are overwhelmingly clear that patients in the real world don't achieve outcomes that are reported in Phase III randomized clinical trials. We at least hypothesize that that's largely due to undertreatment.

The treatment burden is at least responsible for that. The hope is that we have a treatment that's far more durable, that will mean patients will need fewer to no injections over a one-to-multi-year span, and that the real-world outcomes will be much closer to those achieved in Phase III studies. RGX-314 would be more for the patients who have demonstrated a very strong dependence on frequent anti-VEGF treatments—that is, monthly or every six or eight weeks. RS

REFERENCES

1. Nam HJ, Lane MD, Padron et al. Structure of adeno-associated virus serotype 8, a gene therapy vector. J Virol. 2007;81:12260-71
2. Reichel FF, Dauletbekov DL, Klein R, et al., and the RD-CURE Consortium. Mol Ther. 2017;25:2648-2660.
3. Liu Y, Fortmann SD, Shen J, et al. AAV8-antiVEGFfab ocular gene transfer for neovascular age-related macular degeneration. Mol Ther. 2018;26:542-549.

PE: Coming soon to your neighborhood

(Continued from page 42)

payroll, accounts payable and general accounting/tax preparation. Most typically offer other critical business functions, such as strategic planning, revenue cycle management, human resources/benefits management, compliance and information technology.

Bringing formality to financials

Partnering with the right private-equity firm will enable your current administrative team to have a starring role in both the integration process as well as operational and financial reporting post-affiliation. It will bring formality to reporting and financial monitoring.

Most retina groups utilize cash-basis accounting because it offers a reasonable assessment of a group's fiscal health and eases the partners' annual tax filing burdens. Most retina groups also utilize various metrics and benchmarking data to assist in managing the business. Groups considering affiliation should expect a more corporate and frequent approach to financial reporting and key performance indicator (KPI) tracking. Accrual-based accounting, annual operating and capital budgets, and regular communication of KPIs will be the norm.

Depending on a group's level of internal accounting sophistication and its management reporting tools within existing systems, this process brings a potentially significant deviation from the small-business management mentality of most medical practices. But this advanced process also allows for better financial understanding, more accurate projections, identification of critical trends, adjustments of operational processes and development of detailed growth plans—exactly what every practice wishes it had and right in the wheelhouse of private equity.

What path is right for you?

By now, many retina practices have already been solicited by private-equity firms. Some have elected to stay the course. Some have chosen to affiliate with a larger entity, maintaining medical independence but foregoing some business management autonomy.

Which path is right for you? Your present circumstances—competition, referral practice decisions with private equity, the level of sophistication within your group to keep up with and adhere to added regulation and business demands, MIPS (merit-based incentive payment system), fee schedule changes, contract negotiation, recruitment, etc.—may well hold the answers. RS

Can patients take OCT home?

(Continued from page 43)

pressure elevation, vitreous hemorrhage and retinal detachment. Therefore, it would be ideal to be treated only when treatment is needed," says Dr. Kim.

"To achieve this end, the quality of OCT images and the accuracy of AI-based readings of the images will be important," she says of the home-based OCT system.

Ease of use, image quality

Three sites in the United States are evaluating the home-based OCT. "What I hear from them is that it's easy to use by the patients, even in their 80s and 90s," she says. The evaluation sites are also validating image quality compared to in-office OCT and will present those findings at upcoming retina meetings.

Dr. Kim also notes that the notification alert system—when in-home monitoring detects significant retinal fluid changes and how the retina specialist gets that information—is still a work in progress.

Given that Notal already has a platform for its cloud-based ForeseeHome that provides monitoring of changes in metamorphopsia in patients at risk for converting to neovascular AMD, Dr. Kim believes the home system can utilize a similar work flow. "Home OCT is an exciting innovation that has the potential to greatly impact and benefit our patients and their physicians," she says.

REFERENCES

1. Busbee BG, Ho AC, Brown DM, et al. HARBOR Study Group. Twelve-month efficacy and safety of 0.5 mg or 2.0 mg ranibizumab in patients with subfoveal neovascular age-related macular degeneration. Ophthalmology. 2013;120:1046-1056.
2. Martin DF, Maguire MG, Fine SL, et al. Comparison of Age-related Macular Degeneration Treatments Trial (CATT) Research Group. Ranizibumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results. Ophthalmology. 2012;119:1388-1398.

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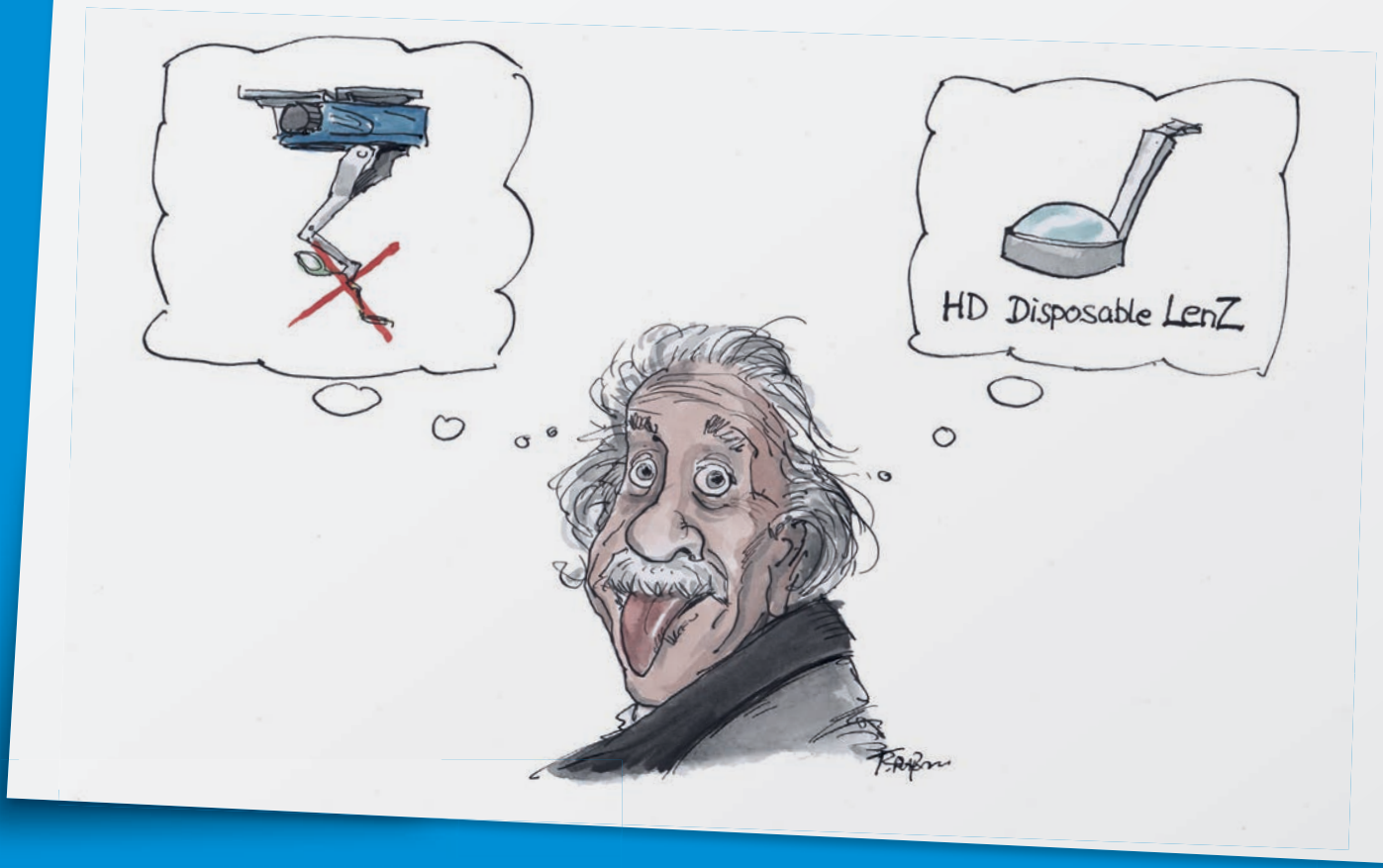

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Reference: 1. Chiang B, Jung JH, Prausnitz MR. The suprachoroidal space as a route of administration to the posterior segment of the eye. *Adv Drug Deliv Rev.* 2018;126:58-66.