Stanford University Network for Diagnosis of Retinopathy of Prematurity (SUNDROP): Five Years of Screening With Telemedicine

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BACKGROUND AND OBJECTIVE: To report the 5-year results of the Stanford University Network for Diagnosis of Retinopathy of Prematurity (SUNDROP) telemedicine initiative.

PATIENTS AND METHODS: Infants requiring retinopathy of prematurity (ROP) screening at six neonatal intensive care units from December 1, 2005, to November 30, 2010, were evaluated with remote retinal photography by an ROP specialist. Every infant received outpatient binocular indirect ophthalmoscope examinations until termination criteria were achieved or until treatment. Outcomes were treatment-warranted ROP (TW-ROP, ETROP type 1) and adverse anatomical events.

RESULTS: Five hundred eleven infants (1,022 eyes) were screened. Fifteen infants had TW-ROP and underwent laser photocoagulation. The TW-ROP cohort had significantly lower birth weight and gestational age (both $P < .001$). No patient progressed to adverse anatomical outcomes and no case of TW-ROP was missed. Telemedicine had 100% sensitivity, 99.8% specificity, 93.8% positive predictive value, and 100% negative predictive value for detection of TW-ROP.

CONCLUSION: Telemedicine demonstrates high diagnostic accuracy for detection of TW-ROP and can complement ROP screening.

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INTRODUCTION

Retinopathy of prematurity (ROP) is a vision-threatening disease of disordered retinal vasculature development in premature and low birth weight infants.[1,2] The underdeveloped retina overcompensates for ischemia at birth by promoting angiogenesis that can damage nearby structures through retinal edema, traction, or detachment.[3,4] At United States schools, ROP accounts for 14% of pediatric blindness.[5] The World Health Organization (WHO) found ROP to be the leading cause of avoidable visual impairment in high-income countries and the second leading cause in middle-income countries,[6] accounting for 15% to 35% of pediatric blindness in some nations.[7-9]

Randomized trials and observational studies demonstrate that cryotherapy,[10,11] laser photocoagulation,[12-15] and intravitreal bevacizumab[16,17] can preserve vision when administered early in the course of disease.[14] Armed with vision-saving treatments, public health efforts have shifted toward screening and promptly identifying high-risk infants. The landmark Early Treatment of Retinopathy of Prematurity (ETROP) trial developed standardized screening time lines based on the natural course of ROP and defined the criteria for initiation of treatment (ETROP type 1).[4,14] In 2013, the American Academy of Pediatrics (AAP) and the American Academy of Ophthalmology (AAO) released updated ROP screening recommendations stating that every infant with birth weight less than or equal to 1,500 g, estimated gestational age

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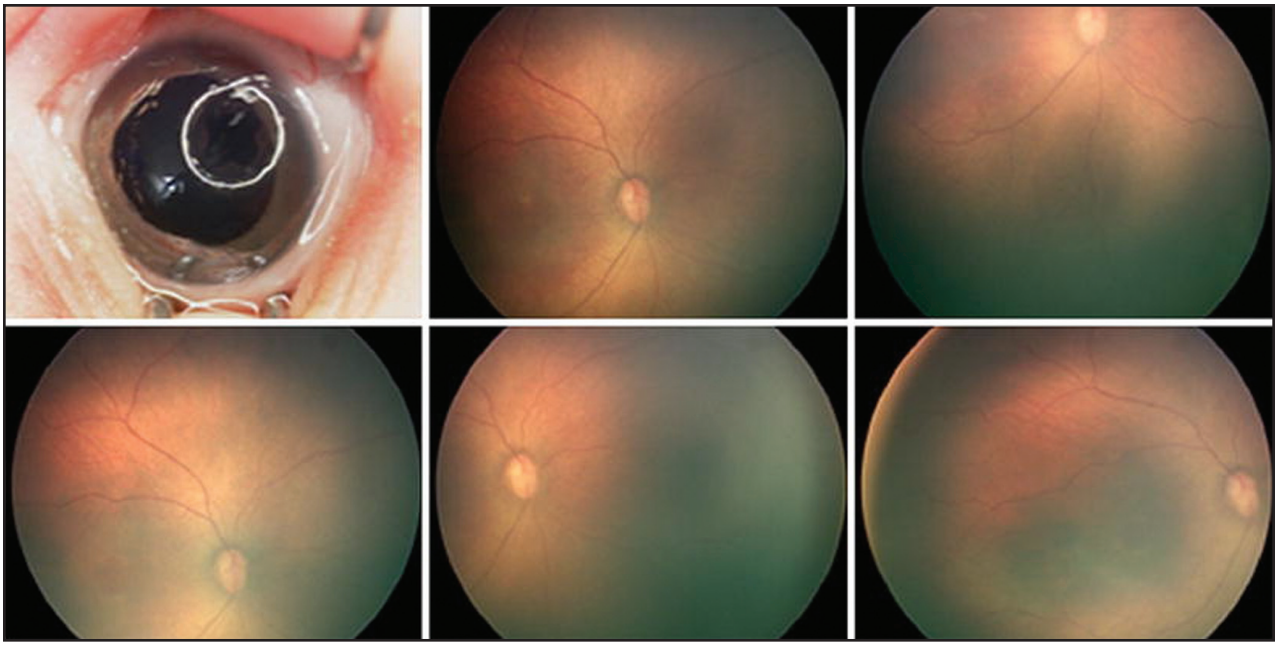


Figure. Images in each eye were external (top left), optic nerve (ON) centered, ON superior, ON inferior (bottom left), ON nasal, and ON temporal. Figure is reproduced with permission from *Graefe's Archive for Clinical and Experimental Ophthalmology*.

less than or equal to 30 weeks, or an unstable clinical course deemed high risk by the attending pediatrician should be screened with serial eye examinations until the infant meets criteria for terminating screening.[18] Although screening and treatment are highly effective at preventing ROP related vision loss, thousands of at-risk infants worldwide remain unscreened because of a shortage of ROP specialists.[19]

The number of neonates requiring screening is increasing because sophisticated neonatal intensive care unit (NICU) technology enables the survival of younger infants worldwide. At the same time, the number of physicians willing and able to care for these patients is dwindling. Pediatric ophthalmologists are already at a shortage in the United States,[8] and a survey by the AAO projects a 17% decline in the current ROP workforce due to legal liability, travel burden, poor reimbursement, and significant time commitments.[20] These shortages are amplified in middle-income countries where there are fewer practicing pediatric ophthalmologists.[19]

The ROP screening burden may be alleviated with the use of wide-angle digital retinal photography interpreted remotely to complement the work of pediatric ophthalmologists and retina specialists. The ROP screening examination relies upon visual analysis of anatomic structures that can be seen in a photograph. Retinal image devices such as the RetCam II (Clarity Medical Systems, Pleasanton, CA) are now able to capture high-resolution digital images from patients in one location and transmit them to a remote expert for interpretation. Telemedicine, the use of electronic technology for remote health care, is promising for ROP screening because it may serve as a cost-effective complement to traditional bedside binocular indirect ophthalmoscope (BIO) examination performed by the ophthalmologist.[21] Among studies comparing telemedicine with concurrent BIO for detection of treatment-warranted ROP, all have found high diagnostic accuracy.[22-28] Most importantly, no infant in any published telemedicine study with disease necessitating intervention has been missed.

The Stanford University Network for the Diagnosis of Retinopathy of Prematurity (SUNDROP) is an active community initiative that uses telemedicine as the sole in-hospital screening technique for high-risk infants born at six satellite NICUs located throughout Northern California. The SUNDROP initiative was developed to reduce blindness and poor visual outcomes from ROP by providing infants in rural and county hospitals with quaternary care. The SUNDROP initiative is the first true implementation of telemedicine for ROP screening in the United States. All infants meeting AAP/AAO criteria are screened with RetCam II images that are sent to the Stanford University Byers Eye Institute reading center for remote interpretation by an ROP specialist, and outcomes are confirmed with outpatient ophthalmology follow-up. This report summarizes the 5-year results of the SUNDROP initiative.

TABLE 1

Comparison of Baseline Characteristics of Infants With and Without Treatment-Warranted Retinopathy of Prematurity in the SUNDROP Telemedicine Initiative

Patient Characteristic	TW-ROP (n = 15), Mean ± SD	No TW-ROP (n = 496), Mean ± SD
Gender		
Male (%)	66.7	54.9
Female (%)	33.3	45.1
Estimated gestational age (weeks)*	24.8 ± 1.7	29.0 ± 2.8
Birth weight (grams)*	678.2 ± 148.5	1,275.0 ± 347.5
Multiplicity**		
Single (%)	73.3	84.7
Twin (%)	26.7	14.1
Triplet (%)	0.0	1.2
Number of exams*	10.3 ± 5.8	3.3 ± 2.9
Number of images*	144.7 ± 47.5	40.5 ± 44.8
Adverse outcomes¥	0	0

TW-ROP = treatment-warranted retinopathy of prematurity.

** P < .001 for variable. P values were obtained by comparing the data for infants with TW-ROP with those without TW-ROP using chi-squared test distributions for categorical variables and Student's t-test for continuous variables.*

TW-ROP was defined by the same criteria as the multicenter, randomized trial Early Treatment of Retinopathy of Prematurity (ETROP) type 1: (1) zone I any stage ROP with plus disease, (2) zone I, stage 3 ROP with or without plus disease, (3) zone II, stage 2 or 3 ROP with plus disease, (4) any plus disease, (5) any stage 4 or higher disease.

*** Multiplicity was defined as monozygotic twins, dizygotic twins, or triplets as opposed to single-born infants (single). Monozygotic and dizygotic twins were lumped into the twin category. There were insufficient counts in cells to run meaningful statistical analysis; therefore, the percentages in each cohort are reported.*

¥ Adverse outcomes were defined as any case of blindness, vision loss, retinal detachment, retrolental mass, macular fold, or other ophthalmic anatomic abnormalities. No infant progressed to any serious outcome at the 5-year mark of the SUNDROP initiative. All 15 TW-ROP patients underwent laser photocoagulation and are monitored in outpatient pediatric ophthalmology at Lucile Packard Children's Hospital.

PATIENTS AND METHODS

Ethical Considerations

The institutional review board at Stanford University School of Medicine approved this retrospective review of the SUNDROP telemedicine initiative. All research was conducted in compliance with human subjects regulations and adhered to the tenets of the Declaration of Helsinki.

Participants and Baseline Characteristics

All infants at six participating NICUs who met AAP/AAO ROP screening criteria[18] were enrolled in the SUNDROP telemedicine initiative. The six NICUs are located throughout Northern California and include level I, II, and III nurseries encompassing community, private, and county hospitals. Thus, the screened infants are a demographically, ethnically, and socioeconomically diverse population. This study includes infants screened from December 1, 2005, to November 30, 2010. The birth weight was obtained from the delivery record and further classified into categories of extremely low birth weight (less than 1,000 g), very low birth weight (1,000-1,499 g) and low birth weight (1,500-2,500 g) consistent with WHO classifications. Gender, estimated gestational age, and multiplicity data were also obtained from the delivery records at each hospital. Births were classified as single, twin (including both dizygotic and monozygotic), or triplet.

Photography Protocol

NICU nurses were trained to take wide-angle (130° lens) retinal photographs using the RetCam II as previously described.[29-33] Retinal images were obtained using published photography protocols with a goal of five or more clearly focused images of each area of the eye, as shown in the Figure (page 111).[25,29-33] In cases of inadequate exposure, artifact, poor visualization of the periphery, or lack of a complete standardized image set, a repeat telemedicine evaluation was performed within 48 hours. In the latter half of the first year, iris images from each eye were included in line with changes in AAP/AAO guidelines.[34] The nurses closely monitored infant's vital signs, cardiopulmonary status, and oxygen saturations during the examination. If bradycardia, apnea, or other abnormalities developed during retinal imaging, the examination was halted and the NICU staff immediately stabilized the infant. Repeat examinations were postponed for 48 hours. In cases in which repeat retinal photography examination could not be performed, the infant was evaluated with bedside BIO.

Data Collection and Management

All patient retinal photographs and data were transferred via secure and encrypted email or by courier. Families and the NICU staff were informed of the im-

TABLE 2

Comparing Premature Infants in the SUNDROP Initiative by Birth Weight

Variable	Extremely Low Birth Weight (< 1,000 g)	Very Low Birth Weight (1,000 – 1,499 g)	Low Birth Weight (1,500 – 2,500 g)
Number (%)	107 (24.0)	250 (56.1)	89 (19.9)
Gender			
Male, n (%)	54 (50.5)	128 (51.2)	58 (65.2)
Female, n (%)	53 (49.5)	121 (48.8)	31 (44.8)
Gestational age* (weeks), mean ± SD	26.3 ± 2.0	29.2 ± 2.6	30.5 ± 2.2
Multiplicity			
Single, n (%)	87 (81.3)	209 (83.6)	81 (91.0)
Twin, n (%)	18 (16.8)	40 (16.0)	8 (9.0)
Triplet, n (%)	4 (3.7)	2 (0.8)	0 (0.0)
Treatment-warranted ROP*, n (%)	15 (100)	0 (0)	0 (0)

** P < .01 for variable. P values were obtained by comparing the data for infants in each birth weight category. For continuous variables, analysis of variance (ANOVA) was performed and a chi-squared test was used to compare categorical variables (TW-ROP).*

Extremely low birth-weight definition is based upon WHO classification criteria of infants born with a birth weight of less than 1,000 g. Very low birth weight was defined as between 1,000 and 1,499 g. Low birth weight was defined as less than 2,500 g that did not fall into the more extreme categories of birth weight. Among the 449 infants with birth weight data available, 446 infants (99.3%) met low birth weight (2,500 g or less) classification criteria. All infants with TW-ROP at 5 years of the SUNDROP initiative were extremely low birth weight.

age interpretation within 24 hours (most often, later in the same day). Study data were collected and managed using Stanford University's REDCap (Research Electronic Data Capture), a secure, Web-based application designed to support data capture in a HIPAA-compliant fashion for research studies.[35] The research was supported by a Center for Clinical Informatics grant.

Inpatient Telemedicine Screening

All infants underwent inpatient retinal photography for ROP screening with remote image evaluation at the Stanford Byers Eye Institute reading center by a single ROP specialist (DMM). Infants meeting AAP/AAO criteria were screened solely with retinal photography until discharge from the hospital unless they had an image interpreted as suggesting treatment-warranted ROP (TW-ROP), defined as ETROP type 1.[14] An interpretation of TW-ROP initiated a mandatory bedside BIO by the ROP specialist within 24 hours. The frequency of screening examinations followed those recommended by the joint criteria statement (eg, weekly screening for a neonate whose images demonstrate zone II, stage 2 ROP without plus disease).[18] All infants were followed up until they met termination criteria delineated by the AAP/AAO: (1) zone III retinal vascularization attained without prior zone I or II ROP, (2) full retinal vascularization, (3) postmenstrual age of 45 weeks, (4) no pre-threshold or worse disease present, or regression of ROP with no abnormal vascular tissue present that is capable of reactivation and progression.[18] Follow-up in high-risk infant clinic allowed complete capture of patient outcomes.

Outcomes

The primary outcomes were TW-ROP and anatomic outcomes (vision loss, retinal detachment, retrolental mass, or macular fold). Images were interpreted using the standardized international classification system criteria[36] by one ROP specialist (DMM). TW-ROP was defined as ETROP type 1 that includes: (1) zone I, any stage ROP with plus disease, (2) zone I, stage 3 ROP with or without plus disease, (3) zone II, stage 2 or 3 ROP with plus disease, (4) any plus disease, or (5) any stage 4 or higher disease.[14] A diagnosis of TW-ROP initiated a subsequent mandatory bedside BIO within 24 hours (usually faster) by the attending ophthalmologist (DMM). Treatment decisions were based exclusively on the bedside BIO examination findings. All patients who required treatment were followed up in outpatient ophthalmology clinic and received serial bedside BIO (they were no longer screened with the SUNDROP telemedicine protocol). The clinical diagnosis determined with bedside BIO was considered

the gold standard reference. All patients received at least one mandatory bedside BIO examination within 1 week of NICU discharge.

Statistical Analysis

All data were analyzed using SAS Enterprise Guide version 5.1 All variables were graphically examined for normal distributions and outliers to determine the appropriate statistical tests. Measures of central tendency and variation were used to describe the study population. All infants who had TW-ROP were compared with the non-ROP cohort with respect to baseline characteristics using *t*-test and chi-squared analyses as appropriate. Statistical significance level was set as a two-tailed test with $\alpha < 0.05$. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated for the detection of TW-ROP in the SUNDROP study during the first 5 years of enrollment. The telemedicine image interpretation was compared to the gold standard BIO results from the outpatient ophthalmology clinic.

RESULTS

Participants

During the 5-year study period, 511 infants (1,022 eyes) were screened for ROP with images interpreted remotely at the Stanford Byers Eye Institute reading center. All 511 infants had complete outcome records with respect to TW-ROP status and adverse anatomical outcomes collected from clinic records. The total number of examinations and images captured was available for 502 infants (98.2%). Details on birth weight and estimated gestational age were available for 424 infants (83.0%). The SUNDROP initiative included 1,783 examinations and 22,215 images; the median number of examinations per infant was 2.0 (mean: 3.55; range: 1 to 20), and the median number of images per patient was 30.0 (mean: 32; range: 6 to 244). The mean birth weight of all patients was 1,255 g (SD: 358 g); mean gestational age was 28 weeks and 6 days (SD: 2.8 weeks); and there were slightly more male than female infants (55% vs 45%). The study included 37 twins (74 infants, 14.5%) and two sets of triplets (six infants, 1.2%).

Treatment-Warranted ROP and Adverse Outcomes

From the 1,783 examinations performed by NICU nurses and reviewed by an ROP specialist (DMM) at the Stanford reading center, 16 infants were classified as having TW-ROP based on telemedicine retinal image interpretation alone. Bedside BIO confirmed TW-ROP in 15 of the 16 infants. All 15 infants were treated with laser photocoagulation, and none of these infants progressed to macular fold, retrolental mass, retinal detachment, or severe vision loss (visual acuity worse than 20/200). The one infant with a false positive finding had ETROP type 2. This infant was followed up with serial examinations until his ROP spontaneously regressed. All 495 patients who did not have TW-ROP on image analysis were confirmed to have no TW-ROP during clinical examination and had no adverse outcomes reported.

Infants with TW-ROP had significantly lower birth weights ($P < .001$) and lower estimated gestational ages ($P < .001$) than infants without TW-ROP (Table 1, page 112). The TW-ROP cohort had a higher proportion of male infants (66.7% vs 54.9%), but this difference was not statistically significant ($P = .14$, Fisher's exact test). There was also a greater percentage of multiples (twins and triplets) in the TW-ROP cohort (26.7% vs 15.3%), but this was not statistically significant ($P = .27$, Fisher's exact test). All infants with TW-ROP met WHO criteria for extremely low birth weight (less than 1,000 g; Table 2, page 113).

Diagnostic Measures for Telemedicine

RetCam II image interpretation yielded one false positive and no false negatives (Table 3). The sensitivity and NPV were 100%. The specificity was 99.8%, and the PPV was 93.8%.

DISCUSSION

The 5-year analysis of the SUNDROP telemedicine initiative exhibits excellent measures of diagnostic accuracy for the detection of TW-ROP with a sensitivity of 100%, specificity of 99.8%, PPV of 93.8%, and NPV of 100% using wide-angle retinal photography interpreted remotely and compared to the gold standard bedside BIO examination findings in outpatient clinic. Infants born at the six nurseries were screened solely with telemedicine as inpatients at a frequency determined by published recommendations until they met termination criteria or required treatment.[18] During the 5-year evaluation period, a single specialist screened 511 premature infants and no case of TW-ROP went undetected, as confirmed by bedside BIO of every infant discharged.[18] The SUNDROP initiative is a community-based ROP screening program led by Stanford University and represents the real-world implementation of telemedicine as a complementary tool for ROP screening.

In the United States, one in every nine infants born in 2012 was premature.[37] Although bedside BIO examination by an ophthalmologist is ideal, the limited ROP workforce is unable to keep up with the growing demand for care. Remote retinal photography may complement the work of ophthalmologists treating

ROP by focusing their resources on infants with potentially vision-threatening disease. Previous studies have found many advantages to telemedicine for ROP screening. Remote image interpretation is faster,[38] is more cost-effective ($3,193 vs $5,617 for BIO for every quality-adjusted life year),[21] is less stressful to infants,[39] reduces the risks and costs of transporting premature infants, provides objective documentation of retinal findings, and provides records for training purposes. Telemedicine is currently being used for diabetic retinopathy care and has reduced the cost to patients and providers, increased access and availability for patients, and yielded no clinically significant sacrifices in the quality of care.[40]

Telemedicine for ROP screening has been evaluated by multiple studies in the last two decades using various cameras, image takers, readers, reading centers, and distances between the patient and physician. Early trials reported mediocre sensitivities and specificities.[41] However, these studies used outdated camera and lens models, had readers of different training levels, and focused on the ability to distinguish between specific stages of ROP.[42-44] Ultimately, the purpose of screening is to detect disease that will alter the clinical course of the patient, which in the case of ROP is TW-ROP. In 2003, Ells et al embraced the tenets of an effective screening program and tested the utility of telemedicine for the detection of treatment-modifying disease. They reported a sensitivity of 100% and specificity of 96%.[22] All studies since then have reported similar diagnostic measures for detection of treatment-modifying disease when compared with simultaneous BIO.[22-25,27]

In light of the growing body of evidence supporting the use of telemedicine for ROP screening, the AAO commissioned an ophthalmic technology assessment report in 2012 to review the published literature pertaining to the use of wide-angle digital photography for ROP screening.[45] The authors reviewed 82 studies, of which 10 met inclusion criteria and were rated as level 1 evidence (independent masked comparison to simultaneous comparison with BIO)[22-25,27] or level 3 evidence (BIO later in the infants course or only infants with ROP).[32,43,45,46] The report found that telemedicine has high diagnostic accuracy for the detection of clinically significant ROP and that the sensitivity for detection of TW-ROP (ETROP type 1 or worse) across all studies was 100%. Taken together, these studies reported the diagnostic accuracy for the detection of TW-ROP with the following estimates (ranges): specificity 98% (93-100), PPV 85% (55-98), and NPV 100% (96-100).[22-25,27,32,43,45,46] The 5-year study results from the SUNDROP initiative are consistent with these estimates.

TABLE 3

Tabulated Diagnostic Measures for RetCam II Examination for Detecting Treatment-Warranted Retinopathy of Prematurity When Compared With Bedside BIO Performed by an Ophthalmologist

Diagnostic Measure	
Sensitivity	100.0%
Specificity	99.8%
Positive predicative value (PPV)	93.8%
Negative predicative value (NPV)	100.0%

TW-ROP = treatment-warranted retinopathy of prematurity.

TW-ROP was defined as ETROP type 1. Retinal image evaluation (telemedicine) classified 16 infants as having TW-ROP. These infants received binocular BIO at the bedside within 24 hours and their final diagnosis and treatment decisions were determined based on the ophthalmic examination at the bedside. Among the 16 infants diagnosed as TW-ROP by telemedicine, 15 infants were determined to require treatment after ophthalmic examination (gold standard) and were classified as having clinical TW-ROP for computing diagnostic measures. All 15 infants were treated with laser photocoagulation, and none of these infants progressed to macular fold, retinal detachment, or severe vision loss (visual acuity worse than 20/200). The one false-positive diagnosis on telemedicine screening was determined to have ROP, however, it was not severe enough to require treatment, and this infant was followed up with close observation and serial examinations until he spontaneously regressed.

The incidence of TW-ROP in this study (15 of 496, 3.0%) is lower than that reported in other studies and national surveys (4% to 12%).[2,4] At initial glance, it may seem that the SUNDROP population is not as sick as other groups. Closer examination of the cohort, however, demonstrates that this is not the case. The SUNDROP initiative serves a socioeconomically and ethnically diverse population stemming from six different NICUs including private, community, and county hospitals. By and large, this is a sick neonatal population with a mean birth weight and gestational age of the TW-ROP cohort similar to that reported in ETROP and other TW-ROP studies.[4,11,46] Among all infants enrolled in SUNDROP, 24% met WHO extremely low birth weight criteria (< 1,000 g). Thus, the apparent low incidence is likely a result of overreferral for screening. In our study, attending pediatricians and neonatologists are able to refer any infant they deem high risk for screening in accordance with the third AAP/AAO criteria. An unstable clinical course is a subjective criterion and more often than not, sick neonates are screened because the equipment is easily accessible and physicians would rather err on the side of caution. The indication for screening is not recorded in the SUNDROP database, and

the screening specialist does not decline screening for any infant referred by the pediatrics team. Therefore, the seemingly low incidence in this population is likely secondary to a watering down of the denominator (total screening population) rather than an indication that the population screened is less sick than others have reported.

There are limitations that must be considered when interpreting the results of this study. The SUNDROP initiative aims to detect disease that modifies treatment and thus only reports TW-ROP. Studies have demonstrated that although there is good agreement between retina specialists about TW-ROP on telemedicine images, agreement is not perfect.[47] Further, a single specialist performed all image interpretation, bedside BIO exams, and treatment, which may introduce bias into the study results.

The barriers to implementation and replication of programs such as the SUNDROP initiative should not be underestimated. The referral center or the nurseries must front capital to purchase a RetCam. The transition from a physician screening at the bedside to a nurse with a camera can be difficult for both health care staff and parents. Our team was able to develop strong community ties and explain the long-term benefits of telemedicine screening for ROP, but this required a trusting and amicable relationship with the hospital administration. The initiative required development of secure, encrypted, HIPAA-compliant electronic transmission systems that are able to reliably and promptly deliver retinal images. A key aspect of remote screening programs is communicating with the multidisciplinary team and clearly delineating the roles and responsibilities of every nurse, pediatrician, administrator, and ophthalmologist. These contracts varied by nursery and required regular meetings to ensure that every high-risk infant was screened and monitored in the pediatric ophthalmology clinic. Finally, for parents and health care staff to feel comfortable with this initiative, the protocol director needed to be available around the clock, interpreting multiple images every day without exception, and willing to travel to the bedside regardless of distance should any infant have a TW-ROP diagnosis on retinal photography.

In our experience, NICU nurses are ideal photographers. They are diligent, detail-oriented, and enthusiastic about being more involved in patient care. The majority of nurses felt comfortable taking images after one or two training sessions. There were occasional instances in which nurses were asked to re-image the retina because the images were not adequate for evaluation; however, most screenings were completed in one session with a median of 12.2 images per examination (goal of six images per eye). Overall, the nursing and health care staff at each nursery worked hard to ensure timely communication of information and cooperate with physician availability for bedside BIO examinations.

The SUNDROP initiative was able to successfully implement two new NICU nurseries since the last published update. The initial high-capital investment in the RetCam II purchase was accepted by new hospitals in light of the published SUNDROP results,[29-33] favorable local reputation of the SUNDROP staff, cost-effectiveness of ROP screening with telemedicine, and the ability to maintain NICU certification. In order to remain accredited, NICU nurseries must offer access to an ophthalmologist trained to screen for ROP, and the two new nurseries were able to meet this mandatory criterion because of their enrollment in the SUNDROP initiative.

Despite some limitations and challenges, the SUNDROP study was successful in meeting its initial goal of delivering quaternary care to all enrolled infants and reducing the burden of visual impairment and blindness in the greater Bay Area. This study's strength is that it represents the true clinical application of remote wide-angle image analysis in screening for ROP without the safety net of simultaneous bedside ophthalmic examination. Confirmation of the practical application of telemedicine in different regions is needed to better understand how this model will need to be adjusted in different practice environments. We now have 5 years of data supporting the use of telemedicine to complement the over-burdened ROP workforce. Telemedicine, as implemented in the SUNDROP initiative, assists the ROP workforce in identifying high-risk infants with vision-threatening disease and ensuring all premature infants have access to quaternary nursery level care, regardless of their birthplace.

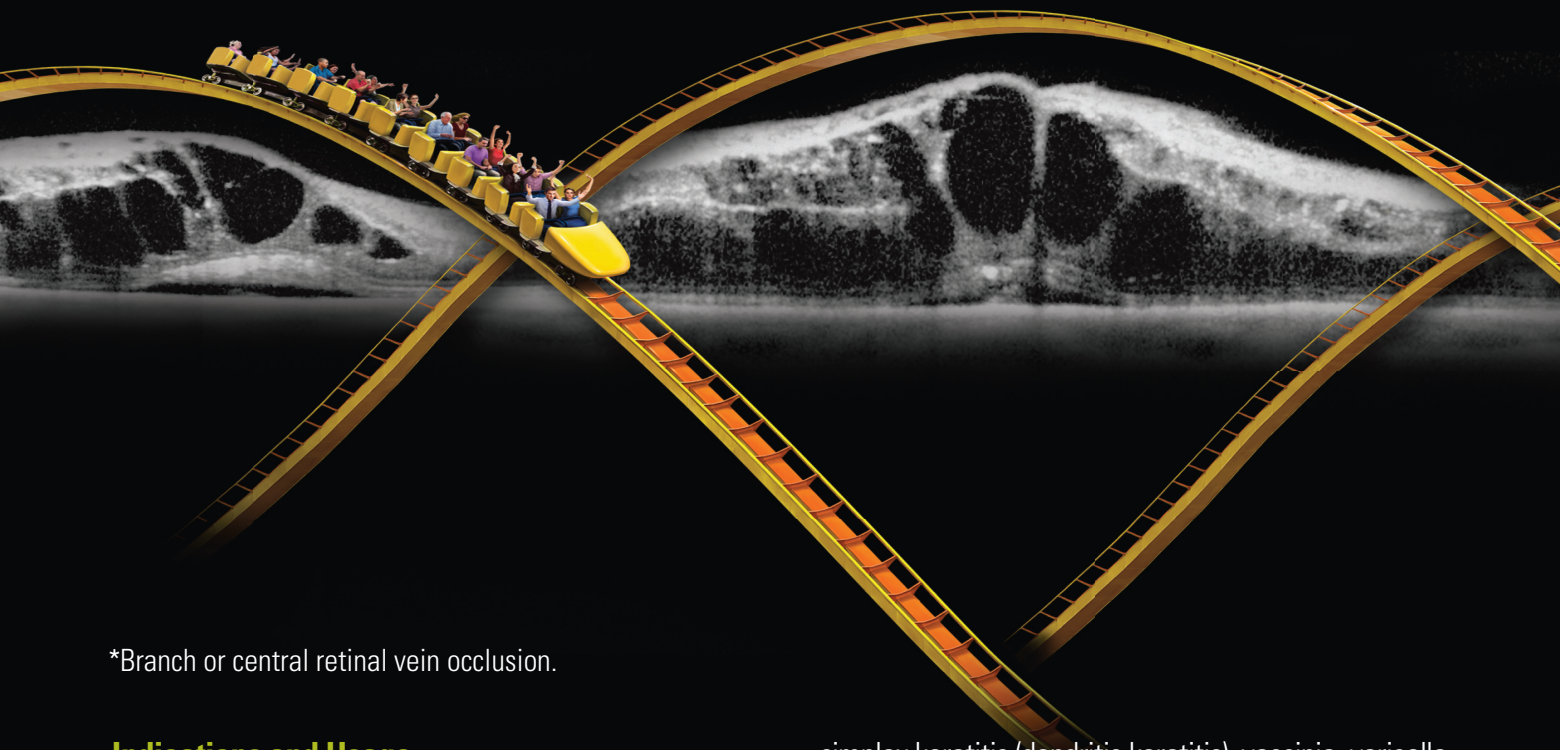
REFERENCES

1. Quiram PA, Capone A Jr. Current understanding and management of retinopathy of prematurity. *Curr Opin Ophthalmol*. 2007;18(3):228-234.
2. Lad EM, Hernandez-Boussard T, Morton JM, Moshfeghi DM. Incidence of retinopathy of prematurity in the United States: 1997 through 2005. *Am J Ophthalmol*. 2009;148(3):451-458.
3. Hartnett ME, Penn JS. Mechanisms and management of retinopathy of prematurity. *N Engl J Med*. 2012;367(26):2515-2526.
4. Good WV, Hardy RJ, Dobson V, et al. The incidence and course of retinopathy of prematurity: findings from the early treatment for retinopathy of prematurity study. *Pediatrics*. 2005;116(1):15-23.
5. Kong L, Fry M, Al-Samarraie M, Gilbert C, Steinkuller PG. An update on progress and the changing epidemiology of causes of childhood blindness worldwide. *J AAPOS*. 2012;16(6):501-507.
6. Foster CGA. Childhood blindness in the context of VISION 2020 The Right to Sight. Bulletin of the World Health Organization.

2001;79. http://www.scielosp.org/scielo.php?script=sci_arttext&pid=S0042-96862001000300011. Accessed March 9, 2013.
7. Zepeda-Romero LC, Barrera-de-Leon JC, Camacho-Choza C, et al. Retinopathy of prematurity as a major cause of severe visual impairment and blindness in children in schools for the blind in Guadalajara city, Mexico. *Br J Ophthalmol*. 2011;95(11):1502-1505.
8. Maida JM, Mathers K, Alley CL. Pediatric ophthalmology in the developing world. *Curr Opin Ophthalmol*. 2008;19(5):403-408.
9. Furtado JM, Lansingh VC, Carter MJ, et al. Causes of blindness and visual impairment in Latin America. *Surv Ophthalmol*. 2012;57(2):149-177.
10. Multicenter trial of cryotherapy for retinopathy of prematurity. Preliminary results. Cryotherapy for Retinopathy of Prematurity Cooperative Group. *Arch Ophthalmol*. 1988;106(4):471-479.
11. Palmer EA, Hardy RJ, Dobson V, et al. 15-year outcomes following threshold retinopathy of prematurity: final results from the multicenter trial of cryotherapy for retinopathy of prematurity. *Arch Ophthalmol*. 2005;123(3):311-318.
12. Laser therapy for retinopathy of prematurity. Laser ROP Study Group. *Arch Ophthalmol*. 1994;112(2):154-156.
13. Hunter DG, Repka MX. Diode laser photocoagulation for threshold retinopathy of prematurity. A randomized study. *Ophthalmology*. 1993;100(2):238-244.
14. Good WV, Early Treatment for Retinopathy of Prematurity Cooperative G. Final results of the Early Treatment for Retinopathy of Prematurity (ETROP) randomized trial. *Trans Am Ophthalmol Soc*. 2004;102:233-248; discussion 248-250.
15. McNamara JA, Tasman W, Brown GC, Federman JL. Laser photocoagulation for stage 3+ retinopathy of prematurity. *Ophthalmology*. 1991;98(5):576-580.
16. Mintz-Hittner HA, Kuffel RR, Jr. Intravitreal injection of bevacizumab (avastin) for treatment of stage 3 retinopathy of prematurity in zone I or posterior zone II. *Retina*. 2008;28(6):831-838.
17. Mintz-Hittner HA, Kennedy KA, Chuang AZ, Group B-RC. Efficacy of intravitreal bevacizumab for stage 3+ retinopathy of prematurity. *N Engl J Med*. 2011;364(7):603-615.
18. Fierson WM, American Academy of Pediatrics Section on O, American Academy of O, American Association for Pediatric O, Strabismus, American Association of Certified O. Screening examination of premature infants for retinopathy of prematurity. *Pediatrics*. 2013;131(1):189-195.
19. Gilbert C. Retinopathy of prematurity: a global perspective of the epidemics, population of babies at risk and implications for control. *Early Hum Dev*. 2008;84(2):77-82.
20. Piechocki KAM. Survey: Physicians being driven awa from ROP treatment. Ocular Surgery News U.S. Edition. 2006. http://www.healio.com/ophthalmology/retina-vitreous/news/print/ocular-surgery-news/%7BEDFA784C-A2AC-4F93-B473-5BE5D07D82CA%7D/Survey-Physicians-being-driven-away-from-ROP-treatment. Accessed March 14, 2013.
21. Jackson KM, Scott KE, Graff Zivin J, et al. Cost-utility analysis of telemedicine and ophthalmoscopy for retinopathy of prematurity management. *Arch Ophthalmol*. 2008;126(4):493-499.
22. Ells AL, Holmes JM, Astle WF, et al. Telemedicine approach to screening for severe retinopathy of prematurity: a pilot study. *Ophthalmology*. 2003;110(11):2113-2117.
23. Chiang MF, Keenan JD, Starren J, et al. Accuracy and reliability of remote retinopathy of prematurity diagnosis. *Arch Ophthalmol*. 2006;124(3):322-327.
24. Wu C, Petersen RA, VanderVeen DK. RetCam imaging for retinopathy of prematurity screening. *J AAPOS*. 2006;10(2):107-111.
25. Photographic Screening for Retinopathy of Prematurity Cooperative G, Balasubramanian M, Capone A, Jr., Hartnett ME, Pignatto S, Trese MT. The Photographic Screening for Retinopathy of Prematurity Study (Photo-ROP): study design and baseline characteristics of enrolled patients. *Retina*. 2006;26(7 Suppl):S4-10.
26. Chiang MF, Wang L, Busuioc M, et al. Telemedical retinopathy of prematurity diagnosis: accuracy, reliability, and image quality. *Arch Ophthalmol*. 2007;125(11):1531-1538.
27. Dhaliwal C, Wright E, Graham C, McIntosh N, Fleck BW. Wide-field digital retinal imaging versus binocular indirect ophthalmoscopy for retinopathy of prematurity screening: a two-observer prospective, randomised comparison. *Br J Ophthalmol*. 2009;93(3):355-359.
28. Dai S, Chow K, Vincent A. Efficacy of wide-field digital retinal imaging for retinopathy of prematurity screening. *Clin Experiment Ophthalmol*. 2011;39(1):23-29.
29. Murakami Y, Jain A, Silva RA, Lad EM, Gandhi J, Moshfeghi DM. Stanford University Network for Diagnosis of Retinopathy of Prematurity (SUNDROP): 12-month experience with telemedicine screening. *Br J Ophthalmol*. 2008;92(11):1456-1460.
30. Silva RA, Murakami Y, Jain A, Gandhi J, Lad EM, Moshfeghi DM. Stanford University Network for Diagnosis of Retinopathy of Prematurity (SUNDROP): 18-month experience with telemedicine screening. *Graefes Arch Clin Exp Ophthalmol*. 2009;247(1):129-136.
31. Murakami Y, Silva RA, Jain A, Lad EM, Gandhi J, Moshfeghi DM. Stanford University Network for Diagnosis of Retinopathy of Prematurity (SUNDROP): 24-month experience with telemedicine screening. *Acta Ophthalmol*. 2010;88(3):317-322.
32. Silva RA, Murakami Y, Lad EM, Moshfeghi DM. Stanford University network for diagnosis of retinopathy of prematurity (SUNDROP): 36-month experience with telemedicine screening. *Ophthalmic Surg Lasers Imaging*. 2011;42(1):12-19.
33. Fijalkowski N, Zheng LL, Henderson MT, Wallenstein MB, Leng T, Moshfeghi DM. Stanford University Network for Diagnosis of Retinopathy of Prematurity (SUNDROP): Four-years of Screening with Telemedicine. *Current Eye Res*. 2013;38(2):283-291.
34. Section on Ophthalmology American Academy of P, American Academy of O, American Association for Pediatric O, Strabismus. Screening examination of premature infants for retinopathy of prematurity. *Pediatrics*. 2006;117(2):572-576.
35. Obeid JS, McGraw CA, Minor BL, et al. Procurement of shared data instruments for Research Electronic Data Capture (REDCap). *J Biomed Inform*. 2013;46(2):259-265.
36. International Committee for the Classification of Retinopathy of P. The International Classification of Retinopathy of Prematurity revisited. *Arch Ophthalmol*. 2005;123(7):991-999.
37. Martin JA HB, Hamilton BE, Sutton PD, Ventura SJ, Mathews TJ, Osterman MJ. Births: Final data for 2008. *Natl Vital Stat Rep*. 2010;59(8):3-71.
38. Richter GM, Sun G, Lee TC, et al. Speed of telemedicine vs ophthalmoscopy for retinopathy of prematurity diagnosis. *Am J Ophthalmol*. 2009;148(1):136-142 e132.
39. Mukherjee AN, Watts P, Al-Madfai H, Manoj B, Roberts D. Impact of retinopathy of prematurity screening examination on cardiorespiratory indices: a comparison of indirect ophthalmoscopy and retcam imaging. *Ophthalmology*. 2006;113(9):1547-1552.
40. Sanchez CR, Silva PS, Cavallerano JD, Aiello LP, Aiello LM. Ocular telemedicine for diabetic retinopathy and the Joslin Vision Network. *Semin Ophthalmol*. 2010;25(5-6):218-224.
41. Kemper AR, Wallace DK, Quinn GE. Systematic review of digital imaging screening strategies for retinopathy of prematurity. *Pediatrics*. 2008;122(4):825-830.
42. Roth DB, Morales D, Feuer WJ, Hess D, Johnson RA, Flynn JT. Screening for retinopathy of prematurity employing the retcam 120: sensitivity and specificity. *Arch Ophthalmol*. 2001;119(2):268-272.
43. Schwartz SD, Harrison SA, Ferrone PJ, Trese MT. Telemedical evaluation and management of retinopathy of prematurity using a fiberoptic digital fundus camera. *Ophthalmology*. 2000;107(1):25-28.
44. Yen KG, Hess D, Burke B, Johnson RA, Feuer WJ, Flynn JT. Telephotoscreening to detect retinopathy of prematurity: preliminary study of the optimum time to employ digital fundus camera imaging to detect ROP. *J AAPOS*. 2002;6(2):64-70.
45. Chiang MF, Melia M, Buffenn AN, et al. Detection of clinically significant retinopathy of prematurity using wide-angle digital retinal photography: a report by the American Academy of Ophthalmology. *Ophthalmology*. 2012;119(6):1272-1280.
46. Lorenz B, Spasovska K, Elflein H, Schneider N. Wide-field digital imaging based telemedicine for screening for acute retinopathy of prematurity (ROP). Six-year results of a multicentre field study. *Graefes Arch Clin Exp Ophthalmol*. 2009;247(9):1251-1262.
47. Scott KE, Kim DY, Wang L, et al. Telemedical diagnosis of retinopathy of prematurity intraphysician agreement between ophthalmoscopic examination and image-based interpretation. *Ophthalmology*. 2008;115(7):1222-1228 e3.

*For macular edema following RVO**

Less "here we go again."



*Branch or central retinal vein occlusion.

Indications and Usage

Retinal Vein Occlusion: OZURDEX® (dexamethasone intravitreal implant) is a corticosteroid indicated for the treatment of macular edema following branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO).

Posterior Segment Uveitis: OZURDEX® is indicated for the treatment of noninfectious uveitis affecting the posterior segment of the eye.

Dosage and Administration

FOR OPHTHALMIC INTRAVITREAL INJECTION ONLY. The intravitreal injection procedure should be carried out under controlled aseptic conditions. Following the intravitreal injection, patients should be monitored for elevation in intraocular pressure and for endophthalmitis. Patients should be instructed to report any symptoms suggestive of endophthalmitis without delay.

IMPORTANT SAFETY INFORMATION

Contraindications

Ocular or Periocular Infections: OZURDEX® (dexamethasone intravitreal implant) is contraindicated in patients with active or suspected ocular or periocular infections including most viral diseases of the cornea and conjunctiva, including active epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, mycobacterial infections, and fungal diseases.

Advanced Glaucoma: OZURDEX® (dexamethasone intravitreal implant) is contraindicated in patients with advanced glaucoma.

Aphakic Eyes with Rupture of the Posterior Lens Capsule: OZURDEX® is contraindicated in patients who have aphakic eyes with rupture of the posterior lens capsule.

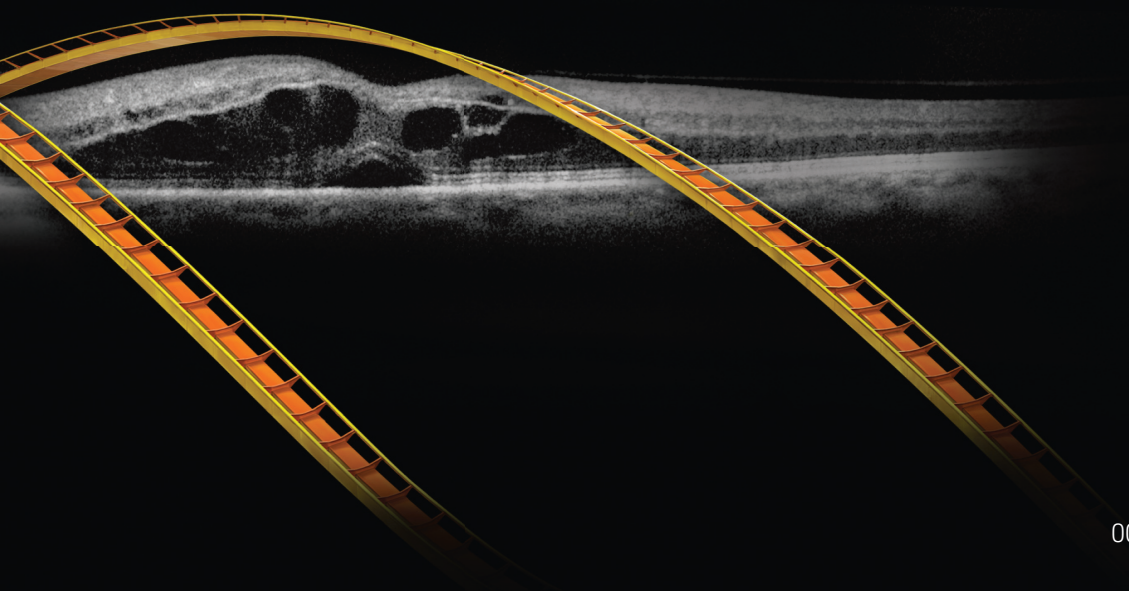
ACIOL and Rupture of the Posterior Lens Capsule: OZURDEX® is contraindicated in eyes with ACIOL (Anterior Chamber Intraocular Lens) and rupture of the posterior lens capsule.

Hypersensitivity: OZURDEX® is contraindicated in patients with known hypersensitivity to any components of this product.

Warnings and Precautions

Intravitreal Injection-related Effects: Intravitreal injections have been associated with endophthalmitis, eye inflammation, increased intraocular pressure, and retinal detachments. Patients should be monitored regularly following the injection.

- When OCT reveals macular edema that persists or recurs in RVO, consider inflammation
- Inject OZURDEX® (dexamethasone intravitreal implant) to help improve visual acuity[1]



OCT images ©2013, Dr. Szilárd Kiss.

IMPORTANT SAFETY INFORMATION (continued)

Warnings and Precautions (continued)

Potential Steroid-related Effects: Use of corticosteroids may produce posterior subcapsular cataracts, increased intraocular pressure, glaucoma, and may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses. Corticosteroids should be used cautiously in patients with a history of ocular herpes simplex.

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

The most common ocular adverse reactions reported by greater than 2% of patients in the first 6 months following injection of OZURDEX® for retinal vein occlusion and posterior segment uveitis include: intraocular pressure increased (25%), conjunctival hemorrhage (22%), eye pain (8%), conjunctival hyperemia (7%), ocular hypertension (5%), cataract (5%), vitreous detachment (2%), and headache (4%).

Increased IOP with OZURDEX® peaked at approximately week 8. During the initial treatment period, 1% (3/421) of the patients who received OZURDEX® required surgical procedures for management of elevated IOP.

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

Ozurdex®

(dexamethasone intravitreal implant) 0.7 mg

Keep the Opportunity in Sight

ALLERGAN Retina

1. OZURDEX® Prescribing Information.

OZURDEX®

(dexamethasone intravitreal implant) 0.7 mg

Brief Summary—Please see the OZURDEX® package insert for full Prescribing Information.

INDICATIONS AND USAGE

Retinal Vein Occlusion: OZURDEX® (dexamethasone intravitreal implant) is a corticosteroid indicated for the treatment of macular edema following branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO).

Posterior Segment Uveitis: OZURDEX® is indicated for the treatment of non-infectious uveitis affecting the posterior segment of the eye.

CONTRAINDICATIONS

Ocular or Periocular Infections: OZURDEX® (dexamethasone intravitreal implant) is contraindicated in patients with active or suspected ocular or periocular infections including most viral diseases of the cornea and conjunctiva, including active epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, mycobacterial infections, and fungal diseases.

Advanced Glaucoma: OZURDEX® is contraindicated in patients with advanced glaucoma.

Aphakic Eyes with Rupture of the Posterior Lens Capsule: OZURDEX® is contraindicated in patients who have aphakic eyes with rupture of the posterior lens capsule.

ACIOL and Rupture of the Posterior Lens Capsule: OZURDEX® is contraindicated in eyes with ACIOL (Anterior Chamber Intraocular Lens) and rupture of the posterior lens capsule.

Hypersensitivity: OZURDEX® is contraindicated in patients with known hypersensitivity to any components of this product.

WARNINGS AND PRECAUTIONS

Intravitreal Injection-related Effects: Intravitreal injections have been associated with endophthalmitis, eye inflammation, increased intraocular pressure, and retinal detachments.

Patients should be monitored regularly following the injection *[see Patient Counseling Information].*

Potential Steroid-related Effects: Use of corticosteroids may produce posterior subcapsular cataracts, increased intraocular pressure, glaucoma, and may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses.

Corticosteroids should be used cautiously in patients with a history of ocular herpes simplex.

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

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

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

The following information is based on the combined clinical trial results from 3 initial, randomized, 6-month, sham-controlled studies (2 for retinal vein occlusion and 1 for posterior segment uveitis):

Adverse Reactions Reported by Greater than 2% of Patients in the First Six Months

MedDRA Term	OZURDEX® N=497 (%)	Sham N=498 (%)
Intraocular pressure increased	125 (25%)	10 (2%)
Conjunctival hemorrhage	108 (22%)	79 (16%)
Eye pain	40 (8%)	26 (5%)
Conjunctival hyperemia	33 (7%)	27 (5%)
Ocular hypertension	23 (5%)	3 (1%)

Adverse Reactions Reported by Greater than 2% of Patients in the First Six Months (continued)

MedDRA Term	OZURDEX® N=497 (%)	Sham N=498 (%)
Cataract	24 (5%)	10 (2%)
Vitreous detachment	12 (2%)	8 (2%)
Headache	19 (4%)	12 (2%)

Increased IOP with OZURDEX® (dexamethasone intravitreal implant) peaked at approximately week 8. During the initial treatment period, 1% (3/421) of the patients who received OZURDEX® required surgical procedures for management of elevated IOP.

Following a second injection of OZURDEX® in cases where a second injection was indicated, the overall incidence of cataracts was higher after 1 year.

USE IN SPECIFIC POPULATIONS

Pregnancy

Teratogenic Effects: Pregnancy Category C: Topical dexamethasone has been shown to be teratogenic in mice producing fetal resorptions and cleft palate. In the rabbit, dexamethasone produced fetal resorptions and multiple abnormalities involving the head, ears, limbs, palate, etc. Pregnant rhesus monkeys treated with dexamethasone sodium phosphate intramuscularly at 1 mg/kg/day every other day for 28 days or at 10 mg/kg/day once or every other day at 3 or 5 days between gestation days 23 and 49 had fetuses with minor cranial abnormalities. A 1 mg/kg/dose in pregnant rhesus monkeys would be approximately 85 times higher than an OZURDEX® injection in humans (assuming 60 kg body weight).

There are no adequate and well-controlled studies in pregnant women. OZURDEX® (dexamethasone intravitreal implant) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether ocular administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. Caution should be exercised when corticosteroids are administered to a nursing woman.

Pediatric Use: Safety and effectiveness of OZURDEX® in pediatric patients have not been established.

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

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

No adequate studies in animals have been conducted to determine whether OZURDEX® (dexamethasone intravitreal implant) has the potential for carcinogenesis.

Although no adequate studies have been conducted to determine the mutagenic potential of OZURDEX®, dexamethasone has been shown to have no mutagenic effects in bacterial and mammalian cells *in vitro* or in the *in vivo* mouse micronucleus test.

PATIENT COUNSELING INFORMATION

In the days following intravitreal injection of OZURDEX®, patients are at risk for potential complications including in particular, but not limited to, the development of endophthalmitis or elevated intraocular pressure. If the eye becomes red, sensitive to light, painful, or develops a change in vision, the patient should seek immediate care from an ophthalmologist.

Patients may experience temporary visual blurring after receiving an intravitreal injection. They should not drive or use machines until this has resolved.

Rx only

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