Pivotal Trials in Ophthalmology

A Guide for Trainees

Jenny C. Dohlman
Alice C. Lorch
Editors

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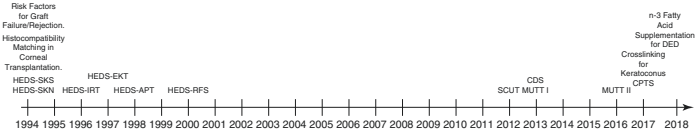
Introduction

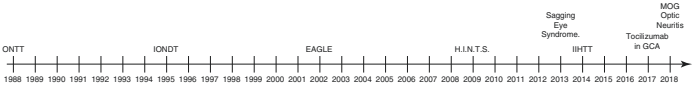
Starting in residency and beyond, it is expected that ophthalmologists are well versed in the landmark clinical trials and research studies that have shaped the way in which ophthalmology is practiced today. *Pivotal Trials in Ophthalmology: A Guide for Trainees* is an introductory text designed to give trainees a comprehensive and accessible overview of important research trials across the subspecialties of ophthalmology and may also serve as a useful reference for practicing ophthalmologists, optometrists, and researchers in the field. Each chapter focuses on a different subspecialty and is authored by a chosen expert in the field, along with one or more trainees. Together, the authors of each chapter selected up to ten studies with which they feel every trainee and practicing ophthalmologist should be familiar; these are summarized and laid out in chronological order. Our hope is that by having trainees work closely with expert clinicians to produce this text, we have produced a resource that is detailed and accurate while remaining concise and accessible when questions arise in clinical practice, in studying for board examinations, or in designing future clinical trials. By including illustrated timelines of the sequence of these studies, we hope to demonstrate how studies have built upon prior knowledge and to depict visually how developments across subspecialties relate to one another.

Glaucoma

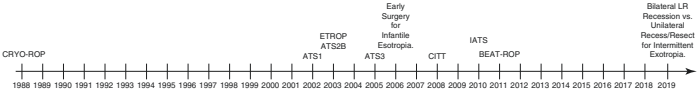
Cornea



Neuro-Ophthalmology

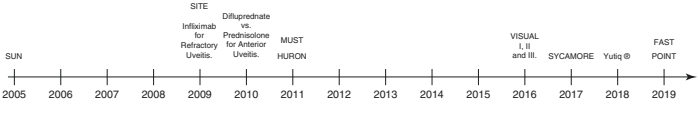


Pediatric Ophthalmology and Strabismus



Retina

Uveitis



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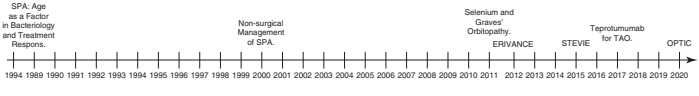
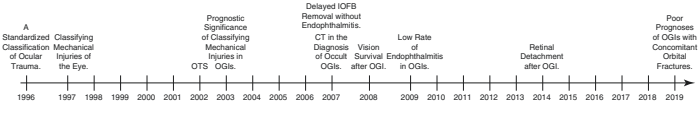


Ocular Trauma



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Chapter 1
Glaucoma

Catherine M. Marando and Lucy Q. Shen

Abstract Over the last 25 years, clinical trials in glaucoma have shaped modern clinical and surgical practice. Glaucoma is well suited to clinical trials given the relative prevalence in the community and the length of follow-up. This chapter briefly summarizes ten key trials that affect how we manage glaucoma today. Early trials explored the natural course of glaucoma and the importance of lowering intraocular pressure in primary open angle glaucoma, normal tension glaucoma, and ocular hypertension. More recent trials investigated the role of laser or filtering surgeries for primary open angle glaucoma and lens extraction for primary angle closure glaucoma.

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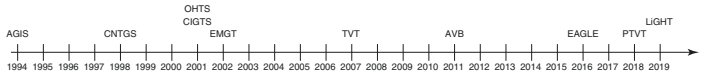

The Advanced Glaucoma Intervention Study (AGIS) – 1994 [1–5]

Purpose

To understand the clinical course after argon laser trabeculoplasty (ALT) and trabeculectomy in patients with advanced open angle glaucoma (OAG) that cannot be controlled on medications alone.

Methods

From 1988 to 1992, investigators at 11 clinical sites in the United States evaluated 789 eyes from 591 patients (56% black and 42% white) between the ages of 35 and 80 years. Patients were included if they had advanced glaucoma on maximum medical therapy and had elevated intraocular pressure (IOP), visual field (VF) defects and/or optic disc rim deterioration. Eyes were randomly assigned to receive one of two treatment sequences: ALT-trabeculectomy-trabeculectomy (ATT) or trabeculectomy-ALT-trabeculectomy (TAT). Subjects would only receive the second or third treatments in the sequence if they demonstrated failure of the first treatment based on elevated IOP, visual field progression and/or optic disc rim deterioration. Visual acuity, visual fields and IOP were assessed three and six months after enrollment, and every six months thereafter. The primary outcome measures were changes in visual acuity and visual fields [1].

Results

Data were reported over a 10-year follow-up period. Black patients had less visual field loss with the ATT sequence compared to the TAT sequence at four years, but did not show this difference for the following six years. However, black patients had significantly better visual acuity with the ATT sequence compared to the TAT sequence throughout the 10-year duration. On the other hand, white patients had less visual field

loss at 10 years with the TAT sequence compared to the ATT sequence. White patients had better visual acuity with the ATT sequence compared to the TAT sequence for the initial four years, but this was confounded by cataract formation [2]. Average IOP greater than 17.5 mmHg was associated with increased progression of visual field as compared to IOP less than 14 mmHg after six years of follow-up time [3].

Trabeculectomy, whether as the first or second intervention, increased risk for cataract formation by 78% [4]. Cataract formation did not alter the study conclusions recommending ATT in black patients and TAT in white patients [5].

In both black and white patients, the need for a second intervention was less in the TAT group (32% black; 18% white) as compared to the ATT group (50% both races). Both black and white patients required fewer topical glaucoma medications in the TAT group compared to ATT group [2].

Key Points

- Based on visual field and visual acuity results, the ATT sequence was recommended for black patients and the TAT sequence was recommended for white patients for treatment of medically uncontrolled glaucoma.
- At the time of the trial, the only topical therapies available were miotics, beta-blockers, epinephrine, and carbonic anhydrase inhibitors. ALT was offered because selective laser trabeculoplasty (SLT) was not yet available.
- Trabeculectomy increased the risk for developing a visually significant cataract.
- Elevated IOP, even less than 20 mmHg, was associated with increased progression of visual field defects. This led to the recommendation to further lower IOP for patients with advanced glaucoma.

Collaborative Normal-Tension Glaucoma Study (CNTGS) – 1998 [6–7]

Purpose

To evaluate the role of intraocular pressure (IOP) in normal tension glaucoma (NTG).

Methods

This randomized clinical trial conducted at 24 centers enrolled 230 patients with unilateral or bilateral NTG as evidenced by glaucomatous cupping of the disc, visual field loss, and a median IOP of 20 mmHg or less in 10 baseline measurements (following a four week washout period of any topical glaucoma medications). Patients were excluded if the pressure was ever recorded as greater than 24 mmHg. Subjects with a visual field defect threatening central fixation were immediately randomized, and all other patients were observed before randomization until they progressed either by visual field or optic disc criteria. Patients were then randomized to either observation or a 30% reduction in IOP by medical or surgical intervention. Beta-blockers and alpha agonists were not used due to the potential for confounding systemic effects. Two physicians independently confirmed optic disc progression based on disc photos. Visual field (VF) progression was based on defined criteria and the analysis was conducted both on defined VF endpoints and in a four-of-five analysis where progression needed to be confirmed on four-of-five follow-up field tests. Patients were observed over 7 years of follow-up. Once progression was detected by optic disc and/or VF criteria, the subject could be treated at the primary clinician's discretion regardless of treatment arm [6].

Results

One hundred and forty-five subjects met criteria for randomization either by showing progression or having a threat to central fixation. Forty-six percent of patients were randomized to treatment and 56% were untreated controls. A threat to central fixation was present in 63% of untreated and 64% of treated patients. However, despite randomization, the baseline IOP was significantly higher in the treatment group than the control group (16.9 vs. 16.1 mmHg, $p = 0.02$). Using disc change or four-of-five visual field change as the combined endpoint, 30% of the untreated controls showed progression versus 18% of the treated patients. Over the 7-year follow-up period, the median survival time from randomization to progression was 2255 days for the treatment group

versus 1837 days for the control group (p = 0.01). To account for increased cataract formation associated with filtering surgery, patients with visually significant cataracts were removed from the analysis. However, this disproportionately removed advanced glaucoma patients from the treatment arm [6].

Adjusted for other variables, the risk ratio for having progression in NTG patients based on visual field was 2.58 (p = 0.0058) for migraine, 2.72 (p = 0.0036) for disc hemorrhage, and 1.85 (p = 0.0622) for female gender [7].

Key Points

- This study demonstrated the need for IOP lowering in normal tension glaucoma to prevent progression.
- However, this was a controversial study given significant differences in baseline IOP between the treatment and observational arms, removal of patients with cataracts from the analysis, and other adjustments.
- Over 7 years of follow-up, progression still occurred in 18% of patients despite treatment achieving a 30% reduction in IOP. Migraine, disc hemorrhage, and female gender were risk factors for rapid visual field progression in patients with NTG.

The Collaborative Initial Glaucoma Treatment Study (CIGTS) – 2001 [8–11]

Purpose

To determine if patients with newly diagnosed open angle glaucoma (primary, pigmentary, or pseudoexfoliative) are managed better with medications or immediate filtration surgery.

Methods

From 1993 to 1997, investigators at 14 clinical sites in the United States enrolled 607 patients aged 25–75 years with newly diagnosed open angle glaucoma. Patients were randomized to treatment with glaucoma medications (n = 307) or

trabeculectomy (n = 300). A target intraocular pressure (IOP) was established using a novel formula that takes into account baseline IOP and visual field (VF) score. Patients were followed at six-month intervals for up to 10 years. If a patient experienced treatment failure (based on specific IOP and VF criteria), then there was a crossover in treatment group. Specifically, failure of medical therapy would progress first to ALT and then to trabeculectomy. In the trabeculectomy arm, failure would progress to ALT and then medications. The primary outcome measure was progressive visual field loss evaluated by changes in mean deviation (MD). A substantial VF loss was defined as a decrease in MD of ≥3 dB. Secondary outcomes included visual acuity and IOP [8].

Results

By eight years, 21.3% of the surgery group and 25.5% of the medicine group showed worsening in VF from baseline. Subjects with worse MD at baseline, such as −10 dB, had better VF outcomes at five to nine years when treated initially with surgery as compared to medicine. Diabetic patients (n = 102) experienced less VF loss over the nine year follow-up period when treated with medical therapy first compared to trabeculectomy. IOP fluctuation over six baseline measurements was predictive of greater VF loss over the follow-up period. Specifically, a range >8.5 mmHg had 96% greater odds of substantial VF loss [9]. Interestingly, at 5 years, 13.9% of patients showed an improvement in VF of ≥3 dB from baseline, which was associated with lower mean IOP, lower minimum IOP and lower sustained levels of IOP at follow-up [10].

Of the patients in the medication arm, self-reported compliance correlated negatively with VF progression, such that those who reported missing medications at two thirds of follow-up visits had approximately 3.5 times the amount of visual field loss compared to those with perfect compliance at eight years [11].

Key Points

- Initial treatment with either surgery or medicine, to achieve a target IOP calculated from baseline IOP and VF severity, produced similar rates of VF loss after eight years.

- At the initiation of the trial, effective medical treatments were limited and trabeculectomy was performed without antimetabolites.
- For patients with moderate to advanced glaucoma at diagnosis, indicated by a lower mean deviation, initial surgery produced better long-term VF outcomes than medical treatment.
- Diabetic patients did better with initial medical therapy rather than surgical treatment.
- Baseline IOP fluctuation was correlated with VF progression at follow-up.
- Better self-reported eye drop compliance was correlated with better VF outcomes.

Ocular Hypertension Treatment Study (OHTS) – 2001 [12–16]

Purpose

To evaluate the safety and efficacy of topical intraocular pressure (IOP) lowering medications in preventing glaucomatous damage in patients with ocular hypertension (OHTN).

Methods

This randomized controlled clinical trial was conducted at 22 centers and enrolled 1636 patients from 1994 through 1996. Subjects aged 40–80 years were included if the IOP was 24–32 mmHg in one eye and 21–32 mmHg in the fellow eye with normal gonioscopy, normal and reliable visual fields (VFs) and normal optic disc photos, which were graded by certified readers. Subjects were randomized to either close observation or topical pressure lowering medications, which were escalated in a stepwise fashion to reach a goal IOP of 20% below baseline and not exceeding 24 mmHg. The choice of medications was at the discretion of the treating physician. Patients were followed every six months with VFs and annual disc photos for a median of 72 months. VFs were considered abnormal if $p < 0.05$ for the pattern standard deviation or the glaucoma hemifield test was outside normal limits confirmed

on three separate VF tests. A masked 'Endpoint Committee' reviewed the history, examination, and results of the VF and disc photos to determine if the patient had converted from OHTN to POAG [12].

Results

Of the 1636 patients randomized, 56.9% were female, 25% were African American, and the mean baseline IOP was 24.9 mmHg. Of those in the medication group, 39.7% required two or more medications and 9.3% required three or more medications. At five years, the cumulative probability of developing POAG was 4.4% in the medication group and 9.5% in the observation group. In the medication group, 6.9% of African American patients developed POAG versus 3.6% of the other participants [13]. Five baseline factors significantly increased risk of conversion from OHT to POAG: older age, higher IOP, thinner central corneal thickness (CCT), larger cup-disc ratio, and higher pattern standard deviation [14].

Follow-up VF testing did not confirm original abnormalities in 85.9% of originally abnormal and reliable VFs, and in fact 66.4% were interpreted as within normal limits on follow-up testing [15].

OHTS phase 2 was an extension study that followed patients over 13 years. Patients initially assigned to treatment remained on treatment and those in the observation group for the first 7.5 years were then started on treatment for the remaining 5.5 years. The cumulative incidence of developing POAG over 13 years was significantly higher in the initial observation group than the initial treatment group (22% vs. 16%, $p = 0.009$), though the slope of the survival curve was unchanged by delaying treatment [16].

Key Points

- The five-year risk of developing POAG from ocular hypertension was reduced ~50% with topical medications.
- However, the risk of conversion to glaucoma remained low in both groups at five years (4.4% treated vs. 9.5% untreated).

- A five-factor model with age, IOP, CCT, cup-disc ratio, and pattern standard deviation can assess risk for developing glaucoma in patients with ocular hypertension.
- 66.4% of originally abnormal VFs were within normal limits on follow-up testing.

Early Manifest Glaucoma Trial (EMGT) – 2002 [17–20]

Purpose

To evaluate the effectiveness of reducing intraocular pressure (IOP) in early, previously untreated, open angle glaucoma and describe the natural course of newly diagnosed glaucoma without treatment.

Methods

A population-based screening of 44,000 people in two major cities in Sweden from 1992 to 1997 identified 255 subjects aged 50–80 years with newly diagnosed and previously untreated early open-angle glaucoma. They excluded subjects with advanced visual field (VF) defects (mean deviation (MD) ≤ -16 dB or threat to central fixation), mean IOP greater than 30 mmHg, visual acuity less than 0.5, or any condition precluding reliable disc photos or visual fields. Subjects were randomly assigned to receive either argon laser trabeculoplasty (ALT) plus topical betaxolol 0.5% two times daily (n = 129) or no initial treatment (n = 126). Subjects were followed every three months with visual field testing and every six months with disc photos for at least four years. Progression was defined as VF progression in three consecutive tests or by optic disc changes [17].

Results

Subjects were followed for a mean of almost 6 years with excellent retention (six patients lost to follow up for reasons other than death). Treatment reduced IOP by approximately

25%, and this effect was larger for subjects with baseline IOPs of 21 mmHg or greater [18]. Disease progression was much more commonly detected by visual field changes (79–100% of all progression depending on disease severity) rather than by optic disc photos [19]. Sixty-two percent of subjects in the control group showed disease progression, which was significantly higher than 45% in the treatment group ($p = 0.007$). IOP reduction was strongly correlated with slowed disease progression. For every 1 mmHg reduction in IOP, the risk of progression decreased by an estimated 10%. The time to progression was 48 months in the controls and 66 months in the treated subjects [18].

Greater risk of progression was independently associated with older age (above the median study age of 68 years), higher baseline IOP, worse baseline mean deviation, exfoliation, disc hemorrhage, and bilateral disease. Of these risk factors, exfoliation conferred the highest correlation with disease progression (hazard ratio 2.31). Eighty-three percent of all patients with exfoliation showed disease progression. Central corneal thickness was not correlated with progression [20].

Treatment had a modest effect on nuclear cataract formation ($p = 0.002$), though there was no significant difference in acuity at four years. Treatment rarely induced systemic side effects (six patients in the treatment group vs. one patient in the control group), including asthma, bradycardia and depression [19].

Key Points

- IOP lowering with ALT and betaxolol halved the risk of progression in patients with early open angle glaucoma compared to observation alone (hazard ratio = 0.50).
- A 1 mmHg reduction in IOP decreased the risk of progression by 10%.
- Some patients still progressed with the treatment regimen, while a small percentage in the observation arm did not progress over a mean follow-up of six years.

- Older age, higher IOP, worse MD, disc hemorrhage and bilateral disease were correlated with disease progression. Exfoliation was most strongly correlated with progression.

The Tube Versus Trabeculectomy Study (TVT) – 2007 [21–23]

Purpose

To compare the safety and efficacy of nonvalved tube shunt surgery to trabeculectomy with mitomycin C (MMC) in patients with previous filtering surgery, cataract surgery, or both.

Methods

This randomized clinical trial conducted at 17 clinical centers enrolled 212 patients between 1999 and 2004. Patients aged 18–85 with inadequately controlled glaucoma with intraocular pressure (IOP) between 18 and 40 mmHg who had previous trabeculectomy, cataract surgery, or both were included in this study. Patients were stratified based on clinical center and type of previous intraocular surgery, and then randomized to receive a 350-mm^2 Baerveldt glaucoma implant or trabeculectomy with mitomycin C (MMC) at 0.4 mg/mL for four minutes. Follow-up examinations were done at set intervals up to 5 years. The primary outcome measures were IOP and rate of complications; the secondary outcome measure was treatment failure. Failure was defined as IOP >21 mmHg or less than 20% reduction from baseline, IOP ≤5 mm Hg, reoperation for glaucoma or loss of light perception vision [21].

Results

The average study age was 71 years, 53% of subjects were female, 45% were white, and 39% were black. At follow-up years one and two, the tube group required significantly more glaucoma medications than the trabeculectomy group, how-

ever there was no significance for the following three years. At five years, the Baerveldt implant produced a 41.4% reduction in IOP with mean IOP of 14.4 mmHg and the trabeculectomy with MMC produced a 49.5% reduction in IOP with mean IOP of 12.6 mmHg, although the difference was not statistically significant [22].

Early post-operative complications were significantly higher ($p = 0.012$) in the trabeculectomy group (37%) than the tube group (21%). The rate of choroidal effusion was very similar between groups (13% trabeculectomy, 14% tube). The trabeculectomy group had higher rates of wound leak (11% trabeculectomy, 1% tube) and hyphema (8% trabeculectomy, 2% tube). At five years, late post-operative complications were similar between groups (36% trabeculectomy, 34% tube) [23].

There were more post-operative interventions in the trabeculectomy group (70%) than the tube group (25%). The most common post-operative procedures in the trabeculectomy group were laser suture lysis (55%), 5-FU injection (25%), and needling (13%). Four patients in the tube group and zero patients in the trabeculectomy group required anterior chamber reformation. The total number of reoperations for complications was similar between groups (18% trabeculectomy, 22% tube) [23].

Cumulative probability of treatment failure was significantly higher in the trabeculectomy group (46.9%) than the tube group (29.8%). The most notable difference in cause of treatment failure between groups was persistent hypotony (31% trabeculectomy, 13% tube), which was defined as IOP $\leq$5 mmHg on two consecutive follow-up visits after three months [22].

Key Points

- Both nonvalved tube surgery and trabeculectomy effectively lowered IOP in patients with previous intraocular surgery.
- Early post-operative complications were more likely in the trabeculectomy group than the tube group.

- Late post-operative complications were similar between groups.
- Treatment failure occurred more frequently with trabeculectomy, in large part due to persistent hypotony.

The Ahmed Versus Baerveldt Study (AVB) – 2011 [24–27]

Purpose

To compare the Ahmed and Baerveldt aqueous drainage devices for the treatment of refractory glaucoma.

Methods

This randomized clinical trial conducted at seven international clinical sites enrolled 238 patients from 2005 to 2009. Patients 18 or older were included if they had inadequately controlled glaucoma despite medical, laser and/or surgical therapy and were planned to receive an aqueous drainage device. Patients were randomized to an Ahmed-FP7 valve or a Baerveldt-350 implant. Patients were followed postoperatively at defined intervals up to five years. The primary outcome was failure, defined as follows: intraocular pressure (IOP) <5 mmHg, IOP >18 mmHg or IOP reduction <20% from baseline (at two consecutive visits at or after three months), a vision threatening complication, need for additional glaucoma procedure, or visual acuity (VA) of no light perception (NLP) [24].

Results

124 patients were randomized to the Ahmed valve and 114 patients to the Baerveldt implant. The baseline characteristics were uniform for each group, except that there were significantly more women in the Baerveldt group ($p = 0.011$) [25].

Over five years, failure occurred significantly more often in the Ahmed group than the Baerveldt group (53.2% vs. 40%, $p = 0.037$). The most common reason was IOP >18 mmHg,

which occurred in 56% of the Ahmed group and 26% of the Baerveldt group. Hypotony resulted in 4% of failures in the Baerveldt group, but none in the Ahmed group ($p = 0.02$) [26]. Both groups had similar IOP within nine months of surgery [25], but subsequently the mean IOP was significantly lower in the Baerveldt group than the Ahmed group (13.6 mmHg vs. 16.6 mmHg at five years, $p = 0.001$) [26].

The Baerveldt group required significantly fewer medications at all visits from follow-up month two through year five [26]. At three years, 25% of the Ahmed group and 50% of the Baerveldt group required no medications ($p < 0.001$) [27].

In the first year, there were fewer patients with post-operative complications in the Ahmed group (44%) than the Baerveldt group (54%). This difference was not significant at one year and five-year follow-up [25, 26]. Persistent corneal edema was more common in the Baerveldt group ($p = 0.004$) during the first year. At five years, there was no significant difference between groups in the rate of choroidal effusion (13% Ahmed and 16% Baerveldt), motility disorder (5% Ahmed and 2% Baerveldt), or endophthalmitis (1% Ahmed and 0% Baerveldt) [25].

Key Points

- Both the Ahmed and Baerveldt implants were effective in lowering IOP in patients with uncontrolled glaucoma.
- The Baerveldt implant may be better for patients with a low IOP target.
- There was a higher risk of hypotony with the Baerveldt implant than the Ahmed valve.
- When selecting an implant, providers must consider the risks and benefits in each patient individually.

Important Correlate

- The Ahmed Baerveldt Comparison (ABC) study was a similar study with data published in 2011 that also found that patients in the Ahmed group required more medications to maintain target IOP, while the Baerveldt group experienced more serious post-operative complications.

These findings also support the need for patient specific risk-benefit analysis before selecting a tube implant.

Effectiveness of Early Lens Extraction for the Treatment of Primary Angle-Closure Glaucoma (EAGLE) – 2016 [28–29]

Purpose

To evaluate the efficacy, safety and cost-effectiveness of early clear-lens extraction versus laser peripheral iridotomy (LPI) as first-line treatment for primary angle-closure glaucoma (PACG).

Methods

This randomized clinical trial conducted at 30 centers in five countries enrolled 419 patients from 2009 through 2011. Phakic patients aged 50 and older were included if they had newly diagnosed PACG or primary angle closure (PAC) with intraocular pressure (IOP) ≥30 mmHg at diagnosis and at least 180° of angle closure by gonioscopy. Patients were excluded if they had advanced glaucoma (mean deviation (MD) < −15 dB or cup-disc-ratio ≥ 0.9), previously diagnosed or secondary angle closure, symptomatic cataract (such that the treating physician would recommend cataract surgery to improve vision), or previous intraocular laser or incisional surgery. Patients were randomized to either cataract surgery within 60 days (may receive medical therapy while awaiting surgery and after cataract surgery) or immediate LPI followed by escalation of medical treatment. All cataract surgeries were performed by glaucoma specialists. Treatment failure was the need for glaucoma filtering surgery. Primary outcome measures were patient-centered health status (European Quality of Life-5 Dimensions [EQ-5D] questionnaire), IOP, and incremental cost per quality adjusted life year (QALY) [28].

Results

208 patients were assigned to clear-lens extraction and 211 were assigned to laser peripheral iridotomy. The two groups were similar in demographics. Overall, 37% had PAC and 67% had PACG. Thirty-one percent were of Chinese and 69% were of non-Chinese ethnicity [29].

At three years, the clear-lens extraction group had significantly better outcomes than the LPI group for both the EQ-5D score (0.870 vs. 0.838, $p = 0.005$) and IOP (16.6 mmHg vs. 17.9 mmHg, $p = 0.004$). The clear-lens extraction group required fewer glaucoma eye drops at three years than the LPI group (0.4 vs. 1.3, $p < 0.0001$). Only one patient in the clear-lens extraction group required incisional filtering surgery versus seven patients in the LPI group. There was no significant difference in visual field severity between groups at three years. Irreversible loss of >10 ETDRS letters was rare in both groups, occurring in only one patient in the clear-lens extraction group and three patients in the LPI group. The health system costs were higher with clean-lens extraction, however the quality-adjusted life years (QALYs) were also higher, therefore the probability of clear-lens extraction being cost-effective was 0.671–0.776. Adverse events were rare and there were no significant differences between groups, except for intolerance to medications (1.4% clear-lens extraction vs. 4.7% LPI, $p = 0.049$) [29].

Key Points

- In patients over age 50 with PACG or PAC with IOP ≥30 mmHg, clear-lens extraction provided better quality of life and IOP control at three years than standard treatment with LPI first.
- Clear-lens extraction was more cost-effective when compared to LPI for patients with PACG or PAC and IOP elevation.
- Glaucoma specialists should consider clear-lens extraction as a treatment option for this patient population.

The Primary Tube Versus Trabeculectomy Study (PTVT) – 2018 [30–32]

Purpose

To evaluate the safety and efficacy of nonvalved tube shunt surgery versus trabeculectomy with mitomycin C (MMC) in patients with uncontrolled glaucoma and no previous incisional ocular surgery.

Methods

This randomized clinical trial conducted at 16 clinical centers enrolled 242 patients from 2008 through 2015. Patients aged 18–85 were included if their glaucoma was inadequately controlled with medical therapy, intraocular pressure (IOP) ≥18 mmHg and ≤40 mmHg, and they had no history of prior incisional ocular surgery (including cataract surgery) in the study eye. Patients were then randomized to receive either a Baerveldt-350 or a trabeculectomy with MMC (0.4 mg/mL for two minutes). Patients were followed up at defined intervals for five years. The primary outcome measure was failure, defined as IOP >21 mmHg or reduced <20% from baseline, IOP ≤5 mmHg, reoperation for glaucoma, or loss of light perception vision. Patients were censored from analysis after reoperation if additional glaucoma surgery was needed [30].

Results

125 patients received a Baerveldt-350 tube and 117 patients received a trabeculectomy with MMC. There were no significant differences in baseline characteristics between groups and only ~5% of patients had a history of failed glaucoma surgery in the fellow eye [31].

At one year, there was a significantly higher failure rate in the tube group than the trabeculectomy group (20% vs. 8%, $p = 0.02$). In both groups, failure was largely due to inadequate IOP reduction or reoperation for glaucoma. IOP was significantly higher in the tube group than the trabeculectomy group (13.8 mmHg vs. 12.4 mmHg, $p = 0.01$). A significant reduction in medical therapy was seen in both groups compared to baseline [31].

At three years, there was no longer any significant difference in failure rate between groups (39% tube vs. 30% trabeculectomy). However, IOP was still significantly higher after tube surgery than trabeculectomy (14.0 mmHg vs. 12.1 mmHg, $p = 0.008$). The trabeculectomy group required 1.2 medications versus the tube group that required 2.1 medications ($p < 0.001$) [32].

Early postoperative complications within the first month were less common in patients after tube surgery than after trabeculectomy (20% vs. 33%, $p = 0.03$) [30]. There was no significant difference in the percentage of patients with late complications (22% tube vs. 25% trabeculectomy). No significant difference was seen in cataract progression between groups by three years [32].

Key Points

- During the first year of follow-up, there was a significantly higher rate of failure with tube surgery than trabeculectomy for eyes with uncontrolled glaucoma and no prior incisional ocular surgery. By three years this difference was no longer significant.
- The trabeculectomy group had lower IOP and required fewer medications than the tube group throughout three year follow-up.
- Early postoperative complications (within the first month) were significantly higher in the trabeculectomy group than the tube group. There was no significant difference in late complications.
- The five-year data has yet to be reported at the time of this publication.

Selective Laser Trabeculoplasty Versus Eye Drops for First-Line Treatment of Ocular Hypertension and Glaucoma (LiGHT) – 2019 [33–34]

Purpose

To determine whether initial treatment with selective laser trabeculoplasty (SLT) is superior to initial treatment with

topical medications for primary open angle glaucoma (POAG) or ocular hypertension (OHT).

Methods

This randomized controlled trial conducted at six centers in the United Kingdom recruited 718 previously untreated patients aged 18 or older with POAG or OHT from 2012 through 2014. Patients were randomized to initial treatment with SLT or eye drops and both eyes were eligible if they met inclusion criteria. For both groups, target IOP was guided by decision support software that took into account disease severity and pre-treatment intraocular pressure. In the laser group, 360 degrees of SLT was performed and titrated to bubble formation. If escalation of care was needed, a second SLT was performed, provided there was some response to the first, before moving to medical therapy. In the eye drops group, prostaglandin analogues were first line therapy, followed by beta-blockers, and then carbonic anhydrase inhibitors or alpha agonists. The primary outcome measure was health-related quality of life (HRQL) and quality-adjusted life years (QALY) [33].

Results

362 patients were assigned to eye drops and 356 patients were assigned to SLT. Baseline characteristics were similar between groups. Of the total eyes evaluated in both groups, ~30% had OHT, ~50% had mild POAG, and the remainder had moderate or severe POAG. At three years, there was no significant difference in the European Quality of Life-5 Dimensions (EQ-5D) score, which takes into account mobility, self-care, usual activities, pain/discomfort, and anxiety/depression [34].

The difference in QALY, a measure of the value of health outcomes, was not statistically significant at three years, though it was slightly higher in the SLT group than the eye drop group. At the end of three years, 11 patients in the eye drop group needed glaucoma surgery versus none in the SLT group. Factoring in the costs of surgery, the slight difference in QALY, and the costs of SLT and eye drops, the authors found that there is a 93–97% probability that SLT first is more cost effective than eye drops first [34].

74.2% of patients in the SLT group were drop-free at three years, while 64.6% of patients in the eye drops group required only one eye drop. Treatment escalations were more common in the eye drops group (n = 348) than the SLT group (n = 299). SLT patients were at target IOP at 93% of visits over three years versus 91.3% of patients in the eye drops group. Algorithm-confirmed disease progression was seen in 5.8% of eyes with eye drops and 3.8% of eyes with SLT. There were no sight-threatening complications, though 1.7% had a transient IOP spike after SLT [34].

Key Points

- There is no difference in quality of life with SLT first versus eye drops first for OHT and POAG.
- SLT was more cost-effective than eye drops in patients with untreated POAG or OHT.
- Within a three-year follow-up period, both SLT and eye drops were effective in controlling IOP and preventing disease progression.

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Chapter 2
Cornea

Kevin K. Ma and Jia Yin

Abstract The cornea is a transparent tissue at the front of the eye that acts as both an important structural barrier and a crucial refractive medium. Its clarity is essential for the eye to perform its function. Many trials have studied how to best protect the cornea from infections, prevent progression of ectasias, ensure optimal ocular surface conditions, and keep the tissue optically clear through transplantation. Key landmark trials are summarized in the following chapter.

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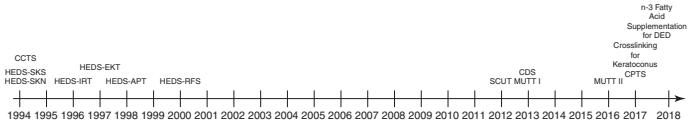

Herpetic Eye Disease Study I (HEDS-I) 1994–1996

Purpose

The HEDS-1 trials were three randomized, placebo-controlled trials conducted to assess the efficacy of topical corticosteroids in treating herpes simplex virus (HSV) stromal keratitis in conjunction with topical trifluridine, the efficacy of adding oral acyclovir in treatment of HSV stromal keratitis for eyes already on topical corticosteroids and trifluridine, and the efficacy of adding oral acyclovir in the treatment of HSV iridocyclitis for eyes on topical corticosteroids and trifluridine.

Herpes Stromal Keratitis, Not on Steroid Trial (HEDS-SKN) – 1994 [1]

Methods

This was a randomized, double-masked, placebo-controlled, multicenter trial of 106 patients with active HSV stromal keratitis who had not received corticosteroids for at least 10 days before enrollment. Participants were assigned to a 10-week tapering regimen of placebo (n = 49) or topical prednisolone phosphate 1% and 0.125% (n = 57). Both groups received topical trifluridine 1%.

Results

The corticosteroid group had a lower risk of persistent or progressive stromal keratouveitis compared to placebo, with a hazard ratio of 0.32 (95% CI 0.18–0.59, $p < 0.001$). The corticosteroid group also had shorter time from randomization to resolution of stromal keratitis compared to placebo (median 26

vs. 72 days, 95% CI of the difference in the medians 14–58 days, $p < 0.001$), while including subjects who were removed from the study and treated with corticosteroids. Delaying initiation of corticosteroid treatment did not affect the visual acuity or rate of recurrence at six months after randomization.

Key Points

- Patients with HSV stromal keratitis given topical corticosteroids had decreased risk of persistent or progressive disease and had faster time to resolution.
- Delaying initiation of topical corticosteroids did not affect the eventual visual acuity or rate of recurrence at six months.

Herpes Stromal Keratitis, on Steroid Treatment (HEDS-SKS) – 1994 [2]

Methods

This was a randomized, double-masked, placebo-controlled, multicenter trial of 104 patients with active HSV stromal keratitis. Participants were assigned to placebo (n = 53) or 400 mg of oral acyclovir five times daily (n = 51). Both groups received topical prednisolone phosphate and trifluridine. Treatment failure was defined as worsening or no improvement of stromal keratitis, or occurrence of an adverse event.

Results

Oral acyclovir did not delay the time to treatment failure (median 84 days, 95% CI 69–93) compared to placebo (median 62 days, 95% CI 57–90). There was no statistically significant difference in the proportion of patients who failed treatment, the proportion of patients whose keratitis resolved, or the time to resolution.

Key Points

- There was no benefit demonstrated to adding oral acyclovir in patients already receiving topical corticosteroids and trifluridine

Herpes Simplex Virus Iridocyclitis, Receiving Topical Steroids (HEDS-IRT) – 1996 [3]

Methods

This was a randomized, double-masked, placebo-controlled, multicenter trial of 50 patients with HSV iridocyclitis. Participants were assigned to a 10-week course of 400 mg oral acyclovir five times daily (n = 22), or placebo (n = 28). Both groups received a tapering regimen of topical prednisolone phosphate 1% or 0.125%, and trifluridine 1%. The trial was stopped because of slow recruitment after only 50 of the initially planned 104 patients were enrolled after more than four years.

Results

The adjusted rate ratio for treatment failure (defined as persistence or worsening of ocular inflammation, withdrawal due to toxicity, or request from patient to withdraw) in acyclovir compared to placebo group during the 10-week treatment period was 0.43 (90% CI 0.18–1.02, p = 0.06). The adjusted rate ratio for treatment failure during the 16-week follow-up period was 0.60 (90% CI 0.29–1.25, p = 0.13).

Key Points

- The study was unable to meet target enrollment, but there was a trend suggesting a benefit of oral acyclovir in the treatment of HSV iridocyclitis in patients already receiving topical corticosteroids and trifluridine.

Herpetic Eye Disease Study II (HEDS-II) 1997–2000

Purpose

Long-term treatment with oral antiviral agents had previously been shown to prevent recurrences of genital and orofacial HSV disease. HEDS-II consisted of two randomized controlled trials evaluating oral acyclovir in preventing the recurrence of ocular HSV disease, as well as one epidemiologic study investigating the risk factors for developing ocular recurrence of disease.

Herpes Simplex Virus Epithelial Keratitis Trial (HEDS-EKT) – 1997 [4]

Methods

This was a randomized, double-masked, placebo-controlled, multicenter trial of 287 patients with HSV epithelial keratitis of one-week duration or less. Participants were assigned to a three-week course of 400 mg oral acyclovir five times daily (n = 153) or placebo (n = 134). Both groups received topical trifluridine 1%. Development of HSV stromal keratitis or iritis was assessed over 12 months of follow-up.

Results

The adjusted rate ratio for the development of stromal keratitis or iritis in the acyclovir group was 1.16 (95% CI 0.56–2.43) compared to the placebo group. Development of stromal keratitis or iritis was more frequent in patients with history of HSV stromal keratitis or iritis than those without (23% vs. 9%, p = 0.01).

Key Points

- There was no apparent benefit of a three-week course of acute oral acyclovir treatment in preventing HSV stromal keratitis or iritis in the subsequent 12 months in patients with HSV epithelial keratitis treated with topical trifluridine.

Acyclovir Prevention Trial (HEDS-APT) – 1998 [5]

Methods

This was a randomized, double-masked, placebo-controlled, multicenter trial of 703 immunocompetent patients with a history of ocular HSV disease within the preceding year. Participants were assigned to receive a 12-month course of 400 mg oral acyclovir two times daily (n = 357), or placebo (n = 346) and were subsequently observed for six months off treatment.

Results

The cumulative probability of recurrence of any type of ocular HSV disease during the 12-month treatment period was 19% in the acyclovir group and 32% in the placebo group ($p < 0.001$). Of the 337 patients with a history of stromal keratitis, the cumulative probability of recurrent stromal keratitis was 14% in the acyclovir group and 28% in the placebo group ($p = 0.005$). The cumulative probability of recurrence of non-ocular HSV disease was 19% in the acyclovir group and 36% in the placebo group ($p < 0.001$). There was no rebound in the rate of HSV disease in the six-month period after treatment with acyclovir was stopped.

Key Points

- Chronic low-dose oral acyclovir significantly reduced the recurrence rate of ocular HSV including HSV stromal keratitis

Ocular HSV Recurrence Factor Study (HEDS-RFS) – 2000 [6]

Methods

Patients in the placebo group of the Acyclovir Prevention Trial (HEDS-APT) with a history of ocular HSV disease within the preceding year were observed.

Results

58 out of 346 subjects (18%) developed epithelial keratitis and 59 out of 346 subjects (18%) developed stromal keratitis during the 18 months of follow-up. A history of previous epithelial keratitis did not significantly affect the risk of epithelial keratitis ($p = 0.84$). Previous stromal keratitis increased the risk of stromal keratitis tenfold ($p < 0.001$) with the risk strongly related to the number of previous episodes ($p < 0.001$).

Psychological stress, systemic infection, sunlight exposure, menstrual period, contact lens wear, and eye injury were not associated with recurrence of ocular HSV disease.

Key Points

- A history of HSV epithelial keratitis was not associated with an increased risk of future recurrence of epithelial keratitis
- A history of HSV stromal keratitis was associated with an increased risk of future recurrence of stromal keratitis
- Psychological stress, systemic infection, sunlight exposure, menstrual period, contact lens wear, and eye injury were not associated with recurrence of ocular HSV disease.

Mycotic Ulcer Treatment Trial I (MUTT I) – 2013 [7]

Purpose

To compare the efficacy of topical natamycin with topical voriconazole in the treatment of filamentous fungal keratitis.

Methods

This was a randomized, double-masked, multicenter trial in South India of 323 patients with smear-positive filamentous fungal keratitis with visual acuity 20/40 to 20/400. Patients were randomized to topical voriconazole 1% or topical natamycin 5% applied every hour while awake until reepithelialization, then four times daily for at least three weeks.

Results

Natamycin-treated cases had a significantly better three-month best corrected visual acuity (BCVA) compared to voriconazole-treated cases (−0.18 logMAR; 95% CI −0.30 to −0.05; p = 0.006). Natamycin-treated cases were less likely to have perforation or require therapeutic penetrating keratoplasty (OR 0.42; 95% CI 0.22–0.80; p = 0.009). While *Fusarium* cases responded better with natamycin (−0.41 logMAR; 95% CI −0.61 to −0.20; p < 0.001); non-*Fusarium* cases fared similarly (−0.02 logMAR; 95% CI −0.17 to 0.13; p = 0.81).

Key Points

- Topical natamycin was associated with significantly better clinical and microbiological outcomes compared to topical voriconazole in smear-positive filamentous fungal ulcers. This difference is primarily attributable to the superior efficacy of natamycin in cases caused by *Fusarium* species.

Mycotic Ulcer Treatment Trial II (MUTT II) – 2016 [8]

Purpose

To compare oral voriconazole to placebo in the treatment of severe filamentous fungal keratitis in eyes already receiving topical antifungals.

Methods

This was a randomized, double-masked, placebo-controlled, multicenter trial in Nepal and India of 240 patients with smear-positive filamentous fungal keratitis with visual acuity 20/400 or worse. Patients were randomized to oral voriconazole (n = 119) or placebo (n = 121). A loading dose of 400 mg voriconazole was given twice daily for 24 hours followed by a maintenance dose of 200 mg twice daily for 20 days; weight-based dosing was later introduced in the trial to reduce adverse effects. Both groups received topical voriconazole 1% and natamycin 5%.

Results

There was no difference in the rate of corneal perforation or the need for therapeutic penetrating keratoplasty in the oral voriconazole group compared to placebo (HR 0.82, 95% CI 0.57–1.18, $p = 0.29$). The group receiving oral voriconazole experienced a greater number of adverse events compared to placebo group (48.7% vs. 23.1%, $p < 0.001$).

Key Points

- The addition of oral voriconazole to topical antifungals in the treatment of severe filamentous fungal keratitis does not appear to be beneficial.

Steroids in Corneal Ulcer Trial (SCUT) – 2012 [9]

Purpose

To evaluate whether there is clinical benefit to the use of adjunctive topical corticosteroids in the treatment of bacterial corneal ulcers.

Methods

This was a randomized, double-masked, placebo-controlled, multicenter trial of 500 patients with culture-positive bacterial corneal ulcers. After receiving topical moxifloxacin for at least 48 hours, patients were randomized to prednisolone phosphate 1% (n = 250) or placebo (n = 250), applied topically four times a day for one week, then twice a day for one week, and then once a day for one week.

Results

In patients randomized to receiving topical corticosteroids, there was no significant difference observed in the primary outcome of three-month best corrected visual acuity (BCVA) (−0.009 logMAR, 95% CI −0.085 to 0.068, p = 0.82). There was also no difference in the secondary outcomes of infiltrate/scar size (p = 0.40), time to re-epithelialization (p = 0.44), or corneal perforation (p > 0.99). In patients with counting-fingers vision or worse at baseline, the corticosteroid group had 0.17 logMAR better BCVA at three months (95% CI −0.31 to −0.02, p = 0.03); in patients with ulcers that were completely central at baseline, the corticosteroid group had 0.20 logMAR better BCVA at three months (95% CI −0.37 to −0.04, p = 0.02).

A secondary analysis of 399 patients evaluated at 12 months found no differences in clinical outcomes by treatment group seen in the above pre-specified regression models. However, a regression model including a *Nocardia*-treatment arm found a mean one-line improvement in BCVA at 12 months among patients on corticosteroids with non-*Nocardia* ulcers (−0.10 logMAR, 95% CI −0.19 to −0.02, p = 0.02).

Key Points

- Adjunctive topical corticosteroid use does not appear to improve vision at three months in patients with bacterial corneal ulcers.
- However, patients with central ulcers or counting-fingers vision or worse may benefit from adjunctive corticosteroid therapy.
- Topical corticosteroids should be avoided in corneal ulcers secondary to *Nocardia*.

Collaborative Corneal Transplantation Studies (CCTS)

Effectiveness of Histocompatibility Matching in High-Risk Corneal Transplantation in the CCTS – 1994 [10]

Purpose

To evaluate the effect of donor-recipient histocompatibility matching and crossmatching on the survival of corneal transplants (penetrating keratoplasty) in high-risk patients. This study included the Antigen Matching Study and the Crossmatch Study.

Methods

The Antigen Matching Study was a prospective, double-masked trial of 419 patients who were allocated corneas based on HLA-A, HLA-B, and HLA-DR typing; ABO status was determined but was not used to allocate grafts. The Crossmatch Study was a prospective, randomized, double-masked trial of 37 patients assigned corneas from either positively or negatively crossmatched donors.

Results

Matching based on HLA-A, HLA-B, and HLA-DR antigens had no effect on overall graft survival, rates of failure due to rejection, or rates of graft rejection episodes. At three years, the ABO-incompatible group had 41% overall graft failures compared to 31% in the ABO-compatible group (RR 1.43, 95% CI 1.00–2.06). The ABO-incompatible group also had 30% fail

due to rejection compared to 16% in the ABO-incompatible group (RR 1.98, 95% CI 1.25–3.13). The positive donor-cornea crossmatch group did not have higher rates of graft failure.

Key Points

- Neither HLA-A, HLA-B, or HLA-DR antigen matching, nor negative donor-cornea crossmatching appeared to reduce the likelihood of corneal transplant (penetrating keratoplasty) failure.
- ABO blood group matching may reduce the risk of cornea graft failure, particularly from rejection, in high-risk patients.

Risk Factors for Corneal Graft Failure and Rejection in the CCTS – 1994 [11]

Purpose

To evaluate suspected risk factors for graft failure from all causes, failure from rejection, and immunologic reactions in high risk patients undergoing corneal penetrating keratoplasty.

Methods

Data from the 419 patients in the Antigen Matching Study, 37 patients in the Crossmatch Study, and one patient who was not randomized were included. Characteristics that were suspected to be risk factors were evaluated using multivariate survival analysis techniques.

Results

Complete information on graft status was available through two years on 95% of patients. The strongest risk factors for graft failure included recipient age younger than 40 years (RR 2.50, 95% CI 1.75–3.58), each additional previous graft (RR 1.20, 95% CI 1.09–1.32), previous anterior segment surgery (RR 2.16, 95% CI 1.37–3.39), pre-operative glaucoma (RR 1.58, 95% CI 1.14–2.21), quadrants of anterior synechiae (RR 1.19, 95% CI 1.07–1.32), quadrants of stromal vessels (RR 1.14, 95% CI 1.01–1.28), primary diagnosis of chemical burn (RR 1.78, 95% CI 1.09–2.88), and ABO incompatibility (RR 1.37, 95% CI 1.00–1.89).

Key Points

- Risk factors for penetrating keratoplasty graft failure include recipient age younger than 40, prior grafts, previous anterior segment surgery, prior diagnosis of glaucoma, presence of anterior synechiae or stromal vessels, primary diagnosis of chemical burns, and ABO incompatibility.

Corneal Donor Study (CDS) 10-Year Data – 2013 [12]

Purpose

To determine whether the success rate of penetrating keratoplasty in corneal endothelial disorders is associated with donor age.

Methods

This was a double-masked, prospective, multicenter trial of 1090 patients assigned corneas from donors 12 to 75 years old using a randomized approach without regard to recipient factors and followed for up to 12 years.

Results

The 10-year success rate was 77% for those receiving grafts from the 707 donors aged 12–65 years, compared to 71% for the 383 donors aged 66–75 years (difference +6%, 95% CI −1 to 12, $p = 0.11$). When analyzed as a continuous variable, there was a higher success rate for those receiving grafts from the 80 donors aged 12–33 years (96%) and lower for those receiving grafts from the 130 donors aged 72–75 years (62%). The relative drop in success rate with donors aged 72–75 years was not evident until after year six.

Key Points

- 10-year analysis of the CDS data suggests there may be higher success rates at the lower extreme (younger than 33 years) and lower success rates at the upper (older than 72 years) extreme of donor age for penetrating keratoplasty in corneal endothelial disorders.

Cornea Preservation Time Study (CPTS) – 2017 [13]

Purpose

To determine whether Descemet stripping automated endothelial keratoplasty (DSAEK) graft success at three years using corneal donor tissue preserved 8 to 14 days is noninferior to that of donor tissue preserved 7 days or less.

Methods

This was a randomized, double-masked, multicenter, noninferiority trial involving 1090 individuals (1330 study eyes) undergoing DSAEK for Fuchs endothelial corneal dystrophy and uncomplicated pseudophakic or aphakic corneal edema. Eyes were randomized to a donor cornea with a preservation time of 7 days or less (0–7d PT), or 8 to 14 days (8–14d PT).

Results

The three-year cumulative probability of graft success was 95.3% (95% CI 93.6–96.9) in the 0-7d PT group and 92.1% (95% CI 89.9–94.2) in the 8-14d PT group. The upper limit of the one-sided 95% CI of the difference was 5.4%, which exceeded the prespecified non-inferiority limit of 4%. Longer PT was associated with a lower rate of graft success, with success rates of 96.5% for 0–4d PT, 94.9% for 5–7d PT, 93.8% for 8–11 PT, and 89.3% for 12–14d PT.

Key Points

- This non-inferiority study was unable to conclude that three-year success rate using donor corneas preserved eight to 14 days was similar to corneas preserved seven days or less.
- The rate of DSAEK success is higher with shorter donor tissue preservation times, but preservation time of up to 11 days appears to have little effect on outcomes.

US Multicenter Clinical Trial of Corneal Collagen Crosslinking for Keratoconus Treatment – 2017 [14]

Purpose
To evaluate the safety and efficacy of corneal collagen crosslinking (CXL) for the treatment of progressive keratoconus.

Methods
This was a randomized, unmasked, sham-controlled, multicenter trial of 205 patients with progressive keratoconus. Participants were randomized to treatment with standard ultraviolet-A riboflavin 0.1% with removal of epithelium (n = 102), or sham treatment with riboflavin 0.1% without removal of epithelium (n = 103). Eyes in control group could cross over to treatment at three months.

Results
The mean maximum keratometry of treated eyes decreased by 1.6 D at one year, compared to an increase of 1.0 D in the control group ($p < 0.0001$). In treated eyes at 12 months, the maximum keratometry decreased by >2.0 D in 28 of 89 subjects (31%), remained within 2.0 D in 56 of 89 subjects (63%), and increased by >2.0 D in five of 89 subjects (6%). At 12 months, corrected distance visual acuity improved by 5.7 letters in the treated group versus 2.2 letters in the control group ($p < 0.01$). Corneal haze was the most frequently reported adverse event in the study.

Key Points
- Corneal collagen crosslinking (CXL) is effective in decreasing disease progression in patients with progressive keratoconus.
- CXL can lead to improved visual function in some patients
- Corneal stromal haze appears to be a concomitant phenomenon in CXL and clears in most cases by 12 months.

n–3 Fatty Acid Supplementation for the Treatment of Dry Eye Disease – 2018 [15]

Purpose
To determine the efficacy and safety of oral n–3 fatty acid (often referred to as omega-3 fatty acids) supplementation in the treatment of dry eye disease.

Methods
This was a randomized, double-masked, placebo-controlled, multicenter trial involving 349 patients with moderate-to-severe dry eye disease. Participants were randomized to daily oral n–3 fatty acids (n = 329) or an olive oil placebo (n = 170).

Results
At 12 months, the mean Ocular Surface Disease Index was not significantly different between the oral n-3 fatty acids (−13.9 ± 15.6 points) and placebo groups (−12.5 ± 18.2 points) (difference −1.9 points, 95% CI −5.0 to 1.1, p = 0.21). There were no significant differences between the groups in mean changes from baseline in the conjunctival staining score (0.0 points, 95% CI −0.2 to 0.1), corneal staining score (0.1 points, 95% CI −0.2 to 0.4), tear break-up time (0.2 seconds, 95% CI −0.1 to 0.5) or Schirmer's test (0.0 mm, 95% CI −0.8 to 0.9).

Key Points
- Among patients with moderate-to-severe dry eye disease, both placebo and n-3 fatty acid groups experienced improved signs and symptoms.
- The patients randomized to n-3 fatty acid supplements did not have significantly better outcomes compared to those randomized to placebo.

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Chapter 3
Neuro-Ophthalmology

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Abstract Neuro-ophthalmology is an academically focused field driven by research. In this chapter we review eight of the most impactful studies within the subspecialty, starting with an in-depth look at Beck's *The Optic Neuritis Treatment Trial (ONTT)*, a hallmark study published in 1988 that changed the initial management of optic neuritis. We then discuss *Head-Impulse—Nystagmus—Test-of-Skew (HINTS) to diagnose stroke in the acute vestibular syndrome* by Kattah et al., which validated the use of a three-step bedside oculomotor exam for the diagnosis of acute vestibular syndrome, a neuro-ophthalmologic emergency. Next we review the *Multicenter Study of the European Assessment Group for Lysis in the Eye (EAGLE) for the Treatment of Central Retinal Artery*

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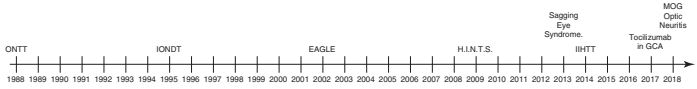
Occlusion by Schumacher et al., which assessed the safety and efficacy of local intra-arterial fibrinolysis compared with conservative standard treatment for angiographically proven acute central retinal artery occlusion. We cover *The Idiopathic Intracranial Hypertension Treatment Trial (IIHTT)* by Wall et al. that assessed the efficacy of acetazolamide for improving vision in patients with IIH and mild visual loss. Four additional studies deemed fundamental to the field of neuro-ophthalmology are also reviewed in this chapter.



Optic Neuritis Treatment Trial (ONTT) – 1988 [1–7]

Purpose

To determine whether oral or intravenous corticosteroids can improve visual outcome and/or accelerate recovery in patients with acute "idiopathic" optic neuritis (ON). In addition, the investigators sought to explore the natural history of patients who suffer from ON and determine their long-term risk of developing multiple sclerosis (MS) [1].

Methods

This was a multicenter, prospective, randomized controlled trial. Patients were eligible if they (a) were between 18 and 46 years (b) had an acute clinical syndrome consistent with unilateral optic neuritis, (c) had visual symptoms for eight days or less, (d) showed evidence of a relative afferent pupillary defect (rAPD) and (e) had a visual field defect in the affected eye. Patients with previous episodes of ON in the affected eye, corticosteroid treatment for either ON or MS and systemic disease other than MS that could cause ON

were excluded [2]. A total of 457 patients were recruited from 15 clinical centers throughout the United States and randomly assigned to one of the three groups: (a) oral prednisone (1 mg/kg/day) for 14 days, (b) intravenous methylprednisolone (250 mg every 6 hours) for three days, followed by oral prednisone (1 mg/kg/day) for 11 days, or (c) oral placebo for 14 days. Primary outcome measures were contrast sensitivity (measured with the Pelli-Robson chart) and visual field performed both on Humphrey Field Analyzer and Goldmann perimeter at one and six months.

Results

A total of 457 patients were randomized from fifteen centers. 77.2% were women and the mean age was 31.8 years. The optic nerve head was normal in 64.7% and showed swelling in 35.3%; 92.2% of patients experienced pain [2]. Patients who received IV methylprednisolone showed a faster return to normal vision compared to placebo ($p = 0.001$ for visual field, $p = 0.02$ for contrast sensitivity). At six months, visual acuity was similar between these two groups, but contrast sensitivity ($p = 0.026$) and visual fields ($p = 0.054$) were still slightly better in the IV methylprednisolone group [3]. Oral prednisone did not show benefit over placebo in terms of visual outcomes at six months, and led to an increased rate of new attacks of optic neuritis in either eye. Longitudinal follow-up of the ONTT cohort showed that treatment did not impact the long-term visual prognosis; 72% of patients recovered to a visual acuity of 20/20 or better in the affected eye, 90% to a visual acuity of 20/40 or better, and no difference was noted between the three groups [4]. Presence of brain lesions on baseline MRI was a strong predictor for the development of MS. At five years, 51% of patients with three or more lesions on initial MRI developed MS compared to 16% of patients with normal baseline MRI [5]. The cumulative risk of developing MS at 15 years was 50%; 25% if MRI was normal at baseline and 72% with one or more lesions on baseline MRI. Overall, normal MRI, white race/ethnicity, male sex,

profound optic disc swelling and presence of atypical clinical features at baseline such as no light perception or absence of periocular pain, were associated with lower likelihood of developing MS [6, 7].

Key Points

- Treatment of acute "idiopathic" optic neuritis with IV methylprednisolone led to faster visual recovery compared to placebo, but did not affect the long-term visual outcome.
- Oral prednisone increased the rate of new attacks of optic neuritis over a 6-month follow up period.
- The visual prognosis of optic neuritis was excellent in all groups, with over 90% of patients recovering to a visual acuity of 20/40 or better in the affected eye at 15 years.
- Cumulative risk of developing MS at 15 years was 50%, and MRI abnormalities at baseline was a strong predictor for conversion to MS.

Ischemic Optic Neuropathy Decompression Trial (IONDT) – 1995 [8–11]

Purpose

To assess the safety and the efficacy of optic nerve decompression surgery (ONDS) in patients with nonarteritic ischemic optic neuropathy (NAION) compared to careful follow-up (control) group.

Methods

This two year, multicenter, single-masked, randomized clinical trial was sponsored by the National Eye Institute. Patients aged 50 years or older, diagnosed with NAION with symptom duration of less than 14 days and visual acuity (VA) equal or worse than 20/64 but better than light perception were eligible to participate as "regular-entry patients". When baseline VA was better than 20/64, patients were followed weekly for up to 30 days. Patients who experienced a decline

in VA to 20/64 or worse within this period were eligible for randomization as "late-entry" participants. Those who maintained VA better than 20/64 were considered eligible for follow-up as part of the "natural history" cohort. Surgery was performed within four days of randomization and involved creation of either two or more slits or a window in the optic nerve sheath in order to release the pressure surrounding the optic nerve [8]. The main outcome measure was a change (gain or loss) of three or more lines of vision on the New York Lighthouse chart at six months.

Results

The preliminary results at six months were based on data from 244 NAION patients (n = 125, careful follow-up; n = 119, ONDS). The most common visual field patterns at baseline and at six months were superior and inferior arcuate defects. Improvement of three or more lines of vision was observed in 42.7% of patients in the careful follow-up group vs 32.6% in the surgery group. Among the careful follow-up group, 12.4% lost three or more lines of vision vs 23.9% in the surgery group. In February 1995, the trial was halted as surgery was found to be ineffective and more importantly potentially harmful; one patient in the surgery group suffered from a central retinal artery occlusion, and two lost light perception immediately after surgery [9]. The 24-month data from the original cohort, in which 174 participants remained, confirmed non-superiority of intervention compared to control. Visual acuity was significantly improved from baseline in both groups despite a gradual decline after the three-month visit [10]. Over a median follow-up of 5.1 years, the incidence of NAION in the fellow eye was 14.7%; a history of diabetes and/or baseline VA of 20/200 or worse were considered important risk factors [11].

Key Points

- Decompression surgery is ineffective and poses a greater risk for poor visual outcomes compared to careful follow-up in patients with NAION.

- Spontaneous improvement was higher than previously reported with 42.7% of patients in the observation group gaining 3 or more lines of vision.
- Incidence of NAION development in the fellow eye was 14.7% over a median period of 5.1 years and was not affected by age, sex, aspirin use, or smoking.

The European Assessment Group for Lysis in the Eye (EAGLE) – 2002 [12–17]

Purpose

To assess the efficacy and safety of local intra-arterial fibrinolysis (LIF) compared with "conservative standard treatment (CST)" in patients with angiographically proven acute (≤20 hours) central retinal artery occlusion (CRAO) [12].

Methods

This was a prospective, multicenter, randomized controlled clinical trial. Patients ages 18–75 years with acute onset of vision loss secondary to CRAO and best corrected visual acuity (BCVA) of less than 0.5 logarithm (Snellen equivalent 20/63) were considered eligible for randomization [13]. The (CST) group was treated with a combination of isovolemic hemodilution (IHD), ocular massage, topical beta-blockers, and systemic acetazolamide; the LIF group underwent local delivery of tissue plasminogen activator (rtPA) via superselective catheterization of the ophthalmic artery done under anticoagulation therapy (heparin 500 IU). Both groups received weighted-adjusted low-dose heparin for five days and acetylsalicylic acid (ASA) 100 mg for four weeks. The primary outcome was the change in best-corrected visual acuity (BCVA) one-month post intervention from the BCVA at baseline. Clinically significant improvement was defined as a decrease in logMAR of ≥0.3. All participants were admitted to the stroke unit for the first 24 hours after intervention,

received standardized and systematic evaluation of vascular risk factors, and were followed up clinically at one, three, and six months [14].

Results

Forty-four patients were randomized to the LIF group and 40 to the CST group. The mean interval between symptom onset and treatment was 10.99 ± 5.49 hours in the CST group and 12.78 ± 5.77 hours in the LIF group. Significant visual improvement was noted in both groups (60% CST vs 57.1% LIF) one month after randomization without significant difference between the groups at one, three, and six months. Analysis of time to treatment administration (both LIF and CST) demonstrated better outcomes in patients with shorter symptom duration (<12 h) [12, 14]. Lack of efficacy along with severe adverse events (e.g. cerebral and cerebellar hemorrhages) in the LIF group led to termination of the trial after the first interim analysis [15]. Evaluation of 34 digital subtraction angiography (DSA) studies from the LIF group (CST group did not undergo DSA) revealed internal carotid artery (ICA) plaques in the cavernous and clinoid portions in 40.6% of the patients, likely representing an embolic source [16]. Coronary artery disease, smoking, age, and CRAO duration of greater than 12 hours were considered key prognostic factors for visual outcome [17].

Key Points

- Local intra-arterial fibrinolysis (LIF) did not show any benefit compared to conservative standard treatment (CST) in terms of visual outcome at one month.
- Serious adverse events in the LIF group, mainly cerebral and cerebellar hemorrhages lead to early termination of the study.
- Early rtPA might lead to greater improvement in vision, but further trials are needed to assess its benefit over conservative management.

Head-Impulse-Nystagmus-Test-of-Skew (H.I.N.T.S.) – 2009 [18]

Purpose
To assess the accuracy of the three-step bedside oculomotor exam Head-Impulse-Nystagmus-Test-of-Skew (H.I.N.T.S.) in differentiating stroke from acute peripheral vestibulopathy (APV) in patients presenting with acute vestibular syndrome (AVS) [18].

Methods
This was a prospective, single-center, cross-sectional study. Eligible patients were identified in two ways: (1) after they presented to the emergency department with clinical features consistent with AVS (rapid onset vertigo, nausea, vomiting, unsteady gait with or without nystagmus), or (2) by review of stroke admissions for cerebellar infarction. Those with at least one stroke risk factor (smoking, hypertension, diabetes mellitus, hyperlipidemia, atrial fibrillation, eclampsia, hypercoagulable state, recent cervical trauma, or prior stroke or myocardial infarction) were included in the study. Patients with a history of recurrent vertigo with or without auditory symptoms were excluded. All patients who consented to screening underwent a neurological and vestibular examination (including horizontal head impulse test (h-HIT), nystagmus observation in different gaze positions and prism cross-over test for ocular alignment assessment) conducted by the same physician. In addition, neuroimaging was obtained in every patient and all were admitted for observation and daily clinical evaluation. The reference standard for diagnosis was presence/absence of stroke on brain MRI with diffusion-weighted imaging (DWI).

Results
In total, 101 patients participated in the study of whom 92 were identified by clinical screening. The mean age of the cohort was 62 years and the age range of those diagnosed with

stroke was 26–92 years. Seventy-five percent of patients were examined within 24 hours of symptom onset. Ninety-seven percent of participants underwent stroke-protocol MRI with DWI and 70% had their imaging done within six hours of study examination. Of the 101 patients included, 76 had a central lesion (69 ischemic strokes, four hemorrhages, two demyelinating lesions and one anticonvulsant toxicity) and 25 had APV. Skew deviation (mean 9.9 prism-diopters, range 3–20 prism-diopters) was present in 30% of patients with brainstem lesions and 4% with pure cerebellar lesions (n = 1 of 24), and 4% (n = 1 of 25) with APV. Of eight patients with false-negative initial MRI, finding a skew predicted the presence of an ischemic stroke in seven. In three patients with lateral pontine strokes in whom abnormal h-HIT suggested a peripheral lesion, presence of skew led to the correct diagnosis in two. Although infrequent, acute auditory symptoms were associated with strokes in the anterior inferior cerebellar artery territory. Craniocervical pain was more frequent in patients with central lesions (38% versus 12%, $p < 0.02$). When considered together as a three-step bedside assessment, the presence of skew deviation, normal h-HIT or direction-changing nystagmus in eccentric gaze had a 100% sensitivity and 96% specificity for detecting stroke, which seems superior to early MRI.

Key Points

- In patients with acute vestibular syndrome (AVS), The Head-Impulse—Nystagmus—Test-of-Skew (H.I.N.T.S.) bedside evaluation is more sensitive than early MRI to detect stroke.
- Presence of a skew deviation is strongly associated with brainstem ischemic lesions and can help to correctly identify stroke when abnormal h-HIT suggests a peripheral lesion.
- Craniocervical pain and acute auditory symptoms are more common with central lesions.

Sagging Eye Syndrome: Connective Tissue Involution as a Cause of Horizontal and Vertical Strabismus in Older Patients– 2013 [19, 20]

Purpose

To assess whether sagging eye syndrome (SES) is caused by an inferior shift of the lateral rectus (LR) extraocular muscle (EOM) pulleys and to examine the anatomic parallels of strabismus in SES [19].

Methods

This was a prospective study of patients with acquired diplopia suspected of having SES. Magnetic resonance imaging (MRI) was used to assess the orbital anatomy of participants clinically diagnosed with SES compared to both age-matched and younger control participants. Exclusion criteria included: prior diagnosis of superior oblique (SO) palsy, thyroid eye disease, trauma, history of strabismus surgery, and significant myopic degeneration (concerning for "heavy eye" syndrome) [20]. Participants underwent orbital MRI at an eye institute to evaluate the rectus EOMs and pulleys (with axial and quasi-sagittal MRI), in addition to the LR–superior rectus (SR) band ligament (with quasi-coronal MRI). Baggy eyelids, deep superior sulcus deformity, aponeurotic ptosis, and blepharoplasty scars were evaluated during the external ocular adnexa exam. Best corrected visual acuity (converted with logMAR), refractive error, stereopsis (Titmus Fly Stereotest), motility exam, Hess screen, slit-lamp exam with fundus torsion measurement and fundoscopy, diagnostic gaze position photography, and saccade exam were performed. Heterotropia was measured at distance and near with prism and cover testing. The primary outcome measures were rectus pulley locations compared with age-matched norms and lengths of the LR-SR band ligament and rectus EOMs. Data were then correlated with facial features, binocular alignment, and fundus torsion.

Results

Fifty-six orbits from 11 men and 17 women (mean age 69.4 years) clinically diagnosed with SES were compared to data from 25 orbits of 14 age-matched control participants and to 52 orbits of 28 younger controls (mean age 23 years) [19]. A significant proportion of SES patient were found to have superior sulcus deformity (64%) and/or aponeurotic blepharoptosis (29%) on external examination. MRI of patient with SES showed significant displacement of the medial rectus (MR) and lateral rectus (LR) pulleys away from the orbital center compared to younger controls ($p < 0.005$). SES patients with divergence paralysis esotropia (DPE), also referred to as *divergence insufficiency*, were found to have *symmetrical* LR sag, while patients with cyclovertical strabismus (CVS) had LR sag that was asymmetrical (>1 mm) between both eyes. Axial MRI showed a 50% elongation of the LR in patients with SES compared to the control groups. The LR-SR band was ruptured in 64% of patients with DPE and 91% of patients with CVS.

Key Points

- Sagging eye syndrome (SES) is a cause of acquired, adult horizontal and/or cyclovertical strabismus due to age-related orbital connective tissue degeneration.
- Patients with SES exhibit significant displacement of all four rectus muscle pulleys away from the orbital center as well as elongation of the EOMs. Rupture of the SR-LR band is seen in most cases.
- Patients with acute or chronic onset of binocular diplopia suggestive of SES without additional acute neurologic deficits may not require emergent neurologic workup.

The Idiopathic Intracranial Hypertension Treatment Trial (IIHTT) – 2014 [21–29]

Purpose

To evaluate the efficacy of acetazolamide in improving vision in patients with Idiopathic Intracranial Hypertension (IIH) and mild vision loss.

Methods

This was a multicenter, randomized, double-masked, placebo-controlled clinical trial. A total of 165 participants between 18 and 60 years of age were enrolled over a three-year period. Patients were eligible if they met the modified Dandy criteria for IIH and had Perimetric Mean Deviation (PMD) between −2 and − 7 dB in the eye with the greatest visual loss on automated visual field testing. All participants received a low-sodium diet and were offered a lifestyle modification program focused on weight reduction before being randomly assigned to the acetazolamide or placebo group. The treatment arm received acetazolamide at an initial dose of 500 mg twice daily followed by increased dosage of 250 mg weekly up to four grams daily. Titration was resumed if papilledema improved to a grade (Frisén scale) of less than one in both eyes and the PMD improved to ≥ −1 dB in each eye, or if patient could not tolerate the medication. The primary outcome measure was the change in PMD between the baseline assessment and the six-month visit in the eye with the worst PMD at baseline. Visual acuity, quality of life (QOL), Frisén papilledema grade, and cerebrospinal fluid (CSF) opening pressure between the two groups we also studied [21].

Results

A total of 165 patients from 38 sites were enrolled in the study of which 161 were women [22]. The average PMD at baseline for the study eye and fellow eye were-3.5 dB and − 2.3 dB, respectively. At 6 months, while the mean PMD improved in the placebo group (0.71 dB), greater improvement was seen in the acetazolamide group (1.43 dB; treatment effect, 0.71 dB; 95% CI, 0 to 1.43; p = 0.05) [23]. Treatment effect was significantly greater in patients with grade 3–5 papilledema at baseline. Visual acuity was relatively unaffected at baseline and no significant differences were noted at the end of the trial [24]. Nerve fiber layer hemorrhages were present in 27.2% of subjects and correlated to the severity of papilledema [25]. Peripapillary retinal pigment epithelium and Bruch's membrane (pRPE/BM) shape normalized in the acetazolamide

group, reflecting a reduction in the pressure differential between the intraocular and retrobulbar space induced by therapy [26]. Headache was present in 139 patients (84%) and similar improvement occurred in both study groups [27]. Improvement in QOL noted by patients in the acetazolamide group was thought to be mediated by its effect on visual field and pulsatile tinnitus [28]. Acetazolamide had a good safety profile and the maximum allowed dose was well tolerated by 44.1% of the treatment group participants [29].

Key Points

- The combination of acetazolamide and weight loss for the treatment of IIH was associated with greater improvement in PMD in patients with mild vision loss compared with placebo.
- Acetazolamide led to improvement in visual field, CSF opening pressure, papilledema, and QOL.
- Acetazolamide was not superior to placebo for headache management in patients with IIH.
- Acetazolamide is considered safe and tolerable for patients with IIH up to 4 g/day.

Trial of Tocilizumab in Giant-Cell Arteritis – 2017 [30–32]

Purpose

To compare the efficacy of tocilizumab versus placebo in inducing sustained glucocorticoid-free remission in patients with giant cell arteritis (GCA) at one year [30].

Methods

The Giant-Cell Arteritis Actemra (GiACTA) trial was a randomized, double-blind, placebo-controlled, phase three clinical trial conducted over 52 weeks [31, 32]. Patients 50 years or older with active giant-cell arteritis diagnosed within six weeks (either newly diagnosed or experiencing a relapse within that time frame), with an erythrocyte sedimentation

rate (ESR) of ≥50 mm/hr, and unequivocal symptoms of GCA or polymyalgia rheumatica (PMR), were considered eligible for randomization. GCA diagnosis required either pathology features of GCA on temporal artery biopsy or evidence of large vessel vasculitis on angiography, computed tomographic or magnetic resonance angiography, or positron-emission tomography. Participants were randomized into one of four double-blinded groups: (1) subcutaneous tocilizumab 162 mg *weekly* with a 26-week prednisone taper (2) tocilizumab 162 mg *every other week* with a 26-week prednisone taper, (3) subcutaneous placebo with a 26-week prednisone taper or (4) subcutaneous placebo with a 52-week prednisone taper. The primary outcome was sustained glucocorticoid-free remission rates at 52 weeks in both tocilizumab groups versus the placebo group that received a 26-week prednisone taper. The secondary outcome was the rate of remission in both tocilizumab groups compared to the 52-week prednisone taper placebo group. Remission and disease activity were assessed at each visit to confirm prednisone taper safety. Sustained remission was defined as the absence of a flare and CRP < 1 mg/dL from weeks 12 to 52 with adherence to the prednisone taper. Flares requiring increased prednisone dose were considered a primary outcome treatment failure.

Results

One hundred patients were randomized to the *weekly* tocilizumab plus 26-week prednisone taper group, 50 to every *other week* tocilizumab plus 26-week prednisone group, 50 to the placebo plus 26-week prednisone taper group, and 51 to the placebo plus 52-week taper group. Sustained remission at week 52 occurred in 56% of the tocilizumab weekly group and 53% of the tocilizumab every other week group, versus 14% of the placebo plus 26-week prednisone taper group and 18% of the placebo plus 52-week prednisone taper group ($p < 0.001$ for the comparisons of either active treatment with placebo). Results of the sensitivity analysis were supportive of the primary and secondary efficacy analysis except for the comparison of the tocilizumab every other week and the placebo group that completed a 52-week taper which met the

criteria for noninferiority, but not superiority. The median cumulative prednisone dose at 52 weeks was 1862 mg in both tocilizumab groups, versus 3296 mg in the 26-week taper placebo group and 3818 mg in the 52-week taper placebo group. Serious adverse events (mainly infections) occurred in 15% of the tocilizumab weekly group, 14% of the tocilizumab every other week group (in which one patient developed a thrombotic stroke while off anticoagulation for surgery and another had an anterior ischemic optic neuropathy), 22% of the 26-week taper placebo group, and 25% of the 52-week taper placebo group.

Key Points

- Tocilizumab given weekly with a 26-week prednisone taper achieved a higher rate of glucocorticoid-free remission at 52 weeks compared to placebo with either a 26- or 52-week taper in patients with GCA.
- At one year, both placebo groups received approximately twice the cumulative amount of prednisone compared to the tocilizumab groups.
- The rate of serious adverse events (mainly infections) was lower in the Tocilizumab groups versus placebo, both for the 26- and 52-week taper.

Myelin Oligodendrocyte Glycoprotein Antibody–Positive Optic Neuritis: Clinical Characteristics, Radiologic Clues, and Outcome – 2018 [33–39]

Purpose

To characterize the clinical phenotype of myelin oligodendrocyte glycoprotein antibody (MOG-IgG) optic neuritis [33].

Methods

This was a multicenter observational case series on patients with MOG-IgG-positive optic neuritis. Patients with a history

of optic neuritis and MOG-IgG seropositivity (MOG-IgG binding index >2.5) were considered eligible for inclusion. MOG-IgG was confirmed with Clinical Laboratory Improvement Amendments–validated, fluorescence-activated cell sorter (FACS) testing in the Mayo Clinic Neuroimmunology Laboratory. Medical records were reviewed for eye pain, fundus appearance at onset, visual acuity (VA) at the worst optic neuritis attack nadir and at final follow-up, number of attacks, other neurologic symptoms, magnetic resonance imaging (MRI) findings, immunotherapy, and outcome. VA was converted from Snellen to logarithm of minimum angle of resolution (logMAR) values for statistical analysis. The primary outcome measures were the clinical and radiologic characteristics as well as visual outcomes.

Results

Eighty-seven MOG-IgG-seropositive patients with optic neuritis were included in this study (76 were seen at Mayo Clinic and 11 by neuro-ophthalmologists at other US sites). Thirty-one patients had previously been reported in a series of 246 recurrent optic neuritis subjects [34]. Average age at symptom onset was 31 years (range 2–79 years) and 50 (57%) were female. The median number of optic neuritis attacks was 3 (range 1–8), median follow-up 2.9 years (range 0.5–24 years), and annualized relapse rate 0.8 per year. Average VA at nadir of worst attack was count fingers (CF) and average final VA was 20/30. Final visual acuity was <20/200 in five patients (6%). Optic disc edema and pain with extraocular movements were each present in 86% of patients. Bilateral simultaneous optic neuritis occurred at least once in 32 (37%).

There were 26 patients (30%) with recurrent optic neuritis in absence of other neurologic symptoms, 10 (12%) with a single optic neuritis attack, 14 (16%) with chronic relapsing inflammatory optic neuropathy, and 36 (41%) with optic neuritis and other neurologic symptoms. MRI demonstrated perineural enhancement with extension to the orbital tissues in 50% and longitudinally extensive enhancement of

the optic nerve in 80%; chiasm was involved in 12% of patients. Persistent MOG-IgG seropositivity occurred in 61 of 62 (98%).

Key Points

- MOG optic neuritis is often recurrent and can present with or without associated neurological symptoms.
- A high percentage of patients experience pain, moderate to severe optic nerve disc edema, and bilateral involvement is common.
- MRI features associated with MOG optic neuritis include perineural and periorbital tissue enhancement along with long-segment (>50%) optic nerve involvement.
- Despite the recurrence and severity of the attacks, most patients with MOG optic neuritis maintain excellent vision [35–39]

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Chapter 4
Pediatric Ophthalmology and Strabismus

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Abstract The field of pediatric ophthalmology and strabismus is broad and includes diseases affecting the anterior segment, the posterior segment, visual development, and efferent function. Among the diverse range of potential topics, we have chosen to focus on four areas: amblyopia, cataract, retinopathy of prematurity, and strabismus. These four areas cover important topics that reflect diseases commonly

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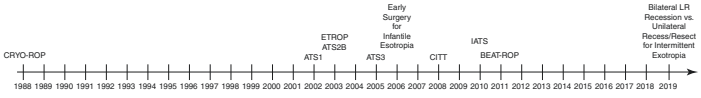
encountered by pediatric ophthalmologists. The clinical studies relevant to each of these topics have been selected as foundational for the influence that these studies play in defining current clinical practice and treatment.



Amblyopia

Amblyopia is characterized by subnormal vision which results from an interruption of normal visual development. Underlying causes may include strabismus, refractive error, or deprivation of visual input during the critical window of visual maturation. Amblyopia is a significant cause of visual impairment in children and in adults but, with early detection and intervention, may be reversed. Current treatment strategies focus on correction of refractive error, when relevant, and penalization of the non-amblyopic eye with occlusion from patching, optical filters, or atropine. The Amblyopia Treatment Studies are a series of randomized controlled clinical trials, 20 of which have been conducted at the time of this publication, that have defined parameters regarding efficacy of treatment and the timeline within which treatment may be effective. These studies have been undertaken by the Pediatric Eye Disease Investigator Group (PEDIG), a multicenter collaborative network focused on advancing an understanding of pediatric ophthalmology and strabismus through evidence based research. Here we review three critical papers from the Amblyopia Treatment Studies that have shaped our understanding of amblyopia treatment and have informed current clinical practice.

Amblyopia Treatment Study 1 (ATS1) – 2002 [1]

Purpose

While occlusion therapy had been the standard of care for amblyopia treatment, pharmacologic penalization was proposed as an alternative form of treatment, particularly when compliance with occlusion therapy was difficult. This study compared the efficacy of patching versus atropine penalization of the non-amblyopic eye in children three to six years of age with moderate amblyopia.

Methods

This randomized clinical trial prospectively enrolled subjects from 47 clinical sites who fulfilled the following inclusion criteria: age < 7 seven years, moderate amblyopia (visual acuity (VA) of 20/40–20/100 in the amblyopic eye), an intereye logMAR difference of ≥ three lines of vision, and no significant prior amblyopia treatment. Exclusion included myopia >0.5 diopters as atropine penalization would be less effective. Participants were randomized to patching or atropine therapy. The primary outcome was logMAR VA at six months. Treatment success was defined as when the amblyopic eye reached a VA of 20/30 or better or improved three lines from baseline.

For the patching group, participants were patched for a minimum of six hours up to full-time patching. For the atropine penalization group, participants received one drop of atropine sulfate 1% in the sound eye daily. For each group, therapy was continued until treatment success, at which point the therapy could be decreased, or when the VA of the amblyopic eye was equal to the sound eye, at which point therapy was discontinued.

Results

This study enrolled 419 participants with a mean age of 5.3 years. Mean VA of the amblyopic eye at enrollment was 20/63 (0.54 logMAR).

At six months, the VA of the amblyopic eye had improved in both groups: 3.16 and 2.84 lines in the patching and atropine groups, respectively. Initially, patching demonstrated more improvement than atropine, but this difference was not statistically significant by six months of treatment. At six months, 79% of the patching group and 74% of the atropine group had met the definition of treatment success with a mean difference in VA of 0.034 logMAR. Patching adherence was good to excellent in 83% of patching and 96% of atropine participants. A parent questionnaire consistently ranked patching as worse for the three subscales measured (adverse effects, compliance, and social stigma with $p \leq 0.002$). Atropine treatment was associated with a 1-line decrease in VA in the sound eye in a larger proportion of subjects compared with patching (15% vs. 7%), and this was attributed most commonly to improper refractive correction.

Follow-Up Studies

Follow-up studies were performed at the two-year mark and at patient ages 10 and 15 years. All studies demonstrated equivalent VA between the two intervention groups [2–4]. Long term studies did not reveal a sustained effect on the sound eye in either the atropine or patching groups. By age 15 years, 60% of amblyopic eyes were 20/25 or better [4]. Age < five at treatment initiation was a predictor of better amblyopic eye VA in long-term follow up [3, 4].

Key Points

- Atropine penalization and patching therapy are effective treatments for moderate amblyopia for children three to six years of age.
- Patching therapy may result in more rapid improvement while atropine may be better tolerated by patients.
- Patching and atropine penalization maintain equivalency in long-term follow up.

Amblyopia Treatment Study 2B (ATS2B) – 2003 [5]

Purpose

This study was designed to compare patching regimens of two hours versus six hours daily in the treatment of moderate amblyopia for children three to six years old due to a lack of consensus on the effective dosage of occlusion treatment with patching.

Methods

This randomized clinical trial prospectively enrolled subjects from 35 clinical sites who fulfilled the following inclusion criteria: age < seven, moderate amblyopia (visual acuity (VA) of 20/40–20/80 in the amblyopic eye), an intereye logMAR difference of ≥3 lines of vision, and minimal prior amblyopia treatment. Participants were randomized to two hours versus six hours of patching daily with one hour of near work as part of the regimen during patching for both groups. The primary outcome was logMAR VA at four months. Treatment success was defined as when the amblyopic eye reached a VA of 20/32 or better or improved three lines from baseline.

Patients were to continue the two versus six hours of patching for the entire four months unless the VA improved to ≤ one line worse than the sound eye, at which point patching could be modified at the investigator's discretion.

Results

This study enrolled 189 participants with a mean age of 5.2 years. There were 95 in the two-hour group and 94 in the six-hour group with 92 (97%) and 89 (95%) participants completing the four month protocol, respectively. Mean VA of the amblyopic eye at enrollment was 20/63 (0.48 logMAR).

At four months, the VA of the amblyopic eye had improved equally in both groups with a mean improvement of 2.40 lines with a mean logMAR acuity difference of 0.001 between treatment groups. Additionally, 62% of each group met the definition of treatment success.

Patching adherence was good to excellent in 83% of the two-hour and 74% of the six-hour group. There was a one line VA decrease in the sound eye of 14% of patients in the two-hour and 15% of patients in the six-hour group. Reverse amblyopia did not occur for subjects in either group. A parent questionnaire consistently ranked patching duration equally for adverse effects and compliance, but worse for social stigma in the six-hour group.

Key Points

- Patching the sound eye two hours daily is equally effective as six hours daily in the treatment of moderate amblyopia in children three to six years of age, and these results inform current patching dosage regimens for amblyopia treatment.
- Decreased patching time is associated with less social stigma.

Amblyopia Treatment Study 3 (ATS3) [6]

Purpose

Historically, amblyopia treatment was believed be most effective during the critical period of visual development, up to age seven years, but the data regarding whether amblyopia treatment would be successful beyond this time were lacking. This study was designed to determine the efficacy of amblyopia treatment in older children, aged seven to 17 years.

Methods

This randomized clinical trial prospectively enrolled subjects from 49 clinical sites who fulfilled the following inclusion criteria: age seven to 17 years, unilateral moderate to severe

amblyopia (visual acuity (VA) 20/40–20/80 and 20/100–20/400), minimal prior amblyopia treatment, and best-corrected VA 20/25 or better in the sound eye. Participants were randomized to treatment versus optical correction alone. In participants ages seven to 12 ("younger group"), treatment consisted of optical correction, patching two to six hours daily, and atropine sulfate 1% daily. In participants ages 13–17 ("older group"), treatment included patching two to six hours daily. One hour of near work during patching was part of the regimen for both treatment groups.

Primary outcome was determination if a participant was a responder, defined as an improvement of VA by ≥ two lines, or non-responder. Secondary outcomes included improvement to VA 20/25 or better for moderate amblyopia and VA 20/40 or better for severe amblyopia.

Results

This study enrolled 507 participants, 404 in the younger group and in the 92 older group. In the younger group, 53% of the treatment group versus 25% of the optical correction group met responder criteria ($p \leq 0.001$) with an equal benefit seen in moderate and severe amblyopia. Thirty-six versus 14% of participants with moderate amblyopia ($p < 0.001$) and 23% versus 5% with severe amblyopia ($p = 0.004$) met secondary outcome criteria in the treatment and optical correction groups, respectively. Younger age was associated with a higher responder rate across categories.

For the older group, 25% percent of the treatment group versus 23% of the optical correction group met responder criteria with similar rates for moderate and severe amblyopia ($p = 0.22$). There was no significant difference in secondary outcomes between the two groups. However, greater improvement with treatment was seen for those who had no prior amblyopia treatment (47% responder vs. 16%; $p = 0.03$).

Follow-Up Studies

Eighty treatment responders from the above group were followed with 84% completing one year of follow-up [7]. At the

beginning of the observation, participants had a mean improvement of 3.4 lines with 45% reaching a VA of 20/25 or better. By one year, the cumulative probability of losing ≥ two lines was 7% while 82% remained two lines better than pre-treatment [7]. All patients remained better than their pre-treatment VA [7].

Key Points

- For children ages 7–12 with moderate or severe amblyopia, optical correction, patching, and atropine may further improve visual acuity, with the greatest response and improvement in younger patients. These results extend the period for which amblyopia treatment may be effective, thereby supplanting historically accepted age norms for cessation of treatment.
- For children ages 13–17 with moderate or severe amblyopia and no prior treatment, optical correction and patching may further improve visual acuity. However, with prior amblyopia treatment, there does not appear to be benefit to treatment beyond optical correction alone.

Pediatric Cataract

Infantile cataracts require urgent treatment because of the potential for significant deprivation amblyopia. The standard treatment for visually significant cataracts in this age group has been lens removal and refractive correction with contact lenses and/or aphakic spectacles. An intraocular lens (IOL) may then be placed during a secondary surgery later in childhood when visual development is more mature and calculation of the appropriate IOL may be more predictable. In spite of timely removal of the cataract, visual development may still be limited if there is poor compliance with the post-operative regimen of refractive correction and patching, when needed. Further, the need for additional surgery for lens re-proliferation, aphakic glaucoma, and the development of strabismus are several considerations that may adversely impact long-term visual development in this

setting. Given the potential challenges of compliance and advancements with IOLs for treatment of pediatric cataracts, the Infant Aphakia Treatment Study Group performed the seminal Infant Aphakia Treatment Study (IATS) to compare the efficacy of primary IOL implantation versus aphakia and contact lens (CTL) correction for unilateral infantile cataracts. We summarize this trial below, and provide a limited review of the extensive number of follow-up studies which provided long-term data for this surgical intervention.

Infant Aphakia Treatment Study (IATS) – 2010 [8]

Purpose

This study was designed to evaluate the visual outcomes and complications associated with treatment of unilateral, infantile cataract with lens removal and contact lens correction (CTL) versus primary intraocular lens (IOL) placement.

Methods

This randomized, multicenter clinical trial prospectively enrolled infants aged 28–209 days at time of surgery with a unilateral, visually significant cataract (≥3 mm central opacity) from 12 clinical sites. Participants were randomized to primary IOL or aphakia with CTL correction. The primary outcome was grating visual acuity (VA) at one year of age.

For the IOL group, surgery consisted of lens aspiration, placement of an AcrySof SN60AT IOL, posterior capsulectomy, and anterior vitrectomy. Spectacle correction was given for residual refractive error with a goal overcorrection of 2.0D for near focus.

For the aphakia group, surgery consisted of lensectomy and anterior vitrectomy. A Silsoft or rigid gas-permeable CTL was fit with a goal overcorrection of 2.0D for near focus.

All participants were instructed to wear their refractive correction full-time and had standardized instruction regarding patching the non-operated eye to treat deprivation amblyopia.

Results

This study enrolled 114 participants with a median age at surgery of 1.8 months. There was no significant difference in the primary outcome of visual acuity (median VA 0.80 logMAR for aphakia, 0.97 logMAR for IOL; $p = 0.19$). In the untreated eye, the median VA in both groups was 0.66 logMAR.

The IOL group had significantly more intraoperative complications (28% vs 11%; $p = 0.03$), and need for additional intraocular interventions within one year (63% vs 12%; $p < 0.001$). Additionally, 77% of the IOL group had ≥ one adverse event compared to 25% of the aphakia group ($p < 0.001$). The rate of glaucoma was not significantly different between groups (12% IOL versus 5% aphakia; $p = 0.32$).

Follow-Up Studies

At 10.5 years follow up, data for 110/114 patients demonstrated a median logMAR VA of 0.89 and 0.86 for the IOL and aphakia groups, respectively ($p = 0.82$) [9]. Participants had a VA of ≥20/40 in 22% of the IOL group versus 27% of the aphakia group, and 44% of each group had a VA ≤20/200 [9].

Five-year complications rates included an adverse event rate of 81% versus 56% ($p = 0.008$) and an additional surgery rate of 72% versus 16% ($p < 0.0001$) for IOL and aphakia groups, respectively [10]. Five-year glaucoma rates were similar between the two groups, 19% versus 14% for IOL and aphakia groups, respectively [11]. At five years, 81% of participants developed strabismus with no significant difference in the rate of orthotropia [12].

As a follow-up study to IATS, the Toddler Aphakia and Pseudophakia Study (TAPS) was a retrospective study assessing IOL implantation in children aged six months to two years. Of 56 patients, 91% received an IOL, additional surgery was needed in 14%, and median VA was 0.80 logMAR in the operative eye. Toddlers between 13 and 24 months were more likely to develop good VA (>20/40) compared with the seven to 12 month cohort (19% versus 0%). Compared to the IOL cohort of IATS, the older patients had lower intraocular complications, lower adverse events, lower reoperations, and a

lower glaucoma suspect rate (2%) thereby supporting the relative safety of IOL implantation in pediatric patients between six months and two years of age [13].

Key Points

- There was no significant difference in one-year or 10-year visual acuity between the patients with an intraocular lens (IOL) placed earlier than six months of age versus those left aphakic with contact lens correction.
- Those with an IOL had a five times higher rate of intraoperative complications and need for additional intraocular procedures at one year raising concern for early (< six months) implantation of IOLs for treatment of infantile cataracts.
- Follow-up studies suggest that IOL implantation after age six months is associated with lower overall complication rates but similar visual outcomes.

Retinopathy of Prematurity

Retinopathy of prematurity (ROP) is a disorder characterized by abnormalities in the development of the retinal vasculature and retina itself with the potential for profound vision loss from distortion of the retina (i.e. macular dragging or retinal folds) and retinal detachment. ROP remains a significant cause of childhood blindness particularly in industrialized countries where neonatal care has improved overall survival of premature infants. The pathogenesis of ROP is complex and beyond the scope of this section, but involves the activation of endogenous signals for neovascularization of the retina such as vascular endothelial growth factor (VEGF) and exogenous inputs such as oxygen which impact this signaling. Treatment of ROP has focused on ablative therapies such as cryotherapy and laser to avascular retina and more recently, on therapies focused on inducing regression of neovascularization through injection of anti-VEGF medications. Here, we present three clinical trials that have helped to shape our current treatment of ROP: the Multicenter Trial of Cryotherapy

for ROP (CRYO-ROP), Early Treatment of ROP (ETROP), and Bevacizumab Eliminates the Angiogenic Threat of ROP (BEAT-ROP). To understand these articles we must first address the definition and classification of ROP from the International Classification of Retinopathy of Prematurity (ICROP), which was first proposed in 1984 and last revisited in 2005 [14]. ICROP classified ROP as follows [14]:

- Location, or zone: zone I a circle centered around the optic disc with a radius twice the distance from nerve to macula, zone II a circle with a radius from the nerve to the nasal ora serrata, and zone III comprising the residual temporal crescent of retina
- Severity of disease, or stage: stage 1 a demarcation line, stage 2 a three-dimensional ridge, stage 3 extraretinal fibrovascular proliferation, stage 4 a partial retinal detachment, and stage 5 total retinal detachment
- Extent of disease in clock hours
- Presence of plus or pre-plus disease: a defined amount of posterior pole retinal vascular arterial tortuosity and venous dilation in comparison to standard photographs

This classification is used as the basis for uniform diagnosis and consensus amongst providers.

Multicenter Trial of Cryotherapy for Retinopathy of Prematurity (CRYO-ROP) – 1988 [15]

Purpose

This study was designed to test the safety and efficacy of cryotherapy for the treatment of retinopathy of prematurity (ROP) based on initial evidence from Japan dating to the early 1970s.

Methods

This randomized, multicenter clinical trial evaluated infants for eligibility with a low birth weight (<1251 g) who were screened for ROP at 23 clinical centers. On reaching "threshold" disease, defined as five contiguous or eight cumulative

clock hours of stage 3 ROP in zone I or II with plus disease, infants were randomized in the study. For bilateral disease, one eye was randomly assigned to receive cryotherapy. For asymmetric disease where only one eye reached threshold, that eye was randomized to cryotherapy versus no treatment. Cryotherapy was performed within 72 hours of randomization to prevent further progression to stage 4 ROP and, if a second cryotherapy session was indicated, it was performed within 17 days of the first treatment. Infants were followed at three and 12 months for presence of an unfavorable structural outcome, defined as a retinal fold involving the macula, retinal detachment (RD) involving zone I, or a retrolental mass.

Results

Overall, 3862 infants met eligibility criteria for ROP monitoring and ultimately, 291 infants were randomized into the trial, 172 of whom completed the three-month evaluation. The average birth weight was 801 g and 82% had symmetric disease. The mean age of treatment after delivery was 11.4 weeks, and treatment consisted of 52 applications of cryotherapy on average per eye.

Adverse outcomes were significantly reduced with cryotherapy treatment (rate of 21.8% with cryotherapy compared to 43% in untreated eyes; $p < 0.00001$). In infants with symmetric disease, treatment resulted in a 50% reduction of adverse outcomes. Given the strength of these statistics, enrollment was stopped early.

Ocular side effects of treatment included retinal or vitreous hemorrhage (19.1%), conjunctival or subconjunctival hematoma (10.2%), conjunctival laceration (5.1%), and proptosis from diffusion of the local anesthetic (1.3%). Systemic side effects included bradycardia/arrhythmia (8.9%) and cyanosis (1.9%). No deaths or inadvertent damage of the central retinal artery, optic nerve, macula, or eye muscle were noted.

Follow-Up Studies

After the initial CRYO-ROP trial, 97% of surviving children (247/255) completed a 10-year examination, 202 with bilateral and 45 with asymmetric disease [16]. Overall cryotherapy

was associated with a 28.5% reduction in unfavorable outcomes for visual acuity (VA) (20/200 or worse; $p < 0.001$) and a 43.2% reduction in abnormalities of the anatomy of the fundus ($p < 0.001$) [16]. A visual acuity of 20/40 or better was equivalent between the control and treatment groups ($p = 0.63$). Control eyes had a higher rate of RD (41.4%) while the treated eye rate remained stable (21.7%; $p < 0.001$) at 10 years [16].

Key Points

- Treatment of "threshold" ROP with cryotherapy reduced unfavorable outcomes by 50% demonstrating the value of managing ROP with cryotherapy.
- Treatment with cryotherapy did not improve the number of eyes with vision better than 20/40, but did reduce the number of eyes with vision less than 20/200 in long-term follow up.

Early Treatment of Retinopathy of Prematurity (ETROP) - 2003 [17]

Purpose

In light of the favorable results of the CRYO-ROP clinical trial, there was a strong desire to further lower the complication rate from retinopathy of prematurity (ROP) by considering earlier treatment. This study was designed to assess outcomes for treatment of high-risk "prethreshold" ROP compared to the conventional treatment, as defined by CRYO-ROP [15].

Methods

This multicenter, randomized clinical trial evaluated infants for eligibility with a low birth weight (<1251 g) who were screened for ROP at 26 clinical sites. If one eye developed prethreshold disease (defined as zone I that did not meet threshold criteria, i.e. zone II stage 2 with plus, zone II stage 3 without plus, or zone II stage 3 with plus less than five contiguous or eight cumulative clock hours [15]), data from that infant were then entered into a risk-analysis program

(RM-ROP2) to predict the likelihood of an unfavorable outcome. Infants with a risk of unfavorable outcome of ≥15% were considered "high risk prethreshold" and then randomized into the study. For infants with one eligible eye, the eye was randomized to early treatment versus conventional treatment [15]. For infants with two eligible eyes, one eye was randomly chosen to receive early treatment. Treatment was performed within 48 hours and included peripheral retinal ablation by laser or cryotherapy.

Infants were followed for a primary outcome of grating visual acuity (VA) and a secondary outcome of structural disease. VA was measured via Teller acuity cards and defined as favorable (≥1.85 cycles/degree) or unfavorable (<1.85 cycles per degree, light perception, or no light perception). An unfavorable structural outcome included CRYO-ROP criteria [15] or requirement for a vitrectomy or buckle procedure.

Results

Of the 828 infants that developed prethreshold disease, 401 were randomized into the study. Bilateral disease was noted in 317 infants while asymmetric disease was noted in 84. Average age of treatment was 35.2 weeks post-menstrual age (PMA) for the early treatment group and 37.0 weeks PMA for the control group.

An unfavorable visual outcome at nine months was noted in 14.5% of early treatment compared to 19.5% of control eyes ($p = 0.01$). An unfavorable structural outcome at nine months was noted in 9.1% versus 15.6% for early treatment versus control, respectively ($p < 0.001$). The early treatment group had approximately twice the rate of systemic complications (apnea, bradycardia, arrhythmia, and cyanosis).

Early treatment was found to be most beneficial for a subgroup of prethreshold ROP. Based on these results, this study proposed an improved clinical algorithm defining type 1 (zone I any stage with plus, zone I stage 3 without plus, or zone II stage 2 or 3 with plus) as those that received more benefit and type 2 (zone I stage 1 or 2 without plus, zone II stage 3 without plus) as those that did not. They recommended treatment for type 1 and close observation for type 2.

Follow-Up Studies

Follow up at age six years was performed on 342 of 370 surviving participants [18]. Overall, a statistically significant decrease in unfavorable outcomes was noted for type 1 eyes only (25.1% early treatment versus 32.8% control) [18]. For all eyes, there was a decrease in unfavorable structural outcomes for the early treatment group (8.9%) compared to the control group (15.2%) [18]. A natural history follow-up of those patients with untreated prethreshold disease demonstrated higher rates of progression to threshold disease in those fitting the criteria for type 1 disease, further supporting a classification of type 1 and type 2 ROP [19].

Key Points

- Accurate clinical staging of ROP is essential in predicting risk of unfavorable outcomes.
- Early peripheral retinal ablation was associated with improved visual acuity in eyes with type 1 ROP, and this study provided a clinical algorithm defining type 1 and type 2 ROP as discussed above.
- Early peripheral retinal ablation was associated with decreased unfavorable structural outcomes through the most recent follow-up at six years.

Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity (BEAT-ROP) – 2011 [20]

Purpose

Research has demonstrated that elevated vascular endothelial growth factor (VEGF) is an important signal for neovascularization in retinopathy of prematurity (ROP), particularly from ages 31 to 44 weeks postmenstrual age (PMA). Historically, treatments have focused on ablation of avascular retina to reduce signaling for neovascularization, but these therapies, such as cryotherapy and laser, result in permanent loss of the peripheral visual field and may induce myopia.

Further, a treatment which might induce regression of ROP rather than ablation of retina would be favored when the ROP is in zone I or has significant plus disease. This study was designed to determine the efficacy of bevacizumab (monoclonal antibody to VEGF-A) monotherapy in the treatment of zone I or II, stage 3 with plus disease ROP.

Methods

This multicenter, randomized clinical trial evaluated infants for eligibility with a birth weight < 1500 g and a gestational age ≤ 30 weeks at 15 clinical sites. Infants who developed stage 3 ROP with plus disease in zone I or II in both eyes were enrolled and randomized by infant to treatment with conventional laser therapy or intravitreal bevacizumab (0.625 mg in 0.025 ml) in both eyes. The primary outcome was recurrence of ROP by 54 weeks PMA, based on data from CRYO-ROP [15] and ETROP [17] indicating that the timeframe to recurrent stage 3+ ROP was before 55 weeks PMA.

Results

This study enrolled 150 infants, 67 with zone I and 83 with zone II disease. Seventy-five were randomized to each group (laser therapy or bevacizumab). Of these subjects, 143 survived to the 54 week PMA examination. The recurrence rate including both zone I and zone II disease was 26% for the laser group and 6% for the bevacizumab group (OR with bevacizumab 0.17; 95% CI 0.05–0.53; p = 0.002) and was significantly higher for zone I disease (46% vs. 6% recurrence; OR with bevacizumab 0.09; 95% CI, 0.02–0.43; p = 0.003), but not for zone II disease (12% vs. 5%; OR with bevacizumab 0.39; 95% CI, 0.07–2.11; p = 0.27). Average time to recurrence was 6.2 versus 16.0 weeks for laser and bevacizumab groups, respectively. For bevacizumab treatment, recurrence was noted in two zone I eyes (one complicated by macular dragging) and four zone II eyes (one infant with bilateral retinal detachments (RD)). For laser treatment, recurrence was noted in 23 zone I eyes (16 with macular dragging, two with RDs) and 9 zone II (six macular dragging, no RDs).

Key Points

- Intravitreal bevacizumab is significantly better than conventional laser treatment for retinopathy or prematurity (ROP) when disease is zone I, stage 3, with plus disease, but not for zone II disease.
- The rate of recurrence of ROP for bevacizumab is lower than conventional laser therapy and delayed compared to laser therapy.
- This study did not examine the local and systemic safety of treatment with bevacizumab in a neonate.
- Treatment with bevacizumab allows for the possibility of normal vascularization of the peripheral retina.

Strabismus

Strabismus refers to ocular misalignment that may result in reduction of vision (strabismic amblyopia), loss of binocular vision/stereopsis, diplopia, and torticollis. Management of strabismus may include glasses, prisms, orthoptic exercises, and surgery, when appropriate. Surgical goals vary based on the timing and type of strabismus. For example, when strabismus occurs early in visual development, a primary goal is preservation or restoration of binocular visual potential. However, surgical method and strategy will be influenced by surgeon preference, and large, randomized controlled trials focusing on surgical strategy and outcomes for strabismus are limited. Here, we examine three key papers for the treatment of three distinct types of strabismus: infantile esotropia, convergence insufficiency, and intermittent exotropia.

Long-Term Motor and Sensory Outcomes After Early Surgery for Infantile Esotropia – 2006 [21]

Purpose

Historically, the safety and efficacy of strabismus surgery in infants was controversial. However, in 1966, Ing et al. demonstrated that early surgery for esotropia before one year of age was safe and would promote the development of binocularity

[22]. Since that seminal paper, the appropriate timing for surgery for infantile esotropia has continued to be examined, with a focus on the impact of early surgery on improved stereopsis compared with later surgery and the possibility of more predictable motor outcomes. This study was designed to assess the sensory and motor outcomes in a group of infants who underwent surgery by six months of age ("early" surgery) compared to a conventional intervention between seven and 12 months of age ("standard" surgery).

Methods

This prospective, non-randomized cohort study assessed children referred from eight pediatric ophthalmologists who met criteria, as informed by the Congenital Esotropia Observational Study (CEOS) [23], for constant esotropia, including a large angle deviation of ≥40 prism diopters (PD) on at least two pre-surgical visits after age 11 weeks and with ≤ + 3.00 diopters of refractive error. Exclusion criteria included paralytic strabismus, neurological defects, or other coexisting diseases. The type of surgical intervention was not specified. Motor success (ocular alignment) was defined as horizontal alignment within 6 PD and was evaluated beyond one year of follow up. Sensory outcomes, including visual acuity, motor fusion, and stereoacuity, were assessed.

Results

128 infants were enrolled: 50 underwent early surgery and 78 standard surgery. The median deviation was 45 PD at the initial pre-operative visit and 55 PD at the final preoperative visit. Characteristics between the early and standard groups were similar, with the exception of age at presentation (16.6 vs. 24.4 weeks; $p < 0.001$) and age at surgery (24.1 vs. 38.0 weeks; $p < 0.001$).

Post-operatively, there was no difference between the two groups in ocular alignment, need for additional surgery, presence of dissociated vertical deviation, amblyopia, or spectacle wear through most recent follow-up. However, there was a difference in motor fusion and stereoacuity. For the early versus standard groups, respectively, peripheral fusion was 77.8% versus 61.4% ($p = 0.02$), central fusion 14.8% versus

2.3% (p = 0.009), and Randot stereopsis 38.0% versus 16.0% (p = 0.003). While 20% of the early group achieved Randot stereopsis of 200 arcseconds or better compared to 9.3% of the standard group (p = 0.05), neither group had high-grade stereopsis of 60 arcseconds or better (4% vs. 1.3%; p = 0.19).

Key Points

- Surgery for constant infantile esotropia by age six months has similar motor and refractive outcomes to that of standard surgical intervention at age seven to 12 months, which suggests that the accuracy of assessment or target angle for surgery is not adversely impacted when early surgery is pursued.
- Early surgical intervention for constant infantile esotropia is associated with a higher prevalence of peripheral fusion, central fusion, and stereopsis, supporting prior work that early surgery is critical for promoting normal visual development.

Convergence Insufficiency Treatment Trial (CITT) – 2008 [24]

Purpose

Convergence insufficiency (CI) refers to a pattern of exodeviation for which the strabismus angle is worse at near than at distance. CI may adversely impact near work and may be associated with symptoms of diplopia and asthenopia. This study was the first large study designed to compare home-based versus office-based treatment for CI.

Methods

This randomized, placebo-controlled study enrolled children ages nine to 17 from nine clinical sites. Inclusion criteria were an exodeviation greater at near than at distance by ≥4 prism diopters (PD), a receded near point of convergence (NPC) ≥ 6 cm, insufficient positive fusional vergence (PFV) at near, and a convergence insufficiency symptom survey

(CISS) score ≥ 16. Patients were randomized to one of four treatment groups. The CI symptom score at 12 weeks was the primary outcome with NPC and PFV evaluated as secondary outcomes.

There were two home-based groups: home-based pencil pushups (HBPP), and home-based computer vergence/accommodative therapy and pencil pushups (HBCVAT+). The HBPP involved bringing a pencil to within 2–3 cm of the brow while trying to keep a target of a 20/60 letter clear and single. This treatment was to be performed for 15 minutes, five days a week. HBCVAT+ performed pencil pushups but for five minutes, five days a week. In addition, a computer-based home therapy system (HTS) used for 15 minutes, five days a week, provided procedures involving accommodative therapy and fusional vergence that supplemented the pencil pushups.

Office-based procedures (OBVAT) focused on typical accommodative therapy and vergence treatments performed during a weekly 60-minute in-office visit. In addition, patients were given home procedures to perform for 15 minutes, five days a week. Office-based placebo therapy (OBPT) had the same time allocated as OBVAT in the office and at home, but the procedures did not have therapeutic value.

Results

221 participants enrolled with a median age of 11.8 years. At baseline they had a mean of 2 PD of exodeviation at distance with 9.3 PD at near, a NPC break-point of 14.2 cm (recovery 17.9 cm), and a PFV break point of 12.7 cm (recovery 8.8 cm). The final follow-up at 12 weeks was completed by 99% of participants.

Overall, the OBVAT group reported lower mean symptoms level by CISS survey, which was found to be statistically significant compared with each of the other treatment groups (6.8 points lower than OBPT, 7.9 lower than HBPP, 8.4 lower than HBCVAT+). The OBVAT group had the greatest improvement in NPC break-point (pair-wise for all groups, $p \leq 0.005$) and PFV at near (pair-wise for all groups,

$p < 0.001$). When combining the CISS score with secondary measures of NPC and PFV to develop a composite outcome after 12 weeks, the OBVAT group did significantly better with 73% considered "successful" or "improved" compared to 43% HBPP, 33% HBCVAT+, and 35% OBPT ($p < 0.002$).

Key Points

- Treatment of convergence insufficiency in children age nine to 17 was most successful, both in symptoms and also in quantitative measures of vergence and accommodation, with office-based therapy performed weekly with home reinforcement compared to office placebo or only home-based therapies.

A Randomized Trial Comparing Bilateral Lateral Rectus Recession Versus Unilateral Recess and Resect for Basic-Type Intermittent Exotropia – 2019 [25]

Purpose

Basic-type intermittent exotropia refers to a pattern of intermittent exotropia for which the angle of distance and near deviations is essentially equal. Surgical management for this type of strabismus is varied, and data to inform surgical strategy have been lacking. This study, performed by the Pediatric Eye Disease Investigator Group (PEDIG), was the first of its kind to compare in a large cohort the long-term outcomes of the most common surgical treatments for intermittent exotropia (IXT): a bilateral lateral rectus recession (BLRc) versus unilateral lateral rectus recession with medial rectus resection (R&R).

Methods

This multicenter, randomized clinical trial enrolled children ages three to <11 years with IXT, no prior strabismus surgery, and near Randot stereoacuity of 400 arcseconds or better from 35 clinical sites. Patients with basic-type IXT and an angle of deviation between 15 and 40 prism diopters (PD)

were included. Participants were randomized within one day of surgery to a BLRc or R&R procedure. For surgery, adjustable suture technique was not permitted. Participants were followed at one week, eight weeks, and then every six months for three years. The primary outcome measure was presence of a suboptimal surgical outcome, defined as persistent exotropia ≥10 PD, consecutive esotropia ≥6 PD, or loss of two octaves of stereoacuity during the study period up to three years follow-up.

Results

197 participants were enrolled with a mean age of 6.2 years and mean angle of exotropia of 28 PD. By three years postoperatively, 46% of patients undergoing BLRc and 37% of patients undergoing R&R had a cumulative probability of a suboptimal surgical outcome, most commonly for residual or recurrent exotropia. At the three-year visit, regardless of prior visits, 29% of patients undergoing BLRc and 17% of patients undergoing R&R met criteria for suboptimal surgical outcome, although these findings were not statistically significant.

Complete or near-complete resolution of the IXT at three years was noted in 30% of BLRc and 45% of R&R, slightly favoring the R&R group. Persistent consecutive esotropia was more common in patients undergoing R&R, but in those patients who did not have a reoperation during the study period, the overcorrection resolved in one of two BLRc patients and seven of seven R&R patients.

There was similar improvement in exotropia control and mean improvement in stereoacuity at distance ($p = 0.82$) and at near ($p = 0.93$) between the two groups. There was no difference between the groups on healthcare-related quality of life via questionnaire.

Key Points

- At three years, there was no statistically significant difference in suboptimal surgical outcomes between bilateral lateral rectus recession (BLRc) and recess and resect (R&R) procedures for the treatment of basic-type intermittent exotropia (IXT) in children ages three to 10.

- BLRc may be associated with higher rates of recurrent exotropia while R&R may be associated with higher rates of post-operative esotropia, though these differences did not reach statistical significance.
- R&R may be associated with higher rates of complete resolution of IXT, though this finding did not reach statistical significance.

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Chapter 5
Retina

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Abstract In the last 20 years, the field of retina has experienced tremendous innovation in the available clinical tools. Though there are many excellent trials investigating various treatment modalities in multiple retinal subspecialties, the current chapter discusses 10 pivotal trials that shape practice today. Summarized below is a combination of carefully chosen historically important, clinically relevant, and epidemiologically significant articles that span a wide range of pathology.

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Results of the Endophthalmitis Vitrectomy Study (EVS) –1995 [1]

Purpose

Historically, intravitreal antibiotics were widely accepted in the management of bacterial endophthalmitis. However, the role of pars plana vitrectomy (PPV) in the initial management of bacterial endophthalmitis was unclear. The Endophthalmitis Vitrectomy Study (EVS) explored the role of initial PPV and the role of intravenous antibiotics in acute post-operative endophthalmitis.

Methods

This was a randomized multi-center trial of 420 patients who developed bacterial endophthalmitis within six weeks of cataract surgery (95%) or secondary lens implantation (5%). Participants were assigned to four treatment groups: initial PPV or vitreous tap (TAP), with or without intravenous antibiotics. Treatment was begun six hours after clinical examination and all patients underwent a diagnostic anterior chamber paracentesis. After the initial PPV or TAP, all patients received an intravitreal injection (INJ) of vancomycin and amikacin, and subconjunctival injection of vancomycin, ceftazadime and dexamethasone. Patients in the systemic antibiotic group received intravenous ceftazidime and amikacin for five to 10 days. The primary endpoint was change in best-corrected visual acuity (BCVA) and ocular media clarity from baseline, and was assessed at three-month and final (nine to 12 month) follow-up. Media clarity was assessed both clinically and by photographic grading.

Results

At three-month and final follow-up, there was no statistically significant difference in BCVA based on treatment assignment. However, subgroup analysis showed that patients with

light perception (LP) vision did better after PPV/INJ, with three times (33% vs. 11%) greater chance of achieving BCVA ≥20/40, two times (56% vs. 30%) greater chance of achieving BCVA ≥20/100, and half the risk (20% vs. 47%) of severe visual loss (5/200). In terms of media clarity, PPV/INJ led to superior clarity at three months (86% vs. 75% TAP/INJ) and at final visit (90% vs. 83% TAP/INJ). 69.3% of cultures were confirmed positive with the majority being gram positive (~94%). There was no difference in visual acuity outcome or media clarity between patients who did and did not receive intravenous antibiotics. Ocular and systemic serious adverse events (SAEs) did not vary substantially between treatment groups. One participant experienced expulsive hemorrhage in the TAP/INJ group while in the PPV/INJ group, two participants each experienced a dislocated intraocular lens and another had a macular infarct.

Follow-up Studies

The current standard regimen for intravitreal antibiotics in cases of suspected bacterial endophthalmitis includes vancomycin for gram-positive coverage and ceftazadime for gram-negative coverage; amikacin has been replaced due to potential retinal toxicity. A subsequent analysis [2] in the EVS showed that ~94% of cases were gram positive (majority coagulase-negative staphylococci) and the remaining 6% were Gram-negative bacteria. Vancomycin was active against all gram-positive isolates while amikacin and ceftazidime were equivalent against gram-negative isolates. The benefit of intravenous antibiotics remains unclear given that bacterial endophthalmitis is predominantly caused by gram-positive organisms, and treatment with intravenous ceftazidime and amikacin (which cover primarily gram-negative organisms) is not the primary treatment choice.

Key Points

- In acute bacterial endophthalmitis after cataract surgery or secondary lens implantation, initial PPV/INJ did not provide benefit over TAP/INJ in the patients with hand motion vision or better.

- However, in patients with LP vision, initial PPV/INJ provided substantial benefit over TAP/INJ.
- Intravenous antibiotics (ceftazadime & amikacin) provide no added visual benefit in acute postoperative bacterial endophthalmitis.

Ranibizumab and Bevacizumab for Neovascular Age-Related Macular Degeneration (CATT) – 2011 [3]

Purpose

In 2006, the efficacy and safety of intravitreal ranibizumab (Lucentis®) were established (MARINA [4], ANCHOR [5]) for neovascular age-related macular degeneration (AMD). Ranibizumab is a monoclonal antibody fragment that binds vascular endothelial growth factor (VEGF) A while bevacizumab (Avastin®) is a monoclonal antibody that also binds VEGF A. Intravenous bevacizumab was approved by the Food & Drug Administration (FDA) for colon cancer but not for ophthalmic (intravitreal) use; nonetheless it was widely used off-label due to its similar therapeutic target, lower cost, and promising results of previous non-randomized studies. However, the comparative intraocular safety, efficacy, and duration of therapy were unknown. The CATT trial explored the safety profile and efficacy of bevacizumab as compared to ranibizumab.

Methods

This was a randomized, single-blinded, multi-center trial of 1185 patients with active choroidal neovascularization (NV), diagnosed by both fluorescein angiography (FA) and optical coherence tomography (OCT). Participants were randomly assigned to four treatment groups: (1) 0.5 mg ranibizumab monthly, (2) 1.25 mg bevacizumab monthly or either medication (3, 4) only when signs of NV were present (as needed). The primary endpoint was noninferiority based on change of BCVA at one year from baseline. Secondary outcomes included percentage of participants with decrease in visual acuity of ≥15 Early Treatment Diabetic Retinopathy Study

(ETDRS) chart letters from baseline, percentage gaining ≥15 letters during the first 36 weeks, number of injections, foveal thickness on OCT, and annual drug costs.

Results

At one year, bevacizumab was noninferior to ranibizumab in the mean change in visual acuity letter score from baseline, both when the injections were given monthly or as needed. Similarly, ranibizumab as needed was equivalent to monthly ranibizumab and monthly bevacizumab. However, the comparison of bevacizumab as needed to bevacizumab monthly or ranibizumab monthly was inconclusive.

For secondary outcomes, the proportions of patients either losing ≥15 letters or gaining ≥15 letters did not differ between groups. While all treatments significantly reduced intraretinal or subretinal fluid, monthly or as needed ranibizumab decreased subfoveal thickness more than monthly bevacizumab (196 μm vs. 164um, $p = 0.03$). Monthly ranibizumab also had a higher rate of fluid free patients compared to monthly bevacizumab (43.7% vs. 26%, $p < 0.001$). There were a total of 11.7 (ranibizumab monthly) and 11.9 (bevacizumab monthly) injections, as compared to 6.9 and 7.7 injections in the ranibizumab and bevacizumab as needed groups, respectively. However, the annual costs for study drug per patient differed significantly, as the cost of ranibizumab ($23,000 for monthly treatment and $13,800 as-needed) was >35 times that of bevacizumab ($595 for monthly treatment and $385 as-needed).

In terms of serious systemic adverse events (SAEs), there was no overall mortality difference between the groups. However, there was a small increased risk for bevacizumab (24.1%) as compared to ranibizumab (19.0%) for any serious SAEs once the dosing-regimen groups were combined ($p = 0.04$). The largest difference was attributed to hospitalizations for infections and gastrointestinal disorders, although a drug-related mechanism was not well understood. Both arterial and venous thrombotic events and ocular adverse events were similar between the groups; however, safety results should be taken with caution, as the study was not powered to detect differences in adverse events based on a specific drug.

Follow-up Studies
The follow-up studies (CATT two-year [6] and CATT five-year [7]) showed similar visual outcomes between bevacizumab and ranibizumab at two years, though there was less gain of visual acuity in the as needed treatment groups. Although visual acuity gains at year one and two were lost at five-year follow up, 50% of eyes had BCVA of 20/40 or better.

Key Points
- Bevacizumab is equivalent to ranibizumab for neovascular AMD in the first year of follow-up when administered on a similar schedule.
- Bevacizumab is significantly cheaper than ranibizumab, which has important economic implications for the treatment of patients with neovascular AMD in the United States.

Intravitreal Aflibercept (VEGF Trap-Eye) in Wet Age-related Macular Degeneration (VIEW 1 & 2) – 2012 [8]

Purpose
Aflibercept is a soluble decoy receptor fusion protein that has substantially higher binding affinity for vascular endothelial growth factor (VEGF) than either bevacizumab or ranibizumab. Intravitreal aflibercept (Eylea®) showed robust resolution of fluid from the central retina and improvement in visual acuity in a Phase 2 (CLEAR-IT 2 [9]) study in patients with neovascular age-related macular degeneration (AMD). Thus, two similar Phase 3 studies (VIEW 1 and VIEW 2) explored the efficacy and safety of aflibercept as compared to ranibizumab.

Methods
This was a randomized, double-masked, multicenter trial of 2419 patients with active subfoveal neovascularization (NV) secondary to choroidal NV. VIEW 1 included patients from the United States of America and Canada while VIEW 2

encompassed Europe, Latin America, Middle East and Asia-Pacific. Participants were randomly assigned to one of four treatment groups: (1) 0.5 mg aflibercept monthly, (2) 2 mg aflibercept monthly or (3) every 2 months, or (4) 0.5 mg ranibizumab monthly. All participants first received three monthly loading doses (at weeks zero, four and eight) and then were subsequently spaced out per treatment group. To establish noninferiority, the prespecified primary endpoint for each study was the proportion of patients who maintained vision at 52 weeks (losing <15 ETDRS letters) with a margin of 10%. The margin was reduced to 7% in the preplanned integrated analysis of both VIEW studies. Secondary outcomes focused on proportion of patients with ≥15 ETDRS letter gain, and anatomic measures (e.g. retinal thickness, persistent fluid).

Results

In both studies, at one year, the proportion of patients who maintained vision was similar among all treatment groups–each aflibercept group achieved statistical noninferiority compared to monthly ranibizumab within the prespecified 10% margin. Analysis of the combination of both studies also met the prespecified 7% noninferiority margin. Important secondary outcomes showed similar proportions of patients achieving both ≥15 ETDRS letter gain as well as dry retinas (absence of intraretinal and subretinal fluid) in all treatment groups. Intraocular and systemic SAEs were similar between both medications.

Follow-up Studies

The VIEW 1 & 2 trials utilized the same dose but switched to an as-needed regimen with defined retreatment criteria and mandatory dosing at least every 12 weeks in year one to two. The results showed a similar small decrease in BCVA in all four treatment groups [10]. The proportions of patients who maintained ≥15 ETDRS letter gain was also similar between treatment groups. Additionally, the decrease in central retinal thickness was maintained at two years.

In 2019, another study (RIVAL [11]) also compared ranibizumab (0.5 mg) to aflibercept (2.0 mg) in wet AMD using a treat-and-extend regimen after an initial three-month

loading dose. Both the change in BCVA from baseline to month 12 and number of injections were similar between the two groups, suggesting neither is superior to the other in terms of visual gains or treatment burden.

The anti-VEGF trials have led to anti-VEGF agents becoming the standard treatment for AMD variants such as polypoidal choroidal vasculopathy (PCV). Given the success of these agents, the previous treatment–photodynamic therapy using verteporfin (PDT) is being used less. EVEREST II [12] and PLANET [13] were recent large multicenter trials in a continuum of other studies that have evaluated anti-VEGF agents in combination with PDT in the treatment of PCV.

Key Points

- Three aflibercept treatment regimens [including monthly (0.5 mg & 2 mg) and every two months (2 mg) after three initial monthly loading doses] were noninferior to monthly ranibizumab in preventing moderate visual acuity loss at one year.
- All three regimens also matched retinal edema and thickness improvement seen with monthly ranibizumab.

Lutein + Zaexanthin and Omega-3 Fatty Acids for Age-related Macular Degeneration (AREDS2) – 2013 [14]

Purpose

Although anti-vascular endothelial growth factor (VEGF) medications are efficacious in treating neovascular age-related macular degeneration (AMD), there are no proven therapies for non-neovascular (dry) AMD. Thus, it is critical to decrease progression from dry AMD to advanced AMD (neovascularization or central geographic atrophy). In 2001, the Age-Related Eye Disease Study (AREDS) [15] showed that daily oral supplementation with high dose antioxidants and zinc reduced the risk of developing advanced AMD at five years by 25% among those with intermediate (category 3) or advanced (category 4) AMD. The AREDS formulation

consisted of vitamin C (500 mg), vitamin E (400 international units), beta-carotene (15 mg), zinc (80 mg as zinc oxide), and copper (2 mg as cupric oxide).

Based on animal and observational studies, other carotenoids (lutein, zeaxanthin) and omega-3 long-chain polyunsaturated fatty acids (DHA & EPA) appeared effective in possibly preventing AMD progression. AREDS2 explored the role of these nutrients in the progression of AMD. A secondary but important goal was to evaluate the elimination of beta-carotene (a carotenoid in the AREDS formulation) given the associated increase in lung cancer rates and mortality in cigarette smokers.

Methods

This was a randomized, double-masked, multicenter trial of 4203 patients at high risk of progression to advanced AMD with either bilateral large drusen or large drusen in one eye and advanced AMD in the fellow eye. Participants were randomized to one of four groups: (1) lutein (10 mg) + zeaxanthin (2 mg), (2) DHA (350 mg) + EPA (650 mg), (3) all four nutrients together, or (4) placebo. All participants also continued daily AREDS supplementation. A secondary randomization placed participants into four further groups: (1) original AREDS formulation, (2) no beta-carotene, (3) lower zinc dose or (4) both a lower zinc dose and elimination of beta-carotene. Baseline serum levels and dietary levels of the study nutrients were measured. The primary outcome was the percentage of participants who developed advanced AMD by five years. One important secondary outcome analysis was comparison of advanced AMD development at five years between original AREDS versus no beta-carotene or reduced zinc formulations.

Results

At five years, the comparison of each treatment group with placebo revealed no statistically significant reduction in progression to advanced AMD or changes in visual acuity; Kaplan-Meier probabilities of progression to advanced AMD by five years were 31%, 29%, 31%, and 30% for placebo, lutein + zeaxanthin, DHA+EPA, and all four nutrients

together, respectively. A subgroup analysis, although not prespecified, revealed a protective role of lutein + zeaxanthin in participants with the lowest dietary intake of these nutrients (HR 0.74, 95% CI 0.59–0.94; p = 0.01). However, the protective effect was not observed with increased lutein + zeaxanthin intake. The secondary randomization analysis showed that eliminating beta-carotene and lowering zinc did not affect progression to advanced AMD.

AREDS2 participants who received AREDS supplementation with beta-carotene had an increase in lung cancer if they were former smokers or quit smoking more than one year prior to the study; there was no increased risk of lung cancer in the lutein + zeaxanthin group.

Key Points

- Addition of either lutein + zeaxanthin or DHA+EPA, or all four nutrients together to the AREDS formulation resulted in similar rates of AMD progression but without further risk reduction.
- In participants with lowest dietary intake of lutein + zeaxanthin, a protective role for advanced AMD progression was observed in the lutein + zeaxanthin supplemental group, though there was no trend with increasing lutein + zeaxanthin intake.
- Eliminating beta-carotene and lowering the zinc dose did not change risk of advanced AMD progression.
- Given the increased risk of lung cancer in former smokers, beta-carotene could be substituted with lutein + zeaxanthin.

Three-Year, Randomized, Sham-Controlled Trial of Dexamethasone Intravitreal Implant in Patients with Diabetic Macular Edema (Ozurdex MEAD) – 2014 [16]

Purpose

Diabetic macular edema (DME) is the most common cause of vision loss in diabetic retinopathy (DR). Historically, the stan-

dard care for DME included focal/grid laser photocoagulation and diabetic glycemic control. The subsequent development of anti-vascular endothelial growth factor (VEGF) agents led to improvements in the treatment of DME (discussed in the next trial). However, inflammatory mediators and other permeability factors in addition to VEGF play a role in DME, suggesting the potential therapeutic role of corticosteroids. Indeed, two studies [17, 18] showed that an intravitreal fluocinolone acetonide insert improved vision in patients with DME. Furthermore, the Diabetic Retinopathy Clinical Research Network (DRCR.net) Protocol I [19] showed similar efficacy of intravitreal triamcinolone or ranibizumab in combination with laser treatment in pseudophakic eyes. The DEX implant (Ozurdex, Allergan) is a sustained-release intravitreal implant of dexamethasone, which is a more potent corticosteroid than triamcinolone. The Ozurdex MEAD study evaluated the safety and efficacy of DEX implant in the treatment of DME.

Methods

Two randomized, multicenter, masked, sham-controlled, trials of 1048 patients with either type 1 or type 2 diabetes, center-involving macular edema, and a BCVA range from 20/50 to 20/200 were conducted. Participants were randomly assigned to one of three treatment groups: (1) DEX implant 0.35 mg, (2) DEX implant 0.7 mg, or (3) sham injection; one eye per participant was randomized to study treatment. DEX or sham was injected at the baseline visit; however, retreatment was possible after six months if there was residual DME.

If a patient lost ≥15 letters or received any other escape therapy (treatment for DME other than study agents), they were required to withdraw from the study. The prespecified primary outcome was the percent of patients with >15 letter improvement in BCVA from baseline at three years. Among other safety measures, intraocular pressure (IOP) and cataract formation were monitored.

Results

At three years, DEX implant was superior to sham, with 22.2% of participants gaining ≥15 letters in the DEX 0.7 mg group, 18.4% in the DEX 0.35 mg group, and 12% in the

sham group ($p < 0.018$). Visual outcomes were consistent over time in pseudophakic patients. In phakic patients the visual benefit was less due to cataract development, although vision improved after cataract surgery. The median number of treatments was four, five and three in the DEX implant 0.7 mg, 0.35 mg and sham groups, respectively.

In phakic eyes, there were significantly more cataract-related adverse events in the DEX 0.7 mg and 0.35 mg as compared to sham (67.9%, 64.1% and 20.4%, respectively). In terms of IOP, about one-third of patients had a clinically significant increase in IOP and approximately 40% required IOP-lowering medications. No implant was removed to control IOP, and three to five (~1–2%) procedures were required for steroid-induced IOP rise in each DEX group. Finally, there was a high rate of patient discontinuation in all groups, but the rate was much higher in the sham group (56.6% vs. 35.9% in DEX 0.7 mg or 33.7% in DEX 0.35 mg) given the lack of efficacy.

Key Points

- Dexamethasone intravitreal implant for the treatment of DME improves visual outcomes when compared to sham over three years.
- Although cataract progression limited visual gains in phakic eyes, cataract removal led to improved and sustained visual acuity.
- The DEX implant provides another tool in addition to anti-VEGF for the treatment of DME.

Aflibercept, Bevacizumab, or Ranibizumab for Diabetic Macular Edema (DRCR.net Protocol T) – 2015 [20]

Purpose

Vascular endothelial growth factor (VEGF) mediates abnormal vascular permeability in diabetic macular edema (DME). In 2012, ranibizumab became the first approved anti-VEGF

treatment for DME, followed by aflibercept in 2014. Similar to its use in AMD, bevacizumab was repackaged and used off-label in the treatment of DME. The DRCR.net Protocol T evaluated the comparative efficacy and safety of intravitreal aflibercept, bevacizumab, and ranibizumab for center-involving DME that caused visual impairment.

Methods

This was a randomized, double-masked, multicenter trial of 660 patients with either type 1 or type 2 diabetes and a BCVA range from ~20/32 to ~20/320. Participants were randomly assigned to one of three treatment groups: (1) aflibercept 2 mg, (2) bevacizumab 1.25 mg, or (3) ranibizumab 0.3 mg. The study drugs were injected at the start (week zero) and then every four weeks unless visual acuity was ≥20/20 and the subfield thickness was below the eligibility threshold. Injections were discontinued if there was no improvement or worsening in response from the past two injections. Focal/grid laser photocoagulation therapy was started at ≥24-week visit for persistent DME. The primary outcome was the mean change in visual acuity one year from baseline.

Results

At one year, the mean improvement in the visual acuity letter score was not significantly different for participants with baseline visual acuities of 20/32–20/40 (aflibercept [+8.0 letters], bevacizumab [+7.5], and ranibizumab [+8.3]). However, in patients with BCVA of 20/50 or worse, the aflibercept group had a larger visual improvement (+18.9 letters) than either bevacizumab (+11.8) or ranibizumab (+14.2). In addition, both aflibercept and ranibizumab decreased central subfield thickness more than bevacizumab, with a final thickness <250 μm in 66%, 36%, and 58% of eyes (aflibercept, bevacizumab, and ranibizumab, respectively).

The median number of injections was nine in the aflibercept group and 10 in the remaining two groups. Focal, grid, or both laser photocoagulation was performed at least once in 37% of aflibercept-treated eyes, 56% of bevacizumab-treated

eyes, and 46% of ranibizumab-treated eyes. However, similar to visual acuity changes, the 20/32–20/40 subgroup had the same number of injections (9) and similar laser photocoagulation rates. Both ocular and systemic SAEs were rare with no significant differences between groups.

Follow-up Studies
The two-year [21] Protocol T results showed that all treatment groups had improved vision from baseline. Like the one-year results, patients with good baseline vision (20/32–20/40) had similar outcomes from any of the three agents. Among eyes with worse baseline vision (≤20/50), aflibercept maintained superior outcomes to bevacizumab but not ranibizumab; with no significant difference between ranibizumab and bevacizumab at two years. In addition, there were more adverse vascular events as defined by the Anti-Platelet Trialists' Collaboration in the ranibizumab group that will require further evaluation in future trials.

Key Points
- Aflibercept, bevacizumab, and ranibizumab are effective and safe treatments for central-involving diabetic macular edema.
- If DME caused mild visual impairment (20/32–20/40), then there was no significant difference in efficacy between the three study drugs. However, if initial visual acuity was ≥20/50, aflibercept was more effective at improving vision at one year with no statistically significant difference between bevacizumab and ranibizumab.

Panretinal Photocoagulation Versus Intravitreous Ranibizumab for Proliferative Diabetic Retinopathy, A Randomized Clinical Trial (DRCR.net Protocol S) – 2015 [22]

Purpose
The standard of care for patients with proliferative diabetic retinopathy (PDR) has historically been panretinal photoco-

agulation (PRP). PRP decreases vascular endothelial growth factor (VEGF) levels by destroying peripheral retina, which can lead to permanent peripheral visual field loss and at times, can exacerbate diabetic macular edema (DME). Given the success of intravitreal anti-VEGF agents in DME and improvement in severity and progression of diabetic retinopathy [23], these agents were proposed to be efficacious for PDR. Thus, Protocol S evaluated the potential efficacy (noninferiority) of ranibizumab compared to PRP in patients with PDR.

Methods

This was a randomized, single-masked, multicenter trial of 305 patients (394 study eyes) with either type 1 or type 2 diabetes and at least one eye with PDR; eyes with DME were allowed. Participants with one study eye were randomly assigned to either: (1) PRP with ranibizumab as needed for DME or (2) ranibizumab 0.5 mg; participants with two study eyes had one eye randomly assigned to PRP and the other eye to ranibizumab. In the PRP group, the procedure (either pattern scan or traditional single shot laser) was started at baseline with additional PRP allowed for increased neovascularization (NV). In the ranibizumab group, injections were given every four weeks through week 12 and then re-treated as necessary based on NV; treatment failure permitted PRP use. DME was treated with ranibizumab at randomization–thereafter, either ranibizumab or focal/grid photocoagulation could be used at investigator discretion. The primary outcome was change in visual acuity from baseline to two years.

Results

At two years, the mean improvement in the visual acuity letter score from baseline was +0.2 in the PRP group and +2.8 in the ranibizumab group ($p < 0.001$), meeting the prespecified noninferiority criterion. While 6% of eyes in the ranibizumab group received PRP, 53% of eyes in the PRP group received ranibizumab for DME. As expected, the PRP group had significantly more peripheral visual field loss (531 dB vs. 213 dB in ranibizumab).

In terms of PDR progression, vitreous hemorrhage occurred more in the PRP group and more vitrectomies were performed (15% of eyes vs. 4% of eyes in ranibizumab group). The rates of inactive or regressed NV at the disc or elsewhere, iris NV and neovascular glaucoma were similar between the ranibizumab and PRP groups. There were no significant SAEs between the two groups.

Follow-up Studies

A secondary analysis [24] of the two-year Protocol S data showed a higher cumulative probability of worsening PDR in the PRP group (42%) versus ranibizumab (34%). Importantly, eyes in the pattern scan laser group were at higher risk for worsening PDR than eyes in the single-spot group (60% vs. 39%, $p = 0.008$ respectively). However, eyes were not assigned randomly to pattern scan or single-spot PRP, so there could be potential bias and confounding.

The five-year [25] Protocol S showed that although there was substantial loss to follow up, visual acuity was similar between both groups. The ranibizumab group had lower rates of vision-impairing DME (cumulative probabilities of 22% vs. 38% in PRP group). Regarding visual field loss, the differences between the two groups diminished over time. Severe vision loss or serious sequelae of PDR were infrequent in both groups. Altogether, these results supported either treatment for PDR.

Intravitreal aflibercept also appears promising as another treatment for PDR. A Phase 2B non-inferiority trial (CLARITY) [26] in the United Kingdom showed that aflibercept was both non-inferior and superior to PRP in BCVA change at one year from baseline.

Key Points

- Ranibizumab was noninferior to PRP in terms of visual acuity change at two years in the treatment of PDR, providing another treatment alternative to PRP.
- Because few eyes in the ranibizumab group received PRP while more than half of eyes in the PRP group received

ranibizumab for DME, the trial essentially evaluated ranibizumab versus PRP plus ranibizumab as needed in the treatment of PDR.
- When choosing treatment for PDR, various patient specific factors should be considered including visit frequency, adherence, and cost.

Five-Year Safety and Performance Results from the Argus II Retinal Prosthesis System Clinical Trial (Argus II) – 2016 [27]

Purpose

Prior to this study, there was no existing proven therapy for the treatment of end-stage Retinitis Pigmentosa (RP) in which the outer retina had substantially degenerated. Retinal prosthesis is one tool that was designed to replace the function of photoreceptors and stimulate secondary retinal neurons, ultimately forming a visual image. In 2002, the first generation retinal prosthesis (Argus® I) was implanted epiretinally in six subjects, showing an increase in spatial vision [28]. The next generation device, Argus® II, evaluated the long-term safety and efficacy of the Argus II System in RP patients with bare light perception (LP) or no light perception (NLP).

Methods

This was a prospective, single-armed, multi-center nonrandomized clinical trial of 29 patients with RP and one patient with choroideremia with bare LP or NLP vision. The Argus II System was implanted in the worse-seeing eye. The primary endpoint for efficacy was visual function as tested by three custom-designed assessments. Additionally, two "real-world" secondary visual function assessments were evaluated. All testing was completed with the Argus II System ON and OFF. In terms of safety, all SAEs due to the device or surgical implantation were recorded.

The Argus II System has multiple components; briefly, the intraocular electrode array is placed epiretinally over the

macula and communicates with a receiving antenna outside the eyes fixed by a scleral band. A small camera mounted on a pair of glasses transmits visual information to a processing unit worn on a belt or shoulder. The data generated is sent via radio-frequency telemetry link from an external antenna on the glasses to the receiving antenna on the eye. The electrode then stimulates inner retinal neurons to generate action potentials that travel through the established visual pathway.

Results

As a group, patients performed better on the three visual function tests with the system ON versus OFF (using their residual visual capacity). They also performed better with the system ON on an individual basis. These results were consistent with the previous three-year data. Finally, patients also performed better with the system ON on "real-world" visual functional assessments.

At five years, 60% of participants had no SAEs; the remaining events were treated with standard ophthalmic care. However, one patient developed a rhegmatogenous retinal detachment in the implanted eye approximately 4.5 years post-implant, causing neovascular glaucoma one year later. Two devices failed ~ four years post-implant, losing the communicating ability between the external and internal antennas. Three devices were explanted, two due to recurrent conjunctival erosion and the third due to chronic hypotony and ptosis.

Key Points

- The Argus II Retinal Prosthesis System functions reliably for at least four years and provides basic visual function to patients with severe vision loss from RP.
- The Argus II System has an acceptable safety profile with few devices failures and explants at 5 years.

Efficacy and Safety of Voretigene Neparvovec (AAV2-hRPE65v2) in Patients with RPE65-Mediated Inherited Retinal Dystrophy: A Randomized, Controlled, Open-Label, Phase 3 Trial – 2017 [29]

Purpose

Inherited retinal dystrophies are rare in the population but cause significant visual impairment. Leber congenital amaurosis (LCA), a RP subtype, has an earlier onset characterized by rapidly progressive vision loss during childhood. Mutations in many genes can lead to LCA; biallelic mutations of the *RPE65* gene, which encodes an enzyme crucial for the visual cycle, leads to disruption of the cycle and eventual blindness.

Using a recombinant Adeno-associated virus (AAV), proof-of-principle for gene augmentation therapy was established and a Phase I trial was safe in all participants. In keeping with progress, the Phase 3 trial of voretigene neparvovec (Luxturna) evaluated safety and efficacy of sequential, bilateral, subretinal administration of voretigene neparvovec in participants with biallelic RPE65-mediated inherited retinal dystrophy.

Methods

This was a randomized, open-label, controlled trial involving two centers and five surgeons, with 29 pediatric and adult patients with a genetically confirmed biallelic *RPE65* gene mutation. Amongst other criteria, participants were required to have bilateral best corrected visual acuity (BCVA) of ≤20/60, and able to perform a standardized multi-luminance mobility test (MLMT). Because of the poor baseline vision of the participants, visual acuity was not a meaningful measure of functional vision. Thus the MLTM, which evaluated a participant's ability to navigate a path filled with obstacles, provided a quantifiably measure of visual acuity, visual field and light sensitivity. Separated

by age and baseline MLMT, participants were randomized to a 2:1 assignment of intervention to control. In the treatment group, a subretinal injection of voretigene neparvovec was performed in the first eye followed by the second eye one to two weeks later. The control group became eligible for bilateral treatment one year after baseline evaluation. The primary endpoint was the change in bilateral MLMT performance (change in lux score for the lowest passing light level) at one year relative to baseline. Secondary efficacy endpoints included full-field sensitivity threshold testing (FST), BCVA and visual field testing.

Results

At one year, the mean change in bilateral MLMT score was 1.8 and 0.2 lux, in the treatment and control groups, respectively ($p = 0.0013$); monocular MLMT scores were similar to bilateral scores. The mean FST increased >2 log units by 30 days and remained stable over the one year – there was no change in the control group. BCVA, averaged over both eyes, showed a mean improvement of 8.1 letters for intervention participants and 1.6 letters for control participants, but was not significant ($p = 0.17$). Finally, the mean sum total degrees of Goldmann visual field (III4e) nearly doubled in the intervention group and decreased in the control group. No viral vector-related SAEs occurred; while most ocular adverse events were mild and resolved, 10% exhibited a retinal tear and 15% developed a cataract.

Key Points

- In this first ever randomized Phase 3 gene therapy trial for a genetic disease, bilateral subretinal AAV resulted in improvement in visual function in patients with LCA (RPE65-mediated inherited retinal dystrophy).
- This landmark study demonstrated proof-of-concept for targeted gene therapy in inherited retinal degeneration.
- No viral vector-related SAEs occurred at the one-year observation period.

Effect of Bevacizumab Versus Aflibercept on Visual Acuity Among Patients with Macular Edema Due to Central Retinal Vein Occlusion- The SCORE2 Randomized Clinical Trial – 2017 [30]

Purpose

Retinal vein occlusion (RVO) is a prevalent retinal vascular disease affecting millions of adults worldwide. Macular edema is the most common cause of vision loss following a RVO. A multitude of studies have investigated the efficacy of anti-vascular endothelial growth factor (VEGF) agents for RVO related macular edema: BRAVO [31] and CRUISE [32] studies demonstrated the efficacy of intravitreal ranibizumab in branch retinal vein occlusion (BRVO) and central retinal vein occlusion (CRVO), respectively, while COPERNICUS [33] & GALILEO [34] showed efficacy of monthly aflibercept for the treatment of macular edema in patients with CRVO.

Similar to its use in AMD, bevacizumab was being used off-label for macular edema from vein occlusions given its previously studied safety profile as well as its efficacy in other retinal diseases. Thus, the SCORE2 trial evaluated the efficacy of bevacizumab as compared to aflibercept for the treatment of center-involving macular edema due to central or hemiretinal vein occlusion (HRVO).

Methods

This was a randomized, single-masked, multicenter trial of 362 patients with either CRVO or HRVO, with center-involving macular edema and best corrected visual acuity (BCVA) from ~20/40–20/400. Participants were randomly assigned 1:1 to intravitreal bevacizumab 1.25 mg every four weeks for six months versus intravitreal aflibercept 2.0 mg every four weeks for six months. Participants were further stratified in three baseline groups of good (20/40–20/63),

moderate (20/80–20/100), or poor (20/125–20/400) BCVA. To establish noninferiority, the prespecified primary outcome was a change in ETDRS visual acuity letter score from baseline, with a noninferior margin of five letters at six months.

Eyes that responded well (prespecified protocol-defined) at six months were randomized to continue monthly treatment or treat-and-extend with same assigned drug. If eyes responded poorly, then the bevacizumab group was switched to aflibercept and the aflibercept group to intravitreal dexamethasone implant.

Results

Of the 362 participants, 85.5% were diagnosed with a CRVO while 14.4% had a HRVO. At six months, bevacizumab was noninferior to aflibercept in terms of a prespecified gained visual acuity score of five letters ($p = 0.001$). In the bevacizumab group, 61% of eyes had >15 letter gain versus 65% in the aflibercept group. There was no difference in treatment effect between the different baseline visual strata. In addition, both groups showed similar reduction in subfield central thickness from baseline and both received approximately six injections the first six months. However, resolution of macular edema was higher in the aflibercept group (54.4%) than bevacizumab (28.5%). Ocular and systemic SAEs were rare in both groups.

Follow-up Studies

Patients who had a protocol-defined "good response" in the first six months of the SCORE2 trial underwent randomization to either continue monthly injections or treat-and-extend (TAE) for an additional six months. The one-year results [35] showed similar visual acuity change from month six to month 12 between monthly aflibercept versus TAE and monthly bevacizumab versus TAE. The TAE schedule led to approximately two fewer injections in each drug group. While promising, caution is warranted due to the large range of the confidence intervals for the visual acuity differences between the monthly and TAE groups, suggesting that the two different dosing regimens may not have similar vision outcomes.

Key Points

- In patients with CRVO or HRVO and secondary center-involving macular edema, intravitreal bevacizumab was noninferior to aflibercept after six months of monthly treatment.
- Although more eyes had resolution of macular edema in the aflibercept group, this difference did not change visual acuity outcomes.

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Chapter 6
Uveitis

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Abstract This is an exciting time in the field of uveitis. There has been an explosion in novel therapies and a wealth of new research in the past several years, perhaps more so than in any other field within ophthalmology.

Uveitis is a broad, diverse, heterogenous field that encompasses infectious, inflammatory and malignant disorders that affect all parts of the eye and orbit. This chapter will highlight clinical studies on the treatment of noninfectious causes of uveitis. The studies presented here focus primarily on uveitis involving the posterior segment, as this subset of inflammation is associated with higher rates of ocular complications and vision loss, and is more difficult to control.

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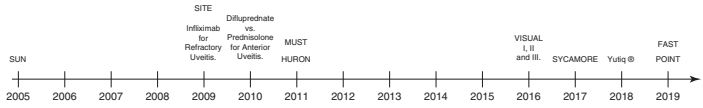
The approach to uveitis treatment is multifactorial and involves topical, local and systemic therapy. The studies presented here explore each of these modalities, with an emphasis on local and systemic therapy. Corticosteroids remain the mainstay of treatment to acutely control inflammation but prolonged systemic use is associated with significant systemic and ocular complications. Therefore, treatment often requires systemic steroid-sparing therapy, in the form of antimetabolites, T-cell inhibitors, and biologic agents inhibiting tumor necrosis factor, many of which will be reviewed here.

The heterogeneity within the field of uveitis, and the fact that individual etiologies are generally rare, dictates that large trials must "lump" rather than "split" diagnoses. This is currently one of the greatest challenges for clinical trial work within uveitis.

Even newer biologic agents targeted toward specific interleukins, T-cells and B-cells are also being studied in uveitis, though space limitations preclude them from being discussed here. Furthermore, this chapter does not review many excellent studies on specific uveitic entities. For additional reading on these therapies, we direct you to the textbook *Treatment of Noninfectious Uveitis* (Editors Phoebe Lin and Eric Suhler, 2019).



Standardization of Uveitis Nomenclature (SUN) Working Group – 2005 [1]

Purpose

To standardize clinical data reporting for uveitis to enhance the comparability of clinical research from different centers and strengthen the field's understanding of disease course and treatment.

Methods

The SUN working group included 50 physicians from 35 centers in 13 countries. Members were surveyed to determine areas of agreement and disagreement within the field. Forty-five members participated in the first workshop, held November 2004. Areas that were addressed included (1) terminology, (2) grading inflammation and documenting complications, and (3) outcomes and results reporting. Results were adopted when there was consensus among the entire group. If no consensus was reached, the topic was deferred for future meetings.

Results

Terminology: The working group established that an anatomic classification of uveitis based on site(s) of inflammation be used. The term "anterior uveitis" should refer to inflammation occurring primarily in the anterior chamber (AC), "intermediate uveitis" for inflammation in the vitreous, and "posterior uveitis" for inflammation of the retina or choroid. The term "panuveitis" should only be reserved for inflammation in all three anatomic regions.

The working group also standardized temporal descriptors for describing disease onset ("sudden" or "insidious"), duration ("limited" or "persistent"), and clinical course ("acute," "recurrent" or "chronic"). The group agreed to develop a reference set of standardized photographs to describe keratic precipitates.

Grading Inflammation and Documenting Complications: Systems for grading AC cells and AC flare were developed. For AC cell, a grade of 0 should be assigned if no cells, 0.5+ for 1–5 cells, 1+ for 6–15 cells, 2+ for 16–25 cells, 3+ for 26–50 cells, and 4+ for >50 cells in a 1 mm × 1 mm slit beam. A similar grade 0 to 4+ scale was developed for anterior chamber flare. The presence or absence of hypopyon should be recorded separately. The National Eye Institute system for grading vitreous haze was adopted [2].

Standardized diagnostic requirements were established to document complications, such as cystoid macular edema,

epiretinal membrane, and subretinal neovascularization, with a preference for use of ancillary studies including optical coherence tomography, fluorescein angiography and indocyanine green angiography. The term "glaucoma" should be used only if there is evidence of glaucomatous optic nerve damage or visual field loss, and should be distinguished from "elevated intraocular pressure (IOP)." A normal range for IOP was not agreed upon, however, a rise of 10 mm Hg was accepted as significant.

Outcomes and results reporting: Definitions of inactive disease (grade 0), improvement (two-step decrease in the level of inflammation or a decrease to inactive), and worsening (two-step increase in the level of inflammation or an increase to the maximum grade) were established. Remission was defined as inactive disease lasting for at least three months after cessation of all treatments. Successful corticosteroid sparing was defined as a reduction in the dose of prednisone to ≤10 mg daily while maintaining inactivity. For reporting visual acuity, the use of logarithmic charts was encouraged, with the establishment of key visual acuity thresholds (6/15 or worse, and 6/60 or worse).

Key Points

- The standardization of uveitis nomenclature, grading scales for inflammation, requirements for documenting complications and recommendations for reporting outcomes were established in this consensus workshop.

Infliximab Therapy for Refractory Uveitis – 2009 [3]

Purpose

To evaluate the use of infliximab for control of refractory uveitis.

Methods

This prospective cohort study enrolled 32 patients over the age of nine with refractory uveitis at a single institution. Key inclusion criteria included vision threatening noninfectious

uveitis with failure or intolerance to systemic corticosteroids and at least one other immunosuppressive medication. Key exclusion criteria included prior treatment with any monoclonal antibody.

Patients received loading infusions of infliximab at weeks zero, two and six, at a dose of 5 mg/kg in patients receiving monotherapy, and 3 mg/kg in patients receiving concomitant non-corticosteroid immunosuppression. In patients who had successful control of their uveitis, infliximab was continued every eight weeks, with dose escalation to a maximum of 10 mg/kg for breakthrough inflammation. The patients were followed for one to two years.

Results

The primary outcome was control of uveitis after initial loading treatment at 10 weeks, as determined by a composite score of visual acuity, inflammation, decrease in oral and topical steroid use, and improvement in cystoid macular edema. At 10 weeks, uveitis was successfully controlled in 77% of patients. Of the seven patients who did not meet criteria, five failed due to lack of efficacy, one withdrew to receive non-study infliximab, and one suffered an adverse event.

Of the patients successfully treated after loading therapy, 60% of patients remained on infliximab therapy at one year, and of those patients, 60% remained on infliximab therapy at two years. Serious adverse events were the main reason for discontinuation of treatment, the most common of which was a drug-related lupus-like illness. Three patients were diagnosed with solid malignant neoplasms, although the causation from infliximab was unclear.

Key Points

- Infliximab therapy was effective in controlling refractory uveitis that had failed other immunosuppressive agents.
- Drug-related lupus-like illness was the most common serious adverse event leading to discontinuation of infliximab.
- This prospective cohort study was limited by its small size and lack of a control group.

Systemic Immunosuppressive Therapy for Eye Diseases (SITE) Cohort Study – 2009 [4]

Purpose

To determine the impact of immunosuppressive drugs used in the setting of ocular inflammatory disease on overall mortality and cancer mortality.

Methods

This retrospective cohort study reviewed 7957 patients with non-infectious ocular inflammation who received care at five tertiary care centers between 1979 and 2005. Systemic inflammatory disease, such as sarcoidosis, juvenile idiopathic arthritis, ankylosing spondylitis and rheumatoid arthritis, with associated ocular inflammation was present in 25.0% of patients. Key exclusion criteria included a diagnosis of HIV. Patients with a known oncologic diagnosis prior to cohort entry were excluded from the survival analysis.

Mortality data and cause of death were obtained from the United States National Death Index. Survival analysis was performed for categories of immunosuppressive agents, as well as individual medications, and adjusted for confounding variables such as age, race, sex, smoking status, site of ocular inflammation, systemic inflammatory disease diagnoses, bilateral ocular inflammation, and other medical comorbidities. The data from the cohort were also compared to mortality data from the United States general population, adjusted for age, race and sex.

Results

Of the entire cohort, 2340 individuals were treated with immunosuppressive therapy, comprising 49,486 person-years before exposure, and 17,316 person-years after exposure to immunomodulatory therapy (total 66,802 person-years). In the cohort, there were 936 deaths, 230 (24.6%) of which were attributed to cancer. Both the overall and cancer mortality for both individuals not exposed to immunosuppressive therapy and for the entire cohort was similar to United States

general population (standardized mortality ratio 1.02 95%, CI 0.94–1.11 for unexposed individuals; standardized mortality ratio 1.03, 95% CI 0.96–1.10 for entire cohort).

Individual analysis on a drug-by-drug basis revealed that patients exposed to antimetabolites (azathioprine, methotrexate, mycophenolate mofetil), T-cell inhibitors (cyclosporine), systemic corticosteroids, or dapsone did not have an increase in overall or cancer mortality compared to patients not exposed to immunosuppressive drugs when adjusted for confounding variables, including systemic disease.

In patients who were treated with alkylating agents (cyclophosphamide, chlorambucil), overall mortality was not increased and cancer mortality was non-significantly increased (overall mortality hazard ratio (HR) 1.17, 95% CI 0.85–1.61 and cancer mortality HR 1.74, 95% CI 0.91–3.32). In patients treated with tumor necrosis factor inhibitors (etanercept, infliximab), there was an increase in overall and cancer mortality, though the data were less robust for this sub-group due to exclusion of many patients with systemic co-morbidities (overall mortality HR 1.99, 95% CI 1.00–3.98 and cancer mortality HR 3.83, 95% CI 1.13–13.01).

There was no dose-response, cumulative dose, threshold dose or highest observed dose relationship for antimetabolites, T-cell inhibitors, alkylating agents, dapsone or systemic corticosteroids that was associated with increased overall or cancer mortality.

Key Points

- Use of most immunosuppressive drugs (azathioprine, methotrexate, mycophenolate mofetil, cyclosporine, systemic corticosteroids, and dapsone) was not associated with an increase in overall mortality or cancer mortality.
- Use of alkylating agents (cyclophosphamide, chlorambucil) may be associated with an increase in cancer mortality risk.
- Use of tumor necrosis factor inhibitors (etanercept, infliximab) may be associated with an increased overall and cancer mortality risk.

- The data for mycophenolate mofetil, chlorambucil and tumor necrosis factor inhibitors were limited. Newer agents, such as adalimumab, lacked sufficient data for analysis.

Difluprednate 0.05% vs Prednisolone Acetate 1% for Anterior Uveitis – 2010 [5]

Purpose

To compare the safety and efficacy of difluprednate 0.05% ophthalmic solution against prednisolone acetate 1% ophthalmic suspension for the treatment of anterior uveitis.

Methods

This double-masked, non-inferiority trial randomized 90 patients over the age of two with anterior uveitis at five institutions. Key inclusion criteria included >10 anterior chamber (AC) cells or AC flare grade ≥2+. Key exclusion criteria were infectious and traumatic etiologies, any intermediate, posterior or panuveitis, > two-week time course to symptoms, prior topical steroid or immunomodulatory therapy use, and glaucoma, ocular hypertension or prior history of steroid response. AC cell grade was assessed by a non-SUN criteria grading scheme.

Patients were randomized to either difluprednate 0.05% ophthalmic solution four times daily (plus four doses of vehicle, n = 50), or prednisolone acetate 1% ophthalmic suspension eight times daily (n = 40). Both groups were treated for 14 days, followed by a two-week tapering regimen. Patients were followed for a total of six weeks.

Results

The primary outcome was change in AC cell grade from baseline at day 14. Difluprednate and prednisolone acetate both improved anterior chamber inflammation, with mean AC cell grade improvement by 2.1 grades in the difluprednate arm and by 1.9 grades in the prednisolone arm, demonstrating noninferiority ($p > 0.05$).

Complete clearance of AC cells was seen in 68.8% of patients who received difluprednate, and 61.5% of patients treated with prednisolone (statistics not reported). More patients from the prednisolone acetate arm (17.5%) discontinued treatment for lack of efficacy as compared to difluprednate arm (2%, p = 0.01).

Adverse events were more common in the difluprednate arm compared to the prednisolone acetate arm, including increase in intraocular pressure (IOP) (difluprednate 12% vs. prednisolone arm 5%), as well as punctate keratitis and ocular surface irritation (statistics not reported).

Key Points

- Difluprednate four times daily was noninferior to prednisolone acetate eight times daily for the treatment of acute anterior uveitis.
- Difluprednate was associated with higher rates of adverse events, including elevated intraocular pressure, though statistics were not reported in this study.
- Limitations of this study included: randomization was not balanced between the groups, AC inflammation grading utilized an independent (non-SUN criteria) system, and patients at risk of developing elevated IOP were excluded.

Dexamethasone Intravitreal Implant (Ozurdex ®) (HURON) Trial – 2011 [6]

Purpose

To evaluate the efficacy of dexamethasone implant for treatment of noninfectious intermediate or posterior uveitis.

Methods

This sham-controlled, masked trial randomized 229 patients over the age of 18 with noninfectious intermediate or posterior uveitis. Key inclusion criteria included vitreous haze of ≥1.5+. Key exclusion criteria included elevated intraocular pressure (IOP), glaucoma, ocular hypertension or prior steroid response,

and prior intraocular or periocular steroid injection. Patients were allowed to be on topical treatment, and stable doses of systemic prednisone or immunomodulatory therapy.

Patients were randomized to either the sustained intravitreal dexamethasone implant (Ozurdex ®) 0.7 mg, 0.35 mg or a sham procedure. Patients were followed for 26 weeks.

Results

The primary outcome was proportion of eyes with no vitreous haze at week eight. Patients receiving the dexamethasone implant showed higher rates of no vitreous haze (dexamethasone 0.7 mg 47%, dexamethasone 0.35 mg 36%, and sham 12%, $p < 0.001$). There was no difference between the two dexamethasone implant groups. The effect persisted through week 26.

Secondary outcomes included best corrected visual acuity. Patients in both dexamethasone groups gained more letters compared to sham: the 0.7 mg group maintained a 10–12 letter improvement throughout the 26 weeks ($p < 0.001$), while the 0.35 mg group also gained 10–12 letters initially but dropped to six letters by week 26 ($p < 0.01$ for all time points except week 26); the sham group gained two to four letters ($p < 0.001$). A greater proportion of patients in both dexamethasone groups improved at least 15 letters compared to sham at all time points ($p < 0.001$).

There was no difference in the proportion of eyes with elevated IOP or cataract formation in either group compared to sham.

Key Points

- The dexamethasone implant was effective for treating intermediate and posterior uveitis, although the study was sham-controlled rather than comparing to standard care.
- There were no differences in rates of elevated IOP or cataract formation in patients who received the dexamethasone implant. However, statistics regarding changes in IOP were not reported and patients at risk of elevated IOP were excluded; cataract development data were limited by the short study period.

Multicenter Uveitis Steroid Treatment (MUST) Trial – (2011–2017) [7–11]

Purpose

To compare the efficacy of a fluocinolone acetonide surgical implant versus systemic immunosuppressive therapy for the treatment of noninfectious intermediate, posterior or panuveitis.

Methods

This randomized, controlled, partially-masked Phase 4 trial enrolled 255 patients age 13 and older with noninfectious intermediate uveitis, posterior uveitis and panuveitis from 23 different institutions. Key inclusion criteria included active disease within the past 60 days requiring systemic corticosteroid therapy. Key exclusion criteria included glaucoma, elevated intraocular pressure (IOP), uncontrolled diabetes and scleritis.

Patients were randomized to either a fluocinolone acetonide 0.59 mg surgical implant (Retisert ®) or systemic immunomodulatory therapy. The implant group was treated with topical, periocular or systemic corticosteroids until anterior chamber cell was less than grade 1+, at which point the implant was placed surgically, followed by a steroid taper. The systemic therapy group was treated with oral corticosteroids at 1 mg/kg daily up to a maximum of 60 mg daily until suppression of uveitis was achieved or for a maximum of four weeks, followed by a steroid taper. Immunomodulatory therapy was indicated for inability to taper prednisone below 10 mg daily, intolerable corticosteroid adverse effects or for specific high-risk uveitic diseases; the specific immunomodulatory drug was left to the discretion of the treating physician. Patients were allowed to cross-over into the other treatment group if their assigned treatment failed to adequately control inflammation.

The implant is designed to release medication for 30 months. Patients were followed for two years during the initial study period. Additional data were reported at 4.5 years and seven years of follow up. By the seven-year time point, there was 70% follow up in each group with approximately 20% cross-over rates in each arm.

Results

The primary outcome was best corrected visual acuity (BCVA) at 24 months. There was no difference in BCVA between the groups, with patients receiving the implant improving 6.0 letters, compared to 3.2 letters in the systemic treatment group ($p = 0.16$). At 54 months, there was similar modest improvement of 2.4 letters in the implant group and 3.1 letters in the systemic treatment group ($p = 0.73$). By seven years, the implant group had lost 6.0 letters, compared to the systemic treatment group, which had gained 1.2 letters ($p = 0.006$).

Secondary outcomes included control of inflammation and ocular and systemic complications. Uveitic activity was controlled in 88% of patients in the implant group compared to 71% in the systemic treatment group at 24 months ($p = 0.001$) and continued to be superior in the implant group at 54 months ($p < 0.016$); by seven years, there was no difference between the groups. Fewer patients treated with the implant had macular edema at six months (20%) compared to the systemic treatment group (34%, $p < 0.001$) but there was no difference at any time point thereafter through seven years.

The implant was associated with higher rates of elevated IOP on multiple measures, including IOP >30, IOP increase >10 from baseline, and new diagnosis of glaucoma requiring treatment (HR >4, $p < 0.0001$ for each measure). Surgical treatment for elevated IOP was necessary in 26% of implant-treated patients by 24 months, compared to 3.7% of systemically-treated patients (HR 8.4, $p < 0.0001$). Between two to seven years, an additional 28.4% of implant-treated patients and 11.4% of systemically treated patients underwent IOP-lowering surgery (HR 2.93, $p < 0.001$).

The implant was also associated with higher rates of cataract formation, with 90.7% of phakic implant-treated patients developing cataract at 24 months, compared to 44.9% of systemically-treated patients (HR 4.12, $p < 0.001$). By 24 months, 80% of phakic implant-treated patients underwent cataract surgery, compared to 31% of systemically-

treated patients (HR 3.3, $p < 0.0001$), which increased to 90% in implant-treated patients and 50% in systemically-treated patients by seven years.

The implant-treated group had lower rates of systemic infections requiring prescription therapy (57.4% vs. 72.3% in the systemically-treated group, $p = 0.02$) but no difference in other systemic complications, including death, malignancy, hospitalization, weight change, diabetes mellitus, osteopenia, osteoporosis, fractures, hypertension, hyperlipidemia, or laboratory abnormalities.

Key Points

- Improvement in BCVA was similar for the fluocinolone acetonide surgical implant and systemic therapy groups through 54 months, but favored systemic therapy by seven years.
- Control of uveitis was superior with the fluocinolone acetonide surgical implant for at least 54 months, but similar by seven years.
- The fluocinolone acetonide surgical implant was associated with much higher rates of ocular complications including elevated IOP and cataract formation.
- Long-term comparison data are difficult to interpret, as the fluocinolone acetonide surgical implant is only designed to last 30 months, and by seven years, 50% of patients were either lost to follow up or had crossed over treatment groups.

VISUAL I, II and III trials: Adalimumab in Patients with Uveitis – (2016–2018) [12–14]

Purpose

To assess the efficacy and safety of adalimumab as a glucocorticoid-sparing agent in active (VISUAL I) and inactive (VISUAL II) noninfectious uveitis, with long-term follow up (VISUAL III).

Methods

VISUAL I: This randomized, controlled, double-masked Phase 3 trial enrolled 217 patients over the age of 18 with active noninfectious intermediate, posterior or panuveitis from 18 different countries. Key inclusion criteria included at least one active chorioretinal or retinal vascular lesion, anterior chamber (AC) cell grade ≥2+ and vitreous haze grade ≥2+ despite at least two weeks of prednisone ≥10 mg daily. Patients were permitted to be on stable doses of methotrexate, mycophenolate mofetil, cyclosporine or azathioprine. Key exclusion criteria included prior treatment with anti-tumor necrosis factor agents, prior treatment failure despite prednisone 60–80 mg daily, current treatment with more than one immunosuppressive agent, recent intraocular or periocular steroid treatment, certain subtypes of uveitis, glaucoma, and demyelinating disease. Patients were randomized to adalimumab loading dose of 80 mg followed by 40 mg every two weeks, or placebo, administered subcutaneously. All patients were treated with a prednisone 60 mg daily burst followed by a 15-week taper. Patients were tapered off any topical steroids over 10 weeks. Patients were followed until treatment failure or to 80 weeks.

VISUAL II: This randomized, controlled, double-masked Phase 3 trial enrolled 226 patients over the age of 18 with inactive steroid-dependent noninfectious intermediate, posterior or panuveitis from 62 sites in 21 countries. Key inclusion criteria included the absence of any active inflammatory chorioretinal vascular lesion, AC cell grade of ≤0.5+, and vitreous haze grade of ≤0.5+ on stable doses of prednisone 10–35 mg daily. Patients must have had at least one flare within 28 days of tapering off systemic corticosteroids in the past 18 months. Key exclusion criteria were similar to VISUAL I. Patients were randomized to adalimumab loading dose of 80 mg followed by 40 mg every two weeks or placebo, administered subcutaneously. Patients were required to taper off prednisone by week 19. Patients were followed until treatment failure or to 80 weeks.

VISUAL III: This Phase 3 open label trial extension enrolled 424 patients from VISUAL I and II who had completed or failed treatment. Patients who had withdrawn or discontinued therapy for any other reason were excluded. Patients were treated with adalimumab 40 mg every two weeks and were permitted to receive systemic corticosteroid therapy at any dose, one additional immunomodulatory agent, and two periocular steroid injections. Intravitreal injections were not permitted. Patients were followed for an additional 78 weeks.

Results

VISUAL I: The primary outcome was time to treatment failure at or after week six. Treatment failure was defined as new inflammatory chorioretinal lesions, AC cell or vitreous haze grade ≥0.5+ at week six or a subsequent two step increase, and worsening of best corrected visual acuity (BCVA) by 15 letters. Patients treated with adalimumab were significantly less likely than those who received placebo to fail treatment (HR 0.50; 95% CI 0.36–0.70; $p < 0.001$). This difference was sustained throughout the length of the study. The median time to treatment failure was 24 weeks in patients treated with adalimumab, compared to 13 weeks for those treated with placebo. Secondary outcomes including change in AC cell grade, vitreous haze grade or BCVA were superior in the adalimumab group ($p < 0.01$ for all).

VISUAL II: The primary outcome was time to treatment failure, which was defined as in VISUAL I. Time to treatment failure was significantly improved in patients receiving adalimumab [median not estimated (>18 months)] compared to patients receiving placebo (8.3 months, HR 0.57, 95% CI 0.39–0.84, $p = 0.004$). This difference was sustained throughout the length of the study. Treatment failure occurred in 39% of patients in the adalimumab group, compared to 55% of patients in the placebo group. Patients were more likely to have failed therapy in the placebo group due to loss of visual acuity (21%) compared to the adalimumab group (9%, $p < 0.01$).

VISUAL III: The primary outcome was disease quiescence, defined as no active inflammatory chorioretinal or inflammatory retinal vascular lesions, AC cell grade ≤0.5+, and vitreous haze grade ≤0.5+ in both eyes. Upon entry into VISUAL III, 65% of patients had active disease (e.g. failed VISUAL I or II), while 35% were inactive (e.g. successfully treated in VISUAL I or II). Of those with active disease, 60% achieved quiescence by week 78, of which 66% were corticosteroid-free and 23% were on doses ≤7.5 mg daily. Mean corticosteroid dose decreased from 13.6 mg daily at study entry to 6.1 mg daily by week 12, and 2.6 mg daily by week 78. Of those with inactive disease, 74% maintained quiescence by week 78, of which 93% were corticosteroid-free. Most patients still remained on other immunomodulatory therapy (78% of patients with active disease and 89% of patients with inactive disease at study entry).

In VISUAL I, adverse events were more frequent in patients treated with adalimumab compared to placebo, including serious adverse events (28.8 per 100 person-years in the adalimumab group, compared to 13.6 per 100 person-years in the placebo group). In VISUAL II, there was no difference in the rates of adverse or serious adverse events between the groups. The rates of serious infections were similar between the groups and rare in both VISUAL I and II.

Key Points

- In active uveitis, adalimumab lowered the risk of uveitis flare and vision loss.
- In inactive uveitis, adalimumab decreased the risk of flare or vision loss with steroid withdrawal.
- Study limitations:
  - VISUAL I and II: Patients were required to rapidly taper off of steroid therapies.
  - VISUAL III: The effect of adalimumab alone was unable to be assessed as other immunomodulatory therapies were permitted; the trial extension also lacked a control group.

SYCAMORE Trial: Adalimumab plus Methotrexate for Uveitis in Juvenile Idiopathic Arthritis – 2017 [15]

Purpose

To determine the efficacy of adalimumab when added to methotrexate for the treatment of juvenile idiopathic arthritis (JIA)-associated uveitis.

Methods

This randomized, placebo-controlled, double-masked trial enrolled 90 patients over the age of two with active JIA-related uveitis from multiple centers in the United Kingdom. Key inclusion criteria included active disease defined as anterior chamber (AC) cell grade ≥1+ within the past 12 weeks despite methotrexate and systemic or topical corticosteroids, and stable methotrexate dose for at least 12 weeks. Key exclusion criteria included prior adalimumab use, prior biologic agent use within five half-lives of the drug, and use of more than six topical glucocorticoid drops daily, prednisone greater than 0.2 mg/kg daily or any other immunomodulatory agent other than methotrexate.

Patients were randomized 2:1 to adalimumab 20 mg or 40 mg (according to body weight), or placebo, administered subcutaneously every two weeks. Patients were continued on their prior methotrexate dose. Patients were followed until treatment failure or for 18 months, plus an additional six months thereafter.

A subsequent retrospective case series reported five-year follow up results of 28 patients enrolled at Bristol Eye Hospital, the largest trial center [16].

Results

The primary outcome was time to treatment failure. Treatment failure was defined as worsening or persistent AC inflammation or coexisting ocular condition (e.g. macular edema), use of ineligible medications, or suspension of trial regimen for

more than four cumulative weeks. The trial was stopped early due to meeting its pre-specified endpoint.

The addition of adalimumab to methotrexate significantly delayed the time to treatment failure (HR 0.25, 95% CI 0.12–0.49, $p < 0.0001$). In the adalimumab group, the median time to failure was not reached (>18 months), compared to 24.1 weeks (95% CI 12.4–81.0 weeks) in the placebo group. In the ADM group, 27% of patients failed treatment, compared to 60% of patients in the placebo group ($p < 0.0001$).

Adverse events and serious adverse events were higher in the adalimumab group (10.07 per person years, 0.29 per person years for serious events), compared to the placebo group (6.51 per person years, 0.19 per person years for serious events). Serious adverse events were driven mostly by infectious complications.

In longer term follow-up at Bristol Eye Center, 26 out of 28 patients flared when adalimumab was discontinued. Of the 19 patients in the adalimumab arm of the trial, 12 completed the trial and 11 (92%) flared after cessation of adalimumab (median time to flare 188 days, range 42–413 days). In total, 25 patients from both arms of the trial were restarted on adalimumab due to either primary treatment failure or subsequent uveitis flare during the extended follow-up period, 11 of whom flared while on adalimumab. The median time to flare following the start of adalimumab during the extended follow-up period was 986 days (95% CI 436–1450 days). There was no long-term change in visual acuity, except for one patient who developed a cataract not requiring surgery. Ocular hypertension was present in 11% of patients. No patients developed new posterior synechiae.

Key Points

- The addition of adalimumab to methotrexate lowered the rate of treatment failure in patients with active JIA-associated uveitis.
- Adalimumab treatment was associated with a higher incidence of adverse and serious adverse events.
- Remission of JIA-associated uveitis did not persist when adalimumab was withdrawn after one to two years of

treatment, leaving questions about how and when to discontinue adalimumab.
- The Bristol Eye Center long-term follow up study was small, retrospective in nature, and lacked a control group.

Injectable Fluocinolone Acetonide Insert (Yutiq ®) Trial – 2018 [17]

Purpose
To assess the safety and efficacy of an injectable intravitreal fluocinolone insert on chronic noninfectious intermediate, posterior and panuveitis.

Methods
This multicenter randomized, sham-controlled trial enrolled 129 patients over the age of 18 with noninfectious intermediate, posterior and panuveitis uveitis. Key inclusion criteria included at least two uveitis recurrences within the past year requiring periocular or systemic therapy, or refractory uveitis requiring recurrent periocular treatment or prolonged systemic treatment within the past year, and vitreous haze worse than grade 2+. Key exclusion criteria included glaucoma, ocular hypertension or elevated intraocular pressure (IOP).

Patients were randomized 2:1 to fluocinolone acetonide 0.18 mg injectable insert versus a sham procedure. Patients were required to taper off all systemic corticosteroids or immunomodulatory therapy prior to entry in the study. Patients were followed for 12 months.

Results
The primary outcome was recurrence of uveitis at six months, as determined by use of any type of corticosteroid therapy or systemic immunomodulatory therapy. In the insert group, 27.6% of patients recurred within six months, compared to 90.5% in the sham group ($p < 0.001$). By 12 months, 37.9% of patients in the insert group experience recurrence of uveitis, compared to 97.6% in the sham group ($p < 0.001$). Median

time to first recurrence was 378 days in the insert group (95% CI 362 days – not evaluable), and 70.5 days in the sham group (95% CI 57–91 days).

Additional secondary outcomes included best corrected visual acuity. Change in visual acuity from baseline did not differ between the groups ($p = 0.35$). However, patients receiving the insert were less likely to lose ≥15 letters (14%) than patients in the sham group (31%, $p = 0.02$).

Adverse events included cataract, which occurred in 33% of patients in the insert group, compared to 12% in the sham group ($p < 0.01$). There was no statistically significant difference in measures of elevated IOP between the groups ($p > 0.01$).

Key Points

- The injectable intravitreal fluocinolone acetonide implant was effective at treating uveitis and decreasing the use of adjunctive systemic therapy, but the study was sham-controlled rather than comparing to standard care.
- The implant was associated with higher rates of cataract formation, but not of elevated IOP.
- Study limitations included patients being required to taper off of all immunomodulatory therapies prior to the trial and exclusion of patients at risk of elevated IOP.

Periocular Versus Intravitreal Corticosteroids for Uveitic Macular Edema (POINT) Trial – 2019 [18]

Purpose

To evaluate the efficacy of periocular versus intravitreal corticosteroid treatment for uveitic macular edema.

Methods

This multicenter, randomized controlled trial enrolled 192 patients with active or inactive noninfectious anterior, intermediate, posterior or panuveitis with associated macular

edema. Key inclusion criteria included central macular subfield thickness greater than 2 standard deviations above normal, visual acuity between 20/40 and 5/200, and stable systemic steroid or immunomodulatory therapy. Key exclusion criteria included elevated intraocular pressure (IOP), or treatment for elevated IOP.

Patients were randomized 1:1:1 to periocular triamcinolone 40 mg (via a posterior sub-Tenon's or periorbital floor injection), intravitreal triamcinolone 4 mg or intravitreal dexamethasone 0.7 mg implant. Patients could be retreated at eight to 12 weeks, with crossover at 12–20 weeks if they did not improve or worsened. Patients were followed for 24 weeks.

Results

The primary outcome was the proportional change central macular subfield thickness (as measured by optical coherence tomography) at eight weeks compared to baseline. All groups reduced macular edema at eight weeks: periocular triamcinolone by 23%, intravitreal triamcinolone by 39%, and intravitreal dexamethasone implant by 46%, with both intravitreal triamcinolone and intravitreal dexamethasone proving superior to periocular triamcinolone ($p < 0.0001$). The dexamethasone implant was noninferior to intravitreal triamcinolone. Both intravitreal treatments were also superior to periocular triamcinolone in improving macular edema at weeks four, eight and 12, but not at week 24.

Intravitreal treatment was associated with higher rates of elevated IOP, including increase in IOP of >10 mm Hg from baseline (HR 2.85, 95% CI 1.30–6.28 for intravitreal dexamethasone; HR 1.92, 95% CI 0.86–4.29 for intravitreal triamcinolone). There was no difference between the two forms of intravitreal treatment.

Key Points

- Intravitreal triamcinolone and dexamethasone were superior to periocular triamcinolone for treating uveitic macular edema with a modest improvement in vision.
- Intravitreal corticosteroids were associated with a higher risk of elevated IOP.

- There were no significant differences in outcomes between intravitreal triamcinolone and the intravitreal dexamethasone implant.
- Data subsequent to the eight-week time point are difficult to interpret, as patients could be re-treated at varying intervals.

First-line Antimetabolites as Steroid-sparing Treatment (FAST) Uveitis Trial – 2019 [19]

Purpose
To compare methotrexate versus mycophenolate mofetil as a first-line steroid-sparing agent for the treatment of noninfectious intermediate, posterior and panuveitis.

Methods
This randomized, masked trial studied 216 patients over the age of 16 with noninfectious intermediate, anterior and intermediate, posterior or panuveitis from nine international centers. Key inclusion criteria included active inflammation within 180 days and at time of enrollment, based on anterior chamber (AC) cell, vitreous haze or active chorioretinal lesions that required steroid-sparing therapy. Key exclusion criteria included prior immunosuppressive therapy other than corticosteroids within the past 12 months, prior treatment with any biologic agent, prior periocular or corticosteroid injection within the past four weeks, or prior fluocinolone acetonide surgical implant within the past three years.

Patients were randomized to methotrexate 25 mg weekly or mycophenolate mofetil 3 g daily. Patients were prescribed oral prednisone 1 mg/kg up to 60 mg daily at enrollment and tapered with a goal of tapering and holding at 7.5 mg daily at month six. Patients could use topical prednisolone tapering to ≤2 drops prednisolone acetate daily by month six. Patients could receive periocular or intravitreal corticosteroid injections if indicated for macular edema. Patients were followed

for six months, at which point patients with treatment success were followed for an additional six months. Patients who failed their initial medication were allowed to crossover treatment groups after six months.

Results

The primary outcome was control of inflammation at six months, as determined by AC cell grade ≤0.5+, vitreous haze grade ≤0.5+, absence of inflammatory chorioretinal lesions, reduction in oral steroid usage to ≤7.5 mg daily and topical steroid usage to ≤2 drops prednisolone acetate-equivalent daily, and no evidence of medication intolerability or adverse events. In patients receiving methotrexate, 66.7% achieved treatment success compared to 57.1% of patients receiving mycophenolate ($p = 0.20$). At 12 months, there were higher rates of treatment success in patients who had failed mycophenolate mofetil and switched to methotrexate (69%) compared to patients who had failed methotrexate and switched to mycophenolate (35%, $p = 0.02$).

Additional secondary outcomes included control of inflammation stratified by anatomical location of uveitis (prespecified analysis, $p = 0.004$ for interaction). When considering only patients with posterior or panuveitis, more patients with methotrexate achieved treatment success (74.4% methotrexate, 55.3% mycophenolate mofetil, $p = 0.02$). When considering only patients with intermediate uveitis, more patients receiving mycophenolate mofetil achieved treatment success though the effect was not statistically significant (63.6% mycophenolate mofetil, 33.3% methotrexate, $p = 0.07$). There was no difference in visual acuity or macular thickness between treatment groups.

Liver function test abnormalities occurred more frequently in patients receiving methotrexate (13.0%) compared to mycophenolate mofetil (7.4%). Serious adverse events were infrequent in both groups, with elevated liver function test levels being the most common drug-related serious adverse event (<3%).

Key Points

- There was no statistically significant difference in treatment efficacy between methotrexate or mycophenolate mofetil as first line steroid-sparing immunosuppressive treatment.
- There may be a difference in response to therapy depending on anatomical subtype of uveitis.
- There was insufficient statistical power to compare treatment efficacy between anatomical sub-types of uveitis.

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Chapter 7
Oculoplastics

Edith R. Reshef and Suzanne K. Freitag

Abstract Clinical outcomes in oculoplastics are often fairly subjective and as such, a variety of effective clinical practice methods have emerged predominantly based on individual clinical experience as well as prospective and retrospective case series. Thyroid eye disease and common orbital or periorbital malignancies lend themselves better to clinical trials. This chapter briefly summarizes key studies and trials that have guided the management of orbital cellulitis, periocular basal cell carcinoma, and non-surgical management of thyroid eye disease.

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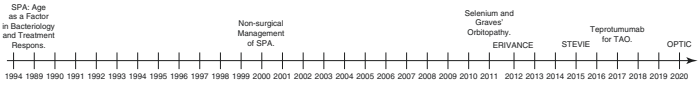

SPI: Age as a Factor in Bacteriology and Response to Treatment [1]

Purpose

To evaluate the role of patient age in the complexity, bacteriology, and responsiveness to treatment of subperiosteal abscess (SPA) secondary to bacterial sinusitis.

Methods

This retrospective study reviewed medical records of 37 patients with a computed tomography diagnosis of SPA at a single institution. Patients were divided into three age groups: younger than nine years old, nine to 14 years old, and 15 years old or older. Responses to therapy and complexity of causative pathogens were assessed for each age group [1].

Results

Among the group of patients younger than nine years old, 83% either cleared their infection without surgical drainage (35%), or had negative cultures from surgical drainage (58%). Of the cases with positive cultures, only single aerobes were isolated. The subgroup of patients ages nine to 14 exhibited an increase in complexity of pathogens. In this group, 25% either cleared their infection without drainage or had negative cultures, and 75% had positive cultures. Of those with positive cultures, four patients had infections refractory to three days of treatment, and three patients had anaerobes isolated from their cultures. The group of patients 15 years or older exhibited the highest complexity of infections, with 100% of patients having persistent posi-

tive cultures after three days of treatment. These infections were often polymicrobial and included anaerobes in every case [1].

Key Points

- Bacteriology and responsiveness to treatment of subperiosteal abscesses seem to increase in complexity with age.
- Expectant observation is recommended for patients younger than nine years old, as they often have single aerobe infections that resolve with intravenous antibiotics alone; surgical intervention becomes warranted for development of visual loss, clinical deterioration after 48 hours, no defervescence within 36 hours, or no improvement after 72 hours.
- Patients older than 15 often require surgical drainage for polymicrobial infections (often including anaerobes).
- Successful nonsurgical management of SPA can be correlated with: age younger than nine, no visual compromise, medial abscess of modest size, no intracranial or frontal sinus involvement.

Criteria for Nonsurgical Management of Subperiosteal Abscess of the Orbit: Analysis of Outcomes [2]

Purpose

To assess the clinical resolution of orbital subperiosteal abscess (SPA) in children younger than 9 years old treated with expectant observation and intravenous antibiotics, based on specific management criteria.

Methods

This prospective case series performed at a single institution applied specific management criteria of SPA to 40 patients younger than nine years old with a computed tomography (CT) confirmed diagnosis of SPA. Expectant observation

with vision and pupil exams every six hours, and treatment with broad-spectrum intravenous antibiotics were applied if all of the following surgical criteria were absent:

1. Age greater than nine years
2. Frontal sinusitis
3. Non-medial SPA
4. Large SPA
5. Suspicion of anaerobic infection (e.g. gas visualized on CT)
6. Recurrence of SPA following prior drainage
7. Chronic sinusitis (e.g. nasal polyps)
8. Acute retinal or optic nerve compromise
9. Infection of dental origin (high suspicion for anaerobic infection)

Patients were treated with four or more days of intravenous antibiotics followed by a three-week course of oral antibiotics, and had 6 months or more of follow-up. Surgical drainage was performed for any one of the following: development of visual loss, absence of defervescence within 36 hours, clinical deterioration after 48 hours, or absence of improvement after 72 hours of medical treatment [2].

Results

Of the 40 patients, three underwent surgical drainage for reasons outside of the study guidelines, and 37 were treated according to the guidelines. Eight of the 37 patients met criteria for prompt surgical drainage. Of the remaining 29 patients, 27 (93.1%) achieved resolution with expectant observation and antibiotics alone. Two patients (6.9%) failed medical therapy and ultimately required surgical drainage. All cases had complete resolution of SPA without sequelae [2].

Key Points

- In patients nine years old or older, orbital SPAs will likely resolve with expectant observation and intravenous antibiotics alone if the above nine surgical criteria are all absent.
- Reverting to surgical intervention in a timely manner based on the above criteria can still yield complete resolution without permanent sequelae.

Selenium and the Course of Mild Graves' Orbitopathy [3]

Purpose
To determine the effect of selenium (antioxidant agent) or pentoxifylline (anti-inflammatory agent) on the clinical course and quality of life of patients with mild Graves' orbitopathy.

Methods
This randomized, double-blind, placebo-controlled trial conducted at six centers in Europe, included 159 patients with mild Graves' orbitopathy of greater than 18 months duration who presented between 2005 and 2009. Patients were randomized to receive sodium selenite (100 μg twice daily), pentoxifylline (600 mg twice daily), or placebo (twice daily) orally for six months, and subsequently followed for six months after treatment completion. The primary outcomes included an assessment of eye changes performed by an ophthalmologist who was blinded to the treatment assignments, and a previously validated Graves' orbitopathy quality-of-life questionnaire completed by the patient. Secondary outcomes included results from a Clinical Activity Score and a diplopia score [3].

Results
At six months, treatment with selenium was associated with less eye involvement ($p = 0.01$), slowed progression of Graves' orbitopathy ($p = 0.01$), and an improved quality of life ($p < 0.001$) and as compared with placebo. The overall ophthalmic outcome improved in 33 of 54 patients (61%) treated with selenium, as compared to 17 of 48 (35%) in the pentoxifylline group, and 18 of 50 patients (36%) in the placebo group. These results persisted six months after treatment was withdrawn ($p = 0.007$ for eye evaluation, and $p < 0.001$ for quality of life). Primary outcomes of treatment with pentoxifylline did not differ significantly from placebo. The mean Clinical Activity Score decreased in all groups, but the reduc-

tions at six and 12 months were significantly greater only in the selenium group. No adverse events were seen with selenium or placebo, but pentoxifylline was associated with frequent skin and gastrointestinal problems [3].

Key Points

- Selenium significantly reduced ocular involvement, slowed progression of disease, and improved quality of life in patients with mild Graves' orbitopathy.
- The clinical improvement from selenium was mainly reflected by improvement of soft-tissue changes and a decrease in eyelid aperture.
- Pentoxifylline did not significantly affect the clinical course or quality of life of patients with mild Graves' orbitopathy.
- The study did not measure selenium levels in the patients either before or after treatment; hence, it is not known if selenium deficiency was present and possibly playing a role.

Efficacy and Safety of Vismodegib in Advanced Basal-Cell Carcinoma (ERIVANCE) [4–6]

Purpose

To evaluate the efficacy and safety of vismodegib (a small molecule inhibitor of the hedgehog pathway) in patients with locally advanced or metastatic basal cell carcinoma.

Methods

This non-randomized, two-cohort, international multicenter phase II trial enrolled 104 patients with either metastatic (n = 33) or locally advanced (n = 71) basal-cell carcinoma for which surgery was deemed inappropriate, across 31 sites from February 2009 to November 2010. All patients received 150 mg of oral vismodegib daily and were followed until dis-

ease progression, unacceptable toxic effects, or study discontinuation. The primary end point was an independently assessed objective response rate (ORR) using previously established guidelines for the metastatic cohort, and using a decrease of greater than or equal to 30% in externally visible or radiographic dimensions, or complete resolution of ulceration, as a response in the locally advanced cohort. Secondary endpoints included investigator-reviewed ORR, duration of response, progression-free survival, overall survival, and safety [4].

Results

Eight patients in the locally advanced cohort were excluded from analysis, as basal cell carcinoma was not identified in baseline specimens. At nine months after completion of accrual, the independently assessed ORRs were 30% in the metastatic basal-cell carcinoma cohort ($p = 0.001$) and 43% in the locally advanced basal-cell carcinoma cohort ($p < 0.001$). The investigator reviewed ORRs were 45% and 60%, respectively. Thirteen patients (21%) in the locally advanced cohort had a complete response, and 54% had no residual disease in biopsy specimens obtained during treatment [4]. After 21 months of follow-up, the ORRs increased from 30.3% to 33.3% in the metastatic cohort, and from 42.9% to 47.6% in the locally advanced cohort [5].

At 39 months, the investigator reviewed ORRs remained comparable to those of preliminary results, with an ORR of 48.5% in the metastatic cohort and 60.3% in the locally advanced cohort. With longer follow-up, the median duration of response increased from 12.9 to 14.8 months in the metastatic cohort and from 7.6 to 26.2 months in the locally aggressive cohort. Twenty patients (32%) in the locally advanced cohort had a complete response. All patients experienced at least one adverse event. Serious adverse events were noted in 36 patients (34.6%), with eight deaths considered to be unrelated to vismodegib. Common (>30%) adverse events included muscle spasms, alopecia, dysgeusia, weight loss, and fatigue [6].

Key Points

- Vismodegib is an effective treatment in patients with metastatic or locally advanced basal-cell carcinoma for whom surgery is not a viable option.
- Long-term follow-up suggests good response durability, consistent efficacy, and an overall favorable safety profile.
- Common adverse reactions of vismodegib include muscle spasms, muscle spasms, alopecia, dysgeusia, weight loss, and fatigue.

Vismodegib in Patients with Advanced Basal Cell Carcinoma (STEVIE) [7, 8]

Purpose

To assess the safety and efficacy of vismodegib for patients with metastatic or locally advanced basal-cell cancer in a setting representative of clinical practice.

Methods

This single-arm, multicenter, open-label phase II trial enrolled 1232 patients at 167 centers in 36 countries between June 2011 and September 2014. Patients were eligible if they were 18 years or older and had histologically confirmed metastatic or locally advanced basal cell carcinoma deemed ineligible for surgical intervention. All patients received 150 mg of oral vismodegib daily in 28-day cycles until disease progression, unacceptable toxicity, withdrawal of consent, or death. Treatment interruption for up to eight weeks was allowed to manage toxic effects. The primary endpoint was safety, which was assessed on day one of each treatment cycle. Secondary endpoints included investigator-assessed objective response, duration of response, time to response, progres-

sion-free survival, overall survival, and quality of life. Tumors were assessed by physical exam every four to eight weeks [7].

Results

Of the enrolled patients, 1215 patients (1119 locally advanced; 96 metastatic) remained eligible for analysis. Of these, 1192 patients (98%) had one or more treatment-emergent adverse events(TEAE), and TEAEs were the main reason for treatment discontinuation (n = 349). The most common TEAEs included muscle spasms (66%), alopecia (62%), dysgeusia (55%), weight loss (41%), decreased appetite (25%) and asthma (24%). Serious TEAEs occurred in 289 patients (23.8%). Fatal TEAEs occurred in 46 patients (3.8%), but these were determined to be unrelated to vismodegib. Exposure of greater than or equal to 12 months did not lead to an increase in severity or incidence of TEAEs. The majority of common TEAEs resolved by 12 months after treatment discontinuation. After a median follow-up of 17.9 months, investigator-assessed response rates were 68.5% in patients with locally advanced disease, and 36.9% in patients with metastatic disease [8].

Key Points

- Vismodegib is tolerable and effective for patients with metastatic or locally advanced basal-cell carcinoma in a clinical practice setting where treatment interruptions may occur.
- Increased treatment interruption was associated with increased median treatment duration and an increased overall response rate.
- The safety profile and response rates of vismodegib in this large study remain consistent with those reported in the ERIVANCE study.
- Long-term exposure of vismodegib was not associated with worsening severity or frequency of adverse events.

Teprotumumab for Thyroid-Associated Ophthalmopathy [9]

Purpose
To assess the efficacy and safety of teprotumumab (a human monoclonal antibody inhibitor of IGF-IR) in patients with active moderate-to-severe Graves' ophthalmopathy.

Methods
This randomized, double-blinded, placebo-controlled phase II trial conducted at 15 sites included 88 patients with active moderate-to-severe Graves' ophthalmopathy without prior surgical or medical treatment, who presented between July 2013 and September 2015. Patients were excluded if they had evidence of optic neuropathy, severe ocular surface damage, or an improvement in Clinical Activity Score between screening and baseline visits. Patients were randomly assigned to receive either an active drug (teprotumumab) or placebo administered intravenously once every three weeks for a total of eight infusions. The primary end point was the response in the study eye, as measured by a two point reduction or more in the Clinical Activity Score, and a reduction of 2 mm or more in proptosis at week 24. Secondary endpoints included proptosis, patients' responses to the Graves' ophthalmopathy-specific quality-of-life questionnaire (GO-QOL), and the Clinical Activity Score [9].

Results
In this intention-to-treat study, 29 of 42 patients (60%) who received teprotumumab versus nine of 45 patients (20%) who received placebo had a response at 24 weeks ($p < 0.001$). The therapeutic effect of teprotumumab was significantly more rapid, with 18 of 42 patients (43%) responding to teprotumumab at six weeks as compared to two of 45 patients (4%) in the placebo group ($p < 0.001$). The difference in response between the groups increased with every time point. Efficacy of teprotumumab persisted at week 28 (seven weeks after administration of the final dose). Hyperglycemia in dia-

betic patients was the only adverse event associated with teprotumumab, and was controlled by adjustment of medications [9].

Key Points

- A 24-week course of teprotumumab was more effective than placebo in reducing the Clinical Activity Score and improving quality of life and diplopia in patients with active moderate-to-severe Graves' ophthalmopathy.
- The onset of therapeutic effect of teprotumumab is rapid and can be seen as early as six weeks following initiation of therapy.
- Teprotumumab has an overall encouraging safety profile, though patients with diabetes should be monitored for hyperglycemia.

Teprotumumab for the Treatment of Active Thyroid Eye Disease (OPTIC) [10]

Purpose

To further evaluate the efficacy and safety of teprotumumab in patients with active moderate-to-severe thyroid eye disease, specifically assessing proptosis as a primary outcome.

Methods

This randomized, double-blinded, placebo-controlled multicenter phase III trial included 83 patients with active thyroid eye disease without prior medical or surgical treatment that presented across 13 sites in the United States and Europe from October 2017 through August 2018. Patients with prior orbital irradiation or surgery, decreasing visual acuity or evidence of optic neuropathy in the prior six months, glucocorticoid treatment for thyroid eye disease, or prior treatment with rituximab or tocilizumab were excluded. Patients were randomized to receive intravenous infusions of either teprotumumab (10 mg/kg for the first infusion and 20 mg/kg for subsequent infusions) or placebo every three weeks for

21 weeks. The primary outcome was a clinically meaningful reduction of proptosis of ≥2 mm at week 24. Secondary outcomes included an overall response (≥2 mm reduction in proptosis and a point reduction of 2 or more in the Clinical Activity Score), a Clinical Activity Score of 0 or 1 (indicating minimal to no inflammation), the mean change in proptosis across visits, a diplopia response (reduction of ≥1 grade in the Gorman subjective diplopia score) and the mean change in score of the Graves' ophthalmopathy-specific quality-of-life (GO-QOL) questionnaire [10].

Results

In this intention-to-treat analysis, 83% of patients in the teprotumumab group showed a proptosis response, as compared to 10% of patients in the placebo group ($p < 0.001$), with a number needed to treat of 1.36. This response was observed early and increased with time. At week 24, the mean change of proptosis from baseline in the teprotumumab group was −3.32 mm (a between-group difference of −2.79). All secondary outcomes in the treatment group were also significantly better ($p \leq 0.001$), including overall response (78% vs. 7%), Clinical Activity Score of 0 or 1 (59% vs. 21%), diplopia response (68% vs. 29%), mean change in proptosis (−2.82 mm vs. −0.54 mm), and mean change in quality of life score (13.79 points vs. 4.43 points). Six patients in the teprotumumab group underwent orbital imaging which showed a reduction in extraocular muscle volume, orbital fat volume, or both, associated with the reduction in proptosis. Most adverse events associated with teprotumumab were mild and self-limited. These included hyperglycemia, hearing impairment, and weight loss. One patient had a severe infusion reaction that led to withdrawal from the trial [10].

Key Points

- Teprotumumab resulted in better outcomes related to proptosis, the Clinical Activity Score, quality of life, and diplopia as compared to placebo.
- The onset of effect of teprotumumab was rapid.

- Orbital imaging showed a correlation between reduction in proptosis and reduction in extraocular muscle and/or orbital fat volume.
- Serious adverse events related to teprotumumab were uncommon.

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Chapter 8
Ocular Trauma

Noam D. Rudnick and Matthew F. Gardiner

Abstract Ocular trauma is a devastating cause of vision loss with a wide variety of presentations. Randomized controlled trials are uncommon in the field of ocular trauma, since each injury is unique and treatment decisions are generally made on a case-by-case basis. Instead, the majority of studies in this field are retrospective case series, often with a focus on open globe injuries. Early studies established standardized terminology for describing ocular injury. Subsequent research determined key factors that predict visual prognosis after ocular injury, such as presenting visual acuity and the presence of a relative afferent pupillary defect. Additional studies have focused on sequelae of open globe injuries such as retinal detachment, proliferative vitreoretinopathy and endophthalmitis. This research has guided the development of standardized protocols for the diagnosis and management of traumatic ocular injuries.

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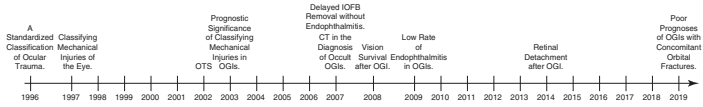

A Standardized Classification of Ocular Trauma – 1996 [1]

Purpose

To develop a standardized system for classifying ocular trauma. This publication was the first to establish consensus terminology and served as the basis for the Birmingham Eye Trauma Terminology (BETT) [2].

Method

A new system for classifying ocular trauma was developed by the authors and was presented internationally starting in 1993. A questionnaire was developed and responses from experts across the world were used to refine the classification system. After a three-year period of optimization, the consensus terminology was finalized [1].

Results

Ocular injuries were first divided into closed globe and open globe injuries. An open globe injury is defined as the presence of a full thickness wound through the cornea or sclera ("eyewall"). Conversely, a closed globe injury is one in which neither the cornea nor the sclera have been breached. A partial thickness eyewall injury is classified as a lamellar laceration. If there is no corneal or scleral wound but internal damage has occurred, then the injury is defined as a contusion. Open globe injuries were further subdivided into rupture or laceration injuries. Rupture occurs when blunt force causes a transient, sudden increase in intraocular pressure leading to a full thickness defect in the eyewall, frequently at its weakest location, and is often accompanied by tissue herniation. A laceration is caused by the direct entry of a sharp object. Laceration injuries were further subdivided into penetrating, intraocular for-

eign body and perforating injuries. Penetrating injury occurs when an object causes an entrance wound through the eyewall but no exit wound is present. An intraocular foreign body injury is a penetrating injury in which an object that causes the entrance wound is retained within the eye. Lastly, a perforating injury is one in which there is both a full thickness entrance wound and a full thickness exit wound [1].

Key Points

- Development of a single international terminology for ocular trauma provides clarity in clinical care and research settings.
- Using this system, open globe injuries can be subdivided into rupture, penetrating, intraocular foreign body and perforating injuries.

A System for Classifying Mechanical Injuries of the Eye – 1997 [3]

Purpose

To expand upon the classification developed by Kuhn et al. [1] to categorize ocular trauma in terms of anatomic and physiologic variables with previously demonstrated prognostic significance.

Methods

A group of 13 ophthalmologists from seven institutions, known as the Ocular Trauma Classification Group, reviewed the ocular trauma literature and developed a new classification system. The intent was to create a simplified system which relied on only a few variables with documented prognostic significance [3].

Results

Separate classification systems for open and closed globe trauma were created, each of which included the following four variables: type of injury, grade of injury, pupillary response and zone of injury. The type of injury was based on

the terminology previously developed by Kuhn et al. [1] and focused on the mechanism of trauma. For open globe injuries, it included rupture, penetrating, intraocular foreign body, perforating and mixed injuries. For closed globe injuries, it included contusion, lamellar laceration, superficial foreign body and mixed injuries. The grade of injury was based on the presenting visual acuity in the affected eye, with five categories ranging from ≥20/40 to no light perception. The pupillary response was defined by the presence or absence of a relative afferent pupillary defect. The zone of injury was based on the anatomical location of the open globe injury or the most posterior structure involved in closed globe injuries. In open globe injuries, Zone I included the cornea and limbus, Zone II included the anterior 5 mm of sclera and Zone III included any scleral injury more than 5 mm posterior to the limbus. In closed globe injuries, Zone I included the conjunctiva, sclera and cornea, Zone II included internal anterior segment structures and Zone III included posterior segment structures [3].

Key Points

- This classification system categorizes open and closed globe injuries based on key anatomic and functional variables with known prognostic utility.
- Because this system relies on only four variables, injuries can be easily categorized with minimal need for ancillary testing.

The Ocular Trauma Score (OTS) – 2002 [4]

Purpose

To develop a reliable method for determining visual prognosis after ocular injuries.

Methods

Over 2500 ocular injuries from the United States and Hungarian Eye Injury Registries were analyzed with attention to over 100 variables that might influence visual prognosis. An ocular trauma score was developed which incorporated six key factors that were determined to make substantial

contributions to final visual acuity and were straightforward to assess on initial examination [4].

Results

The ocular trauma score (OTS) was defined as the sum of numerical values corresponding to presenting visual acuity, presence of globe rupture, endophthalmitis, perforating injury, retinal detachment and relative afferent pupillary defect. The value assigned for visual acuity ranged from 60 (no light perception) to 100 (better than or equal to 20/40). The remaining factors were assigned negative values of different magnitudes. The sum of the raw points yields a number that can be used to stratify visual prognosis into five distinct prognostic groups. Patients with the lowest values have a 74% chance of no light perception vision and only a 1% chance of obtaining visual acuity better than or equal to 20/40 as their final result. Patients with the highest values have a 0% chance of no light perception vision and a 94% chance of obtaining visual acuity better than or equal to 20/40. While initial visual acuity plays a large role in the ocular trauma score, the authors report that the OTC outperforms prognostic methods based on presenting visual acuity alone [4].

Key Points

- The OTS can be used to stratify patients with ocular injuries into prognostic groups based on key presenting factors.
- Key factors in this metric include presenting visual acuity, the presence of globe rupture, perforating injury, endophthalmitis, retinal detachment and a relative afferent pupillary defect.

The Prognostic Significance of a System for Classifying Mechanical Injuries of the Eye in Open-Globe Injuries – 2003 [5]

Purpose

To determine the prognostic significance of the classification system developed by the Ocular Trauma Classification Group

[3], which was based on four key variables: the type of injury, grade of injury, pupil and zone of injury.

Methods

This was a retrospective chart review of open globe injuries presenting to the Wilmer Ophthalmological Institute between December 1985 and January 1993. Eyes were excluded if all four presenting variables were not documented, or if there were fewer than 3 months of follow-up. Based on these criteria, 150 eyes of 150 patients were included in the study. The correlation of each variable in the classification system with final visual acuity was examined. A good visual outcome was defined as visual acuity of 20/40 or better, whereas a poor visual outcome was defined as visual acuity worse than 5/200 [5].

Results

All four variables in the classification system were significant predictors of final visual outcome. For injury type, the probability of obtaining a good visual outcome was highest for penetrating injuries, followed by intraocular foreign body injuries, rupture injuries and finally perforating injuries. As expected, grade of injury was also a significant predictor of final visual outcome, such that presenting visual acuity was correlated with final visual acuity. The presence of a relative afferent pupillary defect was predictive of a poor visual outcome. For zone of injury, more posterior injuries were associated with the worst prognosis. The probability of a good visual outcome was highest for Zone I injuries followed by Zone II and Zone III injuries. A multiple logistic regression model was used to determine which variables were independently associated with visual prognosis. This revealed that the grade of injury (presenting visual acuity) and the pupil exam (presence of a relative afferent pupillary defect) were still significantly associated with final visual outcome after controlling for other variables [5].

Key Points

- The classification system developed by the Ocular Trauma Classification Group has prognostic utility in the setting of open globe injuries.

- Of the variables included in this classification system, presenting visual acuity and the presence of a relative afferent pupillary defect were key predictors of final visual acuity.

Computed Tomography in the Diagnosis of Occult Open-Globe Injuries – 2007 [6]

Purpose
To determine the utility of computed tomography (CT) in the diagnosis of occult open globe injuries, and to determine which specific radiographic signs are most predictive of this diagnosis.

Methods
This was a retrospective chart review of eyes that underwent surgical exploration due to concern for occult open globe injury after evaluation by CT scan between October 1998 and September 2003 at Parkland Memorial Hospital in Dallas, Texas. Eyes with obvious open globe injuries diagnosed at the slit lamp were excluded from this study, as were eyes with metallic intraocular foreign bodies identified on CT scan. In addition to the radiologist that made the original radiographic reading regarding the presence or absence of an open globe injury, the scans were re-evaluated by three masked observers: two neuroradiologists and one ophthalmologist [6].

Results
Forty-eight eyes of 46 patients were included in the analysis. Surgical exploration revealed that an open globe injury was present in 71% of these eyes. The original radiographic reading had a sensitivity of 79% and a specificity of 71% for determining the presence of an open globe injury. Between the three additional expert observers, sensitivity for open globe injury ranged from 56% to 68% and specificity ranged from 79% to 100%. Positive predictive value ranged from 86% to 100% and negative predictive value ranged from 42% to 50%. Positive predictive value was better for patients with blunt trauma compared to patients suffering projectile inju-

ries (94% vs. 75%), whereas negative predictive value was worse for patients with blunt trauma compared to those suffering projectile injuries (33% vs. 70%). CT findings for which there was a statistically significant association with open globe injury included: change in globe contour, globe volume loss, absent/dislocated lens, vitreous hemorrhage and retinal detachment. The most common finding in confirmed open globe injuries was vitreous hemorrhage, and total vitreous hemorrhage was specific to eyes with open globe injuries. Other radiographic findings that were exclusively seen in open globe injuries included moderate change in globe contour, globe volume loss and absence of the lens [6].

Key Points

- CT scans are critical in the workup of potential open globe injuries.
- Certain radiographic findings, such as changes in globe contour and globe volume loss, are highly predictive of open globe injuries.
- CT scans are neither entirely sensitive nor specific for open globe injuries, so ambiguous cases require surgical exploration.

Delayed Intraocular Foreign Body Removal Without Endophthalmitis During Operations Iraqi Freedom and Enduring Freedom – 2007 [7]

Purpose

To determine the long-term outcomes and prognostic factors associated with delayed removal of intraocular foreign bodies (IOFBs) in United States military service members.

Methods

This was a retrospective case series of soldiers deployed during Operation Iraqi Freedom and Operation Enduring Freedom who sustained injuries involving IOFBs. The study

included cases from February 2003 through November 2005. Soldiers with IOFBs underwent primary surgical closure of the globe at a local combat surgical hospital within hours of the injury. After medical stabilization, the patients were subsequently transported to Walter Reed Army Medical Center. Treatment primarily consisted of 20 gauge vitrectomy with IOFB removal, though some patients underwent primary enucleation or observation. The primary outcomes included final visual acuity and the rates of proliferative vitreoretinopathy (PVR) and endophthalmitis [7].

Results

Seventy-nine eyes of 70 soldiers were included in the study. The IOFBs were predominantly metallic, stone/concrete or glass. Overall, 10.1% of eyes had no light perception vision due to severe ocular injury and underwent enucleation, 6.3% of eyes did not undergo IOFB removal because the patient deferred it, while the remaining 83.5% of eyes underwent vitrectomy with IOFB removal. None of the eyes that were enucleated showed evidence of endophthalmitis. Eyes with retained foreign bodies were monitored with serial electroretinography and final visual acuity in these eyes ranged from 20/80 to 20/20. The time from injury to IOFB removal varied widely from two to 661 days, with a median time to removal of 21 days. Mean visual acuity was 20/400 preoperatively and 20/120 postoperatively. Endophthalmitis was not observed in any eyes. Extensive injury involving more than four intraocular structures was the only factor that was significantly associated with a poor visual outcome (visual acuity of 20/800 or worse). Extensive injury and poor presenting visual acuity were both associated with the development of PVR. Time to IOFB removal was not associated with either of these negative outcomes [7].

Key Points

- In a military setting, delayed removal of IOFBs after primary open globe repair does not result in increased rates of endophthalmitis. It remains unknown if these results can be generalized to civilian settings where self-sterilizing hot shrapnel is less common.

- In a military setting, time to IOFB removal is not associated with poor visual outcomes or development of PVR, whereas extensive intraocular injury is key predictor of these negative outcomes.

Vision Survival After Open Globe Injury Predicted by Classification and Regression Tree Analysis – 2008 [8]

Purpose

To develop and validate a prognostic model for predicting visual outcomes after open globe injuries. The authors sought to improve on the Ocular Trauma Score by providing the statistical basis for their model and validating it with an independent cohort.

Methods

This was a retrospective review of patients presenting to the Wilmer Ophthalmological Institute with open globe injuries from January 2001 through December 2004. For patients with bilateral open globe injuries, one eye was randomly selected for inclusion in the initial analysis. The analyzed variables included demographic information, the type and cause of the injury, initial visual acuity, the presence or absence of a relative afferent pupillary defect (rAPD), the anatomical location and length of the wound and the presence of additional ocular, adnexal and orbital injuries. Classification and regression tree (CART) analysis was used to develop a prognostic tree to determine the probability of vision survival (light perception or better) versus complete vision loss (no light perception, enucleation or evisceration). A secondary CART analysis was performed to determine the probability of minimal to severe vision loss (20/400 or better) versus profound vision loss (20/500 or worse, enucleation or evisceration). The models were tested using a validation cohort consisting of open globe injury patients who presented between January 2005 through October 2005, in addition to fellow eyes of patients with bilateral open globe injuries that were excluded from the initial training sample [8].

Results

The training sample consisted of 214 eyes from 214 patients. When CART analysis was used to determine the probability of vision survival versus complete vision loss, the presence of a rAPD was the most predictive variable. The vast majority (96.9%) of eyes without a rAPD maintained some vision. In eyes with an rAPD, poor initial visual acuity was the next highest predictor of complete vision loss, followed by the presence of an eyelid laceration and the presence of a posterior globe injury. In the validation cohort consisting of 51 eyes, the prognostic tree was found to have 85.7% sensitivity for predicting complete vision loss and 91.9% specificity for predicting vision survival. In the secondary CART analysis to determine the probability of minimal to severe vision loss versus profound vision loss, the presence of an rAPD and poor initial visual acuity remained the most predictive variables. However, the next most predictive variables for a poor visual outcome were globe rupture (as compared to laceration injury) and age greater than 38.5 years [8].

Key Points

- Prognostic trees based on a large dataset of open globe injuries can predict visual outcomes with good sensitivity and specificity.
- The presence of a rAPD and poor initial visual acuity are strong predictors of poor visual outcomes in patients with open globe injuries.

Low Rate of Endophthalmitis in a Large Series of Open Globe Injuries – 2009 [9]

Purpose

To quantify rates and risk factors for endophthalmitis in patients with open globe injuries.

Methods

This was a retrospective case series of patients treated surgically for open globe injuries at the Massachusetts Eye and Ear Infirmary from 2000 to 2007. All patients were subject to a standardized protocol which included: initial evaluation in a

dedicated eye emergency room including CT scan of orbits, update of tetanus prophylaxis, admission for IV antibiotics (typically vancomycin q12h and ceftazidime q8h), urgent repair under general anesthesia by the trauma service (or retina service in the case of injuries involving posterior segment intraocular foreign bodies), daily inpatient follow-up and subsequent close outpatient follow up by the trauma service [9].

Results

Of the 675 open globe cases that underwent surgical repair, 558 patients met inclusion criteria (at least 30 days of follow-up, no enucleation within 30 days). Surgery was performed within 24 hours in 80% of cases in which the exact time of injury was known. There were 111 patients (20%) that required lensectomy, and six of these patients underwent intraocular lens placement at the time of the initial surgery. There were 95 patients (17%) with intraocular foreign bodies, and these were uniformly removed during the initial open globe repair. Five patients (<1%) met clinical criteria for endophthalmitis, three of whom had positive cultures (Bacillus cereus, coagulase-negative staphylococcus). Primary lensectomy was not a risk factor for endophthalmitis, but primary intraocular lens placement was associated with increased risk ($p = 0.05$). The presence of an intraocular foreign body at the time of presentation was also associated with an increased rate of endophthalmitis ($p = 0.037$). Other factors that were not associated with a statistically significant difference in the rate of endophthalmitis included: the presence of uveal prolapse, delay in presentation greater than 5 hours, delay in surgical repair greater than 12 hours, or use of vitrectomy during open globe repair [9].

Key Points

- A standardized protocol including 48 hours of intravenous antibiotics and prompt repair by a dedicated eye trauma service resulted in a post-traumatic endophthalmitis rate of less than 1%.
- Risk factors for endophthalmitis include the presence of an intraocular foreign body and primary lens placement at the time of surgical repair.

Retinal Detachment After Open Globe Injury – 2014 [10]

Purpose
To describe the natural history associated with this outcome.

Methods
This was a retrospective chart review of patients who presented to the Massachusetts Eye and Ear Infirmary between February 1999 and November 2011 with open globe injuries. Open globe injuries were repaired urgently and patients were admitted for 48 hours of intravenous antibiotics as described previously [9]. Multivariate logistic regression was used to identify factors associated with development of retinal detachments. Numerous variables were included in this analysis, which included age, gender, mechanism of injury, initial visual acuity, presence of a relative afferent pupillary defect, vitreous hemorrhage, zone of injury and presence of an intraocular foreign body [10].

Results
There were 893 eyes included in this study, and 255 of these eyes were found to develop retinal detachments (29% incidence). Of these eyes, 27% were found to have retinal detachments within 24 hours of open globe repair, 46% within 1 week of repair and 72% within 1 month of repair. Retinal detachment occurred more than 1 year after open globe repair in only 5% of these patients. Multivariate logistic regression revealed that vitreous hemorrhage, poor initial visual acuity on presentation, and more posterior zone of injury were all independently associated with increased risk of retinal detachment. Based on these findings, the Retinal Detachment after Open Globe Injury (RD-OGI) score was developed. In this model, up to 3.5 points were assigned for impairment in visual acuity, up to two points were assigned for posterior zone of injury, and two points were assigned for the presence of vitreous hemorrhage. The probability of retinal detachment ranged from 1% for 0 points to 95% for 7.5 points (maximum) [10].

Key Points

- Predictors of retinal detachment after open globe injury include poor presenting visual acuity, posterior zone of injury and vitreous hemorrhage.
- The RD-OGI score provides an estimate of the probability of retinal detachment after open globe injury and can be used to determine the need for frequent monitoring and referral to a retina specialist.

Poor Prognoses of Open Globe Injuries with Concomitant Orbital Fractures – 2019 [11]

Purpose

To determine whether the presence of an orbital fracture is associated with a worse prognosis for after open globe injury.

Methods

This was a retrospective case series of patients who presented to the Massachusetts Eye and Ear Infirmary for open globe injuries, both with and without concomitant orbital fractures. Chart review of trauma patients between January 2007 and September 2015 yielded 76 patients with combined open globe and orbital fracture injuries. These patients were compared to 77 patients who presented with open globe injuries alone between July 2014 and June 2015. Open globe injuries were repaired by the ocular trauma service and admitted for 48 hours of intravenous antibiotics. Multiple factors including demographic information, mechanism of injury, the presence of an orbital fracture and detailed characteristics of the ocular injury were included in statistical analysis of outcomes data [11].

Results

Patients with combined open globe and orbital fracture injuries were more likely to have incurred blunt force injuries instead of penetrating injuries. Patients without orbital fractures were more likely to have Zone 1 involvement whereas

patients with orbital fractures were more likely to have Zone 2 and Zone 3 involvement as well as involvement of multiple zones. Uveal prolapse was found to be more common in patients with concomitant orbital fractures. Orbital roof fractures were the least frequent wall fractures seen, but they were associated with a higher likelihood of no light perception vision on presentation and the involvement of multiple zones. Patients with orbital fractures were more likely to undergo eventual enucleation/evisceration than patients without fractures (26.3% vs. 6.5%), and multivariate logistical regression revealed that the presence of a fracture was the only factor with a statistically significant effect on the odds of enucleation/evisceration. Excluding patients that underwent enucleation/evisceration, final visual acuity was significantly worse in patients with orbital fractures. The median final best corrected visual acuity was hand motion in patients with orbital fractures versus 20/125 in patients with open globe injuries alone. Patients with orbital fractures were more likely to have no light perception vision (44.6% vs. 7%), and this remained statistically significant after controlling for other factors [11].

Key Points

- Patients with open globe injuries and concomitant orbital fractures are more likely to have posterior ocular injuries that span multiple zones compared to patients with open globe injuries alone.
- The presence of orbital fractures is associated with a worse visual prognosis and higher rates of enucleation.

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