Chapter 2
Cornea

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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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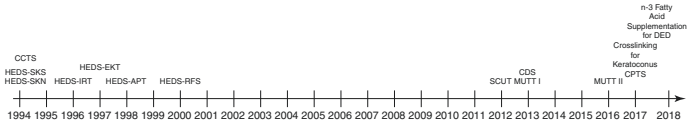

Herpetic Eye Disease Study I (HEDS-I) 1994–1996

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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