Assessing Scientific Literature

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Disclosure

ELZA AG – employment
The challenge of clinical trials (as a medical writer)

Background

ICMJE

GPP

Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals
Updated December 2017

1. About the Recommendations
   A. Purpose of the Recommendations
   B. Who Should Use the Recommendations?
   C. How are the Recommendations Developed?
   D. How are the Recommendations Maintained?

2. Registration
3. Data Sharing
4. Manuscript Preparation and Submission

Good Publication Practice for Communicating Company-Sponsored Medical Research: GPP3

CONSORT
TRANSPARENT REPORTING of TRIALS
Guidelines - ICME

4753 journals adhere (to date)

JCRS - yes

JCRS - no

Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals
Updated December 2017

I. About the Recommendations
A. Purpose of the Recommendations
B. Why Should You Use These Recommendations?

II. Registration
A. Registration of Clinical Trials

III. Manuscript Preparation and Submission

Authorship criteria
Conflicts of Interest
Trial registration
Timely publication (≤12 months of completion)

“Briefly, the ICMJE requires, and recommends that all medical journal editors require, registration of clinical trials in a public trials registry at or before the time of first patient enrollment as a condition of consideration for publication.”
Guidelines: GPP – Good Publication Practice

**Principles of Good Publication Practice for Company-Sponsored Medical Research**

1. The design and results of all clinical trials should be reported in a complete, accurate, balanced, transparent, and timely manner.

2. Reporting and publication processes should follow applicable laws (for example, Food and Drug Administration Amendments Act of 2007) and guidelines (for example, ICMJE recommendations and reporting guidelines found on the Enhancing the QUAlity and Transparency Of health Research [EQUATOR] Network).
For RCTs – but basic principles hold

To enforce

» Transparency
» True randomization
» Sample size generation
» No improper LTFU – higher the rate, the greater the concern
» Follow the patients!
Vigorously debated when presented orally at previous CXL Experts’ meetings

Claim:

“The hot manuscript right now.

“Epithelium-on CXL using this new protocol halted the progression of keratoconus and ectasia after LASIK. It was safer and provided more rapid visual recovery than CXL with epithelial removal, allowing routine bilateral, simultaneous treatment.”
Epi-off vs Epi-on (currently)

Epi-off = Epi-on manuscript
Study design

- Prospective observational study
- Single-arm, open-label

N=592

KC or FFKC
n=512

+ PLE
n=80
CT ≥300 µm

CXLUSA Treatment

UDVA
CDVA
Snellen
Refraction
Pentacam
iTrace

Day week
1
1
1
3
6
12
24
months

END
Patients

Patient Enrolment

N=592

Keratoconus or *forme fruste* keratoconus
n=512

Post-LASIK ectasia
n=80

Unilateral
n=363 (61%)

Bilateral (sequential)
treatment
n=134 (23%)

Bilateral simultaneous
n=95 (16%)

Total bilateral n=229 (39%)

Baseline corneal thickness

* 651 µm

474.8 ± 54.9 µm (mean ± SD)
Median: 474.0 µm

* 302 µm
CXLUSA Treatment protocol

- Instill proparacaine drops (pH=4.64)
- “Gentle brushing” with proparacaine-infused sponge for 15 seconds
CXLUSA Treatment protocol

1. Instill proparacaine drops (pH=4.64)

2. "Gentle brushing" with proparacaine-infused sponge for 15 seconds

3. 1 drop CXLUSA riboflavin q2 minutes onto a different, bespoke sponge for 15–20 minutes

4. Estimate stromal riboflavin concentration at slit lamp with white + cobalt blue light; compare against reference images

Adequate concentration (~15 µg/gm)?

- Yes
- No

Protocol
**Protocol**

- Instill proparacaine drops (pH=4.64)
- 1 drop CXLUSA riboflavin q2 minutes onto a different, bespoke sponge for 15–20 minutes
- "Gentle brushing" with proparacaine-infused sponge for 15 seconds
- Estimate stromal riboflavin concentration at slit lamp with white + cobalt blue light; compare against reference images
- Adequate concentration (~15 µg/gm)?
  - Yes: BSS rinse
  - No: No drops during illumination 365 nm UV at 4 mW/cm², 30 mins, cycled on/off with a proprietary light

"The total energy delivered by this system (3.6 J/cm²)"
CXLUSA Treatment protocol

1. Instill proparacaine drops (pH=4.64)
   - "Gentle brushing" with proparacaine-infused sponge for 15 seconds

2. 1 drop CXLUSA riboflavin q2 minutes onto a different, bespoke sponge for 15–20 minutes
   - Estimate stromal riboflavin concentration at slit lamp with white + cobalt blue light; compare against reference images
   - Adequate concentration (~15 µg/gm)?
     - Yes
     - No drops during illumination
     - 365 nm UV at 4 mW/cm², 30 mins, cycled on/off with a proprietary light
     - BSS rinse

3. Their proprietary riboflavin, as described:
   - No dextran
   - Specific pH
   - Specific concentration
   - Specific osmolarity
   - NaI "as an excipient"*

*"Riboflavin penetration enhancer"
Methods: Outcome measures

- UDVA, CDVA, Kmax
- Total higher-order aberrations (HOAs) and coma
- Progression defined as an increase of >1 D Kmax and >1 line CDVA loss in same eye

“In healthy eyes the repeatability limit, of the maximal corneal curvature Kmax (with the Pentacam HR) were reported to be 0.8 Dioptres (D), however, we found repeatability limits in keratoconic eyes to be 1.97 D [1, 2]. This result means that the current main criteria for progression detection and CXL is inadequate (i.e. a change of 1 D in Kmax after one year of follow-up) [1, 3].

General question: is > +1 D Kmax + 1 line CDVA loss a good enough endpoint assessment?
CXLUSA (JCRS 2018) trial dates

“The study comprised 512 eyes of 308 patients with keratoconus or forme fruste keratoconus and 80 eyes of 55 patients with ectasia after LASIK, who underwent epi-on CXL between October 17, 2013 and May 16, 2016, and were followed through February 20, 2017.”

- 512 eyes
- 308 patients
‘N’s throughout the study

The 12-month and 24-month data analyses included only eyes with preoperative and 12-month or 24-month examinations, respectively. Trends over time were studied using the consistent cohort (eyes with preoperative and 3-, 6-, 12-, and 24-month examinations) to avoid artifacts created by analyzing different eyes at different timepoints. Aberrometry was not performed on all patients because the aberrometer was not available at all treatment sites.

Dropout/LTFU

Consistent cohort (n=115)
And expressed as Kaplan-Meier curves

KC, keratoconus; PLE, post-LASIK ectasia
Why are these patients in the trial if none of the outcomes assessments are at 1 years?

Cannot be part of the “consistent cohort.”
Wait! What about clinicaltrials.gov registration?

- 308 patients (592 eyes)
- October 17 2013 – Feb 20, 2017
- Keratoconus/post-LASIK ectasia
<table>
<thead>
<tr>
<th>NCT Number</th>
<th>Title</th>
<th>Status</th>
<th>Study Result</th>
<th>Conditions</th>
<th>Interventions</th>
<th>Outcome Measures</th>
<th>Sponsor/ Collaborators</th>
<th>Age</th>
<th>Phase</th>
<th>Enrollment</th>
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<th>Study Designs</th>
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<td>Other: Drug Ciprofloxacin or Vigamox or other Drug: Steroid (FML, Pred Forte, Flarex, etc.)</td>
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<td>CXLusa</td>
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</table>

**Pack-CXL**

N=22

Starts 4 y too early
Study Type: Interventional (Clinical Trial)
Actual Enrollment: 1324 participants
Intervention Model: Single Group Assignment
Masking: None (Open Label)
Primary Purpose: Treatment

Official Title: Collagen Crosslinking With Ultraviolet-A in Asymmetric Corneas
Study Start Date: January 2013
Primary Completion Date: February 3, 2017
Actual Study Completion Date: February 3, 2017

Outcome Measures:
1. Change in Best Spectacle Corrected Visual Acuity (BSCVA) Time Frame: 6-9 months
2. Change in Corneal Topography Time Frame: 6-9 months
3. Change in Keratometry Time Frame: 6-9 months
4. Change in Keratometry and Topography and Keratometry Time Frame: 6-9 months
5. Change in Wavefront Refractive and aberrations Time Frame: 6-9 months
Does this mean the Kaplan-Meier curves...
Should it look like this?

Actual Enrollment: 1324 participants

Or was this a completely different trial, unregistered on clinicaltrials.gov?

(not eyes)
But this is a physician-led study

Is it harsh to apply the same conditions to ~4 surgeons running a trial as is done to a pharmaceutical or device company?

“Epithelium-on CXL using this new protocol halted the progression of keratoconus and ectasia after LASIK. It was safer and provided more rapid visual recovery than CXL with epithelial removal, allowing routine bilateral, simultaneous treatment.”
Analyses

“The 12-month and 24-month data analyses included only eyes with preoperative and 12-month or 24-month examinations, respectively.”

“Trends over time were studied using the consistent cohort (eyes with preoperative and 3-, 6-, 12-, and 24-month examinations) to avoid artifacts created by analyzing different eyes at different timepoints.”

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Pre-op</th>
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</table>

“Consistent cohort” – n=115

Is 115 patients the “real” analysis population? Is this enough to investigate these claims with sufficient sensitivity?
Documentation of progression was not required for inclusion in this study;

however, progression was documented by medical history in 283 (92%) patients and by progressive increase in myopic spherical equivalent (>1 D), cylinder (>1 D), or Kmax (>1 D) in the previous 2 years in 172 (56%) patients with keratoconus or forme fruste keratoconus.
“This does not match with out experience”
– Seiler, Hafezi, Randleman, Vinciguerra.

“Only ~1 in every 3 patients that come to our clinics have progressive KC”

“If we cross-linked all of them, 2/3 were stable and would not have progressed!”

“How can you claim that the method works to halt keratoconus progression when you’re treating many patients who are stable?”

Is this a fair criticism of the CXLUSA study?
Treating non-progressive patients skews the numbers

“Documentation of progression was not required for inclusion in this study; however, progression was documented by medical history in 283 (92%) patients and by \textbf{progressive increase} in myopic spherical equivalent (>1 D), cylinder (>1 D), or Kmax (>1 D) in the previous 2 years in 172 (56%) patients with keratoconus or forme fruste keratoconus.”

[\textit{later}]

“At 24 months postoperatively, Kmax increased by more than 1 D in 11 (8.3%) of 133 eyes.”

If 56\% of the cohort may have been progressive \textbf{AND} 8.3\% progressed by common definition \textbf{THEN} Then logically, in a truly progressive cohort, the progression rate was \textbf{\sim}15\% – equivalent/similar to all other epi-on protocols reported to date.”
Statistical Methods

Snellen acuities were converted to logarithm of the minimum angle of resolution (logMAR) notation. Because the distribution of the logMAR values, Kmax values, total HOAs, and coma values are unknown and have not been studied in detail, tests of the hypothesis that the paired differences were not equal to zero were conducted using the Wilcoxon signed-rank test. For testing the differences in multinomial probabilities (percentage of eyes with Kmax decreases < 1 D and increases > 1 D), the normal approximation was used in a Student t test. Error bars in figures and standard deviation reported in the tables are based on the raw values for each timepoint, rather than the differences between timepoints. Therefore, these error bars and plots should not be used to assess the statistical significance of the true differences in these values between timepoints.

• “Significant” results are presented with very low patient numbers
  • Pediatric eyes:
  • 12 months, n=26 / n=19
  • 24 months, n=12 / n=9
How does a busy person read a manuscript?

Most likely

1. Abstract
2. Intro
3. Figures
4. Discussion
5. Results
6. Methods
7. Statistical methods

Least likely

Analysis

“Therefore, these error bars and plots should not be used to assess the statistical significance of the true differences in these values between timepoints.”

Statistical Methods
Snellen acuities were converted to logarithm of the minimum angle of resolution (logMAR) notation. Because the distribution of the logMAR values, Kmax values, total HOAs, and coma values are unknown and have not been studied in detail, tests of the hypothesis that the paired differences were not equal to zero were conducted using the Wilcoxon signed-rank test. For testing the differences in multinomial probabilities (percentage of eyes with Kmax decreases < 1 D and increases > 1 D), the normal approximation was used in a Student t test. Error bars in figures and standard deviation reported in the tables are based on the raw values for each timepoint, rather than the differences between timepoints. Therefore, these error bars and plots should not be used to assess the statistical significance of the true differences in these values between timepoints.

These error bars don’t mean what you think they mean.
Figure 1. Trend in visual acuities over 24 months after CXL. Columns show UDVA and CDVA obtained at 3, 6, 12, and 24 months after CXL for eyes in the consistent cohort (n = 115). Error bars represent standard error of the mean (CDVA = corrected distance visual acuity; CXL = corneal crosslinking; UDVA = uncorrected distance visual acuity).

Figure 2. Trend in Kmax over 24 months after CXL. Columns show Kmax measured at 3, 6, 12, and 24 months after CXL for eyes in the consistent cohort (n = 115). Error bars represent standard error of the mean (CXL = corneal crosslinking; Kmax = maximum keratometry).

Figure 3. Trend in pediatric visual acuities over 24 months after CXL. Columns show UDVA and CDVA measured at 3, 6, 12, and 24 months after CXL for eyes in the consistent cohort (n = 11). Error bars represent standard error of the mean (CDVA = corrected distance visual acuity; CXL = corneal crosslinking; UDVA = uncorrected distance visual acuity).

Figure 4. Trend in pediatric Kmax over 24 months after CXL. Columns show Kmax obtained at 3, 6, 12, and 24 months after CXL for eyes in the consistent cohort (n = 11). Error bars represent standard error of the mean (CXL = corneal crosslinking; Kmax = maximum keratometry).

Figure 5. Eyes with more than 1 D change in Kmax 12 and 24 months after CXL. Columns show the number of eyes with an increase or decrease in Kmax at 12 and 24 months after CXL (CXL = corneal crosslinking; Kmax = maximum keratometry).

Figure 6. Corrected distance visual acuity in eyes with a more than 1 D increase in maximum keratometry 12 months after corneal crosslinking. Columns show the number of eyes with a change in CDVA as shown on the horizontal axis (n = 24) (CDVA = corrected distance visual acuity).

Figure 7. Corrected distance visual acuity in eyes with a more than 1 D increase in maximum keratometry 24 months after corneal crosslinking. Columns show the number of eyes with a change in CDVA as shown on the horizontal axis (n = 11) (CDVA = corrected distance visual acuity).
Small proportion of cross-linked eyes in figures
Is this harsh? Are other epi-off trials any better?

Carporissi et al. JCRS 2013 (TE-CXL, Ricrolin TE) had only 26 eyes
» Found only 12 months of stability
» No control arm
» Progression: ≥2 of the following:
  - UDVA and/or CDVA loss >1 line;
  - ↑ sph and/or cyl >0.5 D;
  - ↑ Kmax > 1 D;
  - ≥10 mm reduction on thinnest point using AS-OCT pachymetry

Souters et al., JCRS 2015 (TE-CXL, Ricrolin TE)
» Compared 35 eyes (Ricrolin TE) vs. 26 eyes epi-off CXL
» 1 D Kmax threshold – no CDVA requirement
» 23% progressed after 12 months

~8 trials in literature
» Generally small n’s – no large LTFU either
» Few have epi-off control arms
» Many have only 1-year data published

Etc.

Analysis

~8 trials in literature

None claim superiority either

Not really (although some define progression better)
Let’s review the abstract

David O’Brart: even non-treated keratoconic eyes can improve in visual acuity. Why? Patients learning the chart during the trial (1)

Very small n’s

Real effect? The inter-measurement variability increases in more highly asymmetric corneas - and 0.48 D is definitely within that variability (which is about 0.7 D)

Remember: “Consistent cohort” = 115 eyes

Not proven in this manuscript

Kmax
Kmax increased by more than 1 D in 24 (7.0%) of 341 eyes at 12 months postoperatively; however, Kmax decreased by more than 1 D in 3 times as many eyes (72 [21.1%] of 341) (P < .0001) (Figure 5). At 24 months postoperatively, Kmax increased by more than 1 D in 11 (8.3%) of 133

Adverse events in this study were rare. Hydrops in one eye 23 months after CXL was clearly a result of the underlying severe ectasia rather than CXL (preoperative CDVA = 20/400 and Kmax = 72.8).
What this paper adds

What was known
- The corneal epithelium prevents absorption of topical riboflavin.
- Traditional CXL requires removal of the corneal epithelium, which can lead to vision-threatening complications.

What this paper adds
- A new CXL technique without epithelial removal effectively stopped progression of keratoconus and ectasia after LASIK.
- The new technique avoided the potential complications of epithelial removal for CXL.

Analysis

This paper reports pain, progression, possible activation of HSV keratitis, and one PK was required. This statement is far too strong.

Misses the fact that this is incredibly rare

Presented data not robust enough to support this; the follow-up is 2 years, and the drop-out/LTFU rate is phenomenal.
General concerns:
• Defining progression (common to most studies)

Specific concerns:
• Drop-out rate
• Treating non-progressive patients (that wouldn’t have progressed)
• No control arm
• Claimed outcomes that are “significant” – but fall within instrumentation noise
• Epi-off CXL’s effects last longer than the 24 month data shown here (CXLUSA have been performing studies since 2009)
• No clinicaltrials.gov registration
• Declarative statements and claims being made that are stronger than the data supports
Nevertheless...

- Small group of good people involved running the trial
- Surgeon-led study
- Limited resources
- No academic/corporate statistician available?
- No large pharma/device support expertise

- Still a sensible rationale for how it might work
- There’s still a potential that this could be the “Holy Grail” of CXL...
- No manuscript or trial design is perfect.

- Next steps? Easy. External validation, as per basic scientific principles.
- Reduces concerns, shows technique is viable

What do you think?
Take-home

• It’s important to stay current
• Read the journals
• Wait to adapt your clinical protocols until these publications have been shown to be safe and effective
• If you want to publish, follow the guidelines and be as transparent as possible