Cross-linking for Corneal Ulcers Treatment Trial (CLAIR)
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Cross-Linking Assisted Infection Reduction

Statistical Analysis Plan

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1. Background

Cross-Linking Assisted Infection Reduction (CLAIR) I for bacterial ulcers, CLAIR II for fungal ulcers are two randomized, masked, clinical trials. The purpose of these studies is to determine differences in microbiological cure for repeat cultures between different medical antimicrobial treatments alone versus antimicrobial treatment plus collagen cross-linking. There will be 1:1 randomization to each of these treatment groups:

CLAIR I. Bacterial Ulcers:

1) Topical 0.5% Moxifloxacin alone
2) Topical 0.5% Moxifloxacin plus cross-linking

CLAIR II. Fungal Ulcers:

1) Topical 5% natamycin alone
2) Topical 5% natamycin plus cross-linking
3) Topical 0.15% amphotericin alone
4) Topical 0.15% amphotericin plus cross-linking

2. Statistical Considerations, Sample Size

We will perform separate analyses for each specific aim for (I) the bacterial ulcers, (II) the fungal ulcers. Enrollment criteria require all study participants to have bacteria on smear from corneal scrapping. Previous studies have shown that 88% of bacterial cultures are positive when initial gram stain is positive.[5] This is consistent with the experience of the microbiology lab at our own institution. We feel that this is a conservative estimate based on prior studies in a similar south Indian setting that have found approximately 90-95% of corneal scrapings with a positive Gram/KOH stain are also culture positive.

There is little current data to inform us about the effect of repeat scrapping on the culture status. In the Mycotic Ulcer Treatment Trial II, approximately 55% of fungal ulcers were culture positive 6 days after enrolling in the trial and receiving treatment. This is an approximately 7.5% reduction is culture positivity on average per day. If we consider initial scrapping to have a similar effect as one day of treatment, we can estimate that there would be an approximately 8% reduction in culture positivity due to repeat scraping in our trial.

SPECIFIC AIM 1 analysis:

CLAIR I Bacterial Trial: McNemar's two-sample paired-proportions test will be used to compare pre- and post- cross-linking cultures on smear-positive bacterial corneal ulcers. In order to detect a 30% difference in repeat culture status (80% in the control group vs. 50% in the crosslinking group), we would need to enroll 78 study participants, assuming a significance level of 0.05 and no loss to follow-up (since the primary outcome occurs the same visit as enrollment).

CLAIR II Fungal Trial: Given the 4 arms of the trial, we have estimated a sample size based on a significance level of 0.0125. In order to detect a 30% difference (80% in control versus 50% in the crosslinking group), we would need to enroll 110 study participants. This assumes no loss to follow-up, since the primary outcome occurs at the same visit as enrollment. In reality, we should have more statistical power since we will also take into account the results of the baseline culture, which we expect to be highly correlated with the follow-up culture.

SPECIFIC AIM 2 analysis: 3-month best spectacle-corrected visual acuity (BSCVA) will be examined in a multiple linear regression model with terms for treatment (dichotomous variable for bacterial and 4-level categorical variable for fungal ulcers) and baseline BSCVA. Similar to above, for the fungal ulcers we will first test for an overall difference between the 4 groups, then pairwise comparisons as indicated, using a Bonferroni correction. 3 and 12-month best spectacle-corrected visual acuity (BSCVA) will be examined in a repeated measures multiple linear regression model with terms for treatment (dichotomous variable for bacterial ulcers and 4-level categorical variable for fungal ulcers) and baseline BSCVA. Similar to above, for the fungal ulcers we will first test for an overall 12-month BSCVA difference between the 4 groups, then pairwise comparisons as indicated, using a Bonferroni correction.

For study participants who experience perforation or undergo therapeutic penetrating keratoplasty (TPK) this will be noted and a BSCVA will be performed prior to performing further surgery. This last observation will be carried forward (LOCF) as the 3-month BSCVA. An enhanced analysis using standard longitudinal modeling methods will be used to handle data from study participants who are lost to follow up. Additional secondary analyses will include:

- Scar size as measured on clinical exam and photographs
- Corneal topography
- Corneal Thickness and scar size as measured by OCT
- IND-VFQ will be compared between the two groups controlling for baseline VFQ
- Analyses of perforations or other adverse events
- A cost effectiveness analysis will be performed.

3. Interim Monitoring

Due to the uncertainty regarding the effect of repeat culture on culture positivity, a masked interim analysis will be conducted to re-evaluate sample size based on day-1 repeat culture positivity when one-third of the data have been collected (note that this interim analysis will not look at outcome by treatment arm). A medical monitor will be appointed at UCSF to monitor any serious adverse events. A small DSMC at UCSF will be appointed to conduct an un-masked interim analysis to evaluate for futility or harm. Either trial may be stopped early without unmasking for temporal reasons or due to low enrollment.