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Performance of automated hyperemia assessment in allergic conjunctivitis interventional study

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Introduction

• Ocular hyperemia is an important efficacy[1], safety[2], and tolerability[3] endpoint in ophthalmic clinical trials.

• Validated subjective standardized scales, e.g. the validated bulbar redness scale[4] and McMonnies/Chapman-Davies scale[5], suffer from intra- and inter-grader variability necessitating large study populations .

• Objective methods of assessing ocular hyperemia offer the potential to reduce the length and/or size of clinical trials.

• A novel automated approach called Imaging System for Ocular Surface (ISOS)[6] may offer a robust method to measure hyperemia grade with the added detail of vessel morphology.

Objective

Explore the reproducibility and sensitivity of automated ocular hyperemia efficacy readout in a double-blind interventional study in allergic conjunctivitis

Methods

• Twenty three subjects were randomly assigned to receive two slit lamp photographs of their right temporal conjunctiva after seven days of either 0.1% Dexamethasone (Maxidex®) ophthalmic solution or vehicle control BID in a double blinded fashion as part of NCT02079649.

• Between slit lamp photographs, subjects were dosed with study medication just before spending 3 hours in an **environmental exposure chamber (EEC)** in which ragweed pollen was circulated at 3500 ± 500 particles per m^3.

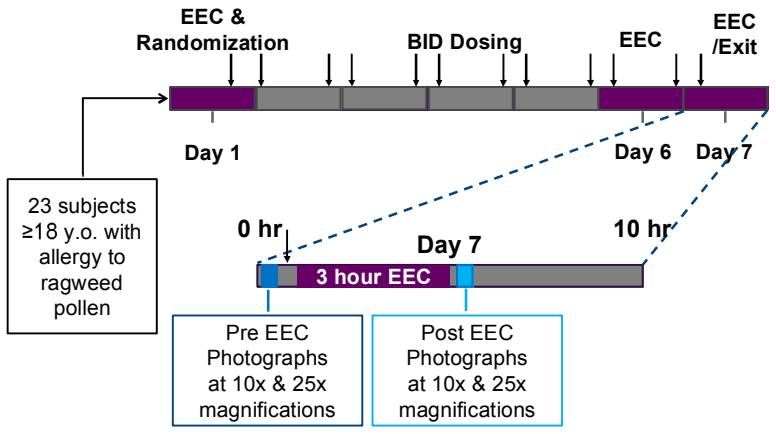

Figure 1. Study Design of Ocular Hyperemia Sub-study

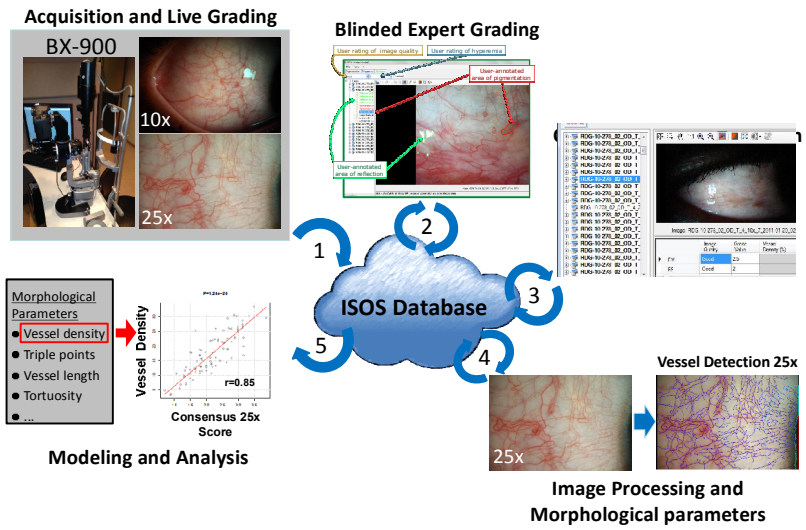

Figure 2. Steps in Data Generation and Analysis

Methods (cont.):

• Photographs were immediately scored using the validated bulbar redness scale from 0 to 4 in 0.5 increments by one of two ophthalmologists (live scoring) and later by three fully-blinded expert graders.

• A consensus expert score was calculated for each 25x photo to minimize grader variability which was estimated by repeated scorings and modeling.

• 35 morphological parameters (e.g. vessel density, length and width, # triple points, etc.) of the conjunctival vasculature were calculated using an automatic vessel segmentation algorithm from each 25x photograph.

• Multivariate linear regression models were used to predict live and expert consensus scores from the morphological parameters.

• The Maxidex® effect was explored via a linear mixed model of change from Pre-EEC relative to vehicle group for hyperemia scores and image descriptors.

• Estimated N-sizes were made based on observed mean change and standard deviation within the Maxidex® treatment group using a paired T-test model.

Results

Pre-EEC	10x	25x
Live Score	1	1
Cons. Expert	2.4	2.1
# Triple Pts		1350
Vessel Density		16.0
Automated Score		2.26

Post-EEC	10x	25x
Live Score	1	1
Cons. Expert	1.9	1.6
# Triple Pts		1003
Vessel Density		12.3
Automated Score		1.7

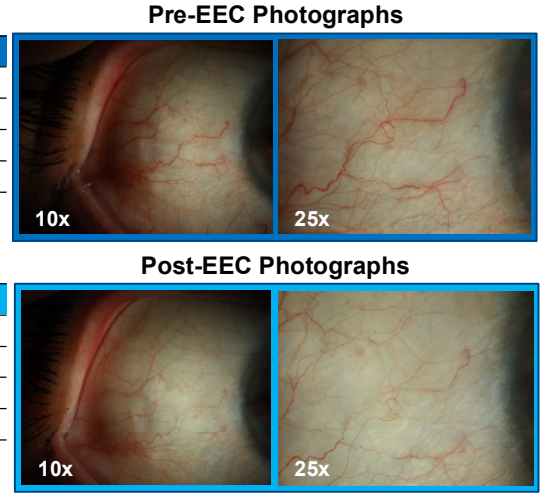

Figure 3. Slit lamp photographs and hyperemia assessments in an example vehicle treated subject

• 13 subjects were randomized to Maxidex® and 10 to vehicle control.

• Intrinsic variability of automated score was similar to consensus expert score and better than that of live and individual expert scorings (Figure 4).

• Live hyperemia score was best predicted by vessel density alone (r=0.68) while consensus expert score was best fit by a linear model (r=0.93) of 14 morphological descriptors (e.g. vessel density, vessel length, # triple points).

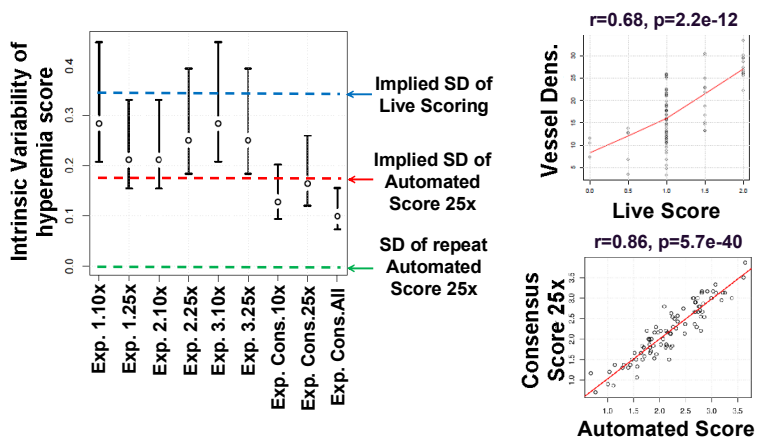

Figure 4. Intrinsic variability of hyperemia scores and best-fit morphological predictions of live and expert consensus scores

Results (cont.):

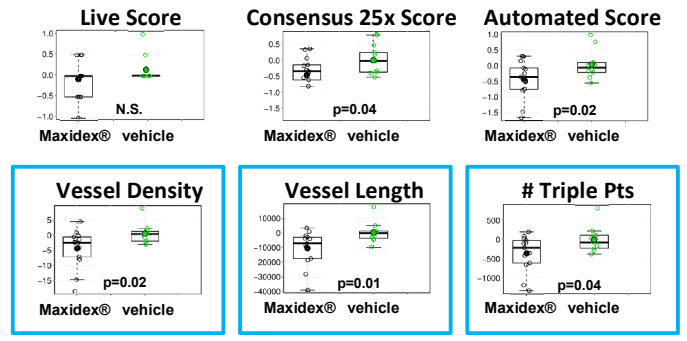

Figure 5. Changes from Pre-EEC in hyperemia scores and vessel morphology for Maxidex® and vehicle treated groups

• A significant Maxidex® response (p<0.05) relative to vehicle was observed in consensus expert and automated scores with further characterization of the response offered by vessel density, vessel length, and # triple points (Figure 5).

• Improved reliability of automated hyperemia readouts offer the potential for reduced study sizes (Table 1).

Measure	Maxidex® Effect (Post-Pre EEC)	N estimate (p<0.05, 80%)
Live Score	-0.077±0.45	270
Expert Cons. Score 25x	-0.44±0.65	19
Automatic Score	-0.40±0.56	18
Vessel density	-4.32±6.35	19
Triple Pts	-351±477	17
Vessel Length	-10048±12341	14

Table 1. N-size estimates based on Maxidex® effect between Post- and Pre-EEC evaluations

Conclusions

• ISOS-based hyperemia assessment offers a deeper understanding of the hyperemia response with a high degree of reliability.

• Its application in additional indications and further implementation enhancements could dramatically improve the efficiency for future clinical trials.

References

1. Nazarov O et al., *Arzneim.-Forsch./Drug Res.* 2003; 53(3).
2. Alagoz G et al., *Ophthalmologica* 2008; 222.
3. Dumbleton K et al., *Optom Vis Sci* 2006; 83(10).
4. Schulze MM et al. *Optom. Vis Sci.* 2007; 84(10).
5. McMonnies CW, Chapman-Davies A, *Am J Optom Physiol Opt* 1987; 64.
6. Tort M et al., *Poster #41, 27th Biennial Cornea Conf. in Boston, MA* 2011.

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Disclosures

• Data was collected as part of NCT02079649, a clinical trial sponsored by Alcon Labs, a Novartis company.

• MJW, CLG, and SC are employees (E) of Novartis Institutes of Biomedical Research.

• BL and RD are employees (E) of ADCIS and consult (C) for Novartis.