EU Regulatory Workshop – Ophthalmology – Clinical Development and Scientific Advice

Dry Eye

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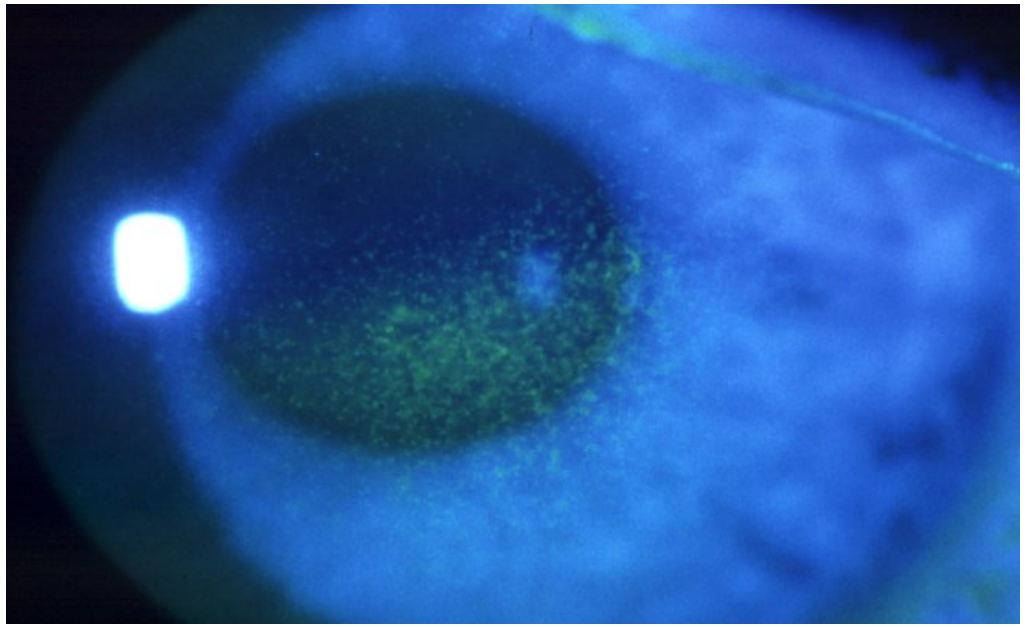


ENDPOINTS - SIGNS VS. SYMPTOMS

Clinical diagnosis grid

TABLE 1

The DEWS Dry Eye Diagnosis Grid* (modified from *The Ocular Surface 2007*)

DRY EYE SEVERITY LEVEL	1	2	3	4
Discomfort, severity, and frequency	Mild/episodic/ environmental stress	Moderate/episodic or chronic/environmental stress or no stress	Severe/frequent or constant without stress	Severe and disabling, constant
Visual symptoms	None or episodic mild fatigue	Annoying and/or activity limiting episodic	Annoying, chronic and/or constant limiting activity	Constant and/or possibly disabling
Lid/meibomian glands	MGD variably present	MGD variably present	Frequent	Trichiasis, keratinization, symblepharon
TFBUT (sec)	Variable	≤ 10	≤ 5	Immediate
Corneal Staining (NEI Scale 0-15)	None to mild	Variable	Central	Severe punctuate erosions
Conjuntival Staining (NEI Scale 0-18)	None to mild	Variable	Moderate to marked	Marked
Schirmer test (no anesthesia) (mm/5 min)	Variable	≤ 10	≤ 5	≤ 2
Recommended management	Patient education, diet modification and lid therapy, artificial tear/gel supplements, environmental control	Add anti-inflammatories, tetracyclines, punctal plugs, moisture chamber spectacles	Add autologous serum, bandage or large-diameter rigid contact lenses, permanent punctual occlusion	Add systemic anti-inflammatory agents, surgical intervention

* The order of the tests represents a common dry eye exam sequence. Recommended management is listed below each grade.

End-points : signs vs symptoms

- Patient perspective
  - To improve, i.e. to have less symptoms
  - Also
    - less frequent application of drops
    - increased quality of life
- Industry perspective
  - To show safety and efficacy
  - To show improvement of signs and/or symptoms

Symptoms

- Factors causing variability

  - Various symptoms are used in different studies
    - Irritation/burning/stinging, foreign body sensation, tearing, itching, dry eye sensation, discomfort etc,
    - Visual acuity related : fatigue, blurred vision

  - Different patients may call the same symptom with a different name
      - E.g. foreign body sensation vs. dryness sensation

  - Symptoms associated with dry eye are not specific to dry eye

Symptoms

- Variation by time
  - By day
  - By time of the day
  - In relation to administration of drops
- Variation by external factors
  - Weather conditions, PC –work, air conditioning, long travels
- Poor correlation between signs and symptoms

Symptoms

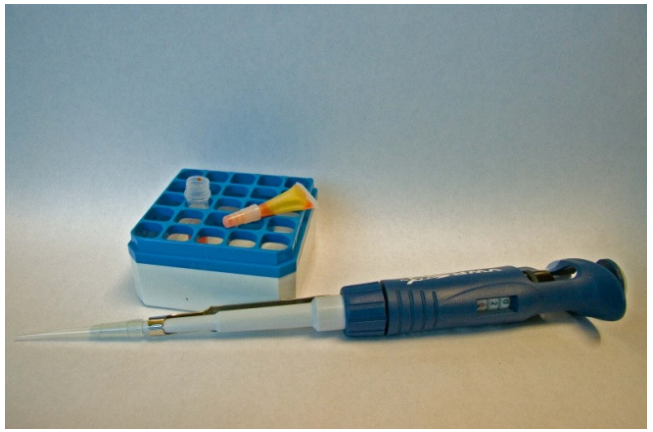
- How to measure ?
  - Frequency vs. severity
  - VAS vs. graded symptom scale vs. validated questionnaires
  - How many symptoms?
    - Too many, too few?
    - Mean/sum of all symptoms/ worst symptom ?

- What is a clinically significant change?
  - Resolution of all symptoms?
  - A reduction in symptoms as compared to baseline?
    - How much ?
      - 20 %, 30% %, 1-2 grade change?
  - A significant change vs comparator?

Signs

- Basic questions
  - What are the signs to be used as inclusion criteria?
  - What is a clinically significant change?

- Staining: conjunctiva, cornea
  - Constant, small volume of the stain (preferably using a micropipette) is preferred to increase reliability of measurements
  - Oxford scale, modified Oxford scale, NEI, van Bijsterveld
    - Established grading scales
- TFBUT
  - Constant, small volume of fluorescein



- Schirmer test
  - With/without anaesthetic
  - Subject to variations (reflex tearing etc)

- Other signs : SBUT: symptomatic break-up time
  - Tear meniscus height/conjunctival folds

Signs

- Osmolarity
  - The best single parameter to diagnose and classify dry eye disease?
    - Lemp et al AJO 2011;151:792-8
  - What is the cut off between normal patients and dry eye disease?
    - 308 mOsms/L
    - 312 mOsm/L
    - 316 m Osm/L
  - Many dry eye patients have consistently high values in osmolarity while intereye variability is sometimes seen
    - If existing, the higher value should be used?
  - Not a standard procedure, test equipment often not available

Signs

Meibomian gland dysfunction (MGD)

- Changes in lipid structure lead to altered tear film stability and evaporative dry eye
  - is thought to be significantly more common than the aqueous-deficient dry eye

- The treatment, if available, should cover both conditions

Signs vs symptoms: end-point

- Various signs and symptoms are used
- Poor repeatability of signs
  - Korb Cornea 2000;19:483-6
  - Nichols et al. Cornea 2000;19:477-82
- Poor correlation between signs and symptoms
  - The international Dry Eye Workshop Ocul Surf 2007,5:65-204
  - Nichols et al Cornea 2004;23:762-70
  - Smith et al.Cornea 2008;27:656-62.
- Development of new pharmaceutical therapies is hampered by the lack of objective tests for response outcomes

Signs vs symptoms: end-point

- A sign only or a symptom only ?
- A sign and a symptom as a co-primary end –points ?
  - Significant change from baseline required for both end-points
  - No approvals so far using this end-point
- Sign and symptom as composite end-point ?
  - More stringent criterion for response than co-primary approach as a significant change is required for both variables for each patient
  - Single component needs to show a positive trend (important also for claims)
- Responder analysis or analysis based on mean values?
  - Responder analysis generally has lower power but is clinically easier to interpret
    - Bigger sample size
    - Responder analysis is a reasonable approach in case the number of drop-outs is not negligible – drop-outs are defined as non-responders
  - If mean change is the primary end-point and statistically significant result is shown, the responder analysis needs only to show a clinically meaningful difference (if used)

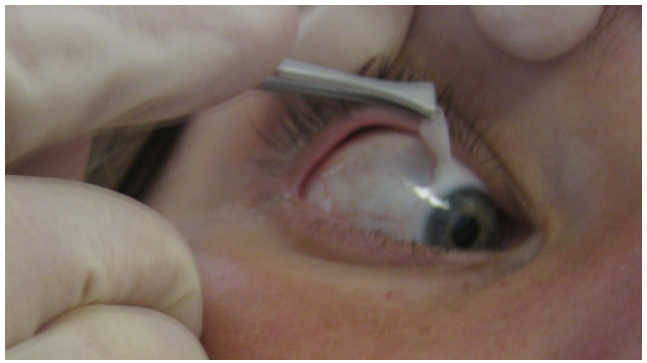
ENDPOINTS ADDRESSING INFLAMMATION

End-points addressing inflammation

- Absence of validated tools to measure topical inflammation on the eye
- So far, to be used as secondary exploratory end-point
- Empirical data are needed to evaluate the association between the biomarker and the clinically relevant end-point
  - How do changes in biomarkers correlate with changes in signs and symptoms?
  - What are clinically significant changes?

End-points addressing inflammation

- Examples on possible biomarkers
  - Possible tear fluid biomarkers (iTRAQ)
    - 6 proteins up-regulated and 4 proteins downregulated in dry eye patients
    - Zhou, Beuerman te al. Journal of proteome Research 2009;8: 4889-4905
  - Tear cytokines and chemokines
    - Five inflammatory molecules were elevated in evaporative-type dry eye patients
    - Salamanca et al. MolVis 2010;16:862-873
  - Conjunctival Impression Cytology
    - HLA-DR (inflammation)
    - MUC5AC (mucin)
    - Multiple publications: Brignole-Baudouin, Baudouin



POTENTIAL TARGETS

Potential target population

- By severity
  - Mild, moderate, severe
  - Challenging to show effect, especially on signs, in mild patients
  - Challenging to show effect in severe patients
    - May be easier in theory, but
      - Concomitant medications may be needed (topical and systemic, inflammatory background)
      - Safety, especially tolerability issues
      - Decreased corneal sensitivity may decrease the possibility to investigate symptoms, but it may deteriorate the signs (decreased blinking)
- Specific patient group, e.g. with inflammatory background
  - Duration of the pivotal studies
    - 3-6 mos for efficacy and 12 mos for safety is suggested if not otherwise justified

COMPARATORS

Comparator

- No active comparators available , i.e. no centrally approved nor uniformly nationally registered pharmacologically active products available for dry eye in Europe → Vehicle controlled studies

- 2-arm studies with the vehicle as the comparator suggested
  - Superiority over vehicle to be shown
  - Difficulty in finding a placebo that does not affect the condition
  - Vehicles often contain components with lubricating action , e.g. glycerol

SUMMARY AND CONCLUSIONS

Summary and conclusions

- Dry eye is a heterogeneous condition
  - Both diagnosis and end-points for clinical trials are diverse
  - The industry would welcome harmonisation of the diagnosis and measures / end-points for clinical trials where possible
- For Industry, flexibility in designing the protocols should be allowed
  - End –points should be justified
    - End-points may be dependent on the mechanism of action of the study drug
  - Development and acceptability of reliable biomarkers would be helpful