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LIMBAL STEM CELL THERAPY
Industry view

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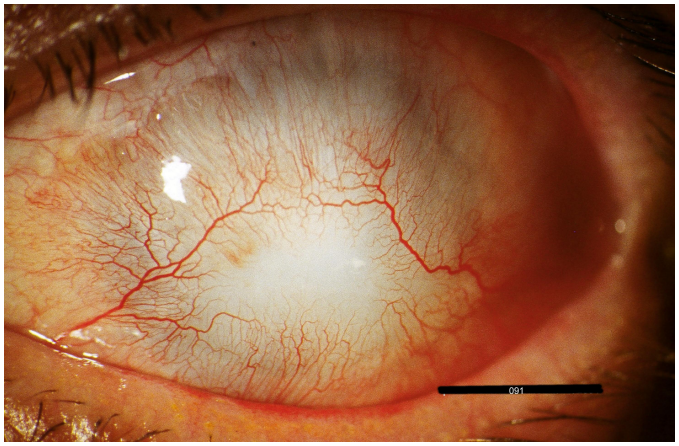
Limbal Stem Cell Deficiency

PRIMARY
- Aniridia
- Multiple endocrine deficiencis
- Neurotrophic keratopathy
- Chronic limbitis
- Congenital erithrokerato dermia

SECONDARY
- Ocular burns
- Steven-Johnson S
- Multiple surgeries
- Extensive microbial invasion
- Ocular cicatricial pemphigoid
- Cryotherapies
- Contact lens wear



- neovascularization
- epithelial defects
- loss of corneal transparency
- chronic inflammation, redness
- fibrovascular pannus
- absence of K3 positive cells (corneal)
- presence of k19 positive cells (conjuunctival)

- decreased vision
- photophobia, tearing, recurrent pain
- chronic inflammation, burning

Challenges to Clinical Development

- Rarity of the condition
- Grading the severity of LSCD
- Absence of a reference treatment
- Difficulties for randomized, treatment masked designs
- Assessment of efficacy and clinical benefit

Rarity of the condition

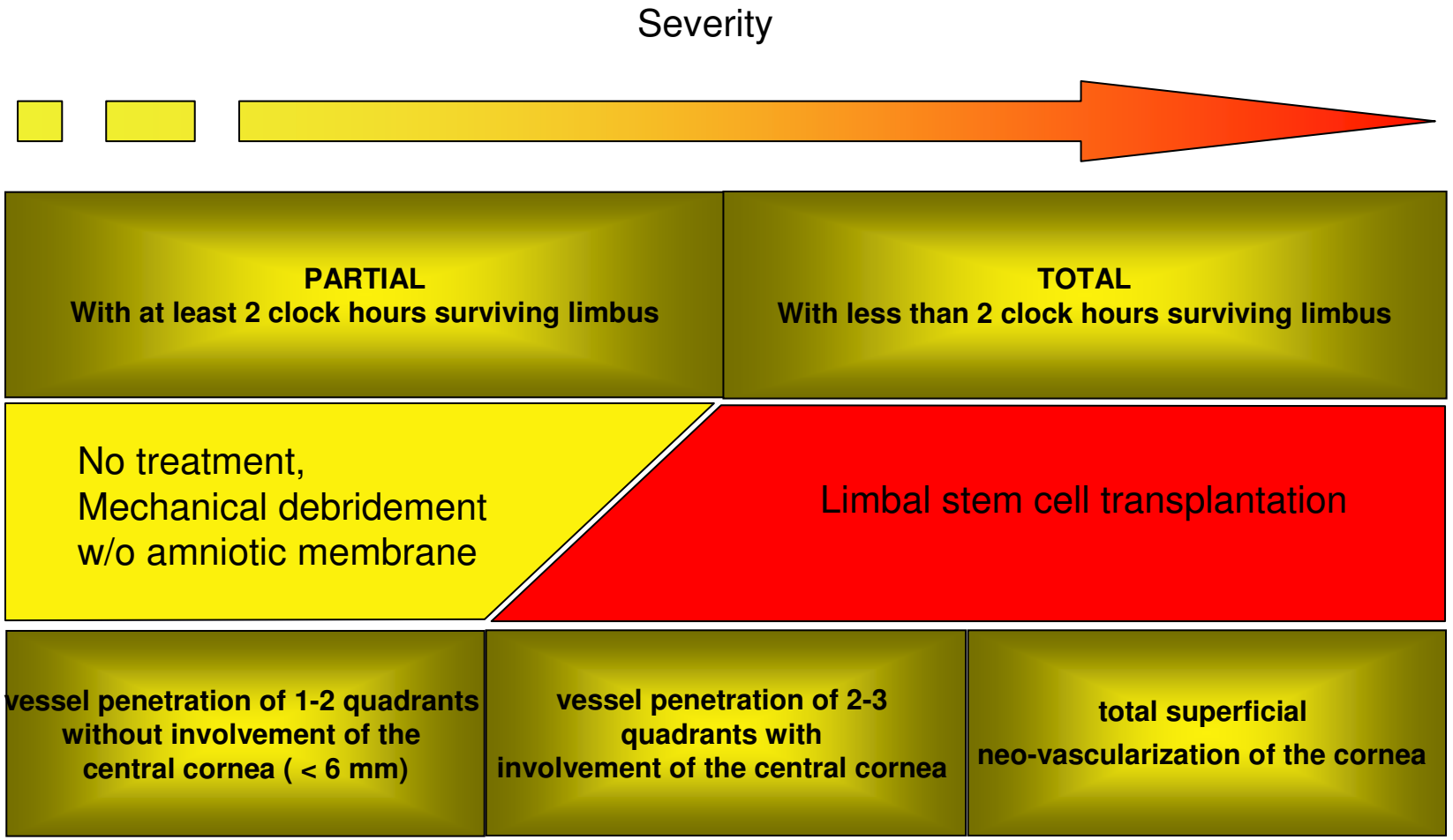
- Orphan condition (less than 0.5 /10.000)
- Most common in the adult population

Should the pediatric population be excluded from the efficacy and full safety analysis ?

PROS
Allow to complete the clinical development without delaying the possibility to treat the adult population

CONS
Exclusion of the pediatric population from the therapeutic indication

How to grade the severity of LSCD ?



How to grade the severity of LSCD ?

Other criteria

Minimum accepted duration of the disease with fully conjunctivalization

Negative outcome of repeated full corneal transplantation

The trial design

- Absence of reference treatment
- Placebo cannot be used. Full corneal transplantation not suitable
- Randomization not possible

May bias be minimized?

•If open-label, choose objective end-points
•Consider independent efficacy evaluation (two assessors)
•Method of blinding, if applicable (masked evaluation of efficacy on photos of the eye)

PROS
Minimize over/under estimation of the clinical data due to the open, not randomized, not controlled design

CONS
• Risk of discrepancies in the judgment between the investigator and the external assessor.
• masked evaluation possible only for efficacy parameters evaluable on photos

End point of efficacy

It is largely accepted that the restoration of the corneal epithelium integrity is the primary objective of the limbal stem cell transplantation

The restoration of a stable and intact corneal epithelium means a resolution of symptoms (pain, photophobia), inflammation and the improvement of visual acuity in patents without scars of the corneal stroma

Assessment of efficacy

Can an intact corneal epithelium (by fluorescein stain) with absence corneal superficial neo-vascularization account for the restoration of the corneal epithelium integrity ?

PROS

- Both parameters are indirect expression of the restoration of limbal stem cells
- Both parameters can be evaluated on photos by independent assessors
- Both parameters easy to evaluate in the routine activity of the clinical centers

CONS

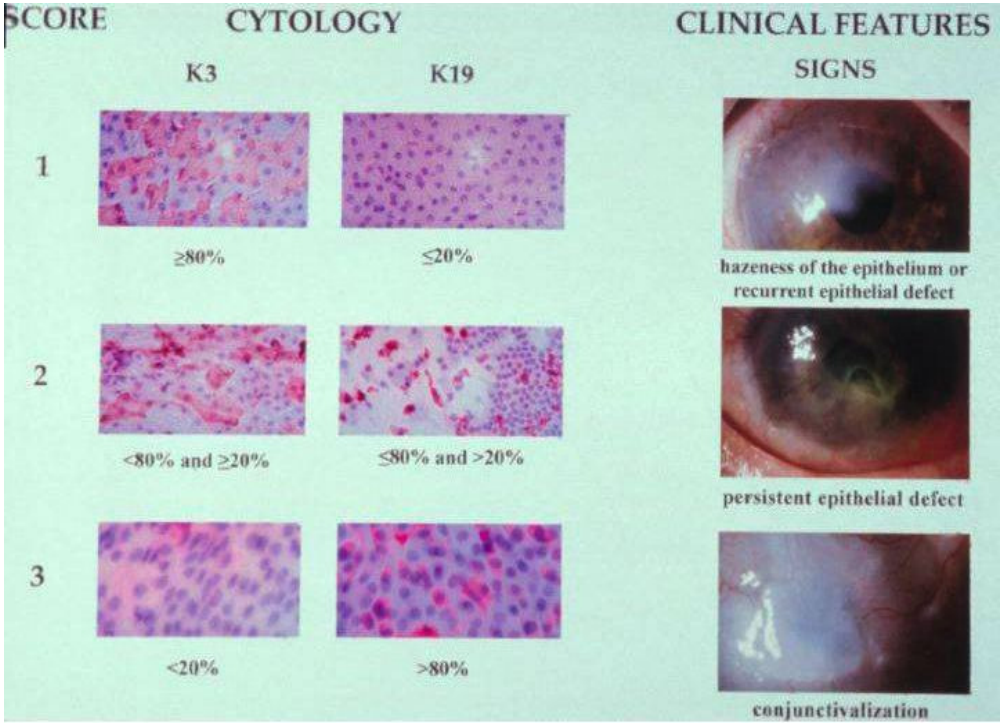
- Both parameters can give false positive (i.e. concomitant herpes infection)
- do not account for the corneal phenotype which is the proof that the limbal stem cell transplantation has restored a self generating corneal epithelium
- Some patients might not derive a tangible clinical benefit from having a stable corneal epithelium

Assessment of efficacy

Which other parameters can be used to evaluate the restoration of the corneal epithelium?

- Corneal phenotype
  1. by corneal impression cytology
  2. by in vivo confocal microscopy

Methods to assess the corneal phenotype (1): Impression cytology



PROS

• directly identifies corneal and conjunctival cells

CONS

•Does not provide information on the overall corneal surface, requires multiple sampling for complete mapping

•Complex and delicate technique, often producing unreliable results. Risk of inadequate sampling.

•Significant discomfort with risk of refusal by the patient

•Risk of ocular surface damage in patients with partial restoration of epithelium

Methods to assess the corneal phenotype (2): In-vivo confocal microscopy

PROS

• results of confocal microscopy correlated well with the impression cytology findings

CONS

• Limited when there is a narrow interpalpebral aperture

•Tolerance is poor in some patients with severe ocular surface disease

•Complex, non-standardized technique, not widely available in surgical centers; requiring expert, dedicated personnel to provide reliable findings from a complete mapping.

•Provides information on cell morphology and density, but not on epithelial cell type (corneal vs conjunctival)

•The approach is more time-consuming than impression cytology

Assessment of efficacy

When the restoration of a stable and intact corneal epithelium integrity should be evaluated ?

The half-time of corneal epithelial replacement is 9 weeks (Sharma A, 1989).

Theoretically the restoration of a stable and intact corneal epithelium might be established 6 months after the LSC transplantation

however,

failure of LSC transplantation has been reported also between 6 and 9 months from transplantation (Rama P, 2010)

Assessment of efficacy: any other variable ?

EFFICACY VARIABLE	How it reflects the primary disease	PRO	CONS
SYMPTOMS	Related to the corneal epithelium instability (recurrent erosions, ulceration) and inflammation	The improvement of symptoms reflects the presence of a stable corneal epithelia and the absence of inflammation and correlate with the Quality of Life	Not present in all patients at the study entry. Patients with a complete fibrovascular pannus have a "quiet eye"
QUALITY OF LIFE	Related primarily to the reduced vision or blindness but also to the improvement of symptoms	The Improvement reflects how the patient perceives the clinical benefit	Do not reflect the primary objective of the treatment (to restore the limbal stem cells)
CORNEAL EPITHELIUM TRANSPARENCY	Related to the "conjunctivalization" of the corneal surface	The presence of a transparent epithelium reflects the presence of corneal epithelium phenotype	Not objective, difficult to standardize and to grade
VISUAL ACUITY	Related to the hazing of the central corneal (superficial and deep)	Express a how the patient perceives the clinical benefit	Patients with stromal haze or retinal disease do not have the improvement of VA
OUTCOME OF THE FULL CORNEAL GRAFT	Related to the severity of the limbal stem cell deficiency	A positive outcome reflects the restoration of the limbal stem cells function	Not applicable in all patients

Assessment of safety

Duration of the follow up

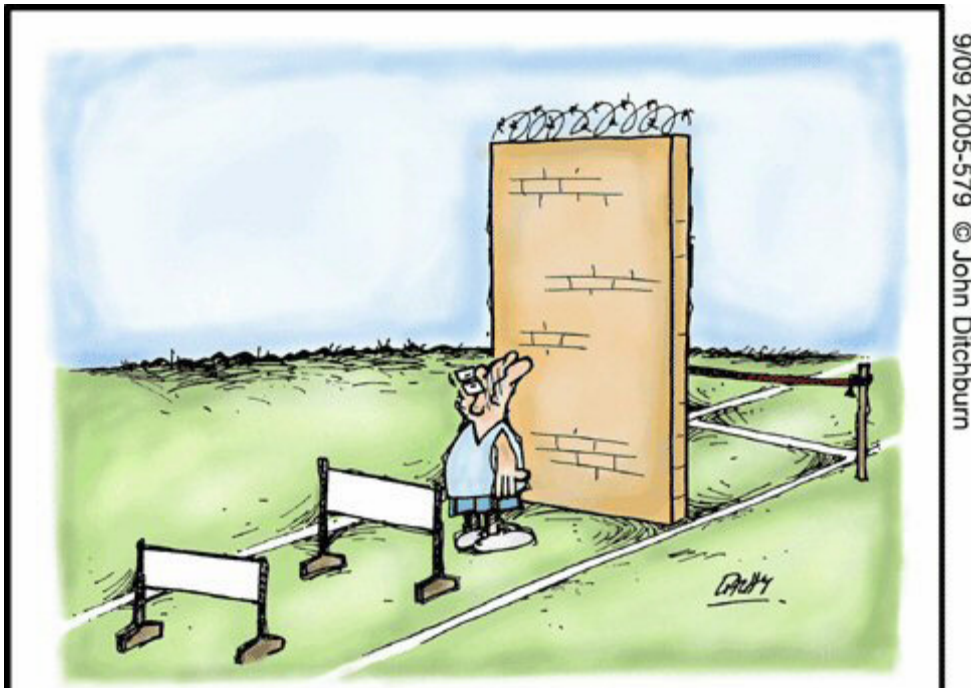
Safety

- Short term (surgery, inflammation, immunoreactions)

- Long term (tumor formation, infections)
    - at least 6 months for chronic treatments (CPMP/ICH/375/95)
    - true cumulative incidence <3% if no SAE reported during 12 months exposure in 100 patients (CPMP/ICH/375/95)
    - longer ?

CONCLUSION

Patients‘ unmet medical need vs. need for evidence



Hurdles should neither be too high…nor too low.

THANK YOU