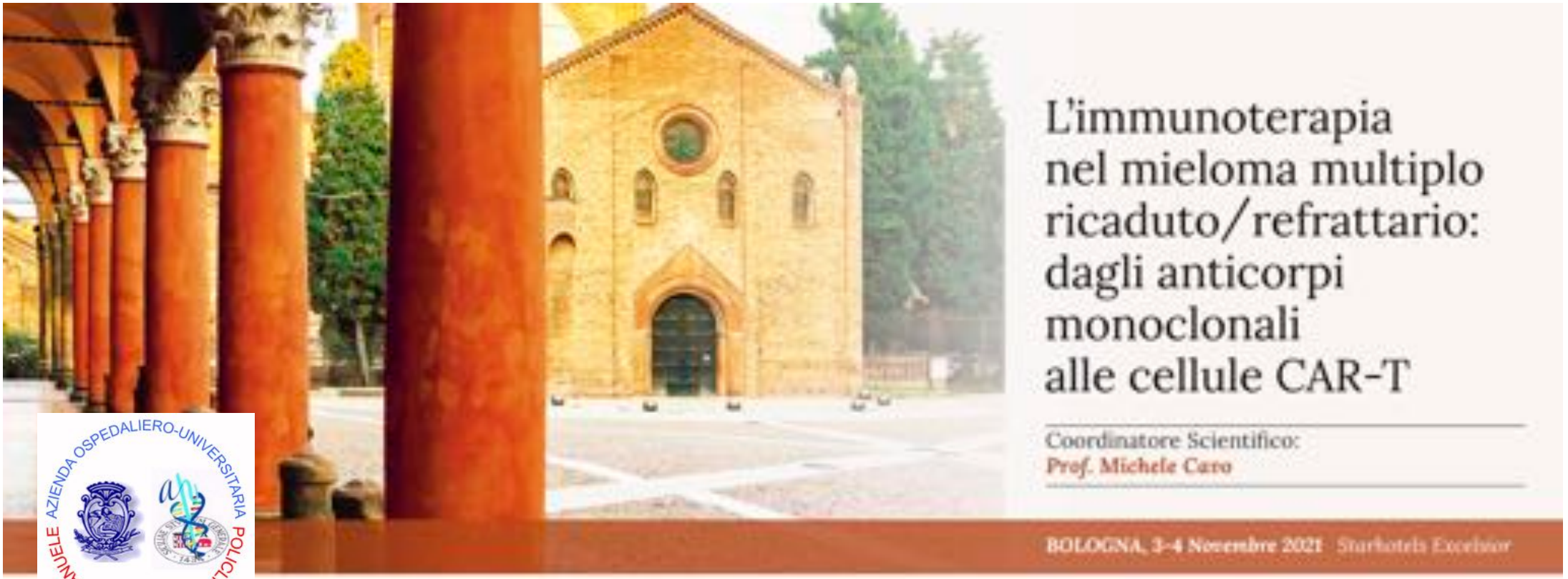
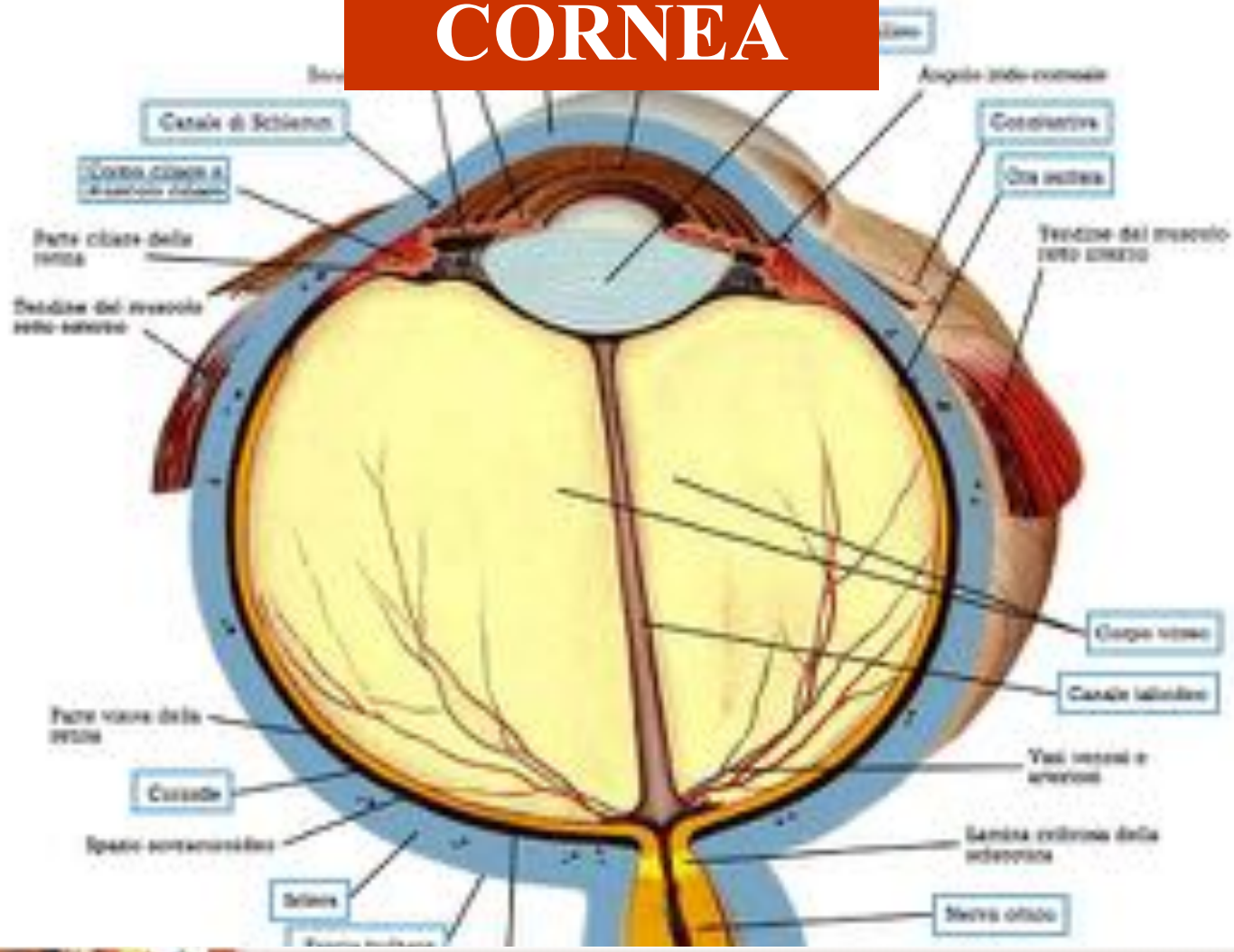


EVENTI AVVERSI E LORO GESTIONE

Caterina Gagliano (Catania)

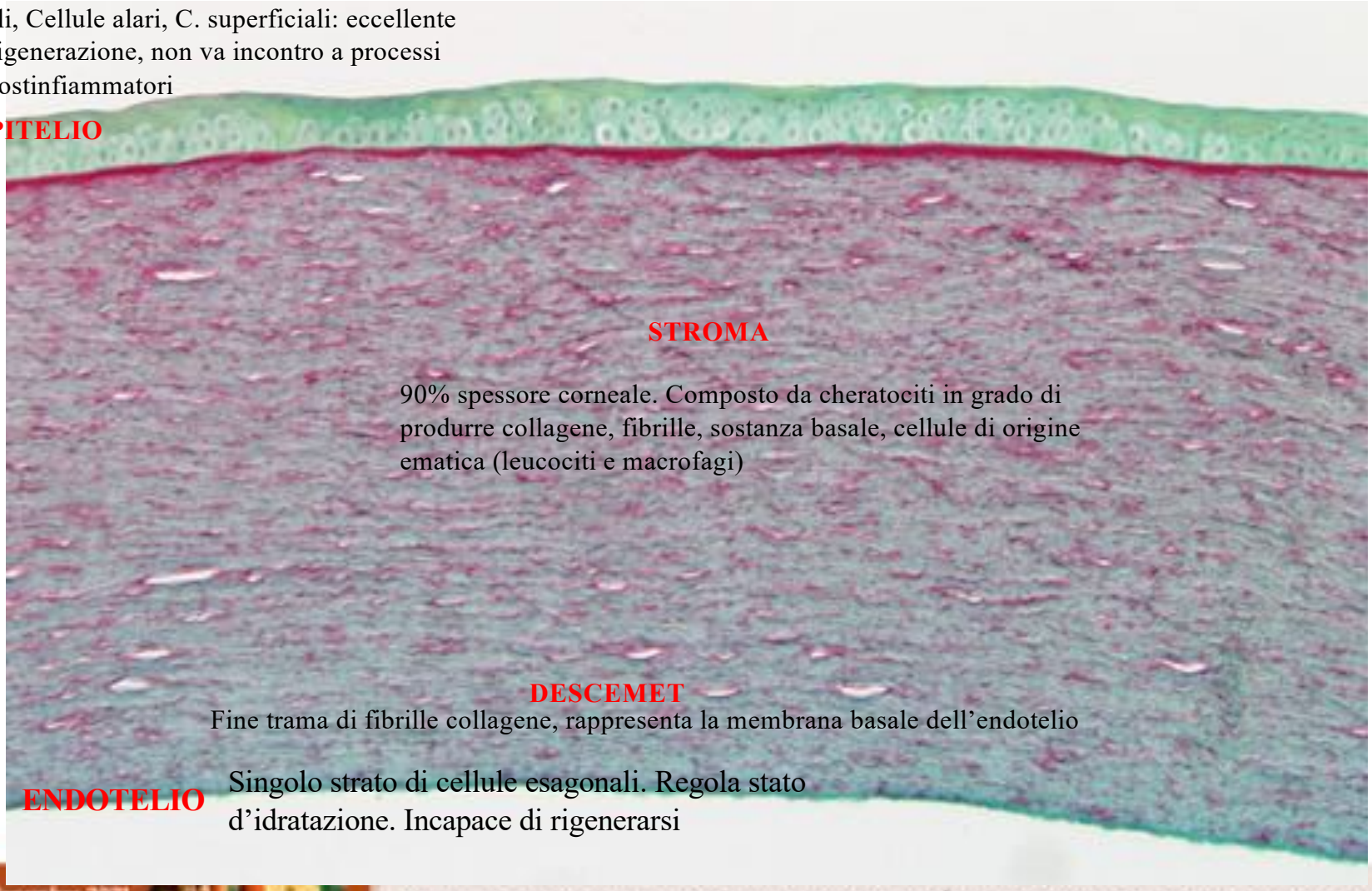
Azienda Ospedaliero – Universitaria
"Policlinico – San Marco"
Clinica Oculistica Universitaria
Direttore: Prof. Teresio Avitabile
Catania

CORNEA


Canale di Schlemm
Congiuntiva
Ora serrata
Parte ciliare della retina
Tendine del muscolo retto esterno
Corpo vitreo
Canale ialoideo
Vasi venosi e arteriosi
Coroide
Sclera
Nervo ottico

Cellule basali, Cellule alari, C. superficiali: eccellente capacità di rigenerazione, non va incontro a processi cicatriziali postinfiammatori

EPITELIO



STROMA

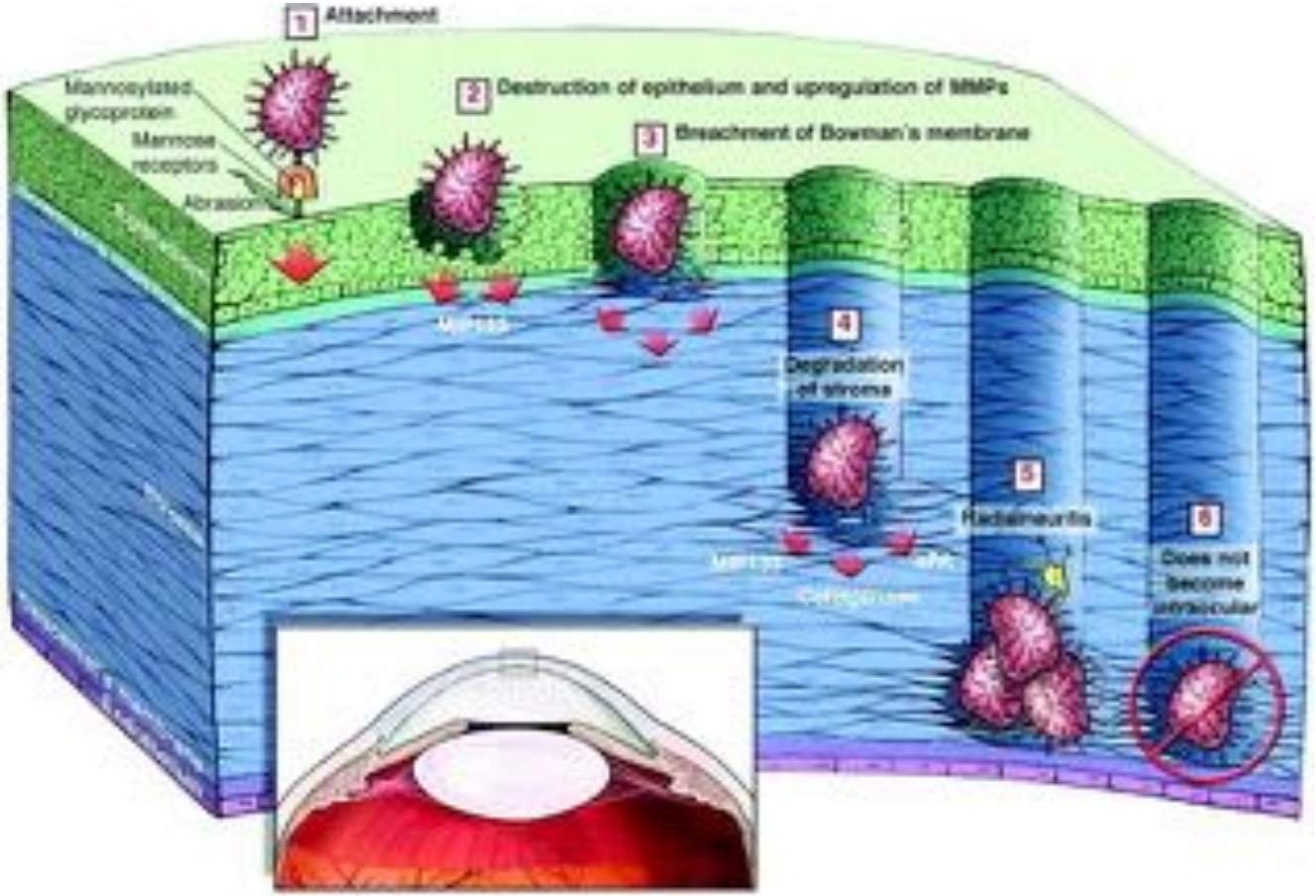
90% spessore corneale. Composto da cheratociti in grado di produrre collagene, fibrille, sostanza basale, cellule di origine ematica (leucociti e macrofagi)

DESCEMET

Fine trama di fibrille collagene, rappresenta la membrana basale dell'endotelio

ENDOTELIO

Singolo strato di cellule esagonali. Regola stato d'idratazione. Incapace di rigenerarsi


1 Attachment
Mannosylated glycoprotein
Mannose receptors
Abrasion
2 Destruction of epithelium and upregulation of MMPs
3 Breachment of Bowman's membrane
4
Degradation of stroma
5
Radial neuritis
6
Does not become vascular

INDAGINI SEMEIOLOGICHE

ESAME ALLA LAMPADA A FESSURA

COLORAZIONE VITALE: floresceina, lisamina, rosa bengala

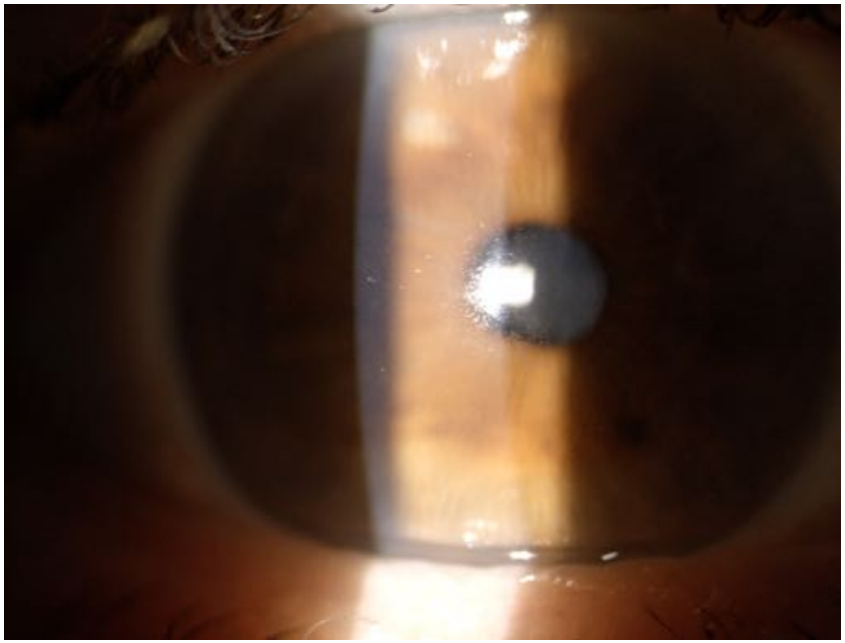
MICROSCOPIA CONFOCALE

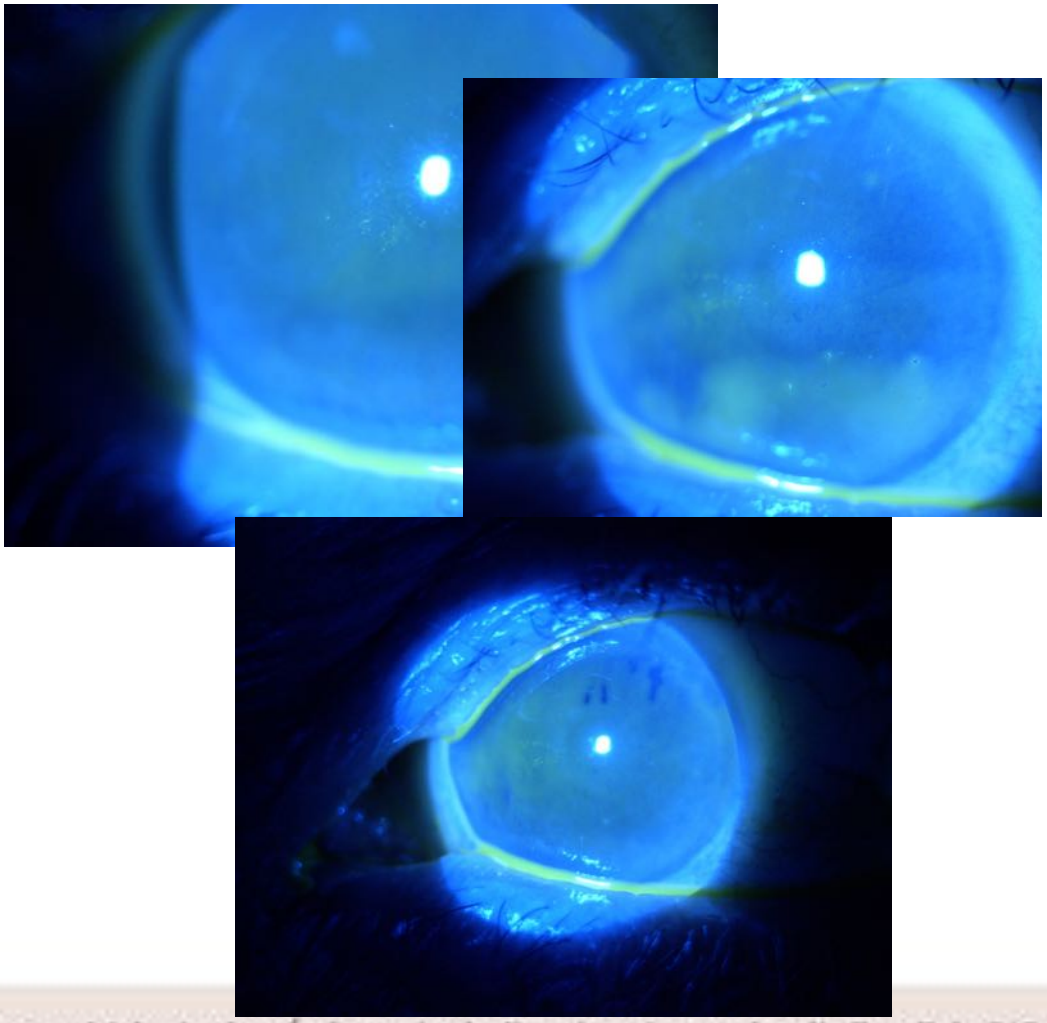
TOMOGRAFIA A COERENZA OTTICA

PACHIMETRIA

TOPOGRAFIA

UBM

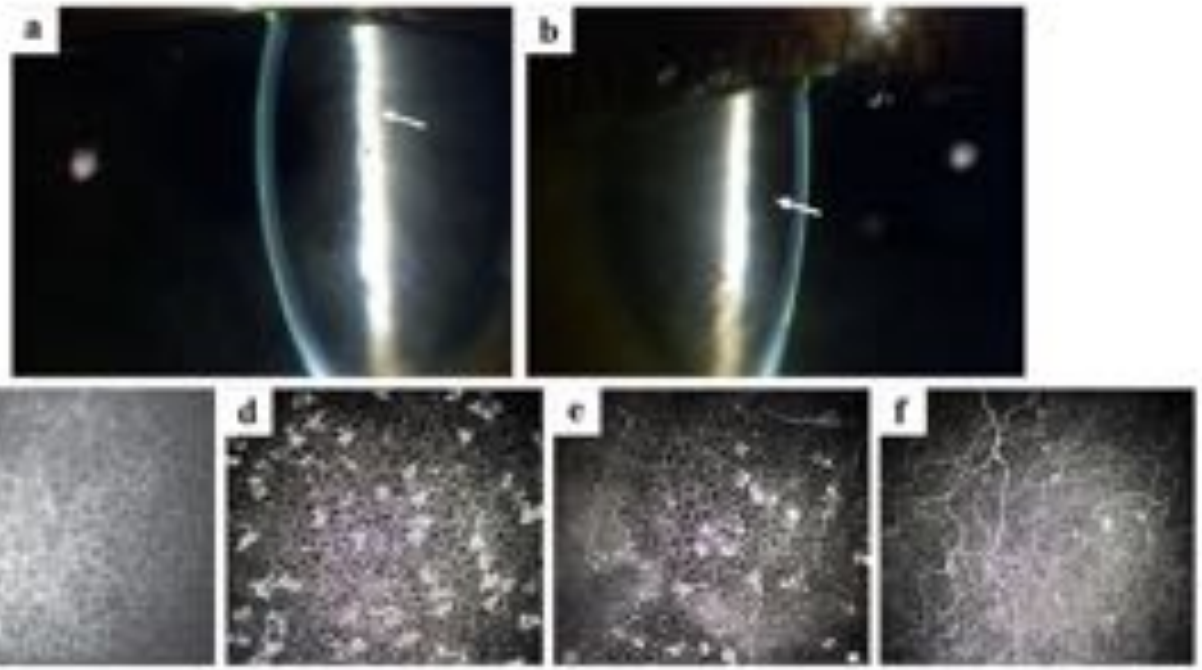




Occhio – Cornea – Microcisti epiteliali (MECs)

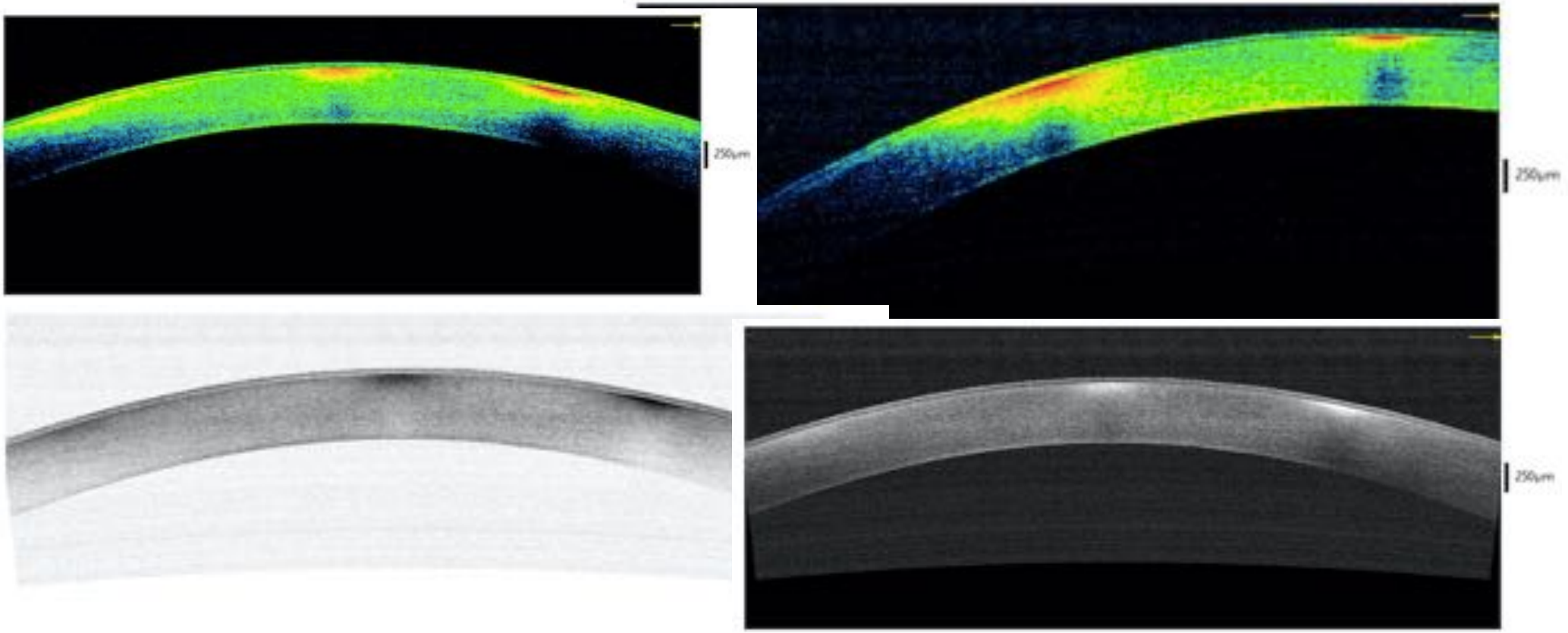
- Quando? Dopo la 4° dose 69% dei soggetti trattati
- Quali esami suggerisce Farooq?

Esame alla Lampada a Fessura



Microscopia confocale della cornea

Tomografia a coerenza ottica (OCT) della cornea



Marquant et al. J Hematol Oncol (2021) 14:159
https://doi.org/10.1186/s13045-021-01172-5

Journal of Hematology & Oncology

CASE REPORT Open Access

Corneal in vivo confocal microscopy to detect belantamab mafodotin-induced ocular toxicity early and adjust the dose accordingly: a case report

Kevin Marquant[1,2], Anne Quinquenel[1,2], Carl Arndt[1,2] and Alexandre Denoyer[1,2,3,4,5*]

Conclusions: Systematic ultrastructural analysis and follow-up of the corneal state during ADCs treatment for multiple myeloma may open new avenues in the therapeutic approach. Early preclinical detection of ocular damage may accurately contribute to finding the correct dose for each patient and not stopping the treatment due to severe ocular adverse effects.

Marquant et al.
https://doi.org/

Journal of
& Oncology

CASE R

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Corne
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Kevin Marqu

Conclusions:
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Table 2 Previous studies using corneal imaging to describe belamaf-induced and other antibody–drug conjugate-induced ocular toxicity

ADC/disease	Authors	Design (n)	Imaging	Findings and limitations
Belantamab mafodotin/MM	Farooq et al. [11]	Retrospective review in the patients' cohort DREAMM-2 (72)	IVCM	Epithelial microcysts and basal opacities
				Largest series, but few IVCM examples
				No quantification
				No space–time kinetics
Belantamab mafodotin/MM	Matsumiya et al. [13]	Case report (2)	OCT	Hyperreflective lesions in some epithelial areas
				Low-resolution imaging
Belantamab mafodotin/MM	Rousseau et al. [10]	Image (1)	IVCM	Epithelial microcysts
				No quantification
				No space–time kinetics
EGFR inhibitor ABT-414/glioblastoma	Parrozzani et al. [14]	Prospective analysis (10)	IVCM	Epithelial microcysts and subbasal nerve plexus disappearance
				Well detailed but no quantification
				Space–time kinetics done
Trastuzumab emtansine/breast cancer	Deblieck et al. [15]	Cross-sectional prospective (12)	IVCM	Microcysts mainly in the peripheral epithelium
				No quantification
				Temporal stability of the lesions
Trastuzumab emtansine/breast cancer	Kreps et al. [16]	Case report (1)	IVCM	No initial images
				Epithelial microcysts and basal deposits
				No quantification
				Stability of the lesions
Mirvetuximab soravtansine/ovarian, peritoneal, and fallopian tube cancer	Corbelli et al. [18]	Case report (5)	OCT and AS-III	Subepithelial changes and corneal hyporeflective dots
				Low-resolution imaging
				No spatial quantification
				Space–time kinetics done

ADC antibody–drug conjugate, AS-III anterior segment-infrared reflectance, IVCM in vivo confocal microscopy, MM multiple myeloma, OCT optical coherence tomography

R-T

CANCER RESEARCH

Translational Science

Modulation of Macropinocytosis-Mediated Internalization Decreases Ocular Toxicity of Antibody–Drug Conjugates

Hui Zhao, John Atkinson, Sara Gulesserian, Zhilan
Hector Aviña, René Hubert, Linnette Capo, Josh Se

DOI: 10.1158/0008-5472.CAN-17-3202 Published A

Abstract

AGS-16C3F is an antibody–drug conjugate (ADC) against ectonucleotide pyrophosphatase/phosphodiesterase 3 (ENPP3) containing the mcMMAF linker-payload currently in development for treatment of metastatic renal cell carcinoma. AGS-16C3F and other ADCs have been reported to cause ocular toxicity in patients by unknown mechanisms. To investigate this toxicity, we developed an *in vitro* assay using human corneal epithelial cells (HCEC) and show that HCECs internalized AGS-16C3F and other ADCs by macropinocytosis, causing inhibition of cell proliferation. We observed the same mechanism for target-independent internalization of AGS-16C3F in fibroblasts and human umbilical vein endothelial cells (HUVEC). Macropinocytosis-mediated intake of macromolecules is facilitated by the presence of positive charges or hydrophobic residues on the surface of the macromolecule. Modification of AGS-16C3F, either by attachment of polyglutamate peptides, mutation of residue K16 to D on AGS-16C3F [AGS-16C3F(K16D)], or decreasing the overall hydrophobicity via attachment of polyethylene glycol moieties, significantly reduced cytotoxicity against HCECs and other primary cells. Rabbits treated with AGS-16C3F showed significant ocular toxicity, whereas those treated with AGS-16C3F(K16D) presented with less severe and delayed toxicities. Both molecules displayed similar antitumor activity in a mouse xenograft model. These findings establish a mechanism of action for target-independent toxicities of AGS-16C3F and ADCs in general, and provide methods to ameliorate these toxicities.

Significance: These findings reveal a mechanism for nonreceptor-mediated toxicities of antibody drug conjugates and potential solutions to alleviate these toxicities. *Cancer Res; 78(8); 2115–26. ©2018 AACR.*

> Ocul Surf. 2021 Jul;21:186-192. doi: 10.1016/j.jtos.2021.06.001. Epub 2021 Jun 6.

Relationships between activated dendritic cells and dry eye symptoms and signs

Harry Levine [1], Jodi Hwang [1], Harrison Dermer [1], Divy Mehra [1], William Feuer [2], Anat Galor [3]

Conclusions: The presence of ≥2 aDCs in the central cornea suggests a systemic immune disorder in individuals with DE symptoms. Topical anti-inflammatory therapy can reduce the number of aDCs in the central cornea.

Ophthalmol Ther
https://doi.org/10.1007/s40123-020-00280-8

ORIGINAL RESEARCH

Corneal Epithelial Findings in Patients with Multiple Myeloma Treated with Antibody–Drug Conjugate Belantamab Mafodotin in the Pivotal, Randomized, DREAMM-2 Study

Asim V. Farooq · Simona Degli Esposti · Rakesh Popat · Praneetha Thulasi · Sagar Lonial · Ajay K. Nooka · Andrzej Jakubowiak · Douglas Sborov · Brian E. Zaugg · Ashraf Z. Badros · Bennie H. Jeng · Natalie S. Callander · Joanna Opalinska · January Baron · Trisha Piontek · Julie Byrne · Ira Gupta · Kathryn Colby

Received: April 21, 2020

Management della tossicità oculare: pronto riconoscimento/diagnosi/monitoraggio

Ophthalmol Ther
https://doi.org/10.1007/s40123-020-00289-z

CORRECTION

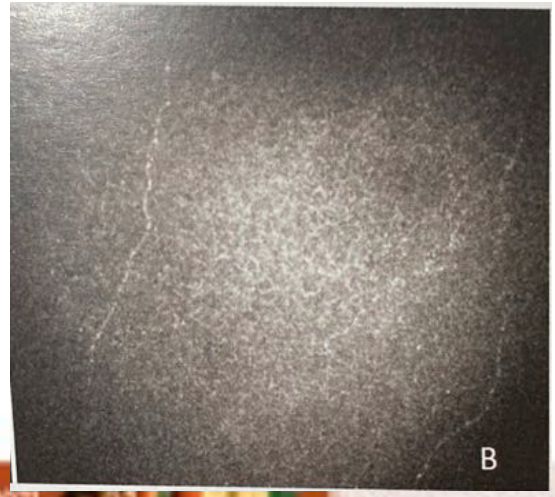
Correction to: Corneal Epithelial Findings in Patients with Multiple Myeloma Treated with Antibody–Drug Conjugate Belantamab Mafodotin in the Pivotal, Randomized, DREAMM-2 Study

Asim V. Farooq · Simona Degli Esposti · Rakesh Popat · Praneetha Thulasi · Sagar Lonial · Ajay K. Nooka · Andrzej Jakubowiak · Douglas Sborov · Brian E. Zaugg · Ashraf Z. Badros · Bennie H. Jeng · Natalie S. Callander · Joanna Opalinska · January Baron · Trisha Piontek · Julie Byrne · Ira Gupta · Kathryn Colby

- Page 10, 2nd column, first paragraph, first sentence reads: "Following the first dose of belamaf 2.5 mg/kg, he presented on day 27 with MECs characterized as mild/patchy in the periphery/mid-periphery on slit lamp microscopy (Fig. 5a, b). IVCM of the involved areas revealed hyperreflective opacities (Fig. 5c)." This should read as "(Fig. 4a, b)" and "(Fig. 4c–f)", respectively.

A cosa son dovute le MICs?

Non sono altro che un processo di apoptosi cellulare indotta nelle forme evaporative di dry eye a cui consegue un'alterazione del plesso nervoso subepiteliale per lo stimolo infiammatorio indotto dalla severa disfunzione lacrimale.



Riduzione delle fibre nervose
Aumento della tortuosità
Ridotta sensibilità della superficie oculare
Attenzione! Maggiore è la riduzione delle fibre nervose minore è la risposta alla terapia lubrificante.

Osservazioni:

- Altri farmaci della stessa categoria ADCs (Antibody Drug Conjugates) provocano le stesse alterazioni (abbondante letteratura!)
- Nelle condizioni di dry eye severo abbiamo frequentemente la presenza di microcisti (MICs)
- Si riporta una percentuale di dry eye del 19% al baseline (inverosimile!); già nella popolazione normale abbiamo 32-36%, in soggetti con terapie oncologiche o che magari hanno avuto una ”GVHD” ????
- Ipotesi: errata interpretazione del fenomeno lacrimazione/epifora???

Table 1 Recommended belamaf dose modifications based on eye examination findings per the KVA scale

Eye examination findings per KVA scale		Recommended dose modifications
Grade 1	Corneal examination finding(s) Mild superficial keratopathy[a] Change in BCVA[b] Decline from baseline of 1 line on Snellen Visual Acuity	Continue treatment at current dose
Grade 2	Corneal examination finding(s) Moderate superficial keratopathy[c] Change in BCVA[b] Decline from baseline of 2 or 3 lines (and Snellen Visual Acuity not worse than 20/200)	Withhold treatment until improvement in both corneal examination findings and changes in BCVA to Grade 1 or better and resume at same dose

Grade 3	Corneal examination finding(s) Severe superficial keratopathy[d] Change in BCVA[b] Decline from baseline by more than 3 lines (and Snellen Visual Acuity not worse than 20/200)	Withhold treatment until improvement in both corneal examination findings and changes in BCVA to Grade 1 or better and resume at a reduced dose
Grade 4	Corneal examination finding(s) Corneal epithelial defect[e] Change in BCVA[b] Snellen Visual Acuity worse than 20/200	Permanently discontinue treatment

BCVA best-corrected visual acuity, *KVA* keratopathy and visual acuity, *MEC* microcystic-like epithelial change
DREAMM-2 utilized a pre-specified scale, the KVA scale, that combined slit lamp examination findings (e.g., keratopathy/MECs) with an assessment of BCVA using Snellen Chart

[a] Mild superficial keratopathy (documented worsening from baseline), with or without symptoms

[b] Changes in visual acuity due to treatment-related corneal findings

[c] Moderate superficial keratopathy with or without patchy microcyst-like deposits, sub-epithelial haze (peripheral), or a new peripheral stromal opacity

[d] Severe superficial keratopathy with or without diffuse microcyst-like deposits involving the central cornea, sub-epithelial haze (central), or a new central stromal opacity

[e] Corneal epithelial defect such as corneal ulcers

Ophthalmol Ther
https://doi.org/10.1007/s40123-020-00288-y

CORRECTION

Correction to: Corneal Epithelial Findings in Patients with Multiple Myeloma Treated with Antibody–Drug Conjugate Belantamab Mafodotin in the Pivotal, Randomized, DREAMM-2 Study

Asim V. Farooq · Simona Degli Esposti · Rakesh Popat · Praneetha Thulasi · Sagar Lonial · Ajay K. Nooka · Andrzej Jakubowiak · Douglas Shoore · Brian R. Zaugg · Ashraf Z. Badros · Benoit H. Jung · Natalie S. Callander · Joanna Opalinska · January Baron · Trisha Piontek · Julie Byrne · Ira Gupta · Kathryn Colby

- Page 5: Table 1, Grade 4, Recommended dose modification currently reads "Permanently discontinue treatment". This should be "Consider treatment discontinuation for a Grade 4 event. Based on a benefit:risk assessment, if continuing treatment with belamaf is being considered, treatment may be resumed at a reduced dose after the event has improved to Grade 1 or better event."

- Page 10, 2nd column, first paragraph, first sentence reads: "Following the first dose of belamaf 2.5 mg/kg, he presented on day 27 with MECs characterized as mild/patchy in the periphery/mid-periphery on slit lamp microscopy (Fig. 5a, b). IVCM of the involved areas revealed hyperreflective opacities (Fig. 5c)." This should read as "(Fig. 4a, b)" and "(Fig. 4c–f)", respectively.

- Page 18: Under "Recommended Monitoring, Diagnosis, and Management Techniques" and "Diagnosis and Staging of MECs" the final sentence currently reads "The eye care professional should also determine if the decline in BCVA is related to belamaf-associated examination finding(s)." This should be "Determine the recommended dosage modification of belamaf based on the worst finding in the worst affected eye. Worst finding should be based on either a corneal examination finding or a change in visual acuity per the KVA scale."

Le ipotesi patofisiologiche del danno corneale nella pubblicazione di Farooq

- On target: presunta attività recettoriale del farmaco su cellule non cancerose (cc corneali con rec HER2? da accertare) che determinerebbe una carica citotossica intracellulare

- Off target: carica citotossica su cellule non cancerose senza antigene con meccanismi di endocitosi, pinocitosi (macropinocitosi), bystender toxicity: spettatore della tossicità

Da dove arriverebbero ADCs per raggiungere

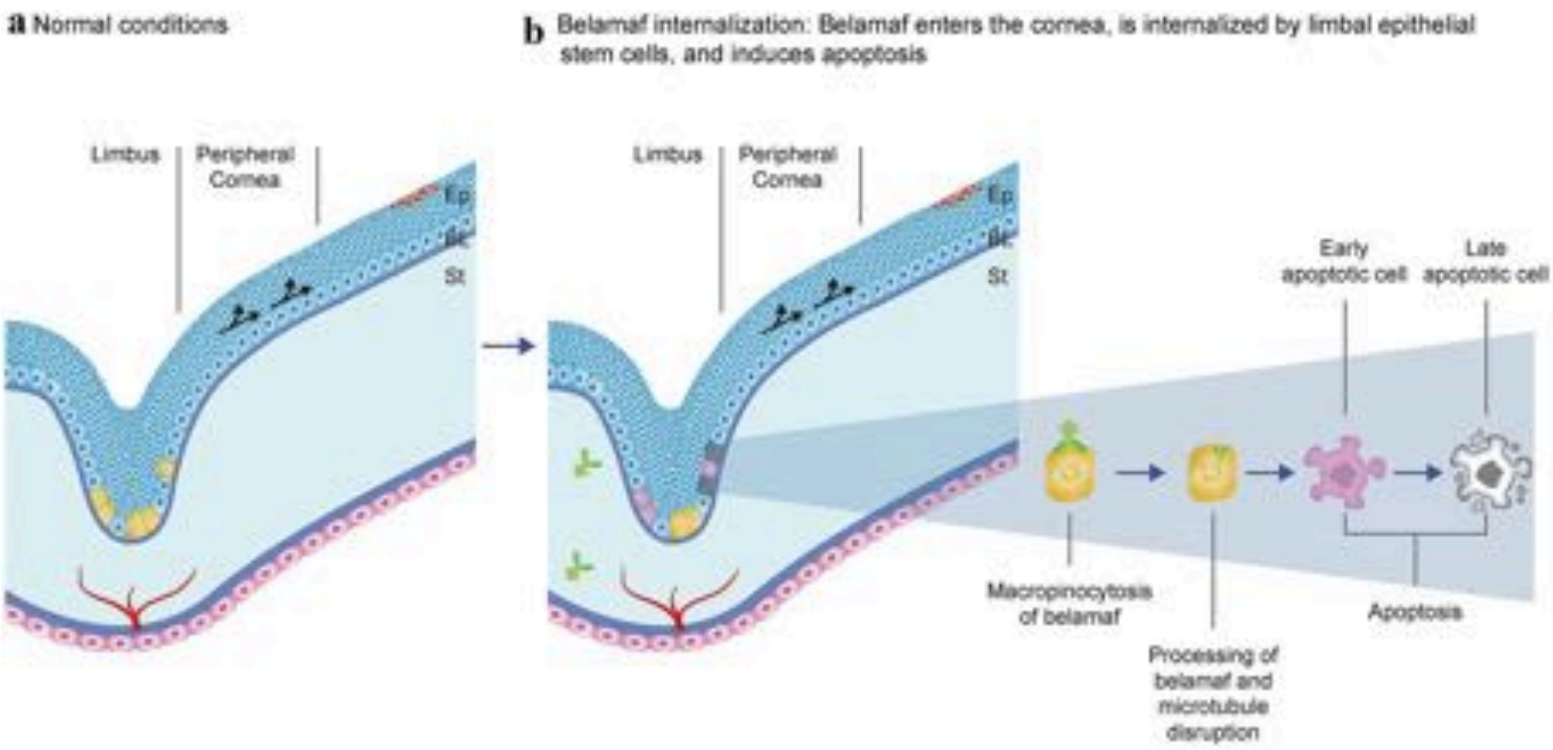
la cornea (avascolare)?

- Attraverso il limbus (vascolarizzato)
- Attraverso le lacrime (Farooq cita, a conferma, studi sulle lacrime del coniglio, ma il coniglio non è un modello utilizzabile!)
- Pathway endocitico, internalizzati in cellule progenitrici (macropinocitosi) – off target – meccanismo determinante nella trombocitopenia

Macropinocitosi e occhio

- Meccanismo di assorbimento
  - di fluidi sulla cornea
    - di nutrienti
  - di farmaci (es. indometacina e FANS in genere)
    - di virus (adenovirus)
- di batteri (pseudomonas, acanthamoeba) che attivano recettori sull'epitelio corneale (EphA2) che inducono
  - macropinocitosi

Macropinocitosi facilitata dal dry eye


a Normal conditions
b Belamaf internalization: Belamaf enters the cornea, is internalized by limbal epithelial stem cells, and induces apoptosis
Limbus
Peripheral Cornea
Ep
Be
St
Limbus
Peripheral Cornea
Ep
Be
St
Early apoptotic cell
Late apoptotic cell
Macropinocytosis of belamaf
Processing of belamaf and microtubule disruption
Apoptosis
c Migration of early apoptotic corneal epithelial cells to peripheral cornea (MECs observed, but no symptoms)
d Migration of early and late apoptotic corneal epithelial cells to central cornea (MECs observed and symptoms reported)
e Migration of new corneal epithelial cells to replace cells that have undergone apoptosis (resolution of MECs and symptoms)

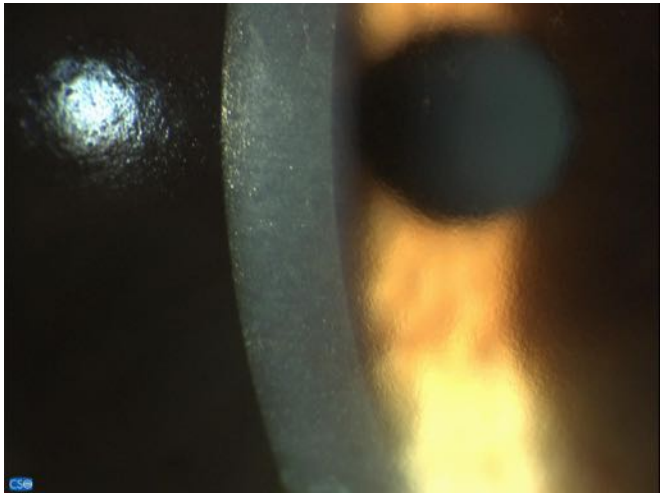
Rivalutazione della patogenesi del danno oculare

1° Concetto: allargare l'attenzione a tutta la superficie oculare e non osservare solo la cornea (es. cardiologo-valvola)
2° Concetto: considerare l'unità funzionale della superficie oculare che comprende:

- le palpebre compreso il margine palpebrale
- la congiuntiva – CALT (Conjunctiva Associated Lymphatic Tissue) assicura la protezione immunitaria della superficie oculare (potrebbe essere l'on-target dell'effetto farmacologico di questa categoria di farmaci che determina come evento avverso una disfunzione lacrimale
- le ghiandole di Meibomio
- le vie lacrimali

Come evidenziare il danno oculare?

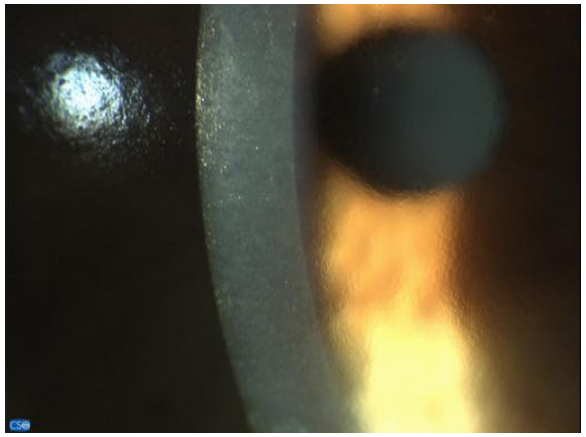
- Lampada a Fessura (LAF)
- Microscopia confocale di cornea (lesioni iperiflettenti, MICs – congiuntiva – ghiandole di Meibomio
- Tomografia a coerenza ottica (OCT) lesioni iperiflettenti LAF guidate , falsi colori
- Meibografia
- Spessore strato lipidico (Keratograph – Lipiview)
- Tempo di rottura del film lacrimale (NIF-BUT)
- Sensibilità corneale

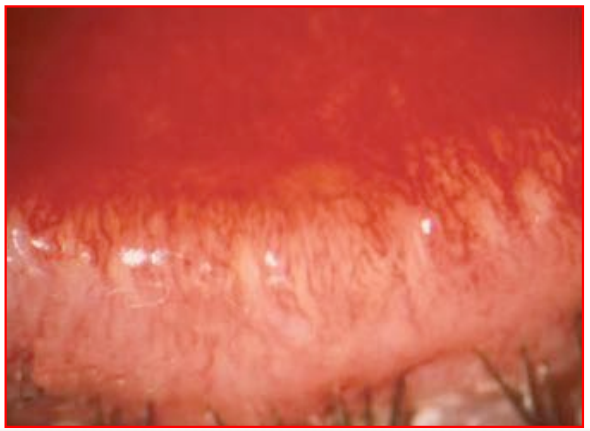


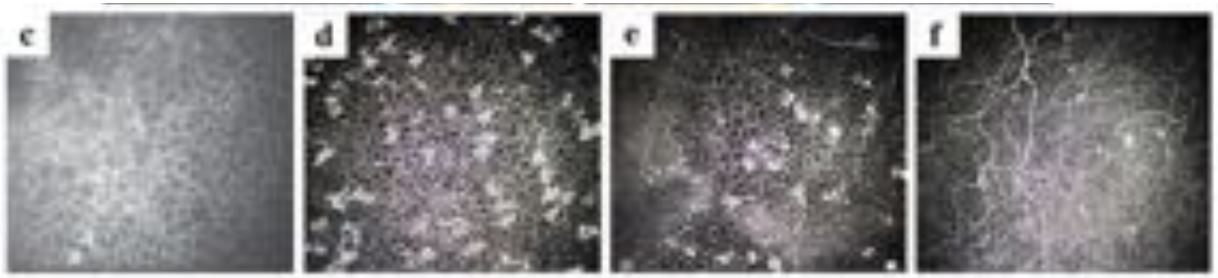
- SINTOMATOLOGIA ED IMPATTO SULLA QUALITÀ DI VITA

Il paziente lamenta lacrimazione perché?

- Patologia infiammatoria grave della superficie oculare (non certo legata alle MICs)
- Ostruzione delle vie lacrimali di deflusso per chiusura e cheratinizzazione del canalino lacrimale

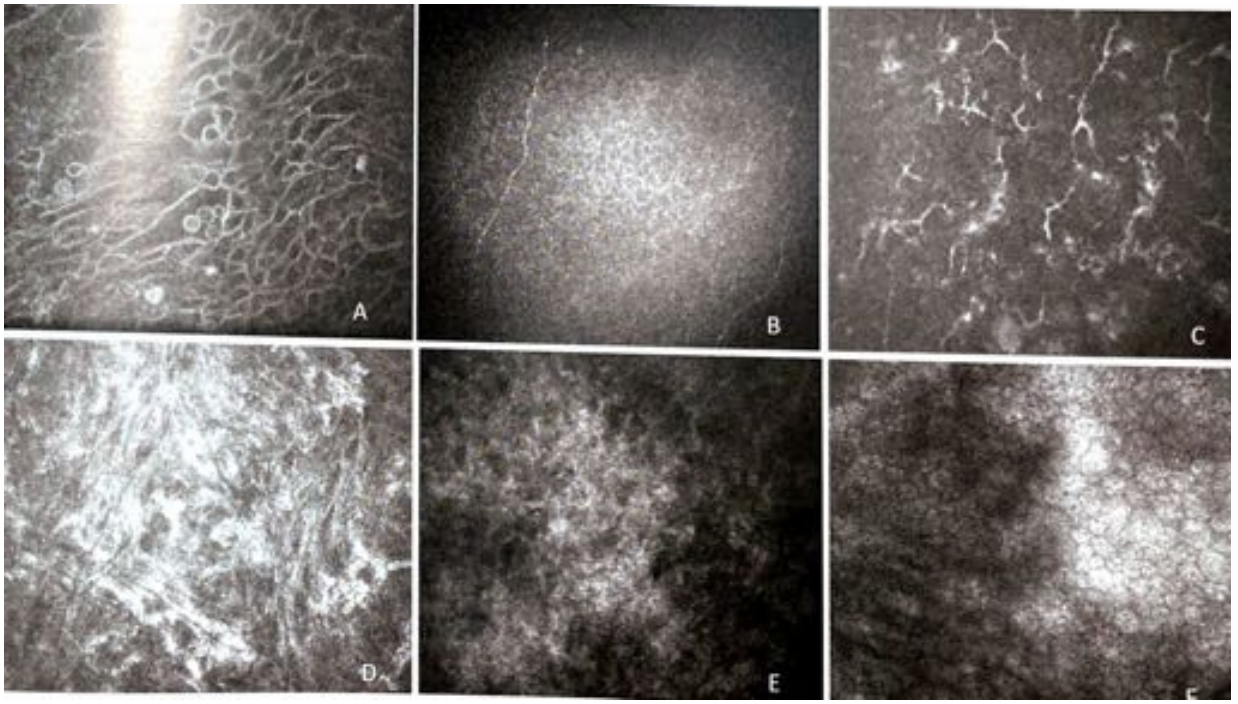


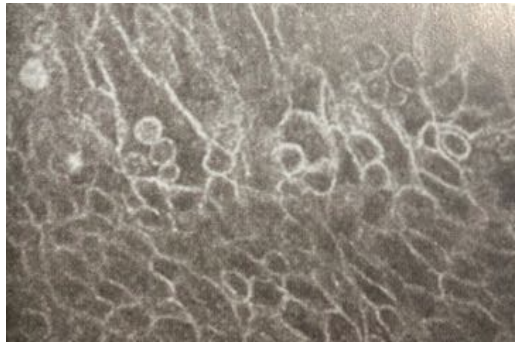




Farooq 2020

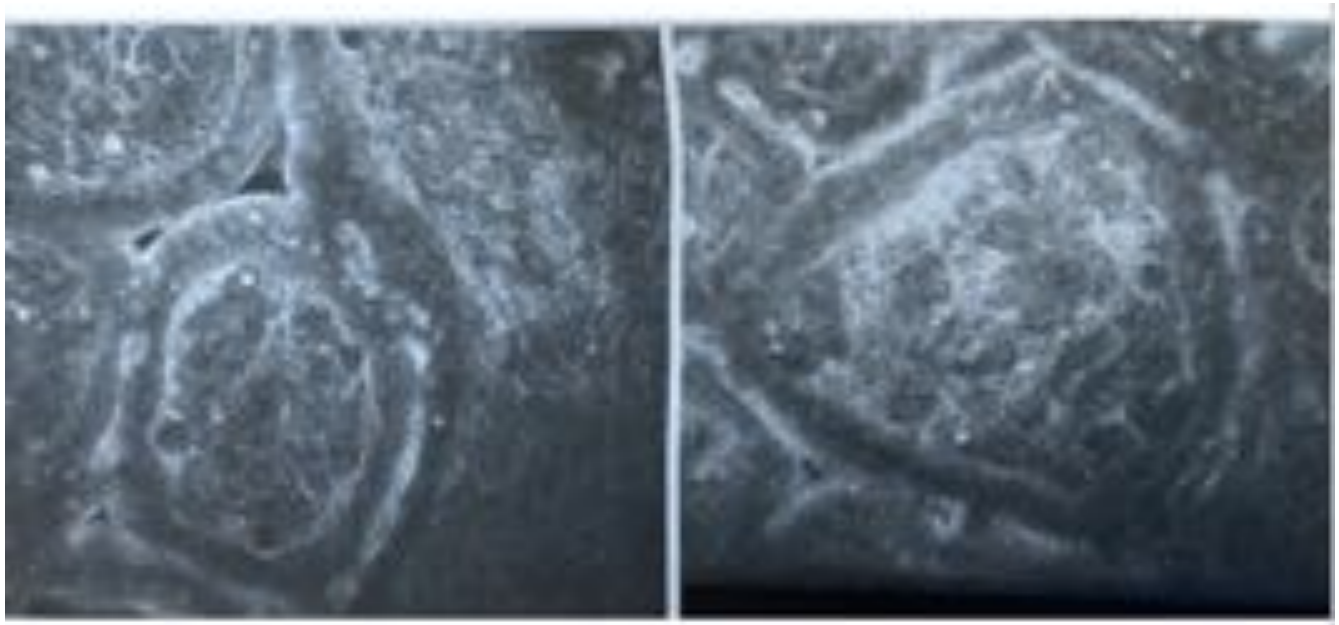
Nubile 2019





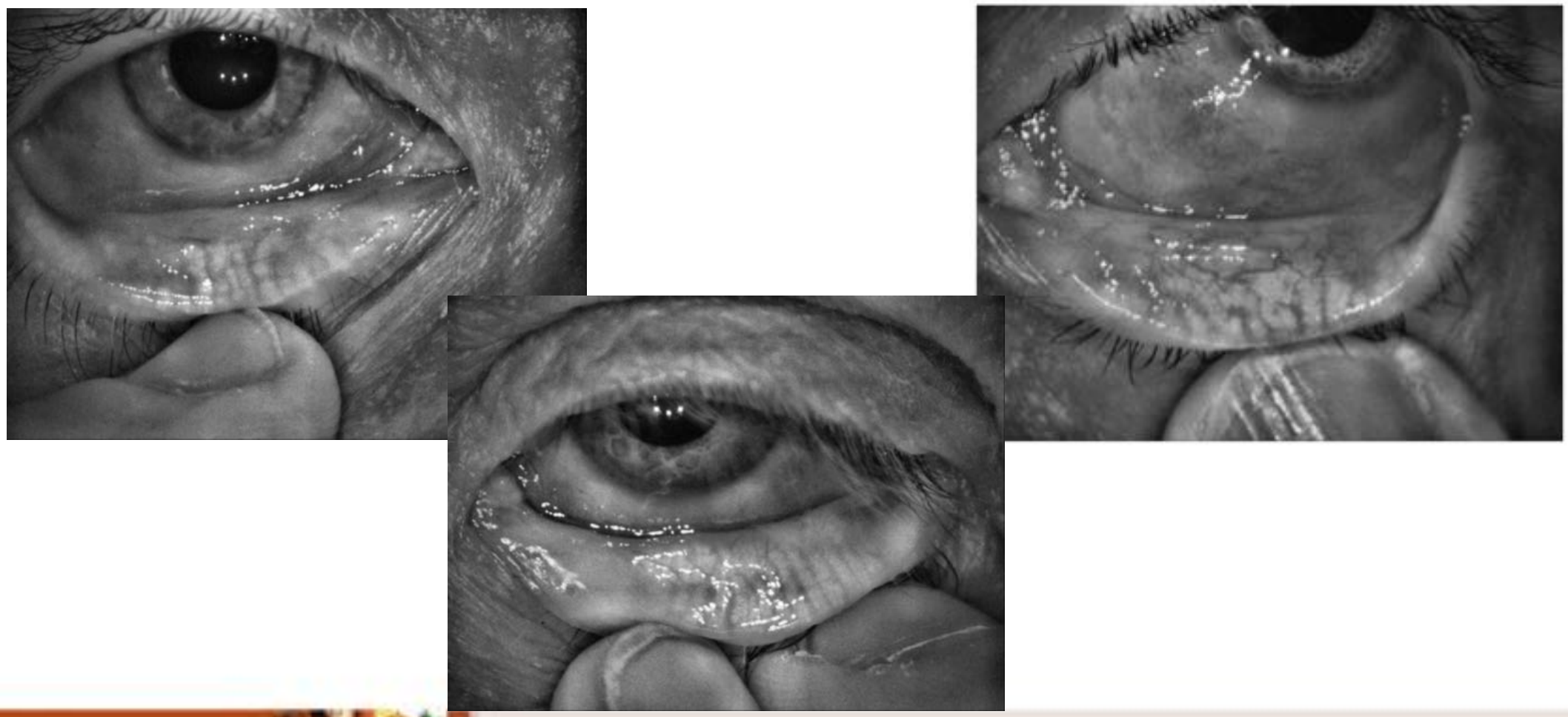
Microcisti (MICs)

Microscopia confocale in vivo per lo studio dei follicoli linfatici congiuntivali



Per la cortesia del Prof. Mario Nubile

Perché le ghiandole di Meibomio si ammalano?



Effetto antimitotico del farmaco

Sindrome sicca di origine autoimmune (Sjogren) Immune-related Adverse Event come nelle terapie con Immune Checkpoint Inibitors (ICIs) che però agiscono sui linfociti B (Nivolumab) o altri

Effetto tossico del farmaco sugli elementi ghiandolari e sulla superficie oculare mediante alta concentrazione raggiunta nelle lacrime

Completa atrofia delle gh. di Meibomio

Microscopia confocale in vivo delle ghiandole di Meibomio

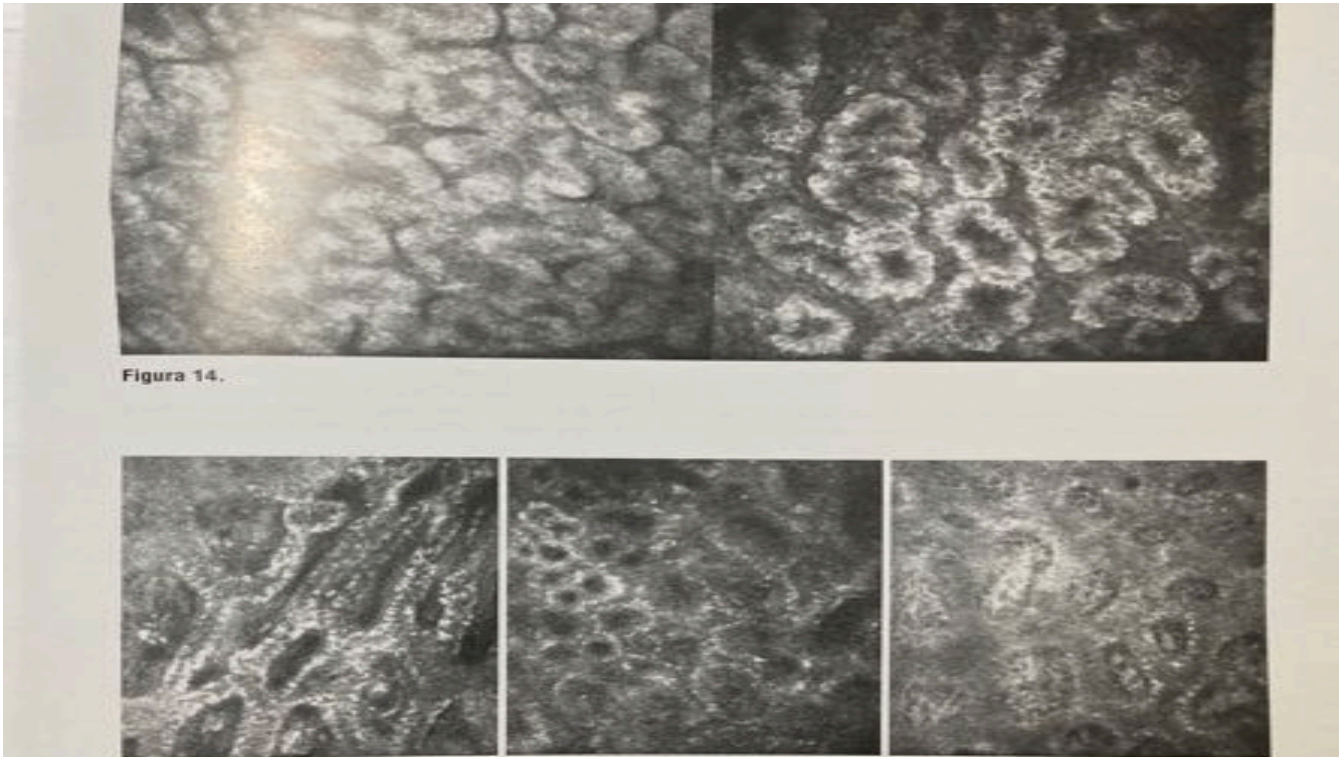
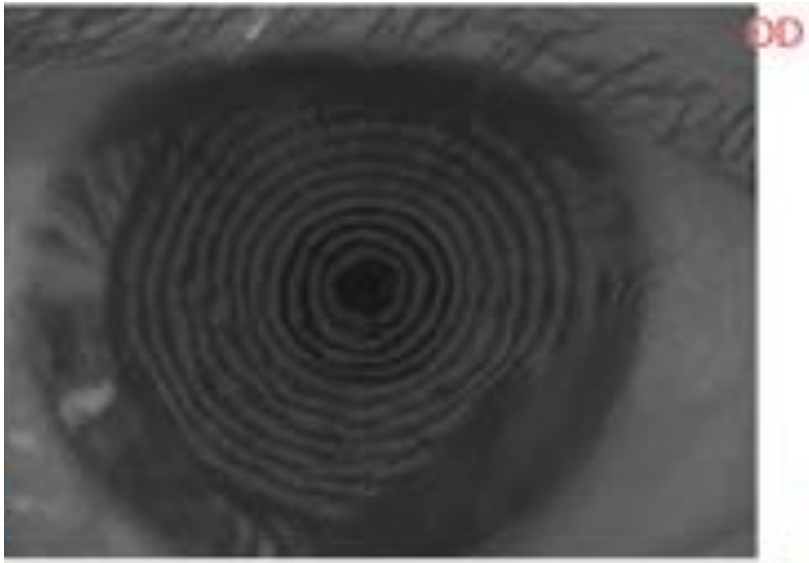
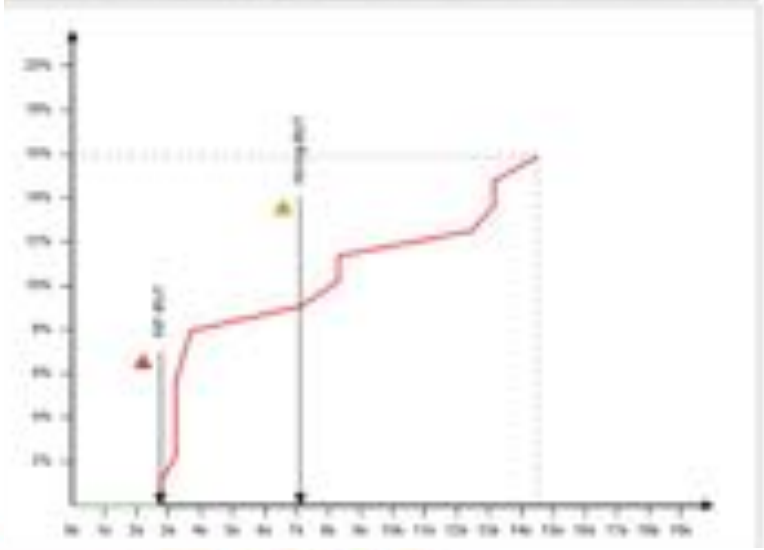
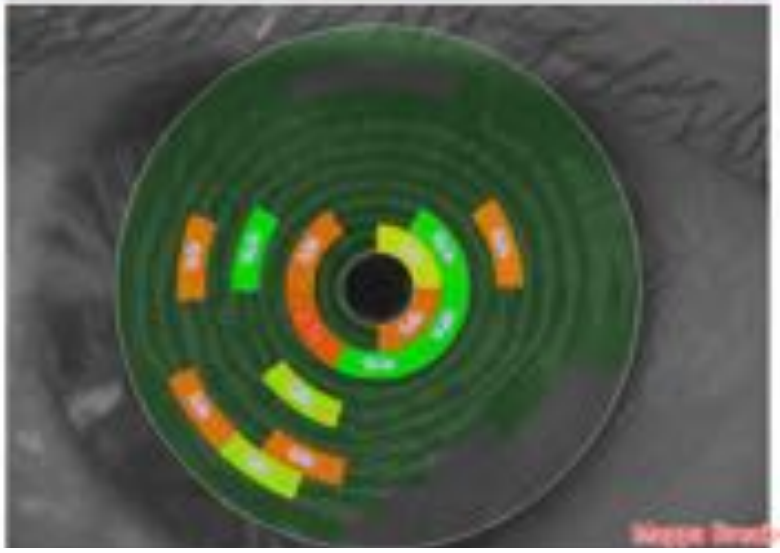


Figura 14.

La Disfunzione delle Ghiandole di Meibomio.
Edizioni SOI 2019



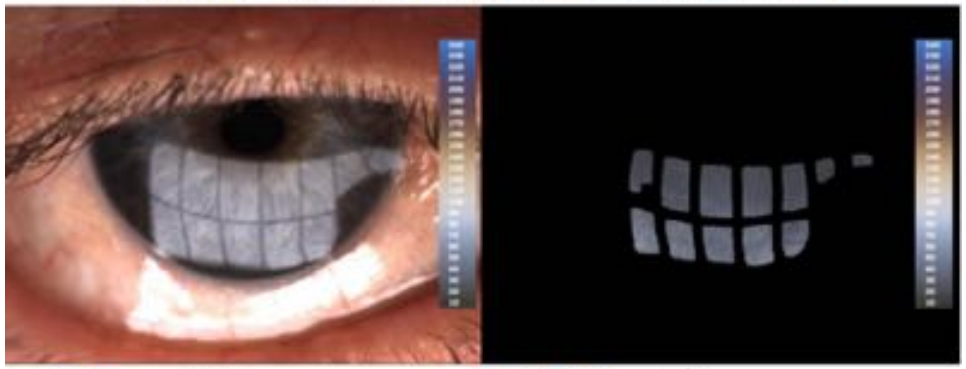




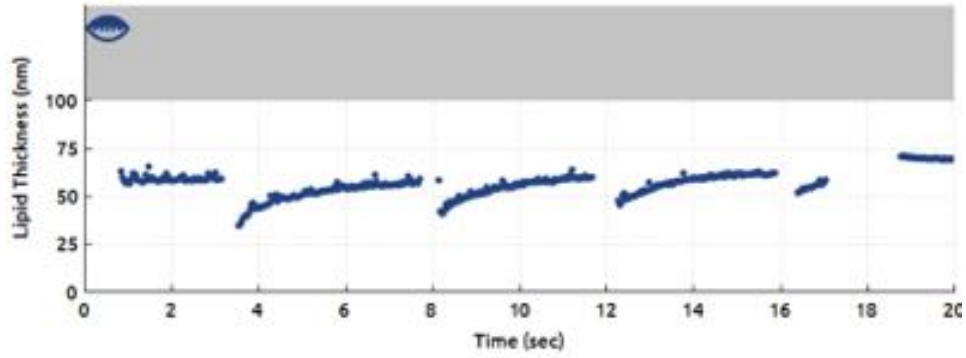
Report Date: 11/12/2019 1:21:10 PM

Spessore dello strato lipidico e funzione dell'ammiccamento

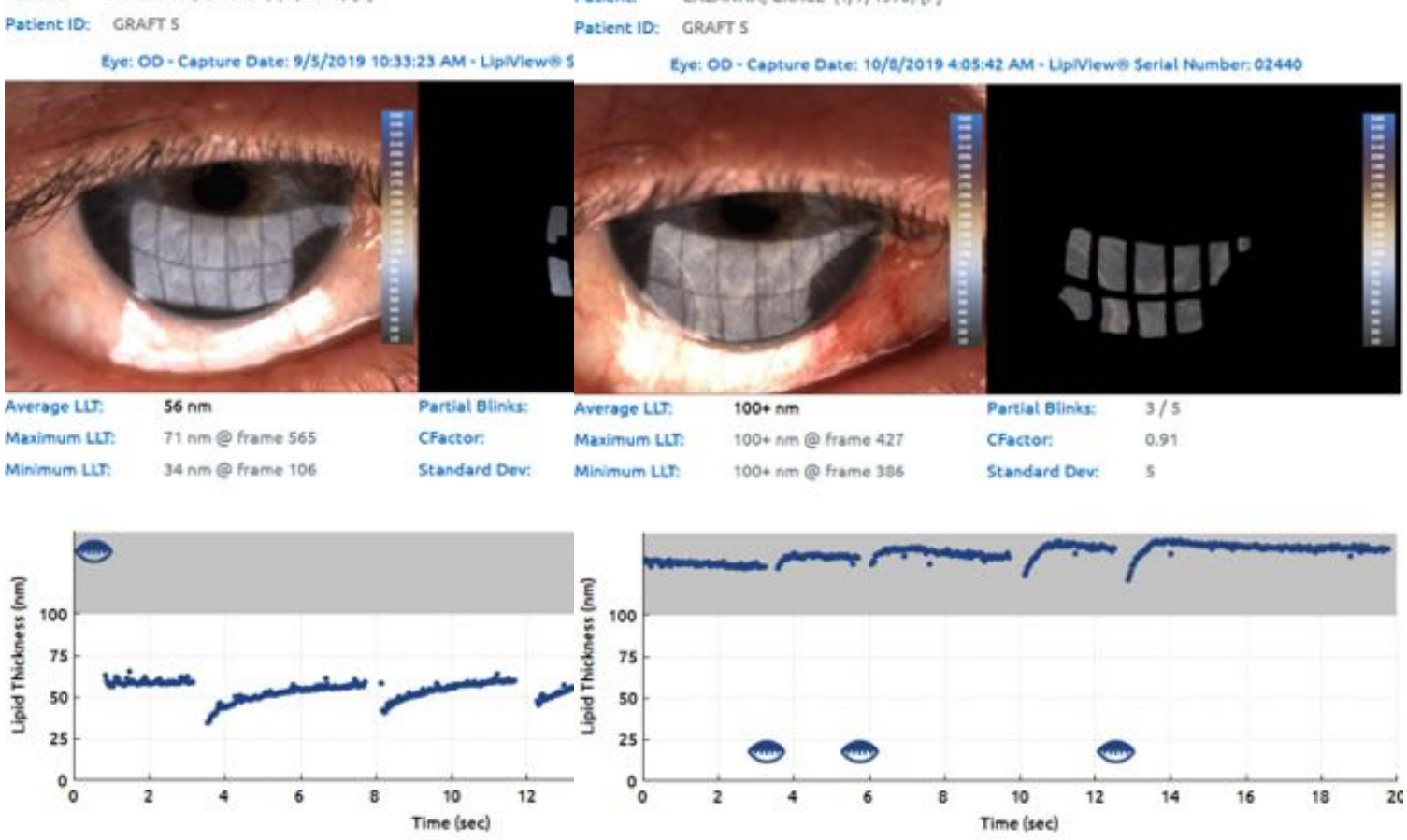
Studio della funzionalità delle ghiandole di Meibomio

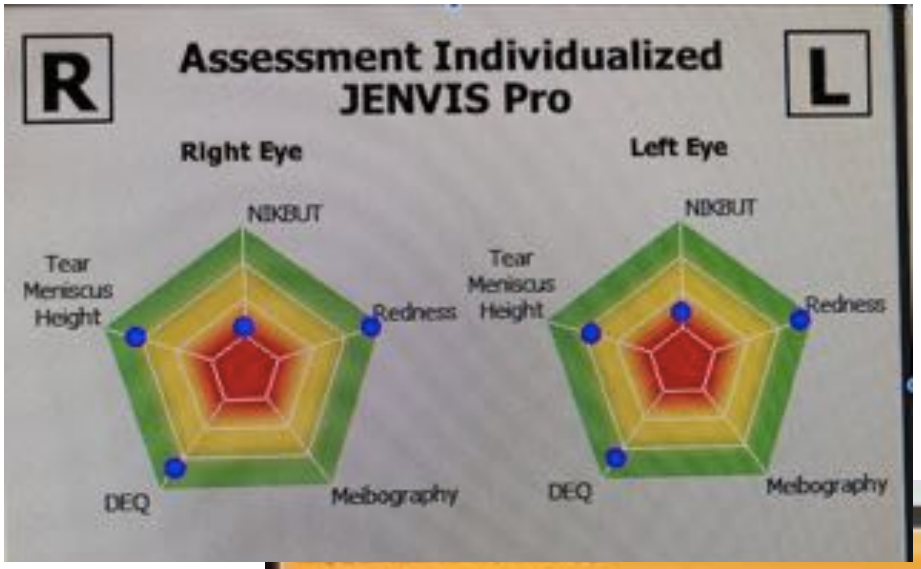


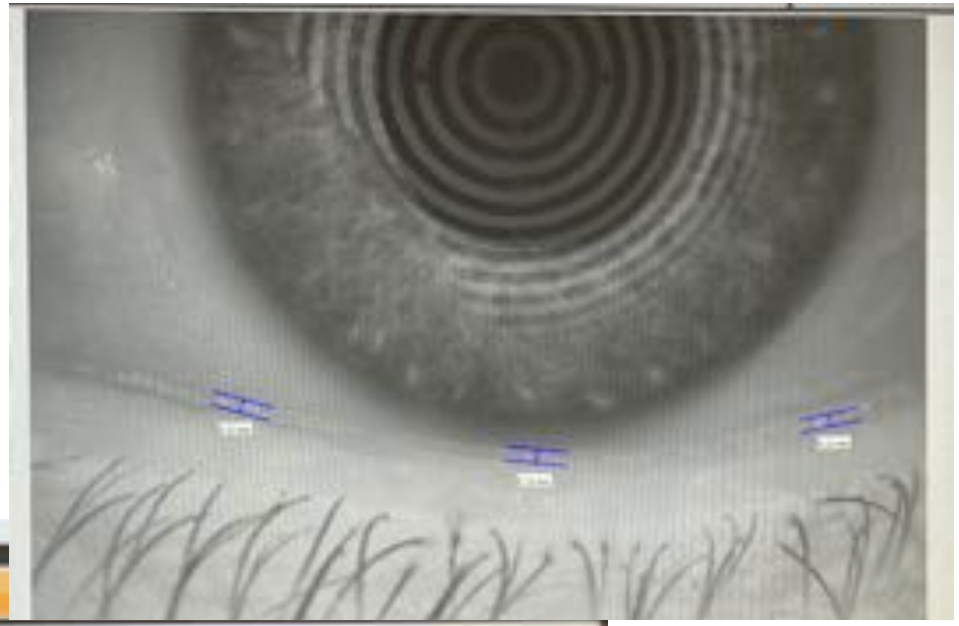
Average LLT:	56 nm	Partial Blinks:	1 / 6
Maximum LLT:	71 nm @ frame 565	CFactor:	0.96
Minimum LLT:	34 nm @ frame 106	Standard Dev:	6

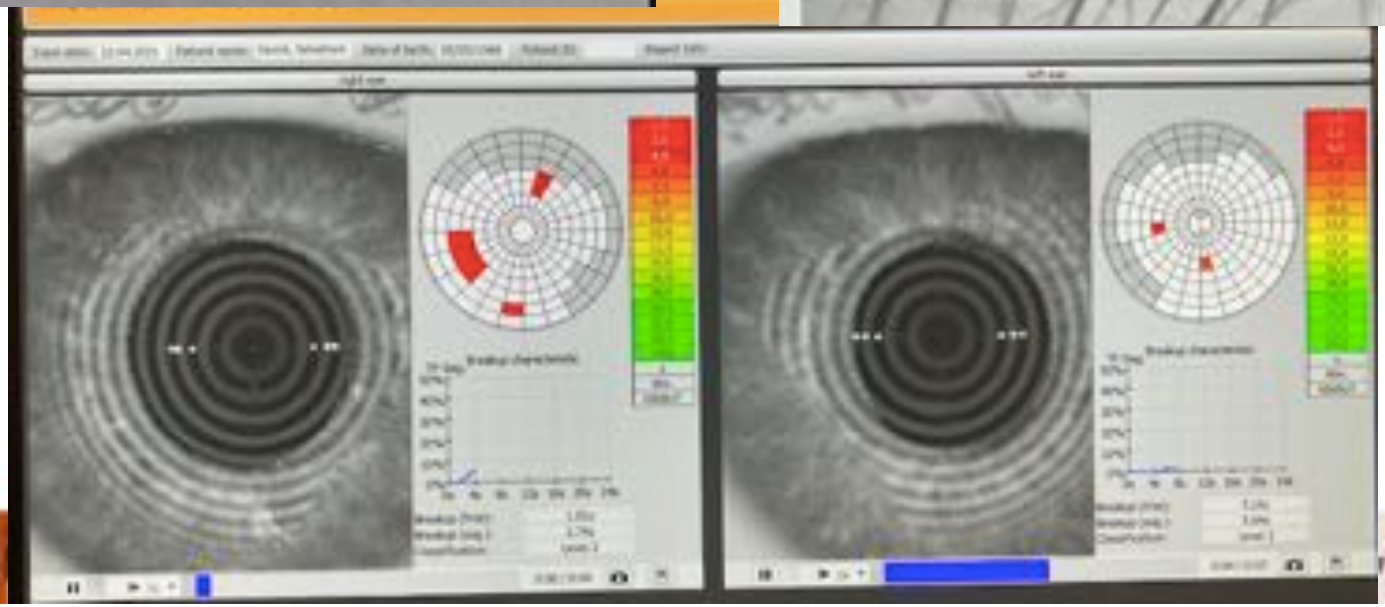


Spessore dello strato lipidico e funzione dell'ammiccamento



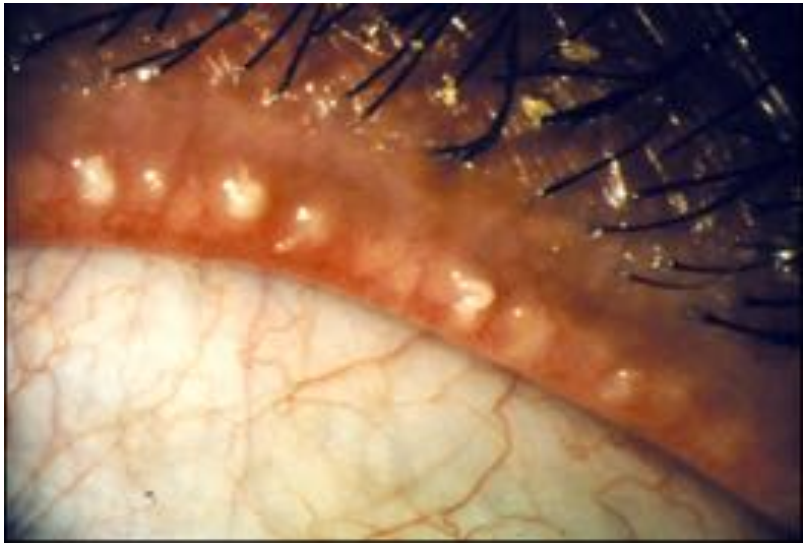

R
Assessment Individualized
JENVIS Pro
L
Right Eye
Left Eye
NIKBUT
Tear Meniscus Height
Redness
DEQ
Meibography
NIKBUT
Tear Meniscus Height
Redness
DEQ
Meibography

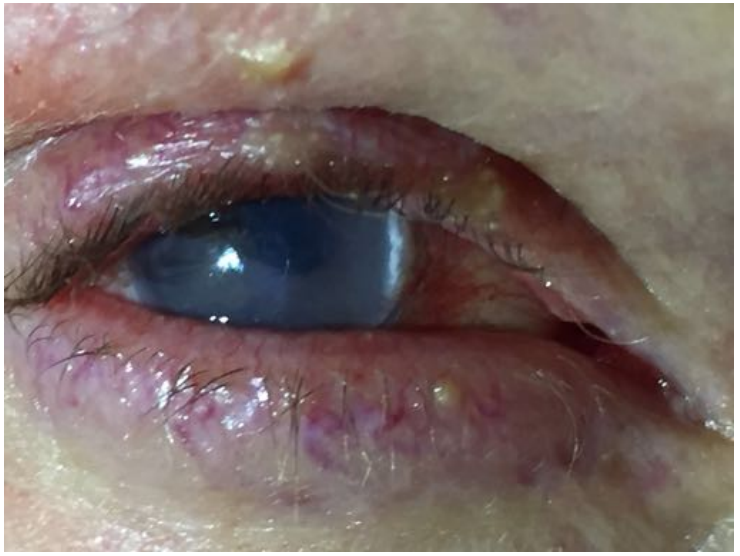




CONSEGUENZE?

- ❑ Secretum addensato
- ❑ Ipercheratinizzazione del condotto terminale e dell'orifizio





Gli orifizi della ghiandola sono ostruiti da tappi di secrezione ispessita, opaca, biancastra contenente materiale cheratinizzato

Epifora per cheratinizzazione ed ostruzione puntino e canalino lacrimale

Nuove entità nosologiche di tipo ostruttivo

Meibomian Gland Disease (MGD):

- Ostruttiva (blocco orifizi ghiandolari)
- Iposecretoria
- Ipercheratinizzazione

Chemotherapy – induced Lacrimal Drenaige obstruction

Strategie di trattamento

Farooq et al. 2020

On target: meccanismo recettoriale – ipotesi di terapia – modificare la struttura molecolare del farmaco?????
Off target: MECs

- agenti che inibiscono la macropinocitosi (imipramina, fenoxibenzamina, vinblastina)
- Corticosteroidi topici
- Sostituti lacrimali senza conservanti
- Riduzione dosi o stop del trattamento

Agiscono sui macrofagi che non sono presenti né sulla cornea né al limbus

Effetti dubbi per ADCs
Non dimostrati effetti su MECs
Inefficaci nella profilassi del danno corneale in DREAMM-2

Strategie di trattamento

Farooq et al. 2020

- Riduzione dosi o stop del trattamento

Grade 4	Corneal examination finding(s)	Permanently discontinue treatment
	Corneal epithelial defect[a]	
	Change in BCVA[b]	
	Snellen Visual Acuity worse than 20/200	

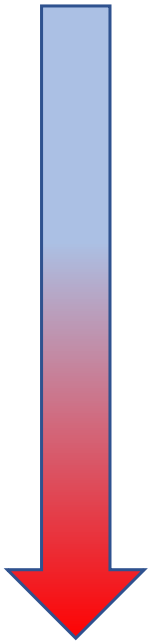
Non si entrava nel merito per stabilire la causa della riduzione visiva che poteva essere legata a cataratta, AMBLIOPIA!!!

Possibile risoluzione del problema corneale con terapia medica o anche chirurgica

I difetti epiteliali, le MICs sono in media periferia

Strategie di trattamento alternative

- Sostituti lacrimali lipidici
- Vitamina A topica (per effetto antiossidante, epiteliotrofico su tessuto ghiandolare ed epitelio corneale, immunomodulante)
- Steroidi topici in collirio ed unguento
- Considerare l'utilizzo degli estratti di sangue cordonale nei soggetti con disepitelizzazione corneale marcata



Profilassi

Maschera oftalmica autoriscaldante

Igiene palpebrale

- ✓ **45°C COSTANTE per 5-7 min**

Impacchi caldo umidi

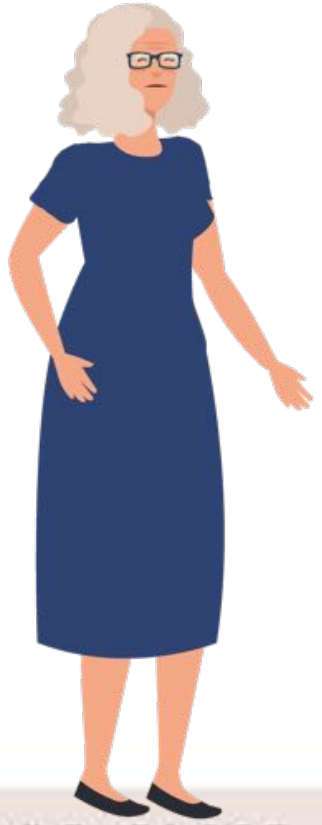
- ✓ **2x/die**

Massaggi sulla cute palpebrale

- ✓ **Fino a 90 riutilizzi**

Caso clinico n.1

M.G. donna anni 69



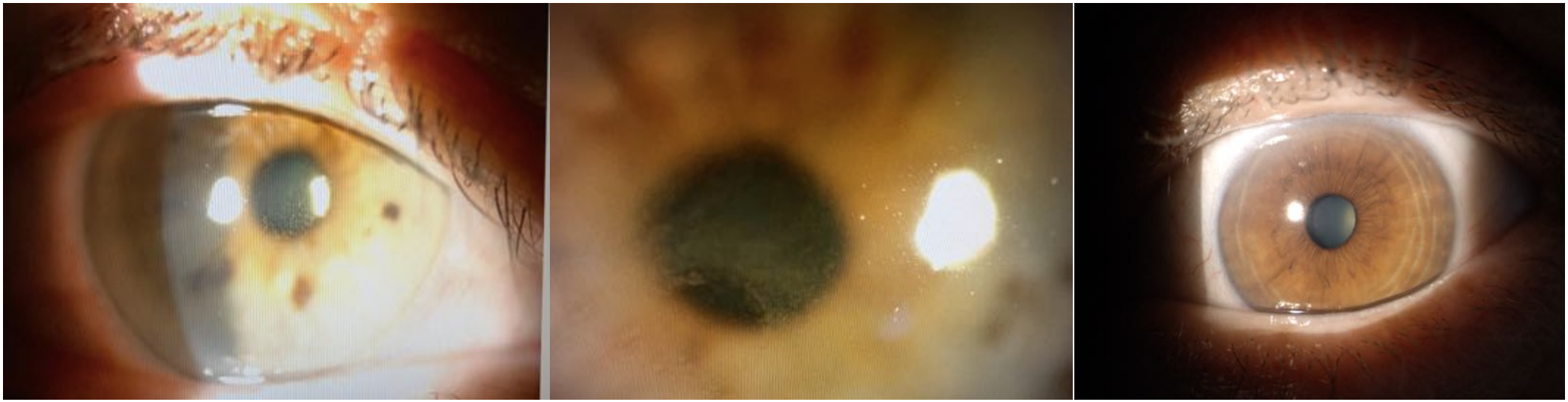
- Diabetica da circa 15 anni. Ambliopia occhio destro. Intervento di cataratta in occhio destro 5 anni fa. Cataratta occhio sinistro.
- Affetta da Mieloma Multiplo Refrattario in terapia con Belantamab da circa 2 mesi.

- Visus Occhio destro 1/20 con correzione 1/10
- Visus occhio sinistro 3/10 con correzione 5/10

- Blefarite anteriore e posteriore. Iperemia congiuntivale e pericheratica.
- Depositi corneali diffusi su tutto l'ambito in media periferia corneale e perilimbari (vedi immagini LAF)

Clinical Case - Female, born 1952

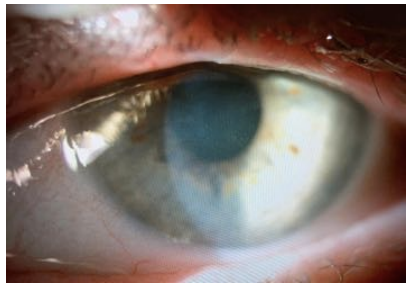
Dopo trattamento topico

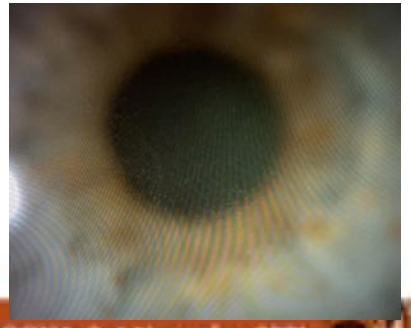


Caso clinico n.2

Donna di 65 anni

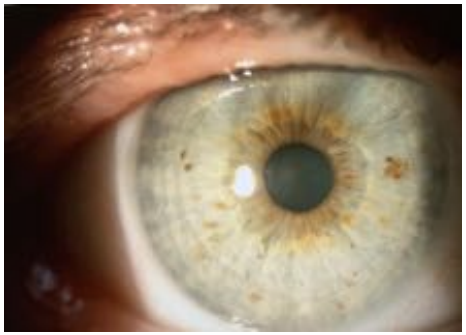
Prima

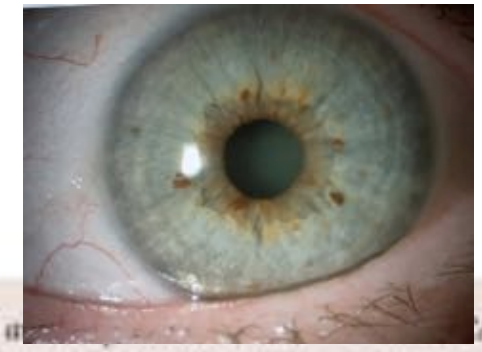


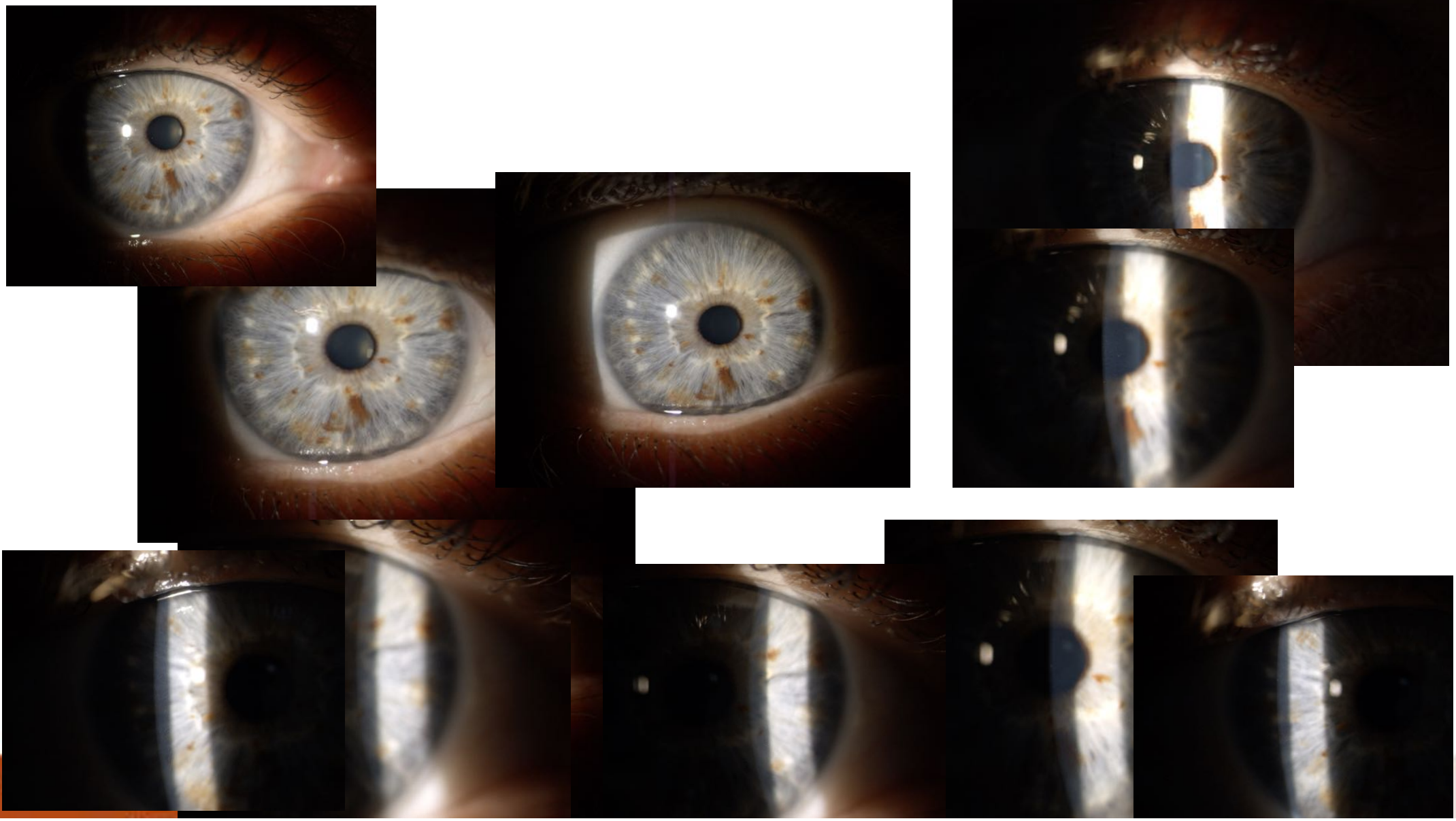


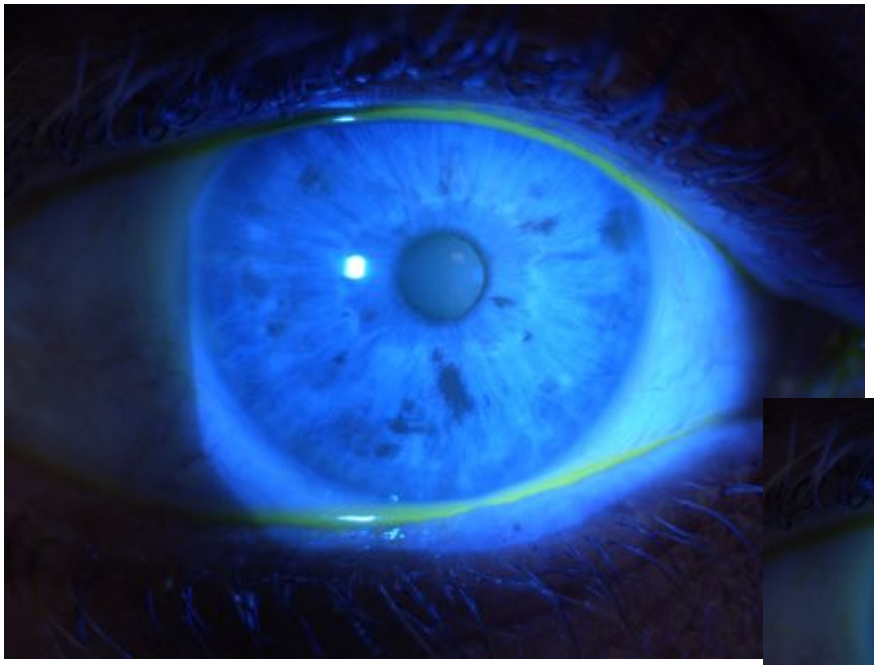
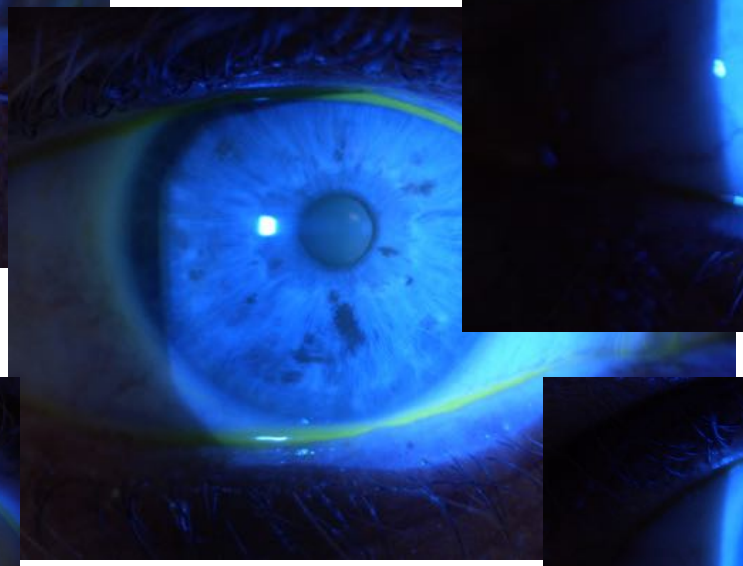
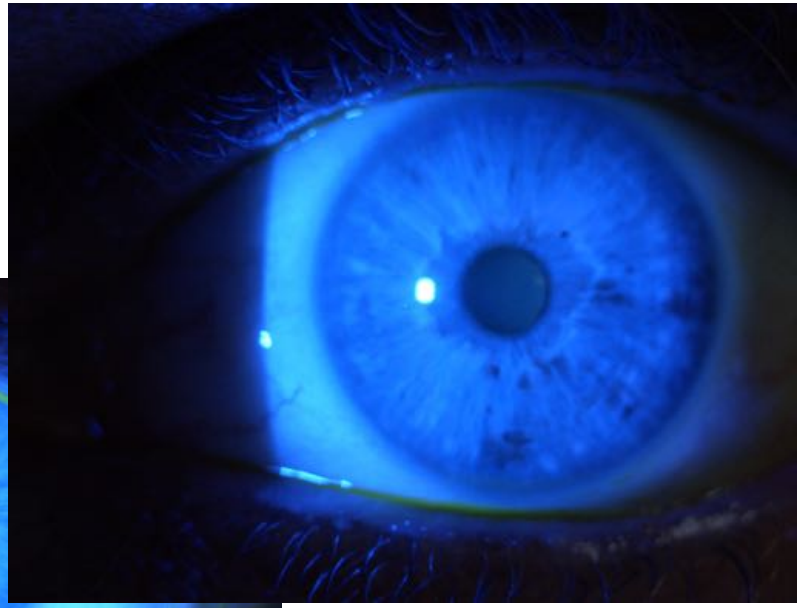
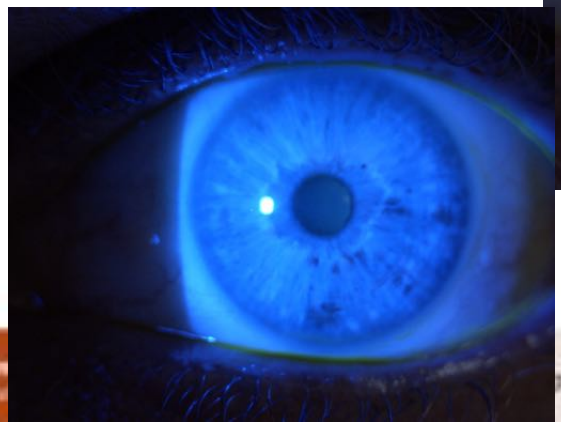
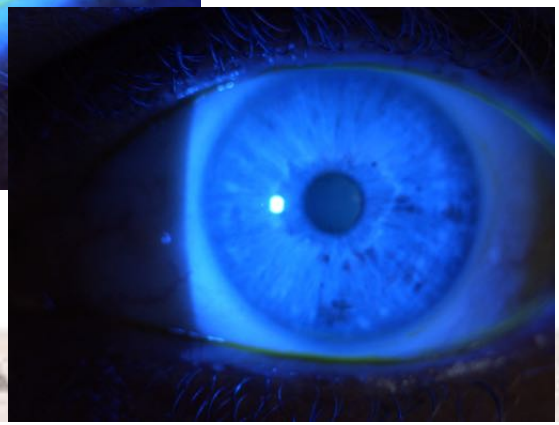
- Donna di 65 anni con MMR in terapia con Belantamab da circa 2 mesi. Riferisce glaucoma da circa 18 anni. La paziente esibisce un esame del campo visivo del 2015 che risulta tubulare in occhio sinistro.
- Visus OD 6/10
- Visus OS conta le dita a 1 metro
- Annebbiamento visivo, bruciore, blefarite, irregolarità del margine palpebrale, microcisti corneali.

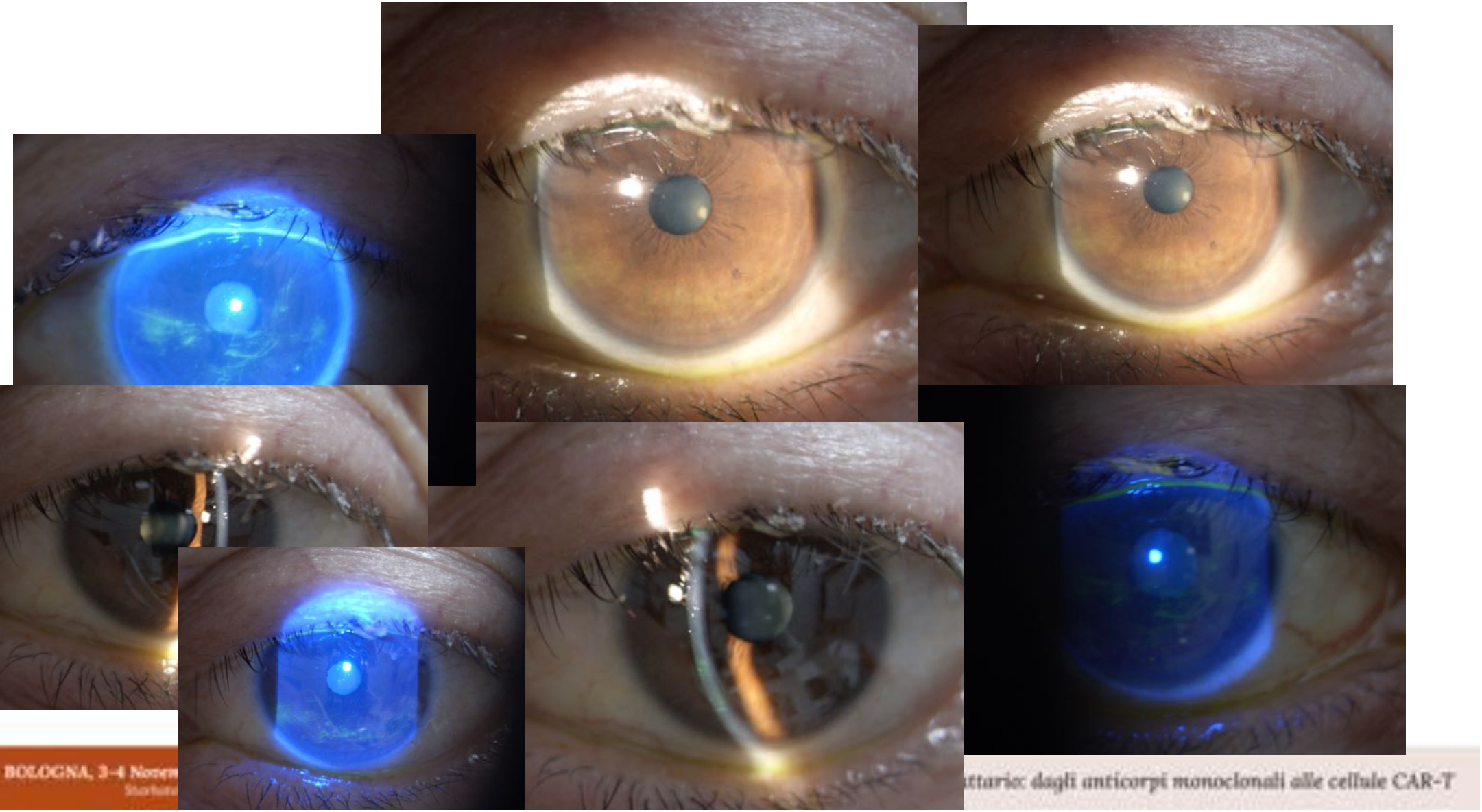
Dopo trattamento topico

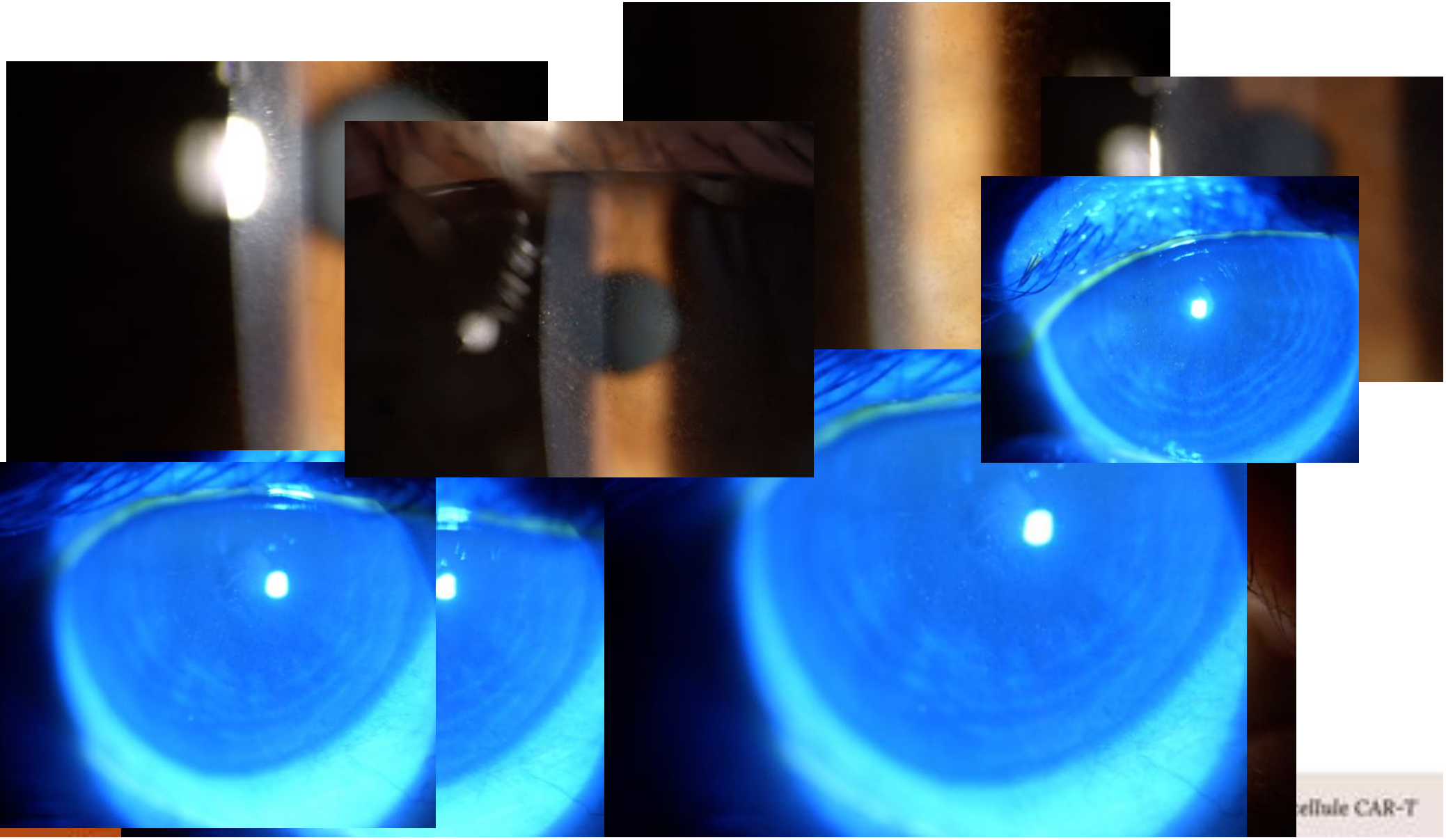


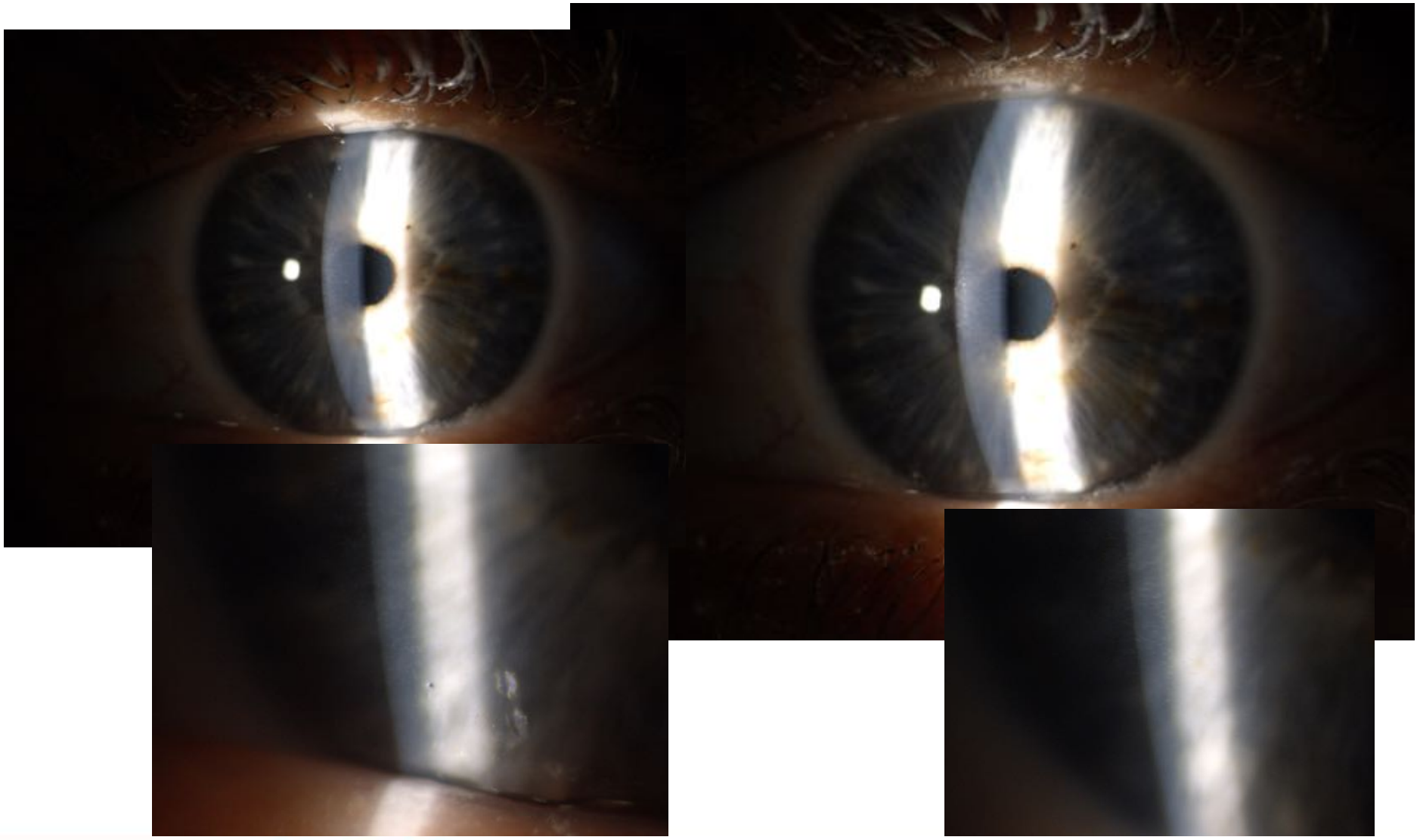





BOLOGNA, 3-4 Nover
ttarie: dagli anticorpi monoclonali alle cellule CAR-T





CONCLUSIONI

- Terapia individualizzata
- È inammissibile pregiudicare la possibilità di un trattamento salvavita per degli eventi avversi oculari assolutamente gestibili
- Opportuni e necessari gli incontri con gli oftalmologi
- Indispensabile l'utilizzo di sostituti lacrimali lipidici
- Necessario l'utilizzo di steroidi anche in unguento in presenza di flogosi palpebrale e MGD severa

Grazie per l'attenzione!