NHS
National Institute for Health Research

Turkish Congress 2013
Uveitis Course

Local Therapy in Uveitis: Benefit and Outcomes

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Moorfields Eye Hospital
London

Intraocular Inflammation

- One of the major challenges
- Difficulties in establishing an etiological diagnosis
- Limited options for management
- Incidence of uveitis has been largely underestimated
- Significant visual loss in a large number of patients, mostly as a consequence of chronic macular edema.

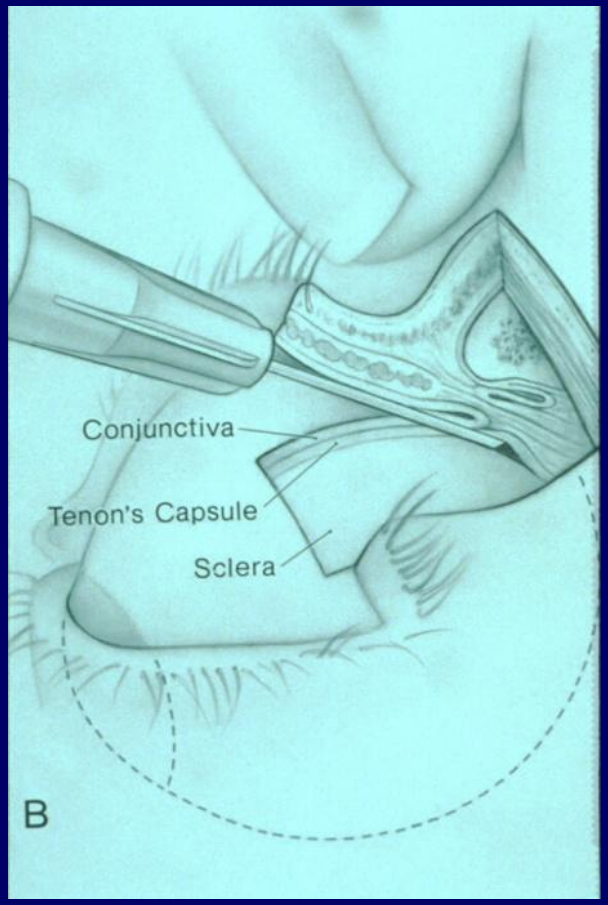
Restricted Drug Bioavailability

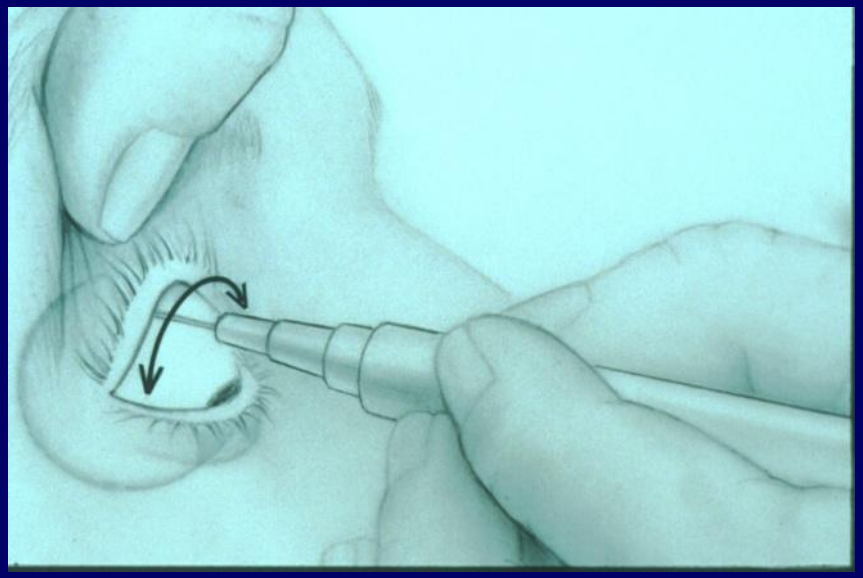
- Ocular barriers:
  - Muco-aqueous layer of tear film
  - Corneal epithelium
  - Iris blood vessels
  - Non-pigmented layer of the ciliary epithelium
  - Retinal pigment epithelium
  - Endothelial of retinal blood vessels

Modalities for Ocular Drug Administration

- **Topical** (drops)
- **Periocular injections**
  - Sub-conjunctival
  - Sub-Tenon's
  - Orbital floor
- **Intraocular injections**
  - Intracameral
  - Intravitreal
- **Intraocular slow-release devices**
  - Retisert (non-biodegradable)
  - Ozurdex (biodegradable)
  - Iluvien (non-biodegradable)

Periocular Injections





Periocular triamcinolone acetonide injections for cystoid macular edema complicating noninfectious uveitis.

Leder HA, Jabs DA, Galor A, Dunn JP, Thorne JE.

- 126 patients (156 eyes) with CMO
- 53% resolution of CMO at 1 month and 57% at 3 months following a single injection
- 1 additional injection in 21 eyes; 2 additional injections in 14 eyes; >2 additional injections in 5 eyes
- 21 eyes: 81% had no CMO 1 month after the second injection and 48% had no CMO 3 months after the second injection
- 23 eyes (15%) failed periocular corticosteroid therapy
- CMO recurred in 53% (median time to recurrence: 20.2 wks)

Intravitreal and orbital floor triamcinolone acetonide injections in noninfectious uveitis: a comparative study.

Roesel M, Gutfleisch M, Heinz C, Heimes B, Zurek-Imhoff B, Heiligenhaus A. Ophthalmic Res. 2009;42(2):81-6.

- Retrospective, 97 chronic, non-responsive CMO
- Single IVTA (4mg) or OFI (40mg)
- Improvement of >2 lines in 50% IVTA and 34% OFI in 3 months
- Improvement of CMO in 100% IVTA and 76% OFI during first month
- CMO reduced in 100% IVTA and 20% OFI at 3 months
- Higher incidence of cataract and high IOP in IVTA

Intraocular Injections

- Mostly, no systemic side-effects
- By-passes all barriers
- High concentration where wanted
- Very efficacious
- Short-lived effect
- Local Toxicity – ideal preparation ?
- Repeated injections – how safe ?

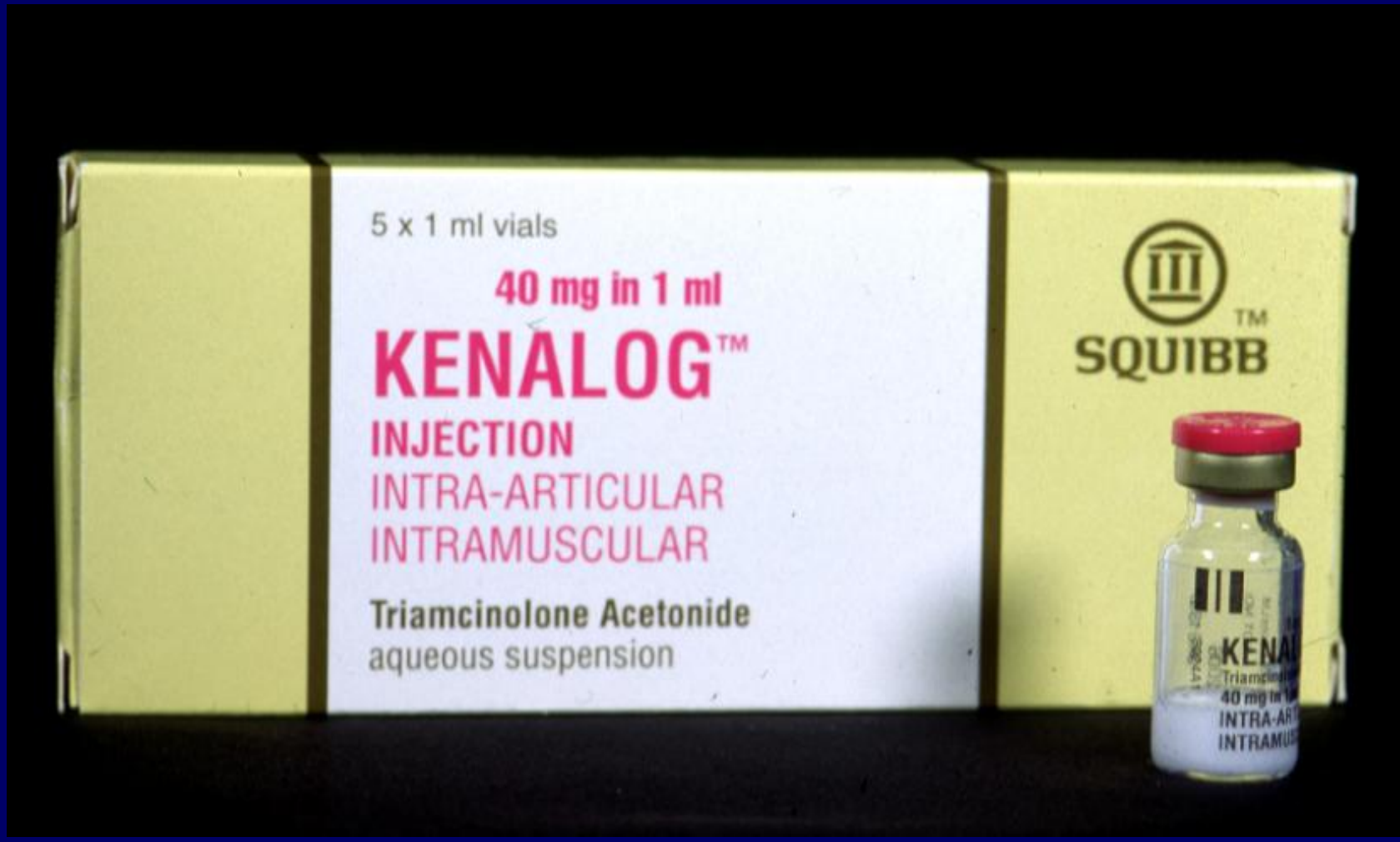
Different Steroid Preparations

- Dexamethasone sodium phosphate is soluble with a half-life of 3 hours (rabbit), and clearance in 3 days.
- Dexamethasone alcohol is less soluble disappearing in 7-14 days.
- TA is hydrophobic with therapeutic levels for up to 3 months

Intraocular Concentration and Pharmacokinetics of Triamcinolone Acetonide after a single intra-vitreal injection.

- Single 4mg dose
- Mean elimination half-life of 18 days in non-vitrectomised eyes
- Half-life of 3 days in vitrectomised eyes
- Measurable concentrations for approximately 3 months (non-vitrectomised)
- Study done in elderly patients with macular oedema

Beer PM et al. Ophthalmology 2003;110:681-686


5 x 1 ml vials
40 mg in 1 ml
KENALOG™
INJECTION
INTRA-ARTICULAR
INTRAMUSCULAR
Triamcinolone Acetonide
aqueous suspension
SQUIBB™

Vitreous pharmacokinetics and retinal safety of intravitreal preserved versus non-preserved triamcinolone acetonide in rabbit eyes.

Oliveira RC, et al

Curr Eye Res. 2012 Jan;37(1):55-61. Epub 2011 Oct 26

- 60 New Zealand white rabbits
- TA-BA (4mg/0.1ml) vs TA-PF (4mg/0.1ml)
- At 7 days median intravitreal triamcinolone concentration was significantly higher in the TA-BA, but no other time points
- There was no evidence of toxic effects on the retina in either group based on ERG or histological analyses

IVTA

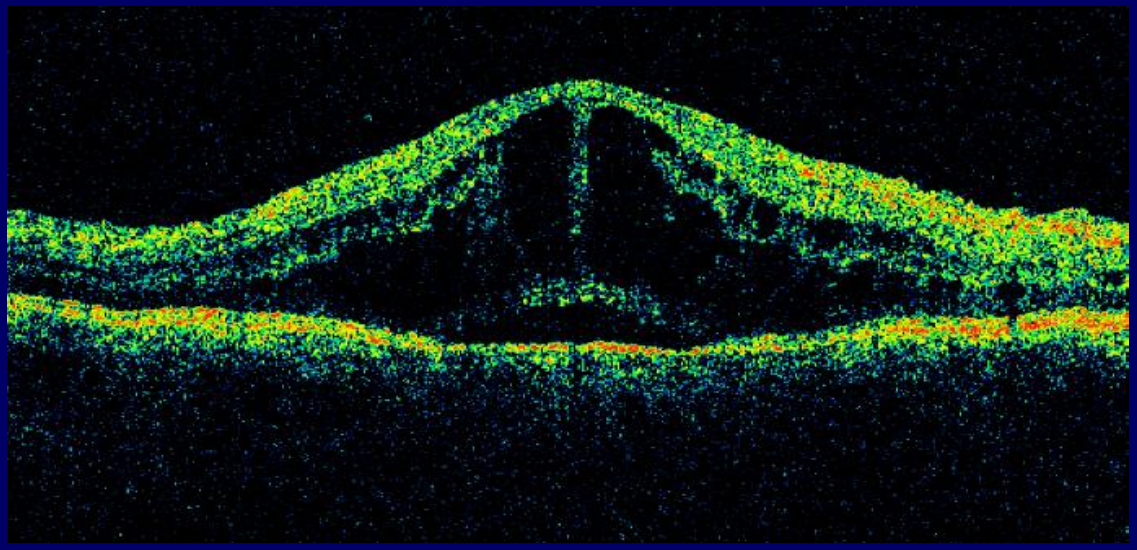
- Range of use: 2mg/0.05ml to 25mg/0.1ml
- Detectable levels up to 2.75 months after single 4mg injection – suggesting reinjection every 3 months may be necessary for sustained therapy
- After a 20-25mg injection, TA is barely detectable in serum samples obtained within 4 to 92 days later.

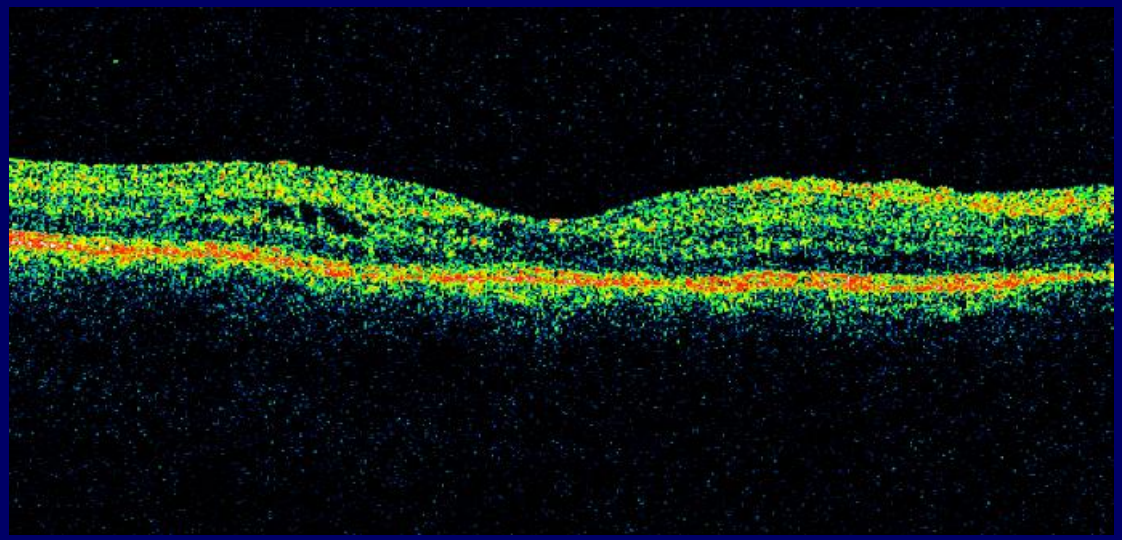
Intravitreal Triamcinolone for Uveitic CME: An Optical Coherence Tomographic Study

- Six patients with CME resistant to Rx (1-11y)
- Three retinal vasculitis, 1 IU, 2 HLA-B27
- 2mg in 0.05 ml of Triamcinolone acetonide
- Monitoring with OCT
- Five complete anat. resolution in 1 week
- Return of edema after 6 weeks to 3 mo.
- Three responded to OFI of 40mg TA afterwards
- Modest visual improvement (chronic disease)
- One needed trabeculectomy

Antcliff RJ, et al. Ophthalmology 2001;108:765-772.

Pre and Post IVT – 1 week





Intravitreal triamcinolone for persistent cystoid macular oedema in eyes with quiescent uveitis

Saskia M Maca MD,[1] Claudette Abela-Formanek MD,[1] Christopher G Kiss MD,[1] Stefan G Sacu MD,[1] Thomas Benesch PhD[2] and Talin Barisani-Asenbauer MD FEBO[1]

[1]Medical University Vienna, Department of Ophthalmology & Optometry, and [2]Medical University Vienna, Department of Medical Statistics, Vienna, Austria

Conclusions: IVTA might be considered as a treatment for patients with chronic CMO when persistent despite previous systemic steroid therapy. Even patients without sustained resolution of CMO after IVTA might benefit in terms of transiently increasing visual acuity, but progression of cataract and rise in intraocular pressure limit repeatability.

Complications

- Endophthalmitis
- Ocular hypertension
- Cataract
- Haemorrhage
- Retinal detachment
- Effect of more injections ???
- Effect of different dosages (2mg to 25mg)

IVTA

- Large number of case reports and small series
- No randomised clinical trials
- Comparison with other routes (periocular) or drugs (anti-VEGF) shows superior efficacy, but transient
- Increased risk of complications

IVTA

- Rapid effect
- No systemic side effects
- Duration of effect limited
- Reinjections required
- Risk of local complications
- **My** Indications:
  - Visually threatening non-infectious retinitis
  - Establish visual prognosis in chronic CMO
  - Intra-operative in cataract surgery

VEGF

- Involved in the pathogenesis in uveitis
- In EAU, VEGF expression markedly increased
- Expression of VEGF is intimately linked to that of major cytokines in the inflammatory cascade
- Increased in aqueous humor of patients with anterior uveitis and CME
- Vitreous levels similar to wet AMD, but much lower than in diabetes.

VEGF

- The importance of VEGF in the development of CMO, CNV and RNV, as well as its involvement in the inflammatory cascade, suggests that its inhibition may have therapeutic potential when these complications occur in the setting of uveitis

- The role of anti-VEGF therapy to treat inflammation is less clear

Anti-VEGF agents

- Most reports on Bevacizumab
- Treatment of recalcitrant CMO
- Some OCT improvement in 1-2 weeks after 1 single injection of 2.5mg
- Variable results reported
- Effect is transient – repeated injections
- No significant systemic side-effects, but Ranibizumab has been associated with subsequent development of uveitis from 0.7 to 1.3%

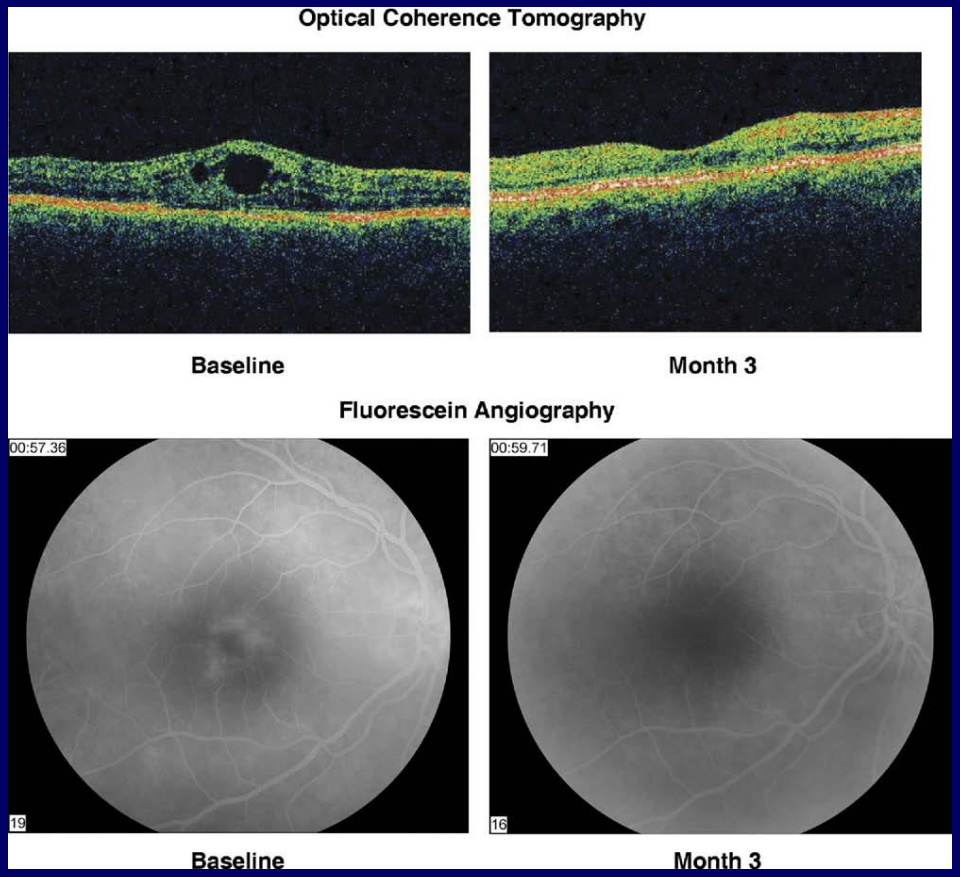
Ranibizumab for Refractory Uveitis-related Macular Edema

NISHA R. ACHARYA, KEVIN C. HONG, AND SALENA M. LEE

• METHODS: Seven consecutive patients with controlled uveitis and refractory CME who had failed corticosteroid treatment were studied. One eligible patient chose not to participate and another did not complete follow-up for nonmedical reasons. Intravitreal ranibizumab injections (0.5 mg) were given monthly for 3 months, followed by reinjection as needed. The primary outcome was the mean change in best spectacle-corrected visual acuity (VA) from baseline to 3 months, and the secondary objective was the mean change in central retinal thickness (CRT) on ocular coherence tomography. Six-month outcomes were also assessed.

• RESULTS: At 3 months, the mean increase in acuity for the 6 patients who completed follow-up was 13 letters (2.5 lines), and the mean decrease in CRT was 357 μm. Both VA and CRT improved significantly between baseline and 3 months ($P = .03$ for each). Although most patients required reinjection, this benefit was maintained at 6 months. There were no significant ocular or systemic adverse effects.

• CONCLUSIONS: Intravitreal ranibizumab led to an increase in VA and regression of uveitis-associated CME in patients refractory to or intolerant of standard corticosteroid therapy. Further studies of this promising treatment are warranted. (Am J Ophthalmol 2009;148: 303–309.



VEGF INHIBITION FOR THE TREATMENT OF UVEITIC CMO

- 9 reports published
- 8 case series
- 1 isolated case report
- Small number of patients
- Follow-up 1 week to 1 year

VEGF INHIBITION FOR THE TREATMENT OF UVEITIC CMO

- Adjunctive treatment with anti-VEGF treatments may be appropriate in cases of uveitis where CMO persists despite adequate control of the inflammatory process

VEGF INHIBITION FOR THE TREATMENT OF UVEITIC CMO

- The quality of evidence for anti-VEGF therapy in the treatment of uveitic CMO is very low
- At this moment, the treatment of uveitic CMO should focus on controlling the underlying inflammation, with the use of steroids and/or immunosuppressive agents

VEGF INHIBITION FOR THE TREATMENT OF UVEITIC CMO

- It is reasonable to consider intravitreal anti-VEGF therapy on a case by-case basis in patients with refractory uveitic CMO in the setting of **inactive** uveitis and in which intravitreal triamcinolone is contraindicated

Intravitreal bevacizumab as first local treatment for uveitis-related choroidal neovascularization: long-term results

Karina Julián,[1] Céline Terrada,[1] Christine Fardeau,[1] Nathalie Cassoux,[1] Catherine Français,[2] Phuc LeHoang[1] and Bahram Bodaghi[1]

[1]Department of Ophthalmology, Pitié-Salpêtrière Hospital, Paris, France
[2]Centre Ophtalmologique de l'Odéon, Paris, France

ABSTRACT.

Purpose: **To report long-term results of intravitreal (IVT) bevacizumab as first local treatment for choroidal neovascularization (CNV) secondary to uveitis.**

Methods: **Files of patients receiving 1.25 mg/0.05 ml bevacizumab as primary local treatment for CNV were retrospectively reviewed. Main outcomes were change in best-corrected visual acuity (BCVA) and central foveolar thickness (CFT), treatment-related adverse events, and number and frequency of injections.**

Results: **Fifteen eyes from fifteen patients were included. Multifocal choroiditis and panuveitis were the diagnosis in seven, ampiginous choroiditis in two, and for six remaining, serpiginous choroiditis, sympathetic ophthalmia, Vogt–Koyanagi–Harada syndrome, punctuate inner choroidopathy, tuberculosis and idiopathic inflammation. In 13 eyes, neovascularization was subfoveal, and peripapillary in two. Intraocular inflammation was strictly controlled in all cases by the time of injections. BCVA improved from logMar 0.53 to logMar 0.29 in 12 eyes (80%), while CFT decreased from 239.06 to 195.2 μm in 13 (87%). Twelve eyes received more than one injection; mean number in this group was 4.25 (2–8), and frequency 1 every 12.97 weeks. There were no adverse events related to bevacizumab or the procedure. Median follow-up was 17.6 months (8–25).**

Conclusions: **First-intention IVT bevacizumab for inflammatory CNV showed transient improvement in BCVA and CFT, in eyes under controlled inflammation. Reinjection was needed in most cases. Further work should conclude about safety related to repeated injections.**

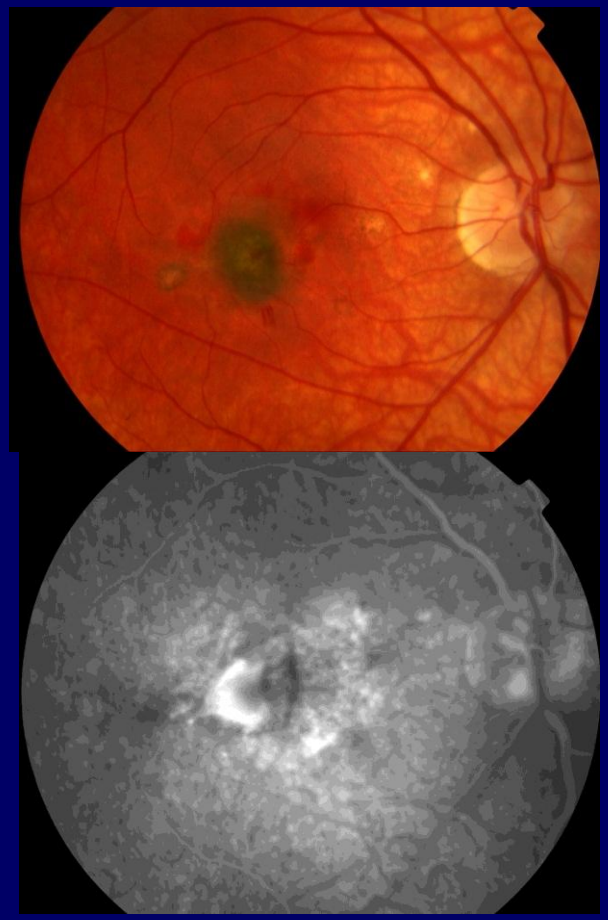
VEGF INHIBITION FOR THE TREATMENT OF UVEITIC CNV

- 11 reports published
- 1 prospective
- 10 retrospective, non-comparative series
- Sample size: 2-96 patients
- Follow-up: 1 to 24 months
- Only one involving Ranibizumab

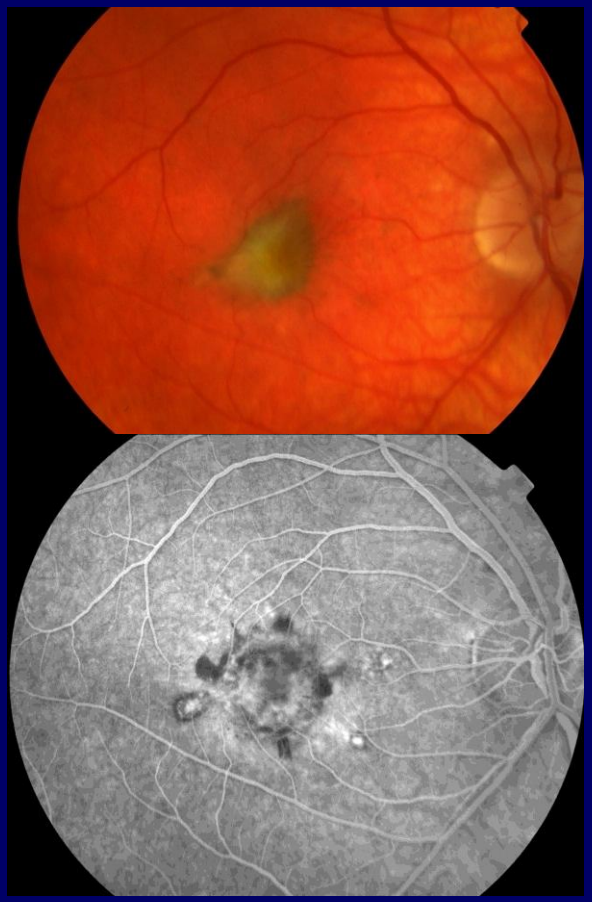
VEGF INHIBITION FOR THE TREATMENT OF UVEITIC CNV

- Treatment of CNV secondary to uveitis should include control of the underlying inflammation
- This is supported by evidence suggesting that treatment with systemic prednisone or immunosuppressive therapy may be of benefit in the treatment of CNV secondary to uveitis

Steroids for CNV



7/10/03
6/18



26/3/04
6/12

VEGF INHIBITION FOR THE TREATMENT OF UVEITIC CNV

- Uncertainty regarding level of inflammatory activity
- Concurrent use of other anti-inflammatory therapy, such as IVTA
- The level of quality of evidence for anti-VEGF therapy in the treatment of uveitic CNV would be rated as very low

VEGF INHIBITION FOR THE TREATMENT OF UVEITIC CNV

- Treatment of the underlying disease will probably reduce the likelihood of recurrent CNV and reduce the need for repeated anti-VEGF treatment

VEGF INHIBITION FOR THE TREATMENT OF UVEITIC RNV

- Very few cases published
- Level of evidence very low
- Treatment of uveitic RNV should focus on treatment of the underlying inflammatory disease, as well as laser photocoagulation to areas of ischaemic retina
- Use only in persistent RNV
- Beware of risk of tractional RD

Conclusions

- Difficult to determine if anti-VEGF therapy is beneficial
- Studies not controlled for disease activity and other treatments - active inflammation might still be present and if treated with corticosteroids and/or immunosuppression, would have resulted in resolution of the CMO

Conclusions

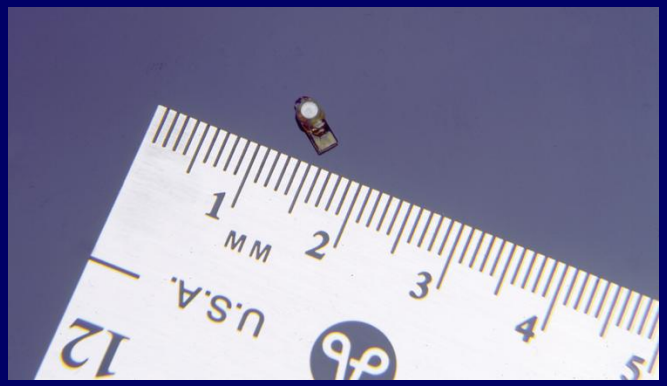
- Treat underlying inflammatory condition
- Anti-VEGF treatments may play a role in the management of uveitic CMO, CNV and RNV in cases with inactive uveitis

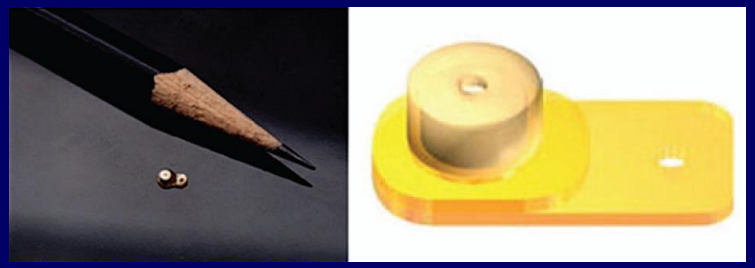
Drug Delivery Systems

- Act as a carrier or vehicle for an entrapped or bound therapeutic agent
- Controls and maintain prolonged release
- Develop organ or site-specific targeting
- New or more convenient routes of administration
- The key is to achieve adequate bioavailability

Retisert

- Designed to last 1000 days.
- Controlled and consistent delivery - drug release rate is 0.6 μg/day initially, which decreases over the first month to a steady state between 0.3-0.4 μg/day up to approximately 30 months
- Local and targeted delivery
- Insignificant systemic dose
- Eliminates long-term systemic side effects





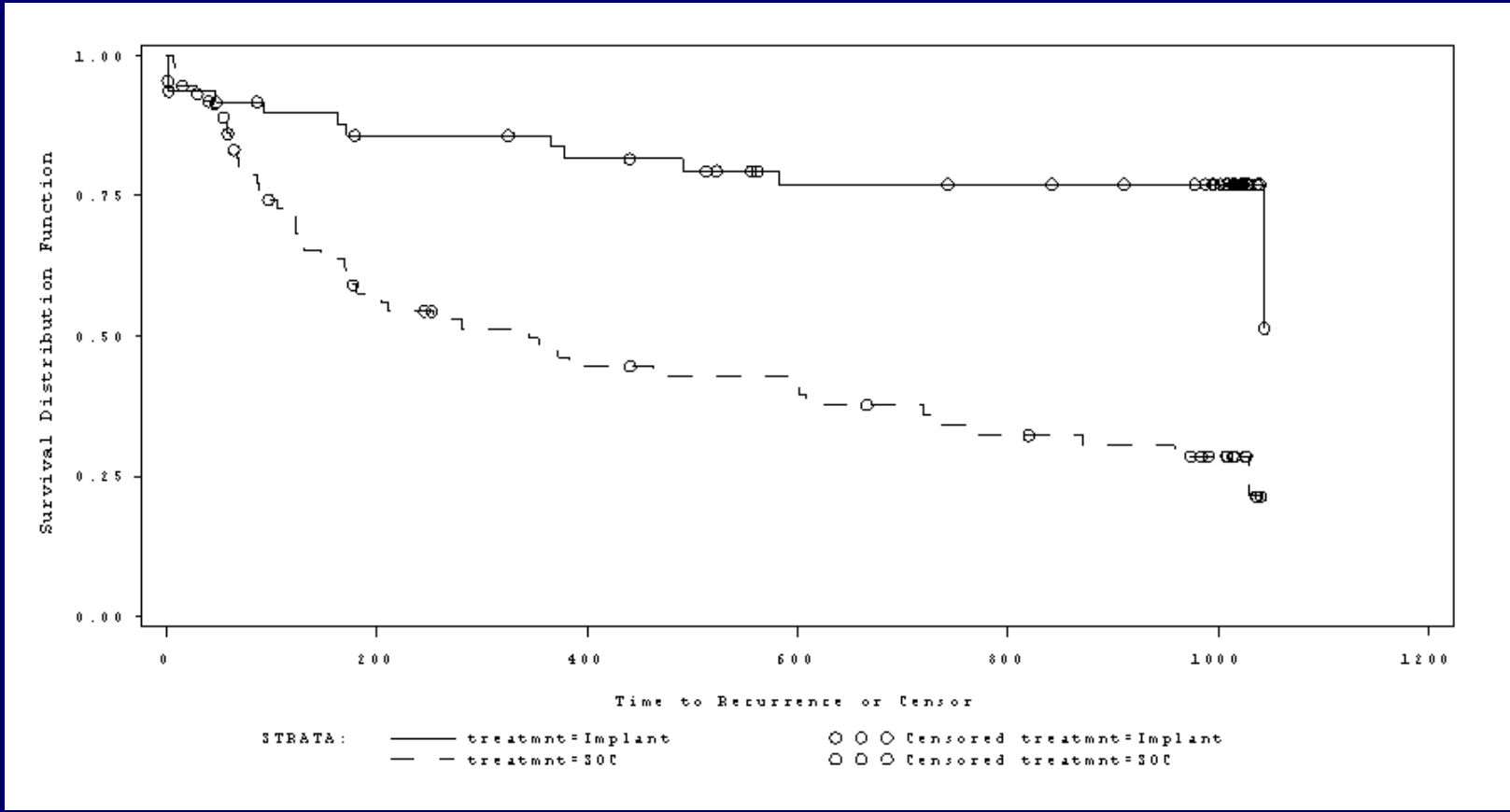
Retisert

- Retisert has been studied in 3 multicenter, randomized, prospective, phase III controlled clinical trials
- Two of them were double-masked and compared 2 doses (0.59 mg vs. 2.1 mg) of the implant in one eye compared to no treatment in control eyes.

Retisert

- Rate of recurrence decreased from 54% before to 7% after Retisert implantation
- Stabilized or improved visual acuity in 80% of patients
- Reduced the percentage of patients requiring systemic corticosteroid therapy from 47-63% to 5-10% after 34 weeks

Time to Recurrence



Supplemental Analysis with failures that were inferred for reasons other than inflammation censored

p=0.0004 (log rank test) adjusted for center and baseline treatment

3-Year Recurrence Data

	Implant	SOC	p-value
• 3Y Rate	36.4%	73.0%	<0.0001
Supplemental	21.2%	71.6%	<0.0001 (Chi-square)
• 3Y Frequency			
Mean ± SD	0.4 ± 0.55	1.5 ± 1.53	<0.0001 (Wilcoxon rank sum)
Median	0	1	
Range	0 to 2	0 to 7	
• Frequency change			
Mean ± SD	-0.7 ± 1.11	0.2 ± 1.76	0.0019 (Wilcoxon rank sum)
Median	-1	0	
Range	-3 to +1	-3 to +5	

Safety - IOP

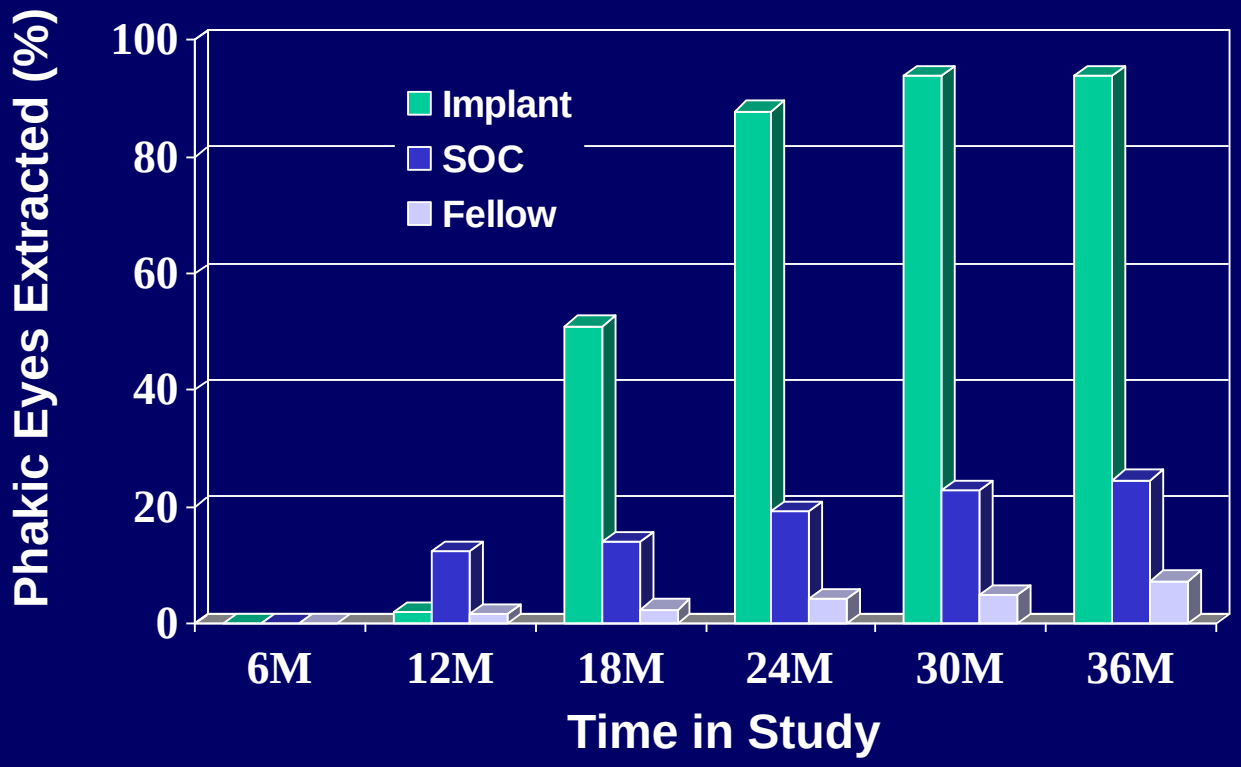
	Topical IOP Lowering Drops	
	@ Enrollment	@3 year
Implant	9.1%	30.5%
SOC	6.8%	8.7%
	p=0.411*	p=0.007*

	Filtering Operations
Implant	28.8%
SOC	2.7%
	P<0.0001*

* CMH χ^2

Safety - Cataract

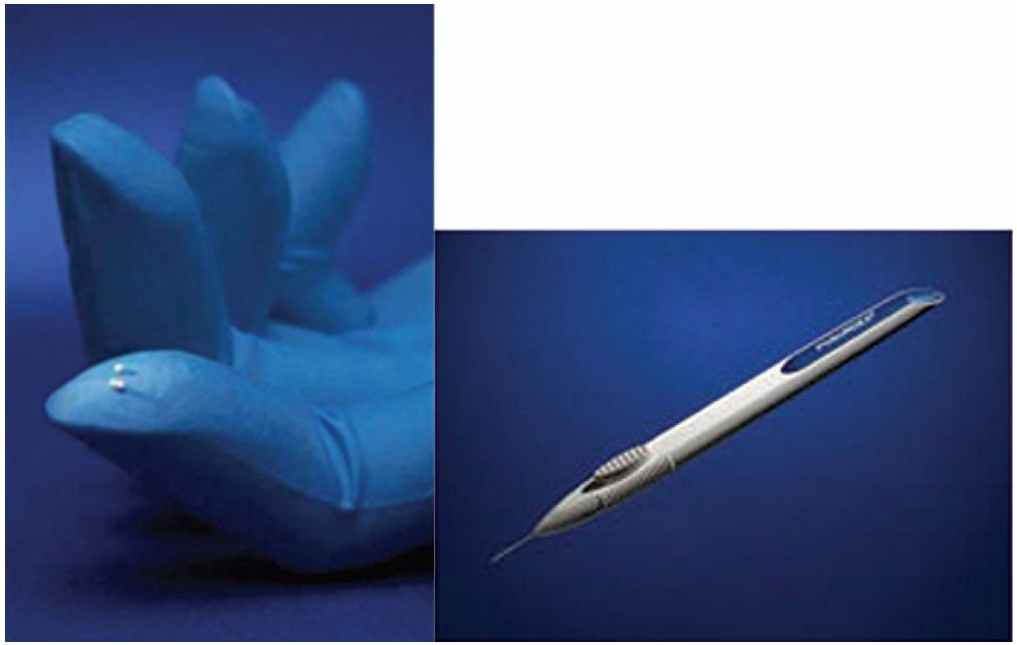
	0.59 mg	SOC	Fellow
Phakic Eyes	49	57	123
Cataracts Extracted	46	14	9
Phakic Eye Extracts	93.9%	24.6%	7.3%



Summary

- Significantly lower rate of recurrence in the implanted eye versus SOC
- Visual acuity stabilized/improved in the majority of implanted eyes
  - VA improved by at least 3 lines in 13.8 % of eyes
  - Similar VA results to SOC w/out need for high dose systemic corticosteroids
- Frequent adverse events
  - Cataract requiring extraction in 94% of implanted eyes
  - IOP rise requiring filter or explantation in 29% of implanted eyes
  - Strict attention to wound integrity critical

OZURDEX™ Phase III in Uveitis: HURON



The HURON Study

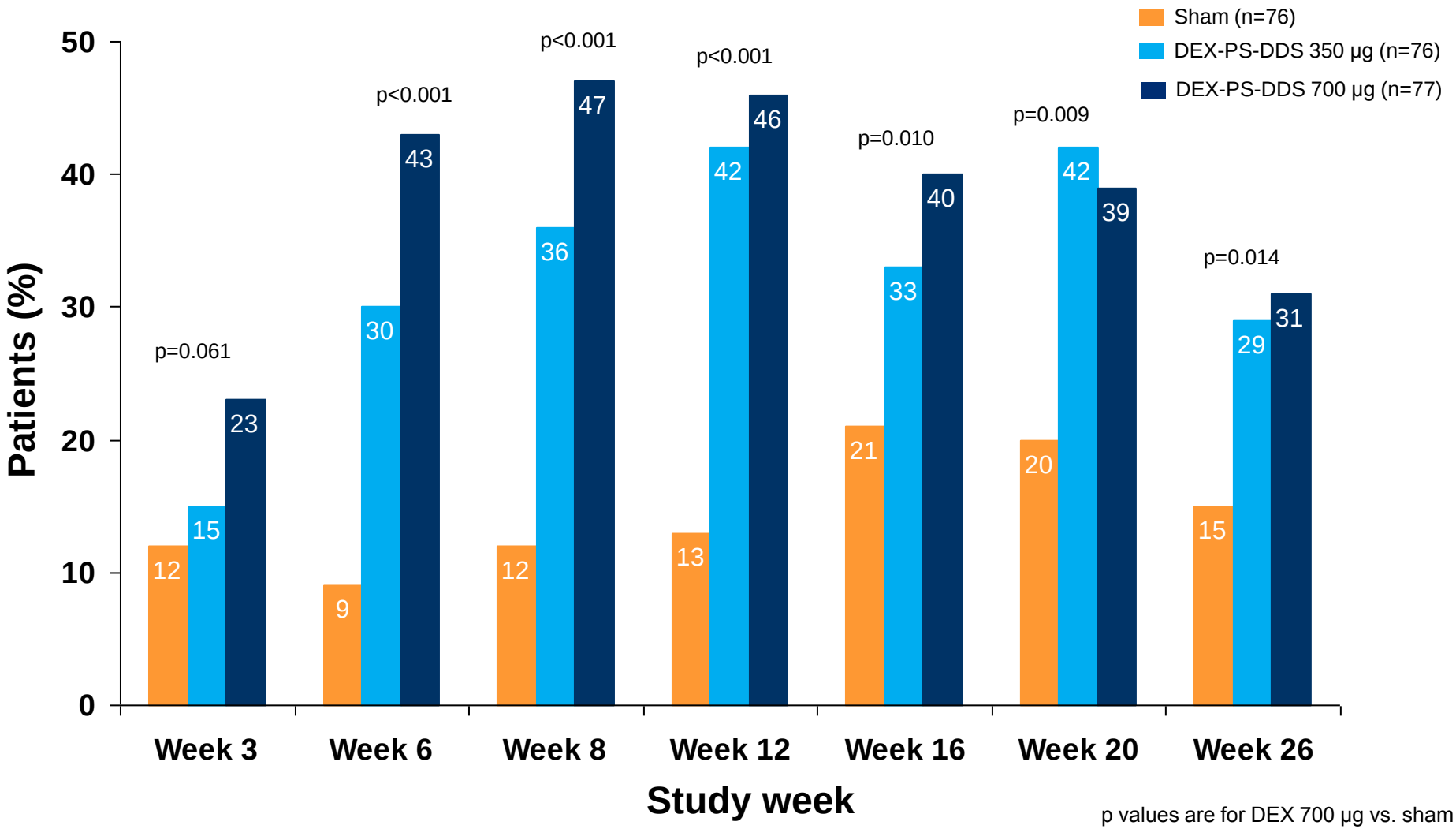
- Pharmacokinetic studies show that OZURDEX™, an intravitreal dexamethasone posterior segment drug delivery system (DEX-PS-DDS), provides sustained release of dexamethasone over 6 months[1]
- **HURON evaluated the efficacy and safety of DEX-PS-DDS in patients with ME due to intermediate and posterior uveitis[2]**
- HURON consists of a 8-week, randomised, prospective, multicentre, masked, sham-controlled, parallel-group Phase III clinical trial followed by a 18-week masked extension[2]

1. Welty DF *et al*. World Ophthalmology Congress 2008. Abstract 6794.
2. Allergan. Data on file.

HURON: Objectives

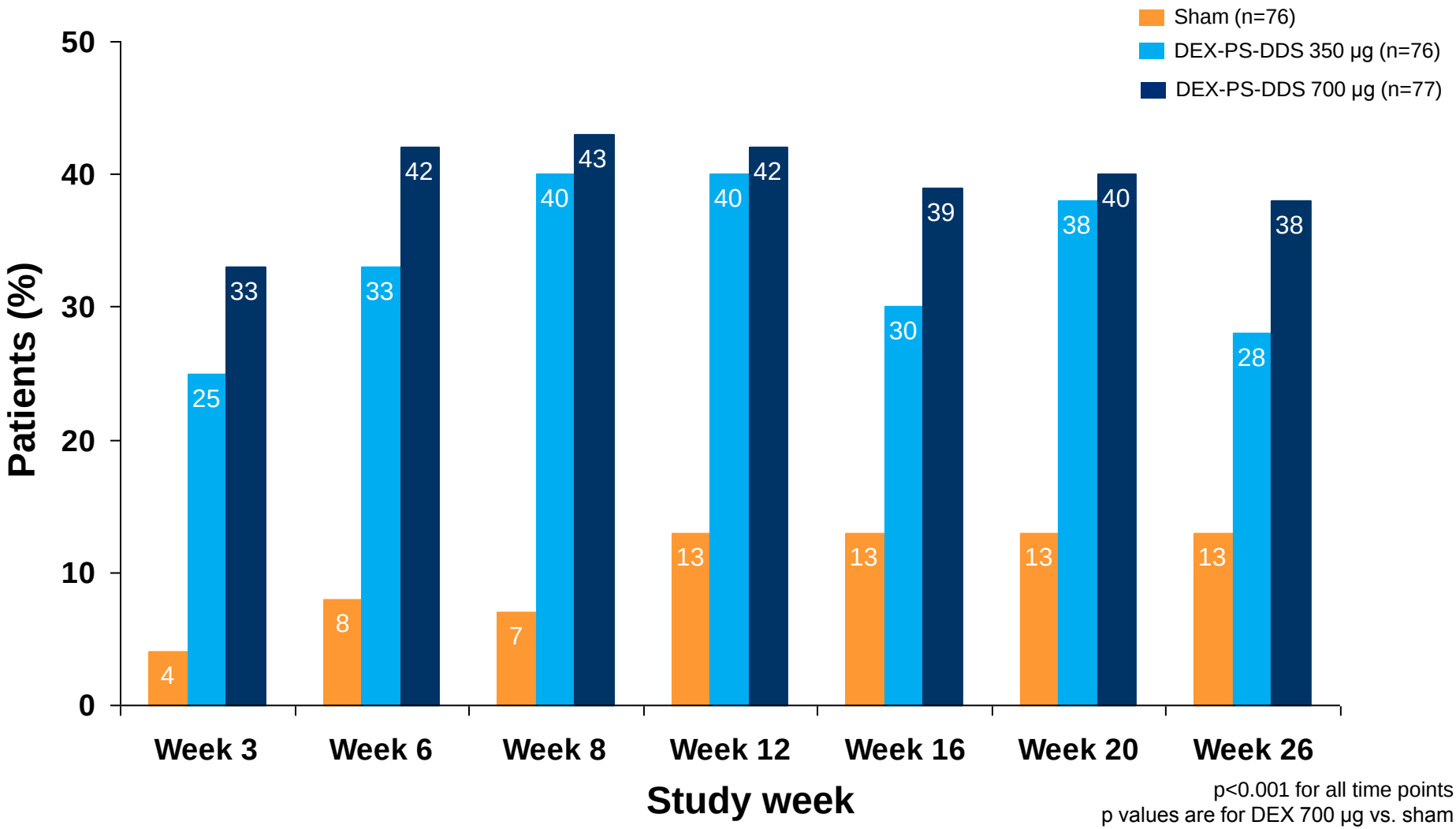
- To evaluate the safety and efficacy of DEX-PS-DDS 350 µg and 700 µg compared with Sham in the treatment of non-infectious ocular inflammation of the posterior segment in patients with intermediate or posterior uveitis

Vitreous haze score of zero



p values are for DEX 700 µg vs. sham

BCVA improvement ≥15 letters from baseline



p<0.001 for all time points
p values are for DEX 700 µg vs. sham

Most common ocular adverse events (reported by ≥2% patients)

Adverse event in study eye	Sham (n=75)	DEX-PS-DDS 350 µg (n=74)	DEX-PS-DDS 700 µg (n=76)
Intraocular pressure increase, n (%)	5 (6.7%)	17 (23.0%)*	19 (25.0%)*
Conjunctival haemorrhage, n (%)	16 (21.3%)	12 (16.2%)	23 (30.3%)
Ocular discomfort, n (%)	6 (8.0%)	3 (4.1%)	10 (13.2%)
Eye pain, n (%)	10 (13.3%)	8 (10.8%)	9 (11.8%)
Cataract, n (%)	4 (5.3%)	6 (8.1%)	9 (11.8%)
Culture neg. endoph. vs. uveitis, n (%)	0 (0%)	0 (0%)	1 (1.3%)
Surgery			
Cataract surgery, n (%)	2 (2.7%)	1 (1.4%)	2 (2.6%)
Glaucoma surgery**, n (%)	0 (0%)	0 (0%)	0 (0%)
Retinal detachment, n (%)	2 (2.7%)	0 (0%)	2 (2.6%)

*Significantly greater with DEX-PS-DDS compared with sham, p≤0.05
** One patient underwent laser iridotomy for narrow angle in DEX-PS-DDS 350 µg group

Patients requiring IOP medications

	Sham	DEX-PS-DDS 350 µg	DEX-PS-DDS 700 µg
Baseline (%)	1.3%	0%	0%
Week 26 (%)	9.2%	7.9%	16.9%

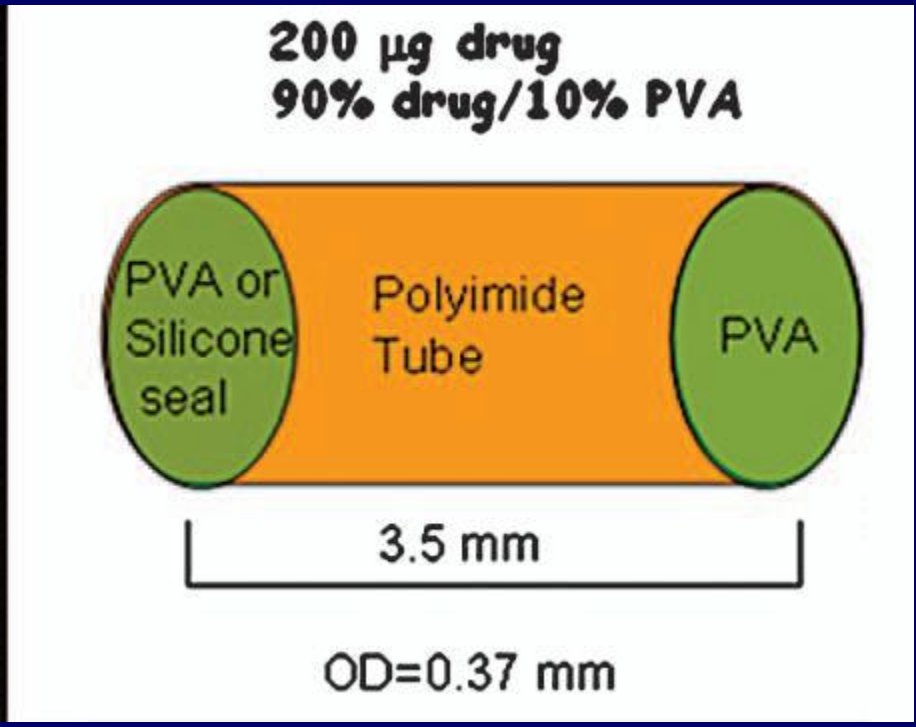
Summary

- DEX-PS-DDS was significantly more effective than sham at eliminating vitreous haze
- Approximately 4 times more patients treated with DEX-PS-DDS 700 µg had complete resolution of vitreous haze compared with sham at the primary timepoint
- With DEX-PS-DDS there was a significant improvement in BCVA by week 3 that persisted through week 26
- DEX-PS-DDS also resulted in statistically significant and clinically relevant improvements in quality of life as measured by NEI VFQ-25

Summary

- IOP increases were relatively low
- Overall efficacy with DEX-PS-DDS 700 µg was greater than with DEX-PS-DDS 350 µg for a **similar safety profile**

Iluvien - FA


200 µg drug
90% drug/10% PVA
PVA or Silicone seal
Polyimide Tube
PVA
3.5 mm
OD=0.37 mm

Iluvien

- Similar to Retisert, Iluvien also contains fluocinolone acetonide (180 µg)
- Iluvien is injected into the eye as an office based procedure using a proprietary inserter with a 25-gauge needle, which allows a self sealing wound

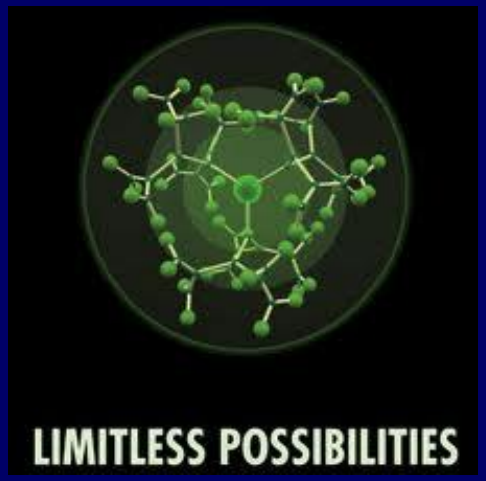
Iluvien

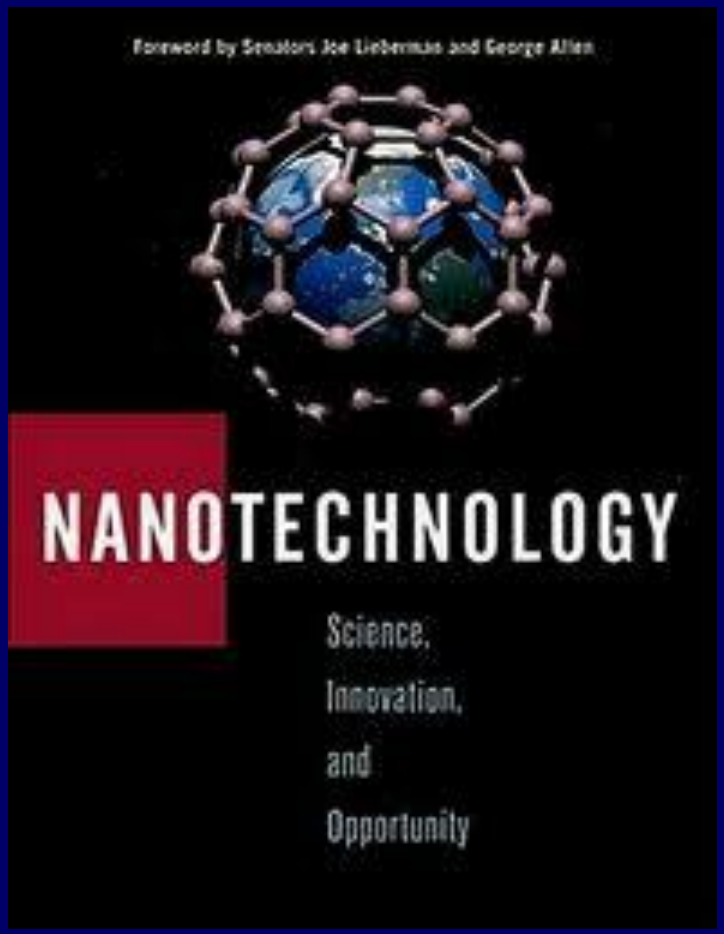
- Releases a low dose of 0.23–0.45 µg/day fluocinolone acetonide for 18 to 36 months after injection
- More favourable ocular hypertension side-effect profile as compared to Retisert

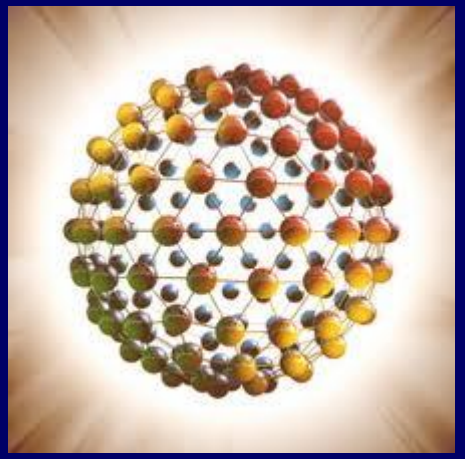
Iluvien

- Two different models of the device releasing high dose (0.45 µg/day) and low dose (0.23 µg/day)

- Currently being investigated in two global phase 3 pivotal clinical trials involving 956 patients which has been granted “fast track” by the FDA.

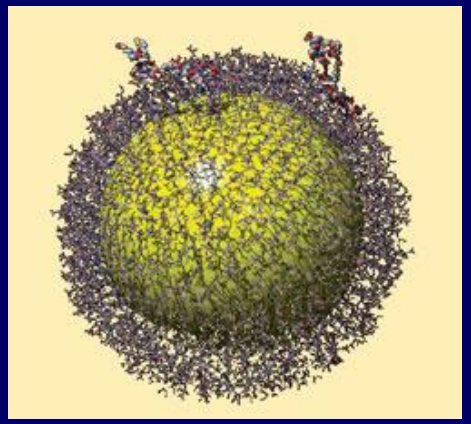

LIMITLESS POSSIBILITIES


Foreword by Senators Joe Lieberman and George Allen
NANOTECHNOLOGY
Science,
Innovation,
and
Opportunity



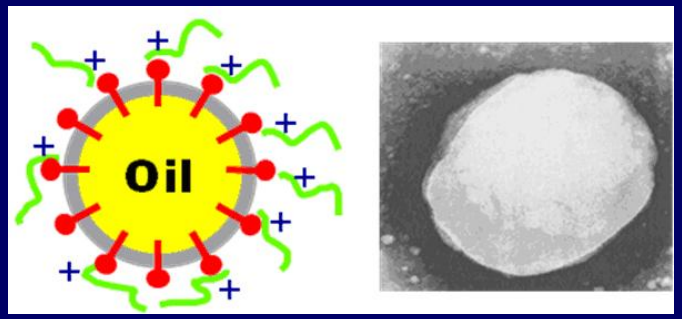
Nanotechnology

Nanoparticles:



- Nanospheres – entrap or adsorb the biologically active molecule onto the surface

- Nanocapsules – a surrounding polymeric wall containing an oil core where the active molecule is dissolved



Nanoparticles Drug Delivery Systems

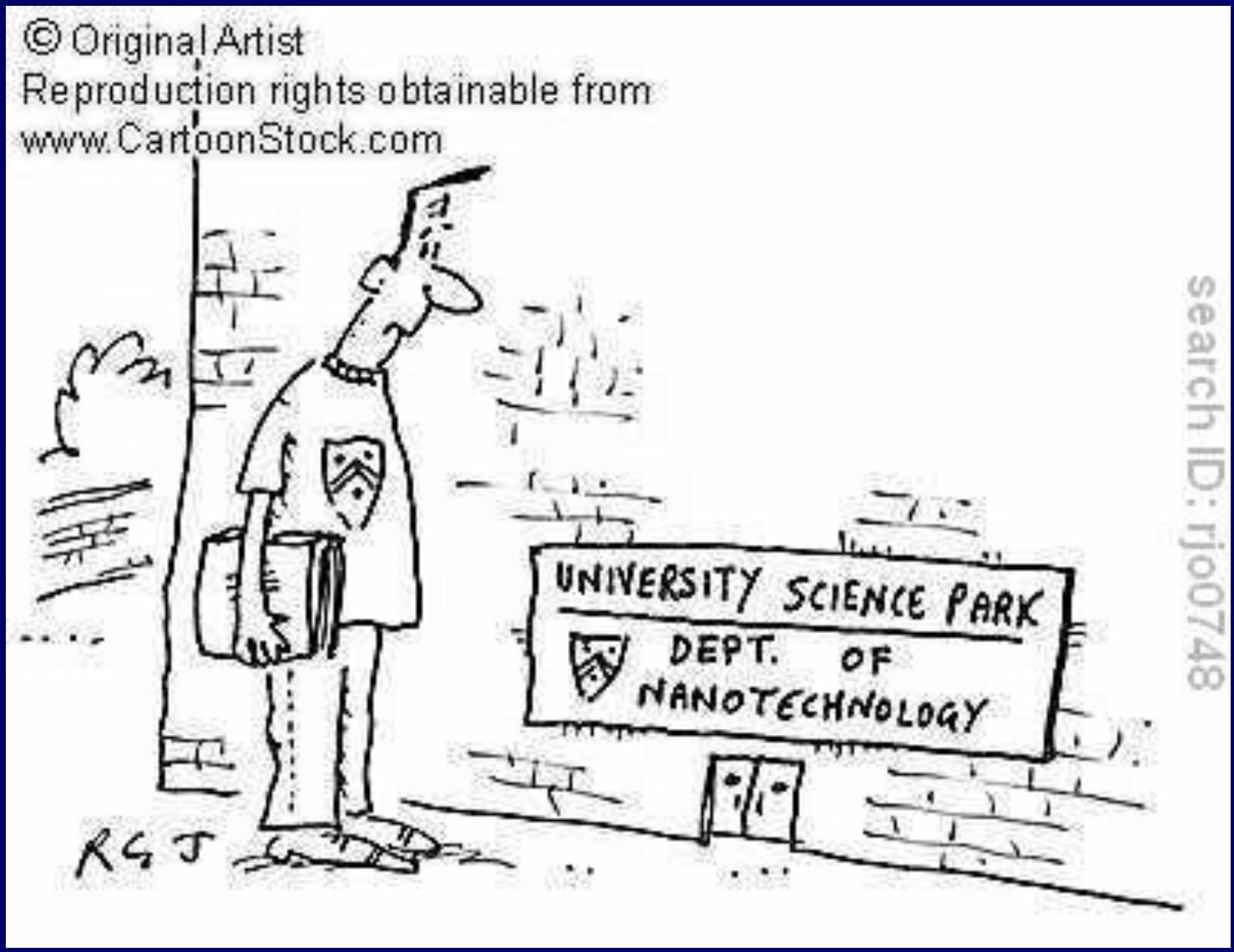
Table 1
Nanoparticulate drug delivery systems (or nanosystems) used as carriers for drug administration.

Nanosystem	Composition	Potential application in the eye
Nanoparticles	Natural or synthetic polymers, metals, lipids, phospholipids	Yes
Liposomes	Phospholipids	Yes
Niosomes	Non-ionic surfactants	Yes
Emulsions	Oil-in-water and water-in-oil mixtures that require surfactants	Yes
Nanosuspensions	Inert polymer resins	Yes
Dendrimers	Synthetic polymers	Yes
Nanoparticle-loaded contact lenses	Different hydrogel-based lenses with nanoparticulate-based drugs incorporated in the lens matrix	Yes
Nanotubes and fullerenes	Carbon-based nanomaterials	Not tested yet
Quantum dots	Semiconductor materials covered with other materials	Yes (diagnostic)

According to Sahoo et al. (2007) and Gaudana et al. (2009).

Conclusions

- Available options can be effective
- But short-lived
- Range of local complications
- Do not cure the disease
- Nanotechnology is now being explored as it presents many advantages over current systems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