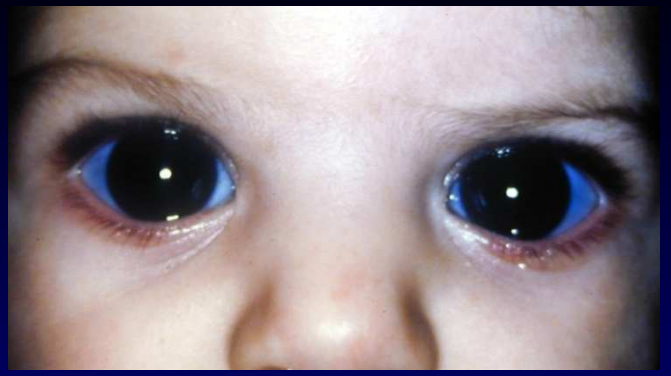
Università degli Studi di Catania
Clinica Oculistica
Direttore: Prof. A. Reibaldi

EFFICACIA E SICUREZZA DELLA TERAPIA A LUNGO TERMINE CON LATANOPROST NEL GLAUCOMA CONGENITO

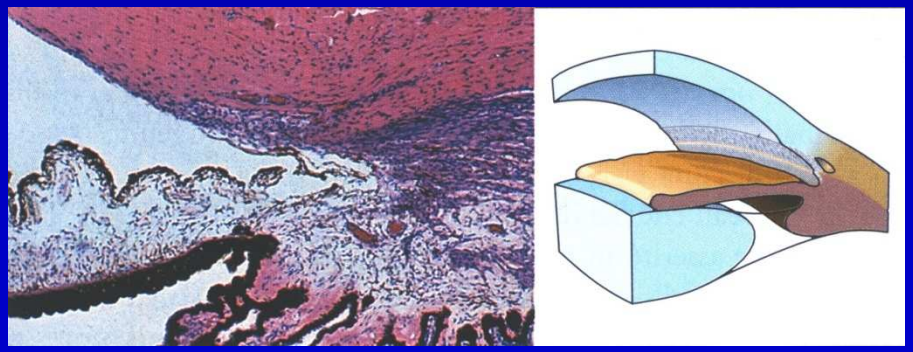
M. Uva, A. Longo, L. Azzaro, A. Reibaldi.

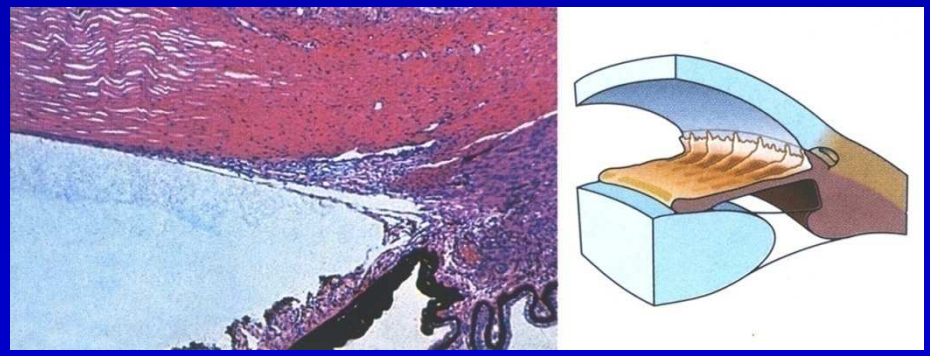
XXXVI CONGRESSO SOSI
ACIREALE 14-16 APRILE 2011

- PRIMARIO (DISGENESIA ISOLATA)
- ASSOCIATO AD ALTRE MALFORMAZIONI
- SECONDARIO



Glaucoma Congenito Primario ad insorgenza precoce (Primary congenital glaucoma)	0-3 anni
Glaucoma Congenito Primario ad insorgenza tardiva (Childhood glaucoma)	3-10 anni
Glaucoma giovanile (Juvenile glaucoma)	>10 anni





DISGENESIA DELL'ANGOLO: DIMINUITO DEFLUSSO ACQUEO

L. Fontana e coll S.O.I. 2005

PATOLOGIA DA TRATTARE CHIRURGICAMENTE

TERAPIA MEDICA POCO UTILIZZATA

scarsa efficacia

161 occhi: <PIO a lungo termine (<21 mmHg) 10% degli occhi. (Turach e coll 1995)

effetti collaterali sistemici

- VOLUME PLASMATICO INFERIORE → MAGGIORE CONCENTRAZIONE PLASMATICA DEL FARMACO
- IMMATURITA' DEL SISTEMA ENZIMATICO EPATICO → FAVORISCE SEQUESTRO PLASMATICO DEL FARMACO
- IMMATURITA' BARRIERA EMATO-ENCEFALICA
- SENSIBILITA' CENTRI BULBARI
- SPESSO IMPOSSIBILE ESEGUIRE MANOVRA DELL'OCCLUSIONE VIE LACRIMALI E/O CHIUSURA PALPEBRALE

DENIS P. J.Fr. Ophtal. 2005

β-BLOCCANTI

timololo, betaxololo, etc

CRISI APNEA, ARRESTO CARDIACO

preferire formulazioni in gel/mucoadesive alla minima concentrazione possibile

INIBITORI ANIDRASI CARBONICA

dorzolamide, brinzolamide

LIMITATA ATTIVITA' IPOTONIZZANTE (?)

SIMPATICOMIMETICI

α2-agonisti

brimonidina

SONNOLENZA
IPOTENSIONE ARTERIOSA

The Effectiveness of Latanoprost for the Treatment of Pediatric Glaucoma

Laura B. Enyedi, MD, Sharon F. Freedman, MD, and Edward G. Buckley, MD

latanoprost, whereas nonresponders showed less than a 15% IOP reduction on latanoprost. ***Results:*** Fifty-seven eyes of 48 pediatric patients with a variety of glaucoma diagnoses and an average age of 7.1 years were included in the study. Of these, 31 eyes of 31 patients had interpretable IOP data; the mean IOP reduction for this group after the addition of latanoprost was 0.9% (0.2 mm Hg). Six patients (6 eyes) were responders, with an average IOP reduction of 8.5 mm Hg (34%), whereas the majority of patients (25) were nonresponders. In the responders, there was a good correlation (r = 0.9) between baseline IOP and the magnitude of IOP reduction. Responders were significantly more likely to have juvenile open-angle glaucoma and to be older than nonresponders. Systemic and ocular side effects were infrequent and mild, and no patient had noticeable iris color changes. ***Conclusions:*** When used in a

AAPOS 1999;3:33-9

Catania University - Italy
Institute of Ophthalmology
Head: Prof. A. Reibaldi

#2163 - B2

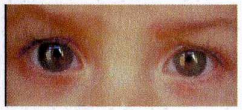
Efficacy and Safety of Latanoprost in Congenital Glaucoma

M.G. Uva, A.Longo, V.Cannemi, A.Reibaldi

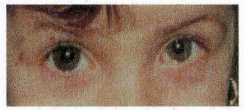
Purpose: Congenital glaucoma is a rare and polimorphous condition whose treatment is primarily surgical. None of ocular hypotensive drugs has been granted approval by the regulatory agencies for use in children, but they are all used on a compassionate basis. To the best of our knowledge in literature there are only four publications about the pediatric use of prostaglandin analogs (Altuna et al. 1998, Yang et al. 1998, Enyedi et al. 1999, 2002). According with the results of these studies latanoprost does not seem as effective in pediatric glaucoma patients as in adults with POAG or ocular hypertension. We wish to report our experience with latanoprost in the treatment of congenital glaucoma.

Methods: In a retrospective way, we analyzed the charts of all patients with primary congenital glaucoma who were given latanoprost 0.005% once-a-day (Lp) at our Institution between January 1997 and July 2002. We excluded from the analysis patients with uncertain or inadequate baseline IOP measurements or who had follow up less than 2 months or underwent surgery within 6 months before of starting latanoprost. The baseline IOP was compared with the final one (at the end of follow up) for each patient and any side effect was reported.

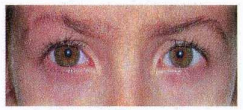
Results: 22 eyes of 14 patients with diagnosis of primary congenital glaucoma were included in this study. The mean follow up was 12.7±14.5 months (range 2-60). The baseline mean IOP was 25.7±3.4 mmHg, the final mean IOP was 18.6±8.1 mmHg with an average IOP decrement of 7.1±7.2 mmHg (28.3%). Six eyes (27.3%) of 5 patients had no useful change in IOP and underwent surgery. Three eyes of 2 patients showed a lasting decrement of IOP even after stopping the treatment with latanoprost (respectively administered for 12 and 16 months). In one of these patients, affected with unilateral congenital glaucoma iris color change and increased eyelash thickness occurred after 10 months of therapy, then latanoprost treatment was discontinued 6 months later, owing to a lasting IOP in the low teens. After a subsequent 36 months follow up time with no therapy, IOP lasted in the low teens and iris pigmentation reversed, as shown in the enclosed photo-gallery (for further details, see the Table I).



Age: 1 year
(after 10 months of Lp-Tx in right eye)



Age: 3,5 years
(after 2 years from discontinuation of Lp-Tx in right eye)



Age: 5,5 years
(after 4 years from discontinuation of Lp-Tx in right eye)

patients	sex	age (yrs.)	prior surgery	prior medications	INTRAOCULAR PRESSURE baseline	final	diff.	var. %	follow-up (begin of Lp-Tx) months	remarks	complications
L.F.	m	13		T 0,5	28	20	8	-28,57	3		
M.D	f	0,6		dorz	28	32	4	14,29	2	TB	irritation
				dorz	22	10	12	-54,25	4		high resp. tract
S.N.	f	3			26	8	18	-69,23	12	Tx discontinued (f.u. 4m)	
					30	9	21	-70,00	12	Tx discontinued (f.u. 4m)	
D.B.F.	f	3	TB (2)	T 0,5 + dorz	24	16	8	-25,00	3		
B.A.	m	3	TB (2)		26	11	15	-57,69	36		
			TB (2)		28	17	11	-39,29	36		
V.V.	f	10			25	15	10	-40,00	10		
					23	15	8	-34,78	10		
S.M.L.	f	7	TB (2) /TE	T 0,5	26	33	7	26,92	24	TE	
			TB (2)	T 0,5	24	16	8	-33,33	60		
S.R.	m	10	GO (2)	T 0,5 + dorz	23	14	9	-39,13	3		
			GO (2)	T 0,5 + dorz	24	16	8	-33,33	3		
L.O.	f	13			30	28	2	-6,67	2	TB	
B.V.	f	10	TB (2)/TE	dorz	32	30	2	-6,25	12	TE	
			TB (2)/TE	dorz	22	22	0	0,00	12	TE	
F.M.	m	16		T 0,5	32	35	3	9,38	9	TE	cong. hyperemia
C.A.R	f	12			22	18	4	-18,18	3		
					23	18	5	-21,74	3		
C.A.	m	10	TB (2)		20	14	6	-30,00	6		
B.L.	f	0,2			28	10	18	-64,29	16	Tx discontinued (f.u. 48m)	> iris pigm. hypertrichosis
mean		7,9			25,73	18,59	8,41	-28,25	12,8		
s.d.		5,1			3,40	8,12	5,99	26,66	14,5		

GO = goniotomy
TB = trabeculotomy
TE = MMC trabeculectomy

Table I

Conclusions: Unlike other authors' experience, e.g. the Enyedi et al. study (1999,2002), involving children with a wide variety of glaucoma diagnoses and showing little IOP effect from this drug, in our study, involving exclusively a case series of primary congenital glaucomas, latanoprost showed an impressive ocular hypotensive effect and appeared to be well tolerated in pediatric patients. In our opinion, the observation of three cases of IOP lowering that lasted after stopping the treatment and the observation of reversal of iris pigmentation are very intriguing even if yet anecdotal.

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Grant Identification: None

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SCOPO DEL LAVORO

Valutare l' efficacia e la sicurezza della terapia topica a lungo termine con latanoprost 0,005% per il trattamento del glaucoma congenito primario

MATERIALI E METODI

Inclusi: pazienti affetti da glaucoma congenito primario seguiti dal gennaio 1997 presso il Centro Glaucoma della Sezione di Oftalmologia del Dipartimento di Specialità Medico-Chirurgiche dell'Università di Catania

Esclusi: pazienti affetti da glaucoma associato a malformazioni oculari o glaucoma secondario, o associato ad altre patologie.

Glaucoma Congenito Primario

- ad insorgenza precoce (<3 anni di vita)
- ad insorgenza tardiva (dai 3 ai 10 anni di vita)

MATERIALI E METODI

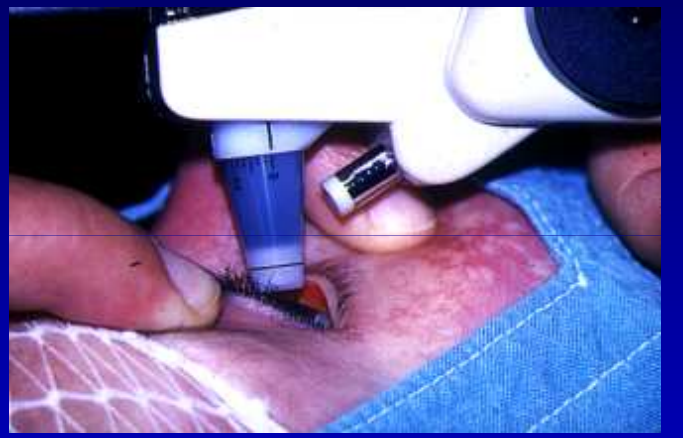
Diagnosi di glaucoma:

- visite ambulatoriali a paziente sveglio
- controllo in narcosi (inalazione con sevoflurane) (Sevorane®, Abbott, U.K.)

➢ **misurazione PIO:**

durante mantenimento e pre-risveglio
tonometro di Perkins

ambulatorialmente: tonometria
sec. Goldmann / tonometro di Perkins



➢ **Gonioscopia:** utilizzato il gonioscopio di Goldmann o il vetro a 4 specchi di Posner (Ocular Instruments Inc., Bellevue, Wa., USA).

➢ **Biometria ad ultrasuoni:** effettuata con ecografo Ophthascan® S (Biophysic Medical, Clermont Ferrand, France).

MATERIALI E METODI

PARAMETRI CONSIDERATI

- parametri demografici (sesso, età)
- dati anamnestici (età alla diagnosi, precedenti terapie o interventi chirurgici)
- dati relativi alla I visita (parametri oculari, IOP basale, terapia in corso)
- trattamenti eseguiti (terapia medica, chirurgica)
- dati relativi all' ultimo controllo

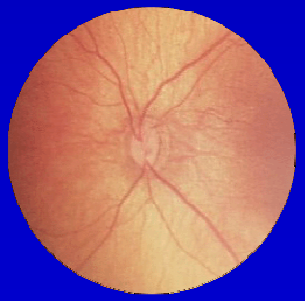
FOLLOW-UP

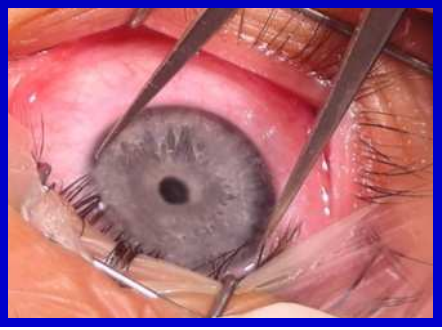
-primo controllo a 1 mese
-controlli periodici ogni 3-6 mesi

OUTCOME CONSIDERATI (IOP, PAPILLA, DATI BIOMETRICI)

-**RESPONDERS:** glaucoma compensato con latanoprost
-**NON RESPONDERS:**

- ✓ aggiunta altro farmaco ipotonizzante (se non controindicato)
- ✓ intervento chirurgico





RISULTATI

26 pazienti (13 m, 13 f) affetti da glaucoma congenito primario
età al momento dell'inizio del trattamento, tra i 2 mesi e i 10 anni.

	GCP precoce	GCP tardivo	Totale
Pazienti	20	6	26
Età alla diagnosi (mesi)	11 ± 14	91 ± 24	
Occhi trattati	33	11	44
Occhi già operati	9	2	11
Età al trattamento (mesi)	46 ± 64	110 ± 47	

RISULTATI

FOLLOW-UP MEDIO:
6,4 ± 3,8 ANNI

	GCP precoce	GCP tardivo	Totale
Occhi trattati	33	11	44
Responders*	12 (36.4%)	6 (54.5%)	18 (40.9%)
Terapia medica addiz.	4 (12.1%)	3 (27.3%)	7 (15.9%)
Chirurgia	14 (42.4%)	2 (18.2%)	16 (36.4%)
terapia post-chir	2		2
*Sospensione terapia	3 (9.1%)		3 (6.8%)

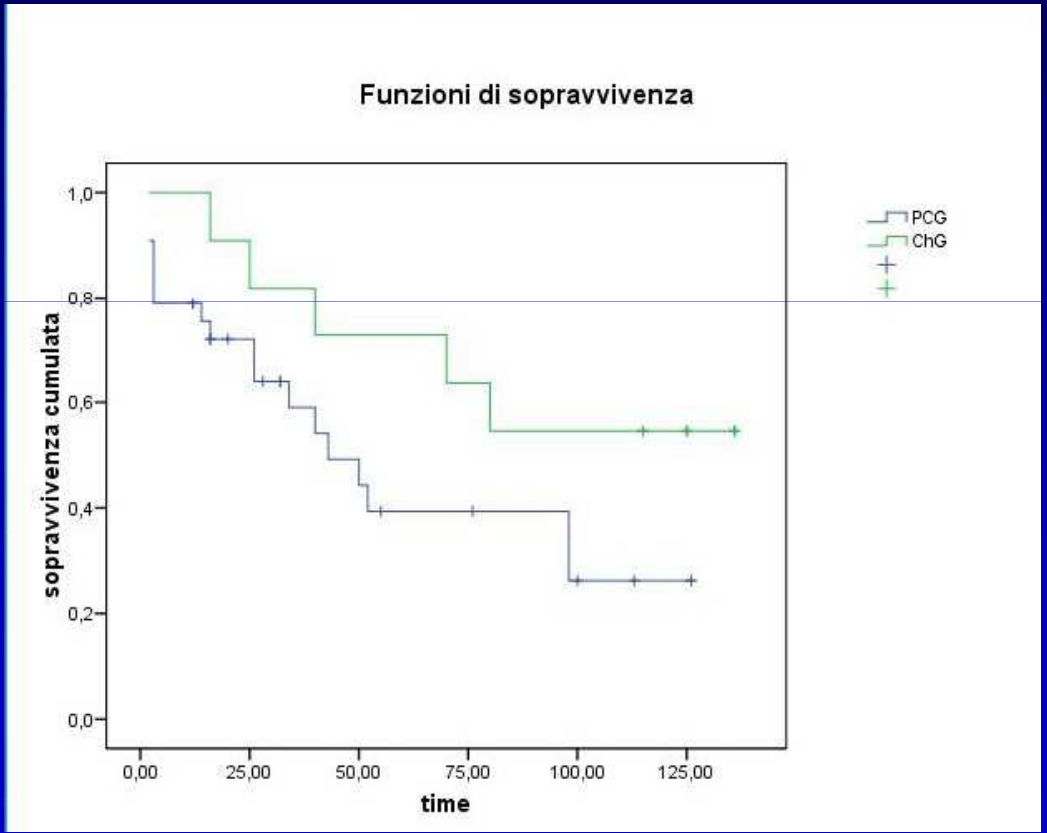
PIO iniziale **23.9 ± 1.7 mmHg**
PIO finale **15.4 ± 1.4 mmHg**
riduzione media **8.8 ± 2.2 mmHg (36.9%).**

RISULTATI

Durata compenso terapia (mesi)	GCP precoce	GCP tardivo	Totale
	42 ± 39*	78 ± 47 *	51 ± 45

*Differenza stat. significativa t-test p=0.16

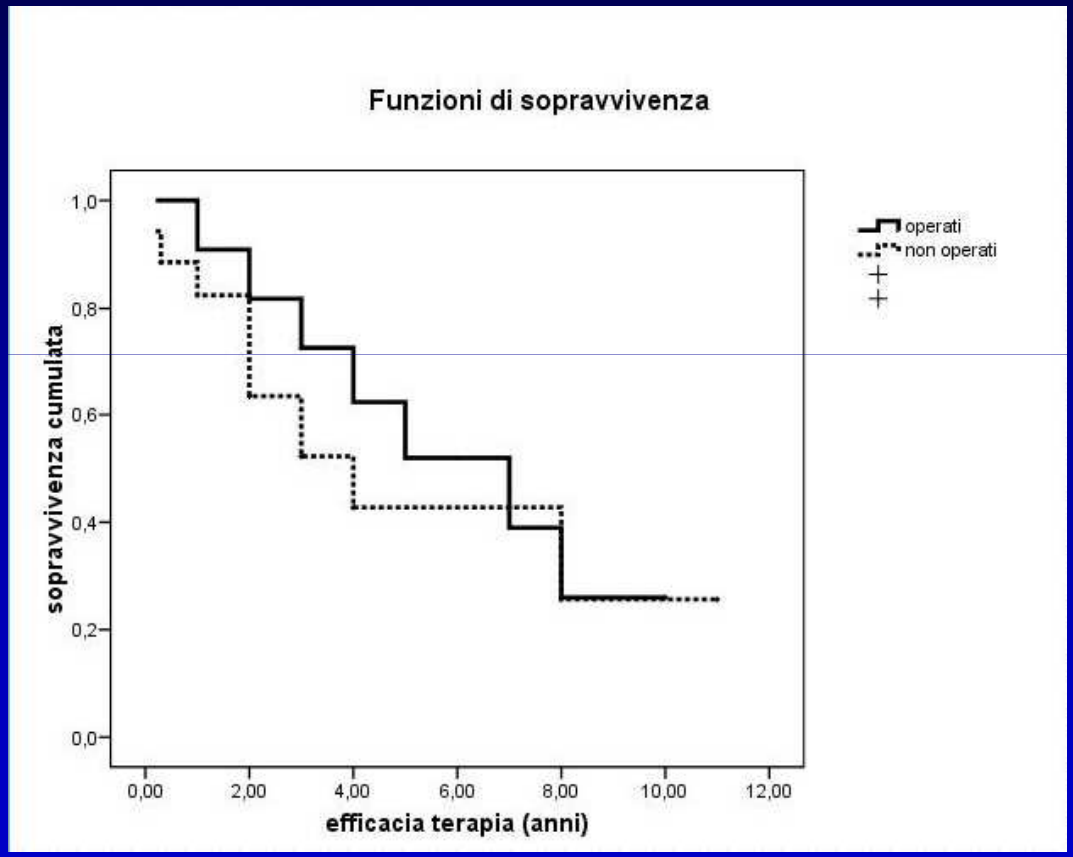
SURVIVAL ANALYSIS



Differenza statisticamente significativa tra GCP precoce e GCP tardivo (log rank test, Mantel-Cox, p=0.041)

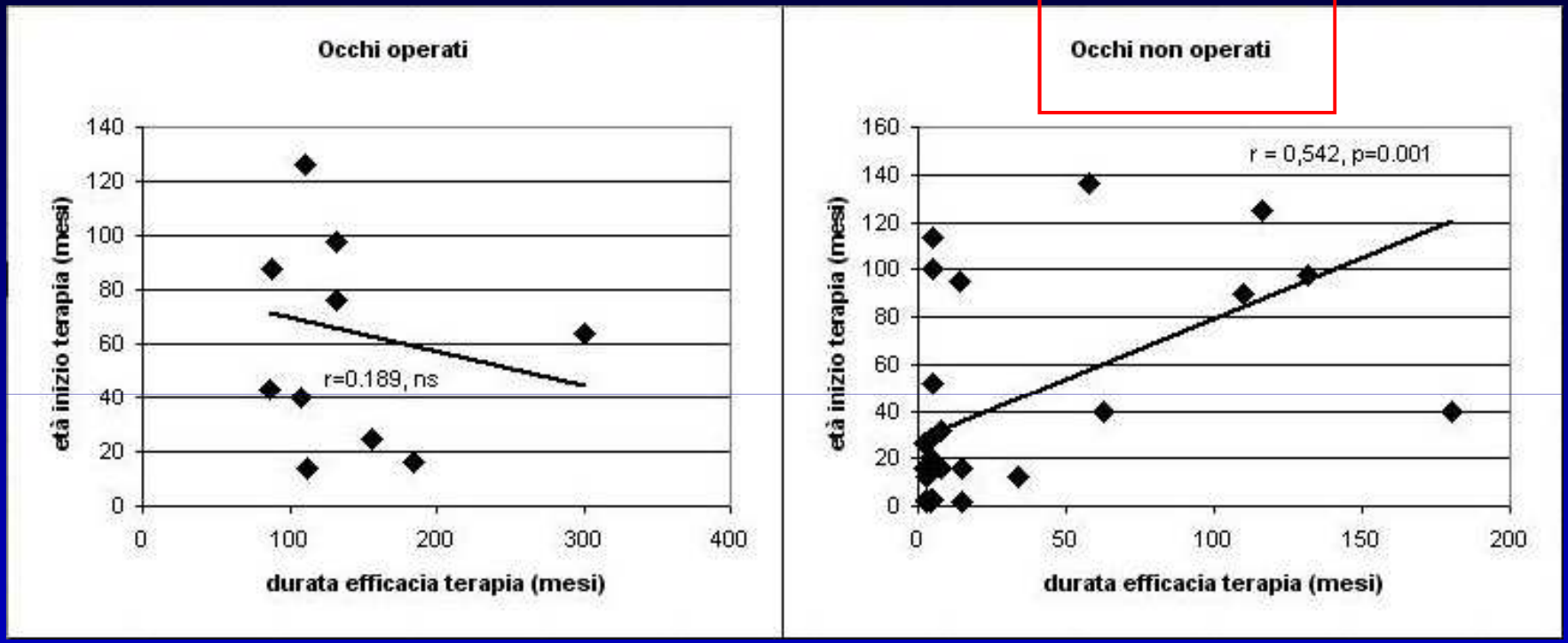
RISULTATI

EFFICACIA IN OCCHI PRECEDENTEMENTE OPERATI



Nessuna differenza tra occhi non operati e occhi operati

RISULTATI



L' analisi multivariata mostra che la lunghezza dell' efficacia del trattamento era correlata all' età all' inizio del trattamento (p=0.014).

SOSPENSIONE TERAPIA

2 pazienti, 3 occhi (età all' inizio della terapia: 2 mesi e 3,5 anni, entrambe sesso F), dopo un periodo di terapia rispettivamente di 16 mesi e di 12 mesi

Ripetuti controlli PIO <10 mmHg

Sospensione terapia

follow-up 7 e 5 anni: pressione normale

?

- **Spontanea regressione (Nagao e coll 2009)**
  maturazione strutture di deflusso in occhi con alterazioni meno gravi.

- **Effetto del farmaco**

EFFETTI COLLATERALI

-1 (4.1 %) caso di irritazione cronica delle alte vie aeree

-4 (8.7%) casi di iperemia congiuntivale transitoria

-1 (4,1%) caso di iperpigmentazione iridea associata ad ipertricosi delle ciglia e sopracciglia, dopo trattamento monolaterale.

Effetti regrediti dopo 3 anni dalla sospensione del trattamento

Effetti a lungo termine?

Età: 1 anno

(dopo 10 mesi di terapia in OD)

Età: 3½ anni

(a 2 anni dalla sospensione)

Età: 5½ anni

(a 4 anni dalla sospensione)

CONCLUSIONI

I dati di questo studio concordano con i dati degli altri studi:

- RESPONDERS: 30%
in accordo con i dati di Enyedi e coll 1999 (dati ad un anno) e Black e coll 2009 (dati a 10 anni)

-RIDUZIONE IOP: 35 %

-Età appare essere un fattore correlato alla risposta terapeutica

-L' uso per diversi anni di tale farmaco non ha prodotto significativi effetti collaterali sistemici o locali.

Non è chiaro perché alcuni pazienti abbiano una buona risposta mentre in altri il farmaco non induce praticamente alcun effetto

↓

Necessità ulteriori studi

PROTOCOL SYNOPSIS

A PHASE 1, OPEN-LABEL STUDY OF LATANOPROST ACID PLASMA CONCENTRATIONS IN PEDIATRIC AND ADULT GLAUCOMA PATIENTS TREATED WITH LATANOPROST 0.005%

Compound:	Xalatan
Compound Name (if applicable):	Xalatan (latanoprost ophthalmic solution)
US IND Number (if applicable):	36,523
Protocol Number:	A6111139
Phase:	Phase 1
Version and Date:	Final 30 November 2007

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Also Included In: Pediatrics / Children's Health
Article Date: 22 Oct 2010 - 2:00 PDT

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Pfizer announced that Xalatan 0.005% (latanoprost) has been approved by the European Commission for reduction of elevated intraocular pressure (IOP) in the treatment of paediatric

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