CONSENSUS CONFERENCE ON ACROMEGALY:
A LINK BETWEEN RESEARCH AND CLINICAL PRACTICE

ACROMEGALY CONTROL AND TREATMENT CONSENSUS: AN EVOLUTIVE PROCESS

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6th AME National Meeting
Italian Association of Clinical Endocrinologists

3 rd Joint Meeting with AACE
American Association of Clinical Endocrinologist

Update in Clinical Endocrinology
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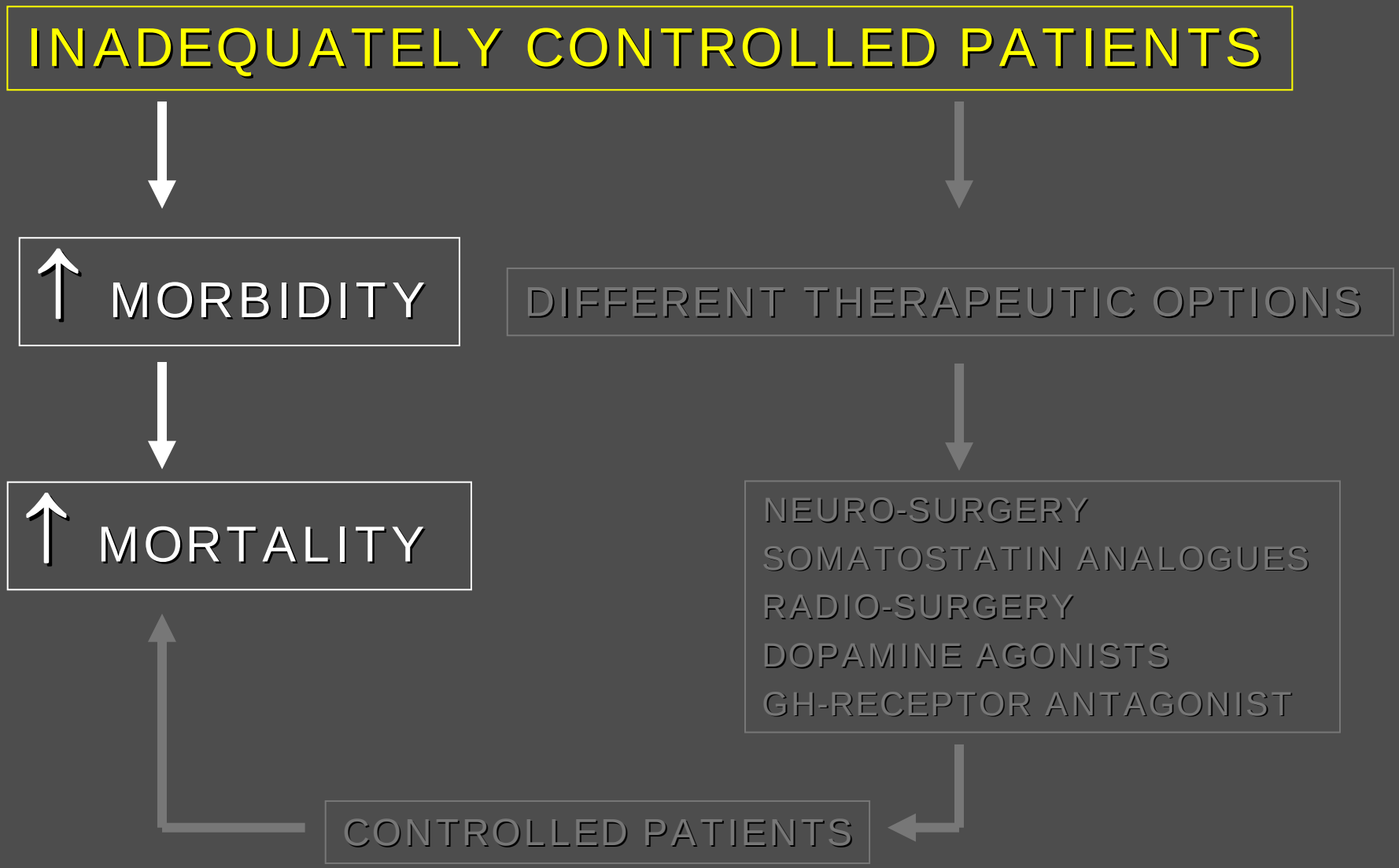
CONSENSUS CONFERENCE ON ACROMEGALY

CORTINA	1999	→ Criteria of Cure
↓		↓
MONTECARLO	2001	→ Treatment Guidelines
↓		↓
SIVIGLIA	2003	→ Medical Therapy
↓		↓
SANTA MONICA	2006	→ Diagnosis and Treatment

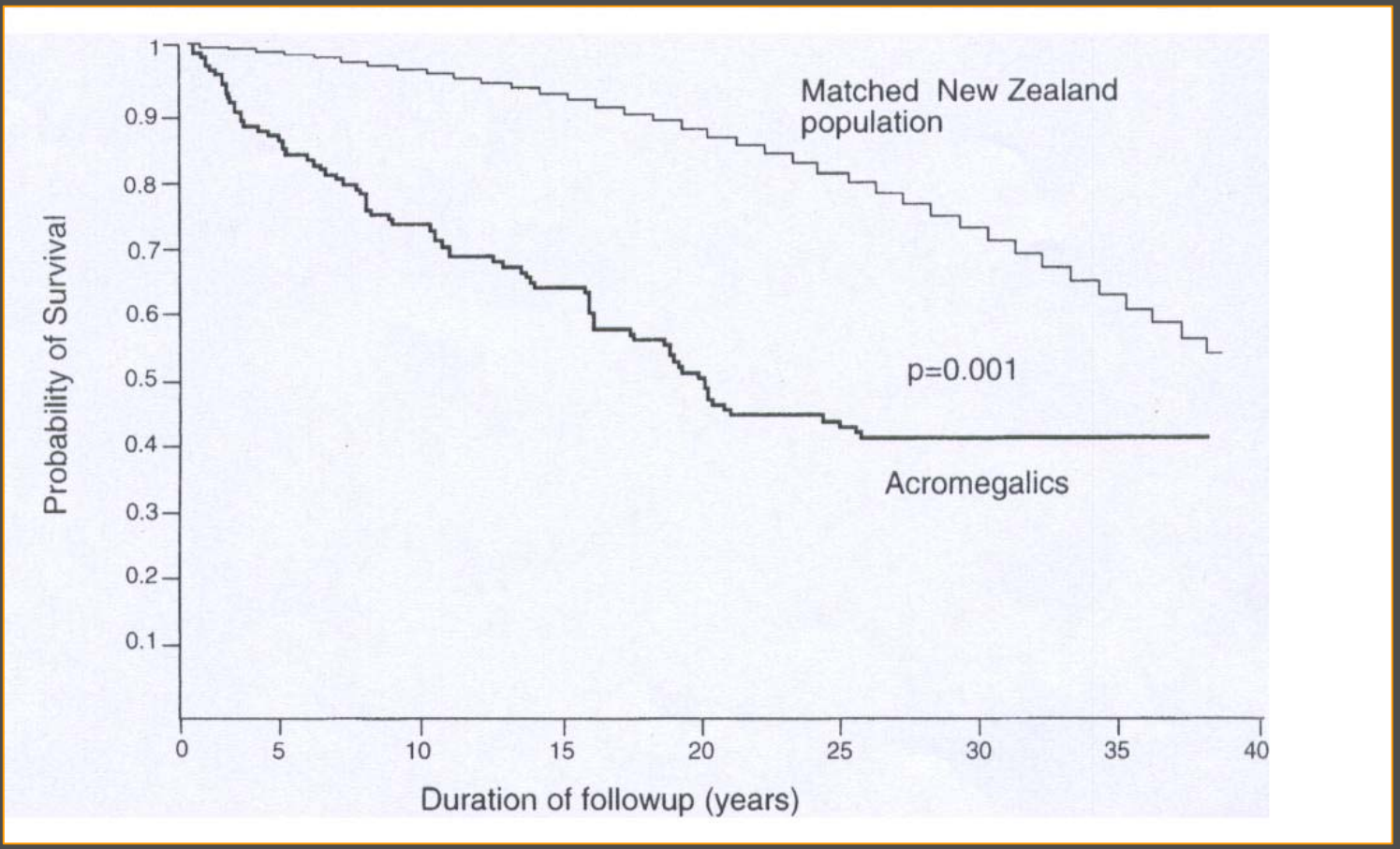
WHY WE NEED TO REDEFINE CONTROL? /1



WHY WE NEED TO REDEFINE CONTROL? /2

MORTALITY

BACKGROUND



I. M. Holdaway and C. Rajasoorya, *Pituitary* 1999

WHY WE NEED TO REDEFINE CONTROL? /3

MORTALITY and AGE AT DIAGNOSIS

BACKGROUND

Mortality and Cancer Incidence in Acromegaly: A Retrospective Cohort Study*

J Clin Endocrinol Metab 1998

STEPHEN M. ORME, RICHARD J. Q. MCNALLY, RAY A. CARTWRIGHT, AND PAUL E. BELCHETZ FOR THE UNITED KINGDOM ACROMEGALY STUDY GROUP†

Department of Endocrinology (S.M.O., P.E.B.), The General Infirmary at Leeds, The Leukemia Research Fund (R.J.Q.M., R.A.C.), Center for Clinical Epidemiology, University of Leeds, Leeds, United Kingdom

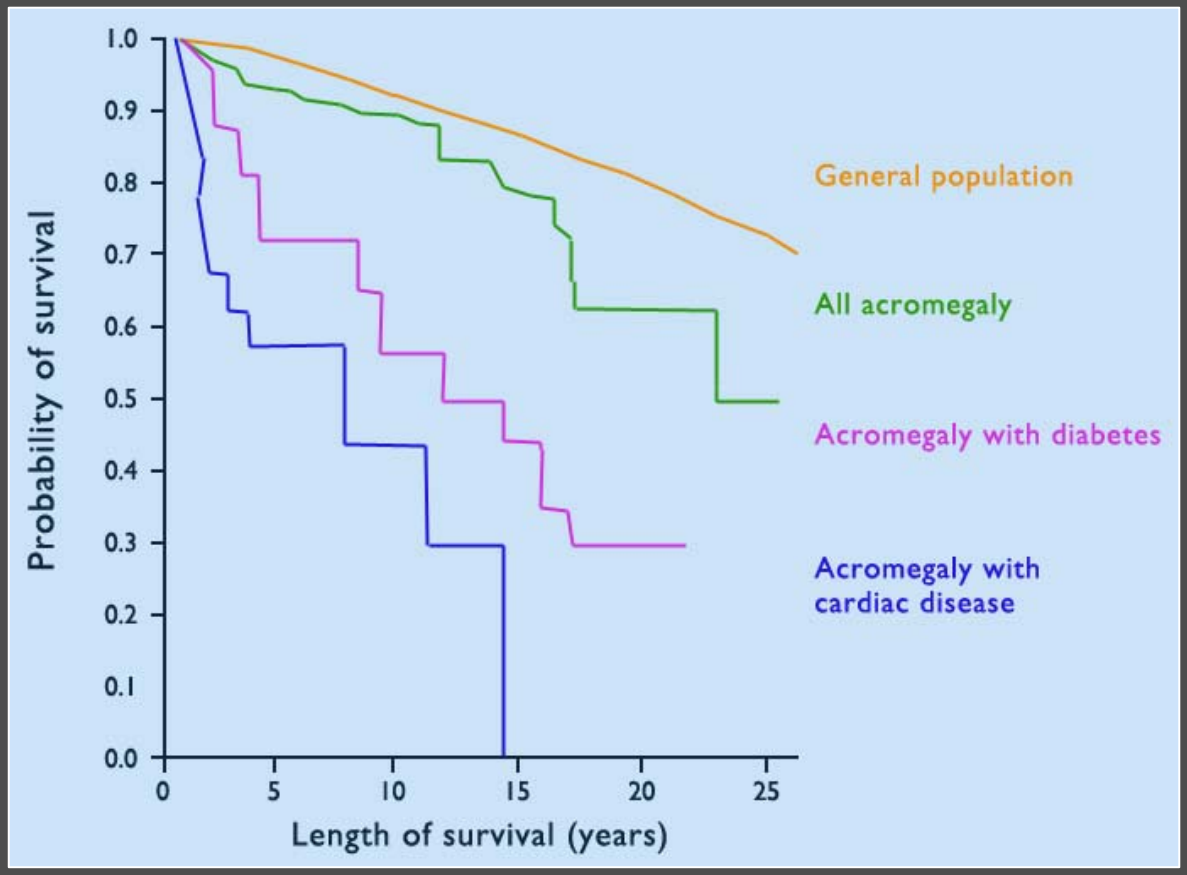
Relationship between age at diagnosis and mortality in acromegalics studied

Cause of death	SMR (95% CI), age at diagnosis:			χ^2 test for linear trend (*P*)
	0–34 yr	35–59 yr	60–84 yr	
Cardiovascular disease	3.81 (2.22–6.10)	1.50 (1.18–1.89)	1.91 (1.39–2.56)	0.38
Cerebrovascular disease	7.36 (3.18–14.51)	2.15 (1.42–3.13)	1.18 (0.54–2.24)	<0.001
Respiratory disease	3.47 (0.95–8.89)	1.97 (1.30–2.87)	1.43 (0.74–2.50)	0.14
Malignant disease	0.92 (0.30–2.15)	1.23 (0.94–1.59)	1.05 (0.63–1.64)	0.88
Overall (all causes of mortality)	2.78 (2.03–3.72)	1.55 (1.35–1.76)	1.43 (1.16–1.75)	0.004

WHY WE NEED TO REDEFINE CONTROL? /4

MORTALITY and COMORBIDITY

BACKGROUND

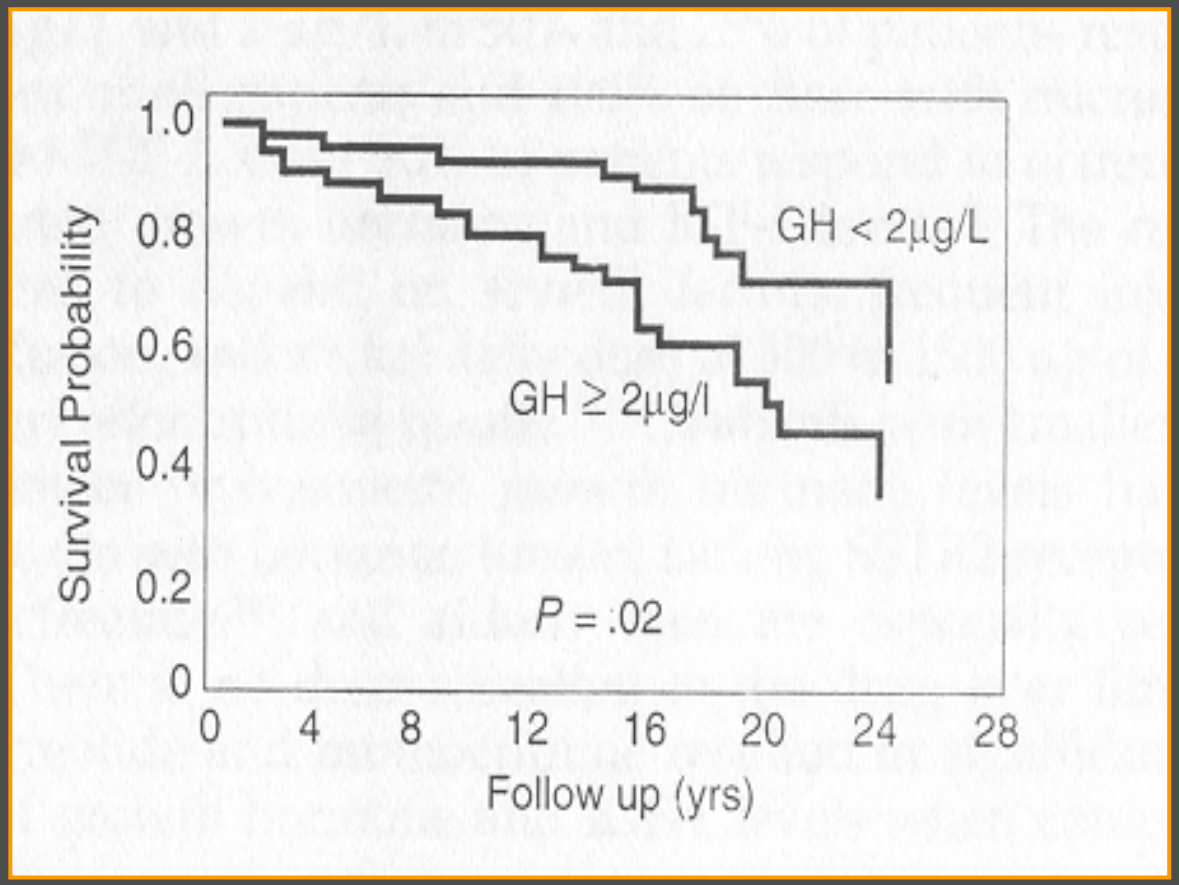


Adapted from Rajasoorya C, et al. *Clin Endocrinol* 1994

WHY WE NEED TO REDEFINE CONTROL? /5

MORTALITY and DISEASE ACTIVITY

BACKGROUND



Rajasoorya C. et al., *Clin Endocrinol* 1994

1970 — GH < 10 µg/L

1980 — GH < 5 µg/L

1990 — GH < 2.5 µg/L

ACROMEGALY CONTROL

HISTORICAL NOTES /2

AUTHOR; YEAR	# OF PATIENTS	BASAL GH < 5 ng/ml	OGTT GH < 2 ng/ml
Arafah et al., 1980	28	20 (78%)	13 (46%)
Tucker et al., 1980	32	24 (75%)	22 (71%)
Quabbe et al., 1982	152 114 micro 38 macro	 68 (60%) 13 (40%)	 39 (39%) 9 (26 %)
Grisoli et al., 1985	100	60 (60%)	43 (43%)
Serri et al., 1985	25 8mico 17 macro	 8 (100%) 14 (82%)	 8 (100%) 13 (76%)

AUTHOR, YEAR	# OF PATIENTS	BASAL GH < 5 NG/ML (%)
Williams et al., 1975	59	39 (66%)
Richards and Thomas, 1980	34	27 (80%)
Balagura et al., 1981	132	76 (58%)
Laws at al., 1985	75	40 (53%)
Roefselma et al., 1985	60	37 (62%)
Fahlbusch and Buchfelder, 1988	38	21 (55%)
Ross and Wilson, 1988	214	117 (54%)
Van't Verlaat et al., 1988	25	14 (56%)

Criteria for Cure of Acromegaly: A Consensus Statement*†

ANDREA GIUSTINA, ARIEL BARKAN, FELIPE F. CASANUEVA, FRANCO CAVAGNINI, LAWRENCE FROHMAN, KEN HO, JOHANNES VELDHUIS, JOHN WASS, KLAUS VON WERDER, AND SHLOMO MELMED

GOALS

- → Reduction of GH levels to less than 1 ng/ml after OGTT
- → Restoration of IGF-I levels to age- and gender- normal levels
- → Adequate control of signs and symptoms
- → Normalization in acromegaly-associated mortality
- → Reduction of pituitary tumor size while preserving other pituitary hormone function
- → Alleviation of the effects of the tumor mass on surrounding structures

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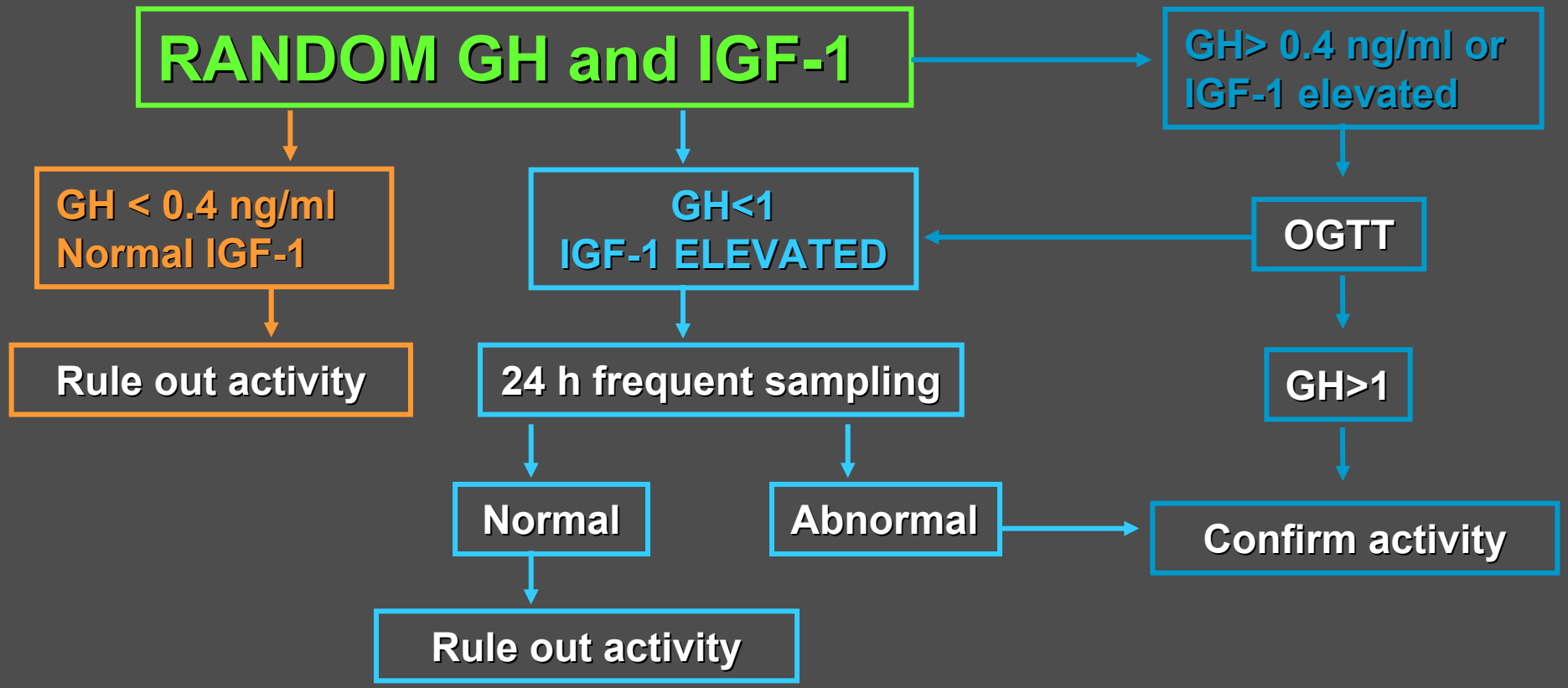
BIOCHEMICAL CRITERIA



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Outcome	Criteria	Management
Controlled	Nadir GH <1 μg/L	Asses GH/IGF-I axis
	Age-sex-normalized IGF-I	Evaluate pituitary function
	No clinical activity	Periodic MRI
		No treatment or no change in current treatment
Inadequately controlled	Nadir GH >1 μg/L	Assess GH/IGF-I axis
	Elevated IGF-I	Evaluate pituitary function
	Clinically inactive	Periodic MRI
		Assess cardiovascular, metabolic, and tumoral comorbidity
		Weigh treatment benefit or consider new treatment *vs.* low risk of elevated GH
Poor control	Nadir GH >1 μg/L	Assess GH/IGF-I axis
	Elevated IGF-I	Evaluate pituitary function
	Clinically active	Periodic MRI
		Actively treat or change treatment

Giustina A. et al., *J Clin Endocrinol Metab* 2000

ACROMEGALY CONTROL

CORTINA /4

Laboratory values at follow-up	Patients in remission	(%)
Directly Postop (d 1–3)		
IGF-I	10 /19	52.6
Nadir GH <1.0 µg/liter	3 /6	50
Random GH ≤ 2.5 µg/liter	28 /48	58.3
Random GH ≤ 5.0 µg/liter	38 /48	79.2
Short-term (6 wk)		
IGF-I	34 /51	66.7
Nadir GH <1.0 µg/liter	19 /37	51.4
Random GH ≤ 2.5 µg/liter	21 /43	48.8
Random GH ≤ 5.0 µg/liter	28 /43	65.1
Long-term (≥ 12 months)		
IGF-I	40 /57	70.2[1]
Nadir GH <1.0 µg/liter	11 /18	61.1
Random GH ≤ 2.5 µg/liter	24 /36	66.7
Random GH ≤ 5.0 µg/liter	31 /36	86.1

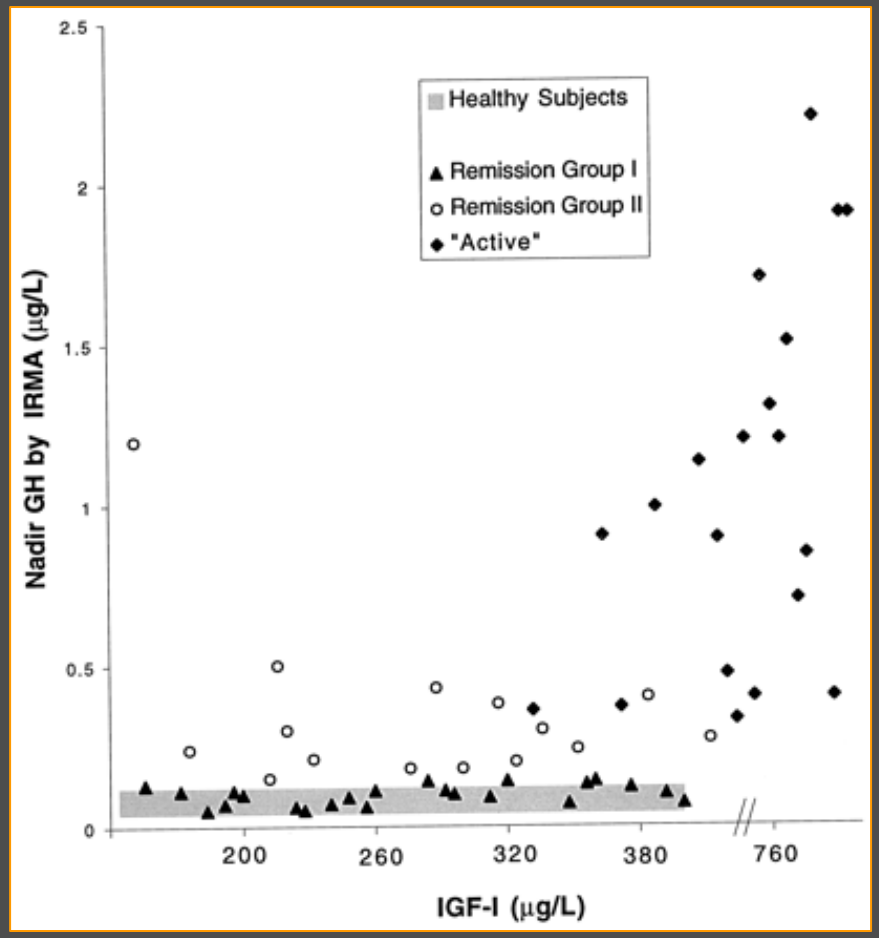
Outcome analysis for 57 surgically treated adenomas

Kreutzer et al., *J Clin Endocrinol Metab* 2001

CONTROL ASSESSMENT AFTER CORTINA

- BIOCHEMICAL EVOLUTION
- CLINICAL EVOLUTION

DISCREPANCY BETWEEN GH AND IGF-1 /1



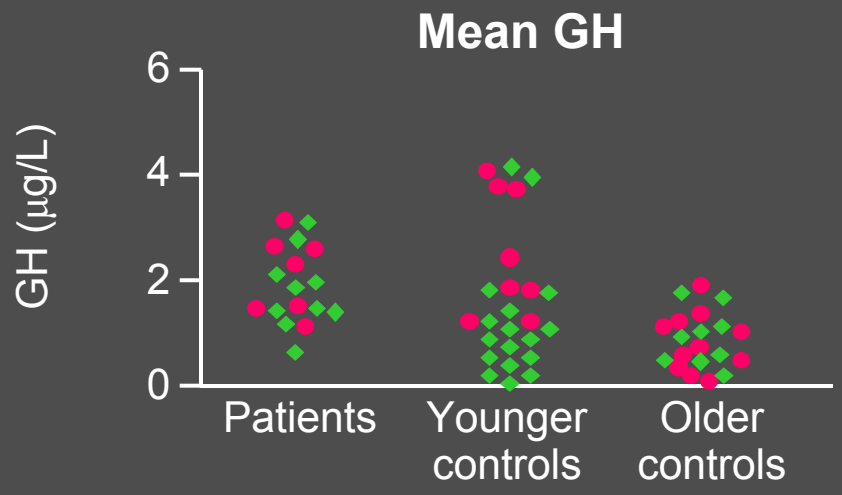
Group I
Remission with normal GH suppression

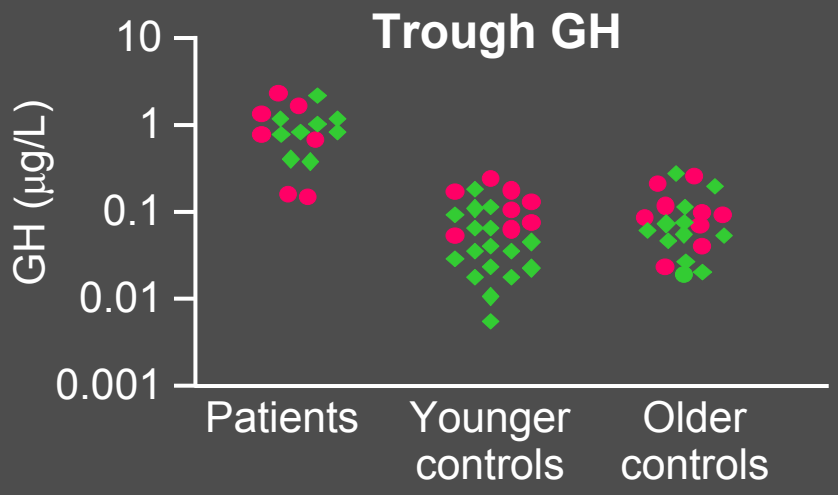
Group II
Remission with abnormal GH suppression

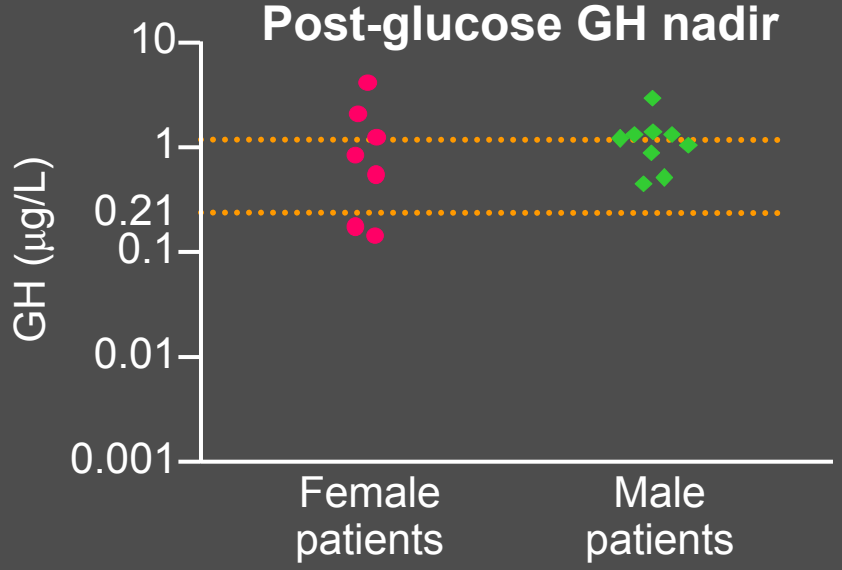
Freda et al., *J Clin Endocrinol Metab* 1998

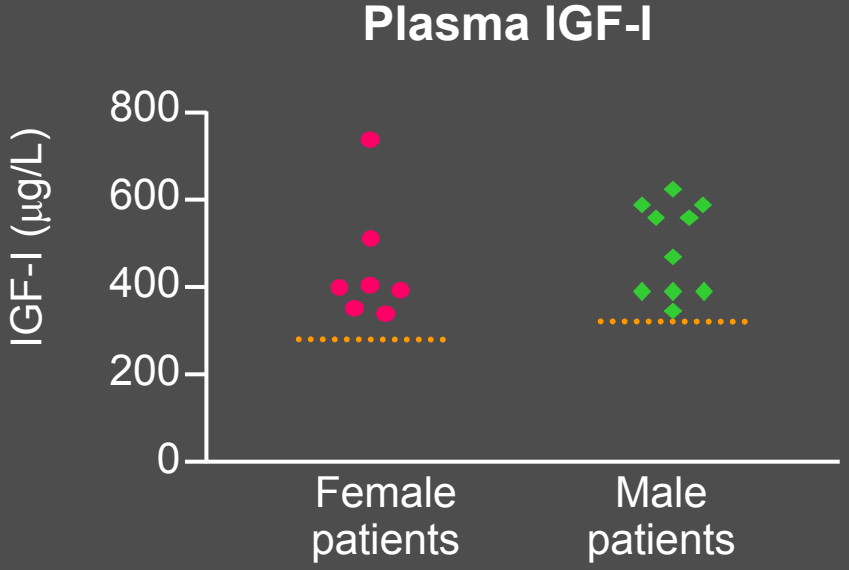
DISCREPANCY BETWEEN GH AND IGF-1 /2
ACROMEGALY WITH NORMAL GH

Dimaraki et al.,
J Clin Endocrinol Metab 2002









DISCREPANCY BETWEEN GH AND IGF-1 /3

HOW FREQUENT IS "MICROMEGALY"?

- Tertiary referral center with particular interest in the phenomenon: 25%

Dimaraki et al., *J Clin Endocrinol Metab* 2002

- Third world country: 2.4%

Mercado et al., *Horm Res* 2004

LIKELY, 5-10%

GH AND IGF-1 NADIR AFTER OGTT
DIFFERENT ASPECTS OF ACROMEGALY

GH during OGTT

→ presence of GH-secreting adenomatous tissue

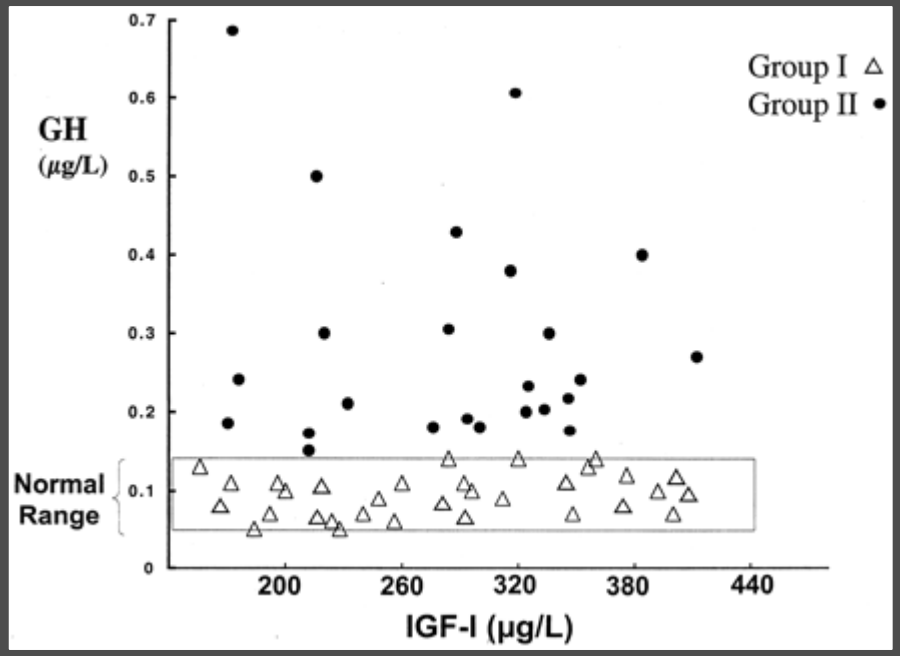
IGF-1

→ activity of the GH secreting adenoma

ASSAYS

	GH	IGF-1
AGE DEPENDENCY	++	+++
SEX DEPENDENCY	+++	++
NUTRITION	+	++
TECHNICAL	+	+++
MEDICATIONS	++	+
NORMAL RANGE	+	+++

NORMALITY GH CUT-OFF AFTER OGTT AND ITS PREDICTIVE VALUE /1

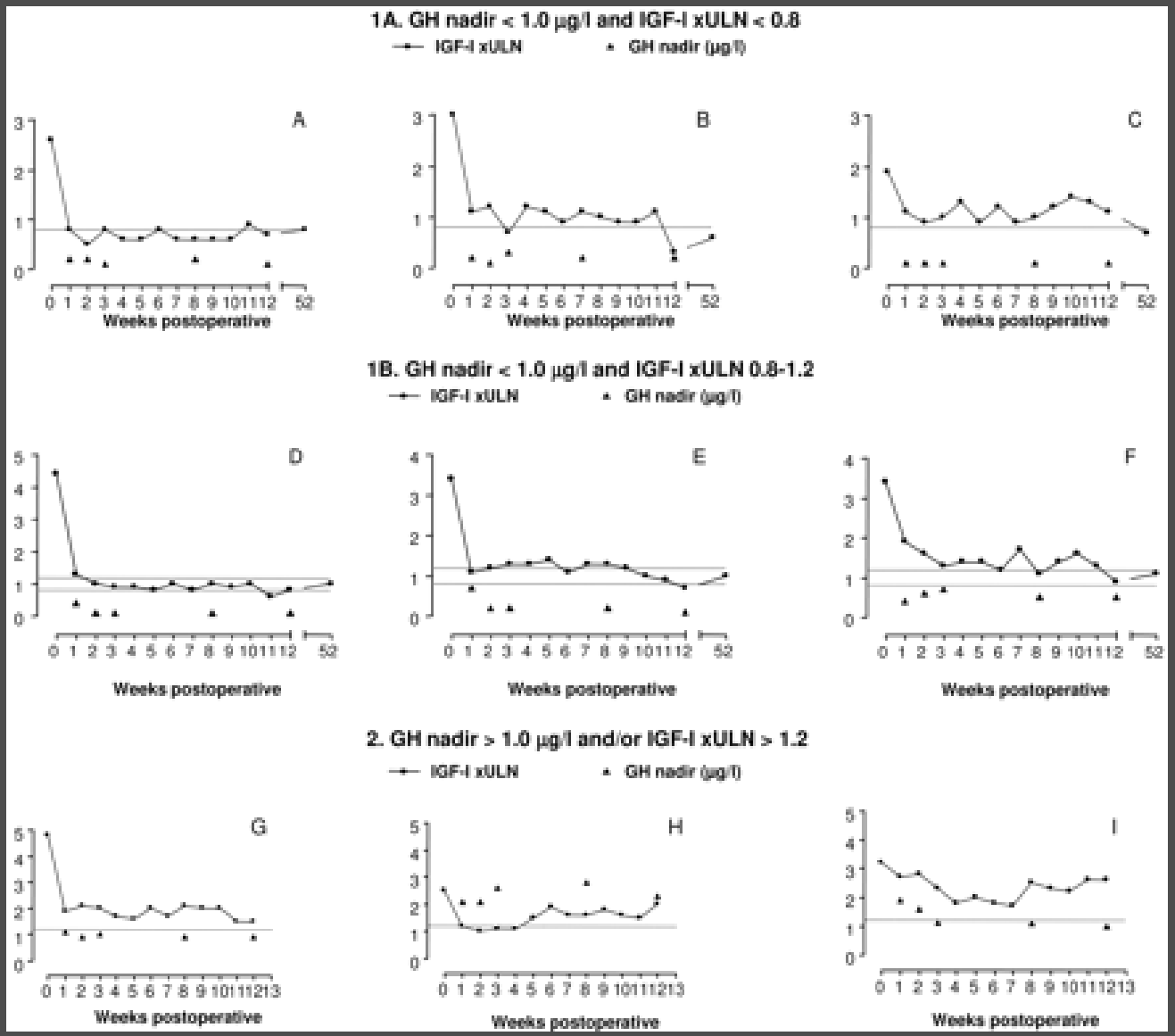


Group I
Nadir GH <0.14 µg/L

Group II
Nadir GH >0.14 µg/L

Freda et al., *J Clin Endocrinol Metab* 2004

GH RESPONSE TO OGTT AND ITS PREDICTIVE VALUE /2



"TIMING"

Feelders et al.,

J Clin Endocrinol Metab 2005

CONSENSUS STATEMENT

Consensus statement: medical management of acromegaly

S Melmed, F Casanueva[1], F Cavagnini[2], P Chanson[3], L A Frohman[4], R Gaillard[5], E Ghigo[6], K Ho[7], P Jaquet[8], D Kleinberg[9], S Lamberts[10], E Laws[11], G Lombardi[12], M C Sheppard[13], M Thorner[11], M L Vance[11], J A H Wass[14] and A Giustina[15]

Cedar-Sinai Research Institute, UCLA School of Medicine, Los Angeles, USA, [1]Santiago de Compostela University, Spain, [2]University of Milan, Italy, [3]Hospital Bicetre; Paris, France, [4]University of Illinois, Chicago, USA, [5]University Hospital CHUV, Lausanne, Switzerland, [6]University of Turin, Italy, [7]Garvan Institute of Medical Research, Australia, [8]Universitè de la Mediterraneè, Marseille, France, [9]NY University Medical Center, New York, USA, [10]University Hospital, Rotterdam, the Netherlands, [11]University of Virginia, Charlottesville, USA, [12]School of Medicine, Naples, Italy, [13]University of Birmingham, UK, [14]Radcliffe Infirmary, Oxford, UK and [15]University of Brescia, c/o 2° Medicina, Spedali Civili, Brescia 25125, Italy

(Correspondence should be addressed to A Giustina; Email: a.giustina@libero.it)

… Improved assay sensitivity now indicates that for control to be achieved the nadir GH level after oral glucose should be considerably below 1 µg/L…

… Furthermore, more data are required with these assays to assess “normality” in males and females. Therefore, **for complete control of GH dynamics to be achieved, nadir values should be below 0.4 µg/L…**

MORTALITY

NEW EVIDENCES

…In the past 2 ys, **3 very large cohort studies** have been published which provide unequivocal evidence for the importance of lowering **GH levels to between 1 and 2.5 µg/l** to achieve a mortality rate comparable to the general population…

- Holdaway (Auckland Hospital, New Zealand) → 208 acromegalic patients
- Ayuk (UK West Midland Pituitary Database) → 419 acromegalic patients
- Kauppinen-Makelin (5 University Hospitals of Finland) → 334 acromegalic patients

MORTALITY

NEW EVIDENCES / ROLE OF GH

Crude death rates in acromegaly related to the lowest GH achieved during follow-up

Lowest GH achieved (µg/liter)	No. of deaths	Death rate per 1000
0–0.5	6	10.5
0.5–1.0	13	9.2
1.0–1.5	5	6.6
1.5–2.0	3	6.7
2.0–2.5	11	23.7
2.5–5.0	30	26.0
5.0–50.0	23	23.3
> 50.0	3	30.8

Ayuk et al. *J Clin Endocr Metab* 2004

MORTALITY

NEW EVIDENCES / ROLE OF GH

Number of deaths in relation to treatment outcome and use of pituitary radiotherapy

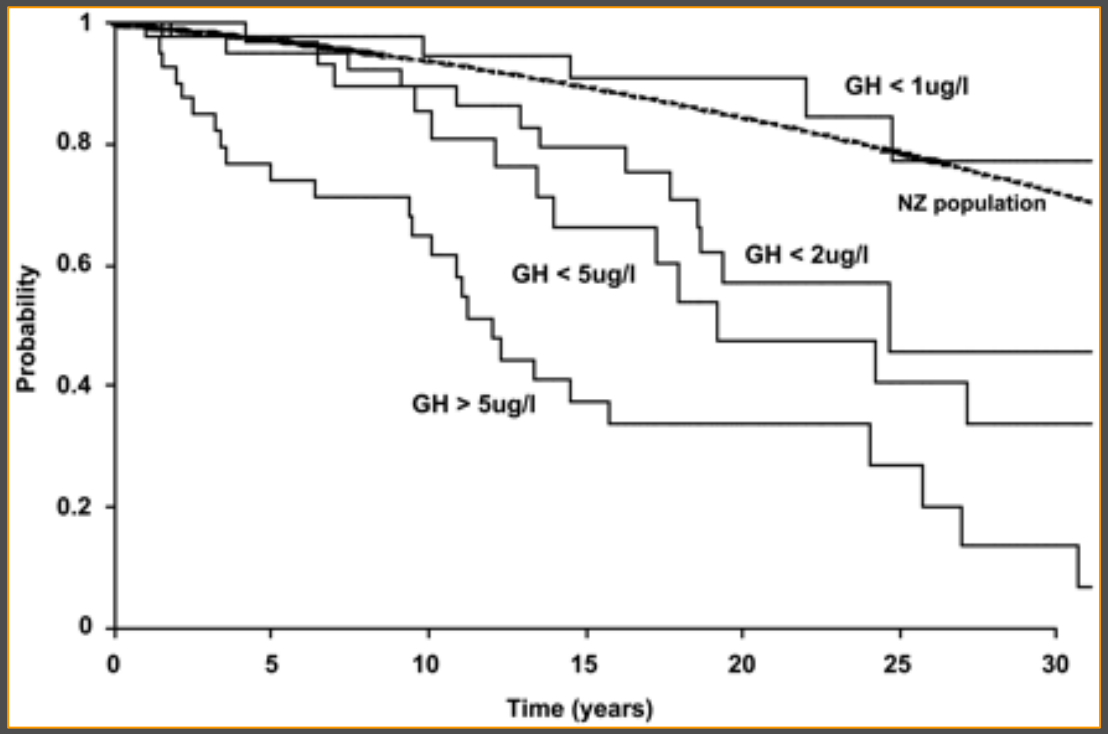
CAUSE OF DEATH	GH (µg/liter)		Radiotherapy	
	< 2.5	≥ 2.5	Yes	No
Coronary artery disease	5	7	4	9
Cerebrovascular diseases	4	3	6	2
Other heart and cardiovascular diseases	1	7	2	7
Malignancy		10	5	7
Pituitary tumor	1	1	1	2
Accidents and violence		5	3	2
Other	2	4	2	4
Total	13	37	23	33

Kauppinen-Makelin at al., *J Clin Endocr Metab* 2005

MORTALITY

NEW EVIDENCES / ROLE OF GH

Probability of survival in acromegaly according to serum GH concentration at last review after treatment (curves different at *P* < 0.0001, by log rank). The *dotted line* represents the probability of survival for the New Zealand population.

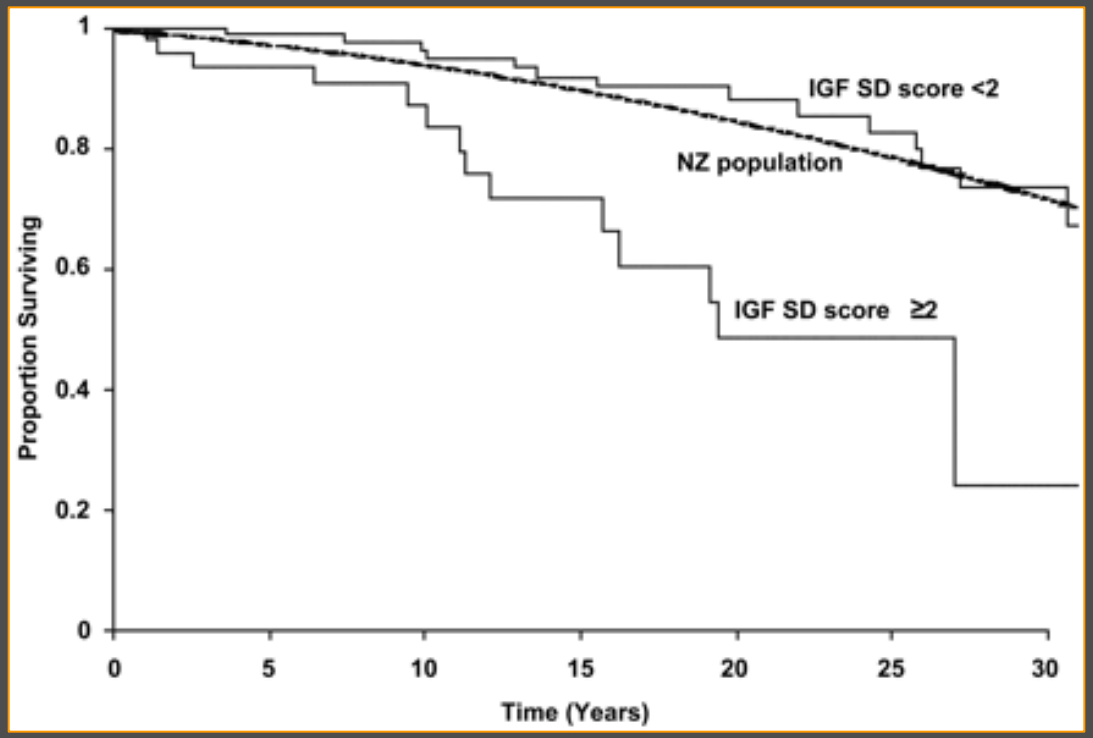


Holdaway et al., *J Clin Endocrinol Metab* 2004

MORTALITY

NEW EVIDENCES / ROLE OF IGF-1

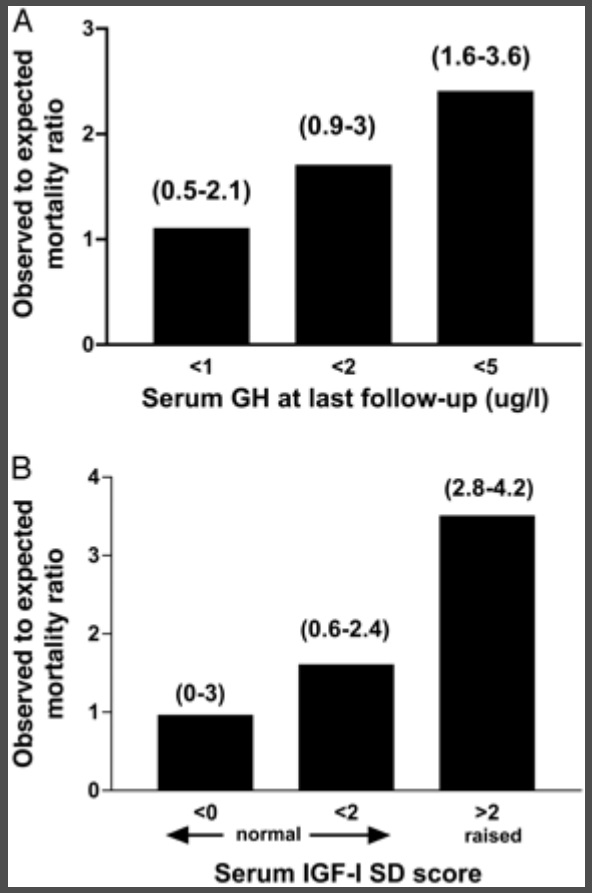
Probability of survival in acromegaly according to serum IGF-I concentration (expressed as SD score) at last review. The *dotted line* represents the probability of survival for the New Zealand population. *P* < 0.001.



Holdaway et al., *J Clin Endocrinol Metab* 2004

MORTALITY

NEW EVIDENCES / GH vs IGF-1



Mortality according to serum GH and IGF-I at last follow-up. A, Influence of GH. B, Influence of IGF-I. *Parentheses* indicate 95% confidence limits.

Holdaway et al., *J Clin Endocrinol Metab* 2004

CURRENT VIEWS

- **Diagnosis**
  - GH < 0.4 µg/L (+ normal IGF-1) excludes acromegaly
  - GH nadir < 1 µg/L during OGTT (+ normal IGF-1) excludes acromegaly
- **Post-treatment monitoring**
  - Controls have GH between 0.1 and 0.2 µg/L during OGTT
  - GH nadir < 1 µg/L after OGTT does not confirm cure
- **Treatment of acromegaly should be directed towards defining safe biochemical endpoints rather than restoring normal physiology**

…mortality is increased in acromegaly largely due to vascular deaths.

On the basis of current evidence a post treatment GH of <2.5 μg/L is associated with normal mortality. In order to reduce mortality it is reccommended that **biochemical targets in all patients should be GH <2.5 μg/L and normal IGF-1.**

The definition of the GH target is based on any parameter when drowing blood –random, fasting, mean of a series of GH measurements, or GH nadir during OGTT.

A lower GH value may be a more appropriate target expecially in younger patients.

More data are required as to whether further treatment is required in patients with normal IGF-1 / abnormal GH or normal GH / abnormal IGF-1…

OPEN ISSUES

- Basal GH cut-off <2.5 μg/L results from aged studies
- What's normal IGF-1 in every single patient?
- OGTT role
  (post-surgery, predictive risk of relapse, other, altro)
- Discrepancy between GH and IGF-1 and inadequately controlled patient according to Cortina criteria
  ("control grey zone")

CONCLUSIONS

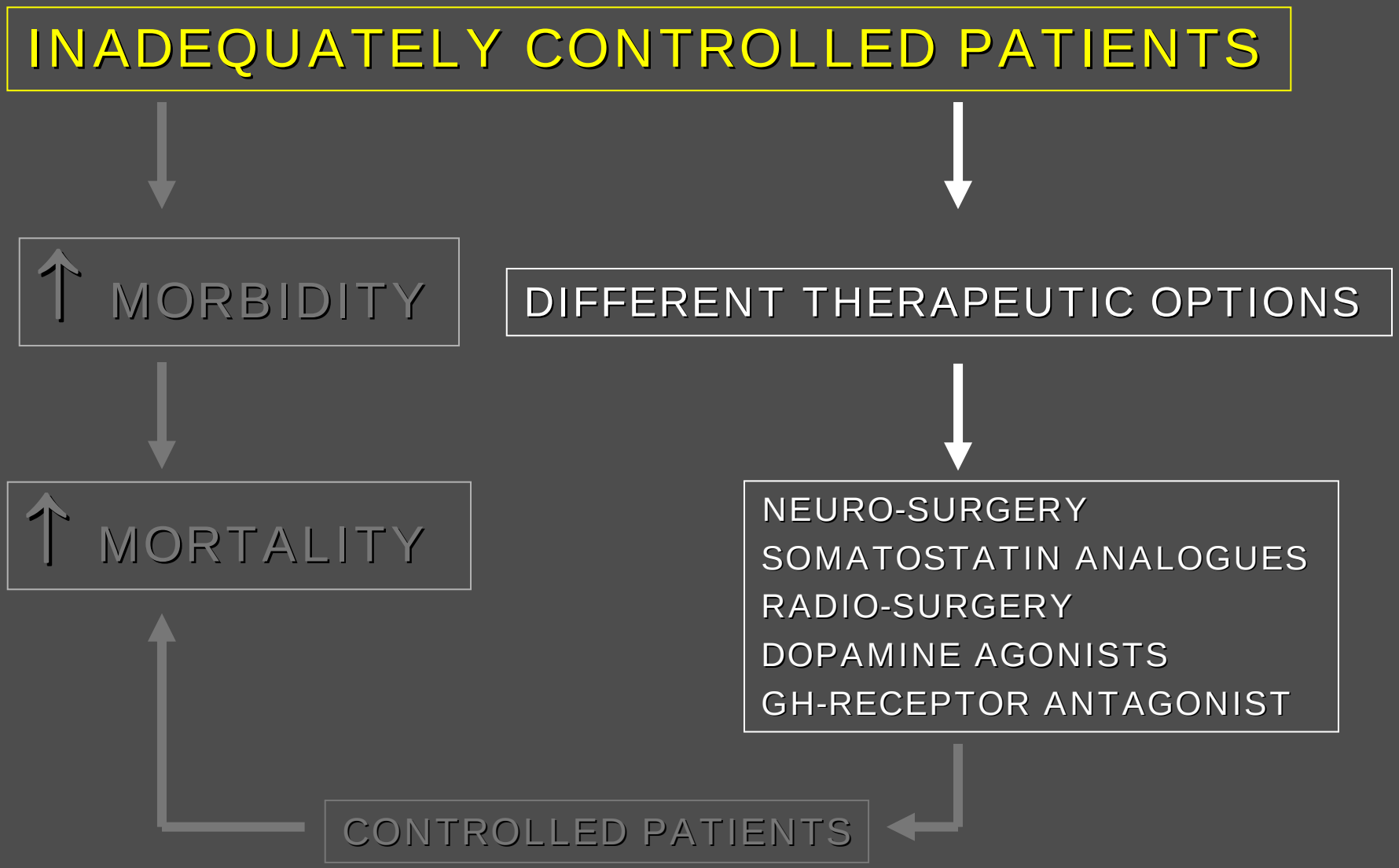
CONTROL

- THE EVOLUTION OF LABORATORY ASSAYS IS FASTER THAN THE POSSIBILITY TO OBTAIN DATA FROM LONG TERM PROSPECTIVE STUDIES

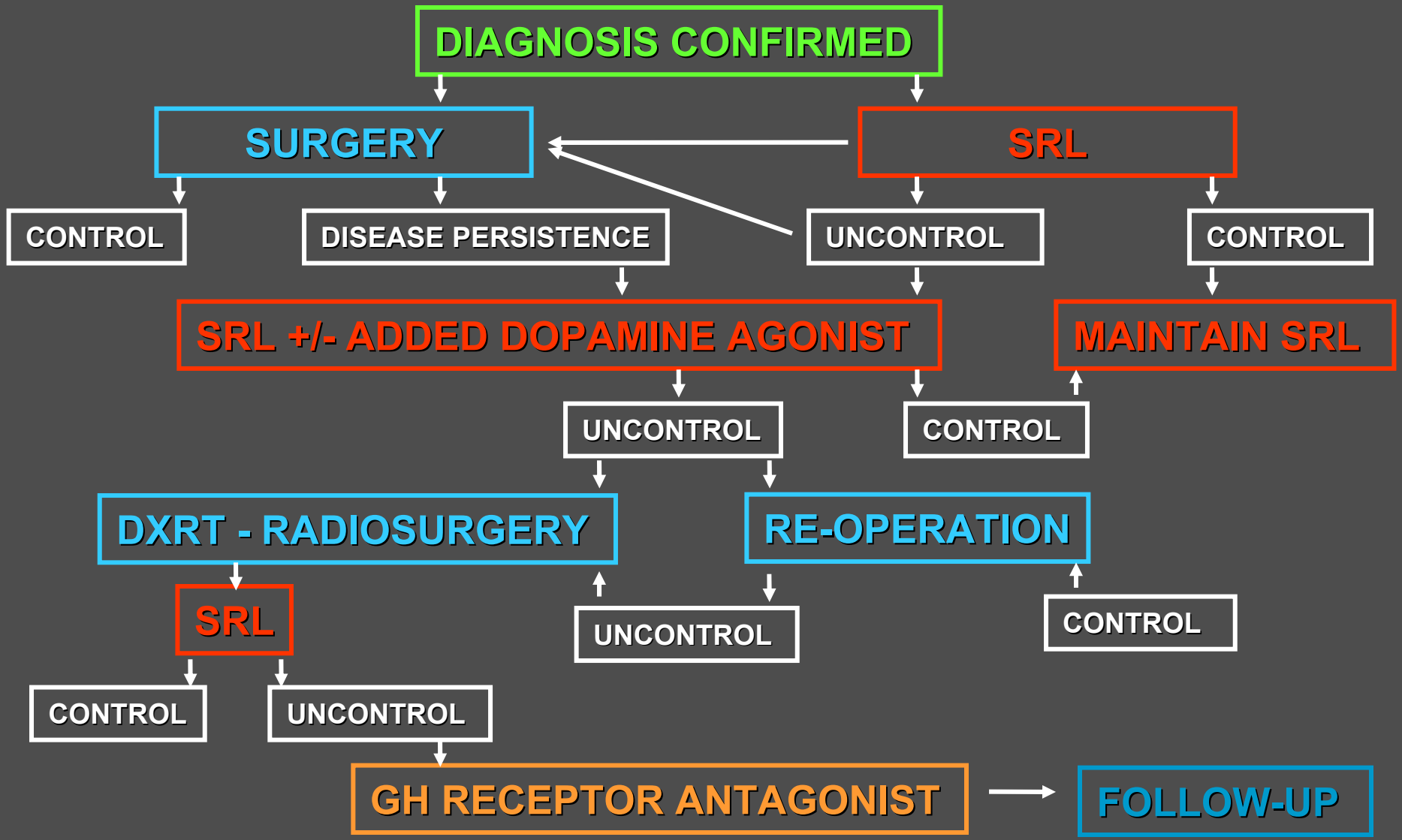
- THIS LEADS, IN OUR OPINION, TO RE-EVALUATE THE IMPORTANCE OF AN ACCURATE BIOCHEMICAL EVALUATION

- BASED ON THESE CONSIDERATIONS AND ON THE AVAILABILITY OF NEW TREATMENTS THERE IS THE CONSTANT NECESSITY FOR RE-ASSESSMENT OF DISEASE CONTROL PARAMETERS

WHY WE NEED TO REDEFINE TREATMENT?



THERAPEUTIC PARADIGM



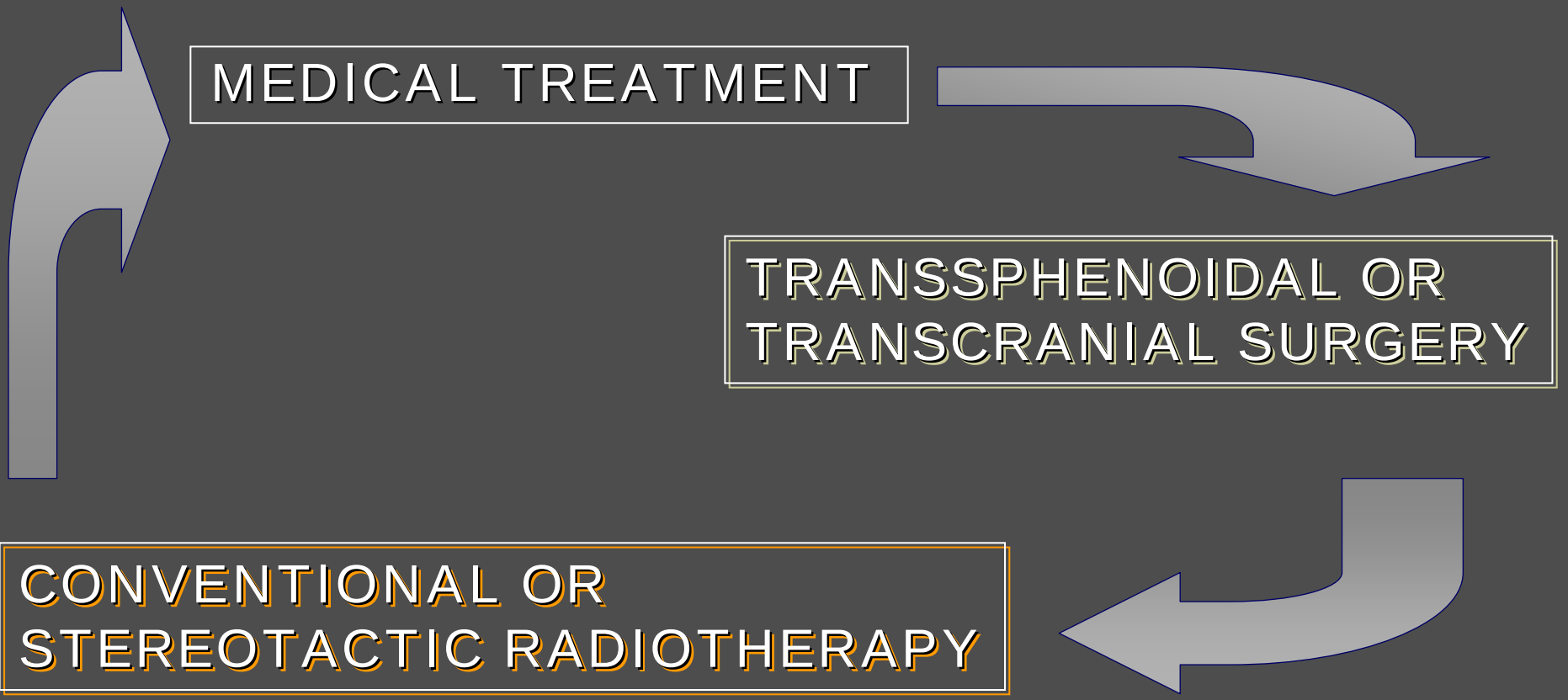
HIGHLIGHTS

→ NEUROSUGERY IS FIRST CHOICE TREATMENT

→ POSSIBILITY OF PRIMARY MEDICAL THERAPY WITH SRLs IN SELECTED PATIENTS

→ INITIAL DATA ON RADIOSURGERY AND PEGVISOMANT

TREATMENT OPTIONS



TRANSSPHENOIDAL SURGERY/1

Complete microadenoma resection

Maximal removal of locally impinging tumor and hyperfunctioning macroadenomas

Reoperation of surgically accessible residual or recurrent tumor remnants visualized by MRI

TRANSSPHENOIDAL SURGERY / 2

MAJOR DETERMINANT OF SURGICAL OUTCOME

INDIVIDUAL SURGICAL EXPERTISE

A RECORD OF PEER-REVIEWED PUBLICATION OF SURGICAL RESULTS

TRAINING EXPERIENCE: > 100 PITUITARY SURGERY CASES
ANNUAL SURGICAL ACTIVITY > 25 CASES/SURGEON

MEDICAL TREATMENT OF ACROMEGALY

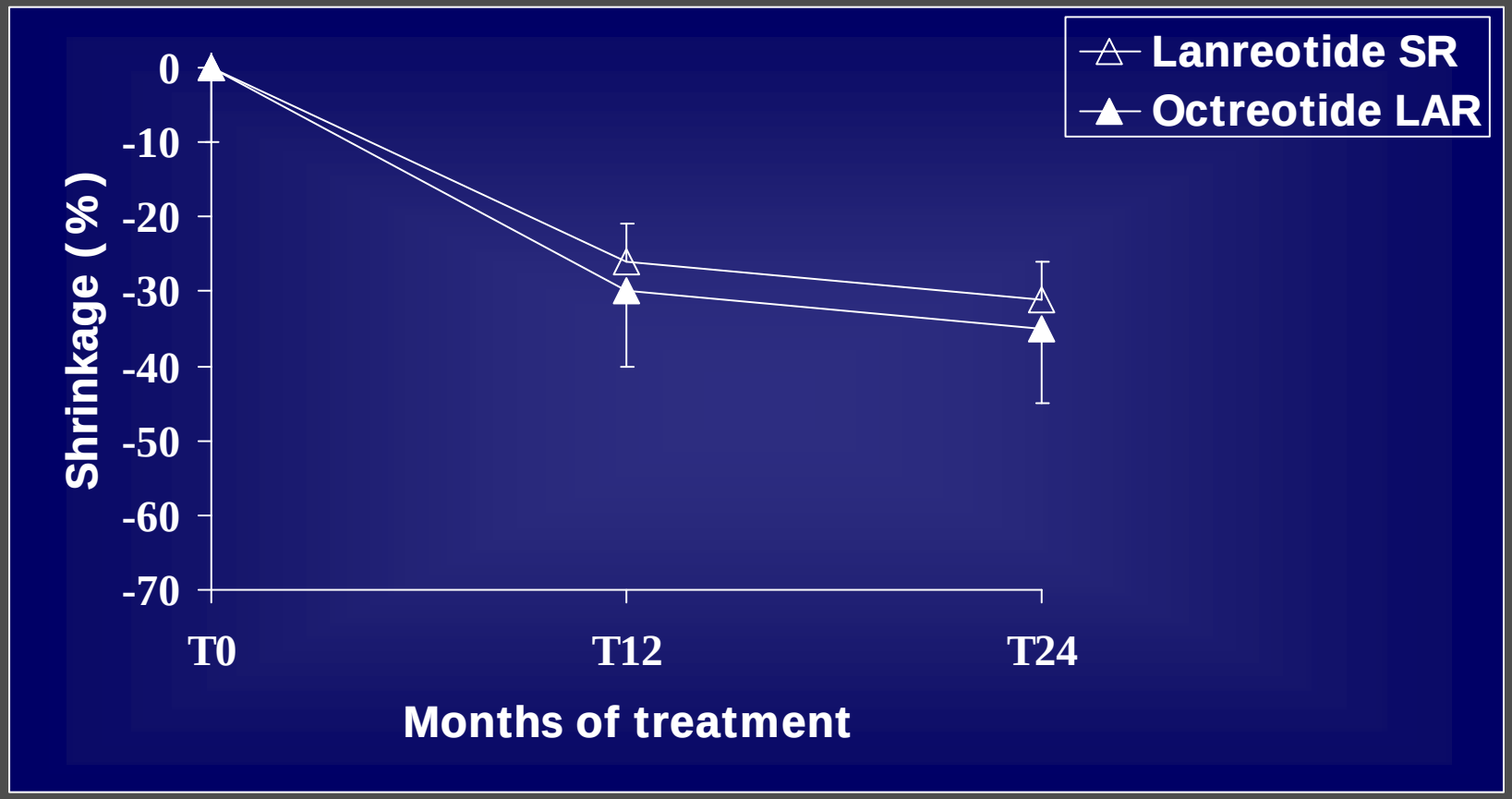
- Somatostatin analogs
  - Lanreotide SR
  - Octreotide LAR
- Dopamine agonist
- GH receptor antagonist

Biochemical data in acromegalic patients undergoing treatment with lanreotide SR and octreotide LAR

	LANREOTIDE	OCTREOTIDE
Macro / microadenomas	6/6	4/4
Basal serum GH levels (mU/l)	60.2±30.6	52.0±31.4
Basal IGF-I levels (ng/ml)	565.7±198.7	567.8±179.0
Patients attaining GH values <5 mU/l at T12	33.3	37.5
Patients attaining GH values <5 mU/l at T24	58.3	50.0
Patients attaining normal IGF-I values at T12	50.0	37.5
Patients attaining normal IGF-I values at T24	66.7	50.0

Amato et al., *Clin Endocrinol* 2002

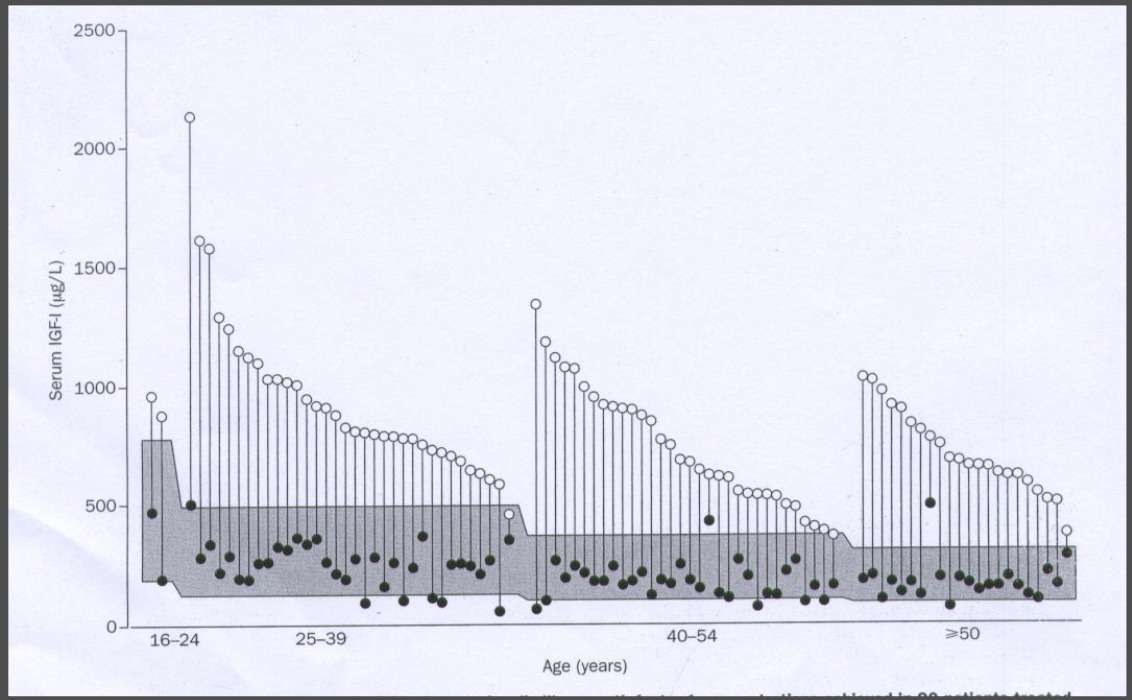
TUMOR SHRINKAGE



Amato et al., *Clin Endocrinol* 2002

GH RECEPTOR ANTAGONIST

Baseline and lowest values of individual serum IGF-1 concentration achieved in 90 patients treated for 12 months

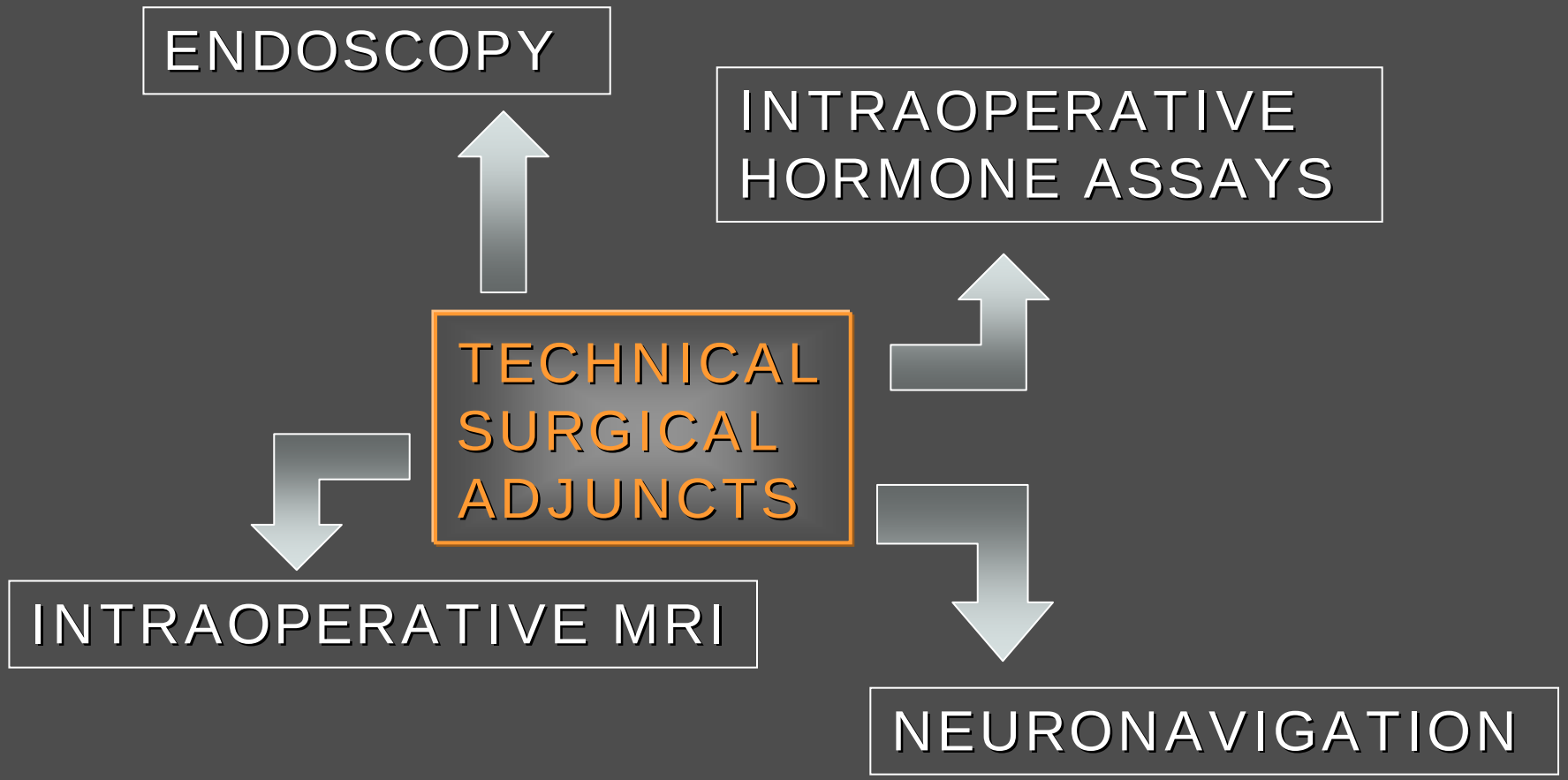


Van der Lely et al. *Lancet* 2001

TREATMENT EVOLUTION AFTER MONTE CARLO

- SURGICAL TREATMENT:
  PROGRESSES AND REASSESSMENT
- PROGRESSES IN MEDICAL TREATMENT

TRANSSPHENOIDAL SURGERY/1



TRANSSPHENOIDAL SURGERY/2

RESULTS

Control > 80% in microadenoma
Control ≤ 50% in macroadenoma

SIDE EFFECTS

Hypopituitarism

Plasma GH and IGF-1 concentration in 53 postoperative acromegalic patients and healthy subjects

Long-Term Biochemical Status and Disease-Related Morbidity in 53 Postoperative Patients with Acromegaly

OMAR SERRI, CATHERINE BEAUREGARD, AND JULES HARDY

Service of Endocrinology (O.S., C.B.) and Service of Neurosurgery (J.H.), Centre Hospitalier de l'Université de Montreal, Notre-Dame Hospital, University of Montreal, Montreal, H2L 4M1 Canada

	Acromegaly		Healthy subjects (n = 20)	P
	Remission (n = 34)	Active (n = 19)		
IGF-I (μg/liter)	163 ± 11	425 ± 38	137 ± 8	<0.001
Basal GH (μg/liter)				
Mean	1.1 ± 0.2	2 ± 0.3	0.9 ± 0.4	NS
Range	0.02–6.3	0.4–4.7	0.2–7.1	
Nadir GH (μg/liter)				
Mean	0.25 ± 0.07	1.2 ± 0.2	0.04 ± 0.00	<0.001
Range	0.02–1.5	0.25–2.9	0.02–0.15	

Serri et al., *J Clin Endocrinol Metab* 2004

Biochemical evaluation of disease activity after pituitary surgery in acromegaly: a critical analysis of patients who spontaneously change disease status

Ana Laura Espinosa-de-los-Monteros*, Ernesto Sosa*, Sonia Cheng*, Raquel Ochoa*, Carolina Sandoval*
Gerardo Guinto†, Victoria Mendoza*, Irma Hernández*, Mario Molina* and Moisés Mercado*

	First evaluation (1–11 months)	Last evaluation (6–108 months)
Active	42 (33·3%)	42 (33·3%)
Cured	51 (40·4%)	52 (41·2%)
Discordant		
↑IGF-1/normal GHn	5 (3·9%)	5 (3·9%)
↑GHn/normal IGF-1	28 (22·2%)	27 (21·4%)
Total	126 (100%)	126 (100%)

Espinosa de los Monteros et al., *Cinical Endocrinol* 2006

MEDICAL TREATMENT EVOLUTION

DO COMBINED MODALITIES OF MEDICAL MANAGEMENT IMPROVE OUTCOME?..

PRINCIPLES DETERMINING MEDICAL TREATMENT

MARKEDLY ELEVATED PRL LEVELS → DOPAMINE AGONIST

AGGRESSIVE TUMOR MASS WITH COMPRESSIVE SYMPTOMS → SRLs

SEVERE HEAD-ACHE → SHORT-ACTING SC. SOMATOSTATIN ANALOG

FAILED SURGERY IN AGGRESSIVE TUMOR → SRLs + PEGVISOMANT

MEDICAL TREATMENT EVOLUTION SIVIGLIA / 2

PRESURGICAL TREATMENT

...Pressure of compressive symptoms, acute visual disturbances or apoplexy with neurologic consequence are clear controindications for delaying a surgical procedure...

PATIENTS WITH RESTRICTIVE COMORBIDITIES OR OTHER DEBILITATING FEATURES
- Congestive heart failure
- Cardiomiopathy
- Severe sleep apnea
- Respiratory or intubation problems

Experienced endocrinologist + anesthesiologist

→ DURATION INDIVIDUALLY DETERMINED
→ INSUFFICIENT EVIDENCE THAT IT IMPROVES PERIOPERATIVE MORBIDITY
→ DATA WITH PRESURGICAL SRLS TREATMENT ARE LIMITED
→ BENEFIT ON WELL CAPSULATED ADENOMA
→ NO CONSENSUS ON PEGVISOMANT
→ “MASK” RESIDUAL DISEASE POSTOPERATIVELY
→ SURGICAL OUTCOME 4 MONTHS AFTER INTERRUPTION OF SRLS

Necessity of a randomized,prospective study: treated vs untreated presurgically patients

PRIMARY MEDICAL TREATMENT / 1

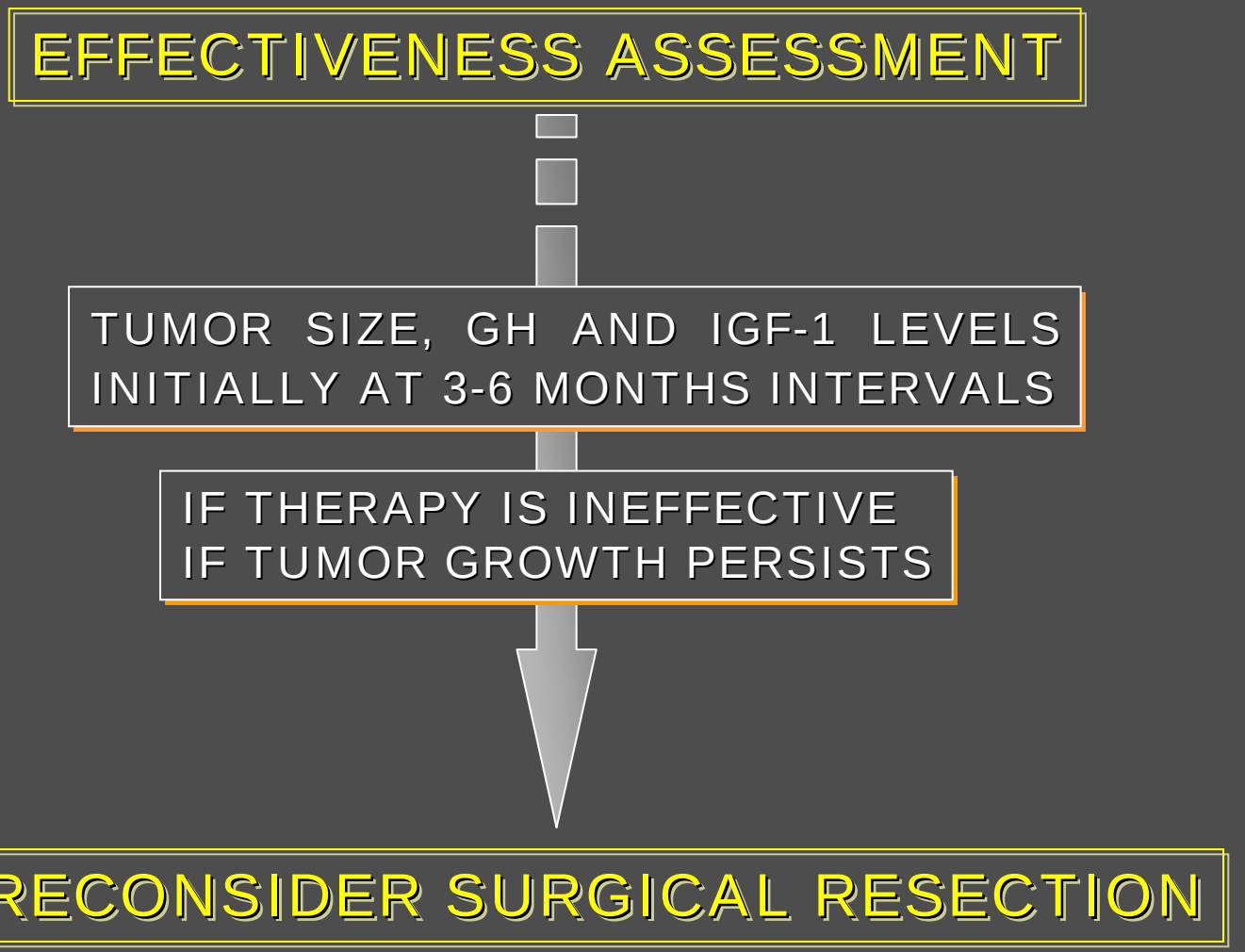
MEDICAL TREATMENT INDICATIONS

- SRLs ARE RECOMMENDED
- DOPAMINE AGONIST FOR PRL-COSECRETING TUMORS

CANDIDATES FOR PRIMARY MEDICAL TREATMENT

- NO RISK OF VISUAL IMPAIRMENT FROM THE TUMOR
- POOR CANDIDATES FOR SURGERY
- TUMORS NOT CONTROLLED BY SURGERY (sinus cavernous)
- PRESERVATION OF INTACT PITUITARY FUNCTION (fertility)

PRIMARY MEDICAL TREATMENT / 2



PATIENT CONCERNS

- → DETERMINATION OF COST/BENEFIT RATIO
- → LONG-TERM OUTCOME OF POOR DISEASE CONTROL AND INCIDENCE OF SUBSEQUENT COMPLICATIONS
- → ASSESSMENT OF QUALITY OF LIFE
- → PATIENT-ORIENTED SUPPORT GROUP
- → POTENTIAL SIDE EFFECTS OF THERAPY

NON GH-LOWERING TREATMENTS

...Comorbidities of acromegaly should be assessed at the time of diagnosis... they may not always improve with treatment of acromegaly...

HYPERTENSION
- Treated according to established guidelines
- ACE inhibitors in diabetes, impaired glucose tolerance, microalbuminuria, cardiac hypertrophy
- Aggressive treatment in cranial irradiation

DIABETES
- Treated in the standard manner
- Carbohydrate tolerance improves with GH control

DYSLIPIDEMIA
- Treated with diet and conventional lipid-lowering drugs

NEW EVIDENCES ON SOMATOSTATIN ANALOGS / 1

Long-Acting Somatostatin Analog Therapy of Acromegaly: A Meta-Analysis

Pamela U. Freda, Laurence Katznelson, Aart Jan van der Lely, Carlos M. Reyes, Shouhao Zhao, and Daniel Rabinowitz

Department of Medicine (P.U.F., C.M.R.), Columbia University, College of Physicians and Surgeons, New York, New York 10032; Departments of Neurosurgery and Medicine (L.K.), Stanford University Medical Center, Stanford, California 94305; Department of Internal Medicine (A.J.v.d.L.), Erasmus Medical Center, The Netherlands; and Department of Statistics (S.Z., D.R.), Columbia University, New York, New York 10027

BIOCHEMICAL EFFICACY OF SOMATOSTATIN ANALOG THERAPY

	% of subjects meeting efficacy criteria		Mean GH levels		Mean IGF-I levels	
	GH	IGF-I normalization	Pretherapy	On therapy	Pretherapy	On therapy
Octreotide LAR						
Unselected (n = 126)	54 ± 0.002[a]	63 ± 0.002[b]	15.8 ± 2.9	4.1 ± 0.8	601 ± 35	330 ± 75
Preselected (n = 486)	58 ± 0.003	68 ± 0.003	10.2 ± 2.3	2.3 ± 1.1	735 ± 48	313 ± 35
All subjects (n = 612)	57 ± 0.05[c]	67 ± 0.05[d]	12.6 ± 3.9	3.2 ± 1.53	644 ± 66	327 ± 30.5
Lanreotide SR						
Unselected (n = 609)	48 ± 0.002	42 ± 0.002	15.1 ± 6.0	5.3 ± 2.4	689 ± 95	432 ± 97
Preselected (n = 305)	50 ± 0.005	56 ± 0.003	19.7 ± 4.0	3.5 ± 0.5	735 ± 48	321 ± 24
All subjects (n = 914)	48 ± 0.04	47 ± 0.03	16.9 ± 3.2	5.9 ± 1.3	741 ± 51	442 ± 30
Octreotide (sc) (primary therapy only)						
All subjects (n = 266) (unselected, n = 252, preselected, n = 14)	53 ± 0.05	54 ± 0.05	40.8 ± 4.3	8.76 ± 1.0	693 ± 66	288 ± 41

Freda et al., *J Clin Endocrinol Metab* 2005

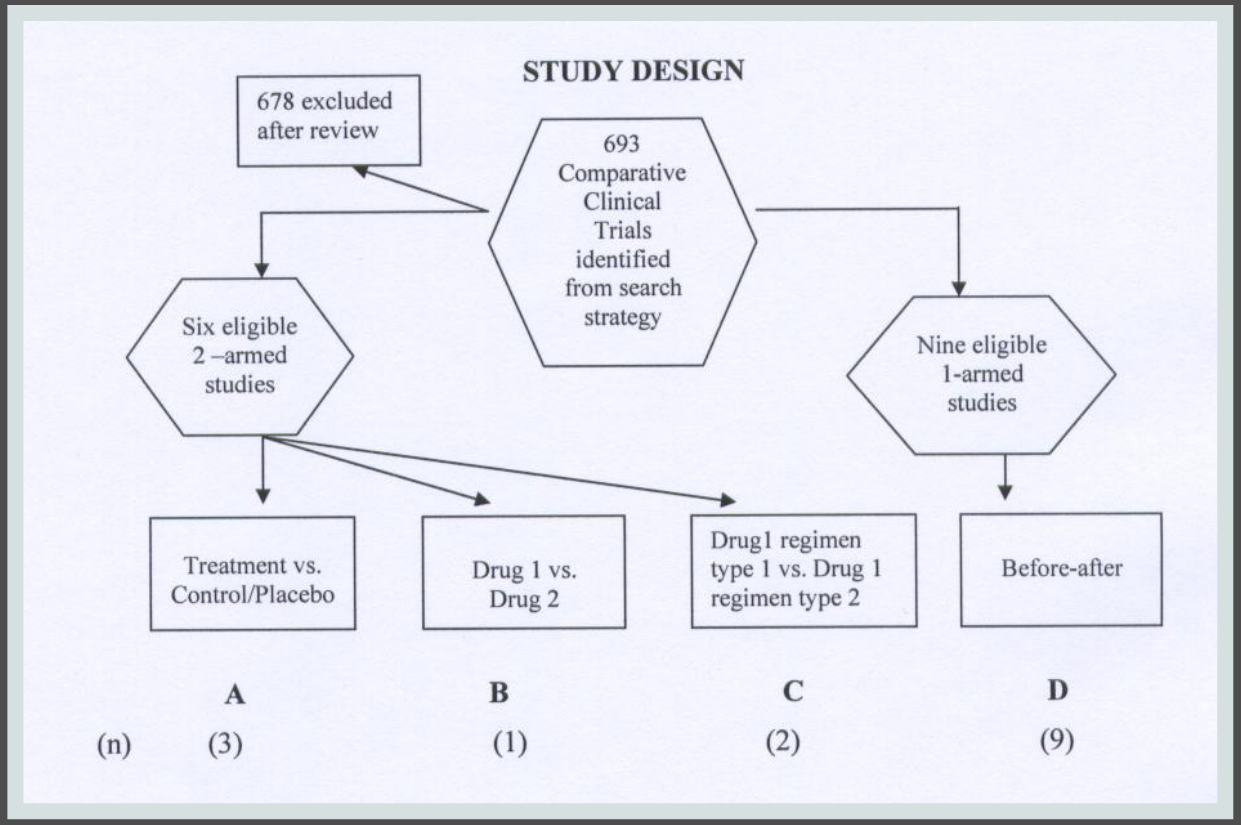
NEW EVIDENCES ON SOMATOSTATIN ANALOGS / 2

SHRINKAGE /1

CLINICAL REVIEW: A Critical Analysis of Pituitary Tumor Shrinkage during Primary Medical Therapy in Acromegaly

Shlomo Melmed, Richard Sternberg, David Cook, Anne Klibanski, Philippe Chanson, Vivien Bonert, Mary Lee Vance, David Rhew, David Kleinberg, and Ariel Barkan

Department of Medicine, Cedars-Sinai Research Institute, David Geffen School of Medicine, University of California (S.M., V.B.), Los Angeles, California 90048; Zynx Health, Inc. (R.S., D.R.), Los Angeles, California 90024; Department of Medicine, Oregon Health & Science University (D.C.), Portland, Oregon 97205; Department of Medicine, Massachusetts General Hospital (A.K.), Boston, Massachusetts 02114; Department of Endocrinology, Hospital Bicetre (P.C.), Paris, France 94275; Department of Medicine, University of Virginia Health Science Center (M.L.V.), Charlottesville, Virginia 22901; Department of Medicine, New York University Medical Center (D.K.), New York, New York 10010; and Department of Medicine, Veterans Administration Medical Center, University of Michigan (A.B.), Ann Arbor, Michigan 48105



Melmed S et al., *J Clin Endocrinol Metab* 2005

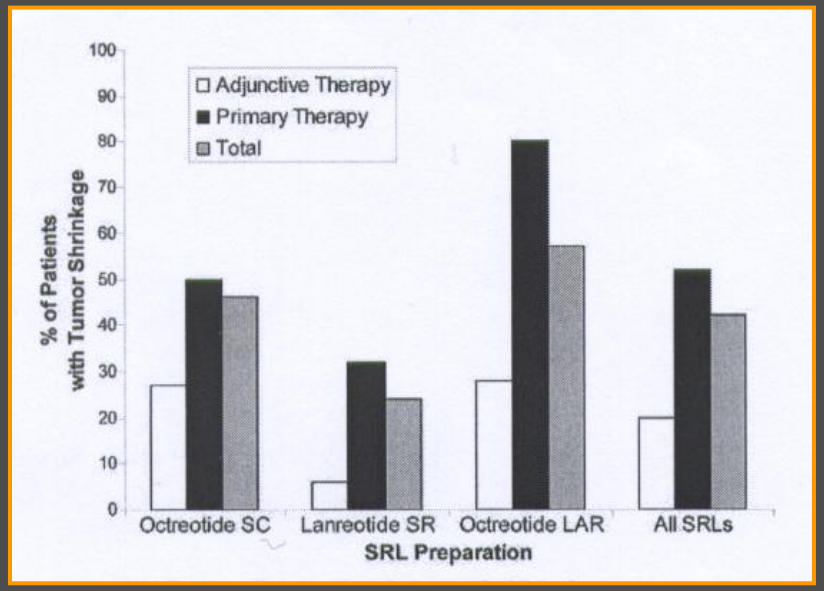
NEW EVIDENCES ON SOMATOSTATIN ANALOGS / 3

SHRINKAGE /2

CLINICAL REVIEW: The Antitumoral Effects of Somatostatin Analog Therapy in Acromegaly

John S. Bevan

Department of Endocrinology, Aberdeen Royal Infirmary, Aberdeen AB25 2ZN, Scotland, United Kingdom



Bevan JS, *J Clin Endocrinol Metab* 2004

CLINICAL REVIEW: A Critical Analysis of Pituitary Tumor Shrinkage during Primary Medical Therapy in Acromegaly

Shlomo Melmed, Richard Sternberg, David Cook, Anne Klibanski, Philippe Chanson, Vivien Bonert, Mary Lee Vance, David Rhew, David Kleinberg, and Ariel Barkan

Department of Medicine, Cedars-Sinai Research Institute, David Geffen School of Medicine, University of California (S.M., V.B.), Los Angeles, California 90048; Zynx Health, Inc. (R.S., D.R.), Los Angeles, California 90024; Department of Medicine, Oregon Health & Science University (D.C.), Portland, Oregon 97205; Department of Medicine, Massachusetts General Hospital (A.K.), Boston, Massachusetts 02114; Department of Endocrinology, Hospital Bicetre (P.C.), Paris, France 94275; Department of Medicine, University of Virginia Health Science Center (M.L.V.), Charlottesville, Virginia 22901; Department of Medicine, New York University Medical Center (D.K.), New York, New York 10010; and Department of Medicine, Veterans Administration Medical Center, University of Michigan (A.B.), Ann Arbor, Michigan 48105

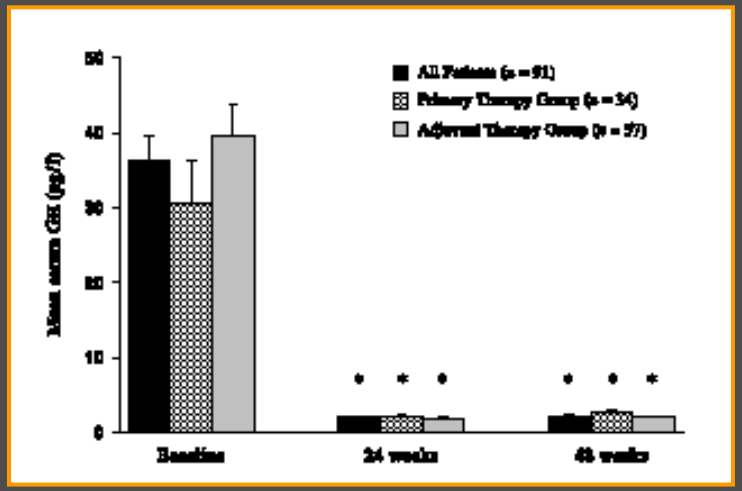
Study	Arm	N=total number of patients enrolled in study	Median or mean shrinkage in volume calculated for all patients enrolled in study.
Lucas et al 2003	Lanreotide 30 mg	104	10%‡
Bevan et al 2002	Phase 1: Octreotide	27	20 MA: 43%‡ 7 mA: 49%‡
Amato et al 2002	Lanreotide 30 mg	10	30%†
Amato et al 2002	Octreotide LAR	10	34.8%†
3 studies		**151**	†mean; ‡median
§Weighted mean % shrinkage in tumor size when calculated for all patients enrolled in a study = 19.4%			

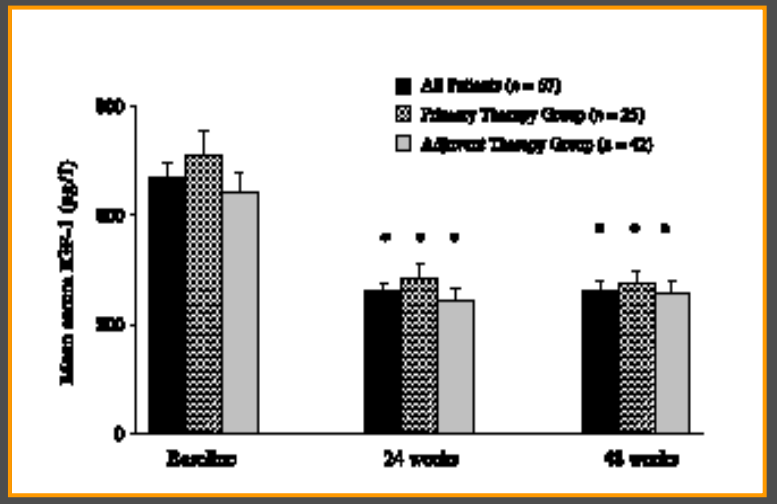
Melmed S et al., *J Clin Endocrinol Metab* 2005

PRIMARY TREATMENT

Efficacy of Sandostatin® LAR® (long-acting somatostatin analogue) is similar in patients with untreated acromegaly and in those previously treated with surgery and/or radiotherapy

John Ayuk, Susan E. Stewart, Paul M. Stewart, Michael C. Sheppard and the European Sandostatin® LAR® Group

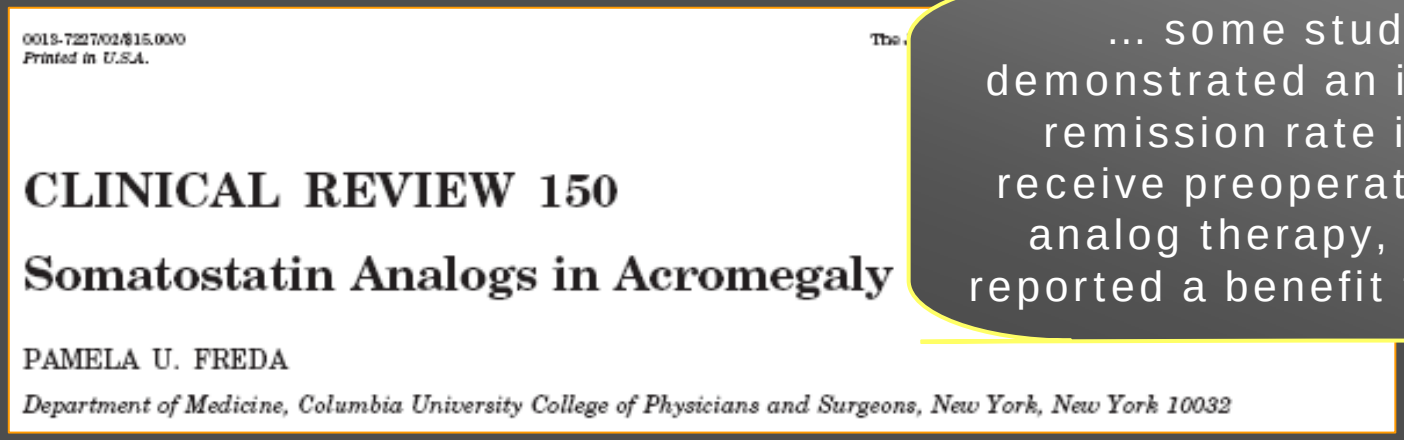




Ayuk et al., *Clin Endocrinol* 2004

NEW EVIDENCES ON SOMATOSTATIN ANALOGS / 5

PRE SURGICAL TREATMENT



0013-7227/02/$15.00/0
Printed in U.S.A.

CLINICAL REVIEW 150

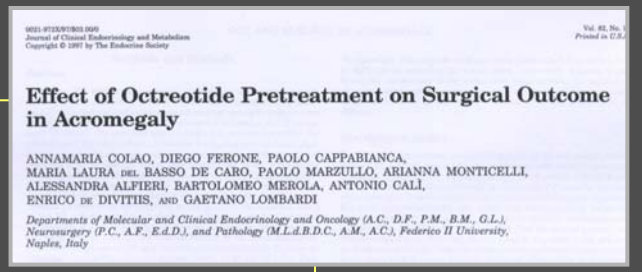
Somatostatin Analogs in Acromegaly

PAMELA U. FREDA

Department of Medicine, Columbia University College of Physicians and Surgeons, New York, New York 10032

... some studies have not demonstrated an improved surgical remission rate in patients who receive preoperative somatostatin analog therapy, but others have reported a benefit to pre-treatment...

Freda PU, JCEM 2002



0021-972X/97/$03.00/0
Journal of Clinical Endocrinology and Metabolism
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Vol. 82, No. 1
Printed in U.S.A.

Effect of Octreotide Pretreatment on Surgical Outcome in Acromegaly

ANNAMARIA COLAO, DIEGO FERONE, PAOLO CAPPABIANCA, MARIA LAURA DEL BASSO DE CARO, PAOLO MARZULLO, ARIANNA MONTICELLI, ALESSANDRA ALFIERI, BARTOLOMEO MEROLA, ANTONIO CALÌ, ENRICO DE DIVITIIS, AND GAETANO LOMBARDI

Departments of Molecular and Clinical Endocrinology and Oncology (A.C., D.F., P.M., B.M., G.L.), Neurosurgery (P.C., A.F., E.d.D.), and Pathology (M.L.d.B.D.C., A.M., A.C.), Federico II University, Naples, Italy

RATIONAL

- ↓ GH SECRETION
- ↓ ACROMEGALY SYMPTOMS
- ↑ PATIENT GENERAL CONDITION BEFORE SURGERY
  - ↓ ANESTHETIC RISK
  - ↓ SURGICAL COMPLICATIONS
  - ↓ HOSPITALIZATION
- TUMOR SHRINKAGE

0021-972X/99/$03.00/0
The Journal of Clinical Endocrinology & Metabolism
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Vol. 84
Printed in

Direct Postoperative and Follow-Up Results of Transsphenoidal Surgery in 19 Acromegalic Patients Pretreated with Octreotide Compared to Those in Untreated Matched Controls

N. R. BIERMASZ, H. VAN DULKEN, AND F. ROELFSEMA

Department of Endocrinology, Leiden University Medical Center, 2333AA Leiden, The Netherlands

NEW EVIDENCES ON SOMATOSTATIN ANALOGS / 6

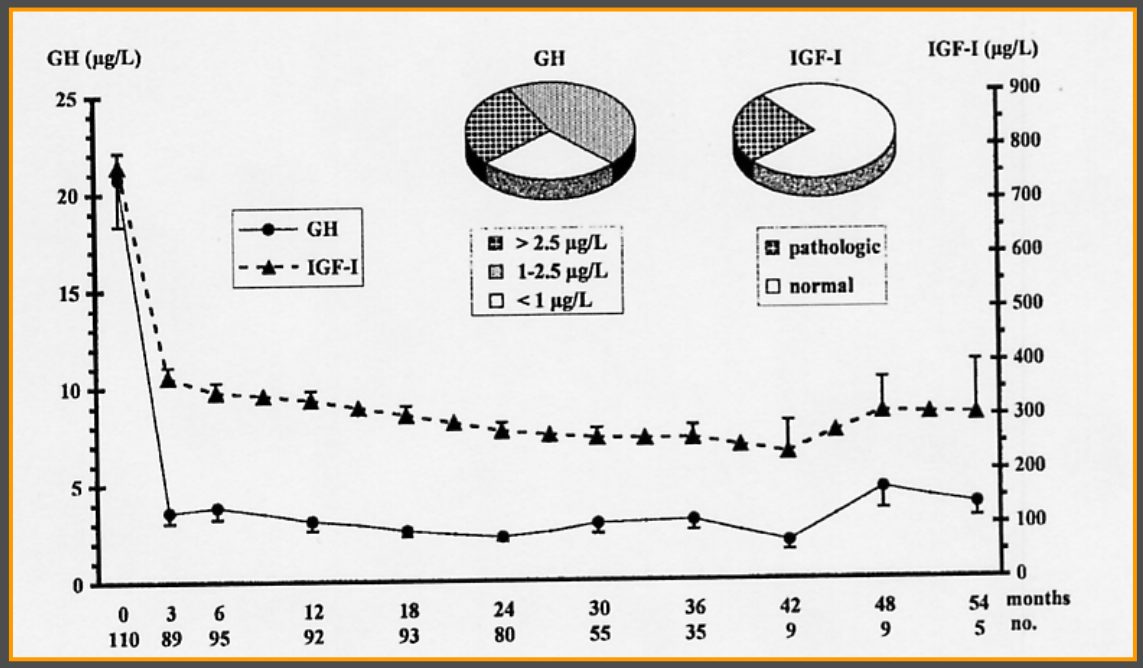
TACHIPHILAXIS

Four-Year Treatment with Octreotide-Long-Acting Repeatable in 110 Acromegalic Patients: Predictive Value of Short-Term Results?

RENATO COZZI, ROBERTO ATTANASIO, MARCELLA MONTINI, GIORGIO PAGANI, GIOVANNI LASIO, SANDRO LODRINI, MICHELA BARAUSSE, MASCIA ALBIZZI, DANIELA DALLABONZANA, AND ALBERTO M. PEDRONCELLI

Division of Endocrinology, Ospedale Niguarda (R.C., R.A., M.B., D.D.), I-20162 Milan, Italy; Endocrine Unit, Ospedali Riuniti (M.M., G.P., M.A., A.M.P.), Bergamo I-24100, Italy; and Department of Neurosurgery, Carlo Besta Institute (G.L., S.L.), Besta I-20133, Milan, Italy

GH AND IGF-1 TREATMENT
4 YEAR TREATMENT

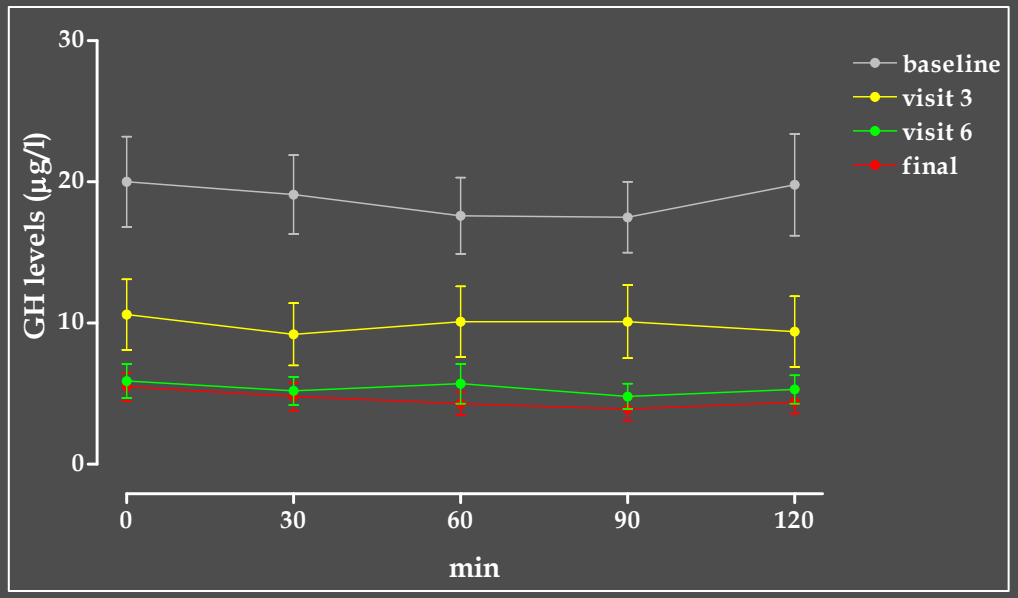


Cozzi et al., *J Clin Endocrinol Metab* 2003

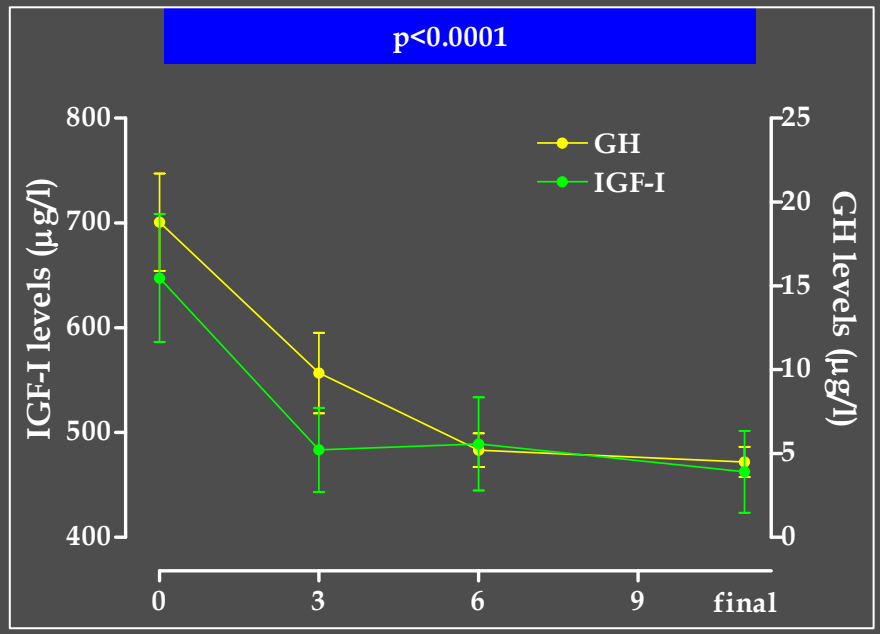
NEW EVIDENCES ON SOMATOSTATIN ANALOGS / 7

Italian Multicenter Study On Lanreotide Autogel

GH LEVELS



IGF-I LEVELS



NEW EVIDENCES ON SOMATOSTATIN ANALOGS / 8

RESISTANCE

DOSES AND TIMING OF TREATMENT

SHORTENING THE INTERVALS BETWEEN OCTREOTIDE LAR 30 MG INTRAMUSCOLAR INJECTIONS FROM 28 TO 21 DAYS MAY IMPROVE GH CONTROL IN PATIENTS WITH ACTIVE ACROMEGALY

S. Bonadonna, F. Manelli, A. Burattin, S. Villa, E. Agabiti Rosei, A. Giustina

JEI 2003

DIFFERENT RECEPTOR SUBTYPES EXPRESSION

Differential Inhibition of Growth Hormone Secretion by Analogs Selective for Somatostatin Receptor Subtypes 2 and 5 in Human Growth-Hormone-Secreting Adenoma Cells in vitro

Giovanni Tulipano[a] Carlo Bonfanti[b] Gabriella Milani[a] Bruno Billeci[d] Angelo Bollati[c] Renato Cozzi[g] Giulio Maira[e] William A. Murphy[h] Claudio Poiesi[b] Sergio Turazzi[f] Andrea Giustina[a]

[a]Endocrine Section, Department of Internal Medicine, [b]Institute of Microbiology, [c]Neurosurgery, University of Brescia; [d]Divisions of Neurosurgery Hospital of Treviso; [e]Policlinico Gemelli, Roma; [f]Ospedale Maggiore, Verona, and [g]Division of Endocrinology, Niguarda Hospital, Milano, Italy, and [h]Peptide Laboratory, Tulane University, New Orleans, La., USA

Neuroendocrinology 2001

MUTATION OF DIFFERENT RECEPTOR SUBTYPES

Mutation of Somatostatin Receptor Type 5 in an Acromegalic Patient Resistant to Somatostatin Analog Treatment

EMILIA BALLARÈ*, LUCA PERSANI*, ANDREA G. LANIA, MARCELLO FILOPANTI, ENZA GIAMMONA, SABRINA CORBETTA, SIMONA MANTOVANI, MAURA AROSIO, PAOLO BECK-PECCOZ, GIOVANNI FAGLIA, AND ANNA SPADA

JCEM 2001

ALTERATION OF POST-RECEPTOR MECHANISM

PHOSPHORILATION OF βARRESTIN RECEPTOR

Differential β-Arrestin Trafficking and Endosomal Sorting of Somatostatin Receptor Subtypes*

Received for publication, December 10, 2003, and in revised form, February 25, 2004
Published, JBC Papers in Press, March 4, 2004, DOI 10.1074/jbc.M313522200

Giovanni Tulipano, Ralf Stumm, Manuela Pfeiffer, Hans-Jürgen Kreienkamp‡, Volker Höllt, and Stefan Schulz§

From the Institut für Pharmakologie und Toxikologie, Otto-von-Guericke-Universität, 39120 Magdeburg, Germany and Institut für Zellbiochemie und klinische Neurobiologie, Universitätskrankenhaus Hamburg-Eppendorf, Universität Hamburg, 20246 Hamburg, Germany

JBC 2004

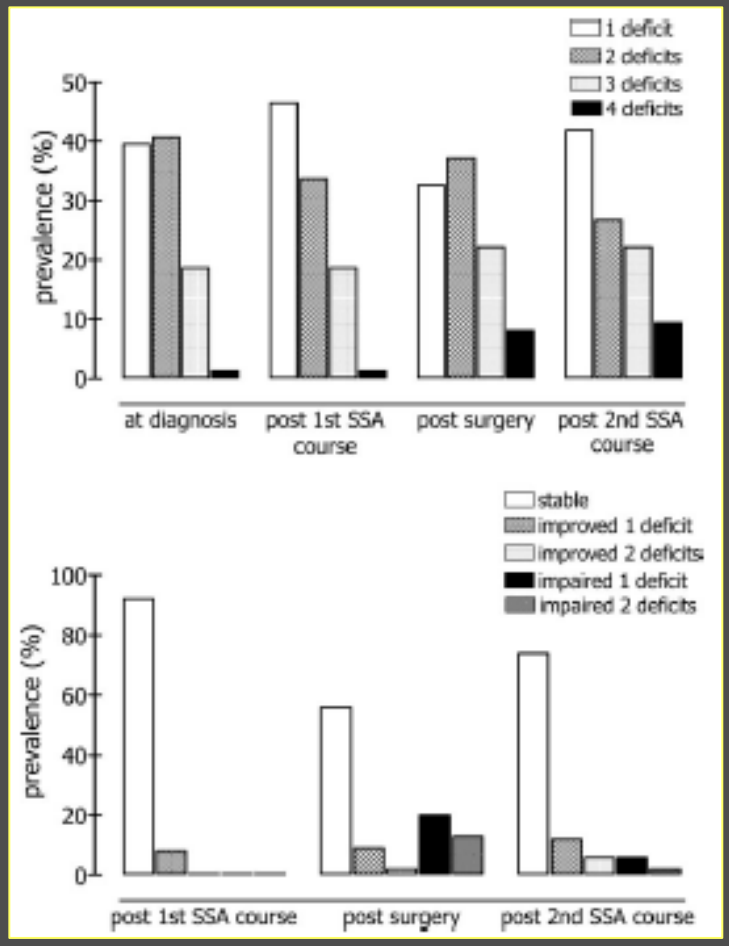
DEBULKING EFFECT

Partial Surgical Removal of Growth Hormone-Secreting Pituitary Tumors Enhances the Response to Somatostatin Analogs in Acromegaly

Annamaria Colao, Roberto Attanasio, Rosario Pivonello, Paolo Cappabianca, Luigi M. Cavallo, Giovanni Lasio, Alessandro Lodrini, Gaetano Lombardi, and Renato Cozzi

Departments of Molecular and Clinical Endocrinology and Oncology and Neurological Sciences, Section of Neurosurgery (P.C., L.M.C.), University Federico II (A.C., R.P., G.L.), 80131 Naples, Italy; Division of Endocrinology, Hospital Niguarda Ca Granda (R.A., R.C.), 20162 Milan, Italy; and Division of Neurosurgery, Neurologic Institute Carlo Besta (G.L., A.L.), 20162 Milan, Italy

Prevalence of pituitary failure during the study



Colao et al., *J Clin Endocrinol Metab* 2006

COMORBIDITIES: ACROMEGALIC CARDIOMIOPATHY

Systemic Complications of Acromegaly: Epidemiology, Pathogenesis, and Management

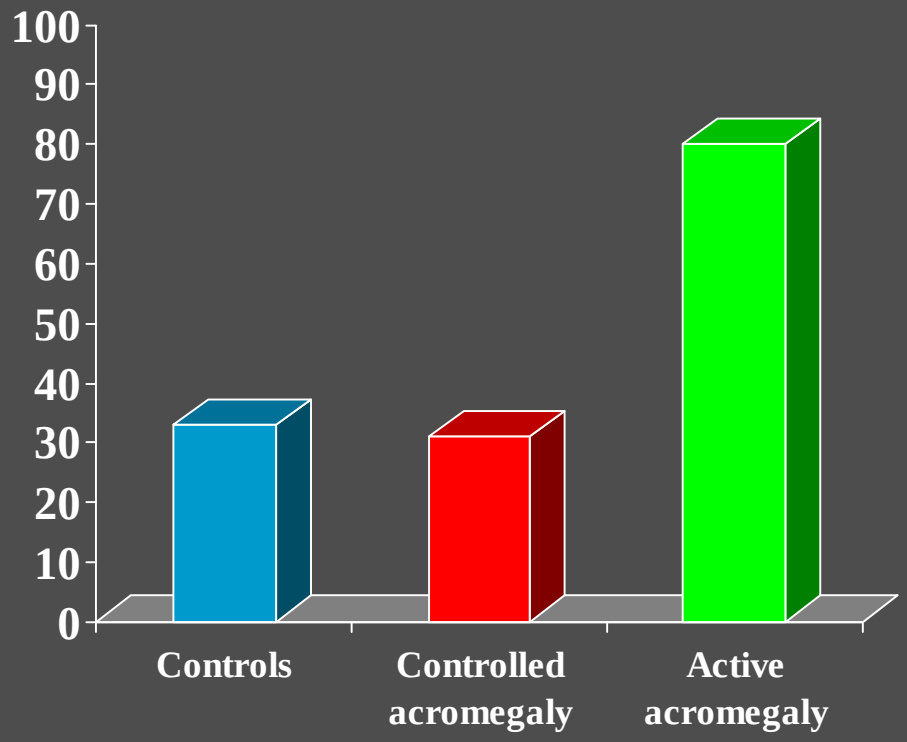
ANNAMARIA COLAO, DIEGO FERONE, PAOLO MARZULLO, AND GAETANO LOMBARDI

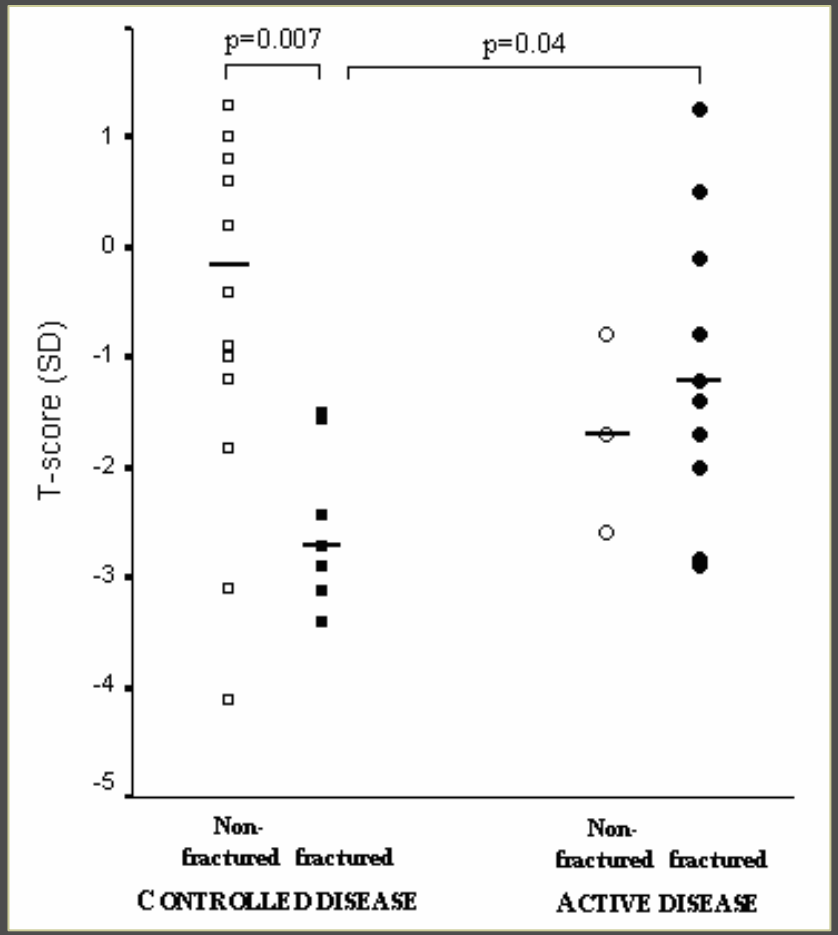
Department of Molecular and Clinical Endocrinology and Oncology (A.C., P.M., G.L.), "Federico II" University of Naples, 80131 Naples, Italy; and Department of Endocrinological and Metabolic Sciences and Center for Excellence for Biological Research (D.F.), University of Genova, 16132 Genova, Italy

Year	Ref.	No. of patients	Treatment	Follow-up	Methods	Results			
						LVH	Diastolic function	Systolic function	Others
1985	185	11	RT	3–17 yr	ECG, ECHO	n.a.	n.a.	n.a.	↑ Cardiovascular events
1989	192	9	OCT	12 months	ECHO	↓	n.a.	↔	↓ HR and BP
1991	193	5	OCT	6 months	ECHO	↓	↑	↔	No change in contractility
1992	188	16	OCT	2 months	ECHO	↓	n.a.	↓	Only in patients with hypertrophy
1993	194	11	OCT	6 months	ECG, ECHO	↓	↑	↔	↔ BP
1994	187	6	OCT	6 months	ECG, ECHO	↓	↑	↔	↑ Treadmill exercise, ↔ BP
1999	196	30	OCT	12 months	ERA	n.a.	↔	↑	↓ HR only in controlled patients
1999	189	13	LAN	12 months	ECHO	↓	↑	↔	↔ BP
1999	195	13	LAN	12 months	ECHO	↓	↑	↔	↔ BP
2000	191	15	OCT-LAR	6 months	ECHO, ERA	↓	↑	↔	Only in controlled patients, ↓ HR
2001	193	30	Surgery	6 months	ECHO	↓	↑	↔	↓ BP only in controlled patients
2001	184	18	Surgery/OCT	5 yr	ERA	n.a.	↔	↑	Only in controlled patients
2002	97	25	OCT-LAR	6 months	ECHO, ERA	↓	↑	↓	↓ HR, when disease duration <5 yr
2002	146	19	LAN	6 months	ECHO	↓	↑	↔	↓ Arrhythmias from 33.3 to 16.5%
2003	199	22	OCT-LAR	12 months	ECHO, ERA	↓	↑	↑	Mostly in young patients

Colao et al., *Endocr Rev* 2004

COMORBIDITIES: OSTEOPOROSIS





Bonadonna et al., *JBMR* 2005

QUALITY OF LIFE

VALIDITY AND CLINICAL APPLICABILITY OF THE ACROMEGALY QUALITY OF LIFE QUESTIONNAIRE, ACROQOL: A 6-MONTH PROSPECTIVE STUDY.

→ Better AcroQoL in treated patients with controlled disease

Webb et al., *Eur J Endocrinol.* 2006

QUALITY OF LIFE IN TREATED PATIENTS WITH ACROMEGALY.

→ ↓HRQoL even in treated acromegalic patients. Positive influence of IGF-1 normalization and GH nadir after OGTT within 0.3 and 1 ng/ml

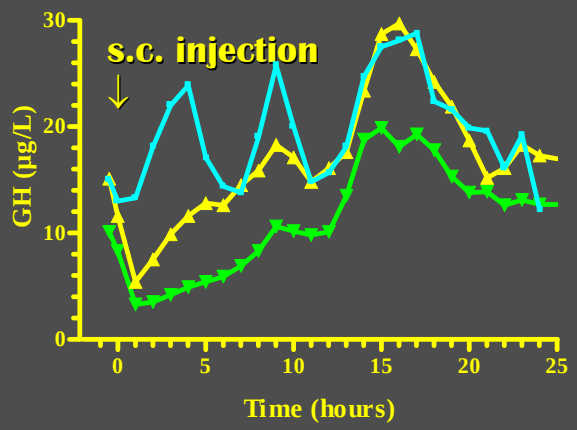
Kauppinen-Makelin R et al., *J Clin Endocrinol Metab* 2006

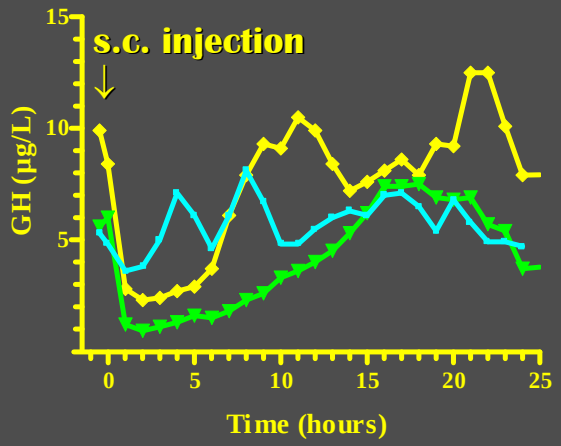
Prediagnosis	Postdiagnosis/presurgery	Postsurgery
Emotional lability	Guilt	Unmet expectation
Anxiety	Social withdrawal	Social withdrawal
Sleep disordered	Body image distortion	Body image distortion
Loss of control over oneself	Anger toward medical inefficiencies	Battle fatigue
Enhanced sociability	Loss of control of one's future in doctor's hand	Anger, depression
Self esteem disintegration	Fear of death	Diminished interest in life
Hypochondria	Relief, Burden, Sleep disordered, Fear of brain damage, Depression, Helplessness,	Word loss

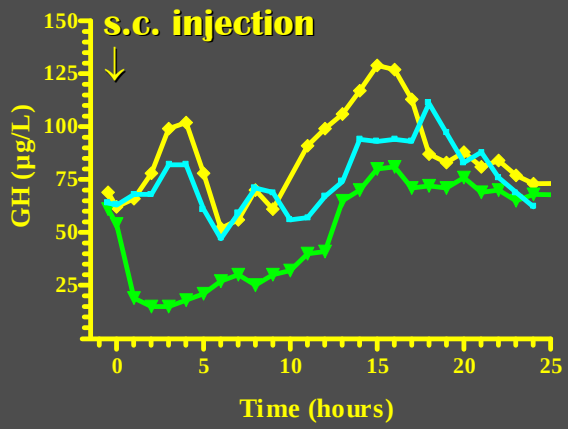
Furman K and Ezzat S, *Psychother Psychosom* 1998

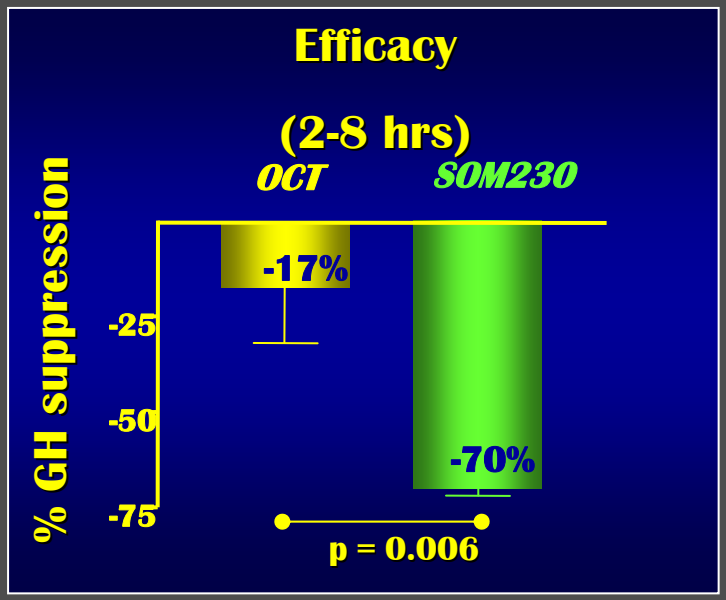
NEW ANALOGUES / 1

24 HOUR GH LEVELS IN 3 PATIENTS FOLLOWING A SINGLE S.C. INJECTION OF 100μG OCT(—) OR 250μG SOM230(—) IN COMPARISON WITH CONTROL DAY(—)



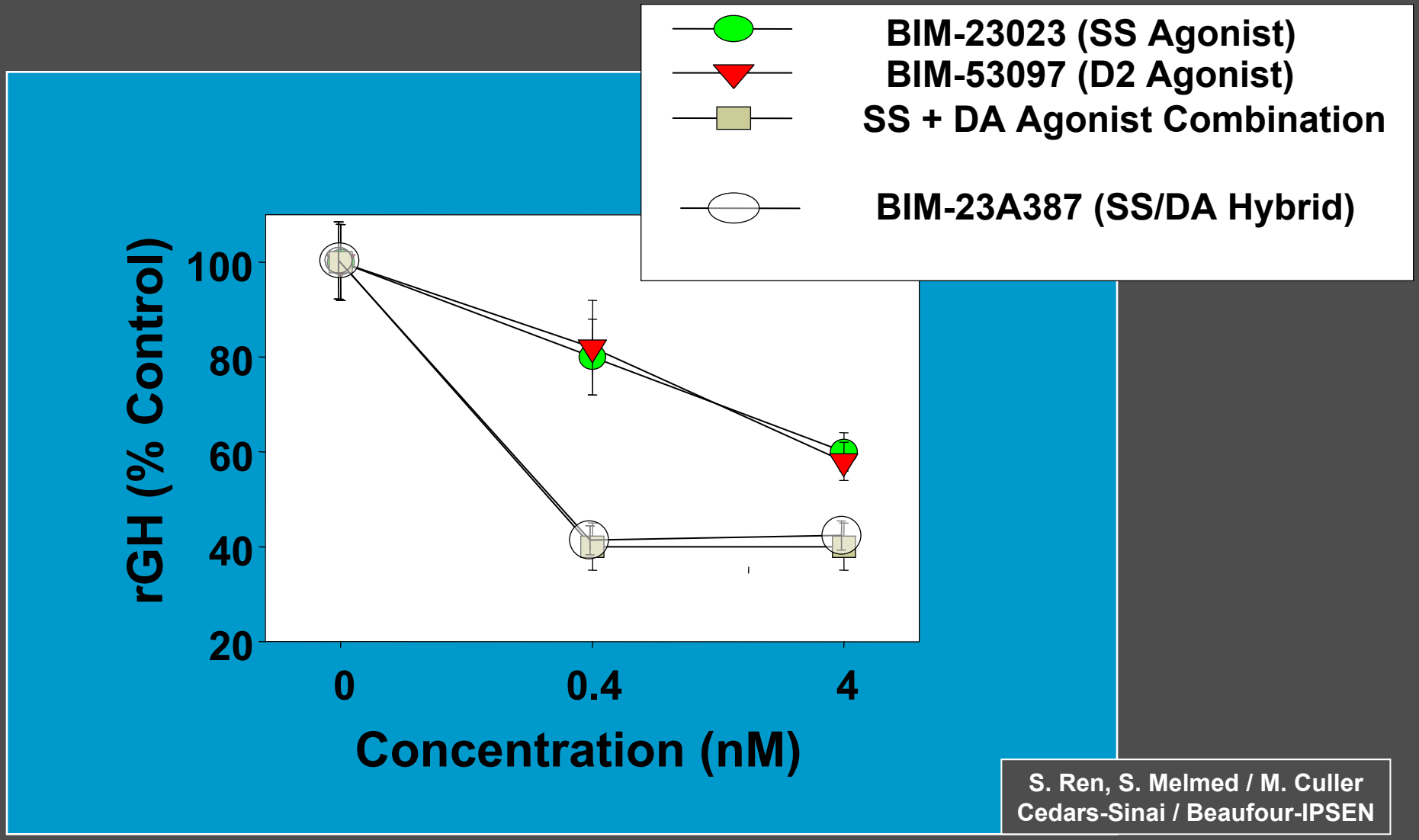






Van der Hoek et al., *J Clin Endocrinol Metab* 2004

Enhanced GH Suppression with SS/DA Hybrid Molecule



S. Ren, S. Melmed / M. Culler
Cedars-Sinai / Beaufour-IPSEN

POST SOMATOSTATIN ANALOGUES

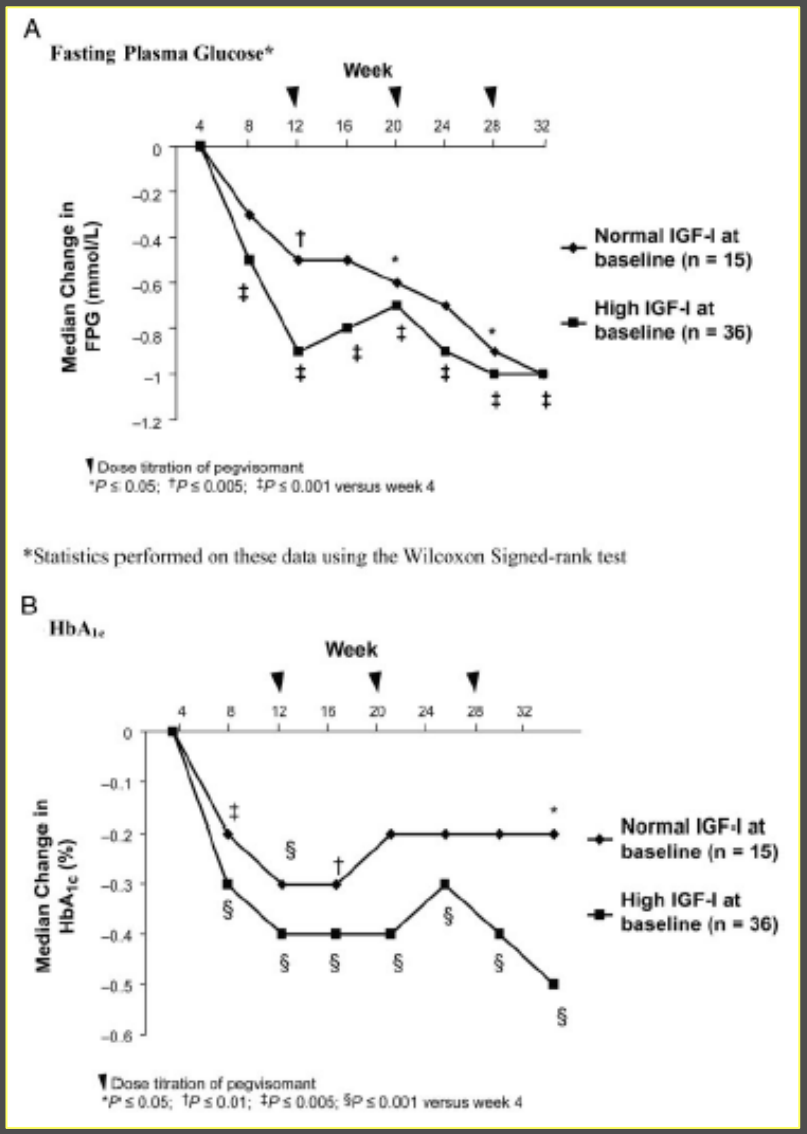
GLUCOSE HOMEOSTASIS

Glucose Homeostasis and Safety in Patients with Acromegaly Converted from Long-Acting Octreotide to Pegvisomant

Ariel L. Barkan, Pia Burman, David R. Clemmons, William M. Drake, Robert F. Gagel, Philip E. Harris, Peter J. Trainer, Aart Jan van der Lely, and Mary Lee Vance

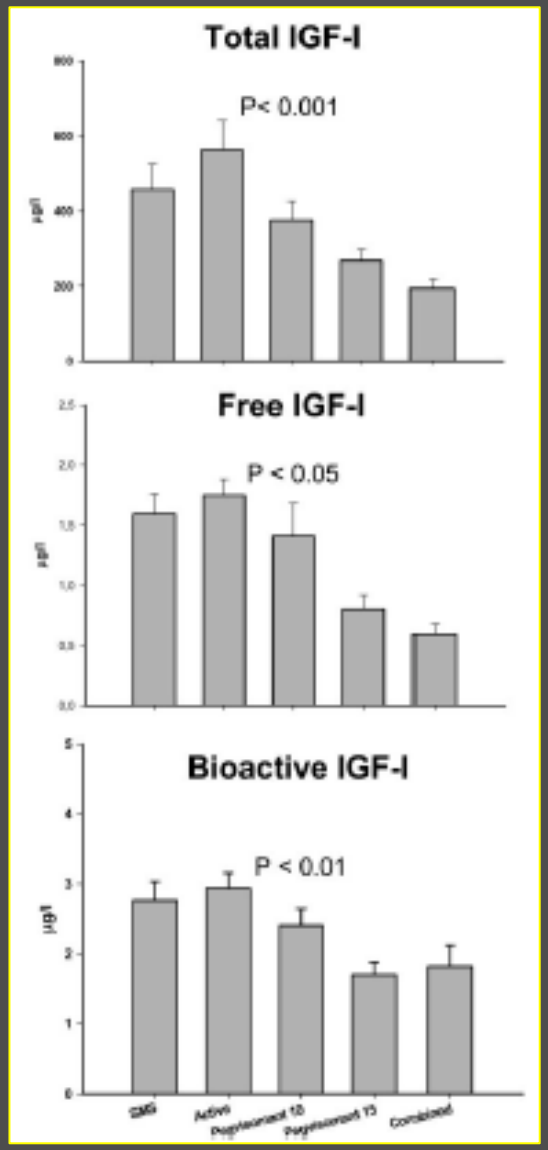
Departments of Internal Medicine and Neurosurgery (A.L.B.), University of Michigan Medical Center, Ann Arbor, Michigan 48109-0354; Pfizer, Inc. (P.B., P.E.H.), New York, New York 10017-5755; Division of Endocrinology/Metabolism, University of North Carolina School of Medicine (D.R.C.), Chapel Hill, North Carolina 27599; Department of Endocrinology, St. Bartholomew's Hospital (W.M.D.), London EC1A 7BE, United Kingdom; Department of Endocrinology (W.M.D., P.J.T.), Christie Hospital, Manchester M20 4BX, United Kingdom; Division of Internal Medicine, University of Texas M. D. Anderson Medical Center (R.F.G.), Houston, Texas 77030; Erasmus Medical Center Rotterdam (A.J. v.d.L.), 3000 CA Rotterdam, The Netherlands; and Department of Internal Medicine, University of Virginia Health Sciences Center (M.L.V.), Charlottesville, Virginia 22908

Median change in fasting plasma glucose (FPG) and HbA1c in patients with normal IGF-1 concentrations (n=15) compared with patients with high IGF-1 concentrations (n=36)



NEW EVIDENCE ON PEGVISOMANT / 2

CO-TREATMENT



Cotreatment of Acromegaly with a Somatostatin Analog and a Growth Hormone Receptor Antagonist

Jens Otto Lunde Jørgensen, Ulla Feldt-Rasmussen, Jan Frystyk, Jian-Wen Chen, Lars Østergård Kristensen, Claus Hagen, and Hans Ørskov

Medical Department M (Endocrinology and Diabetes) (J.O.L.J., J.F., J.-W.C., H.Ø.), Aarhus University Hospital, DK-8000 C Aarhus, Denmark; Department of Endocrinology, Rigshospitalet (U.F.-R.), DK-2200 Copenhagen, Denmark; Department of Medicine and Endocrinology, Herlev Sygehus (L.Ø.K.), DK-2730 Copenhagen, Denmark; and Department of Endocrinology (C.H.), Odense University Hospital, DK-5000 Odense, Denmark

11 patients on SMS therapy:

- 2 month off therapy
- 6 wk treatment with 10 mg-pegvisomant
- 6 wk treatment with 15 mg-pegvisomant
- 3 month treatment with 15 mg-pegvisomant + SMS

Mean serum levels of total (top panel), free (middle panel), and bioactive (bottom panel) IGF-1 at the end of each study period

CURRENT VIEW

PAY ATTENTION TO HORMONAL LEVELS
AND
TREAT COMPLICATIONS WITH SPECIFIC DRUGS
(particularly metabolic and cardiovascular complications)

COMORBIDITIES MAY NOT ALWAYS BE TOTALLY TREATED
BY GH AND IGF-1 CONTROL

CURRENT VIEW

NEUROSURGICAL TREATMENT

..Transsphenoidal surgery is the procedure of choice for the initial management of acromegaly.. anyhow there are some concerns regarding surgery...

→ AVAILABILITY OF EXPERIENCED PITUITARY SURGEON
→ NOT ALWAYS AVAILABLE

→ TUMORS HAVING HIGH LIKELIHOOD OF POSTOPERATIVE CONTROL
ADENOMA (diffusely invasive macro-adenoma)
→ 2/3 OF ADENOMAS ARE MICRO-ADENOMAS

→ NO ANHESTESIOLOGIC RISK
→ FREQUENT CARDIOPULMONARY COMPLICATIONS

CONFIRM ADVANTAGE OF SURGERY...

BUT INDIVIDUALLY DETERMINED

CURRENT VIEW

SOMATOSTATIN ANALOGUES

ADJUVANT TREATMENT
→ IF NEUROSURGICAL FAILURE

PRIMARY TREATMENT
→ IF LOW CHANCES OF NEUROSURGERY EFFECTIVENESS
→ IF PATIENT REFUSES SURGICAL THERAPY

OCTREOTIDE LAR = LANREOTIDE SR (Autogel) (↑ compliance)

CURRENT VIEW

PEGVISOMANT

...has not to be considered only an alternative to analogs, but another step in medical treatment...

SOMATOSTATIN ANALOGUES → SHRINKAGE

\+

PEGVISOMANT → BIOCHEMICAL EFFECTS

...some advantages in cost-effectiveness and cost-benefits in co-treatment: weekly pegvisomant administration with reduced doses of somatostatin analogues...

CURRENT VIEW

PRE-SURGICAL TREATMENT

SHORT SRLs TREATMENT BEFORE SURGERY

Correction/amelioration of systemic comorbidities: decrease anesthesiological risk

Not shown to improve long-term surgical cure rates and perioperative outcomes

ACROMEGALY TREATMENT

OPEN ISSUES

→ Medical treatment effects on mortality

→ Primary medical therapy role and modality

→ Differential effects of various treatments on adenomas vs complicances

→ Role of new treatments

→ Specific/intensive treatment of co-morbidities

CONCLUSIONS / 1

TREATMENT

→ THE NECESSITY OF A STRICT DISEASE CONTROL JUSTIFIES MULTI-MODAL THERAPIES, BOTH "GH-LOWERING" AND "NOT GH-LOWERING".

→ NEW MEDICAL THERAPIES WILL PROBABLY ALLOW TO INCREASE COMPLIANCE AND EFFECTIVENESS OF TREATMENT (RESISTANT PATIENTS).

→ THERAPEUTICAL PHYLOSOPHY OF ACROMEGALY HAS CHANGED OVER THE YEARS FROM "DISEASE ORIENTED" TO "PATIENT ORIENTED".
FUTURE CHALLENGE IS TO OBTAIN EVIDENCE BASED CRITERIA TO PROPOSE TO EACH SINGLE PATIENT THE TREATMENT OR THE TREATMENT COMBINATION WHICH MOST LIKELY GUARANTEE TO REACH THE CLINICAL TARGET.

CONCLUSIONS / 2