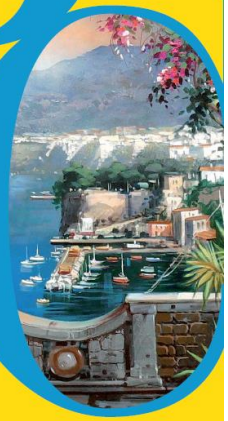
INFORMAZIONI GENERALI

Luogo e data:
Sorrento (NA) 27-30 maggio 2014
Hilton Sorrento Palace - Sala Capri
Via S. Antonio 13 – Sorrento

Altogether to Beat Cushing's Syndrome

AB



Iacopo Chiodini
Fondazione Cà Granda - Ospedale Maggiore Policlinico di Milano
Dip. Scienze Cliniche e di Comunità, Università degli Studi di Milano

2. LA SINDROME DI CUSHING IN FORME PECULIARI

14.30-15.30 **SESSIONE 3: IL CUSHING CICLICO**
Moderatori: **Emanuela Arvat, Franco Grimaldi**

14.30-14.45 L'ENIGMA DELL'EZIOPATOGENESI
Claudio Urbani

14.45-15.00 LA SFIDA DELLA DIAGNOSI
Giuseppe Reimondo

15.00-15.15 L'IPOTESI DELLA TERAPIA E DEL FOLLOW-UP
Paolo Marzullo

15.15-15.30 Discussione

15.30 -16.00 Pausa Caffè

16.00-17.00 **SESSIONE 4: IL CUSHING IATROGENO**
Moderatori: **Alfredo Scillitani, Massimo Terzolo**

16.00-16.15 LE CONDIZIONI CLINICHE E I FARMACI CORTICOSTEROIDEI
Roberto Baldelli

16.15-16.30 LA TERAPIA CON GLUCOCORTICOIDI: L'EQUILIBRIO "SOPRA LA FOLLIA"
Iacopo Chiodini

16.30-16.45 L'APPROCCIO TERAPEUTICO ED IL FOLLOW-UP
Alberto Ambrogio

16.45-17.00 Discussione

17.00-18.00 **SESSIONE 4: IL CUSHING DOPO LA GUARIGIONE**
Moderatori: **Dario Giugliano, Andrea Isidori**

17.00-17.15 LA DEFINIZIONE DI GUARIGIONE
Monica De Leo

17.15-17.30 IL DANNO RESIDUO FISICO
Giovanni Vitale

17.30-17.45 IL DANNO RESIDUO PSICHICO ED ESTETICO
Laura Trementino

17.45-18.00 Discussione

TERAPIA CON GC

van Staa TP et al. QJM 2000

- Maggior parte soggetti assume GC per brevi periodi o in maniera intermittente;
- Il 22% dei soggetti assume GC per periodi ≥ 6 mesi;
- I soggetti più anziani assumono GC per periodi più lunghi rispetto ai giovani:
  - 2.5% dei soggetti ≤ 30 anni assume GC per ≥ 2 anni
  - 20% dei soggetti ≥ 70 anni assume GC per ≥ 2 anni
- 7.3% dei soggetti assume GC per un periodo ≥10 anni;
- 2.6% dei soggetti assume GC per un periodo ≥20 anni;
- La dose media di GC è di 8 mg di prednisone/die o equivalenti

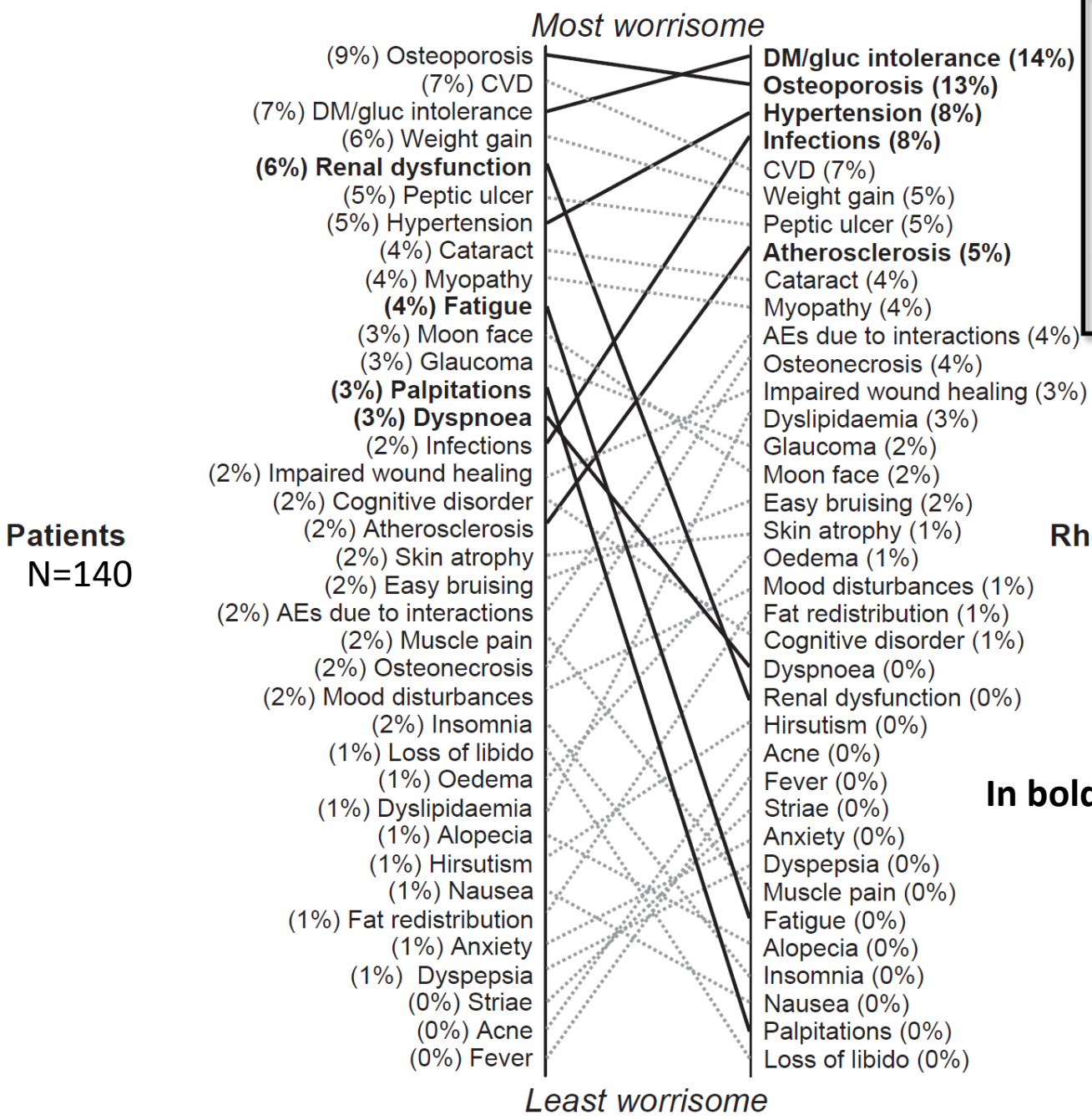
Forse… «andare al massimo non è sempre andare a gonfie vele»

EULAR EVIDENCE-BASED AND CONSENSUS-BASED RECOMMENDATIONS ON THE MANAGEMENT OF MEDIUM TO HIGH DOSE (> 7.5 PREDNISONE EQ) GLUCOCORTICOID THERAPY IN RHEUMATIC DISEASES

Education and prevention	
1	Explain to patients (and their family and/or carers, including healthcare professionals) the aim of medium/high-dose GC treatment, and the potential risks associated with such therapy
2	Discuss measures to mitigate such risks, including diet, regular exercise and appropriate wound care
3	Patients with, or at risk of, GC-induced osteoporosis should receive appropriate preventive/therapeutic interventions
4	Patients and the patients' treatment teams should receive appropriate, practical advice on how to manage with GC-induced hypothalamic-pituitary-adrenal axis suppression
5	Provide an accessible resource to promote best practice in the management of patients using medium/high-dose GCs to general practitioners
Dosing/risk-benefit	
6	Before starting medium/high-dose GC treatment consider comorbidities predisposing to AEs. These include diabetes, glucose intolerance, cardiovascular disease, peptic ulcer disease, recurrent infections, immunosuppression, (risk factors of) glaucoma and osteoporosis. Patients with these comorbidities require tight control to manage the risk/benefit ratio
7	Select the appropriate starting dose to achieve therapeutic response, taking into account the risk of undertreatment
8	Keep the requirement for continuing GC treatment under constant review, and titrate the dose against therapeutic response, risk of undertreatment and development of AEs
9	If long-term medium/high-dose GC therapy is anticipated to be necessary, actively consider GC-sparing therapy
Monitoring	
10	All patients should have appropriate monitoring for clinically significant AEs. The treating physician should be aware of the possible occurrence of diabetes, hypertension, weight gain, infections, osteoporotic fractures, osteonecrosis, myopathy, eye problems, skin problems and neuropsychological AEs

Duru N et al, Ann Rheum Dis 2013; 72:1905-1913

HOW TO IMPROVE THE PATIENTS AWARNESS OF ADVERSE EVENTS OF GLUCOCORTICOID THERAPY IN RHEUMATIC DISEASES



Patients
N=140

Rheumatologists
N=110

In bold: discordant scores

Van dr Goes MC et al, Ann Rheum Dis 2010

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Duru N et al, Ann Rheum Dis 2013; 72:1905-1913

LIFESTYLE EVIDENCES

- **PHYSICAL EXERCISE**
  (Grossman JM et al, Arthritis Care Res 2010)
- **SMOKE**
  (Kanis JA et al, Osteoporos Int 2005)
- **ALCOHOL INTAKE**
  (Kanis JA et al, Osteoporos Int 2005)
- **DIETARY CALCIUM INTAKE**
  (Tang BM et al, Lancet 2007)
- **WOUND CARE**
  (Dixon WG et al, Ann Rheum Dis 2011)

Non è definibile una….
«vita spericolata, una vita come Steve McQueen»

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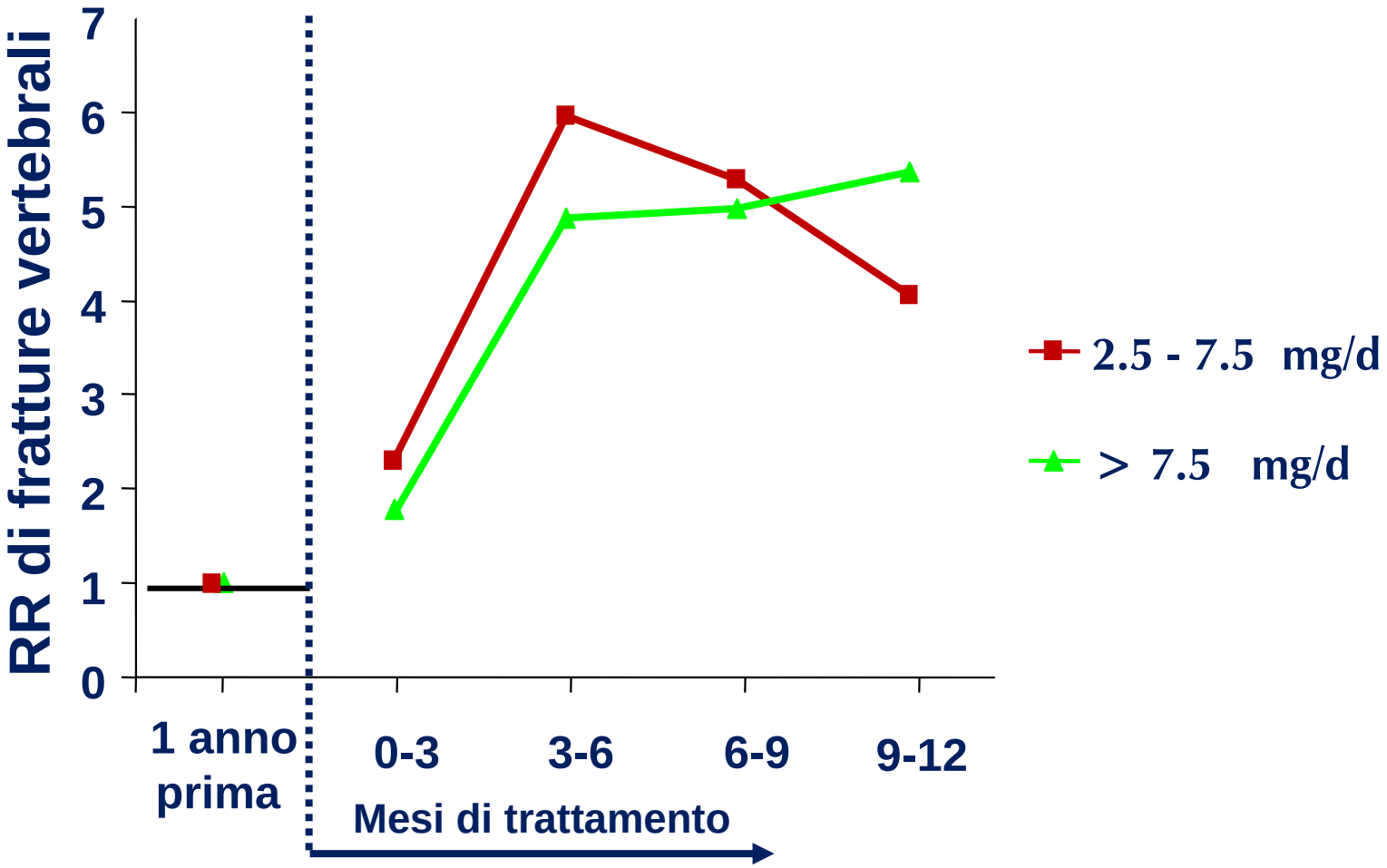
Duru N et al, Ann Rheum Dis 2013; 72:1905-1913

RAPIDO AUMENTO DEL RISCHIO FRATTURATIVO NELLA GIO



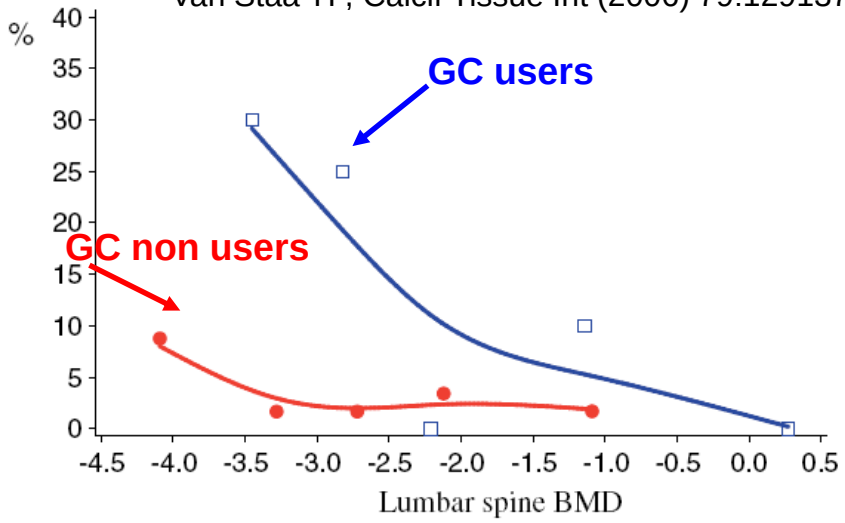
van Staa et al, Osteoporosis Int 2002

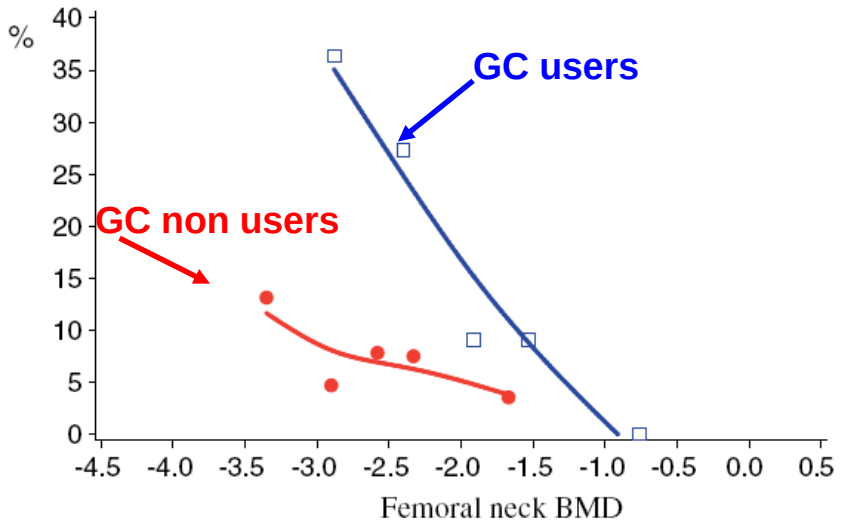
INCIDENZA DI FX VERTEBRALI IN SOGGETTI CHE ASSUMONO O NON ASSUMONO GC IN CRONICO PER OS

- **Rispetto alla osteoporosi involutiva vi è ridotta qualità dell'osso**
  Dalle Carbonare et al, J Bone Miner Res 2001

- **Il rischio di frattura è solo parzialmente spiegato dalla riduzione della densità minerale**
  Selby et al, J Bone Miner Res 2000; Kanis, J Bone Miner Res 2004

Van Staa TP, Calcif Tissue Int (2006) 79:129137





SIOMMMS

SOCIETÀ ITALIANA DELL'OSTEOPOROSI, DEL METABOLISMO MINERALE E DELLE MALATTIE DELLO SCHELETRO

Linee Guida per la Diagnosi, Prevenzione e Terapia dell'Osteoporosi

TABELLE SINOTTICHE: OSTEOPOROSI CORTISONICA

Livelli di evidenza

Intervento farmacologico	Obiettivo terapeutico			
	BMD	Fx -vert	Fx- non vert	Fx- Femorali
alendronato	1	1[a]		
risedronato	1	1[ab]		
clodronato	1[c]	2[c]		
teriparatide	1	1		
zoledronato	1[d]			

a= non "primary end-point" ; b= Emerge solo da meta-analisi di 2 trials

Livelli di evidenza

1 Disamina generale sistematica o meta-analisi di studi controllati randomizzati

2 Studio controllato randomizzato che non risponde ai criteri del Livello 1

3 Studio clinico non randomizzato o studio di coorte

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Duru N et al, Ann Rheum Dis 2013; 72:1905-1913

DO PATIENTS ON GCs REQUIRE PREOPERATIVE STRESS DOSES ?

Although hypothalamic–pituitary–adrenal axis suppression may vary greatly from person to person, it should be anticipated in any patient receiving more than 7.5 mg of prednisolone equivalent daily for more than 3 weeks

(Cooper MS AND Stewart PM. N Engl J Med 2003)

Duru N et al, Ann Rheum Dis 2013; 72:1905-1913

PATIENTS ON GCs DO NOT REQUIRE PREOPERATIVE STRESS DOSES IN THEY CONTINUE THEIR DAILY DOSE BETWEEN 5 AND 16 MG PREDNISONE

Table. Studies Investigating the Use of Perioperative Corticosteroids

Source	No. of Patients	Design	Patient Description	Previous Corticosteroid Treatment[a]	Surgical Procedure	Corticosteroid Treatment	Abnormal Corticotropin Level, No. (%)	Hemodynamic Profile
Jasani et al,[10] 1968	21/20[b]	P CC	RA	7 mg/3 y	Synovectomy	Stopped 18 h before surgery; restarted 6 h after surgery	9 (43)	1 Hypotensive collapse[c]
K								
S								
B								
B								
Fr								
M								
G								
				(placebo)		25 mg		
Thomason et al,[18] 1999	20/40[f]	RCT double-blind crossover	Organ transplant	8 mg/3 y	Gingival, local anesthesia	Usual daily dose placebo or hydrocortisone 100 mg	ND	No difference between groups

Conclusions:

- **Patients receiving therapeutic doses of corticosteroids do not routinely require stress doses of corticosteroids so long as they continue to receive their usual daily dose of corticosteroid.**
- **Adrenal function testing is not required in these patients because the test is overly sensitive and does not predict which patient will develop an adrenal crisis.**
- **Patients receiving physiologic replacement doses of corticosteroids require supplemental doses of corticosteroids in the perioperative period.**

Marik PE and Varon J, Arch Surg 2008

European Journal of Endocrinology (2010) **162** 91–99 ISSN 0804-4643

CLINICAL STUDY

Post-surgical hypocortisolism after removal of an adrenal incidentaloma: is it predictable by an accurate endocrinological work-up before surgery?

Cristina Eller-Vainicher[1], Valentina Morelli[1], Antonio Stefano Salcuni[1], Massimo Torlontano[2], Francesca Coletti[3], Laura Iorio[4], Antonello Cuttitta[5], Angelo Ambrosio[5], Leonardo Vicentini[6], Vincenzo Carnevale[7], Paolo Beck-Peccoz[1], Maura Arosio[1,3], Bruno Ambrosi[4], Alfredo Scillitani[2] and Iacopo Chiodini[1]

60 PATIENTS WITH ADRENAL INCIDENTALOMAS OPERATED ON FOR THE SIZE OF THE ADENOMA AND/OR FORE THE PRESENCE OF SUBCLINICAL HYPERCORTISOLISM

Indeed, we demonstrated that any patient with elevated UFC and MSC levels has a 100% probability to develop post-surgical adrenal insufficiency. Conversely, no parameters or combination of parameters have enough diagnostic accuracy to reliably exclude the possibility of post-surgical hypocortisolism, which can occur in up to the 50.0% of patients with no or only one altered parameter of HPA axis secretion.

EULAR evidence-based and consensus-based recommendations on the management of medium to high-dose glucocorticoid therapy in rheumatic diseases

Duru N et al, Ann Rheum Dis 2013; 72:1905-1913

«..... to be cautious, adequate GC replacement is recommended by the task force in acute situations for patients on chronic medium/high-dose GC treatment; GC therapy should not be stopped without tapering. Evidence supporting superiority of a specific replacement or stress scheme is not available. Pragmatically, one could choose to increase the dosage for 3 days, or, depending on the clinical situation, switch to intravenous hydrocortisone (eg, starting two times 25 mg daily for patients on 10 mg prednisone daily, or three times 50 mg daily for patients on high-dose GC therapy) .....»

«liberi, liberi, siamo noi, però liberi da che cosa…»

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Duru N et al, Ann Rheum Dis 2013; 72:1905-1913

SCREENING OF COMORBIDITIES

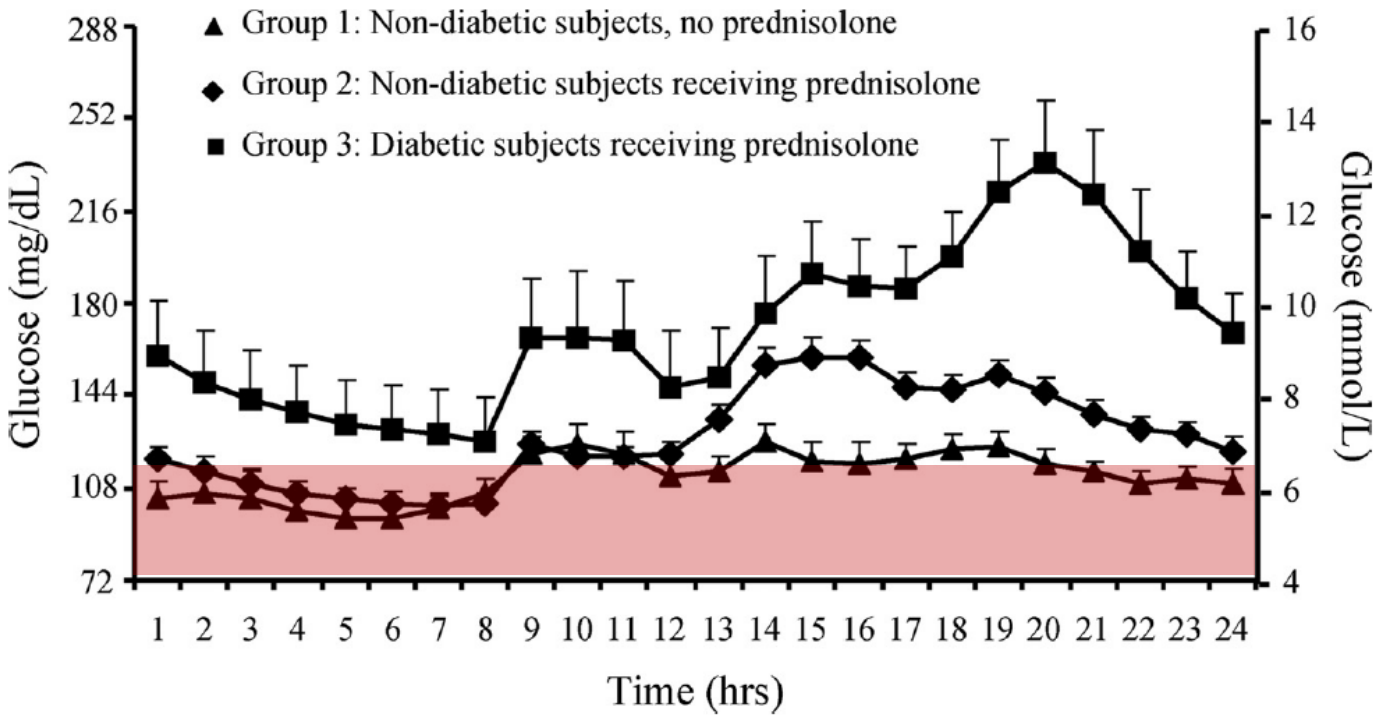
When it is decided to start glucocorticoid treatment, comorbidities and risk factors for adverse effects should be evaluated and treated where indicated.

- **Hypertension**
- **Diabetes**
- **Peptic ulcer**
- **Recent fractures**
- **Presence of cataract or glaucoma**
- **Presence of (chronic) infections**
- **Dyslipidemia**
- **Comedication with non-steroidal anti-inflammatory drugs**

Even though the above-mentioned risk factors for GC associated AEs are well known, and there is obvious face validity trying to prevent these from occurring by assessing and treating comorbidities and risk factors at baseline, there is no evidence to show that this is effective (category IV).

Hoes JN et al AnnRheum Dis 2007

HALF OF PATIENTS WITHOUT KNOWN DIABETES, TREATED WITH 20 MG PREDNISOLONE A DAY, DEVELOP HYPERGLICEMIA WITHIN 24 HOURS



Glucose ≥ 200 within 24 hours:

Group 1: 1/13 (8%)

Group 2: 21/40 (53%),

Group 3. 7/7 (100%)

Burt MG et al, J Clin Endocrinol Metab 2011

PATTERNS OF AES RATES (%) BY DOSE OF GLUCOCORTICOID INTAKE

	No glucocorticoids in past 12 months	Patients with glucocorticoid intake for >6 months		
		<5 mg/day	5–7.5 mg/day	>7.5 mg/day
Patient characteristics				
No of cases	307	101	281	90
Female	79%	82%	77%	72%
Age, in years (mean)	58.4	60.9	60.4	61.5
Disease duration, in years (mean)	10.8	9.7	13.2	10.7
Severe disease, physician rating	6%	11%	23%	39%
In women	5%	13%	24%	39%
In men	8%	0%	19%	40%
Patterns of adverse event rates (%) by dose of glucocorticoids				
"Linear" rising				
Cushingoid phenotype*	2.7	4.3	15.8	24.6
Ecchymosis*	6.8	17.4	23.5	24.6
Leg oedema*	9.5	11.6	20.2	26.2
Mycosis	4.5	5.8	6.6	8.2
Parchment-like skin*	3.2	10.1	15.8	21.3
Shortness of breath	9.5	10.1	12.6	16.4
Sleep disturbance*	20.7	33.3	37.2	44.3
Threshold at				
<5 mg/day				
Eye cataract	2.7	10.1	7.7	8.2
5–7.5 mg/day				
Epistaxis*	1.4	1.4	6.6	4.9
Weight gain*	9.5	8.7	22.4	21.3
>7.5 mg/day				
Depression, listlessness	12.6	10.1	13.7	19.7
Glaucoma	2.7	2.9	2.7	6.6
Increase in blood pressure	18.9	18.8	16.4	23.0

Allora: se non posso avere una «… vita spericolata..», almeno vorrei evitare una vita piena di guai…»

Huscher D et al, An Rheum Dis 2009

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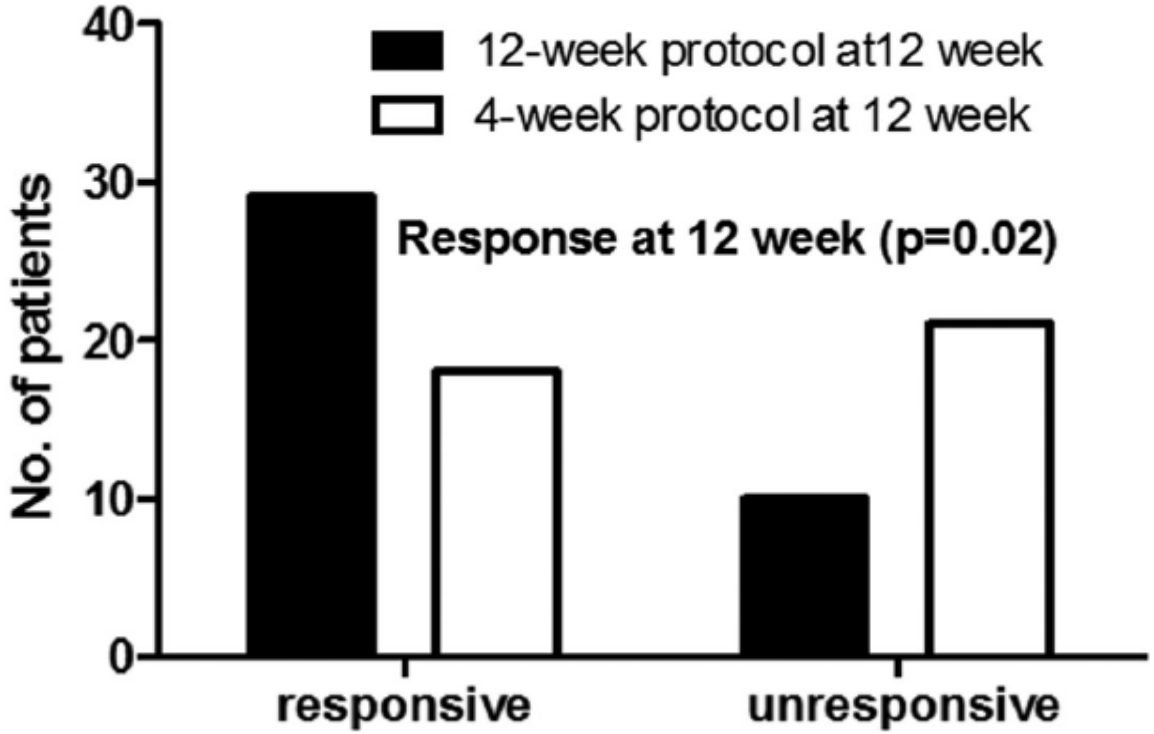
Duru N et al, Ann Rheum Dis 2013; 72:1905-1913

IMPROVEMENT IN RESPONSE RATE IN 80 PATIENTS WITH GRAVES' OPHTHALMOPATHY RANDOMIZED TO A TREATMENT WITH A CUMULATIVE DOSE OF 4.5 gr METHYLPREDNISOLONE IN A 4 OR 12 WEEKS PROTOCOL



Zhu W et al, J Clin Endocrinol Metab 2014

IMPROVEMENT IN RESPONSE RATE IN 80 PATIENTS WITH GRAVES' OPHTHALMOPATHY RANDOMIZED TO A TREATMENT WITH A CUMULATIVE DOSE OF 4.5 GR METHYLPREDNISOLONE IN A 4 OR 12 WEEKS PROTOCOL BUT SIMILAR SIDE EFFECTS

Table 4. Treatment associated adverse effects in the 4th week, 8th week and 12th week.

		weekly protocol (n = 39)			daily protocol (n = 39)			P value
		4th week	8th week	12th week	4th week	8th week	12th week	
Weight gain	0.5 kg	0	1	1	2	1	1	0.68
	1 kg	6	3	5	6	5	7	
	2 kg	3	5	5	2	5	4	
	3 kg	2	4	6	4	8	4	
Bone mineral density	Bone loss	0		1	0		0	-
	Osteoporosis	0		0	0		0	
	Hypertension	1	2	0	1	1	1	1
Glucose regulation	IFG	1	1	0	1	0	0	-
	IGT	1	2	2	3	3	3	1
	DM	1	0	2	1	0	0	0.49
Lipids (mmol/liter)	TC≥6.22	4	2	4	7	3	2	0.42
	TG>2.26	4	1	5	3	2	2	0.24
	LDL>4.14	3	1	3	5	1	3	1
	HDL<1	0	1	1	0	0	0	1
Liver function (U/liter)	ALT>40	1	2	0	4	0	2	0.49
	ALT>100	0	1	0	1	0	0	
	AST>40	0	1	0	1	0	1	1
	AST>100	0	0	0	0	0	0	
Hypokalemia		5	5	11	4	7	7	0.56
Hyperuricemia		0	1	1	2	0	0	0.49

Zhu W et al, J Clin Endocrinol Metab 2014

BENEFITS AND RISK OF LOW DOSE GC THERAPY IN RA

	No GCs in past 12 months, %	Patients with GC intake for >6 months		
		<5 mg/day, %	5–7.5 mg/day, %	>7.5 mg/day, %
Cushingoid phenotype	2.7	4.3	15.8	24.6
Ecchymosis	6.8	17.4	23.5	24.6
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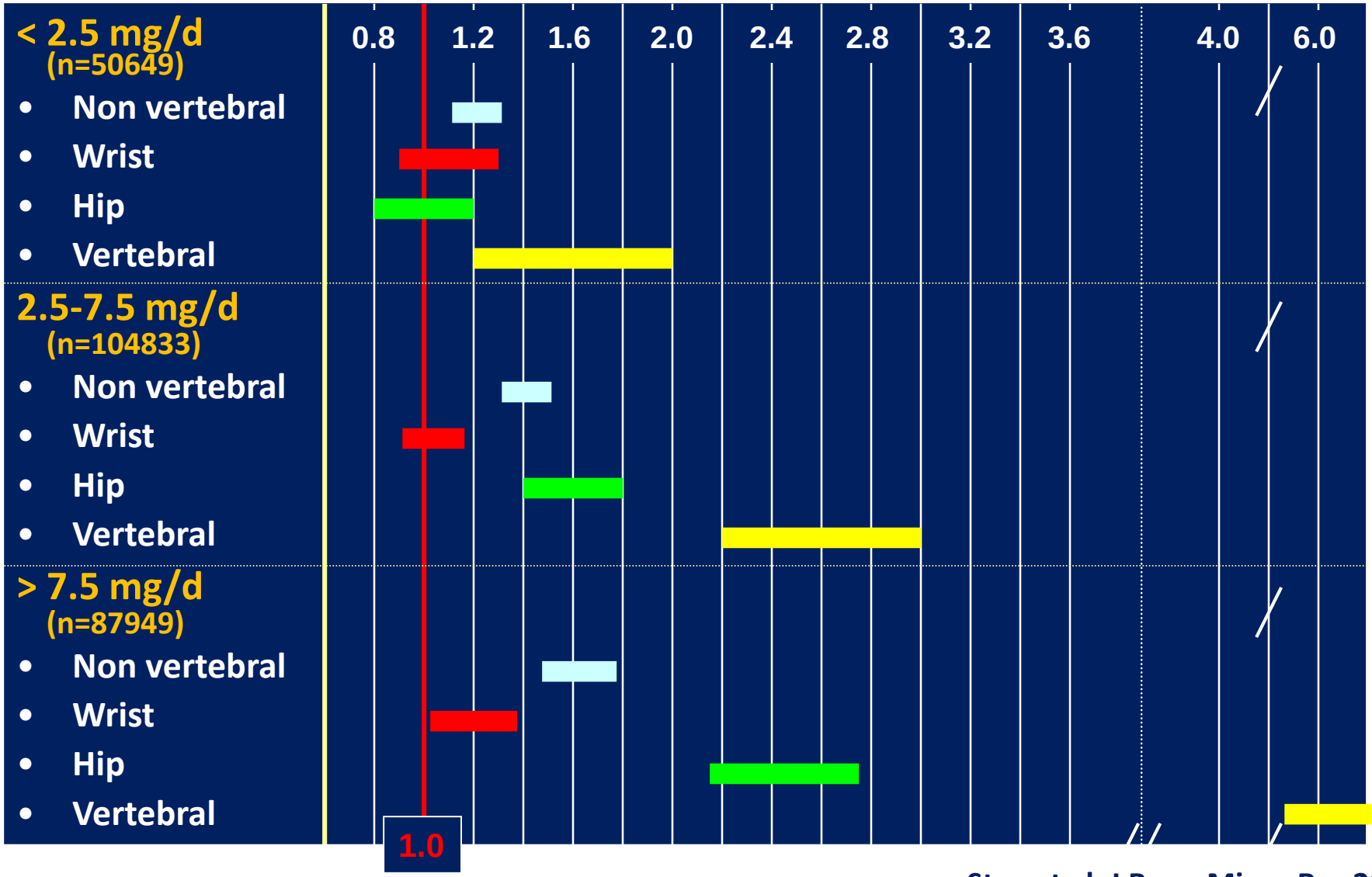
Epistaxis	1.4	1.4	6.6	4.9
Weight gain	9.5	8.7	22.4	21.3
Depression, listlessness	12.6	10.1	13.7	19.7
Glaucoma	2.7	2.9	2.7	6.6
Increase in blood pressure	18.9	18.8	16.4	23.0

GCs: glucocorticosteroids. Modified from Huscher *et al.* [36] with permission from the copyright holder, BMJ Publishing Group Ltd

Kavanaugh A and Wells AF, Rheumatology 2014

FRACTURE RATE (BY DAILY PREDNISONE DOSE) COMPARED TO CONTROLS (BARS REPRESENT THE CI)



van Staa et al, J Bone Miner Res 2000

WAY OF ADMINISTRATION	Reference
TOPICAL	Joe EK, Dermatol Online 2003
	Abma EM et al, Neth J Med 2002
	Ermis B et al, Clin Endocrinol 2003
	Castanedo-Cazares JP et al, Int J Dermatol 2003
	Weber SL, Endocr Pract 1997
PERIOCULAR	Ozerdem U et al, Am J Ophtalmol 2000
INHALED	White A et al, Ann Intern Med 2004
	Wilson AM et al, Chest 2000
	Kennedy MJ et al, Ann Allergy Asthma Immunol 2002
	Drake AJ et al, BMJ 2002
INTRANASAL	Findlay CA et al, BMJ 1998
	Perry RJ et al, Arch Dis Child 2002
	Nutting CM et al, Postgrad Med J 1995
INTRA-ARTICULAR/INTRADERMAL	Jansen TL et al, Neth J Med 2002
	Kumar S et al, Pediatrics 2004
	Teelucksingh S et al, Ann Trop Paediatr 2002

NO CLEAR GUIDANCE ON HOW TO WEIGH DOSES, BENEFITS AND RISKS OF GC THERAPY

- **Keep the dose as low as needed to achieve therapeutic effect in each individual patient**
- **Specific treatment goals may require different GC regimes or different periods of treatment.**
- **Regular checks of the requirement for GC therapy are needed**

«…Voglio trovare un senso a questa condizione, anche se questa condizione un senso non ce l'ha…»

FACTORS INFLUENCING GC THERAPY

- **Type of disease**
- **Indication and goals of treatment**
- **Initial response to treatment**
- **Development of AES**
- **Individual patient characteristics**

Duru N et al, Ann Rheum Dis 2013; 72:1905-1913

BclI polymorphism of the glucocorticoid receptor gene is associated with decreased bone mineral density in patients with endogenous hypercortisolism

Ágnes Szappanos*, Attila Patócs*,†, Judit Tõke*, Belema Boyle*, Márta Sereg*, Judit Majnik*, Gábor Borgulya§, Ibolya Varga†, István Likó‡, Károly Rácz* and Miklós Tóth*

Role of glucocorticoid receptor polymorphism in adrenal incidentalomas

Eur J Clin Invest 2010; 40 (9): 803–811

Valentina Morelli[1], Francesca Donadio[1], Cristina Eller-Vainicher, Valentina Cirello, Luca Olgiati, Chiara Savoca, Elisa Cairoli, Antonio Stefano Salcuni, Paolo Beck-Peccoz and Iacopo Chiodini

European Journal of Endocrinology (2012) **166** 35–42 ISSN 0804-4643

CLINICAL STUDY

Association of glucocorticoid receptor polymorphism A3669G with decreased risk of developing diabetes in patients with Cushing's syndrome

Laura Trementino, Gloria Appolloni, Carolina Concettoni, Marina Cardinaletti, Marco Boscaro and Giorgio Arnaldi

Bone 45 (2009) 1098–1103

HSD11B1 polymorphisms predicted bone mineral density and fracture risk in postmenopausal women without a clinically apparent hypercortisolemia

Joo-Yeon Hwang [a,1], Seung Hun Lee [b,d,1], Ghi Su Kim [b,d], Jung-Min Koh [b,d], Min Jin Go [a], Young-Jin Kim [a], Hyung-Cheol Kim [a], Tae-Ho Kim [b,c], Jung Min Hong [b], Eui Kyun Park [b,c], Jong-Young Lee [a,*], Shin-Yoon Kim [e,*]

Steroids. 2012 Nov;77(13):1345-51

The rs4844880 polymorphism in the promoter region of the HSD11B1 gene associates with bone mineral density in healthy and postmenopausal osteoporotic women.

Feldman K, Szappanos A, Butz H, Grolmusz V, Majnik J, Likó I, Kriszt B, Lakatos P, Tóth M, Rácz K, Patócs A.

Journal of Steroid Biochemistry & Molecular Biology 123 (2011) 79–84

Contents lists available at ScienceDirect

Journal of Steroid Biochemistry and Molecular Biology

journal homepage: www.elsevier.com/locate/jsbmb

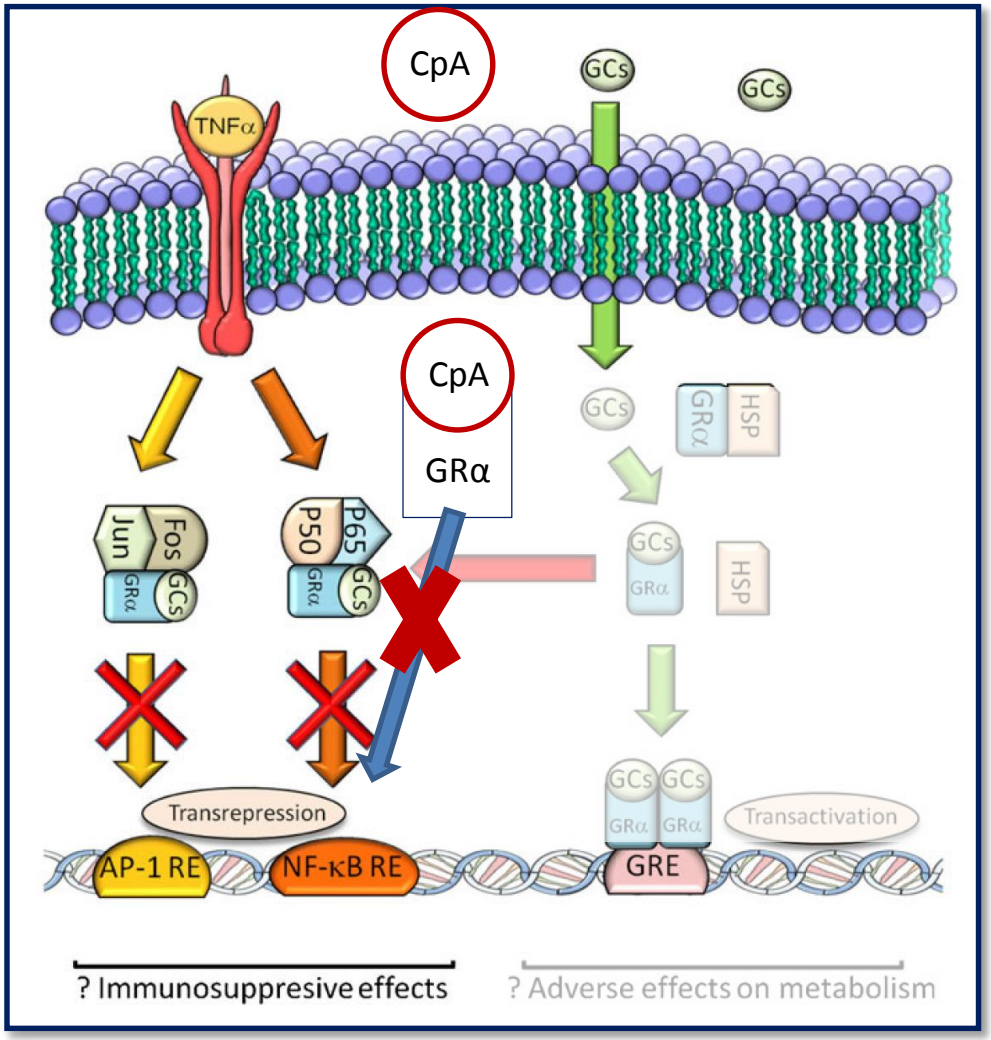
The 83,557insA variant of the gene coding 11β-hydroxysteroid dehydrogenase type 1 enzyme associates with serum osteocalcin in patients with endogenous Cushing's syndrome

Ágnes Szappanos [a], Attila Patócs [b,a], Péter Gergics [a], Rita Bertalan [a], Andrea Kerti [a], Bence Ács [a], Karolina Feldmann [a], Károly Rácz [a], Miklós Tóth [a,*]

«…ognuno col suo viaggio, ognuno diverso…», ma…

Selective Glucocorticoid Receptor Agonists: Glucocorticoid Therapy With No Regrets?

Mark S Cooper,[1] Hong Zhou,[2] and Markus J Seibel[2,3] JBMR 2012



Compound A binds to the GR and has mostly preserved transrepression capability, but lacks the ability to induce GRE-mediated transactivation

«…c'è chi dice no!…»

COMPOUND A

Affinity for GR

Ki = 6.4 nM (L929sA) and Ki = 81.8 nM (BWTG3)

CpdA inhibited [3H]DEX binding to GR by 85% in DU145 cells

Inhibited cytokines/chemokines/adhesion molecules

IL-6, IL-8, E-selectin, TNFα, ICAM, IL-1β, IFNγ, MCP-1, IP10, IL-17, IL-23, MIP1α

In vivo animal models

- Zymosan-induced paw swelling
- CIA (collagen-induced arthritis)
- EAE (experimental autoimmune encephalomyelitis)
- EAN (experimental autoimmune neuritis)

Side effects addressed

- Reduced hyperglycemia/hyperinsulinemia
- Reduced HPA axis suppression
- Metabolite-induced GR-independent apoptosis
- Favorable bone marker profile *in vitro*[a]
- No acquired glucocorticoid resistance or unresponsiveness

De Bosscher K, Curr Op Pharmacol 2010

Selective Glucocorticoid Receptor Agonists: Glucocorticoid Therapy With No Regrets?

Mark S Cooper,[1] Hong Zhou,[2] and Markus J Seibel[2,3] JBMR 2012

CAVEATS

- **Theraputic window:** at high concentrations the drug degrades to a alkylating agent.
- **Some of the anti-inflammatory effects of GCs are mediated by transactivation**
- **Studies in a inflammatory setting are lacking**
- **SEGRAs has to be examined in each inflammatory condition.**
- **HPA axis suppression with long term treatment:** the inhibition of ACTH secretion by high levels of GCs is via transrepression
- **Negative consequences in humans by prolonged ‘‘deficiency’’ of GR transactivation**

FONDAZIONE IRCCS
CÀ GRANDA
OSPEDALE MAGGIORE
POLICLINICO

UNIVERSITÀ DEGLI STUDI DI MILANO

THANK YOU

«….colpa d'Alfredo (Scillitani) che con i suoi discorsi seri ed opportuni mi ha sempre dato un sacco di occasioni…»