Glucocorticoids in the management of autoimmune disorders

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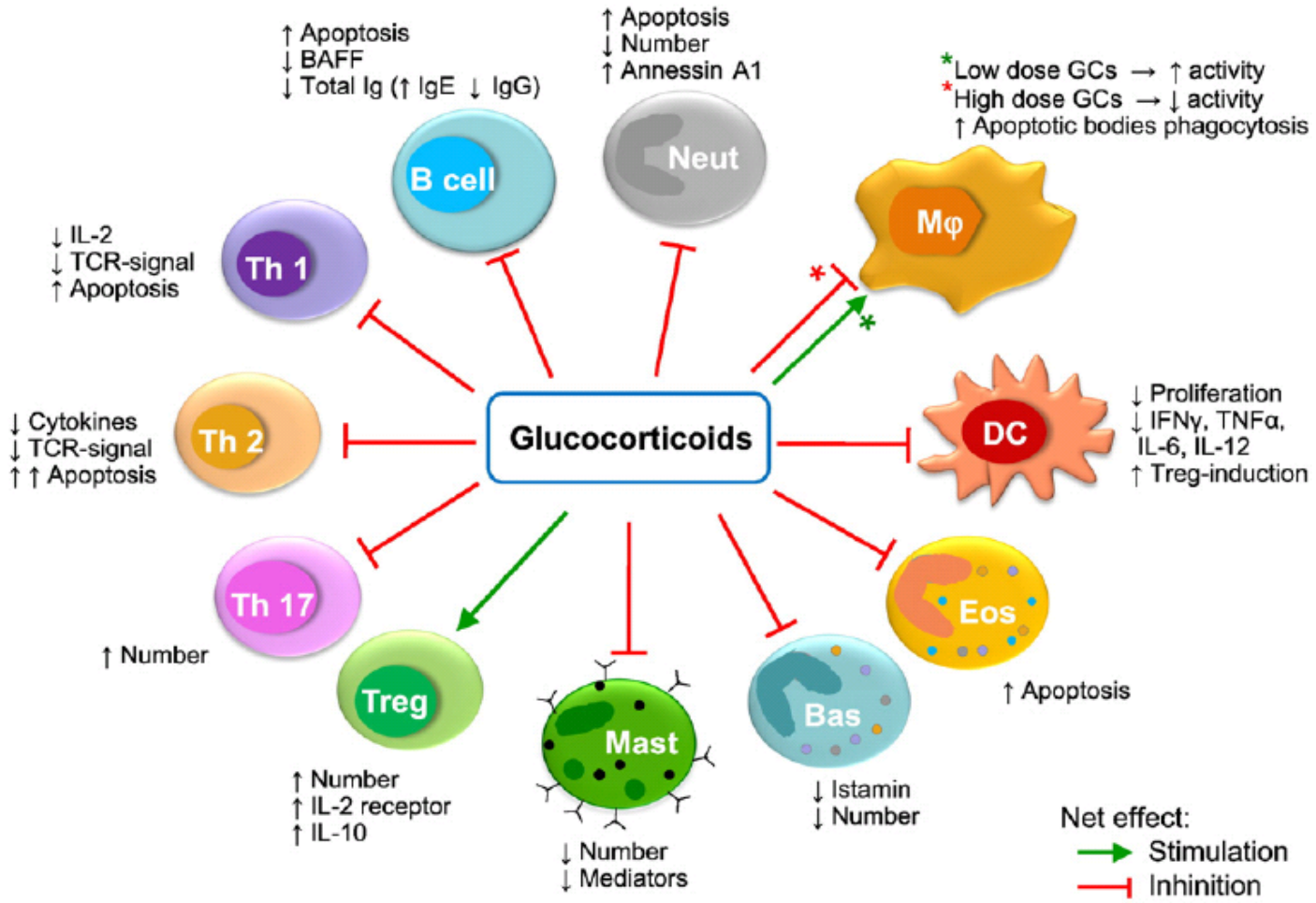
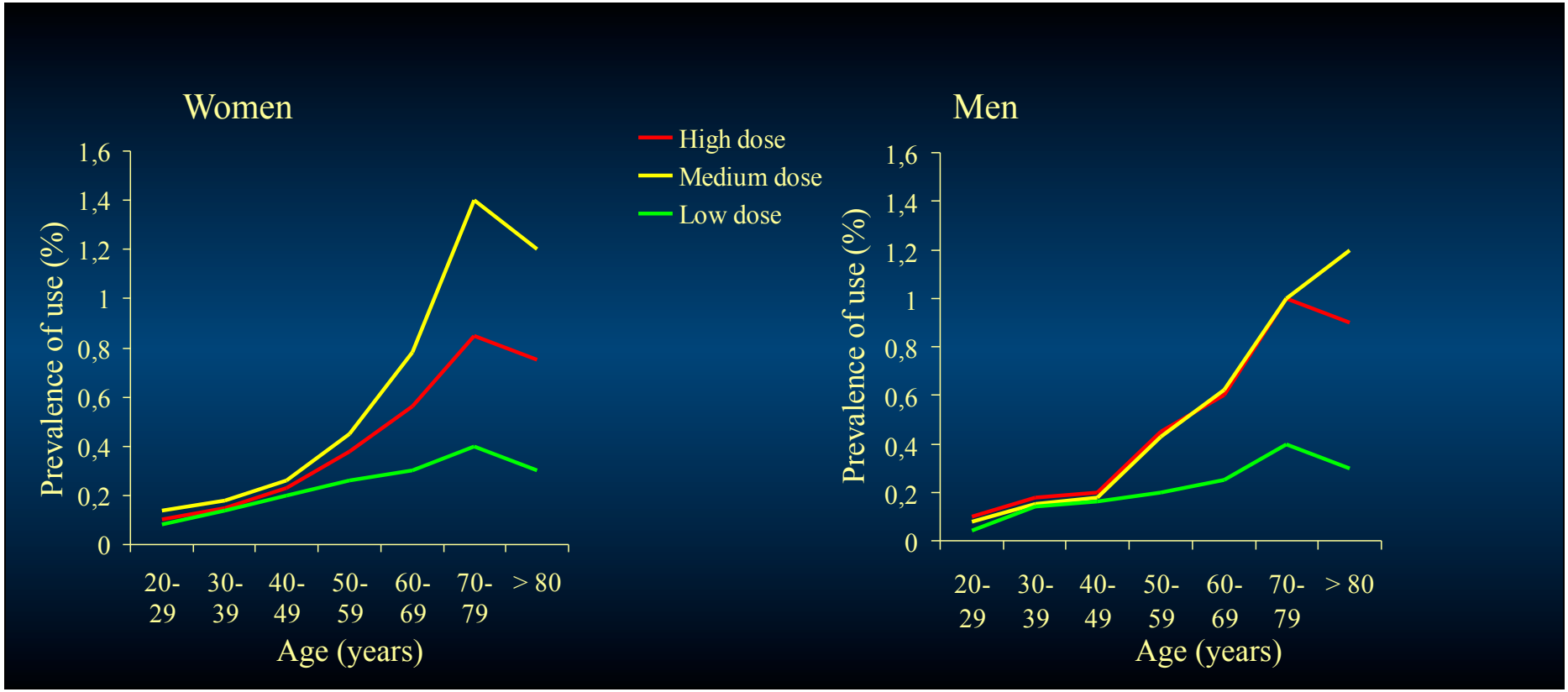
The kaleidoscope of Glucocorticoid effects on immune system



Zen M *Autoimmunity Rev* 10:305 2011

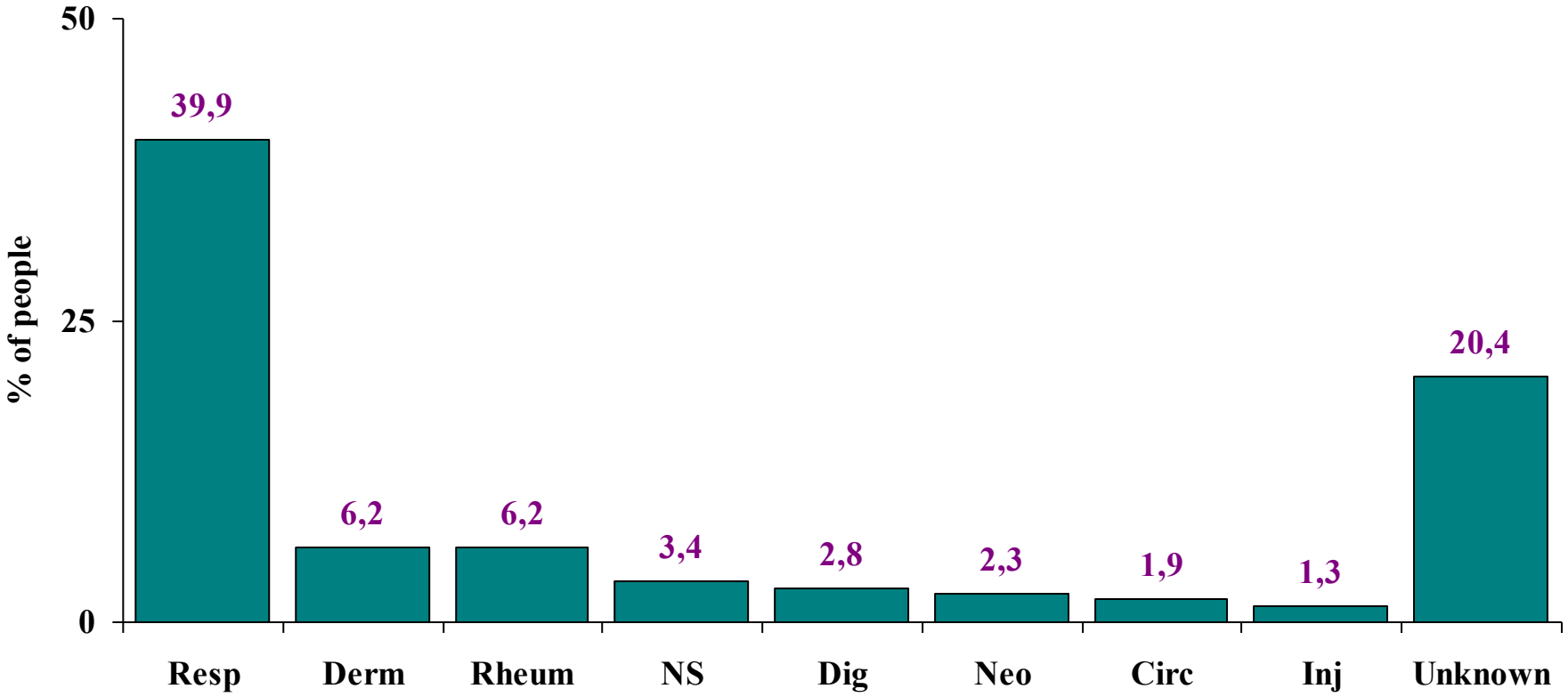
Use of oral corticosteroids in the General Practice Research Database population

(683 practices- 244.235 steroid users) stratified by dose, age and gender



Van Staa TP et al. *Q J Med* 2000

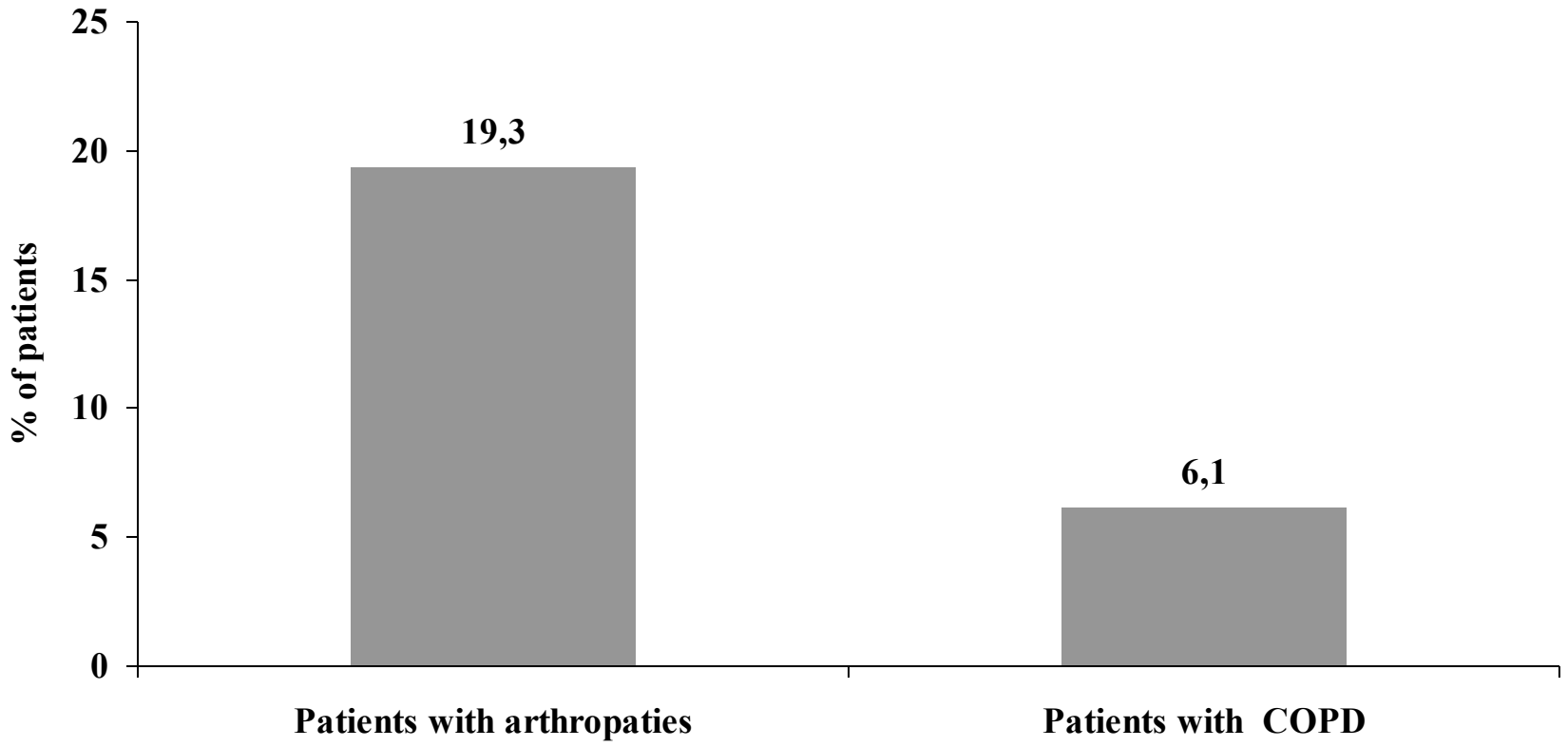
Indications for oral corticosteroid treatment in the General Practice Research Database (GRPD)



Van Staa TP et al., *Q J Med* 2000

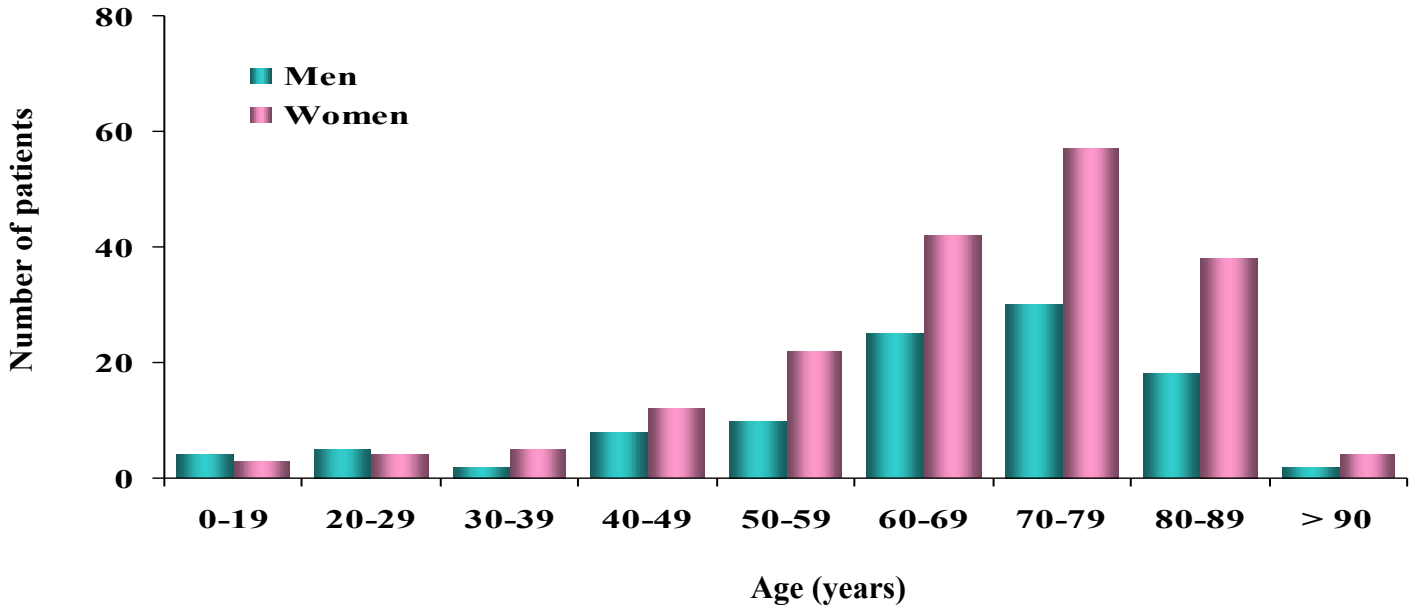
Percentage of patients who continued oral corticosteroid treatment for > 2 years, according to concomitant disease

General Practice Research Database Population



Van Staa TP et al., *Q J Med* 2000

Age and sex distribution of patients taking continuous oral corticosteroids
A population survey on 65,786 patients registered with a GP



Prevalence in the community based population : 0.5 %
Prevalence in PM women : 1.7 %

Walsh et al. *BMJ* 1996

General use of Glucocorticoids in Clinical Rheumatology

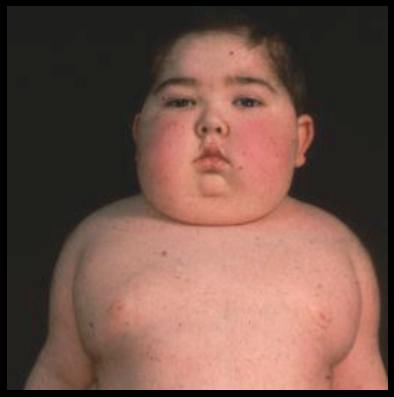
	Low	Medium	High	Pulse	Local
Arthritides					
• Gout	Infrequent	Frequent	Frequent	=	Frequent
• JIA	=	Infrequent	Infrequent	=	Infrequent
• Pseudogout	=	=	=	=	Frequent
• Psoriatic A.	=	Frequent	=	=	Frequent
• Reactive A.	=	=	=	=	Frequent
• Rheumatic Fever	=	Frequent	Frequent	=	=
• Rheumatoid A.	Frequent	Frequent	Infrequent	=	Frequent
Connective Tissue Disorders					
• Demato/polymyositis	=	=	Basic Strategy	Infrequent	=
• MCTD	Frequent	Infrequent	=	Infrequent	Infrequent
• Polymyalgia Rheum.	=	Basic strategy	=	=	=
• Sjogren Syndrome	=	=	Infrequent	=	=
• Systemic Lupus Er.	Frequent	Basic strategy	Infrequent	Frequent	=
• Systemic Sclerosis	=	Infrequent	=	=	=
Systemic Vasculitides	=	=	Basic strategy	Infrequent	=

Low : ≤ 7.5 mg/d in Prednisone
Medium: ≥ 7.5 but ≤ 30 mg/d in Prednisone
High : > 30 mg/d in Prednisone

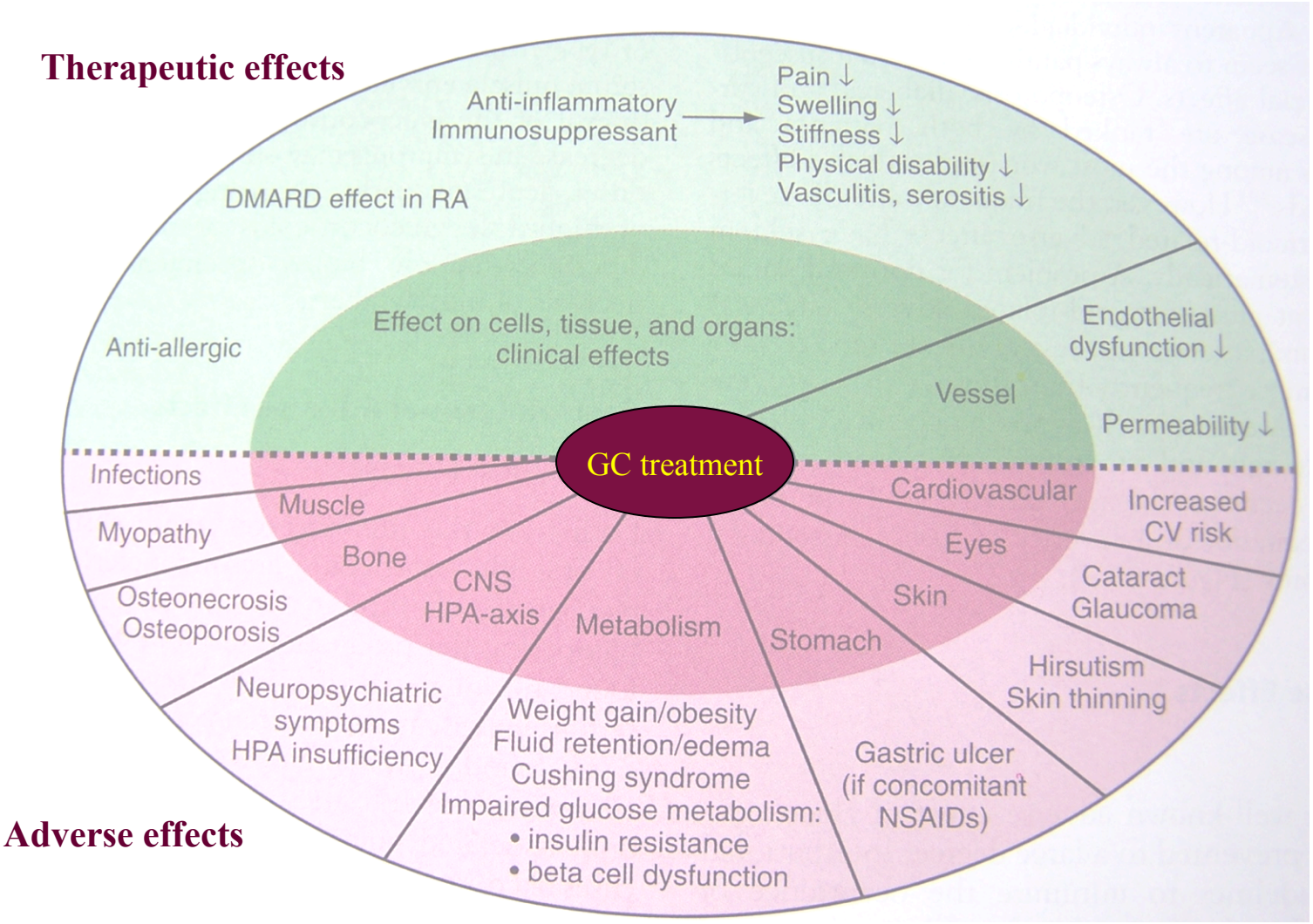
Modified from: Kelley's Textbook of Rheumatology, Elsevier 2013

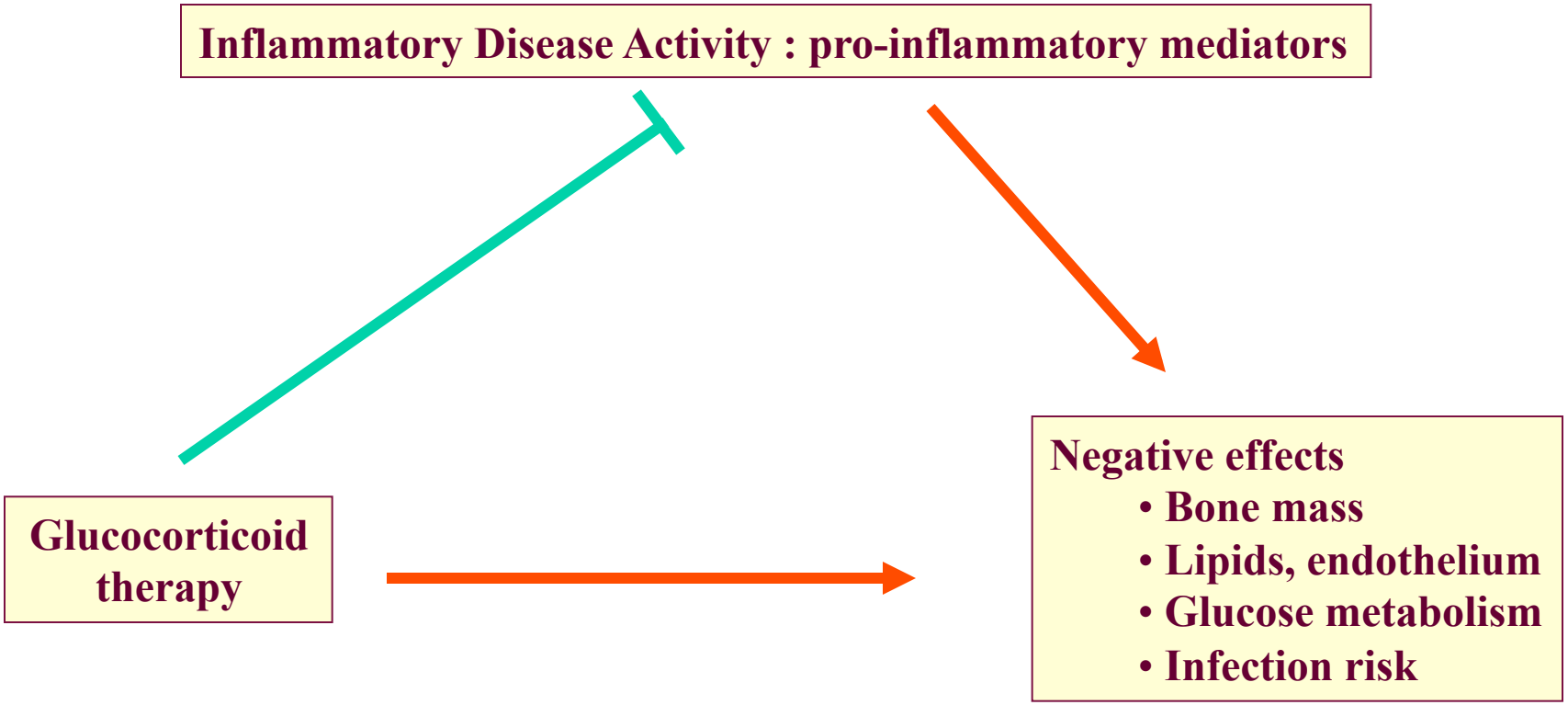
Some current definitions of CS therapy in chronic rheumatic diseases

- The silent companions of Rheumatologists…….
- CS in Rheumatoid Arthritis: win a battle, lose the war
- The two edged sword of CS therapy…….



The spectrum of glucocorticoid therapy





Glucocorticoid therapy, inflammatory disease and adverse effects: an interplay making it hard in non randomized trials to discriminate the negative effects of glucocorticoids from negative effects of the disease itself

Glucocorticoids in clinical Rheumatology

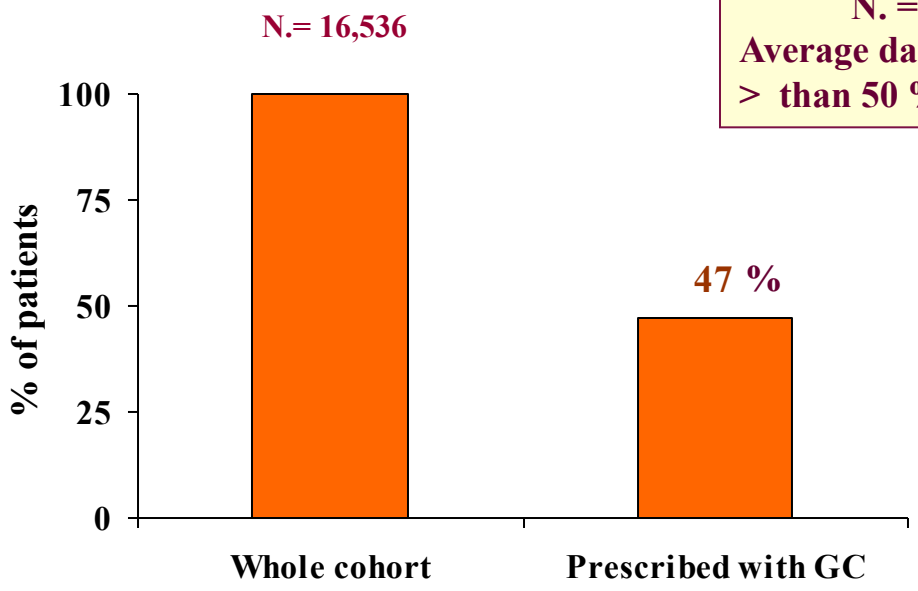
- **Rheumatoid Arthritis**

RESEARCH ARTICLE Open Access

Half of UK patients with rheumatoid arthritis are prescribed oral glucocorticoid therapy in primary care: a retrospective drug utilisation study

Rachel J. Black[1,2,5*], Rebecca M. Joseph[1,3], Benjamin Brown[4], Mohammad Movahedi[1], Mark Lunt[1] and William G. Dixon[1,3,4,6]

N. =7,777 patients with RA
Average daily dose 7.5 mg (IQR 5-15.3 mg)
> than 50 % prescribed with > 10 mg/day

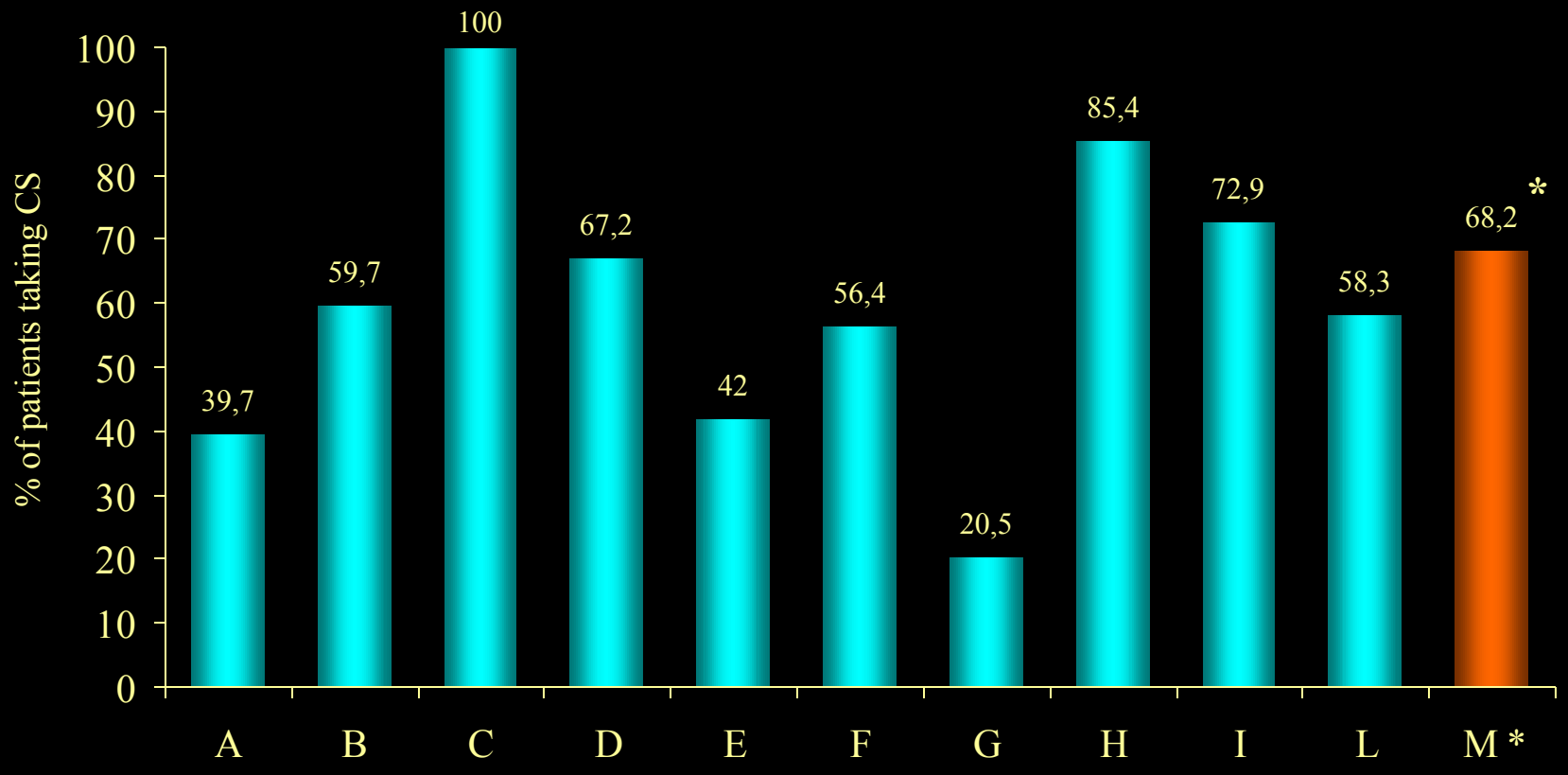


Black RJ et al. *Arthritis Res Ther* 2015

Corticosteroids prescriptions for RA at Italian Centers

(907 RA patients, 10 Centers, average 6MP daily dose 5.7 ± 3.6 mg)

(* 925 RA patients, 21 Centers, average Predn. daily dose 5.5 ± 4.5 mg)



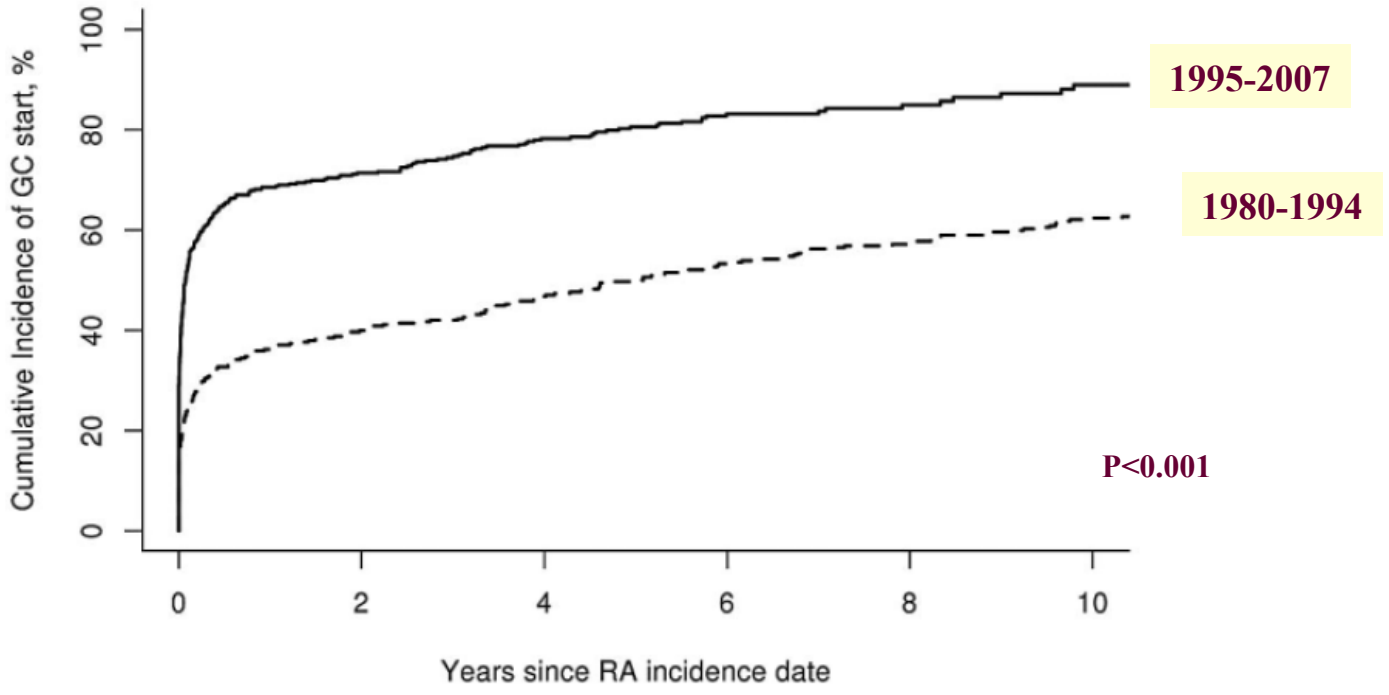
Grassi W et al. *Clin Rheumatol* 1998

* Sinigaglia et al. *J Rheumatol* 2000

Time Trends in Glucocorticoid Use in Rheumatoid Arthritis: Results From a Population-Based Inception Cohort, 1980–1994 Versus 1995–2007

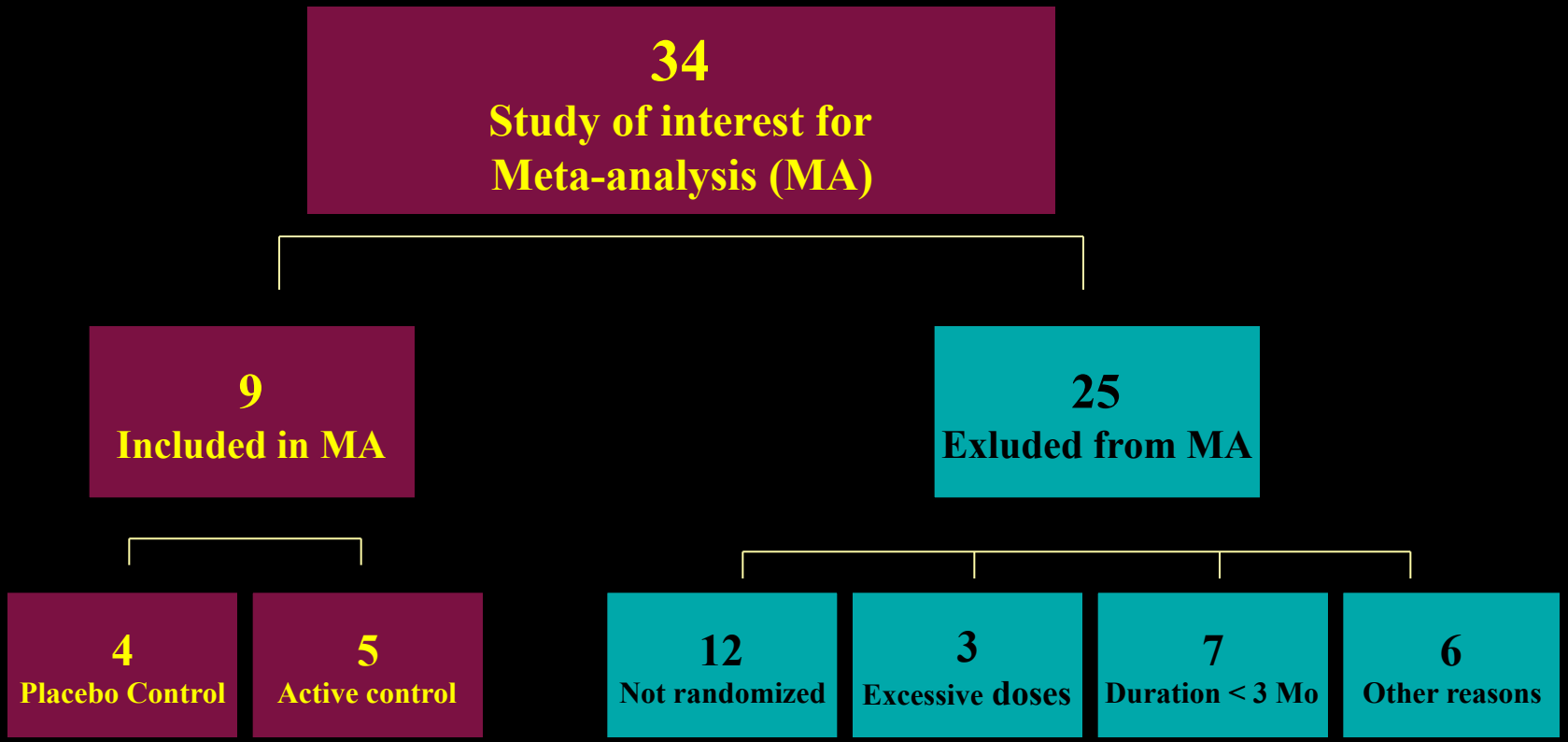
ASHIMA MAKOL, JOHN M. DAVIS III, CYNTHIA S. CROWSON, TERRY M. THERNEAU, SHERINE E. GABRIEL, AND ERIC L. MATTESON

Cumulative incidence of start of glucocorticoids according to time period of RA incidence



Maikol A et al. *Arthritis Rheum* 2014

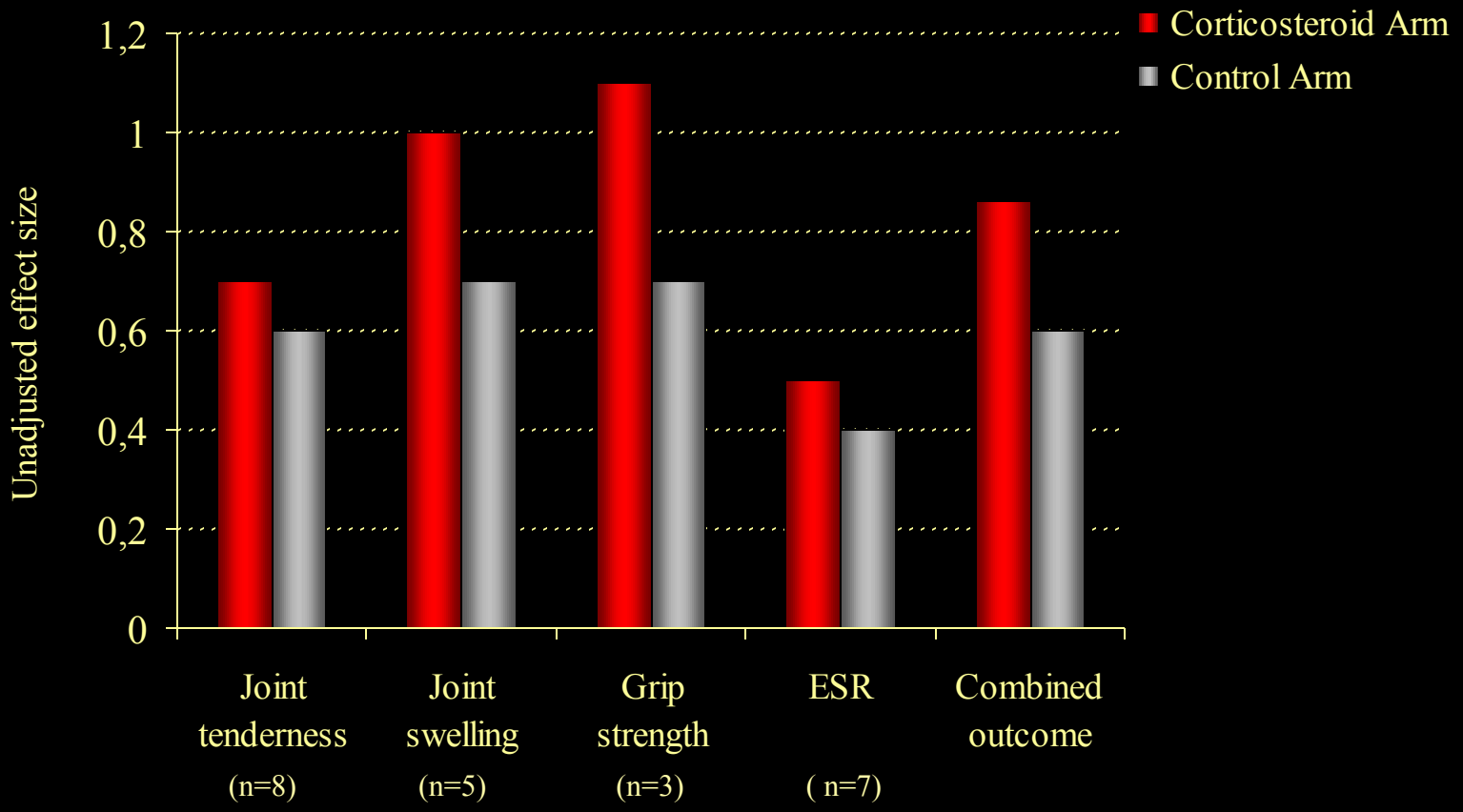
Low-dose Corticosteroids in Rheumatoid Arthritis
A meta-analysis of their moderate-term effectiveness



Saag KG et al. *Arthritis Rheum* 1996

Low-dose Corticosteroids in Rheumatoid Arthritis
A meta-analysis of their moderate-term effectiveness

Unadjusted effect size comparing the pooled CS treatment arms and the control treatment – 9 studies



Saag KG et al. *Arthritis Rheum* 1996

DX

Reported trials since 1980 examining the effects of oral CS on radiographic progression in Rheumatoid Arthritis

Study, year	Treatment	Control	Effect on progression	Design
Harris et al.,1983	Prednisone, 5 mg/day + DMARDs	Placebo	**NO**	DB,RCT
Million et al., 1984	Prednisolone, 10.3 mg/day + DMARDs	No prednisone	**YES**	RCT
Kirwan, 1995	Prednisolone, 7.5 mg/day + DMARDs	Placebo + DMARD	**YES**	DB,RCT
Boers, 1997	Prednisolone, 60 mg/day and taper + MTX + SSZ	Placebo + SSZ	**YES**	DB,RCT
Hansen et al., 1999	Prednisolone, 6 mg/day + DMARDs	DMARD	**NO**	RCT
Paulus et al., 2000	Prednisone, ≤ 5 mg/day	Placebo	**NO**	RCT
Van Everdingen et al., 2002	Prednisolone, 10 mg/day	Placebo	**YES**	DB,RCT
Capell et al., 2004	Prednisone, 7 mg/day + SSZ	Placebo + SSZ	**NO**	DB,RCT

Reported trials since 1980 examining the effects of oral CS on radiographic progression in Rheumatoid Arthritis

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Boers, 1997	Prednisolone, 60 mg/day and taper + MTX + SSZ	Placebo + SSZ	**YES**	DB,RCT
Van Everdingen et al., 2002	Prednisolone, 10 mg/day	Placebo	**YES**	DB,RCT

Randomised controlled trials of Glucocorticoids added to DMARDs in early arthritis

Study	N	Glucocorticoid regimen	Trial duration (years)	Outcome	Results in glucocorticoids group (%)	Results in control group (%)	p Value
Machold, 2010[9]	383	Single IM 120 mg methylprednisolone	1	Drug-free persistent clinical remission (both at 12 and 52 weeks)	16.2	17.8	0.685
Fedorenko, 2011[10]	141	Prednisolone 10 mg/day or Prednisolone 10 mg/day +methylprednisolone 1 g IV first day	1	'Clinical EULAR remission' at 12 weeks*	21.3 (oral GC)	3.1	0.027
					28.6 (oral GC+IV GC)		0.006
				'Clinical EULAR remission' at 52 weeks*	37.5 (oral GC)	11.4	0.012
					29.4 (oral GC+IV GC)		0.133
Montecucco, 2012[11] Todoerti, 2010[12]	220	Prednisone 12.5 mg/day for 2 weeks tapered to 6.25 mg/day for the follow-up period†	1	DAS28≤3.2 at 52 weeks	80.2	75.5	0.44
				DAS28<2.6 at 52 weeks	44.8	27.8	0.02
Bakker, 2012[13]	236	Prednisone 10 mg/day†	2	ACR70 at 104 weeks	38	19,	0.002
				SHS erosion score at 104 weeks	0 (0–0)	0 (0–2)	0.022
				SHS total score at 104 weeks	0 (0–3)	0 (0–4)	0.32

Studies were of glucocorticoids added to MTX except for the study of Machold *et al* concerning glucocorticoids added to no other therapy, NSAIDs or DMARDs at the investigators' discretion.
*Study only reported as an abstract at the 2011 EULAR congress: definition of 'Clinical EULAR remission' unclear.
†Tight control, treatment to target.
DAS28, Disease Activity Score in 28 joints; DMARDs, disease-modifying antirheumatic drugs; GC, glucocorticoids; IM, intramuscular; IV, intravenous; MTX, methotrexate; NSAIDs, non-steroidal anti-inflammatory drugs; SHS, median Sharp–van der Heijde score (interquartile range).

Gaujoux-Viala C et al. *Ann Rheum Dis* 2014; 73:510

OPEN ACCESS

EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update

Josef S Smolen,[1,2] Robert Landewé,[3,4] Ferdinand C Breedveld,[5] Maya Buch,[6,7] Gerd Burmester,[8,9] Maxime Dougados,[10] Paul Emery,[6,7] Cécile Gaujoux-Viala,[11] Laure Gossec,[12] Jackie Nam,[6,7] Sofia Ramiro,[13,14] Kevin Winthrop,[15] Maarten de Wit,[16] Daniel Aletaha,[1] Neil Betteridge,[16] Johannes W J Bijlsma,[17] Maarten Boers,[18] Frank Buttgereit,[8,9] Bernard Combe,[19] Maurizio Cutolo,[20] Nemanja Damjanov,[21] Johanna M W Hazes,[22] Marios Kouloumas,[16] Tore K Kvien,[23] Xavier Mariette,[24] Karel Pavelka,[25] Piet L C M van Riel,[26] Andrea Rubbert-Roth,[27] Marieke Scholte-Voshaar,[16] David L Scott,[28] Tuulikki Sokka-Isler,[29,30] John B Wong,[31] Désirée van der Heijde[5]

Level of Evidence	Grade of Recommendation
1a	A

Recommendation 9 : Glucocorticoids

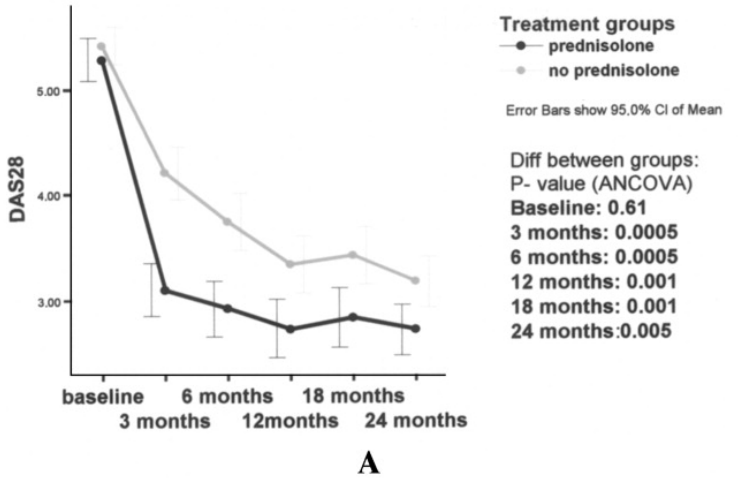
- **Low-dose glucocorticoids should be considered as part of the initial treatment strategy (in combination with one or more DMARDs) for up to six months, but should be tapered as rapidly as clinically feasible**

Smolen J et al. *Ann Rheum Dis* 2013

Low-Dose Prednisolone in Addition to the Initial Disease-Modifying Antirheumatic Drug in Patients With Early Active Rheumatoid Arthritis Reduces Joint Destruction and Increases the Remission Rate

A Two-Year Randomized Trial

Björn Svensson,[1] Annelies Boonen,[2] Kristina Albertsson,[3] Désirée van der Heijde,[2] Catharina Keller,[4] and Ingiäld Hafström,[3] for the BARFOT Study Group



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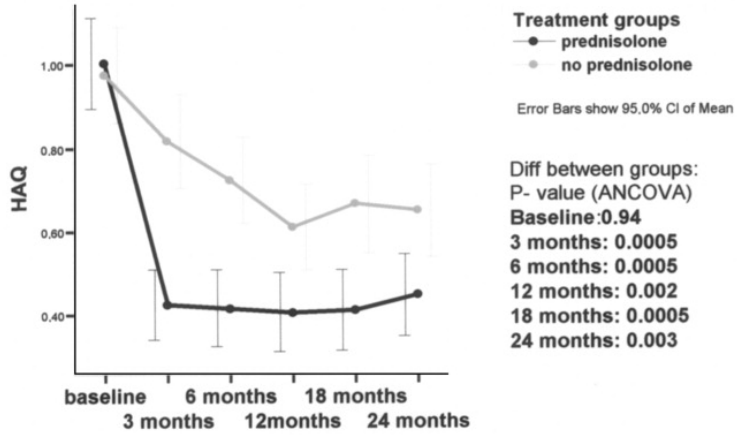
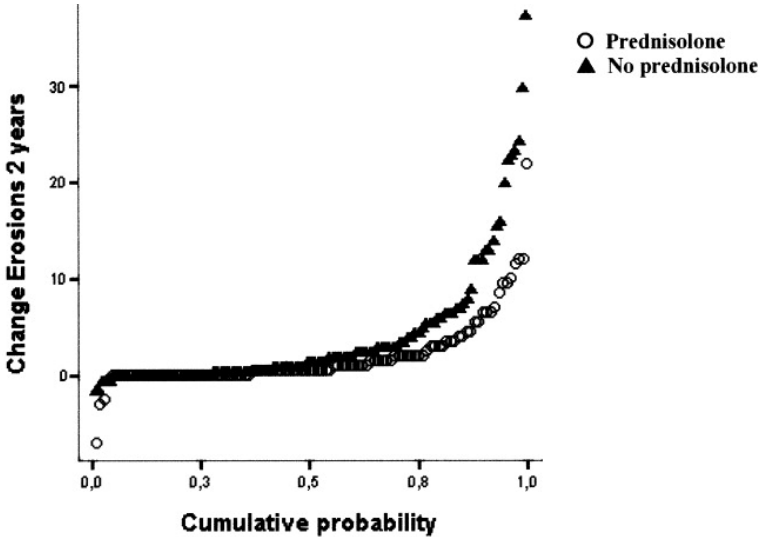




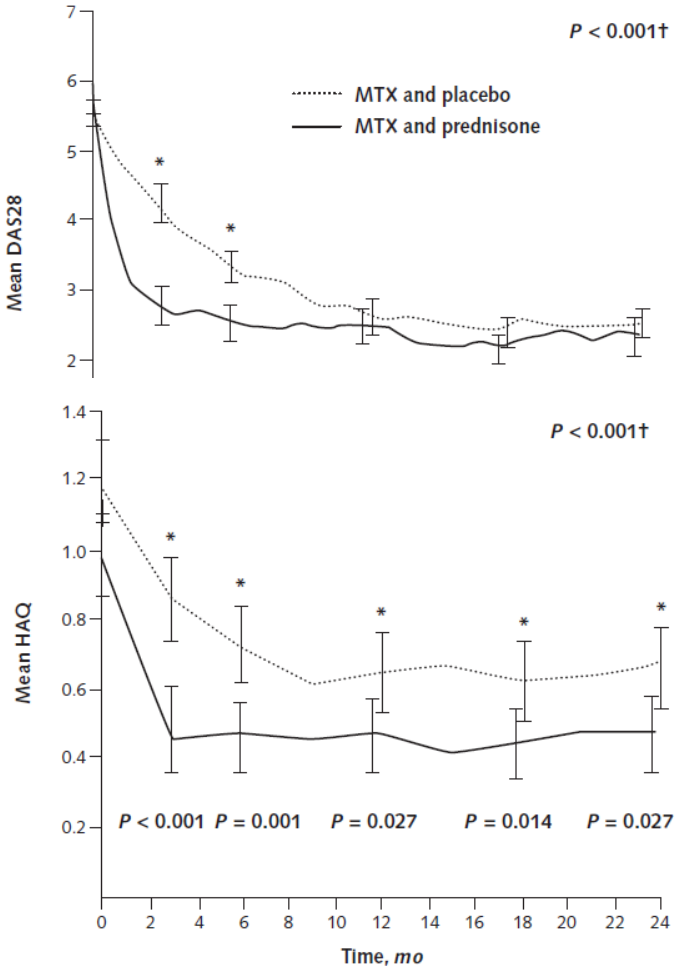
Svensson B et al. *Arthritis Rheum* 2005

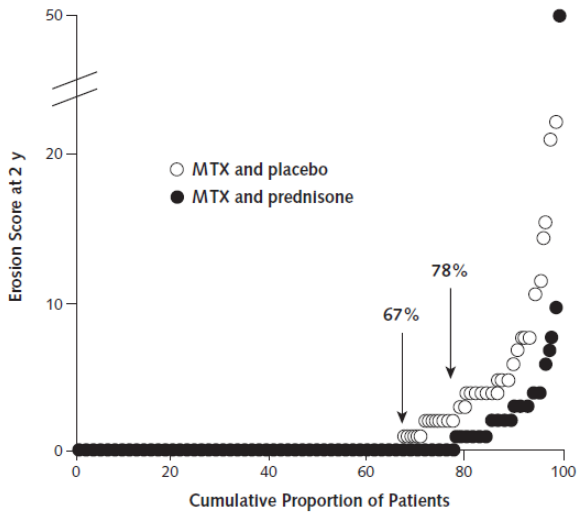
Annals of Internal Medicine | ORIGINAL RESEARCH

Low-Dose Prednisone Inclusion in a Methotrexate-Based, Tight Control Strategy for Early Rheumatoid Arthritis

A Randomized Trial

Marije F. Bakker, PhD; Johannes W.G. Jacobs, PhD, MD; Paco M.J. Welsing, PhD; Suzanne M.M. Verstappen, PhD; Janneke Tekstra, PhD, MD; Evelien Ton, MD; Monique A.W. Geurts, MD; Jacobine H. van der Werf, MD; Grietje A. van Albada-Kuipers, MD; Zalima N. Jahangier-de Veen, PhD, MD; Maaike J. van der Veen, PhD, MD; Catharina M. Verhoef, PhD, MD; Floris P.J.G. Lafeber, PhD; and Johannes W.J. Bijlsma, PhD, MD, on behalf of the Utrecht Rheumatoid Arthritis Cohort Study Group*





Bakker MF et al. *Ann Intern Med* 2012

Keys to optimizing the outcome of treatment

James R. O' Dell: Therapeutic Strategies for Rheumatoid Arthritis
New Engl J Med 350:2591, 2004

- Make an early diagnosis
- Start DMARDs therapy as early as possible (within 3 months after onset of symptoms)
- Strive for remission (no joint symptoms) in all patients
- Use Corticosteroids as a bridge to effective DMARDs therapy
  - Prednisone at doses > 10 mg/day is rarely indicated for joint diseases
  - Avoid using corticosteroids without DMARDs
  - Minimize duration and dose by tapering to the lowest dose that controls the disease
  - Always consider prophylaxis to avoid Osteoporosis
- Recognize and treat coexisting illnesses
- Facilitate communication between primary care physician and rheumatologist

Glucocorticoids and Rheumatoid Arthritis

Joana Fonseca Ferreira, MD[a], Alaa Abdelkhalik Ahmed Mohamed, MD[b], Paul Emery, MA, MD, FRCP, FRCPE, FMedSci[c,*]

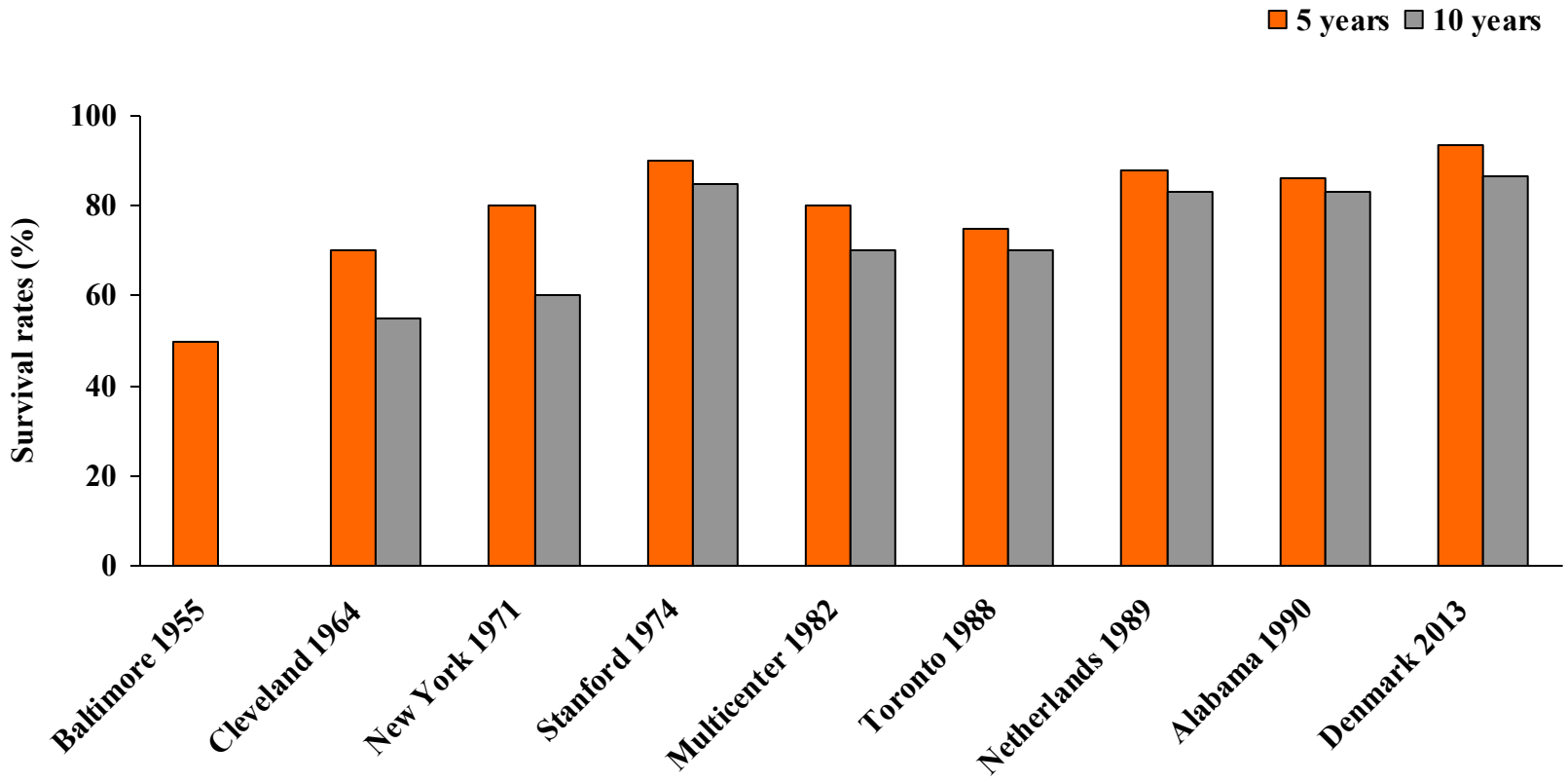
- **GCs improve pain, morning stiffness and fatigue**
- **In early Rheumatoid Arthritis, low-dose GCs can prevent joint damage**
- **In clinical practice, low doses of GCs can be used in RA as a maintenance therapy**
- **Medium and high doses could be used initially as a bridge therapy**
- **Very high doses or pulse therapy are reserved for acute life-threatening or organ-threatening complications**

Rheum Dis Clin N Am 42 (2016) 33–46

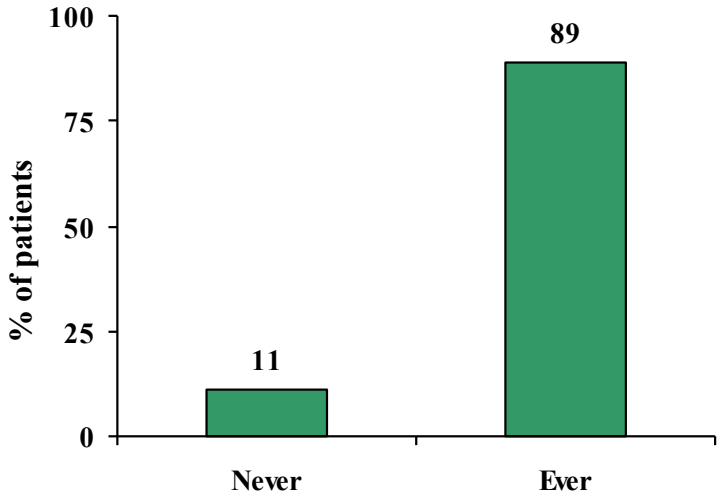
Glucocorticoids in clinical Rheumatology

- **Systemic Lupus Erythematosus**

Survival rates in Systemic Lupus Erythematosus



Glucocorticoids use in the Hopkins Lupus Cohort (N.= 539)



Prednisone use during different periods after diagnosis

Prednisone use	Years after SLE diagnosis 0–5 years*	6–10 years†	11–15 years‡
Percentage of time			
Never	56 (17%)	37 (21%)	15 (18%)
1–49%	57 (18%)	19 (11%)	10 (12%)
50–99%	90 (27%)	19 (11%)	10 (12%)
Always	119 (37%)	101 (57%)	46 (57%)

Zonana-Nacach A et al. *Arthritis Rheum* 2000

Review

The use of glucocorticoids in Systemic Lupus Erythematosus. After 60 years still more an art than science

Remco K.M.A.C. Luijten *, Ruth D. Fritsch-Stork, Johannes W.J. Bijlsma, Ronald H.W.M. Derksen

Department of Rheumatology and Clinical Immunology, University Medical Center Utrecht, The Netherlands

- **GCs constitute the corner-stone in SLE treatment**
- **After 60 years of experience consensus about appropriate dosages, route of administration and tapering regimens has not been reached**
- **GC therapy, especially in higher dosages, comes at a considerable price in terms of side effects**

Luijten R et al. *Autoimmunity* ***Rev*** **2013**

SLE: Corticosteroids dosing per manifestation

A systematic Literature Research

Luijten R et al. *Autoimmunity Rev* 2013

Indication		Range oral pred	Level of evidence
General	Fever	10–100 mg	2b
	Lymfadenopathy	20–30 mg	4
Mucocutaneous	Bullous	30–90 mg	4
	Erythema multiforme	20–60 mg	4
	Discoid LE	10 mg–1 mg/kg	4
	SCLE	40 mg–1 mg/kg	4
	Lupus panniculitis	32–40 mg	4
	Necrotizing vasculitis	0.5–1 mg/kg	2b
Neuropsychiatric	Myelitis	20 mg–1 mg/kg	4
	Psychosis	20 mg–2 mg/kg	2b
	NP-SLE general	10 mg–2 mg/kg	2a/b
Nephritis	WHO classes III + IV + V	10 mg–2 mg/kg	1A
	WHO pure class V	10 mg–2 mg/kg	1B
Haematologic	Thrombocytopenia	25 mg–1 mg/kg	2b
	Auto-immune anemia	10 mg–2 mg/kg	2b
	Pure red cell aplasia	0–1 mg/kg	4
	Hemophagocytosis syndrome	60–100 mg (1–2 mg/kg)	4
	TTP/ITP	0–100 mg	4
Gastro-intestinal	Pancreatitis	10 mg–1.5 mg/kg	4
	Auto-immune hepatitis	20–60 mg	4
	Lupus enteritis	10 mg–1 mg/kg	2b
	Gastro-intestinal vasculitis	40–100 mg	4
	Protein losing enteropathy	40–60 mg (0.8-1 mg/kg)	2a
	Lupus peritonitis	40–100 mg	4
Ocular	Neuromyelitis optica (devic)	25 mg–2 mg/kg	4
Other	Lupus cystitis	20–60 mg	4
Pulmonary	Pleuritis	33.6 mg–2 mg/kg	2b
	Shrinking lung syndrome	20–40 mg	4
	Pulmonary hemorhage	40 mg–3 mg/kg	2b
Cardiovascular	Myocarditis	30 mg–1 mg/kg	3a/4
	Pericarditis	30–60 mg	2b
Musculoskeletal	Polyarthritis	Low-dose—10 mg	4
	Myositis	60 mg	5

RHEUMATOLOGY

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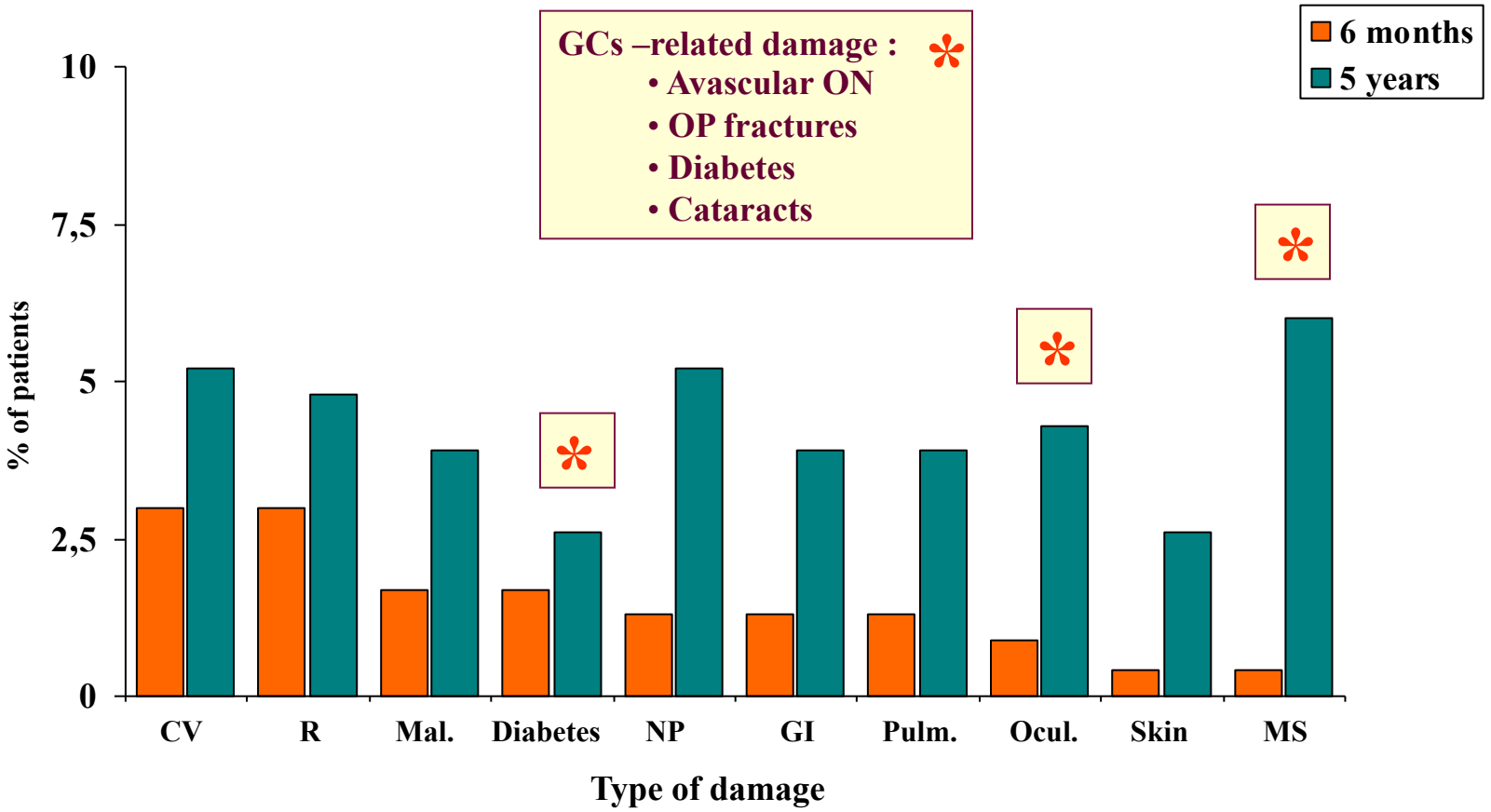
doi:10.1093/rheumatology/keu148
Advance Access publication 27 March 2014

Original article

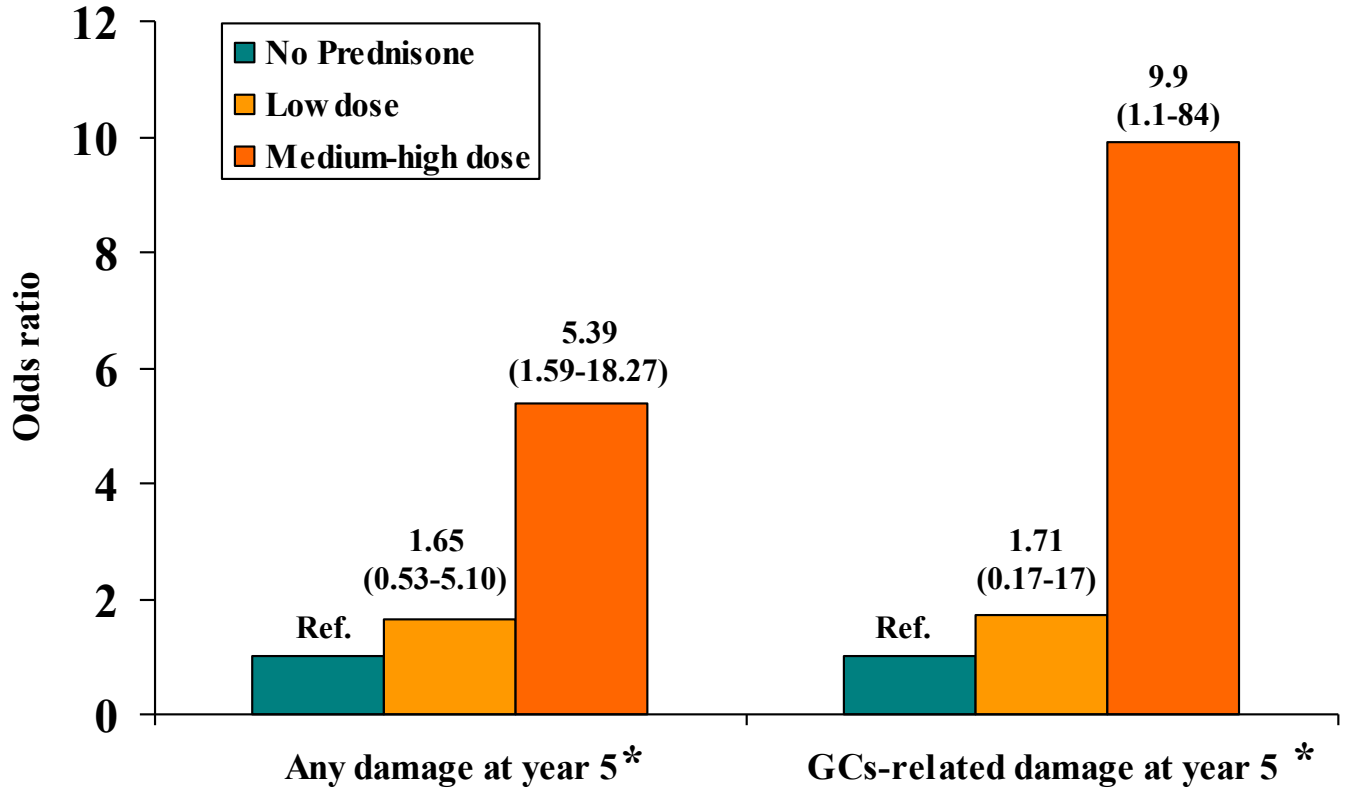
Glucocorticoids and irreversible damage in patients with systemic lupus erythematosus

Ioana Ruiz-Arruza[1], Amaia Ugarte[1], Ivan Cabezas-Rodriguez[1], Jose-Alejandro Medina[1], Miguel-Angel Moran[1] and Guillermo Ruiz-Irastorza[1]



Ruiz-Arruza I et al. *Rheumatology (Oxford)* 2014

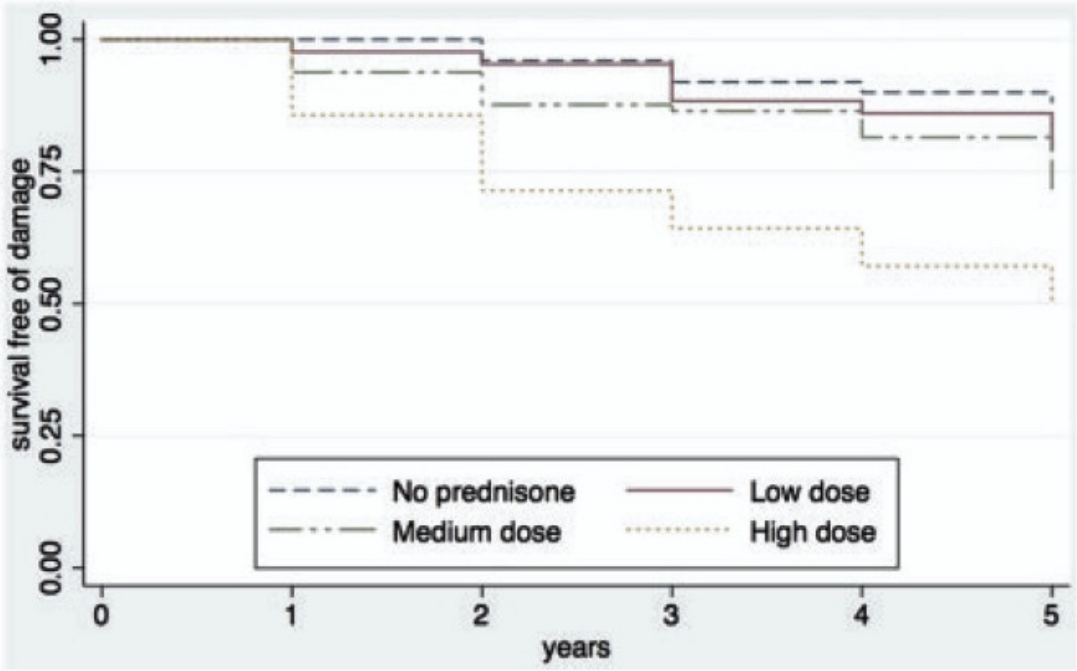
Prednisone dose category and damage accrual at 5 years in 230 SLE patients



* Adjusted by gender, age at diagnosis calendar year of diagnosis, mean SLEDAI, presence of early damage, proliferative nephritis

Ruiz-Arruza I et al. *Rheumatology (Oxford)* 2014

Kaplan-Meier survival free-of-damage curves according to prednisone dose received during the first year of follow-up in 230 SLE patients



Low dose: ⩽7.5 mg/day; medium dose: ⩽30 mg/day; high dose: >30 mg/day.

Ruiz-Arruza I et al. *Rheumatology (Oxford)* 2014

The chronic damage in systemic lupus erythematosus is driven by flares, glucocorticoids and antiphospholipid antibodies: results from a monocentric cohort

F Conti⇑F Ceccarelli, C Perricone, I Leccese, L Massaro, V A Pacucci, S Truglia, F Miranda, F R Spinelli, C Alessandri, G Valesini

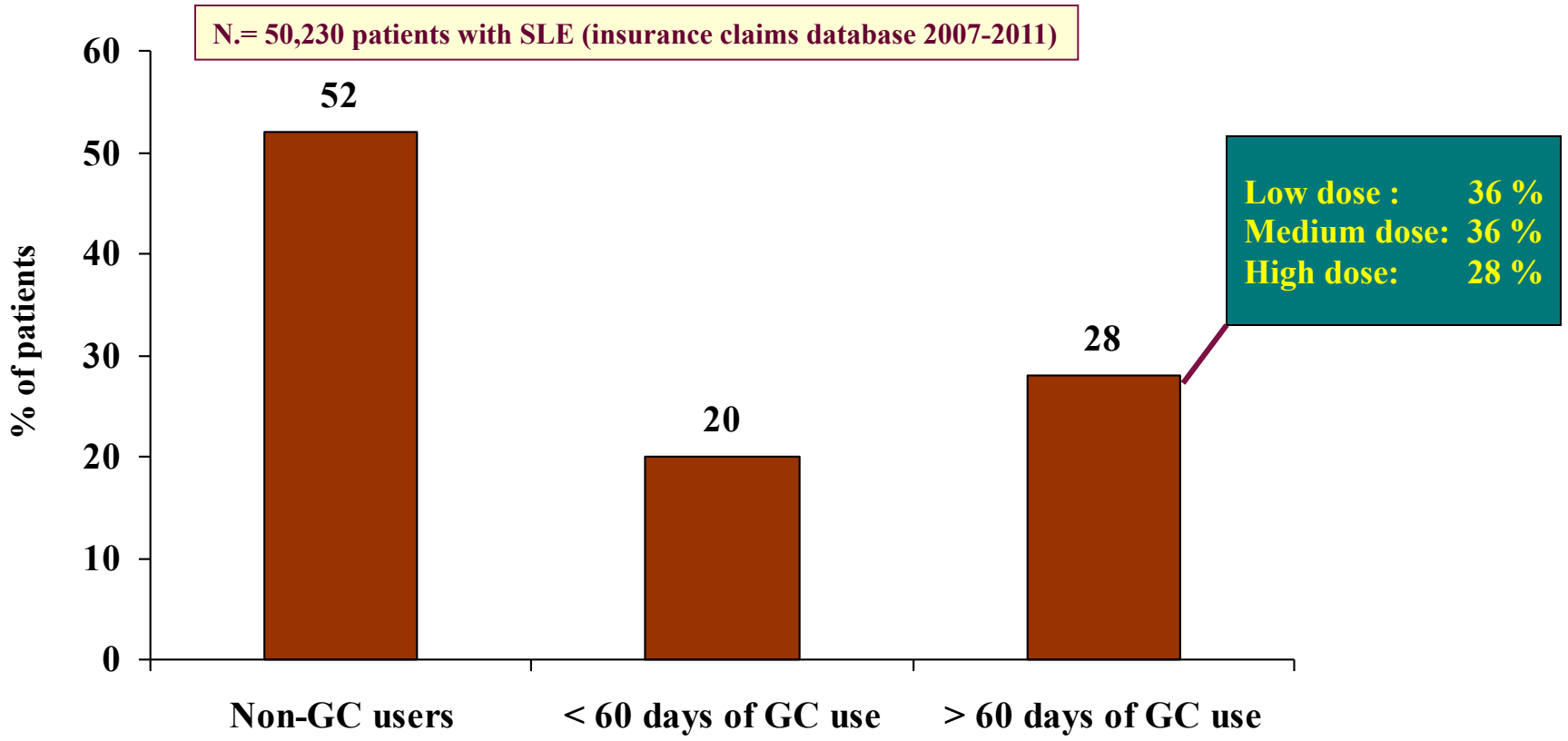
Lupus Clinic, Reumatologia, Dipartimento di Medicina Interna e Specialità Mediche, Sapienza Università di Roma, Rome, Italy

Results We evaluated 349 SLE patients (M/F 25/324, mean age ± SD 42.7 ± 12.4 years, mean disease duration ± SD 164.9 ± 105.2 months). Among the enrolled patients, 125 (35.8%) showed a SDI ≥ 1 (mean SDI ± SD 1.7 ± 0.9, range 0–5). The musculo-skeletal was the most frequently involved organ/system in SDI score (41/349 patients, 11.7%), with deforming/erosive arthritis in 21/349 (6.0%). The presence of chronic damage was associated with age ($P < 0.001$), disease duration ($P < 0.001$), number of flares ($P = 0.02$) and with the use of glucocorticoids ($P = 0.02$).

Conti F et al. *Lupus* 2016

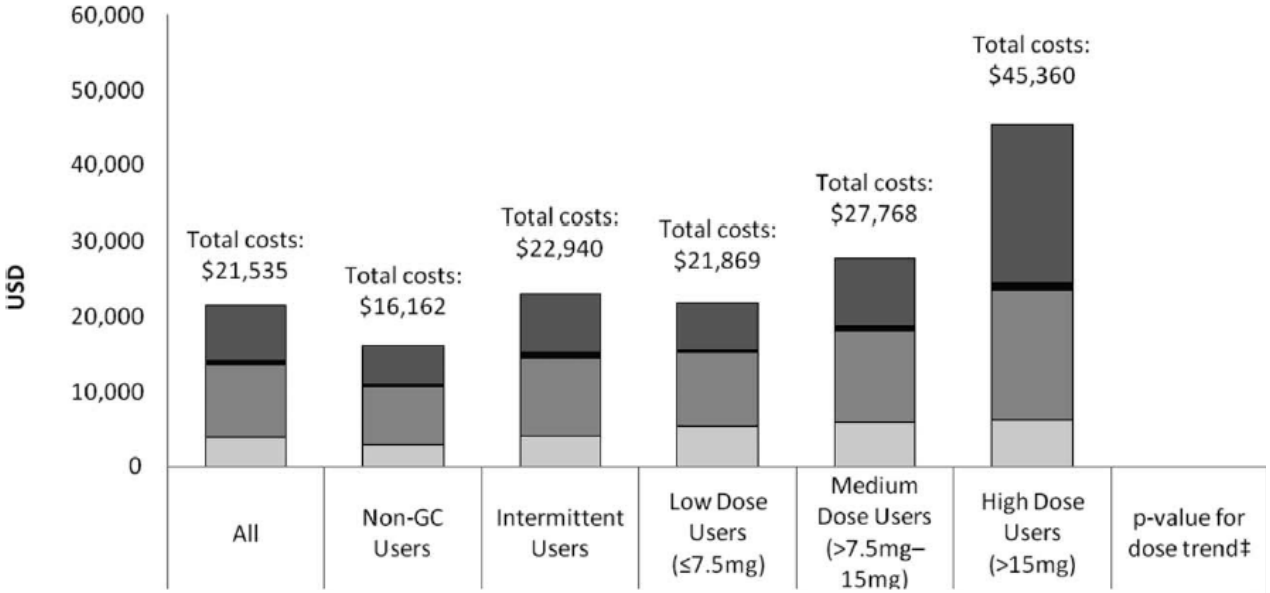
Glucocorticoid Use in Patients With Systemic Lupus Erythematosus: Association Between Dose and Health Care Utilization and Costs

SHIH-YIN CHEN,[1] CHAN-BUM CHOI,[2] QIAN LI,[3] WEI-SHI YEH,[1] YUAN-CHI LEE,[3] AMY H. KAO,[1] AND MATTHEW H. LIANG[4]



Chen S-Y et al. *Arthritis Care Res* 2015

Average health care costs during 1-year follow-up by study cohorts stratified according to GC use



	All	Non-GC Users	Intermittent Users	Low Dose Users (≤7.5mg)	Medium Dose Users (>7.5mg–15mg)	High Dose Users (>15mg)	p-value for dose trend‡
Total costs: mean (SD)	21,535 (46,539)	16,162 (36,970)	22,940* (50,028)	21,869* (44,139)	27,768* (48,387)	45,360* (76,268)	<0.01
Inpatient: mean (SD)	7,412 (33,964)	5,167 (26,018)	7,720* (39,947)	6,249† (30,245)	9,026* (33,153)	20,887* (57,575)	<0.01
ED: mean (SD)	545 (1,981)	397 (1,556)	770* (2,712)	425* (1,347)	652* (1,920)	969* (2,763)	<0.01
Outpatient mean (SD)	9,630 (21,455)	7,653 (18,551)	10,456* (19,141)	9,832* (23,338)	12,170* (23,963)	17,232* (33,523)	<0.01
Pharmacy: mean (SD)	3,948 (7,503)	2,945 (6,533)	3,995* (6,129)	5,363* (9,188)	5,921* (9,916)	6,272* (9,385)	<0.01

Chen S-Y et al. *Arthritis Care Res* 2015

Glucocorticoids in clinical Rheumatology

- **Polymyalgia rheumatica and Giant cell Arteritis**

Glucocorticoids for Management of Polymyalgia Rheumatica and Giant Cell Arteritis

Eric L. Matteson, MD, MPH[a,b,*], Frank Buttgereit, MD[c], Christian Dejaco, MD, PhD, MBA[d,e], Bhaskar Dasgupta, MD[f]

KEY POINTS

- Polymyalgia rheumatica (PMR) and giant cell arteritis (GCA) are diseases of older persons most common in persons of Northern European ancestry. There is considerable clinical overlap between the diseases, and there are many disease mimics.
- Advanced imaging can be useful in support of the diagnosis of the diseases.
- In PMR, typical ultrasonographic findings include subdeltoid bursitis and bicipital tendonitis, which resolve on successful treatment.
- Prompt initiation of treatment is important to avoid complications of visual loss in GCA and severe functional impairment in PMR.
- The course of the diseases is variable. They generally require treatment with glucocorticoids for 1 to 3 years and often longer.

Rheum Dis Clin N Am 42 (2016) 75–90

Provisional European League Against Rheumatism/American College of Rheumatology classification criteria for the polymyalgia rheumatica scoring algorithm (required criteria: age ≥50 y, bilateral shoulder aching, and abnormal C-reactive protein or erythrocyte sedimentation rate)

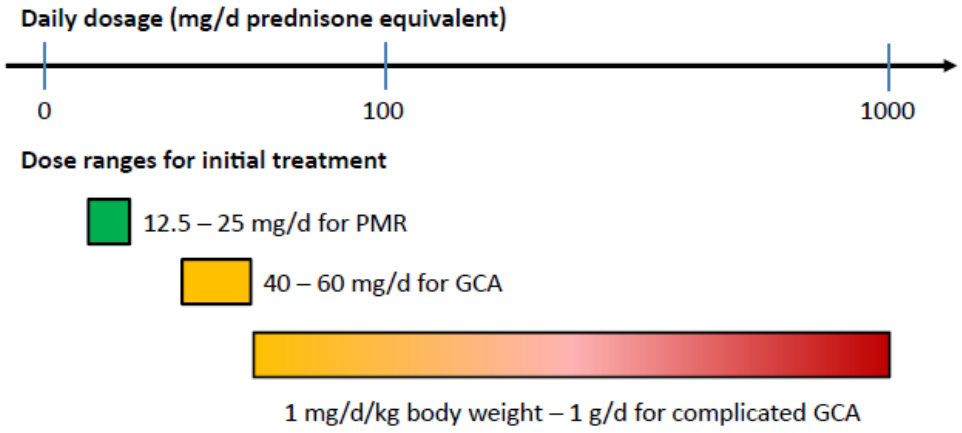
Dasgupta B ey al. *Ann Rheum Dis* 2012

Criteria	Points Without Ultrasonography (0–6)	Points with Ultrasonography[a] (0–8)
Morning stiffness duration >45 min	2	2
Hip pain or limited range of movement	1	1
Absence of RF or ACPA	2	2
Absence of other joint involvement	1	1
≥1 shoulder with subdeltoid bursitis and/or biceps tenosynovitis and/or glenohumeral synovitis (either posterior or axillary) and ≥1 hip with synovitis and/or trochanteric bursitis	n/a	1
Both shoulders with subdeltoid bursitis, biceps tenosynovitis, or glenohumeral synovitis	n/a	1

ACR classification criteria for GCA

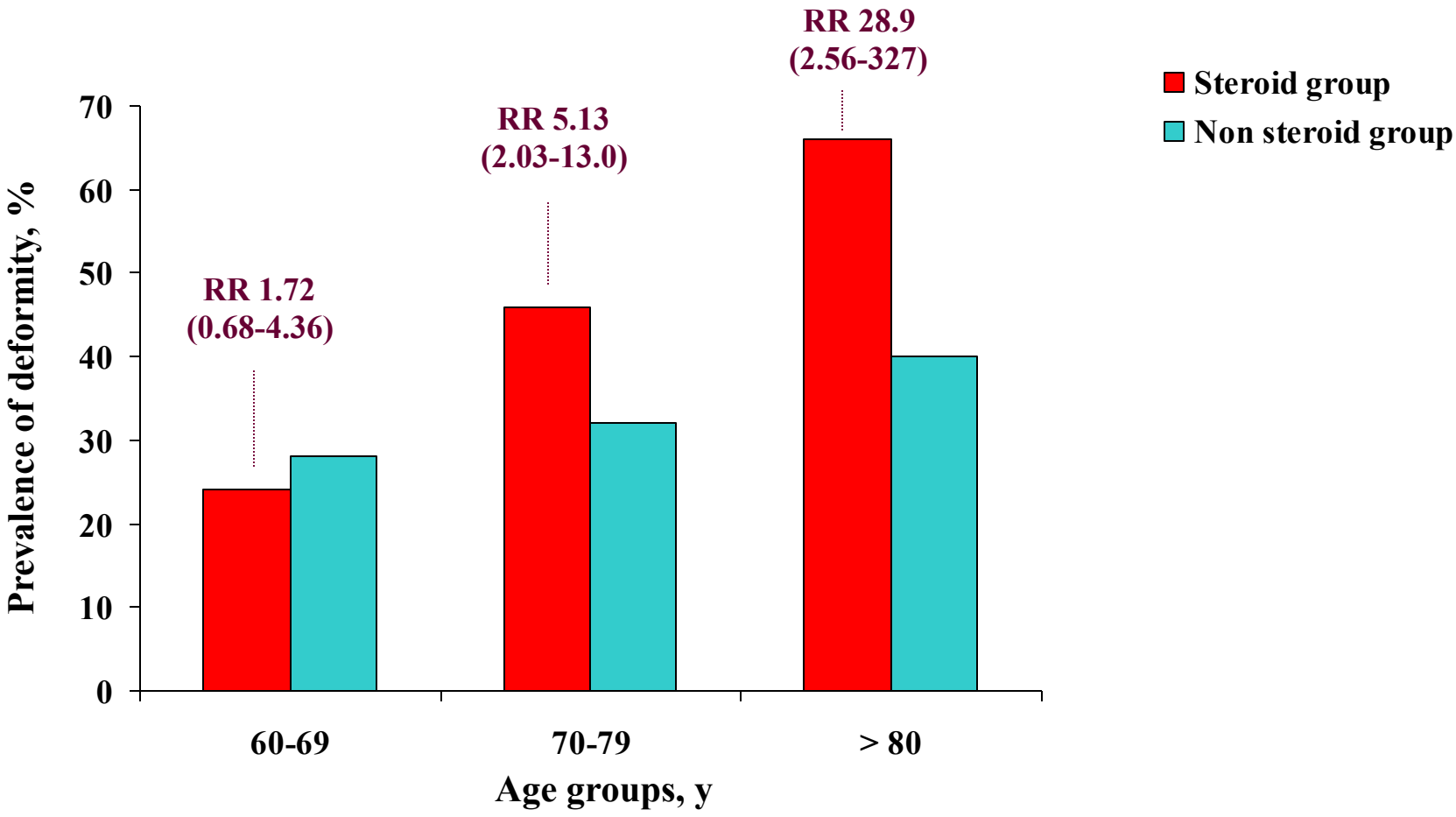
Hunder GG et al. *Arthritis Rheum* 1990

1. Age at onset of disease greater than 50 years
2. New headache
3. Temporal artery abnormality (tenderness to palpation or decreased pulse)
4. Increased ESR greater than 50 mm/h
5. Abnormal findings on biopsy of the temporal artery. The histopathology of the artery shows vasculitis with predominant mononuclear cells or granulomatous inflammation usually with multinucleated giant cells



Rheum Dis Clin N Am 42 (2016) 75–90

Prevalence of vertebral deformity in corticosteroid treated and control patients according to age



Naganathan V et al. *Arch Intern Med* 2000

Giant Cell Arteritis: Beyond Corticosteroids

Lauren Steel[1] · Asad Khan[1] · Bhaskar Dasgupta[1,2,3]

Key Points

The initial management for reasonably suspected giant cell arteritis (GCA) remains high-dose glucocorticoid therapy to prevent ischaemic complications including sight loss.

The treatment with glucocorticoids is usually required long-term, with a gradual tapering regimen. As a consequence, patients may be exposed to the burden of glucocorticoid toxicity, especially in the face of multiple flares that require an increase in the glucocorticoid doses.

Process	Cell/factor involved	Potential target	Drug in clinical trial
Disease initiation	Dendritic cell	TLR-4	
	T cell (Th1, Th17)	IFN-γ	
	Macrophage	IL-6	Tocilizumab (GiACTA)
	Neutrophil	IL-17	
	NKG2D cell	CTLA-4	Abatacept
Disease amplification	NK receptor (CD161)	IFN-γ	
	Notch receptor	IL-17	
	Rho kinase	IL-1 receptor	Anakinra
	B effector cells	IL-1b	Gevokizumab
	Giant cell	NOTCH receptor inhibitor	
	Protease production	TNF-α	
		IL-23	
		MMP-9/MMP-2	
		ET-1	
Vessel injury and occlusion	Giant cell		
	Endothelial cell	PDGF	
	Smooth muscle cell	VEGF	
	Platelet leukocyte interactions	T cells (CD8)	

Steel L et al *Drugs Aging* 2015

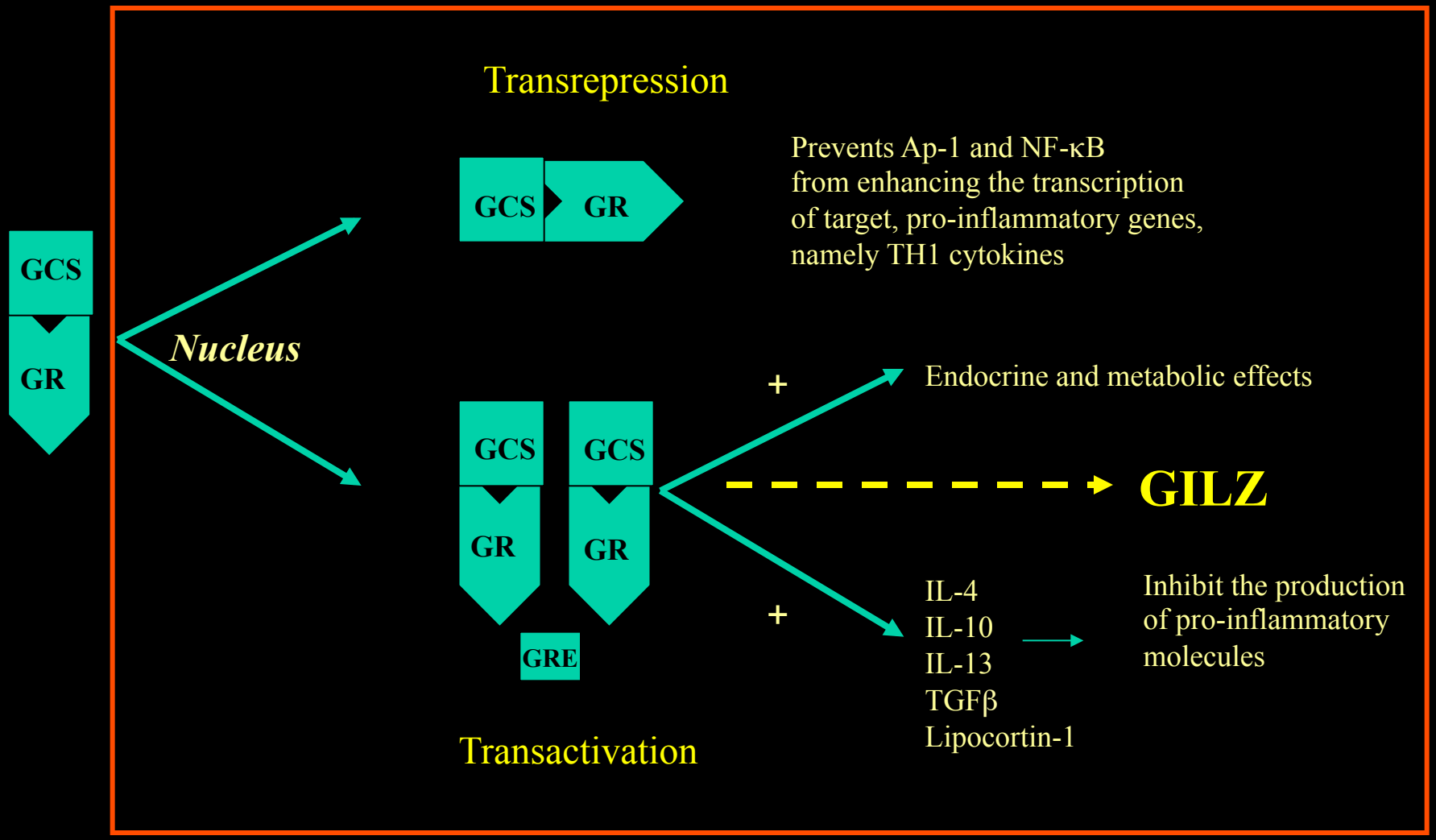
Aging Clin Exp Res (2016) 28:1–16
DOI 10.1007/s40520-015-0522-1

REVIEW

Balancing benefits and risks of glucocorticoids in rheumatic diseases and other inflammatory joint disorders: new insights from emerging data. An expert consensus paper from the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO)

Cyrus Cooper[1,2] · Thomas Bardin[3] · Maria-Luisa Brandi[4] · Patrice Cacoub[5,6] · John Caminis[7] · Roberto Civitelli[8] · Maurizio Cutolo[9] · Willard Dere[10] · Jean-Pierre Devogelaer[11] · Adolfo Diez-Perez[12] · Thomas A. Einhorn[13] · Patrick Emonts[14] · Olivier Ethgen[15] · John A. Kanis[16] · Jean-Marc Kaufman[17] · Tore K. Kvien[18] · Willem F. Lems[19] · Eugene McCloskey[16] · Pierre Miossec[20] · Susanne Reiter[21] · Johann Ringe[22] · René Rizzoli[23] · Kenneth Saag[24] · Jean-Yves Reginster[25]

Transrepression dampens the pro-inflammatory reaction, while transactivation induces behavioral, cardiovascular and metabolic side effects



GILZ as a Mediator of the Anti-Inflammatory Effects of Glucocorticoids

*Simona Ronchetti, Graziella Migliorati and Carlo Riccardi**

***Frontiers in Endocrinology* 2015**

Role of GILZ in immune regulation, glucocorticoid actions and rheumatoid arthritis

Elaine Beaulieu and Eric F. Morand

***Nat Rev Rheumatol* 2011**

EXTENDED REPORT

Glucocorticoid-induced leucine zipper (GILZ) inhibits B cell activation in systemic lupus erythematosus

Sarah A Jones,[1] Andrew E J Toh,[1] Dragana Odobasic,[1] Marie-Anne Virginie Oudin,[1] Qiang Cheng,[1] Jacinta P W Lee,[1] Stefan J White,[2] Brendan E Russ,[3] Simona Infantino,[4,5] Amanda Light,[4,5] David M Tarlinton,[4,5] James Harris,[1] Eric F Morand[1]

***Ann Rheum Dis* 2015**

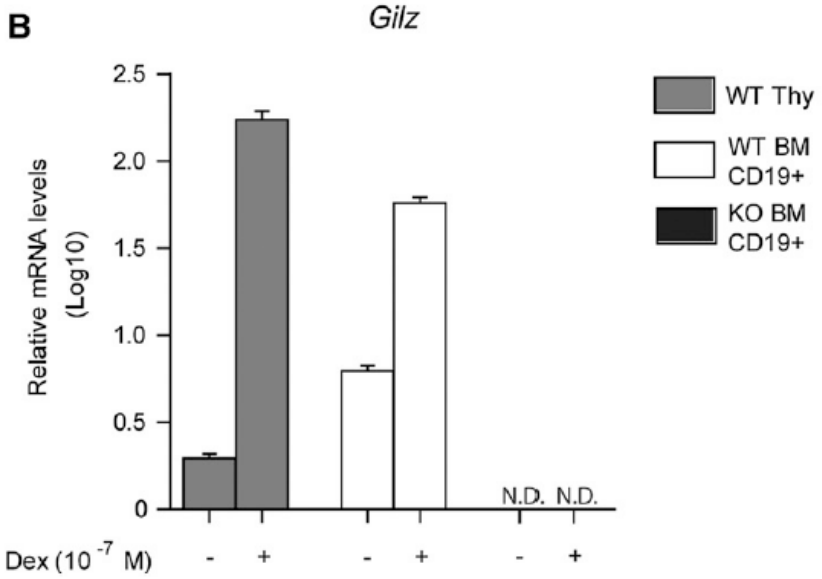
IMMUNOBIOLOGY

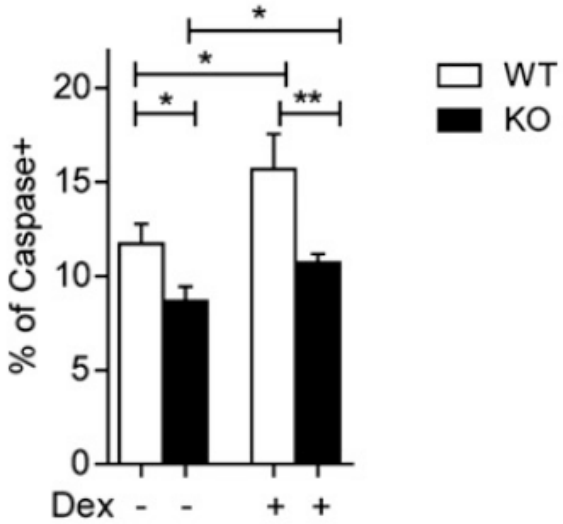
Lack of glucocorticoid-induced leucine zipper (GILZ) deregulates B-cell survival and results in B-cell lymphocytosis in mice

Stefano Bruscoli,[1,*] Michele Biagioli,[1,*] Daniele Sorcini,[1] Tiziana Frammartino,[1] Monica Cimino,[1] Paolo Sportoletti,[2] Emanuela Mazzon,[3] Oxana Bereshchenko,[1] and Carlo Riccardi[1]

Key Points

- GILZ-deficient mice develop B-cell lymphocytosis.
- GILZ deficiency precludes GC-mediated B-cell apoptosis.



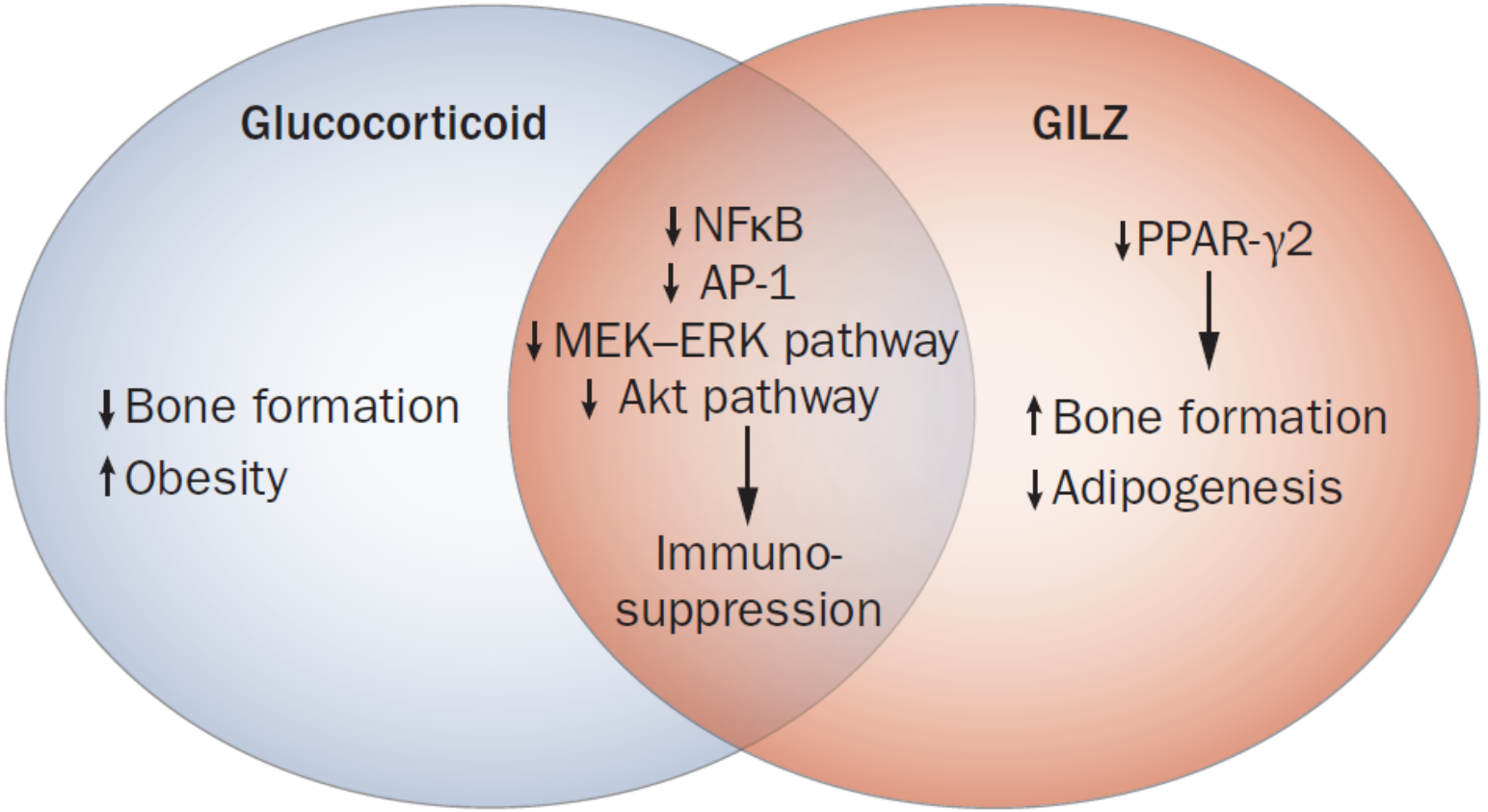


Bruscoli S et al. *Blood* 2015

Immunomodulatory effects of Glucocorticoid-induced leucine zipper protein

Cell type	Function of GILZ	Reference(s)
T lymphocytes	Immunosuppressive Anti-proliferative Inhibits T-cell activation	Mittelstadt *et al.* (2001)[9], Ayroldi *et al.* (2001),[12] Riccardi *et al.* (2001),[14] D'Adamio *et al.* (1997),[15] Asselin-Labat *et al.* (2004)[32]
Macrophages	Anti-inflammatory	Berrebi *et al.* (2003)[21]
Monocytes	Anti-inflammatory	Hamdi *et al.* (2007),[35] Ehrchen *et al.* (2007)[62]
Mast cells	Anti-inflammatory	Godot *et al.* (2006)[36]
Dendritic cells	Immunosuppressive	Cohen *et al.* (2006)[37]
Epithelial cells	Anti-inflammatory	Eddleston *et al.* (2007),[18] Bhalla *et al.* (2006),[63] Soundararajan *et al.* (2005),[64] Chivers *et al.* (2006),[65] Wang *et al.* (2004)[66]
Mesenchymal stem cells	Osteogenesis	Shi *et al.* (2003),[56] Zhang *et al.* (2008)[57]

Potentially different metabolic effects of Glucocorticoids and GILZ



Beaulieu E et al. *Nat Rev Rheumatol* 2011

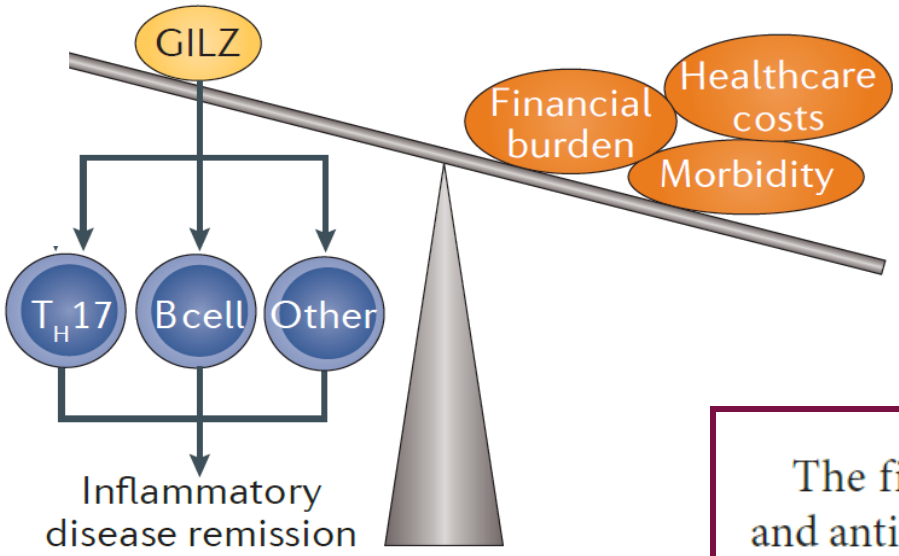
GLUCOCORTICOIDS IN 2015

New answers to old problems

Sarah A. Jones and Eric F. Morand

***Nat Rev Rheumatol* 2016**

Glucocorticoids

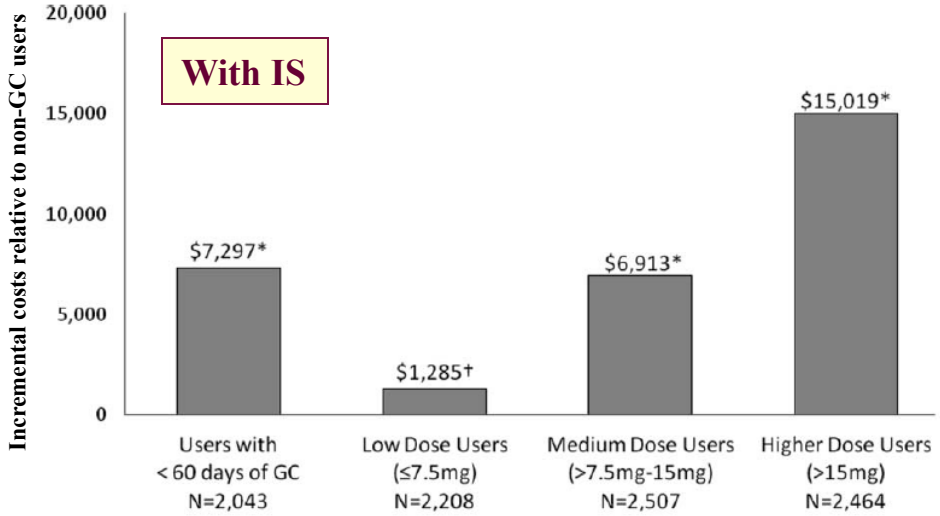


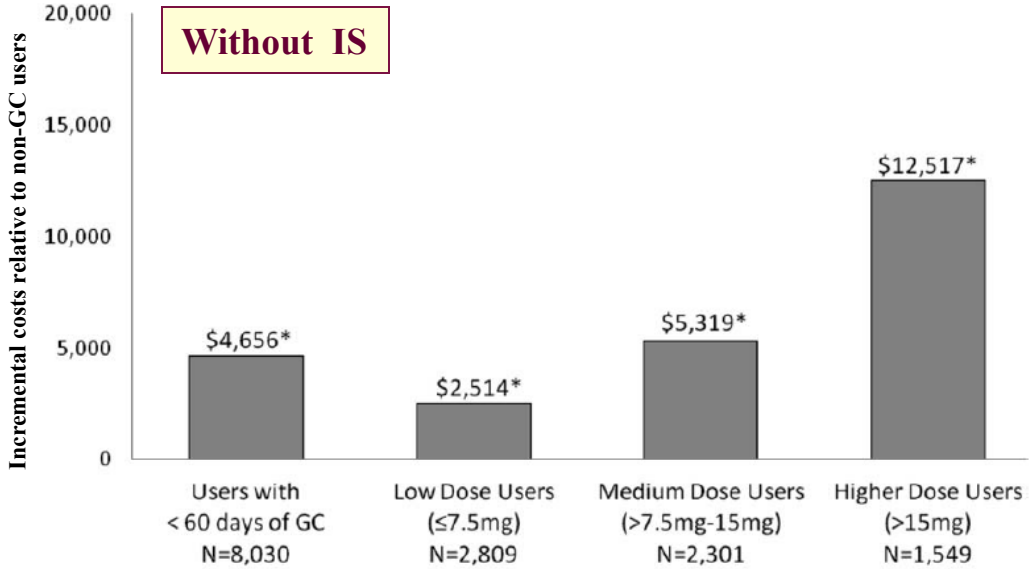
The findings that GILZ exerts immunomodulatory and anti-inflammatory effects that mimic the inhibitory actions of glucocorticoids, while restricting adipocyte differentiation and potentially promoting bone formation, suggest that a non-glucocorticoid GILZ-based therapy might yield the highly desirable goal of having the beneficial effects of glucocorticoids without the associated toxicity.

Beaulieu E et al. *Nat Rev Rheumatol* 2011

Back up

Adjusted incremental total costs during 1-year follow-up by study cohorts stratified by prednisone dose compared with non GC-users in patients with or without use of immunosuppressants





Chen S-Y et al. *Arthritis Care Res* 2015

Philip S. Hench
The Nobel Prize in Physiology or Medicine 1950

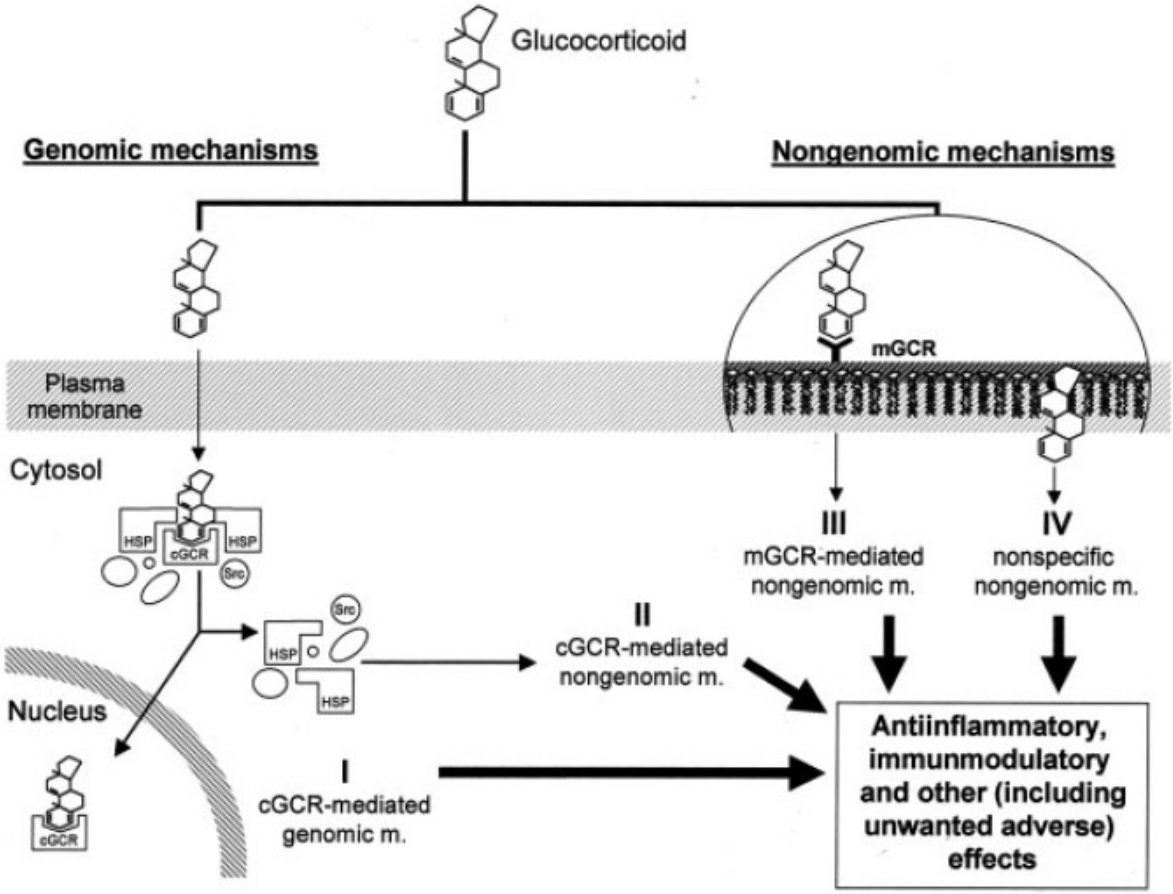


Figure 1. Mechanisms of the cellular actions of glucocorticoids. As lipophilic substances, glucocorticoids pass very easily through the cell membrane into the cell, where they bind to ubiquitously expressed cytosolic glucocorticoid receptors (cGCR). This is followed by either the classic cGCR-mediated genomic effects (I) or by cGCR-mediated nongenomic effects (II). Moreover, the glucocorticoid is very likely to interact with cell membranes either specifically, via membrane bound glucocorticoid receptors (mGCR) (III), or via nonspecific interactions with cell membranes (IV). HSP = heat-shock protein; m. = mechanism.

Current knowledge on the relationship between clinical dosing and cellular actions of Glucocorticoids

Terminology*	Clinical application†	Genomic actions (receptor saturation)‡§	Nongenomic actions§	
			Nonspecific	cGCR-mediated
Low dose (≤7.5 mg/day)	Maintenance therapy for many rheumatic diseases	+ (<50%)	–	?
Medium dose (>7.5 to ≤30 mg/day)	Initial treatment for primary chronic rheumatic diseases	++ (>50 to <100%)	(+)	(+)
High dose (>30 to ≤100 mg/day)	Initial treatment for subacute rheumatic diseases	++(+) (almost 100%)	+	+
Very high dose (>100 mg/day)	Initial treatment for acute and/or potentially life-threatening exacerbations of rheumatic diseases	+++ (almost 100%)	++	+(+?)
Pulse therapy (≥250 mg for 1 or a few days)	For particularly severe and/or potentially life-threatening forms of rheumatic diseases	+++ (100%)	+++	+(++?)

* Values represent mg of prednisone equivalent per day. See ref. 9 for further information.
† See ref. 9.
‡ See ref. 10.
§ cGCR = cytosolic glucocorticoid receptor; ? = unknown; – = not relevant; (+) = perhaps relevant, but of minor importance; + = relevant; +(+?) = relevant or perhaps even very relevant; +(++?) = relevant or perhaps even very or most relevant; ++ = very relevant; ++(+) = very relevant to most relevant; +++ = most relevant.

Buttergeit F et al *Arthritis Rheum* 2004