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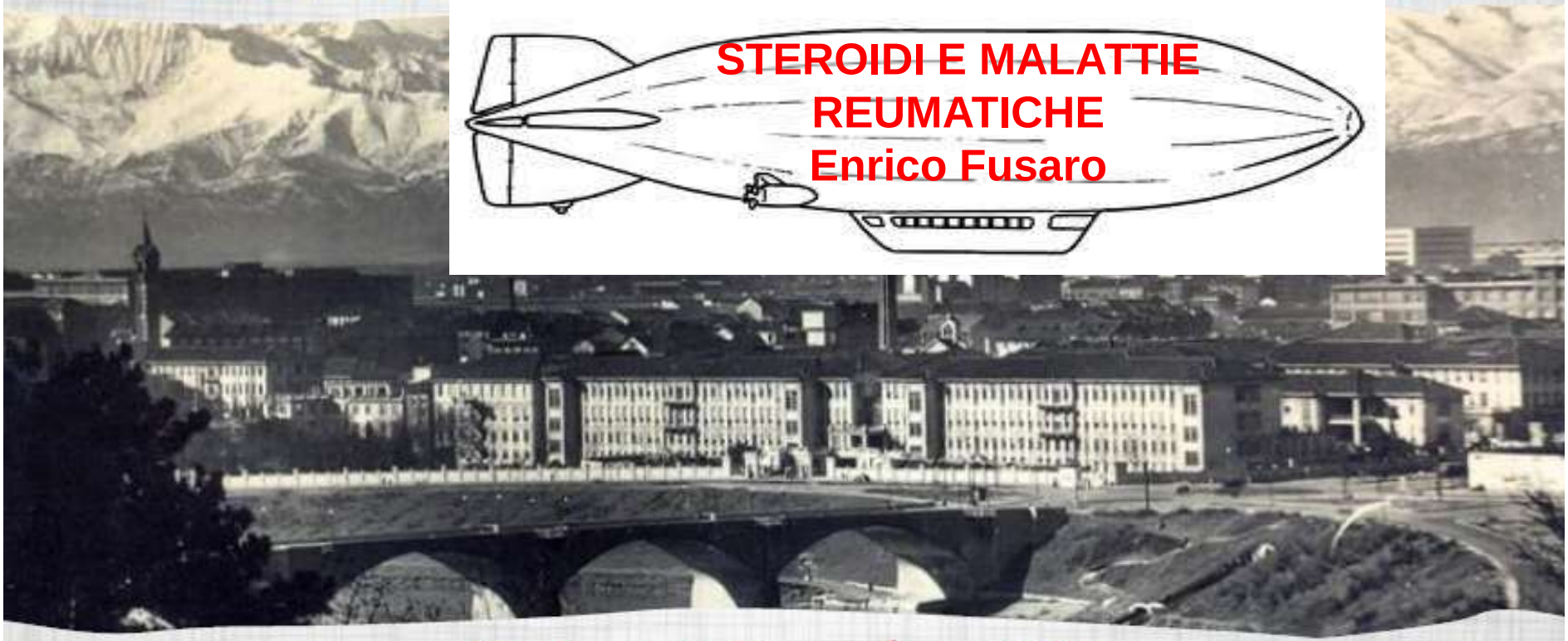
UNIVERSITÀ DEGLI STUDI DI TORINO

APPROCCI INTERDISCIPLINARI IN REUMATOLOGIA

4ª edizione

INFETTIVOLOGIA E MALATTIE REUMATICHE



STEROIDI E MALATTIE REUMATICHE

Enrico Fusaro

Torino, 7-8 ottobre 2016

The Nobel Prize in Physiology or Medicine 1950
Edward C. Kendall, Tadeus Reichstein, Philip S. Hench

Share this:

Edward C. Kendall - Facts

Edward Calvin Kendall

Born: 8 March 1886, South Norwalk, CT, USA

Died: 4 May 1972, Princeton, NJ, USA

Affiliation at the time of the award: Mayo Clinic, Rochester, MN, USA

Prize motivation: "for their discoveries relating to the hormones of the adrenal cortex, their structure and biological effects"

The Nobel Prize in Physiology or Medicine 1950

The Nobel Prize in Physiology or Medicine 1950
Edward C. Kendall, Tadeus Reichstein, Philip S. Hench

Share this:

Tadeus Reichstein - Facts

Tadeus Reichstein

Born: 20 July 1897, Wloclawek, Poland

Died: 1 August 1996, Basel, Switzerland

Affiliation at the time of the award: Basel University, Basel, Switzerland

Prize motivation: "for their discoveries relating to the hormones of the adrenal cortex, their structure and biological effects"

The Nobel Prize in Physiology or Medicine 1950
Edward C. Kendall, Tadeus Reichstein, Philip S. Hench

Share this:

Philip S. Hench - Facts

Philip Showalter Hench

Born: 28 February 1896, Pittsburgh, PA, USA

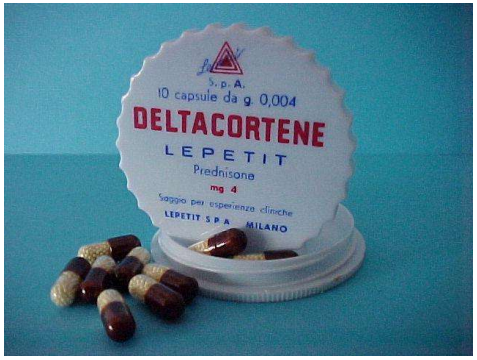
Died: 30 March 1965, Ocho Rios, Jamaica

Affiliation at the time of the award: Mayo Clinic, Rochester, MN, USA

Prize motivation: "for their discoveries relating to the hormones of the adrenal cortex, their structure and biological effects"

Prize motivation: "for their discoveries relating to the hormones of the adrenal cortex, their structure and biological effects"

Hench PS, Kendall EC, Slocum CH, *et al* (1949) The effect of a hormone of the adrenal cortex (17-hydroxy-11-dehydrocorticosterone: Compound E) and the pituitary adrenocorticotropic hormone on rheumatoid arthritis. Preliminary report. *Proceedings of the Staff Meeting of the Mayo Clinic* **24**, 181–97.



"miracle cure for arthritis"

Raoul Dufy (1877-1953)

Cortisone can reverse the inflammatory changes in AR. (Hench PS, *Merck Rep.* ***1950***)

never as be the initial agent …(but) only after the failure of conservative measures (Hollander JL*, Arthritis* ***1966***)

Low doses of GC can be safely used.(Townsend HB*, Clin Exp Rheum* ***2004***)

'Glucocorticoids added at low to moderately high doses to sDMARD monotherapy [or combinations of sDMARDs] provide benefit as initial short term treatment, but should be tapered as rapidly as clinically feasible.' (EULAR recommendations for the management of rheumatoid arthritis. Smolen JS et al, *Ann Rheum Dis* ***2010****).*

Low-dose glucocorticoids should be considered as part of the initial treatment strategy (in combination with one or more csDMARDs) for up to 6 months, but should be tapered as rapidly as clinically feasible (EULAR recommendations for the management of rheumatoid arthritis. Smolen JS, et al. Ann Rheum Dis **2013**;0:1–18)

–, rare use;
1, infrequent use, for therapy-resistant disease, complications, severe fl are, major exacerbation, and for bridging the lag-time of recently started therapy;
2, frequently added to/used as the basic therapeutic strategy;
3, basic part of the therapeutic strategy

	Initial oral dose			Intravenous, very high dose or pulse therapy	Intra-articular injection
	Low	Medium	High		
Arthritides					
Gouty arthritis, acute	–	2	2	–	2
Juvenile idiopathic arthritis	–	1	1	–	1
Osteoarthritis	–	–	–	–	1
Acute calcium pyrophosphate crystal arthritis	–	–	–	–	2
Psoriatic arthritis	–	1	–	–	2
Reactive arthritis	–	–	–	–	1
Rheumatic fever	–	1	1	–	–
Rheumatoid arthritis	2	2	1	1	2
Collagen disorders					
Dermatomyositis, polymyositis	–	–	3	1	–
Mixed connective tissue disease	–	1	–	1	1
Polymyalgia rheumatica	–	3	–	1	–
Sjögren's syndrome, primary	–	–	1	–	–
Systemic lupus erythematosus	–	2	1	1	–
Systemic sclerosis	–	1	–	–	–
Systemic vasculitides					
In general	–	–	3	1	–

–, rare use;
1, infrequent use, for therapy-resistant disease, complications, severe fl are, major exacerbation, and for bridging the lag-time of recently started therapy;
2, frequently added to/used as the basic therapeutic strategy;
3, basic part of the therapeutic strategy

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Psoriatic arthritis	–	1	–	–	2
Reactive arthritis	–	–	–	–	1
Rheumatic fever	–	1	1	–	–
Rheumatoid arthritis	2	2	1	1	2
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Sjögren's syndrome, primary	–	–	1	–	–
Systemic lupus erythematosus	–	2	1	1	–
Systemic sclerosis	–	1	–	–	–
Systemic vasculitides					
In general	–	–	3	1	–

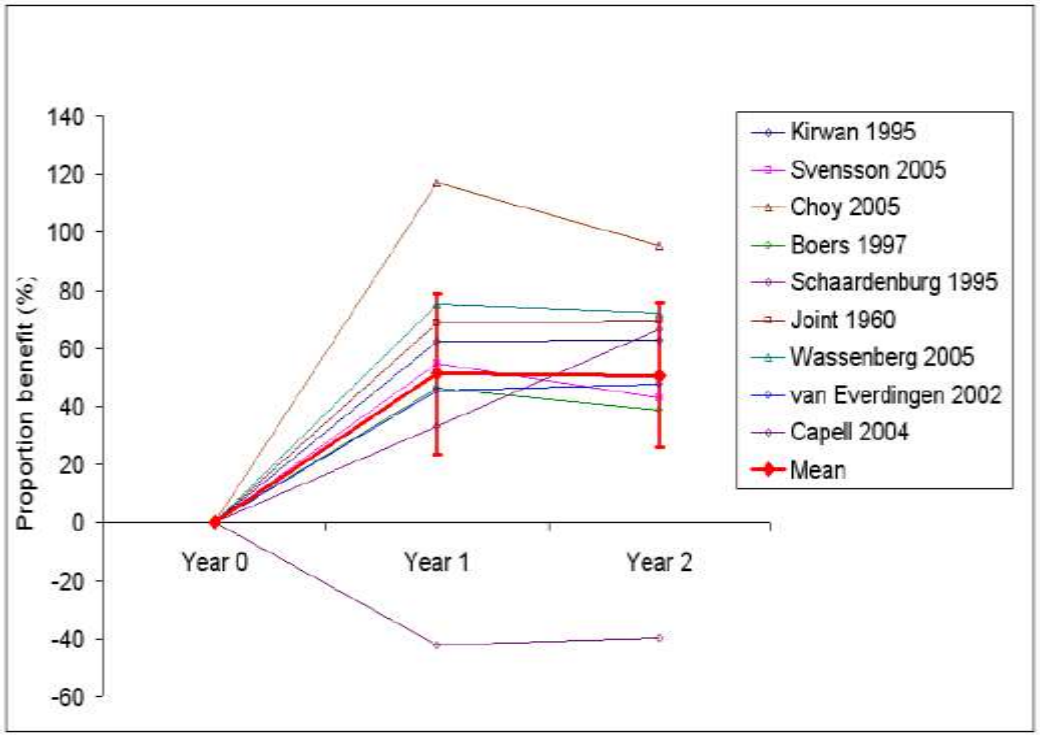
Significant reduction in progression of radiologic joint damage when GC added to antirheumatic treatment

THE COCHRANE COLLABORATION®

1 & 2-year benefit, %

Low dose GC+DMARD vs DMARD

Erosions at 2 years



Kirwan JR, Bijlsma JWJ, Boers M, Shea BJ. Cochrane Library 2007

ARD Online First, published on October 25, 2013 as 10.1136/annrheumdis-2013-204573

OPEN ACCESS

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

6 months

Table 1 2013 Update of the EULAR recommendations (the table of 2010 recommendations can be seen in the online supplement or the original publication)

Overarching principles

A. Treatment of RA patients should aim at the best care and must be based on a shared decision between the patient and the rheumatologist
B. Rheumatologists are the specialists who should primarily care for RA patients
C. RA incurs high individual, societal and medical costs, all of which shoul

Recommendations

1. Therapy with DMARDs should be started as soon as the diagnosis of RA
2. Treatment should be aimed at reaching a target of remission or low dise
3. Monitoring should be frequent in active disease (every 1–3 months); if t been reached by 6 months, therapy should be adjusted
4. MTX should be part of the first treatment strategy in patients with activ
5. In cases of MTX contraindications (or early intolerance), sulfasalazine or
6. In DMARD-naive patients, irrespective of the addition of glucocorticoids,
7. Low-dose glucocorticoids should be considered as part of the initial trea be tapered as rapidly as clinically feasible
8. If the treatment target is not achieved with the first DMARD strategy, in the absence of poor prognostic factors, change to another csDMARD strategy should be considered; when poor prognostic factors are present, addition of a bDMARD should be considered
9. In patients responding insufficiently to MTX and/or other csDMARD strategies, with or without glucocorticoids, bDMARDs (TNF inhibitors*, abatacept or tocilizumab, and, under certain circumstances, rituximab†) should be commenced with MTX
10. If a first bDMARD has failed, patients should be treated with another bDMARD; if a first TNF inhibitor therapy has failed, patients may receive another TNF inhibitor* or a biological agent with another mode of action
11. Tofacitinib may be considered after biological treatment has failed
12. If a patient is in persistent remission after having tapered glucocorticoids, one can consider tapering‡ bDMARDs§, especially if this treatment is combined with a csDMARD
13. In cases of sustained long-term remission, cautious reduction of the csDMARD dose could be considered, as a shared decision between patient and physician
14. When therapy needs to be adjusted, factors apart from disease activity, such as progression of structural damage, comorbidities and safety issues, should be taken into account

7. Low-dose glucocorticoids should be considered as part of the initial treatment strategy (in combination with one or more csDMARDs) for up to 6 months, but should be tapered as rapidly as clinically feasible

As much as necessary
As little as possible

Get in quickly
Get out fast

Research Article

Effects of Anti-TNF Alpha Drugs on Disability in Patients with Rheumatoid Arthritis: Long-Term Real-Life Data from the Lorhen Registry

Matteo Filippini,[1] Chiara Bazzani,[1] Fabiola Atzeni,[2] Piercarlo Sarzi Puttini,[2] Antonio Marchesoni,[3] Ennio Giulio Favalli,[3] Roberto Caporali,[4] Lorenzo Cavagna,[4] and Roberto Gorla[1]

The baseline difference between the patients receiving steroids (867/1033, 83.93%) or not (166/1033, 16.07%) was statistically significant (ΔHAQ > MID; $P < 0.05$), but there was no difference after 42 months (ΔHAQ > MID; P = ns).

HAQ < 0.5 (1st year)	Univariate analysis		HAQ < 0.5 (1st year)	Multivariate analysis	
	OR (95% CI)	P		OR (95% CI)	P
Age (≥65 versus <65 years)	[0.974 (0.962–0.985)]	<0.0001	Age (≥65 versus <65 years)	[0.978 (0.965–0.99)]	0.0004
Gender (F versus M)	[0.354 (0.248–0.505)]	<0.0001	Gender (F versus M)	[0.417 (0.282–0.617)]	<0.0001
Disease duration (years)	[1.004 (0.985–1.023)]	ns	Disease duration	[0.998 (0.976–1.02)]	ns
DAS28 (high versus moderate versus low)	[0.622 (0.542–0.713)]	<0.0001	DAS28 (high versus moderate versus low)	[0.724 (0.626–0.837)]	<0.0001
DMARDs (no versus yes)	[1.248 (0.724–2.151)]	ns	DMARDs (no versus yes)	[0.85 (0.453–1.596)]	ns
Steroids (no versus yes)	[2.109 (1.445–3.078)]	0.0001	Steroids (no versus yes)	[1.775 (1.153–2.734)]	ns
Adalimumab versus infliximab	[1.495 (1.045–2.138)]	ns	Adalimumab versus infliximab	[1.547 (1.041–2.297)]	0.0307
Etanercept versus infliximab	[1.048 (0.69–1.59)]	ns	Etanercept versus infliximab	[0.871 (0.538–1.41)]	ns
HAQ < 0.5 (5th year)	Univariate analysis		HAQ < 0.5 (5th year)	Univariate analysis	
	OR (95% CI)	P		OR (95% CI)	P
Age (≥65 versus <65 years)	[0.978 (0.964–0.991)]	0.0014	Age (≥65 versus <65 years)	[0.982 (0.967–0.996)]	0.0142
Gender (F versus M)	[0.474 (0.31–0.726)]	0.0006	Gender (F versus M)	[0.571 (0.362–0.901)]	0.016
Disease duration	[1.002 (0.979–1.025)]	ns	Disease duration	[0.995 (0.97–1.022)]	ns
DAS28 (high versus moderate versus low)	[0.729 (0.624–0.853)]	0.0001	DAS28 (high versus moderate versus low)	[0.79 (0.668–0.936)]	0.0063
DMARDs (no versus yes)	[0.702 (0.322–1.53)]	ns	DMARDs (no versus yes)	[0.627 (0.255–1.54)]	ns
Steroids (no versus yes)	[1.851 (1.182–2.898)]	0.0071	Steroids (no versus yes)	[1.832 (1.102–3.045)]	0.0195
Adalimumab versus Infliximab	[0.607 (0.383–0.962)]	ns	Adalimumab versus infliximab	[0.554 (0.337–0.911)]	0.019
Etanercept versus infliximab	[0.607 (0.364–1.011)]	ns	Etanercept versus infliximab	[0.502 (0.284–0.888)]	0.017

BioMed Research International
Volume 2014, Article ID 416892, 8 pages
http://dx.doi.org/10.1155/2014/416892

Japan College of Rheumatology
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Taylor & Francis

ORIGINAL ARTICLE

Effectiveness and safety of tocilizumab in achieving clinical and functional remission, and sustaining efficacy in biologics-naive patients with rheumatoid arthritis: The FIRST Bio study

Naoki Ishiguro[1], Tatsuya Atsumi[2], Masayoshi Harigai[3], Tsuneyo Mimori[4], Norihiro Nishimoto[5], Takayuki Sumida[6], Tsutomu Takeuchi[7], Yoshiya Tanaka[8], Ayako Nakasone[9], Nobuhiro Takagi[10], and Hisashi Yamanaka[11]

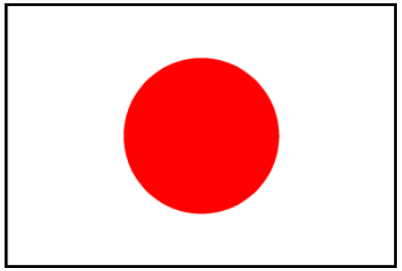

Table 1. Characteristics of patients with RA participating in the FIRST Bio study.

Characteristics	Patients receiving TCZ ($N = 839$)
Concomitant oral corticosteroid use, n (%)[a]	440 (52.4)
Corticosteroid dose, mg/d, mean (SD)	5.4 (3.2)
Corticosteroid dose, mg/d, min–max	0.5–25.0

EXTENDED REPORT

Adalimumab: long-term safety in 23 458 patients from global clinical trials in rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis and Crohn's disease

Gerd R Burmester,[1] Remo Panaccione,[2] Kenneth B Gordon,[3] Melissa J McIlraith,[4] Ana P M Lacerda[5]

Characteristics	Rheumatoid arthritis	Juvenile idiopathic arthritis	Ankylosing spondylitis	Psoriatic arthritis*	Psoriasis	Crohn's disease	All patients
N	14 109	212	1684	837	3010	3606	23 458
Mean age, years	53.5	11.2	43.1	48.4	44.7	37.4	48.6
Mean disease duration, years	9.8†	3.9†	10.9	14.6†	19.3	11.1†	11.4†
Female, %	78.9	80.2	27.5	47.4	33.2	59.7	65.3
Receiving concomitant immunosuppressant agents, %	65.9	64.6	38.2	69.3	2.8	43.2	52.5
Receiving concomitant systemic steroids, %	64.4	53.3	35.5	26.8	4.9	34.6	48.7
From US sites, %	23.1	47.6	8.6	25.3	37.5	37.6	26.4
Exposure, PYs	23 942.6	604.9	1985.6	997.5	5061.8	4138.0	36 730.5
Median duration of exposure, years	0.7	2.6	0.4	0.4	0.7	0.5	0.6
Maximum duration of exposure, years	11.8	6.9	5.1	3.5	5.7	5.5	11.8
>2 Years of exposure, N (%)	2503 (17.7)	109 (51.4)	354 (21.0)	312 (37.3)	1228 (40.8)	703 (19.5)	5209 (22.2)
>5 Years of exposure, N (%)	1646 (11.7)	64 (30.2)	140 (8.3)	0	86 (2.9)	35 (1.0)	1971 (8.4)

Ann Rheum Dis 2013;**72**:517–524. doi:10.1136/annrheumdis-2011-201244


S. p. A.
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mg 4
Saggio per esperienze cliniche
LEPETIT S P A MILANO

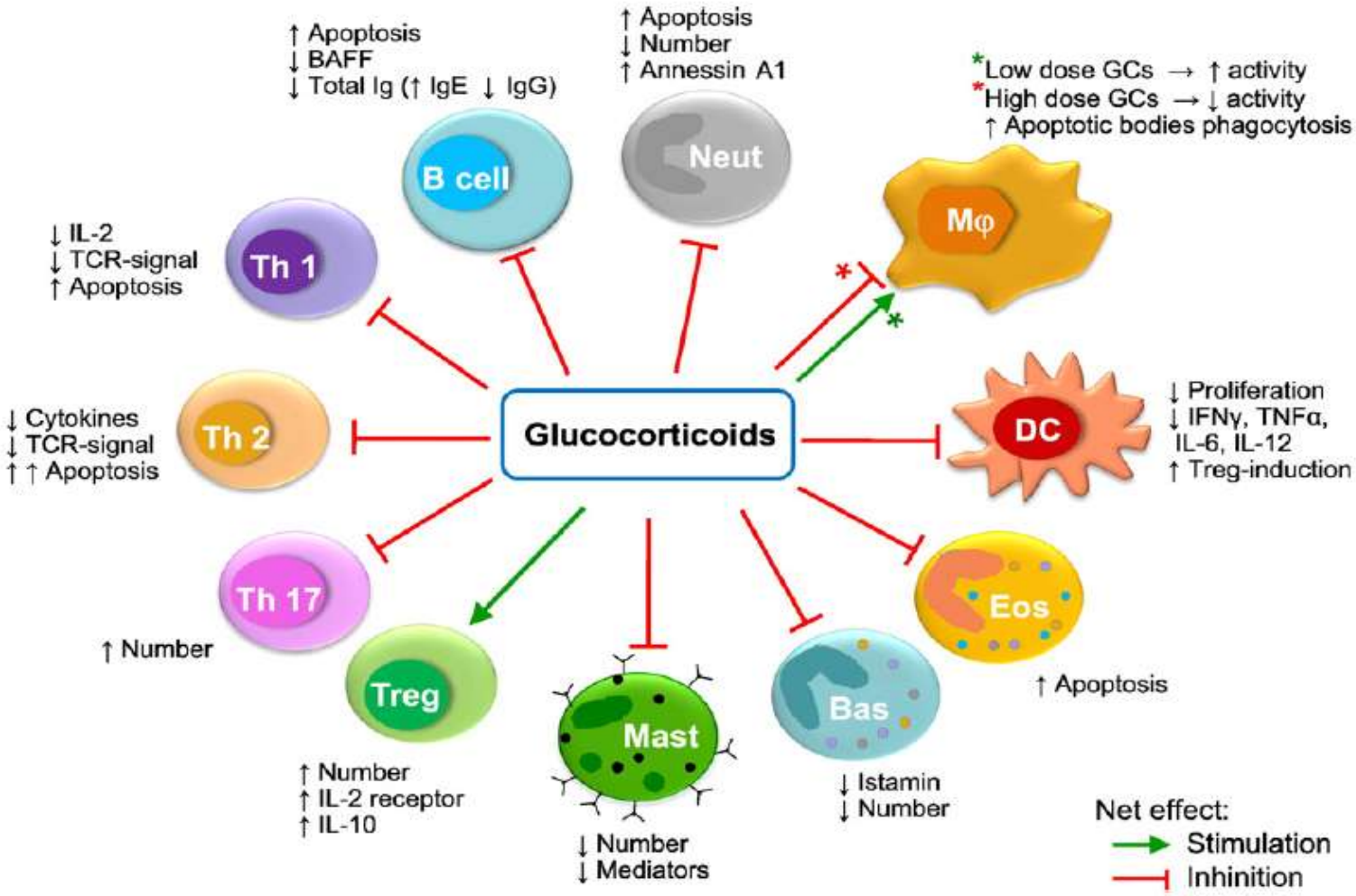
Published in final edited form as:
Arthritis Rheum. 2012 September ; 64(9): 2847–2855. doi:10.1002/art.34530.

Development and Validation of a Risk Score for Serious Infections in Patients with Rheumatoid Arthritis

Cynthia S. Crowson[*,#], Deana D. Hoganson[*], Patrick D. Fitz-Gibbon[#], and Eric L. Matteson[*,#]
[*]Division of Rheumatology
[#]Department of Health Sciences Research

- **Corticosteroid use was associated with a higher risk for serious infection in a dose-dependent fashion**. For corticosteroid use < 10 mg daily prednisone equivalent, the HR was 1.74 (1.35, 2.24) compared to patients not taking corticosteroids. With doses >10 mg daily, the HR increased to 3.60 (95% CI 1.90, 6.81) compared to those not using corticosteroids.

EFFETTI DEI GC SUL SISTEMA IMMUNITARIO



ARTHRITIS & RHEUMATISM
Vol. 63, No. 1, January 2011, pp 1-9
DOI 10.1002/art.30070

Arthritis & Rheumatism

An Official Journal of the American College of Rheumatology
www.arthritisrheum.org and wileyonlinelibrary.com

REVIEW

Exogenous and Endogenous Glucocorticoids in Rheumatic Diseases

Frank Buttgereit,[1] Gerd-Rüdiger Burmester,[2] Rainer H. Straub,[3] Markus J. Seibel,[4] and Hong Zhou[5]

EFFETTI "GENOMICI" DEI GCs

EFFETTI "NON GENOMICI" DEI GCs

EFFETTI "GENOMICI" DEI GCs

EFFETTI A LENTA REALIZZAZIONE

Passaggio attraverso la membrana plasmatica

↓

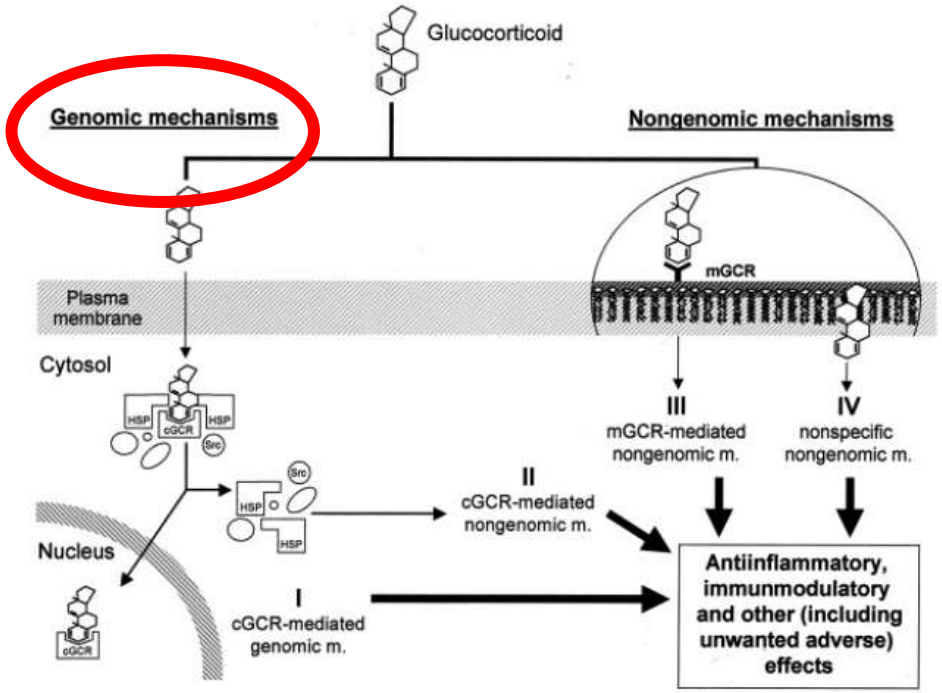
Legame con i recettori dei GCs

↓

Formazione di un complesso che entra nel nucleo

↓

Variazione genetica mediante



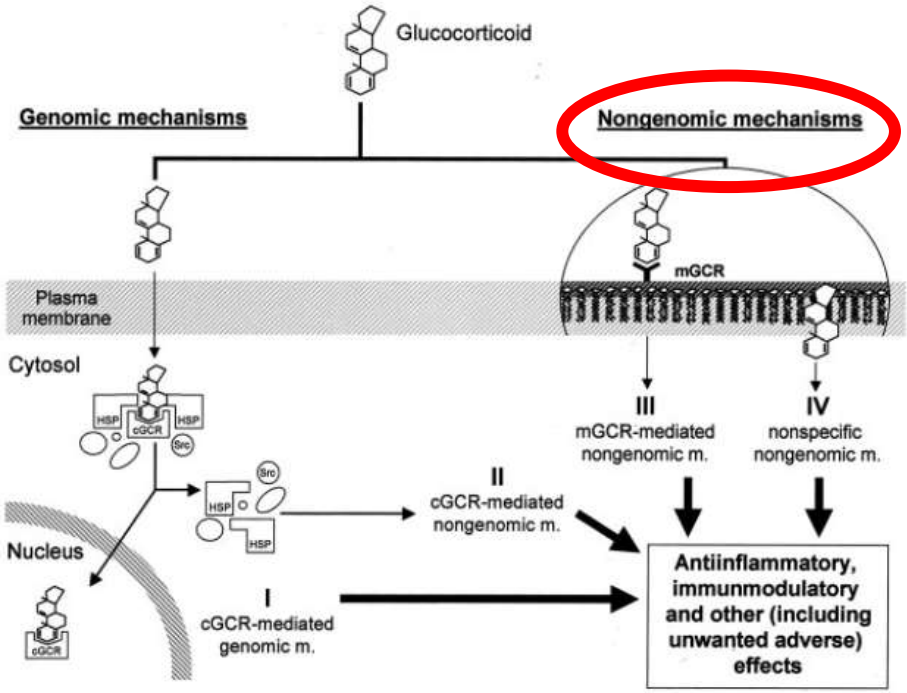
→ Trans-attivazione
(> Sintesi di molecole anti-infiammatorie)

→ Trans-repressione
(< Sintesi di sostanze pro-infiammatori

EFFETTI “NON GENOMICI” DEI GCs

Effetti mediati dal legame dei GCs con i recettori di membrana

Relazione tra il numero di Monociti positivi ai recettori di membrana dei GCs e l’attività dell’A.R.



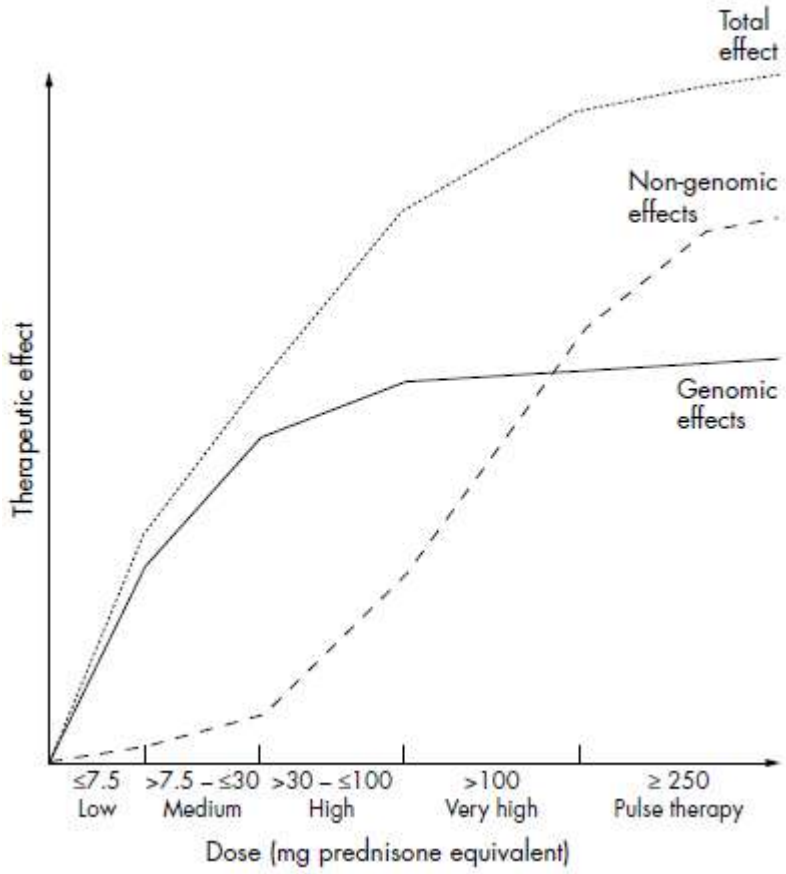
EFFETTI A RAPIDA REALIZZAZIONE

EXTENDED REPORT

Standardised nomenclature for glucocorticoid dosages and glucocorticoid treatment regimens: current questions and tentative answers in rheumatology

F Buttgereit, J A P da Silva, M Boers, G-R Burmester, M Cutolo, J Jacobs, J Kirwan, L Köhler, P van Riel, T Vischer, J W J Bijlsma

Ann Rheum Dis 2002;**61**:718–722



ARTHRITIS & RHEUMATISM
Vol. 46, No. 9, September 2002, pp 2287–2293
DOI 10.1002/art.10524

Frequency of Infection in Patients With Rheumatoid Arthritis Compared With Controls

A Population-Based Study

Michele F. Doran, Cynthia S. Crowson, Gregory R. Pond, W. Michael O'Fallon, and Sherine E. Gabriel

Table 4. All physician-documented infections in 609 rheumatoid arthritis (RA) and 609 non-RA subjects

Infection type	Patients, no.		Infections, no.		Incidence/100 person-years (all events/person)		Rate ratio*	95% confidence interval†
	RA	Non-RA	RA	Non-RA	RA	Non-RA		
Total	471	456	2,417	2,124	32.05	24.04	1.33	1.26–1.41
Bacteremia/septicemia	53	39	60	47	0.78	0.51	1.50	1.10–2.08
Septic arthritis	22	2	31	2	0.40	0.02	14.89	6.12–73.71
Osteomyelitis	11	1	13	1	0.17	0.01	10.63	3.39–126.81
Pneumonia	179	135	311	218	4.02	2.39	1.68	1.46–1.95
Lower respiratory tract	244	227	624	638	8.07	6.99	1.16	1.05–1.27
Urinary tract infections	234	224	658	662	8.72	7.49	1.16	1.05–1.30
Urosepsis/pyelonephritis	28	29	38	40	0.49	0.44	1.12	0.77–1.63
Skin/soft tissue	245	187	537	328	6.95	3.59	1.93	1.72–2.17
Gastroenteritis	49	88	63	119	0.82	1.30	0.63	0.48–0.81
Intra-abdominal	28	28	29	29	0.38	0.32	1.18	0.77–1.82
Other	42	34	53	40	0.69	0.44	1.56	1.11–2.22

OPEN ACCESS

EXTENDED REPORT

Adalimumab: long-term safety in 23 458 patients from global clinical trials in rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis and Crohn's disease

Gerd R Burmester,[1] Remo Panaccione,[2] Kenneth B Gordon,[3] Melissa J McIlraith,[4] Ana P M Lacerda[5]

	Rheumatoid arthritis	Juvenile idiopathic arthritis	Ankylosing spondylitis	Psoriatic arthritis	Psoriasis	Crohn's disease
N	14 109	212	1684	837	3010	3606
Exposure, PYs	23 942.6	604.9	1985.6	997.5	5061.8	4138.0
Serious infections	4.6	2.0	1.4	2.8	1.7	6.7
Active tuberculosis	0.3	0	0	0.2	0.1	<0.1
Opportunistic infections	<0.1	0	0	0	0	<0.1
Demyelinating disorder	<0.1	0	<0.1	0	0	0.1
Lupus-like syndrome	<0.1	0	0.1	0	0	<0.1
CHF	0.2	0	0.1	0	<0.1	0
New onset/worsening of psoriasis	<0.1	0	<0.1	0.1	<0.1	<0.1
Malignancies excluding lymphoma and NMSC	0.9	0	0.2	0.2	0.6	0.5
Lymphoma	0.1	0	<0.1	0.2	<0.1	<0.1
NMSC†	0.2	0	0.3	0.1	0.1	<0.1
Melanoma	<0.1	0	<0.1	0	0.2	0
Any AE leading to death	0.8	0	<0.1	0.3	0.2	0.1

*Rates in events/100 PYs.
†Only serious NMSC events.
AE, adverse event; CHF, congestive heart failure; NMSC, non-melanoma skin cancer; PYs, patient-years.

Published in final edited form as:
Arthritis Rheum. 2012 September ; 64(9): 2847–2855. doi:10.1002/art.34530.

Development and Validation of a Risk Score for Serious Infections in Patients with Rheumatoid Arthritis

Cynthia S. Crowson[*,†], Deana D. Hoganson[*], Patrick D. Fitz-Gibbon[†], and Eric L. Matteson[*,†]
[*]Division of Rheumatology
[†]Department of Health Sciences Research

- Several comorbidities were associated with the risk of serious infections, including **chronic lung disease** (HR: 1.56; 95% CI: 1.24, 1.95; adjusted for all other predictors in the risk score), **diabetes mell**itus (HR: 1.35; 95% CI: 1.01, 1.81), **alcoholism** (HR: 1.50; 95% CI: 1.05, 2.16), **coronary heart disease** (HR: 1.47; 95% CI: 1.08, 2.01), **heart failure** (HR: 1.70, 95% CI: 1.34, 2.16), and **peripheral vascular disease** (HR: 1.50; 95% CI: 1.13, 2.10).

- The presence of one comorbidity was associated with an increased risk of infection (HR: 1.96; 95% CI: 1.55, 2.49), with an additional risk for more than 1 comorbidity (HR: 2.79; 95% CI: 2.17, 3.58).

Predictor	Level	Model developed in Original Cohort[†] Hazard Ratio (95% CI)	Model assessed in Validation Cohort[‡] Hazard Ratio (95% CI)
Age	Age< 60 years	Reference	Reference
	60 ≤ age < 80 years	1.50 (1.15, 1.95)	1.53 (0.98, 2.40)
	age ≥ 80 years	2.36 (1.71, 3.24)	2.18 (1.21, 3.91)
Previous serious infection	Never or >3 years ago	Reference	Reference
	In the past year	3.48 (2.67, 4.54)	10.13 (6.00, 17.12)
	In the past 2–3 years	1.95 (1.45, 2.63)	5.59 (2.69, 11.64)
Extraarticular manifestation of RA [*]		1.86 (1.33, 2.60)	1.59 (0.88, 2.87)
Erythrocyte sedimentation rate (ESR)	ESR < 30 mm/hr	Reference	Reference
	30 ≤ ESR ≤ 50 mm/hr	1.20 (0.93, 1.55)	1.50 (0.98, 2.32)
	ESR > 50 mm/hr	1.84 (1.45, 2.34)	1.05 (0.54, 2.03)
Corticosteroid dose	None	Reference	Reference
	≤ 10 mg daily	1.74 (1.35, 2.24)	2.14 (1.42, 3.23)
	> 10 mg daily	3.60 (1.90, 6.82)	3.97 (1.79, 8.82)
Comorbidities [**]	None	Reference	Reference
	One	1.96 (1.55, 2.49)	1.25 (0.77, 2.05)
	More than one	2.79 (2.17, 3.58)	2.67 (1.45, 4.90)

Variabilità inter-individuale della risposta ai GC

STESSA DOSE

DIVERSA EFFICACIA CLINICA

DIVERSA INTENSITA' DEGLI EFFETTI COLLATERALI

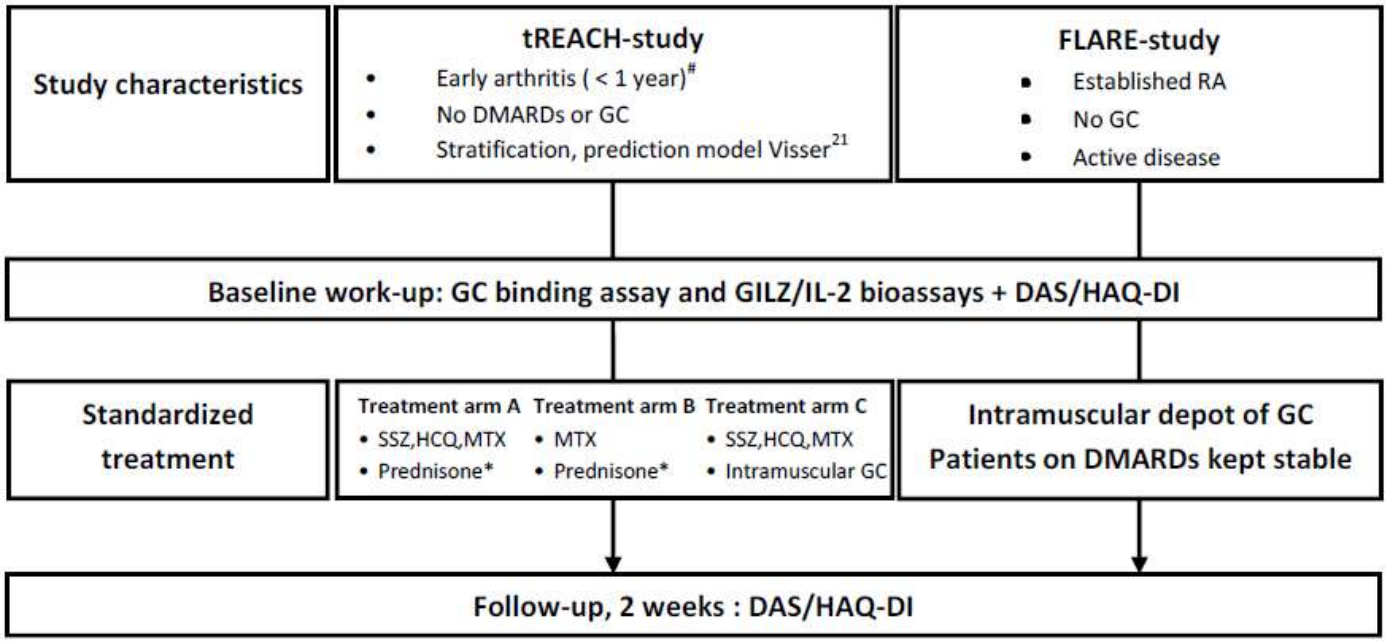
Quax et al. Arthritis Research & Therapy 2012, 14:R195
http://arthritis-research.com/content/14/4/R195

arthritis research&therapy

RESEARCH ARTICLE Open Access

In vitro glucocorticoid sensitivity is associated with clinical glucocorticoid therapy outcome in rheumatoid arthritis

Rogier AM Quax[1*], Jan W Koper[1], Pascal HP de Jong[2], Ramona van Heerebeek[1], Angelique E Weel[3], Anne M Huisman[4], Derkjen van Zeben[4], Frank H de Jong[1], Steven WJ Lamberts[1], Johanna MW Hazes[2] and Richard A Feelders[1]



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Abstract

Introduction: Genetic and disease-related factors give rise to a wide spectrum of glucocorticoid (GC) sensitivity in rheumatoid arthritis (RA). In clinical practice, GC treatment is not adapted to these differences in GC sensitivity. *In vitro* assessment of GC sensitivity before the start of therapy could allow more individualized GC therapy. The aim of the study was to investigate the association between *in vitro* and *in vivo* GC sensitivity in RA.

Methods: Thirty-eight early and 37 established RA patients were prospectively studied. *In vitro* GC sensitivity was assessed with dexamethasone-induced effects on interleukin-2 (IL-2) and glucocorticoid-induced leucine zipper (GILZ) messenger RNA expression in peripheral blood mononuclear cells (PBMCs). A whole-cell dexamethasone-binding assay was used to measure number and affinity ($1/K_D$) of glucocorticoid receptors (GRs). *In vivo* GC sensitivity was determined by measuring the disease activity score (DAS) and health assessment questionnaire disability index (HAQ-DI) score before and after 2 weeks of standardized GC treatment.

Results: GR number was positively correlated with improvement in DAS. IL-2-EC_{50} and GILZ-EC_{50} values both had weak near-significant correlations with clinical improvement in DAS in intramuscularly treated patients only. HAQ responders had lower GILZ-EC_{50} values and higher GR number and K_D.

Conclusions: Baseline cellular *in vitro* glucocorticoid sensitivity is modestly associated with *in vivo* improvement in DAS and HAQ-DI score after GC bridging therapy in RA. Further studies are needed to evaluate whether *in vitro* GC sensitivity may support the development of tailor-made GC therapy in RA.

Infection Risk and Safety of Corticosteroid Use

RANDOMIZED CONTROLLED TRIALS

Jameel Youssef, MD*, Shannon A. Novosad, MD, Kevin L. Winthrop, MD, MPH

Rheum Dis Clin N Am 42 (2016) 157–176

Table 1
Recent randomized controlled trials in patients with rheumatoid arthritis treated with systemic corticosteroids*

Author, Year, Country, Duration	Population	Arms of Study	Type of Infection/ Outcome	Outcome (Percentage of Infections in Each Treatment Arm)
Capell et al,[21] 2004, UK, 2 y	RA patients not on DMARDs, n = 167	1. SSZ plus prednisone 7 mg 2. SSZ plus placebo	• Infections leading to discontinuation	• None reported
Choy et al,[22] 2008, UK, 2 y	Early RA patients on MTX within 2 y of diagnosis, n = 467	1. MTX 2. MTX plus cyclosporine 3. MTX plus step-down prednisolone 4. MTX plus cyclosporine and pr	• Serious infections • Respiratory tract infections	• 5.9%, 2.5%, 3.4%, and 1.7% serious infections in the 4 arms, respectively • 46.1%, 42.8%, 42.6%, and 47.4% respiratory tract infections in the 4 arms,
Durez et al,[23] 2007, Belgium, 46 wk	Early RA patients, n = 44	1. M 2. M 3. M 2,		
Gerlag et al,[24] 2004, the Netherlands, 2 wk	RA patients on DMARDs, n = 21	1. Pr ok 2. Pl		
Kirwan et al,[25] 2004, Belgium and Sweden, UK, 12 wk	Patients with RA, n = 143	1. Bu 2. Bu 3. Pr 4. Pl		
Sheldon,[26] 2003, UK, 4 wk	Patients with RA, n = 26	1. Bu 2. Pl		
Svensson et al,[1] 2005, Sweden, 2 y	Early RA patients on DMARDs, n = 250	1. DMARD plus prednisolone 7.5 mg 2. DMARD, no prednisolone	• Withdrawal due to adverse events	• 0.7% Infections in the nonprednisolone arm (1 abscess) • No discontinuations due to infection in the prednisolone arm
van Everdingen et al,[27] 2002, the Netherlands, 2 y	Previously untreated patients with early RA, n = 81	1. Prednisolone, 10 mg 2. Placebo	• Infections treated with antibiotics	• 42.5% Infections in the prednisolone arm • 53.6% Infections in the placebo arm
Wassenberg et al,[2] 2005, Germany, Austria, and Switzerland, 2 y	Patients with RA of <2 y duration, n = 192	1. Prednisolone, 5 mg, plus DMARD therapy 2. Placebo plus DMARD therapy	• Adverse events	• 3.1% Bronchitis infections and 1% influenza infections in the prednisolone arm • 3% Influenza infections in the placebo arm
Buttgereit et al,[28] 2013, Europe and US, 12 wk	Patients with RA on DMARDs, n = 350	1. MR prednisone plus DMARDs 2. Placebo plus DMARDs	• Incidence of infection, nasopharyngitis, and bronchitis	• Incidence of infection in the prednisone group 13% vs 12% in the placebo • Incidence of pharyngitis 4.8% in the prednisone group vs 3.4% in the placebo • Incidence of bronchitis 1.3% in the Prednisone groups vs 4.2% in the placebo
Bakker et al,[29] 2012, the Netherlands, 2 y	Patients with RA, DMARDs naïve, n = 239	1. MTX plus prednisone, 10 mg daily 2. MTX plus placebo	• Infections treated with antibiotics	• 0.8% Infections in the prednisone group • No infections in the placebo group

"No significant increased risk of infection was noted in the corticosteroid arms in most of the trial"

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Rheum Dis Clin N Am 42 (2016) 157–176

OBSERVATIONAL STUDIES

Table 2
Recent observational studies evaluating risk of infections in patients with rheumatoid arthritis treated with systemic corticosteroids

Author, Year, Country, Duration, Study Type	Population	Prednisone or Prednisone Equivalent Dose	Infections	Results	Risk Ratios[a]
Wolfe et al,[32] 2006, US, 2001–2004, prospective	RA, n = 16,788	PEQ ≤5 PEQ 5–10 PEQ >10	Pneumonia requiring hospitalization	Increased risk of infection; dose dependent	HR of hospitalization for pneumonia: • Any PEQ, HR 1.7 (95% CI, 1.5–2) • PEQ ≤5, HR 1.4 (95% CI, 1.1–1.6) • PEQ 5–10, HR 2.1 (95% CI, 1.7–2.7)
Curtis et al,[35] 2007, US, 5/1998–12/2003, retrospective					
Franklin et al,[37] 2007, NOAR, 1990–1999, prospective					
Schneeweiss et al,[33] 2007, US, 1/1995–12/2003, prospective					

Table 2 (*continued*)

Author, Year, Country, Duration, Study Type	Population	Prednisone or Prednisone Equivalent Dose	Infections	Results	Risk Ratios[a]
Smitten et al,[14] 2008, US, 1/1999–7/2006, retrospective	RA patients (n = 24,530) compared with 500,000 non-RA patients	PEQ ≤5 6–10 >10	Any infection requiring hospitalization	Increased risk of infection; dose dependent	RR of hospitalization for infection risk as per PEQ: • PEQ ≤5, RR 1.32 (95% CI, 1.06–1.63) • PEQ = 6–10, RR 1.94 (95% CI, 1.53–2.46) • PEQ >10, RR 2.98 (95% CI, 2.41–3.69)
Greenberg et al,[38] 2010, US, CORRONA, 10/2001–9/2006, prospective	Patients with RA on DMARDs, n = 7971	PEQ <10 PEQ >10	Overall infections (includes both Opportunistic	Increased risk of overall infections with PEQ >10	IRR of overall infections as per PEQ: • Any dose, IRR 1.05 (95% CI, 0.97–1.15) • PEQ >10, IRR 1.30 (95% CI, 1.11–1.53)
Dixon et al,[31] 2012, Quebec, 1985–2003, nested case-control	RA >65 y old, n = 16,207				
Dixon et al,[20] 2011, N/A, up to 1/2010, meta-analysis	21 RCTs 42 Observation studies				
Grijalva et al,[30] 2011, US, 1998–2007, retrospective	1—RA, n = 10,484 2—Pso or SpA, n = 3215	Any dose	Infection requiring hospitalization In patients on DMARDs	Increased risk of infection; dose dependent in RA group and Pso/SpA group	HR of serious infection risk as per PEQ: • RA group: PEQ 0–<5, HR 1.32 (95% CI, 1.10–1.58) PEQ 5–10, HR 1.78 (95% CI, 1.47–2.15) PEQ >10, HR 2.95 (95% CI, 2.41–3.61) • Pso and SpA group: 0–<5, 1.15 (0.75–1.77) 5–10, 2.01 (1.08–3.73) >10, 2.77 (1.44–5.32)
Xie et al,[39] 2012, China, 1/2009–2/2011, retrospective	RA, n = 2452	Any dose	Nosocomial infections	Increased risk of infection	OR of nosocomial infections by multivariate analysis: 1.02 (95% CI, 1.01–1.03)
van Dartel et al,[40] 2013, DREAM, 2005–2010, prospective	Patients with RA, n = 2044	Any dose	SBI	Increased risk of infection	• HR of SBI by multivariate analysis: HR 1.54 (95% CI, 1.08–2.20) • HR of SBI by univariate analysis: HR 1.78 (95% CI, 1.26–2.53)
Widdifield et al,[34] 2013, Ontario, 1992–2010, nested case control	RA ≥66 Y/O, n = 86,039	PEQ ≤5 PEQ 6–9 PEQ 10–19 PEQ ≥20	Serious infections	Increased risk of infection; dose dependent	Adj OR of serious infections as per PEQ: • PEQ ≤5, OR 3.96 (95% CI, 3.67–4.27) • PEQ 6–9, OR 4.28 (95% CI, 3.70–4.96) • PEQ 10–19, OR 5.98 (95% CI, 5.42–6.59) • PEQ ≥20, OR 7.57 (95% CI, 6.87–8.34)

Observational studies have consistently demonstrated an increased risk of serious infections (generally defined as infections requiring hospitalization or intravenous [IV] antibiotics or resulting in disability or death), **sometimes even with prednisone equivalent (PEQ) doses of 5 mg or less daily.**

On the other hand, other studies have found an increased risk only with higher doses of corticosteroids.

as well as a dose dependent and duration-dependent stepwise increase in the risk of serious bacterial infections.

Work from Strangfeld and colleagues suggested that for patients with RA, the risk of serious infections decreased over time in biologic users because the use of biologic agents allowed for decreased prednisone utilization and/or dosage over time

Strangfeld A, et al. Treatment benefit or survival of the fittest: what drives the time-dependent decrease in serious infection rates under TNF inhibition and what does this imply for the individual patient? Ann Rheum Dis 2011;70(11):1914–20.

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

N Duru,[1] M C van der Goes,[1] J W G Jacobs,[1] T Andrews,[2] M Boers,[3] F Buttgereit,[4] N Caeyers,[5] M Cutolo,[6] S Halliday,[2] J A P Da Silva,[7] J R Kirwan,[8] D Ray,[9] J Rovensky,[10] G Severijns,[5] R Westhovens,[11] J W J Bijlsma[1]

Duru N, *et al. Ann Rheum Dis* 2013

Table 2 The recommendations with strength of recommendation and level of evidence

	Proposition	SOR VAS; mean (95% CI)	SOR A+B %	LoE
	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	91 (81 to 101)	100	III
2	Discuss measures to mitigate such risks, including diet, regular exercise and appropriate wound care	75 (57 to 93)	75	III/IV
3	Patients with, or at risk of, GC-induced osteoporosis should receive appropriate preventive/therapeutic interventions	91 (84 to 99)	100	I-A
4	Patients and the patients' treatment teams should receive appropriate, practical advice on how to manage with GC-induced hypothalamic-pituitary-adrenal axis suppression	84 (67 to 101)	92	IV
5	Provide an accessible resource to promote best practice in the management of patients using medium/high-dose GCs to general practitioners	80 (69 to 91)	75	IV
	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	85 (76 to 94)	83	IV
7	Select the appropriate starting dose to achieve therapeutic response, taking into account the risk of undertreatment	85 (76 to 95)	92	I-A/IV
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	82 (72 to 94)	92	IV
9	If long-term medium/high-dose GC therapy is anticipated to be necessary, actively consider GC-sparing therapy	REJECTED		
	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	85 (79 to 92)	75	IV

Infection Risk and Safety of Corticosteroid Use

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Table 3
Prevention strategies

Disease	Prevention Strategies
Influenza	Annual vaccination in those with rheumatic diseases[88]
HZ	Vaccine in all patients with rheumatic diseases ages ≥50[75,77,78]
Pneumococcal pneumonia	In patients without prior vaccination, 1 dose of PCV13 in those on chronic steroid therapy should be given followed by PPSV23 ≥8 wk later. A second dose of PPSV23 is indicated 5 y after first dose.[88]
PJP	Treat with TMP/SMX (160 mg/800 mg) 3 times a week if on PEQ >16 mg daily for more than 8 wk.[45]
TB	Screen for latent TB using either TSTs or IGRAs[a] in those anticipated to start long-term corticosteroid therapy (10 mg for at least 1 mo) and treat for latent TB if positive.[81] If already on chronic steroid therapy, screen with IGRA and be aware of risk of false-negative results with TSTs or IGRAs.

Abbreviations: PCV13, 13-valent pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine.

[a] IGRA is preferred if patient has a history of bacille Calmette-Guérin vaccine.

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Development and Validation of a Risk Score for Serious Infections in Patients with Rheumatoid Arthritis

Cynthia S. Crowson[*,#], Deana D. Hoganson[*], Patrick D. Fitz-Gibbon[#], and Eric L. Matteson[*,#]

[*]Division of Rheumatology

[#]Department of Health Sciences Research

Predictor	Level	Coefficient
Age	Age< 60 years	0
	60 ≤ age < 80 years	0.404
	age ≥ 80 years	0.857
Previous serious infection	Never or >3 years ago	0
	In the past year	2.138
	In the past 2–3 years	1.670
Extraarticular manifestation of RA		0.620
Erythrocyte sedimentation rate (ESR)	ESR < 30 mm/hr	0
	30 ≤ ESR ≤ 50 mm/hr	0.180
	ESR > 50 mm/hr	0.611
Corticosteroid dose	None	0
	≤ 10 mg daily	0.553
	> 10 mg daily	1.281
Comorbidities	None	0
	One	0.675
	More than one	1.024

Pharmacodynamics of glucocorticoids

C. Strehl, C.M. Spies, F. Buttgereit

- Conventional GCs can be improved by a targeted delivery via carrier systems (*e.g.* long circulating liposomes); by this route, GCs accumulate directly at the site of inflammation

- GCs can be linked to nitric oxide (NO) which can enhance anti-inflammatory effects of GCs, while it is slowly released from these drugs

- Selective glucocorticoid receptor agonists (SEGRAs) cause a receptor conformation preferring GCR/protein interaction rather than GCR/DNA binding, which leads to induced transrepression processes, whereas transactivation remains unchanged

- A new, modified-release prednisone tablet formulation has been developed to prevent the circadian increase of proinflammatory cytokine levels, thereby improving signs and symptoms of rheumatoid arthritis such as the duration of morning stiffness

Clin Exp Rheumatol 2011; 29 (Suppl. 68): S13-S18.

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Journal of Controlled Release 200 (2015) 20–26

Contents lists available at ScienceDirect

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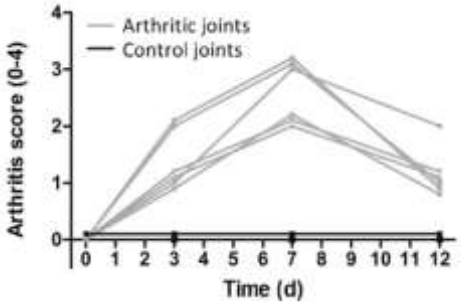
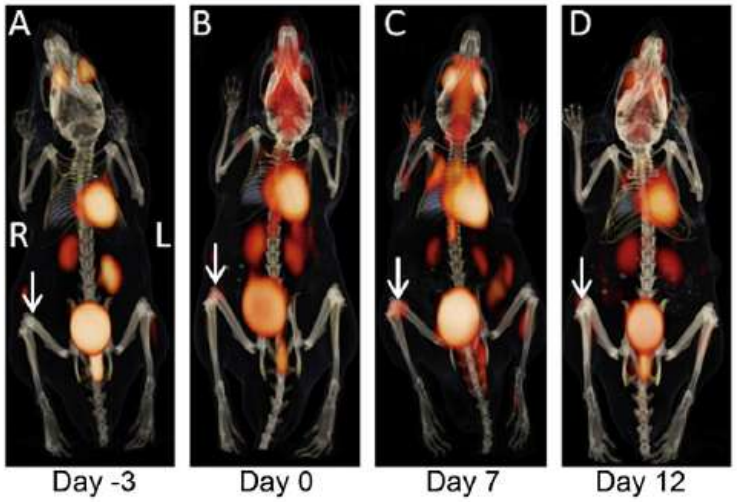
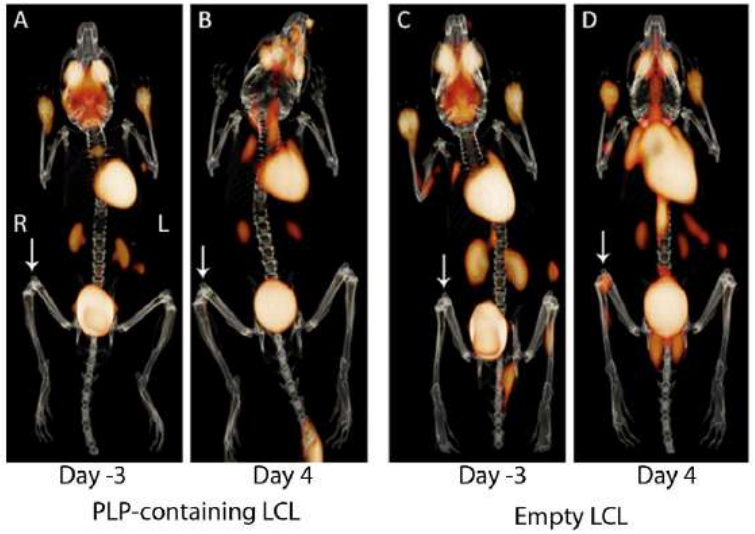
journal homepage: www.elsevier.com/locate/jconrel

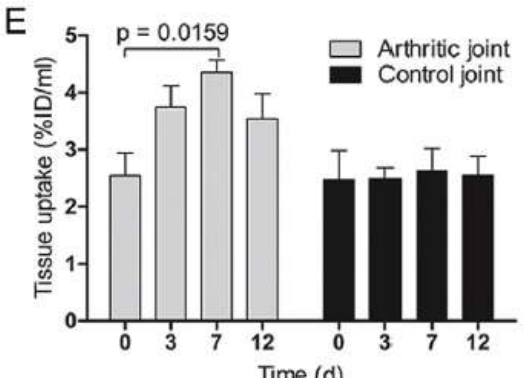
[18]F FDG PET/CT imaging to monitor the therapeutic effect of liposome-encapsulated prednisolone in experimental rheumatoid arthritis

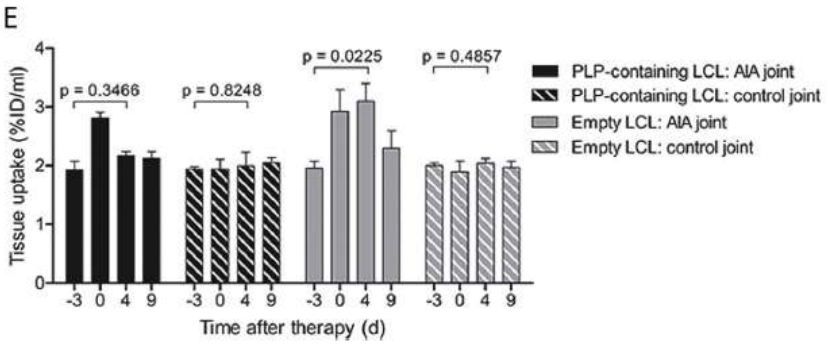
Tessa van der Geest [a,*], Josbert M. Metselaar [b,c], Danny Gerrits [a], Peter L. van Lent [d], Gert Storm [e], Peter Laverman [a], Otto C. Boerman [a]











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Pharmacology & Therapeutics 152 (2015) 28–41

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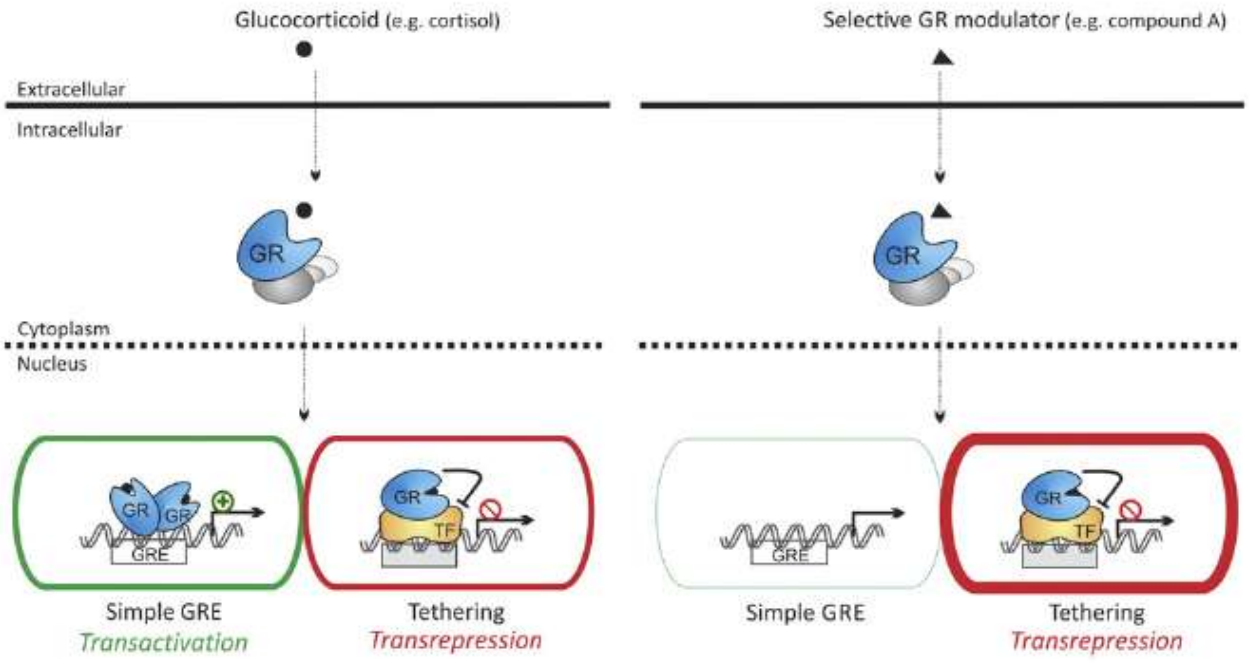
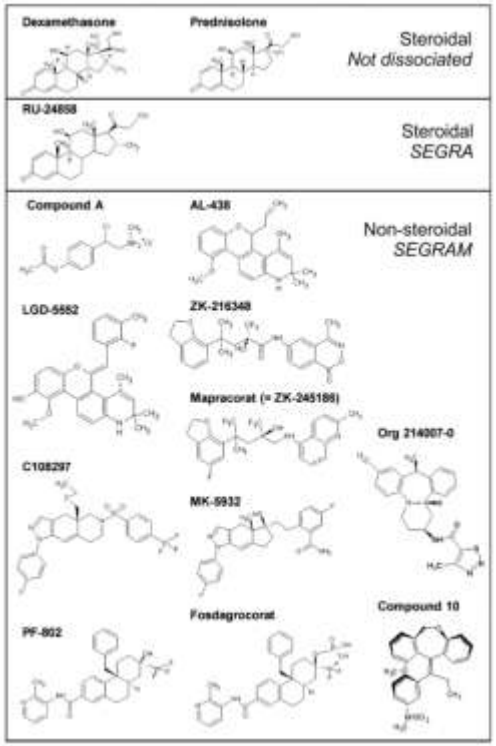
Selective glucocorticoid receptor modulation: New directions with non-steroidal scaffolds

Nora Sundahl [a], Jolien Bridelance [a,1], Claude Libert [b,c], Karolien De Bosscher [d,*,2], Ilse M. Beck [a,2]

Selective glucocorticoid receptor agonists (SEGRAs)





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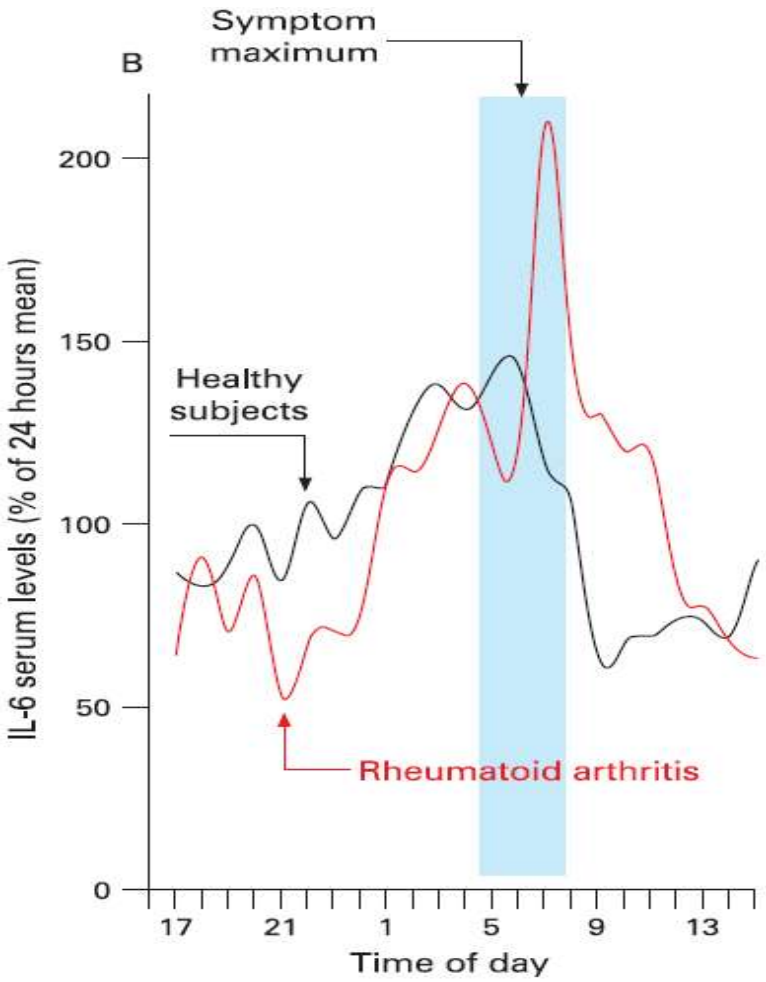
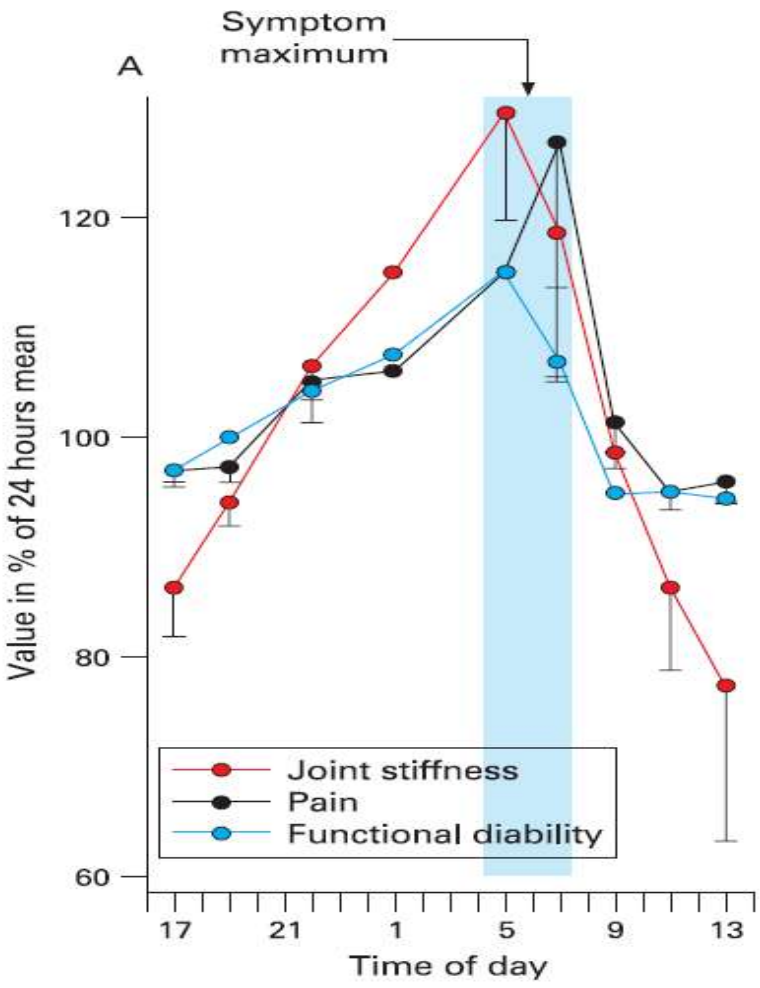
Ritmo Circadiano dei Sintomi e Interleuchina-6





Conclusioni

- I cortisonici rimangono uno dei cardini della terapia delle patologie reumatologiche infiammatorie.
- Dose, durata del trattamento, età e comorbilità aumentano il rischio infettivo
- Un uso razionale delle molecole che abbiamo a disposizione può consentire un aumento della efficacia terapeutica a fronte di minori effetti collaterali.
- E' ipotizzabile che ulteriori progressi in tal senso possano derivare dallo sviluppo di nuove molecole sintetizzate alla luce delle più recenti conoscenze dei meccanismi d'azioni di tali farmaci

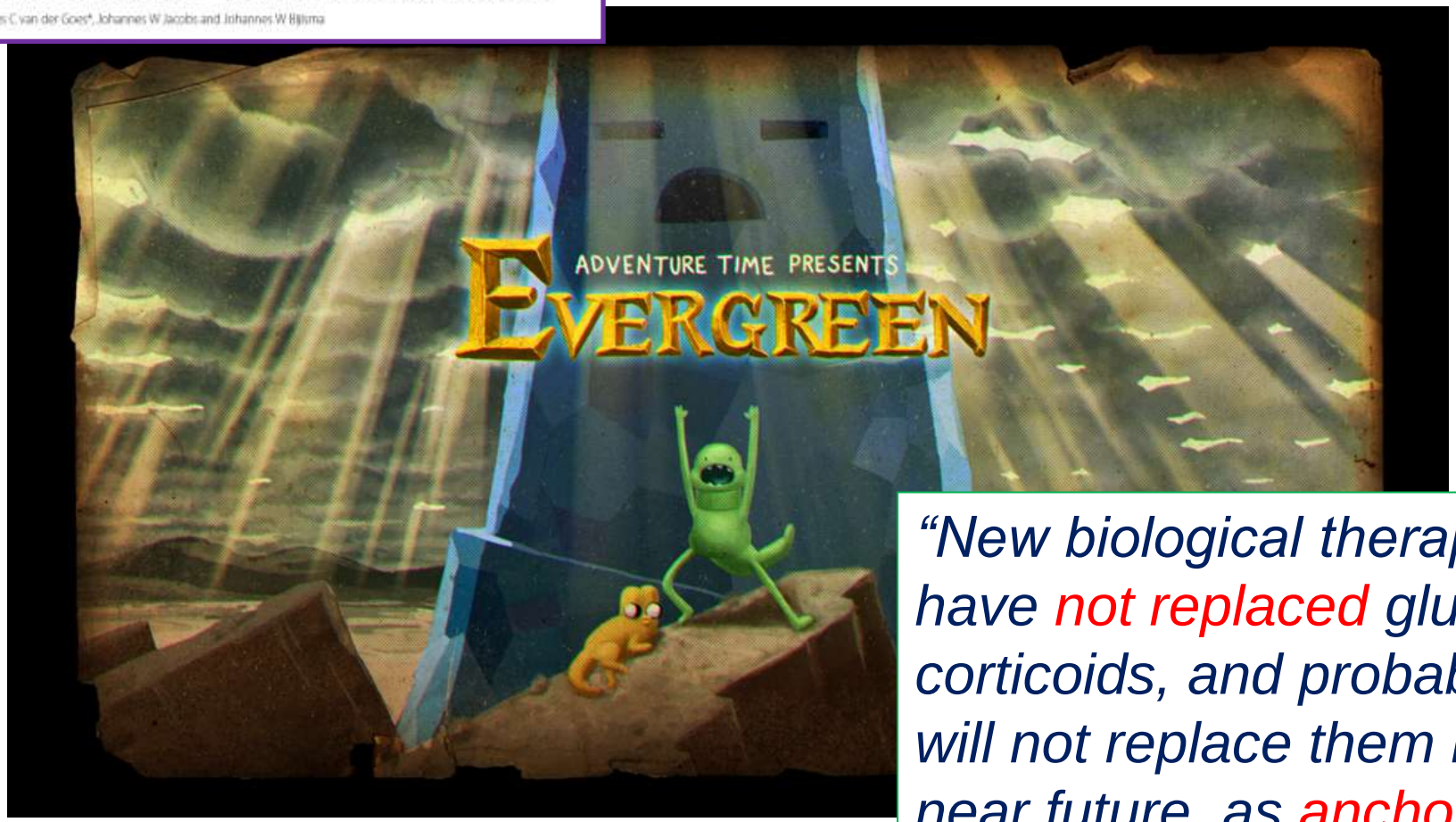
van der Goes et al. Arthritis Research & Therapy 2014, 16(Suppl 2):S2
http://arthritis-research.com/content/16/S2/S2

arthritis research & therapy

REVIEW

The value of glucocorticoid co-therapy in different rheumatic diseases – positive and adverse effects

Marlies C van der Goes*, Johannes W Jacobs and Johannes W Bijlsma



"New biological therapies have not replaced gluco-corticoids, and probably will not replace them in the near future, as anchor drugs in therapeutic strategies for rheumatic diseases"

S.C.
Reumatologia
AO
Città della Salute
e della Scienza
di Torino

AZIENDA OSPEDALIERO - UNIVERSITARIA
Città della Salute e della Scienza di Torino

REUMATOLOGIA E MALATTIE NEOPLASTICHE

Torino Marzo 2017