Steroids Sparing Effect of Biologics In Rheumatoid Arthritis

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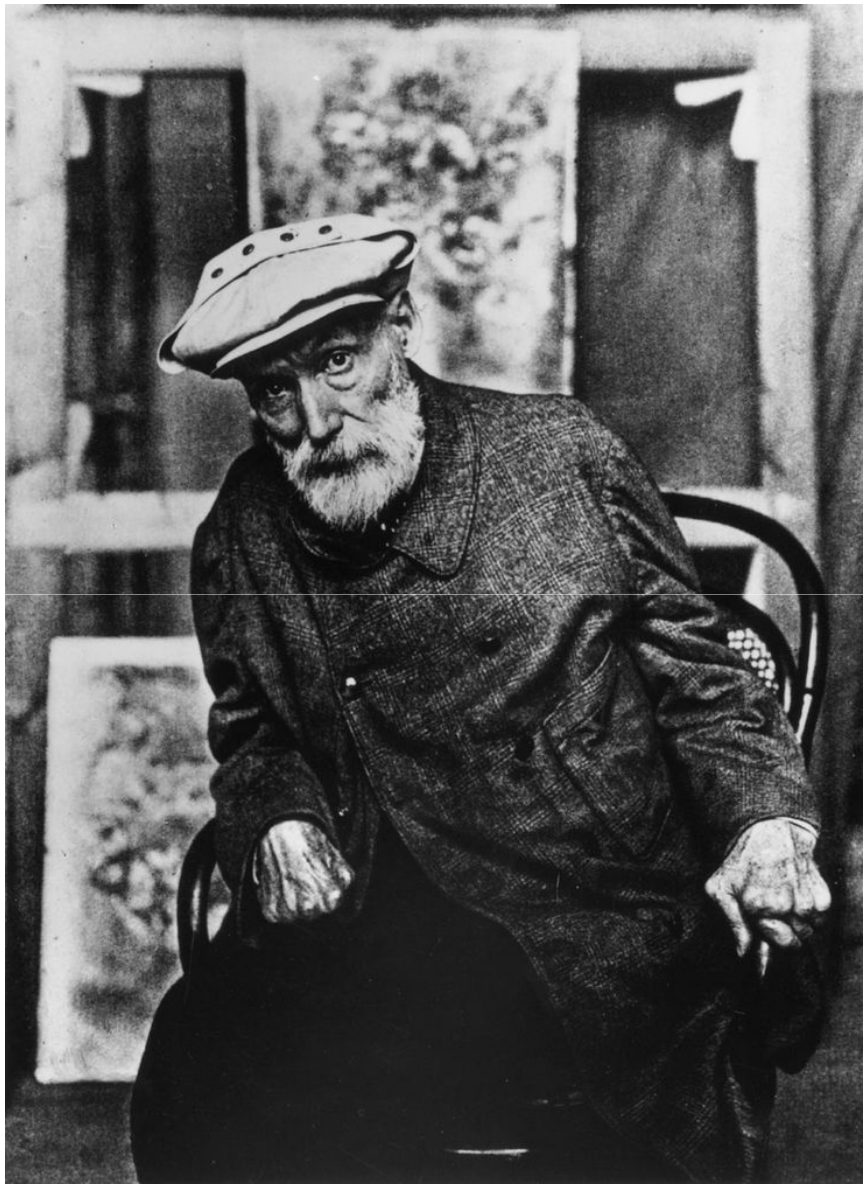
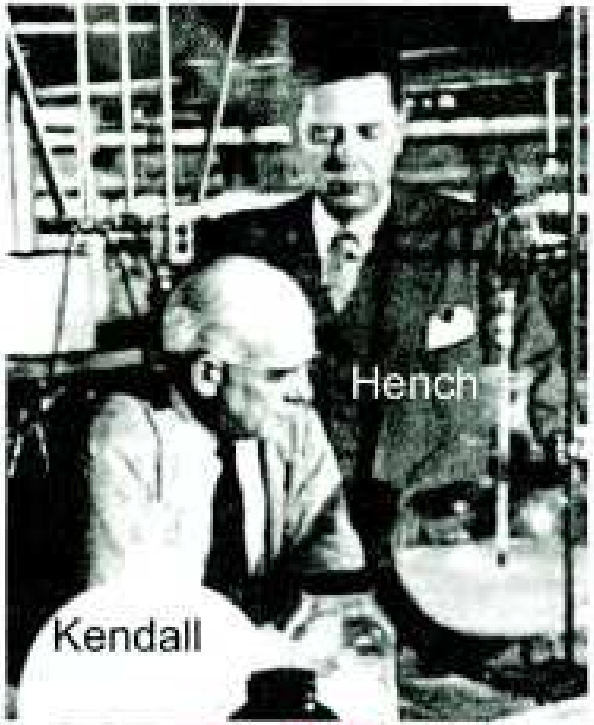
Conflict of interest

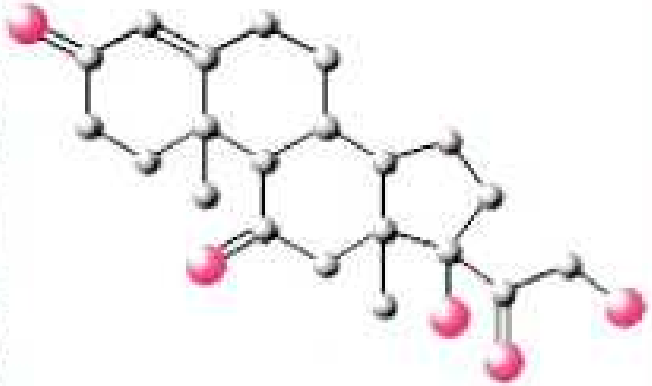
- Clinical trials: Abbvie, Bristol Myers Squibb, Lilly, MSD, Novartis, Pfizer, Roche-Chugai, UCB
- Advisory Boards : Bristol Myers Squibb, Lilly, Roche Chugai, UCB
- Lessons: Abbvie, Bristol Myers Squibb, Merck Sharp, Novartis, Pfizer, Roche-Chugai, UCB
- Grant for researchs: Abbvie, Bristol Myers Squibb, Merck Sharp, Novartis, Pfizer, Roche-Chugai, UCB

Plan

- Background
- Recommendation about glucocorticoids
- Do we use glucocorticoids?
- What do patients and rheumatologists think about glucocorticoids?
- Risks of glucocorticoids
- Benefits of glucocorticoids
- Do biologics allow a glucorticoid tapering?







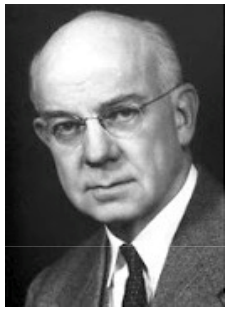
Reichstein

Anemones

Raoul Dufy, self-portrait

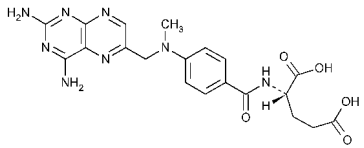
„La cortisone“

1949



HENCH and KENDALL
First use of steroids

1950
1968



Ann. rheum. Dis. (1968), **27**, 64

AMETHOPTERIN (METHOTREXATE) IN CONNECTIVE TISSUE DISEASE—PSORIASIS AND POLYARTHRITIS

BY

G. D. KERSLEY

Bath

Methotrexate (amethopterin), a folic acid reductase inhibitor, affects primarily the tissues that are growing most rapidly. When in prolonged contact with the cell, its interference with the supply of available folic acid reduces the DNH content and hence holds up preparation for mitosis and division. Apart from neoplastic cells, the rapid epidermal proliferation of psoriasis is particularly susceptible; after this the brunt of the attack falls on the endothelium of the oral mucosa and gastro-intestinal tract, the hair follicles, and later the blood-forming elements—especially the granulocytes. The drug is easily absorbed orally and the greater part is excreted in the urine within 12 hours. Impaired renal function potentiates its effect, pregnancy is a contraindication, and over-dosage should be treated with folinic acid (Leucovorin).

Folic acid antagonists were first used in the treatment of psoriasis by Gubner, August, and Ginsberg (1951). Further reports on their use in this disease were made by Rees, Bennett, Hamlin, and Maibach (1964), and Ryan, Vickers, Salem, Callender, and Badenoch (1964), three deaths being reported by the former. Shrank and Blendis (1965) gave details of and sepsis. Burrows and Kelly (1967) recorded severe toxicity and leucopenia with recovery in 3 weeks after taking only 2·5 mg. for 4 days.

Present Investigations

A case of severe pustular psoriatic arthritis reacted so well to methotrexate, relapsing when the drug was stopped and improving again when it was restarted, that further investigation of its effect both on the psoriasis and arthritis was prompted.

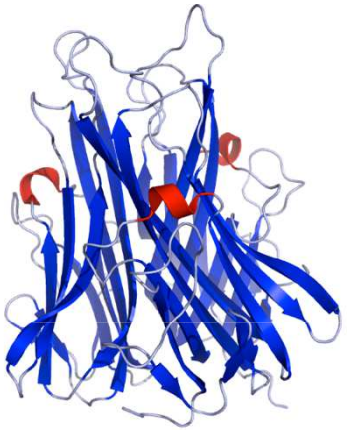
Case Report

A man aged 52 years noticed stiffness after exercise at the age of 30 and had an attack of bilateral sciatica at age 37. In March, 1964, at the age of 48, he developed simultaneously severe psoriasis and arthritis of the right elbow and left shoulder.

When seen in August, 1964, he had a very severe generalized psoriasis, pustular psoriasis of the fingernails and toenails, and extremely swollen and partly subluxated knees and ankles. The neck and back were stiff but there was little pain. He had lost a stone in weight and his temperature rose to 101° F. at night. The erythrocyte sedimentation rate was 120 mm./hr., Hb 70 per cent., and rheumatoid factor tests negative.

MÉTHOTREXATE

1975



1st cytokine identification (TNF)

Background

Low dose corticosteroids are often considered as part of the treatment strategy of RA but should be tapered as rapidly as clinically feasible

Long term glucocorticoids (GC) doses may induce

- psychological, metabolic, gastrointestinal and cardiovascular events
- osteoporosis
- Infection

Rheumatologists starting biologics aim:

- To reach a target of remission or LDA
- To decrease corticosteroids
- No increase in synthetic DMARDs

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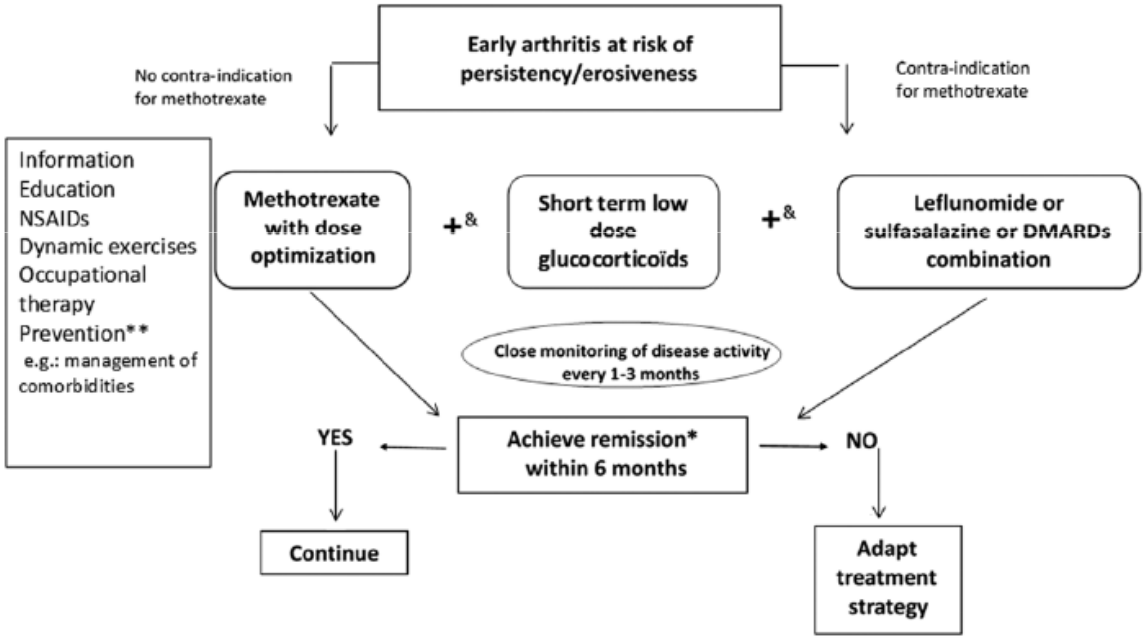
- Benefits of glucocorticoids
- Do biologics allow a glucorticoids tapering?

2016 update of the EULAR recommendations for the management of early arthritis

Bernard Combe,[1] Robert Landewe,[2] Claire I Daien,[1] Charlotte Hua,[1] Daniel Aletaha,[3] Jose María Álvaro-Gracia,[4] Margôt Bakkers,[5] Nina Brodin,[6,7] Gerd R Burmester,[8] Catalin Codreanu,[9] Richard Conway,[10] Maxime Dougados,[11] Paul Emery,[12] Gianfranco Ferraccioli,[13] Joao Fonseca,[14,15] Karim Raza,[16,17] Lucía Silva-Fernández,[18] Josef S Smolen,[3] Diana Skingle,[5] Zoltan Szekanecz,[19] Tore K Kvien,[20] Annette van der Helm-van Mil,[21,22] Ronald van Vollenhoven[23]



Systemic glucocorticoids reduce pain, swelling and structural progression, but in view of their cumulative side effects, they should be used at the lowest dose necessary as temporary (<6 months) adjunctive treatment. Intra-articular glucocorticoid injections should be considered for the relief of local symptoms of inflammation

Combe B, *et al*. *Ann Rheum Dis* 2016;**0**:1–12.

2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis

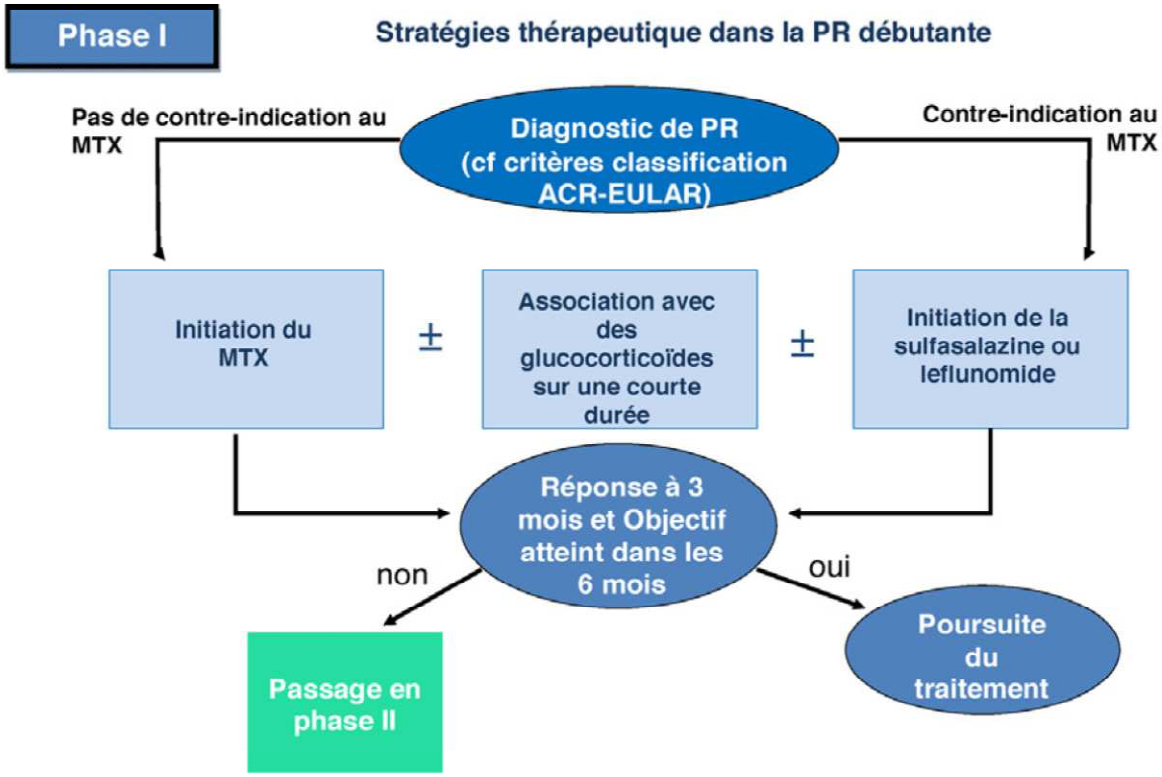
JASVINDER A. SINGH,[1] KENNETH G. SAAG,[1] S. LOUIS BRIDGES JR.,[1] ELIE A. AKL,[2] RAVEENDHARA R. BANNURU,[3] MATTHEW C. SULLIVAN,[3] ELIZAVETA VAYSBROT,[3] CHRISTINE MCNAUGHTON,[3] MIKALA OSANI,[3] ROBERT H. SHMERLING,[4] JEFFREY R. CURTIS,[1] DANIEL E. FURST,[5] DEBORAH PARKS,[6] ARTHUR KAVANAUGH,[7] JAMES O'DELL,[8] CHARLES KING,[9] AMYE LEONG,[10] ERIC L. MATTESON,[11] JOHN T. SCHOUSBOE,[12] BARBARA DREVLOW,[13] SETH GINSBERG,[14] JAMES GROBER,[13] E. WILLIAM ST.CLAIR,[15] ELIZABETH TINDALL,[16] AMY S. MILLER,[17] AND TIMOTHY MCALINDON[3]

Recommendations for patients with symptomatic Early RA	Level of Evidence (evidence reviewed)
1. **Regardless of disease activity level, use a treat-to-target strategy rather than a non-targeted approach (PICO A.1).**	**Low (17)**
2. **If the disease activity is low, in patients who have never taken a DMARD:** • **use DMARD monotherapy (MTX preferred) over double therapy (PICO A.2).** • **use DMARD monotherapy (MTX preferred) over triple therapy (PICO A.3).**	**Low (18-21)** **Low (22-25)**
3. *If the disease activity is moderate or high, in patients who have never taken a DMARD:* • *use DMARD monotherapy over double therapy (PICO A.4).* • *use DMARD monotherapy over triple therapy (PICO A.5).*	*Moderate (18,20,21)* *High (22-25)*
4. **If disease activity remains moderate or high despite DMARD monotherapy (with or without glucocorticoids), use combination DMARDs or a TNFi or a non-TNF biologic (all choices with or without MTX, in no particular order of preference), rather than continuing DMARD monotherapy alone (PICO A.7).**	**Low (26-28)**
5. *If disease activity remains moderate or high despite DMARDs:* • *use a TNFi monotherapy over tofacitinib monotherapy (PICO A.8).* • *use a TNFi + MTX over tofacitinib + MTX (PICO A.9).*	*Low (29)* *Low (30)*
6. *If disease activity remains moderate or high despite DMARD (PICO A.6) or biologic therapies (PICO A.12), add low-dose glucocorticoids.*	*Moderate (31-37)* *Low (31-37)*
7. *If disease flares, add short-term glucocorticoids at the lowest possible dose and for the shortest possible duration (PICO A.10, A.11).*	*Very low (38-43)*

Singh JA, et al. Arthritis Care Res (Hoboken). 2016 Jan;68(1):1-25

Recommandations de la Société française de rhumatologie pour la prise en charge de la polyarthrite rhumatoïde☆

Cécile Gaujoux-Viala[a,*,1], Laure Gossec[b,1], Alain Cantagrel[c], Maxime Dougados[d], Bruno Fautrel[b], Xavier Mariette[e], Henri Nataf[f], Alain Saraux[g], Sonia Trope[h], Bernard Combe[i]



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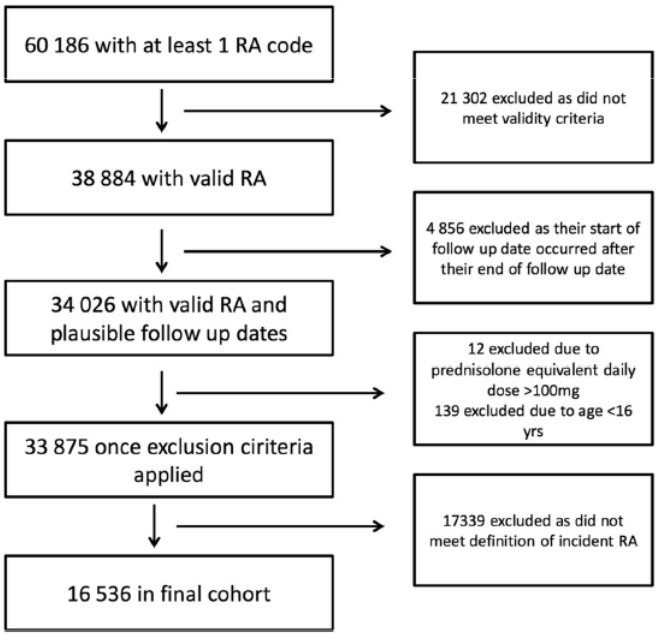
Black *et al. Arthritis Research & Therapy* (2015) 17:375
DOI 10.1186/s13075-015-0895-8

Arthritis Research & Therapy

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]



50% of RA patients treated with glucocorticoids
7.5 mg/day

Table 2 Summary statistics of GC doses and duration of use per patient during follow-up and in the 12 months prior to study entry for those patients ever prescribed GCs (n = 7777)

	Follow-up period		12 months prior to study entry	
Measure*	Median	IQR	Median	IQR
Duration of follow-up (years)	5.29	2.62–8.58	-	-
Cumulative duration of GC use (years)	0.80	0.15–2.56	0.23	0.05–0.67
Proportion of follow-up time on GCs (%)	26.3	3.8–70.0	22.7	5.4–67.2
Average dose** (mg)	7.5	5–15.3	10	5–20
Lowest dose** (mg)	5	2.5–7.5	5	3–15
Highest dose** (mg)	15	7.5–30	15	6–30

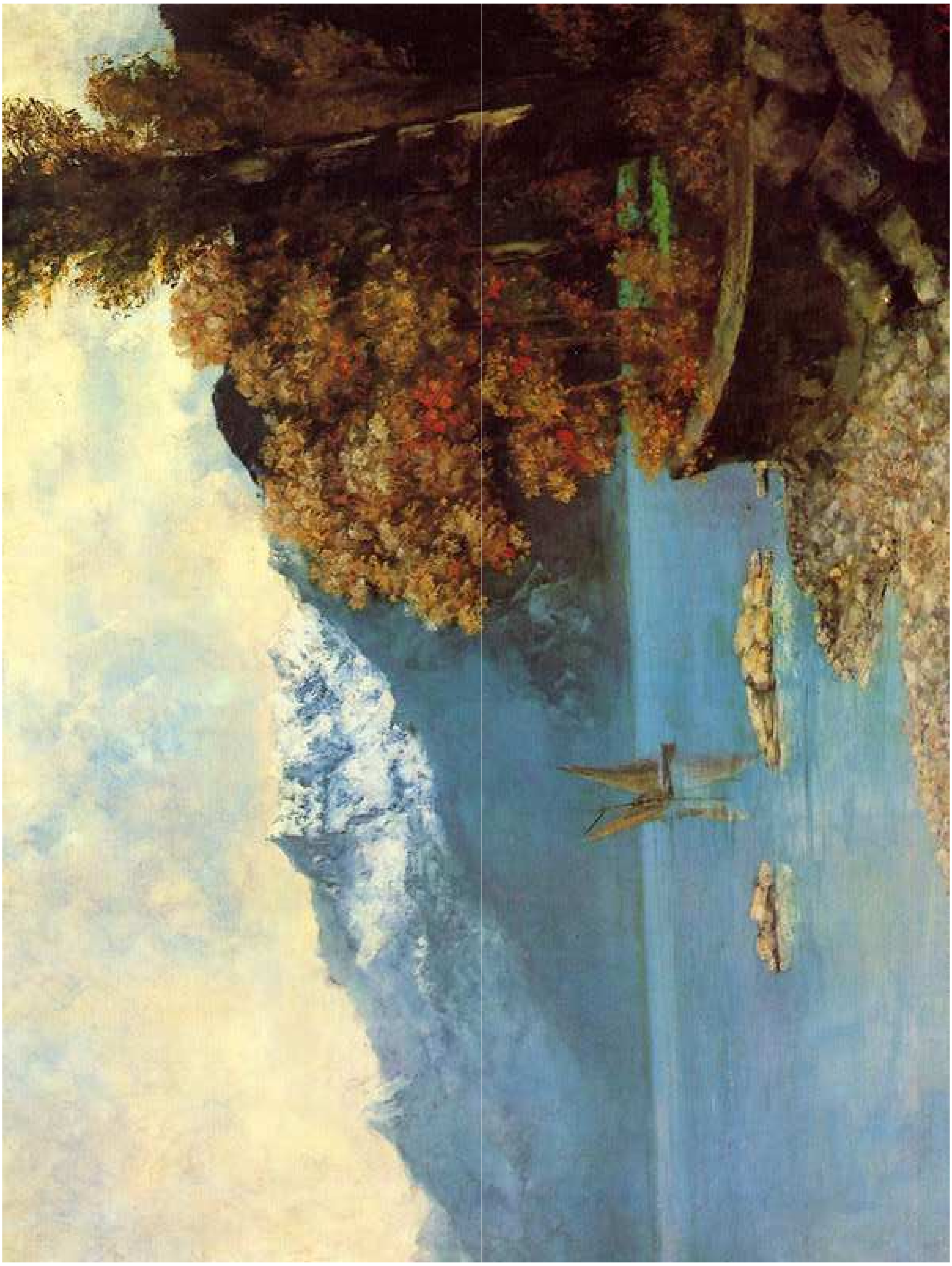
GC glucocorticoid, *IQR* interquartile range
*Summary statistics were obtained by calculating the value for each patient and then determining median values across the whole population
**All doses are prednisolone-equivalent daily doses

More frequently in elderly people, with cardiovascular risk

Table 3 Baseline patient characteristics associated with GC prescriptions

Variable	Ever GC use (number, %)	Never GC use (number, %)	Univariate analysis* (odds ratio, 95 % CI)	Multivariate stepwise analysis (odds ratio, 95 % CI)
Baseline demographics				
Age (decades)			1.02, 1.02–1.02**	1.17, 1.14–1.20
Gender (female)	5313, 68.32 %	6153, 70.25 %	0.94, 0.88–1.00	
Current smoking (versus never)	2147, 27.61 %	2385, 27.23 %	1.04, 1.00–1.08**	1.22, 1.13–1.32
Baseline GC-associated comorbidities				
Osteoporosis	427, 5.49 %	279, 3.19 %	1.42, 1.21–1.66**	
Avascular necrosis	7, 0.09 %	4, 0.05 %	1.68, 0.49–5.78	
Myopathy	14, 0.18 %	10, 0.11 %	1.35, 0.60–3.08	
Diabetes mellitus	603, 7.75 %	699, 7.98 %	0.85, 0.76–0.95**	0.71, 0.62–0.82
Cardiovascular disease	364, 4.68 %	264, 3.01 %	1.22, 1.04–1.44**	1.25, 1.03–1.51
Hypertension	1842, 23.69 %	1754, 20.03 %	0.98, 0.90–1.06	
Hyperlipidaemia	798, 10.26 %	830, 9.48 %	0.93, 0.84–1.04	0.86, 0.76–0.97
Peptic ulcer disease	382, 4.91 %	334, 3.81 %	1.13, 0.97–1.32	
Pancreatitis	46, 0.59 %	43, 0.49 %	1.11, 0.73–1.70	
Depression	1684, 21.65 %	1847, 21.09 %	1.11, 1.03–1.19**	
Insomnia	985, 12.67 %	865, 9.88 %	1.21, 1.10–1.34**	
Psychosis	56, 0.72 %	52, 0.59 %	1.24, 0.84–1.81	
Baseline inflammatory comorbidities				
Chronic obstructive pulmonary disease	540, 6.94 %	189, 2.16 %	2.74, 2.31–3.25**	1.63, 1.33–1.99
Asthma	1492, 19.18 %	925, 10.56 %	2.07, 1.89–2.27**	1.58, 1.42–1.76
Lower respiratory tract infection	1717, 22.08 %	1342, 15.44 %	1.47, 1.35–1.59**	1.22, 1.11–1.34
Inflammatory bowel disease	78, 1.11 %	63, 0.72 %	1.35, 0.96–1.89	
Cutaneous lupus	13, 0.17 %	11, 0.13 %	1.30, 0.58–2.93	
Cutaneous vasculitis	6, 0.08 %	0, 0.00 %	1	
Atopic eczema	1084, 13.94 %	1127, 12.87 %	1.10, 1.00–1.20**	
Baseline DMARD use				
Methotrexate	465, 5.98 %	501, 5.72 %	1.07, 0.93–1.22	0.80, 0.66–0.97
Sulfasalazine	468, 6.02 %	581, 6.63 %	0.91, 0.80–1.03	0.69, 0.58–0.83
Hydroxychloroquine	259, 3.33 %	256, 2.92 %	1.20, 1.00–1.43**	
Leflunomide	105, 1.35 %	71, 0.81 %	1.83, 1.35–2.49**	1.75, 1.18–2.59
Other DMARDs***	277, 3.56 %	151, 1.72 %	2.06, 1.68–2.52**	1.68, 1.28–2.19

GC glucocorticoid, *DMARDs* disease-modifying anti-rheumatic drugs, *CI* confidence interval
*Adjusted for age and gender
**Significant in univariate analysis
***Other DMARDs include gold, penicillamine, cyclosporine, chloroquine and azathioprine



Clin Rheumatol
DOI 10.1007/s10067-016-3468-6

ORIGINAL ARTICLE

Does addition of glucocorticoids to the initial therapy influence the later course of the disease in patients with early RA? Results from the Swiss prospective observational registry (SCQM)

Ruediger B. Mueller[1] · Nazim Reshiti[1] · Toni Kaegi[1] · Axel Finckh[2] · Sarah R. Haile[3] · Hendrik Schulze-Koops[4] · Michael Schiff[5] · Michael Spaeth[6] · Johannes von Kempis[1] · on behalf of the SCQM physicians

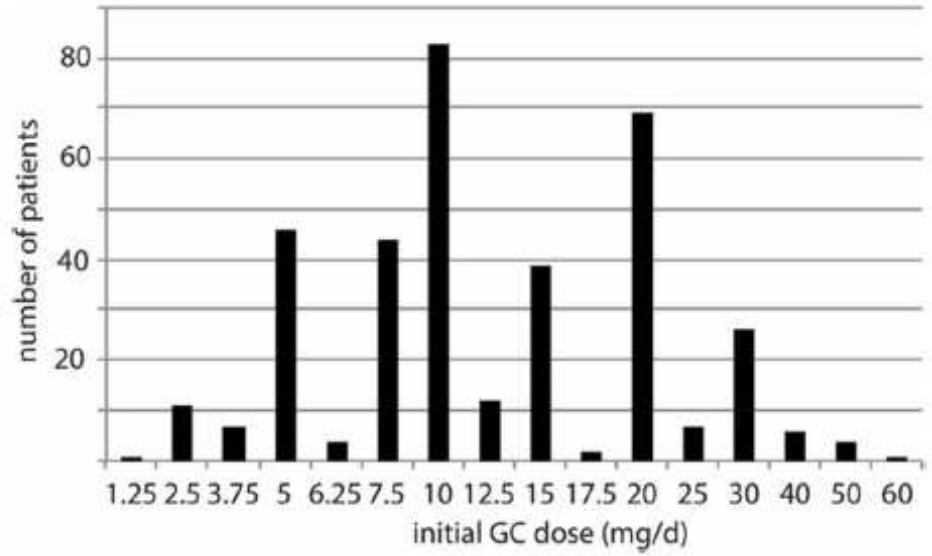


Fig. 1 Initial GC doses. The number of patients initiated on the different GC doses are demonstrated

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More severe RA
disease duration similar

GC use initiated at baseline	Present	Not present	*p* value
Number	363	228	–
Age (years, mean ± SD)	55.1 ± 14.8	51.3 ± 15.2	0.034
Gender (f/m)	257/106	172/56	0.214
Follow-up (months, mean ± SD)	51.4 ± 37.2	50.6 ± 39.1	0.80
Symptom durations (days, mean ± SD)	171.2 ± 98.5	186.9 ± 94.5	0.0529
SJC at onset (mean ± SD)	7.9 ± 6.0	7.1 ± 5.9	0.088
TJC at onset (mean ± SD)	8.0 ± 6.8	7.6 ± 6.6	0.48
DAS-28 at onset (mean ± SD)	4.6 ± 1.6	4.3 ± 1.6	0.011
RF pos. at onset (*n*, %[a])	231, 63.6%	157, 68.9%	0.19
CCP pos. at onset (*n*, %[a])	85, 62.0%	66, 65.3%	0.60
ESR at onset, mm/h (mean ± SD)	30.5 ± 25.3	24.3 ± 20.4	0.0013
CRP at onset, mg/l (mean ± SD)	23.7 ± 12.1	15.8 ± 11.5	0.13
Ratingen score at onset	8.9 ± 9.6	7.1 ± 8.4	0.0614
HAQ-DI at onset	0.94 ± 0.71	0.82 ± 0.65	0.0122
Initial GC dose (av. mg ± SD, range, median)	14.1 ± 9.8, 2.5–50, 10	0 ± 0, 0	–

f female, *GC* glucocorticoid, *m* male, *TJC* tender joint count, *SJC* swollen joint count, *RF* rheumatoid factor, *CCP* antibodies to cyclic citrullinated peptides, *CRP* C reactive protein, *n.a.* not applicable

[a] Calculated on patients with available data

Haugeberg et al. Arthritis Research & Therapy (2015) 17:219
DOI 10.1186/s13075-015-0716-0

arthritis research&therapy

RESEARCH ARTICLE Open Access

Ten years of change in clinical disease status and treatment in rheumatoid arthritis: results based on standardized monitoring of patients in an ordinary outpatient clinic in southern Norway

Glenn Haugeberg[1,2*], Inger Johanne Widding Hansen[1], Dag Magnar Soldal[1] and Tuulikki Sokka[3]

In Norway, 55% in 2004, 61% 2010 and 54% in 2013

Table 4 Treatment is displayed for each year in the 10-year period from 2004 to 2013 for patients with rheumatoid arthritis monitored with outcome measures in an ordinary outpatient clinic

Treatment	2004 (n = 404)	2005 (n = 604)	2006 (n = 620)	2007 (n = 743)	2008 (n = 796)	2009 (n = 969)	2010 (n = 1069)	2011 (n = 1103)	2012 (n = 1113)	2013 (n = 1083)	*P* value (2010–2013
No treatment[a]	44 (10.9)	102 (16.9)	94 (15.2)	110 (14.8)	99 (12.4)	139 (14.3)	122 (11.4)	121 (11.0)	132 (11.9)	106 (9.8)	0.45
Biologic DMARDs (%)	141 (34.9)	170 (28.1)	161 (26.0)	203 (27.3)	234 (29.4)	265 (27.3)	335 (31.3)	342 (31.0)	366 (32.9)	373 (34.4)	0.30
TNF inhibitor	139 (34.4)	170 (28.1)	159 (25.6)	176 (23.7)	192 (24.1)	198 (20.4)	236 (22.1)	221 (20.0)	230 (20.7)	227 (21.0)	0.70
Non-TNF inhibitors	2 (0.5)	0 (0)	2 (0.3)	27 (3.6)	42 (5.3)	67 (6.9)	99 (9.3)	121 (11.0)	136 (12.2)	146 (13.5)	0.016
Synthetic DMARDs (%)	267 (66.1)	349 (58.8)	351 (56.6)	440 (59.2)	471 (59.2)	562 (58.0)	627 (58.7)	667 (60.5)	668 (60.0)	660 (60.9)	0.73
One synthetic DMARD (%)	243 (60.1)	321 (53.1)	342 (55.2)	423 (56.9)	455 (57.2)	547 (56.4)	612 (57.2)	648 (58.7)	649 (58.3)	649 (59.9)	0.88
Two synthetic DMARDs (%)	24 (5.9)	28 (4.6)	9 (1.5)	16 (2.2)	16 (2.0)	14 (1.4)	14 (1.3)	18 (1.6)	17 (1.5)	10 (0.9)	
Three synthetic DMARDs (%)	0 (0)	0 (0)	0 (0)	1 (0.1)	0 (0)	1 (0.1)	1 (0.1)	1 (0.1)	2 (0.2)	1 (0.1)	
Biologic and synthetic DMARDs	100 (24.8)	123 (20.4)	114 (18.4)	142 (19.1)	155 (19.5)	176 (18.2)	216 (20.2)	226 (20.5)	234 (21.0)	233 (21.5)	0.58
TNF inhibitor and synthetic DMARDs	99 (24.5)	123 (20.4)	113 (18.2)	129 (17.4)	132 (16.6)	145 (15.0)	167 (15.6)	170 (15.4)	170 (15.3)	162 (15.0)	0.94
Prednisolone (%)	224 (55.4)	334 (55.3)	369 (59.5)	433 (58.3)	486 (61.1)	589 (60.8)	653 (61.1)	653 (59.2)	617 (55.4)	590 (54.5)	0.005
Prednisolone and synthetic DMARDs (%)	152 (37.6)	208 (34.4)	216 (34.8)	270 (36.3)	297 (37.3)	354 (36.5)	377 (35.3)	394 (35.7)	368 (33.1)	346 (31.9)	0.43
Biologic DMARD and prednisolone	53 (13.1)	61 (10.1)	57 (9.2)	78 (10.5)	90 (11.3)	101 (10.4)	125 (11.7)	125 (11.3)	124 (11.1)	120 (11.1)	0.80

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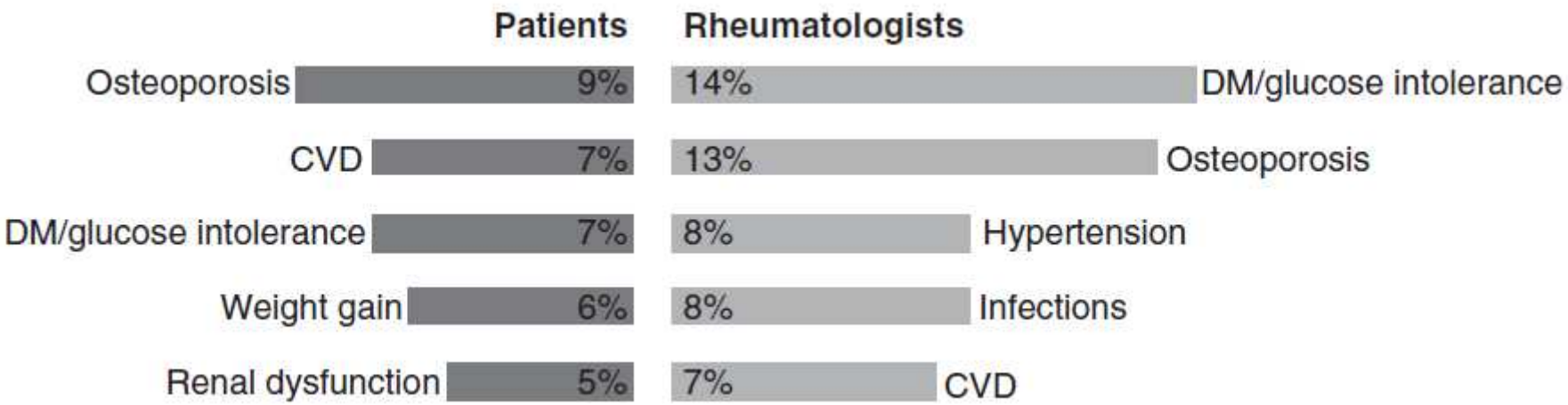
Glucocorticoid safety for treating rheumatoid arthritis

Linda A Rasch MSc, Irene EM Bultink, Lilian HD van Tuyl & Willem F Lems

More frequent secondary effects of steroids according patients and rheumatologists



Expert Opin. Drug Saf. (2015) 14(6):839-844

Glucocorticoids are associated to death

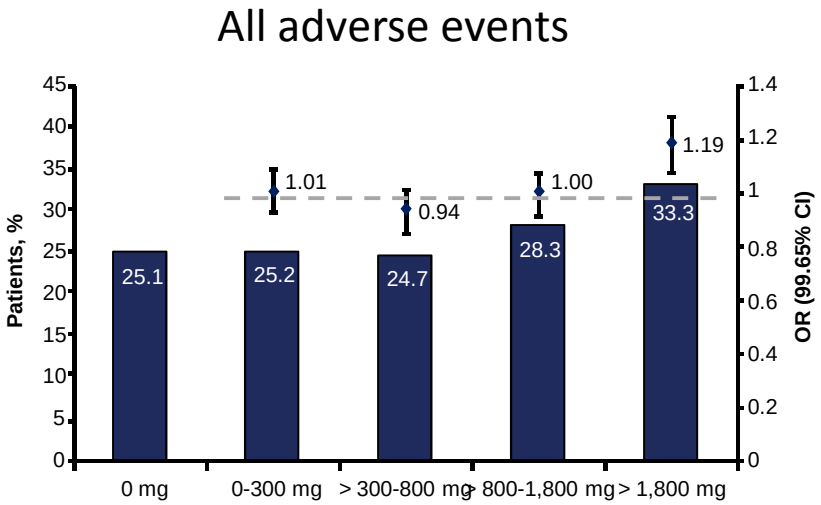
RABBIT
Adjusted risk

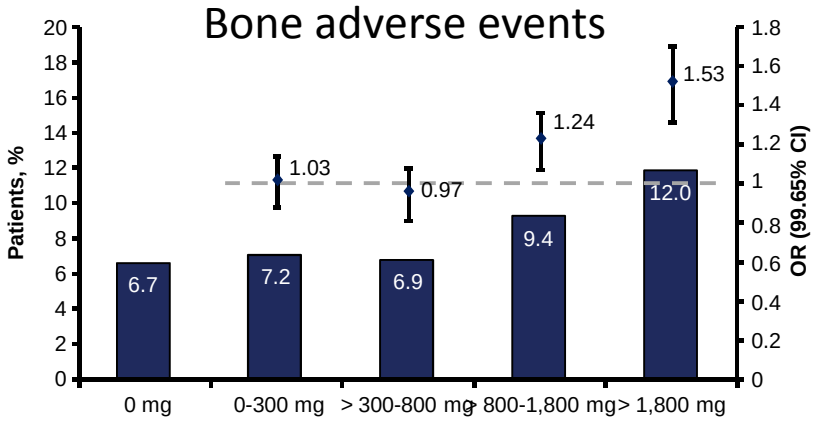
	ajusted HR		Adjusted HR : exposition 6 months before (12 if rituximab)			HR ajusted HR				
	HR	**IC 95 %**	**HR**	**IC 95 %**	**p**	**HR**	**IC 95 %**	**p**	**Death**	**Patient/ yrs**
Prednisone 12 months before evaluation	Ref.		Ref.			Ref.			88	9 036
1-5 mg/d	1,33	1,00-1,76	1,05	0,80-1,38	0,71	1,04	0,79-1,37	0,77	177	13 615
>5-10 mg/d	2,22	1,65-2,98	1,46	1,09-1,95	0,013	1,41	1,06-1,89	0,021	140	7 086
>10-15 mg/d	3,95	2,61-5,98	2,00	1,29-3,11	0,0033	2,01	1,30-3,11	0,0030	37	1 170
>15 mg/d	6,68	4,06-11,0	3,59	2,11-6,13	<0,0001	3,43	2,01-5,86	< 0,0001	21	448
Méthotrexate	Ref.		Ref.			Ref.			96†/78‡	7 021†/6 469‡
Other csDMARDs	2,53	1,95-3,28	1,14	0,86-1,51	0,36	0,98	0,60-1,59	0,92	126†/31‡	3 513†/1 581‡
Anti-TNF	0,77	0,61-0,98	0,64	0,50-0,81	0,0007	NA			182†	16 843†
Rituximab	1,01	0,70-1,46	0,57	0,39-0,84	0,0062	NA			36†	2 599†
Anti-TNF or rituximab	NA		NA			0,77	0,60-0,97	0,0312	330‡	22 370‡
Other biologics	1,02	0,68-1,52	0,64	0,42-0,99	0,043	0,91	0,66-1,25	0,54	25†/51‡	1 654†/2 806‡

Listing J, et al. Ann Rheum Dis 2015;74:415–421.

Cumulated risk
US Database

- > 1,800 mg in 12 months
- 800-1,800 mg





Best et al e EULAR June 2015; Rome, Italy **Poster SAT0344**

Plan

- Background
- Recommendation about glucocorticoids
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- What do patients and rheumatologist think about glucocorticoids?
- Risks of glucocorticoids
- Benefits of glucocorticoids
- Do biologics allow a glucorticoids tapering?

Clin Rheumatol
DOI 10.1007/s10067-016-3468-6

ORIGINAL ARTICLE

Does addition of glucocorticoids to the initial therapy influence the later course of the disease in patients with early RA? Results from the Swiss prospective observational registry (SCQM)

Ruediger B. Mueller[1] · Nazim Reshiti[1] · Toni Kaegi[1] · Axel Finckh[2] · Sarah R. Haile[3] · Hendrik Schulze-Koops[4] · Michael Schiff[5] · Michael Spaeth[6] · Johannes von Kempis[1] · on behalf of the SCQM physicians

More severe RA

GC use initiated at baseline	Present	Not present	*p* value
Number	363	228	–
Age (years, mean ± SD)	55.1 ± 14.8	51.3 ± 15.2	0.034
Gender (f/m)	257/106	172/56	0.214
Follow-up (months, mean ± SD)	51.4 ± 37.2	50.6 ± 39.1	0.80
Symptom durations (days, mean ± SD)	171.2 ± 98.5	186.9 ± 94.5	0.0529
SJC at onset (mean ± SD)	7.9 ± 6.0	7.1 ± 5.9	0.088
TJC at onset (mean ± SD)	8.0 ± 6.8	7.6 ± 6.6	0.48
DAS-28 at onset (mean ± SD)	4.6 ± 1.6	4.3 ± 1.6	0.011
RF pos. at onset (*n*, %[a])	231, 63.6%	157, 68.9%	0.19
CCP pos. at onset (*n*, %[a])	85, 62.0%	66, 65.3%	0.60
ESR at onset, mm/h (mean ± SD)	30.5 ± 25.3	24.3 ± 20.4	0.0013
CRP at onset, mg/l (mean ± SD)	23.7 ± 12.1	15.8 ± 11.5	0.13
Ratingen score at onset	8.9 ± 9.6	7.1 ± 8.4	0.0614
HAQ-DI at onset	0.94 ± 0.71	0.82 ± 0.65	0.0122
Initial GC dose (av. mg ± SD, range, median)	14.1 ± 9.8, 2.5–50, 10	0 ± 0, 0	–

f female, *GC* glucocorticoid, *m* male, *TJC* tender joint count, *SJC* swollen joint count, *RF* rheumatoid factor, *CCP* antibodies to cyclic citrullinated peptides, *CRP* C reactive protein, *n.a.* not applicable

[a] Calculated on patients with available data

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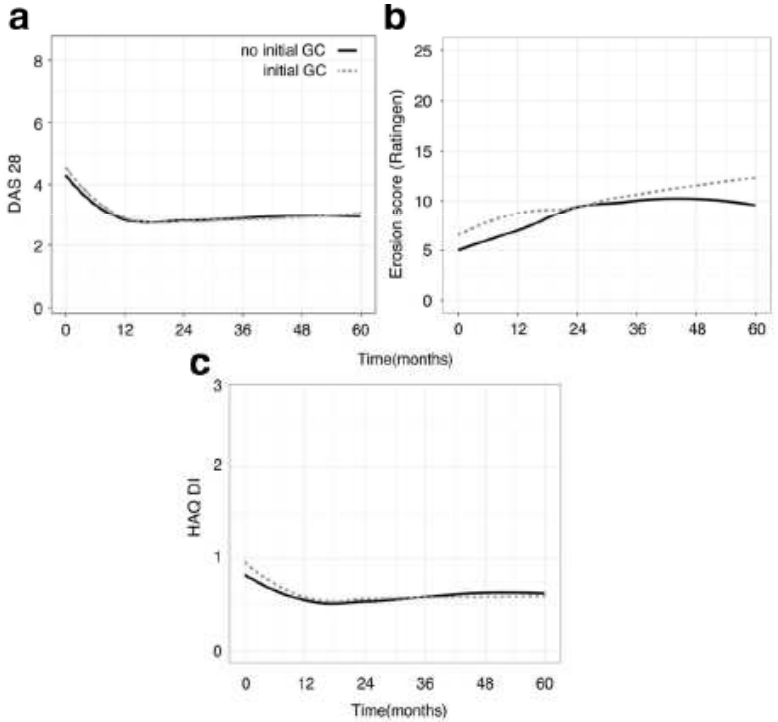


Fig. 2 DAS-28, HAQ scores and radiographic progression over time. Patient groups were analysed separately for initial GC (*dotted grey line*, GC patients) and no initial GC use (*solid black line*, no-GC patients). Loess smoothed time courses of DAS-28 (a), Ratingen (b) and HAQ-DI (c) scores are depicted per group over 60 months of follow-up

Evolution of patients treated or not by glucocorticoïds is similar (DAS 28, HAQ, X-rays)

Suggesting an effect as their prognosis seems worse

Glucocorticoids increase DMARDs maintain

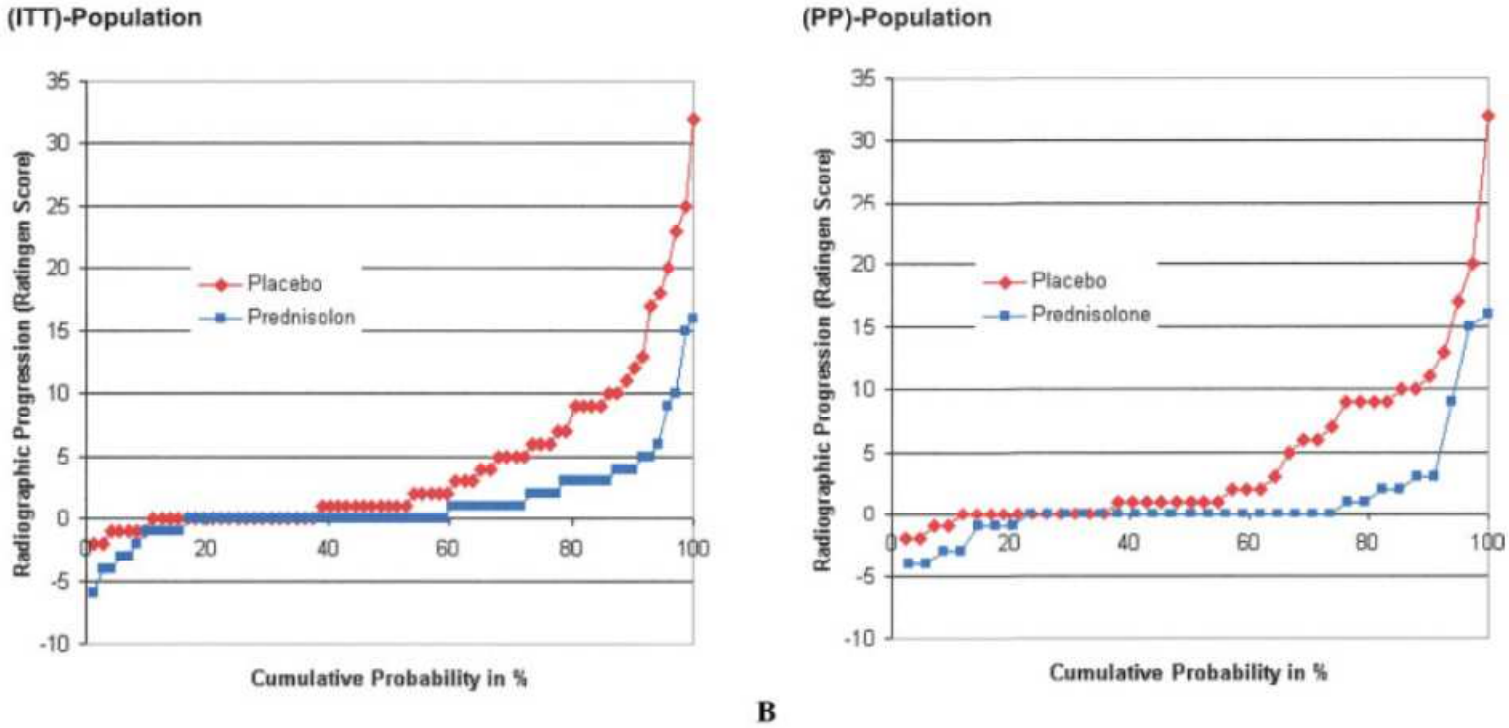
- Sulfasalazine :
  - From **10.4** +/- 2.3 months to **22.5** +/- 1.9 months
- Methotrexate:
  - from **21.8** +/- 2.9 months to **43.3** +/- 2.7 months

Malysheva OA, Wahle M, Wagner U, *et al.* Low-dose prednisolone in rheumatoid arthritis: adverse effects of various disease modifying antirheumatic drugs. J Rheumatol. 2008;35:979-85.

Very Low-Dose Prednisolone in Early Rheumatoid Arthritis Retards Radiographer Two Years

A Multicenter, Double-Blind, Placebo-Controlled Trial

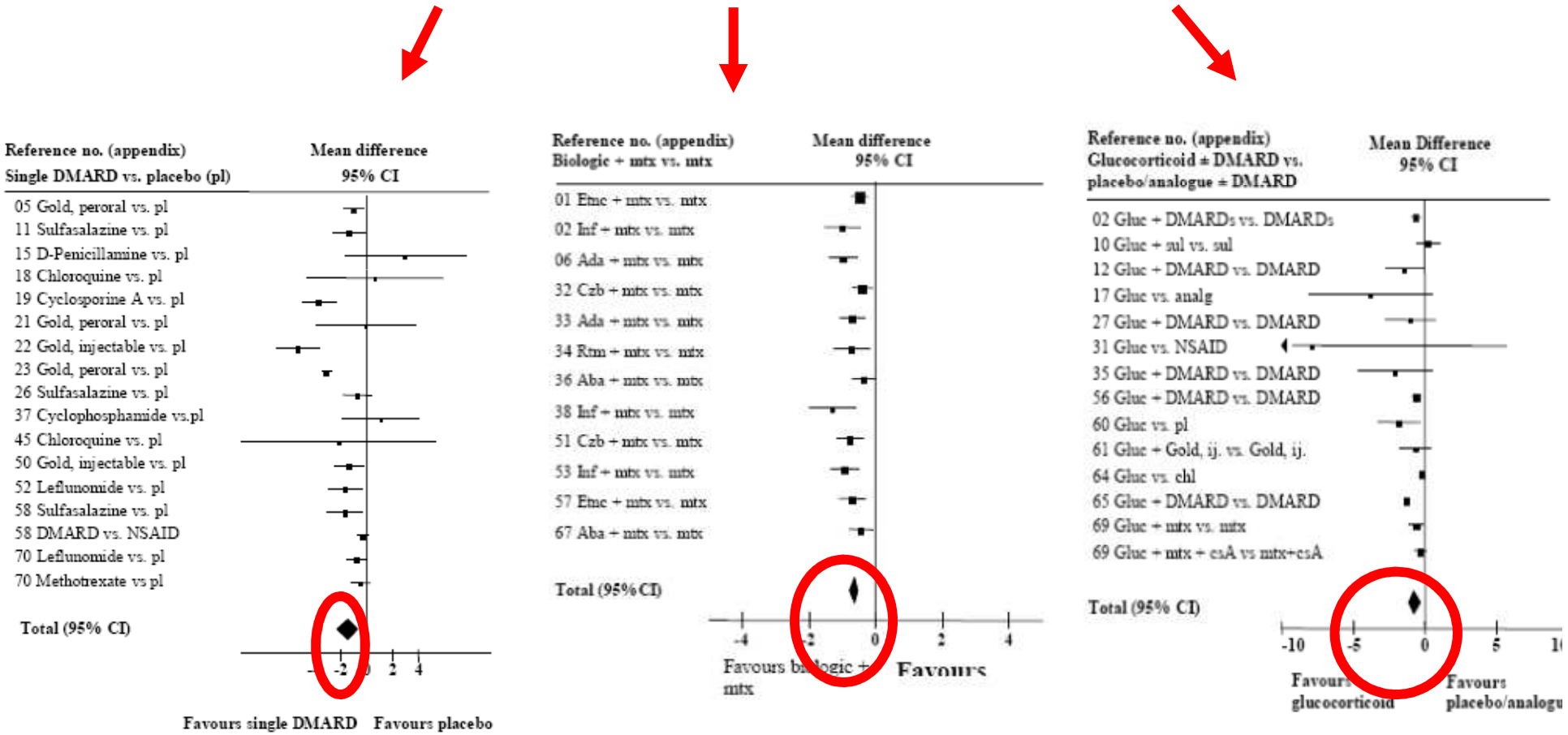
Siegfried Wassenberg,[1] Rolf Rau,[1] Paul Steinfeld,[2] and Henning Zeidler,[3] for the Low-Dose Prednisolone Therapy Study Group



B

Graudal et Jürgens

DMARDs Biologics Prednisone low dose



Graudal N, Jürgens G. Arthritis Rheum 2010;62: 2852

OPEN ACCESS

EXTENDED REPORT

Efficacy of conventional synthetic disease-modifying antirheumatic drugs, glucocorticoids and tofacitinib: a systematic literature review informing the 2013 update of the EULAR recommendations for management of rheumatoid arthritis

Cécile Gaujoux-Viala,[1] Jackie Nam,[2,3] Sofia Ramiro,[4,5] Robert Landewé,[6] Maya H Buch,[2,3] Josef S Smolen,[7,8] Laure Gossec[9]

Table 1 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) 28.6 (oral GC+IV GC)	3.1	0.027 0.006
				'Clinical EULAR remission' at 52 weeks*	37.5 (oral GC) 29.4 (oral GC+IV GC)	11.4	0.012 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 DAS28<2.6 at 52 weeks	80.2 44.8	75.5 27.8	0.44 0.02
Bakker, 2012[13]	236	Prednisone 10 mg/day†	2	ACR70 at 104 weeks SHS erosion score at 104 weeks SHS total score at 104 weeks	38 0 (0–0) 0 (0–3)	19, 0 (0–2) 0 (0–4)	0.002 0.022 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).

Plan

- Background
- Recommendation about glucocorticoids
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- Risks of glucocorticoids
- Benefits of glucocorticoids
- Do biologics allow a glucorticoids tapering?

Long term efficacy and safety of adalimumab plus methotrexate in patients with rheumatoid arthritis: ARMADA 4 year extended study

M E Weinblatt, E C Keystone, D E Furst, A F Kavanaugh, E K Chartash, O G Segurado

Decrease of glucorticoids in patients treated by adalimumab + MTX 6 months in ARMADA

81 patients received glucorticoids

Decrease 63 % (28% stopped), stable 36 %, increased 1 %

Means 5,8 mg/d at inclusion vs 2,7 mg/d at follow up ($p<0.0001$)

Table 4 Efficacy data at last visit for patients with RA in the ARMADA trial/open label extension who were eligible for corticosteroid and/or MTX dosage adjustments*

Drug change	Mean duration of RA at baseline (years)	ACR20 (%)	ACR50 (%)	ACR70 (%)	DAS28 (mean change from baseline)	DAS28 <2.6 (%)	HAQ (mean change from baseline)
Steroid decrease (n=51)	10.8	78	55	28	−2.9	22	−0.67
Steroid no change (n=29)	11.6	76	52	24	−2.5	18	−0.58
MTX decrease (n=92)	11.1	75	55	34	−2.7	27	−0.73
MTX no change (n=110)	12.3	67	44	24	−2.5	16	−0.65
MTX increase (n=15)	14.5	53	33	20	−1.7	7	−0.55
MTX and steroid decrease (n=25)	10.1	76	48	20	−3.0	24	−0.65

*Patients were eligible for corticosteroid and/or MTX dosage reductions after receiving adalimumab treatment for at least 6 months. Last visits were at 8–59 months from the start of adalimumab treatment.

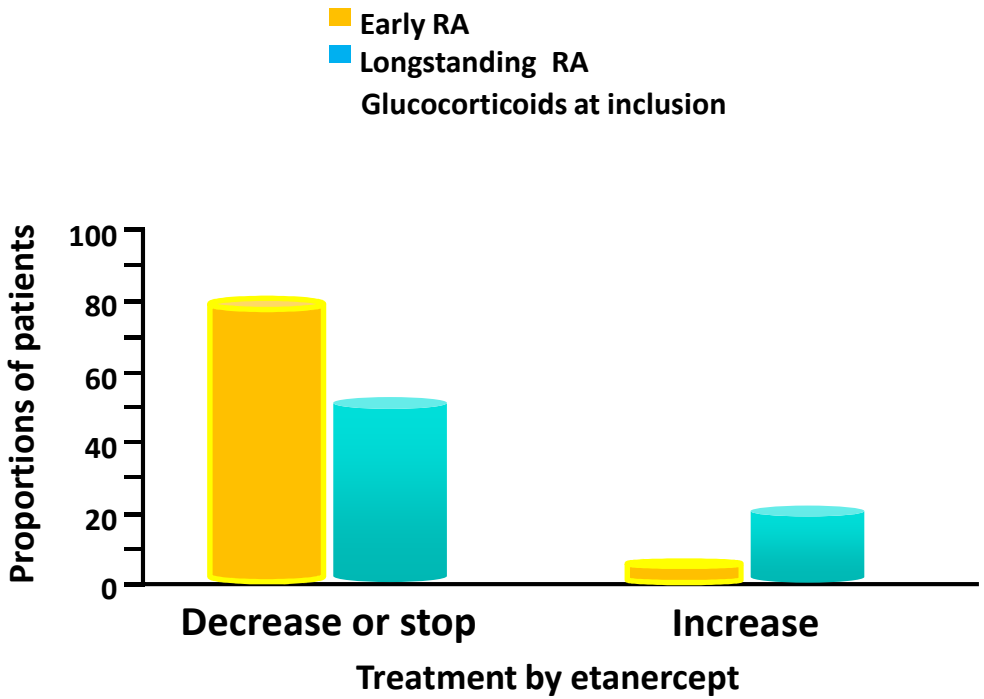
Weinblatt ME, et al. Ann Rheum Dis 2006;65:753-9

Arthritis Care & Research
Vol. 63, No. 3, March 2011, pp 373–382
DOI 10.1002/acr.20372

ORIGINAL ARTICLE

Safety and Efficacy of Etanercept Beyond 10 Years of Therapy in North American Patients With Early and Longstanding Rheumatoid Arthritis

MICHAEL E. WEINBLATT,[1] JOAN M. BATHON,[2] JOEL M. KREMER,[3] ROY M. FLEISCHMANN,[4] MICHAEL H. SCHIFF,[5] RICHARD W. MARTIN,[6] SCOTT W. BAUMGARTNER,[7] GRACE S. PARK,[7] EDWARD L. MANCINI,[7] AND MARK C. GENOVESE[8]



Etanercept is associated to glucocorticoid tapering

Glucocorticoid-sparing effect of first-year anti-TNFα treatment in rheumatoid arthritis (CORPUS cohort)

C. Duquenne[1], D. Wendling[2], J. Sibilia[3], C. Job-Deslandre[4], L. Guillevin[5], J. Benichou[6], R.M. Flipo[7], F. Guillemin[8], A. Saraux[1,9]

The CORPUS cohort is a

French,

non-interventional,

multicenter,

longitudinal,

prospective,

population-based cohort of patients

with RA, spondyloarthritis (SA), or juvenile idiopathic arthritis (JIA),

naive to biologics,

recruited prospectively in private practices and hospitals, between 2007 and 2009, by 102 rheumatologists, internists and pediatricians

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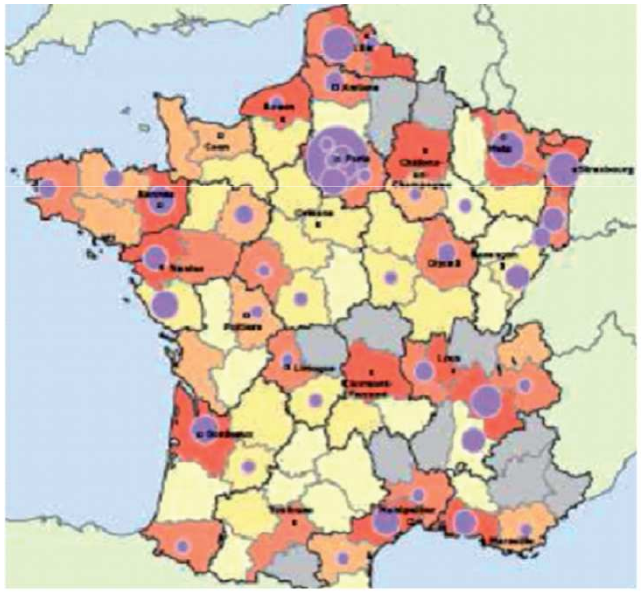
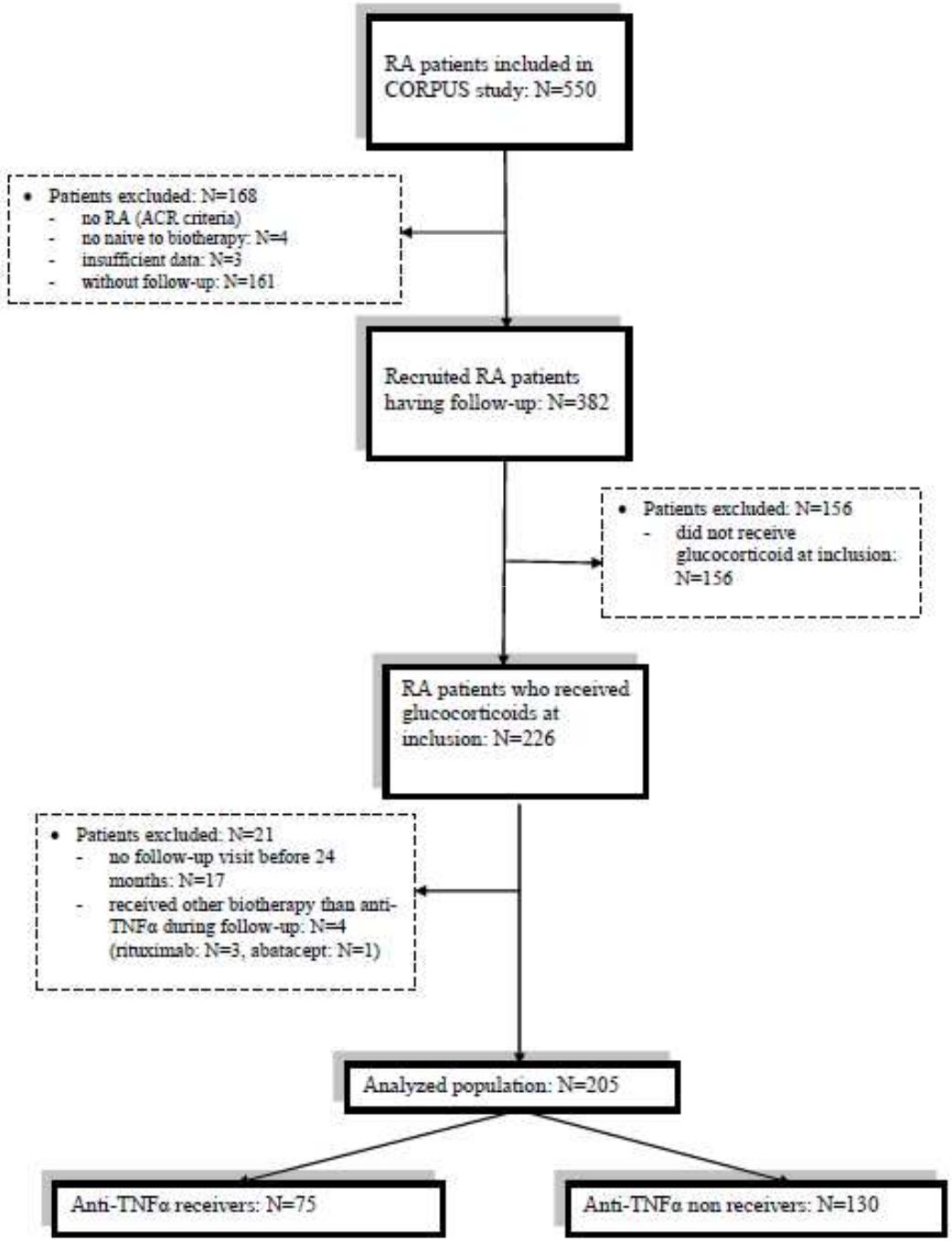


Fig. 1. Number of physicians Corpus (small circle for 0–5 and large circle for 5–20) and number of rheumatologists in France (graduation from yellow to red).

Figure 1: flow chart of the selection to include RA patients who met the inclusion criteria



Which patients with rheumatoid arthritis, spondyloarthritis, or juvenile idiopathic arthritis receive TNF-α antagonists in France? The CORPUS cohort study

A. Saraux[1], J. Benichou[2], L. Guillevin[3], L. Idbrik[4], C. Job-Deslandre[5], J. Sibilia[6], M. Soudant[7], D. Wendling[8], F. Guillemin[7]

Rheumatoid arthritis patients, odds ratio and 95% confidence interval for the risk of receiving biologics in RA patients by multivariate regression analyses

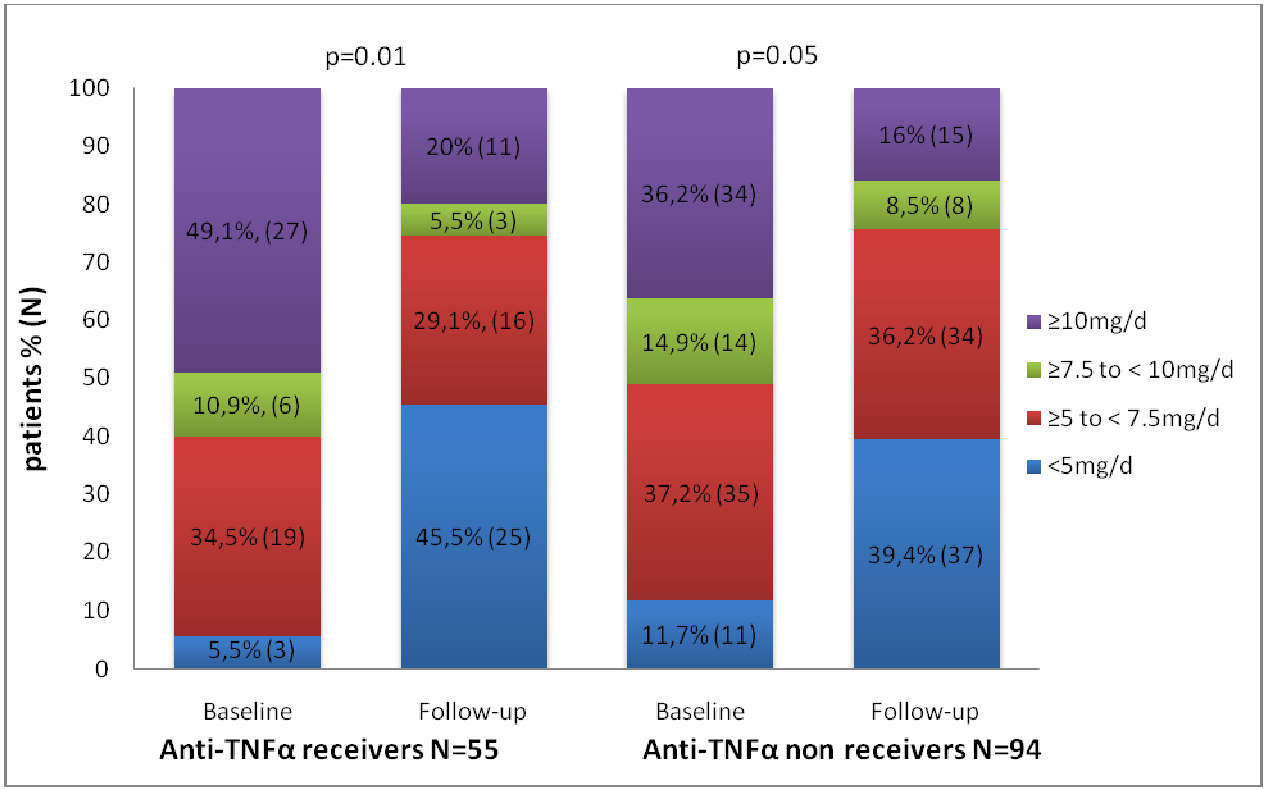
Rheumatoid arthritis	Multivariate Odds ratio	95%CI lower	upper	*p* value
Age (years)	0.93	0.91 -	0.95	<0.0001
Disease duration (years)	1.05	1.02 -	1.09	0.0024
ESR, mm, mean (SD)	1.01	1.000	1.028	0.0499
SF36 PCS [0;100]	0.94	0.91 -	0.98	0.0009
SF36 MCS [0;100]	0.97	0.95 -	0.99	0.0193
Glucocorticoids (yes vs no)	2.36	1.30 -	4.127	0.0046

Corticosteroids are associated to an increased risk to receive biologic during the year

Follow-up data

	Total N=205	anti-TNFα users N=75	anti-TNFα nonusers N =130	*P* value
Decrease or increase in weekly methotrexate dosage between baseline and follow-up***, mg, mean (SD)	+0.5 (4.4)	-1.3 (4.7)	+1.5 (3.9)	<0.01
Time-pattern of sDMARDs intake				
discontinued or decreased, n (%)	48/153 (31.4)	25/56 (44.6)	23/97 (23.7)	0.01
discontinued, n	19	10	9	
decreased, n	29	15	14	
unchanged or increased, n (%)	105/153 (68.6)	31/56 (55.4)	74/97 (76.3)	
unchanged, n	52	21	31	
increased, n	53	10	43	

Prednisone equivalent dosage ranges



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	OR	p
Patient followed by office based practitionner	0.4	<0.05
CRP higher to 10 mg/l at baseline	2.8	0.03
Daily prednisone equivalent dosage at baseline	1.23	<0.01

Factors associated with a lower glucocorticoid requirements (dosage decrease or discontinuation) by multivariate analysis

Glucocorticoid-sparing in patients suffering from rheumatoid arthritis and treated with tocilizumab: the SPARE-1 study

A. Saraux[1], S. Rouanet[2], R.-M. Flipo[3], J.-C. Poncet[4], P. Fardellone[5], P. Hilliquin, I. Idier[6], A. Cantagrel[7]

- *Study design:* French non-interventional, prospective multicenter study with a follow-up period of 12 months.
- *Objective:* Describe in real life the steroid sparing effect in patients treated by TCZ
- *Primary endpoint:* Proportion of patients treated by 5mg/day or less of equivalent prednisone at 12 months without intensification of synthetic DMARDs
- *Patients:*
  - Moderate to severe RA ,
  - >18 years old,
  - TCZ according to their physician,
  - and receiving GCs at a dose greater than 5mg/day of equivalent prednisone for at least 3 months.

Saraux A, et al. Clin Exp Rheumatol 2016; 34 Mar 3

Glucocorticoid-sparing in patients suffering from rheumatoid arthritis and treated with tocilizumab: the SPARE-1 study

A. Saraux[1], S. Rouanet[2], R.-M. Flipo[3], J.-C. Poncet[4], P. Fardellone[5], P. Hilliquin, I. Idier[6], A. Cantagrel[7]

- *Recruitment:* February 2011 - March 2012
- *Treatment :*
  - TCZ and GCs as prescribed in real life.
  - TCZ was administered IV in day-care hospital, usually at a dose of 8mg/kg/4 weeks,
  - no instruction was given regarding GCs dose
- *Collected data*
  - Patients characteristics and co-morbidities at baseline
  - Synthetic DMARDs, GCs, NSAID, TCZ and concomitant treatments every month
  - Tender and swollen joint counts, ESR, CRP, patient visual analogue scale (VAS) for global assessment, patient VAS for pain, physician VAS for global assessment every month
  - Health assessment questionnaire disability index (HAQ-DI) and Rheumatoid arthritis impact of disease (RAID) score at baseline, month 6 and 12
  - Safety: Adverse events (AEs), serious AEs (SAE) and AE of special interest (AESI) as well as withdrawals due to a safety reason

Saraux A, et al. Clin Exp Rheumatol 2016; 34 Mar 3

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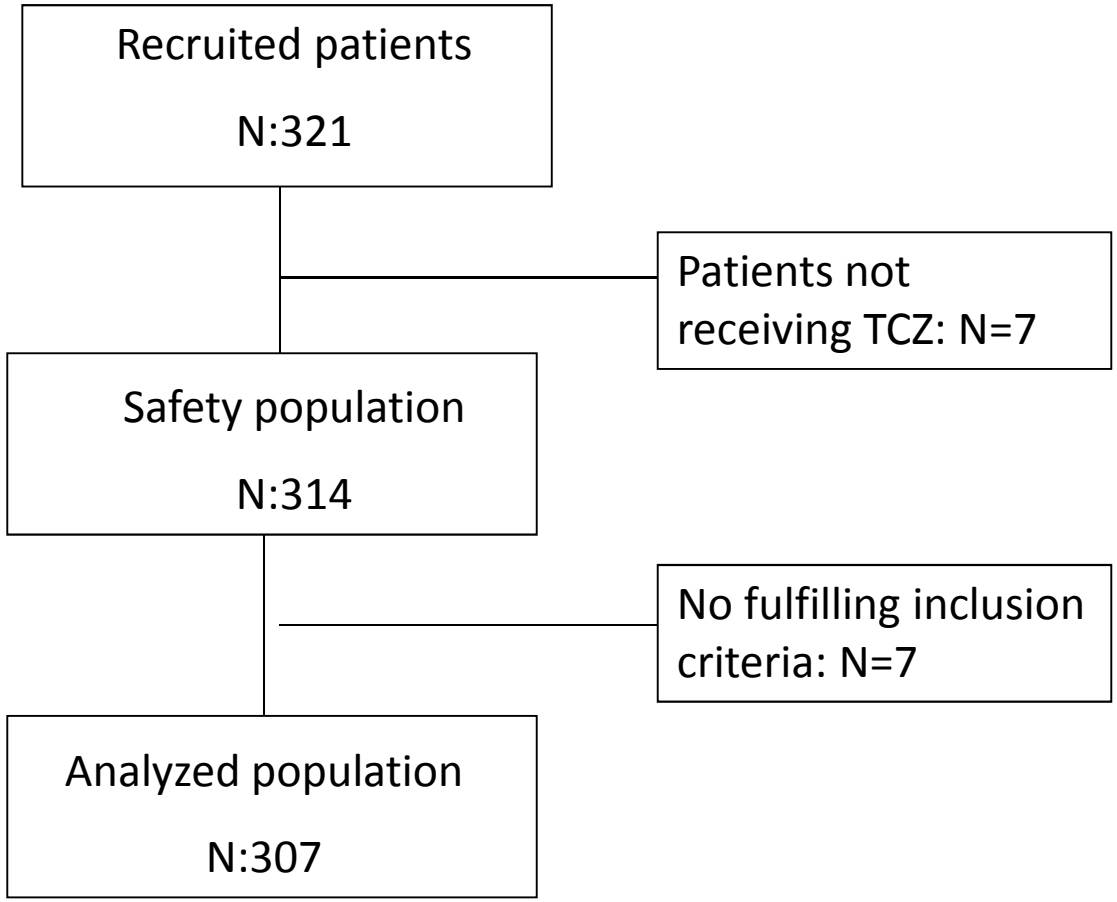
- *Analysis*
  - Patients
    - with at least one TCZ infusion were analyzed for safety data
    - with at least one TCZ infusion fulfilling inclusion criteria were analyzed for all other data
  - Primary endpoint
    - proportion of patients treated by 5mg/day or less of equivalent prednisone at 12 months without intensification of synthetic DMARDs
  - Glucocorticoid dose values in classes at each time point were analyzed using the Last Observation Carried Forward (LOCF) method for handling missing data

Saraux A, et al. Clin Exp Rheumatol 2016; 34 Mar 3

Population



Saraux A, et al. Clin Exp Rheumatol 2016; 34 Mar 3

Population

	Total N=307
Age (years)*	57±14
Women, n (%)	239 (78)
Osteoporosis, n (%) • **Previous fracture, n (%)**** • **Anti-osteoporotic treatment, n (%)**	95 (32) 31/85 (37) 81/95 (85)
RA duration (years)*,**	10±9 8 [3; 15]
RF or ACPA positive, n (%)	249 (82)
Erosive arthritis, n (%)	237 (79)
RA previous treatments* • **Naive, n(%)** • **DMARDs IR, n (%)** • **Biologics IR, n (%)**	 1 (0.3) 87 (29) 216 (71)

*Missing data: 3 patients **Missing data: 10 patients

Saraux A, et al. Clin Exp Rheumatol 2016; 34 Mar 3

Population

	Total N=308
DAS-28 Mean (SD) • **≤ 3.2, n (%)** • **]3.2; 5.1[, n (%)** • **>5.1, n (%)**	5.1±1.3 22 (7) 124 (42) 151 (51)
Glucocorticoid dose at baseline (mg eq. prednisone/day)*	12±7
Glucocorticoid dose at 1st TCZ infusion (mg eq. prednisone/day) Mean (SD) Median [Q1; Q3] **]5; 7.5], n (%)** **]7.5; 10], n (%)** **> 10, n (%)**	15±25 10 [7.5; 15] 79 (26) 136 (44) 92(30)
Associated DMARDs • **Methotrexate (MTX), n (%)**	191 (62) 147 (77)
MTX dose (mg/week) Mean (SD)	17±4
HAQ -DI Mean (SD)	1.6±0.7
RAID Mean (SD)	6.2±2.0

Oral GCs dose at 1st TCZ infusion + GCs bolus at 1st infusion if applicable

Saraux A, et al. Clin Exp Rheumatol 2016; 34 Mar 3

Premature withdrawals

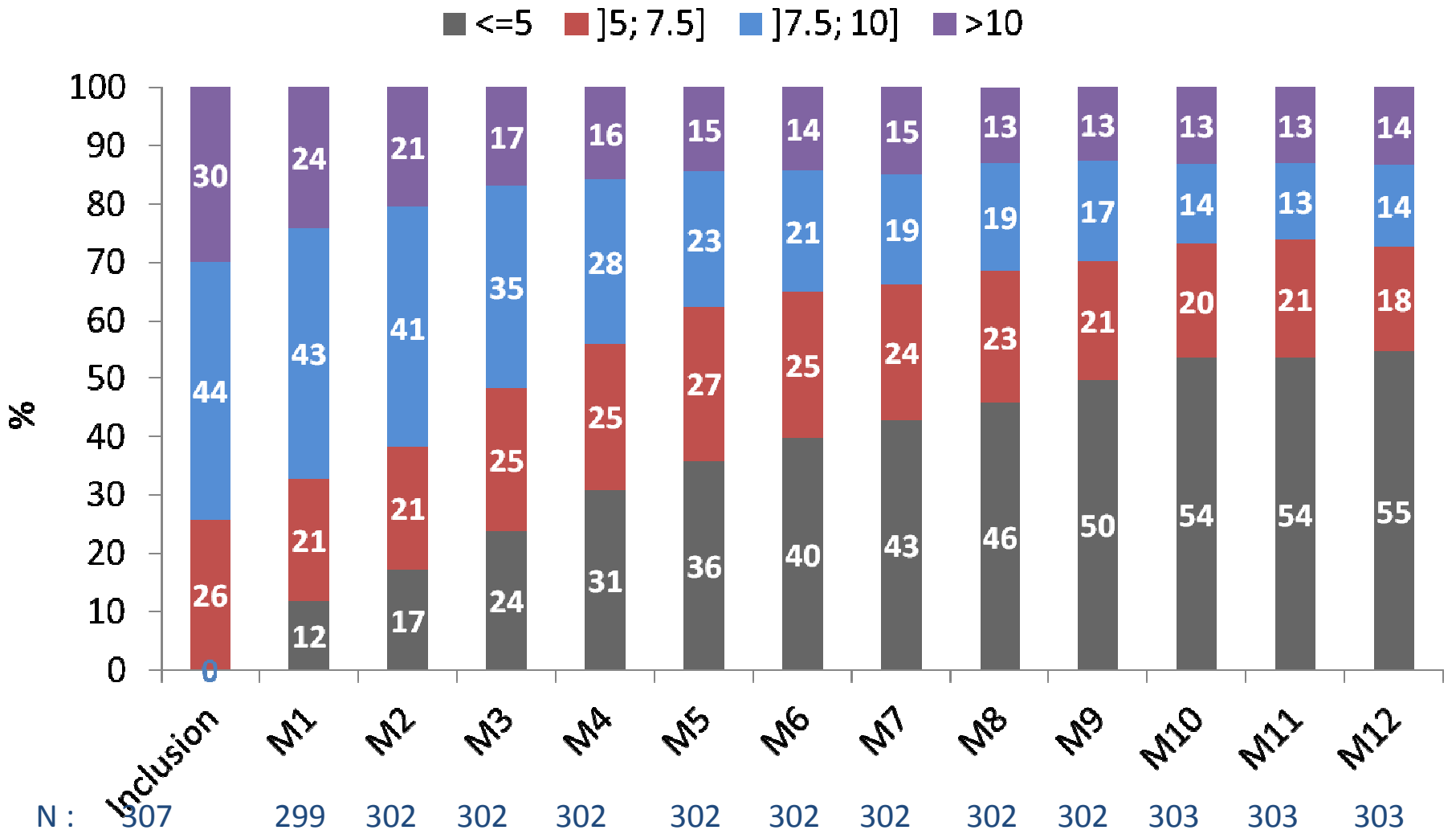
	Total N=307
Premature withdrawals, n(%)	105 (34)
• **Adverse event**	38 (12)
• **Inefficacy**	39 (13)
• **Lost-to-follow-up/moving/refusal to continue the study**	19 (6)
• **Death***	1 (0.3)
• **Other****	8 (3)

* Decubitus complications after osteoporotic fracture in a 82-year old patient
** Including 3 desire of pregnancy

Saraux A, et al. Clin Exp Rheumatol 2016; 34 Mar 3

Evolution of prednisone daily dose

(mg/day of equivalent prednisone)



N : 307 299 302 302 302 302 302 302 302 302 303 303 303

* LOCF

Saraux A, et al. Clin Exp Rheumatol 2016; 34 Mar 3

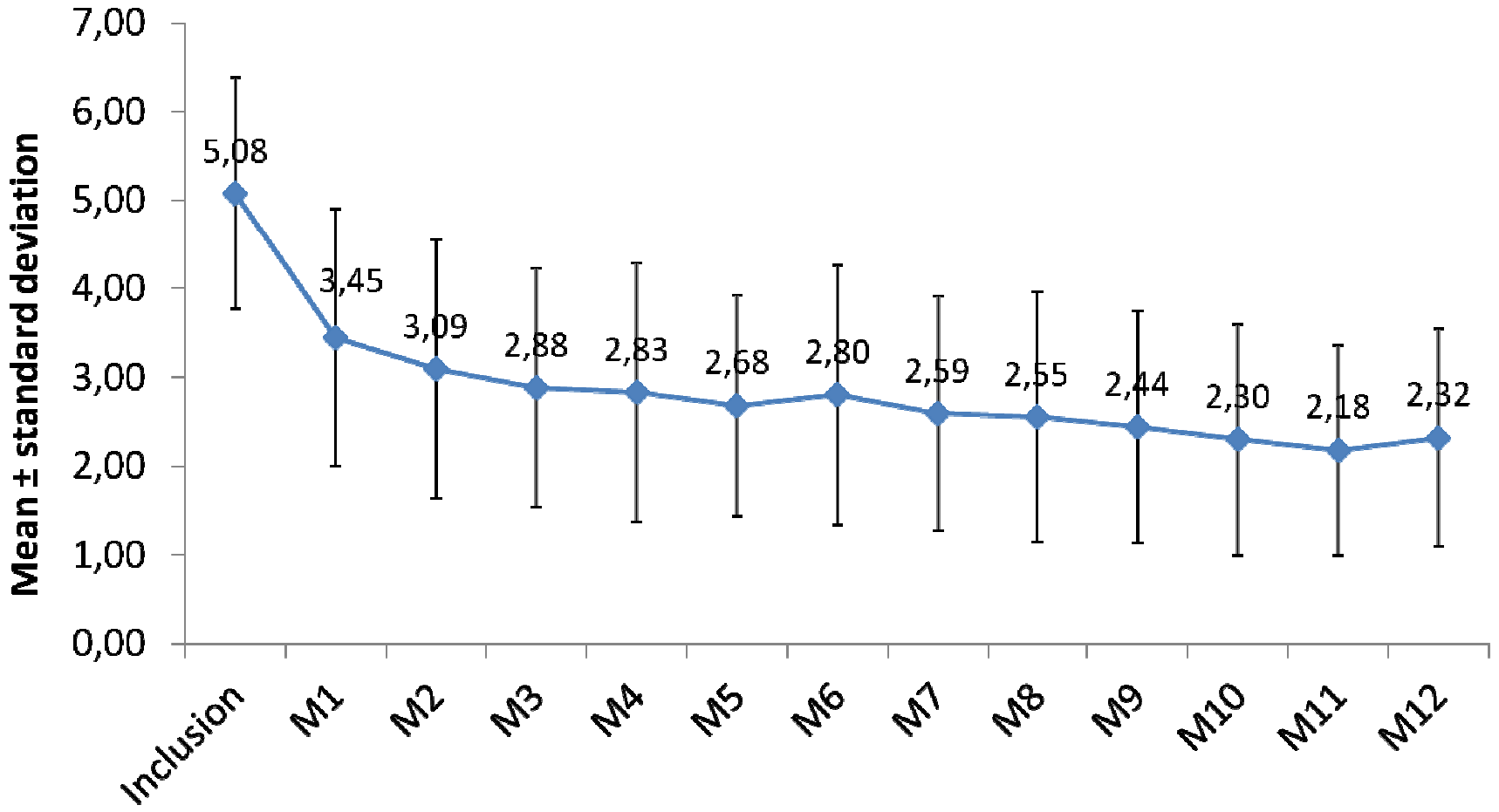
Table II. Proportion of patients who reached a daily glucocorticoid dose ≤5 mg prednisone or equivalent, without intensification of synthetic DMARDs, after 12 months of treatment with tocilizumab (n=307).

	Total n=307
Proportion of patients who reached the targeted glucocorticoid dose (non-assessable response = No) - 95% CI	124 (40.4%) - [34.9 ; 45.9]
Proportion of patients who reached the targeted glucocorticoid dose (LOCF, non-assessable response = No) - 95% CI	157 (51.1%) - [45.6 ; 56.7]
Proportion of patients who reached the targeted glucocorticoid dose (completed patients) – 95% CI (n=184*)	124 (67.4%) - [60.6 ; 74.2]

LOCF: last observed carried forward; CI: confidence interval).
*Amongst the 185 completed patients (*i.e.* patients who underwent the M12 visit with ongoing treatment with tocilizumab), 1 patient had no data reported for the primary criterion analysis.

Saraux A, et al. Clin Exp Rheumatol 2016; 34 Mar 3

DAS-28(ESR) from baseline to month 12



N :	301	280	269	266	248	232	222	217	199	186	181	168	172

Saraux A, et al. Clin Exp Rheumatol 2016; 34 Mar 3

Safety

	Total N=315
At least on AE, n (%)	211 (67)
At least one AE related to TCZ, n (%)	130 (41)
At least one AE of special interest, n (%)	150 (48)
At least one AE of special interest related to TCZ, n (%)	97 (31)
At least one serious AE, n (%)	44 (14)
At least one serious AE related to TCZ, n (%)	23 (7)
At least one serious AE of special interest*, n (%)	24 (8)
At least one serious AE of special interest related TCZ, n (%)	19 (6)

*AEs of special interest as required in the Risk Management Plan (*i.e*. Infections (including all opportunistic and non-serious infections), Myocardial infarction /acute coronary syndrome, Stroke, Gastrointestinal perforations and related events, Malignancies, Anaphylaxis /Hypersensitivity reactions, Demyelinating disorders, Bleeding events, Hepatic events)

Saraux A, et al. Clin Exp Rheumatol 2016; 34 Mar 3

Key messages

- This study is the first prospective study demonstrating in real life that a biologic DMARD (tocilizumab) allows to decrease corticosteroid dosage in RA patients
- 40% of patients could decrease their prednisone dose at 5mg or below at 12 months without increasing disease activity

RHEUMATOLOGY

Rheumatology 2015;54:672–677
doi:10.1093/rheumatology/keu339
Advance Access publication 22 September 2014

Original article

Tocilizumab induces corticosteroid sparing in rheumatoid arthritis patients in clinical practice

Clémentine Fortunet[1,2], Yves-Marie Pers[3], Joseph Lambert[4], Marie Godfrin-Valnet[5], Elodie Constant[6], Hervé Devilliers[7], Philippe Gaudin[4], Christian Jorgensen[3], Béatrice Pallot Prades[6], Daniel Wendling[5] and Jean Francis Maillefert[1,2]

Observationnal multicenter

220 patients
132 steroids

TABLE 1 Baseline characteristics of the study population

Age, mean (S.D.), years	56.7 (14.0)
Gender	25 men, 105 women
Disease duration, mean (S.D.), years	16.3 (10.4)
Erosions on joint X-rays, % of patients	81.9
RF seropositivity, %	71.8
ACPA seropositivity, %	63.1
Previous DMARDs, mean (S.D.)	3.3 (1.6)
Previous biologic therapies, mean (S.D.)	2.3 (1.6)
Associated treatment with MTX, % of patients; mean dose (S.D.), mg/week	46.2; 14.1 (4.4)
DAS28-ESR, mean (S.D.)	5.1 (1.4)
Tender joint count, mean (S.D.)	9.4 (7.3)
Swollen joint count, mean (S.D.)	5.0 (4.7)
Patient's global assessment (VAS 0–100), mean (S.D.)	60.3 (21.3)
ESR, mean (S.D.), mm/h	34.2 (25.7)
CRP, mean (S.D.), mg/l	24.7 (32.7)
CS daily dose, mean (S.D.) prednisone equivalent, mg/day	10.0 (8.2)

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FIG. 1 Evolution of the mean daily CS dose (prednisone equivalent) during the 24 weeks following introduction of tocilizumab

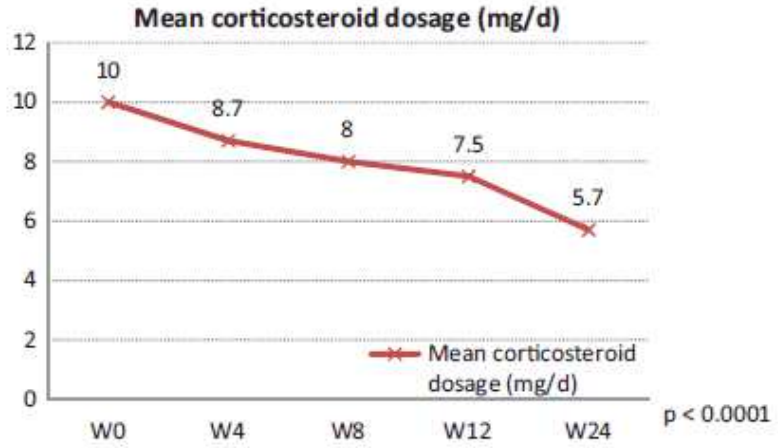
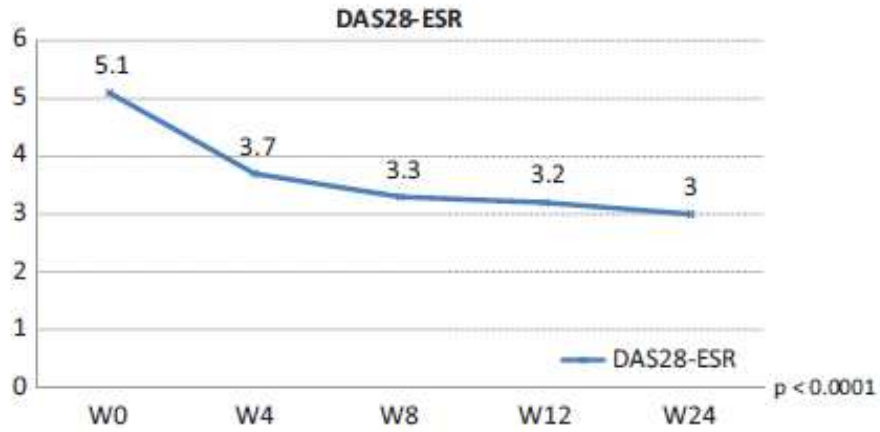


FIG. 2 Evolution of the mean DAS28-ESR during the 24 weeks following the introduction of tocilizumab



RMD Open
Rheumatic & Musculoskeletal Diseases

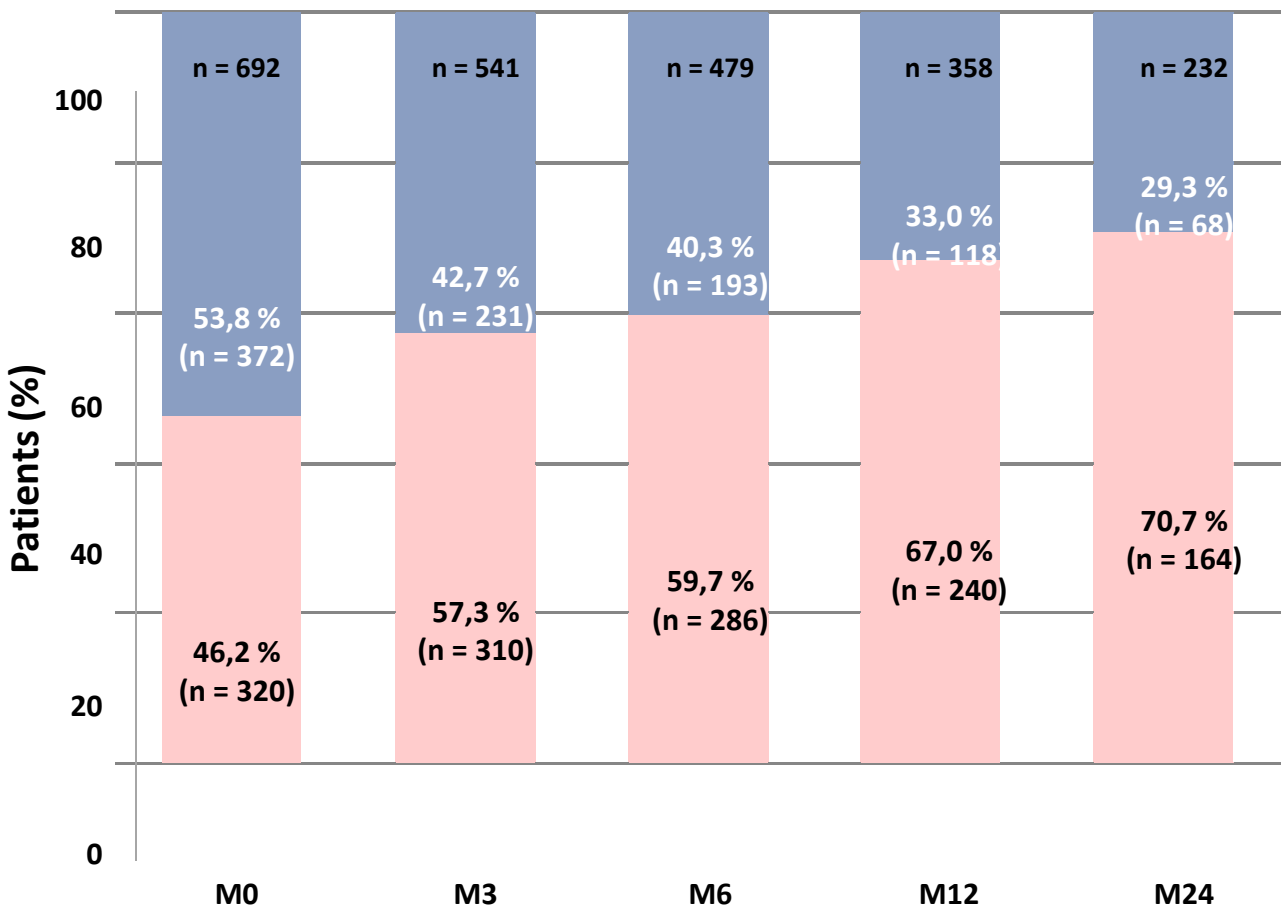
SHORT REPORT

Decreased use of glucocorticoids in biological-experienced patients with rheumatoid arthritis who initiated intravenous abatacept: results from the 2-year ACTION study

Rieke Alten,[1] Hubert Nüßlein,[2] Mauro Galeazzi,[3] Hanns-Martin Lorenz,[4] Michael T Nurmohamed,[5] William G Bensen,[6] Gerd R Burmester,[7] Hans-Hartmut Peter,[8] Karel Pavelka,[9] Mélanie Chartier,[10] Coralie Poncet,[11] Christiane Rauch,[12] Yedid Elbez,[13] Manuela Le Bars[14]

Abatacept ACTION study

% of patients ≤ 5 mg or > 5 mg/d



Conclusion

- Do we use glucocorticoids and when?
  - Yes, frequently….
  - In elderly and in active RA
- What do patients and rheumatologists think about it?
  - Risk are known but not in the same order
- Are there risk and benefits?
  - Benefits are clear
  - Risks are dosage dependent
- What do we recommend?
  - To use it as a bridge…but it is difficult…
- Interest of biologics on glucocorticoids spare
  - Yes, but not so strong

Conclusion