Μείωση και διακοπή κορτικοστεροειδών σε χρονίως θεραπευόμενο ασθενή

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Δεν υπάρχει σύγκρουση συμφερόντων για την συγκεκριμένη ομιλία

No conflict of Interest

Περίπτωση ασθενούς με Ρευματοειδή Αρθρίτιδα

- Γυναίκα 58 ετών με ιστορικό Αρτηριακής Υπέρτασης και Οστεοπόρωσης, χωρίς ιστορικό κατάγματος υπό αγωγή με διφωσφονικά παρουσιάζει φλεγμονώδη αρθρίτιδα νέας έναρξης με υψηλή ενεργότητα DAS 28 (ESR)=5.6 και θετικά anti-CCP αντισώματα σε τίτλο > 300

- Οι ακτινογραφίες δεν ανέδειξαν διαβρώσεις και με διάγνωση Ρευματοειδούς Αρθρίτιδας ξεκίνησε αγωγή με Methotrexate 15 mg/week και Prezolon 10 mg/day

- Τρείς μήνες μετά και αφού έχει γίνει step-up της θεραπείας με μετατροπή της Μεθοτρεξάτης σε υποδόρια στην δόση των 20 mg/week συνεχίζει να λαμβάνει στεροειδή σε δόση 7.5 mg/day και έχει ακόμη ενεργότητα με DAS 28(ESR)=5.2

Περίπτωση ασθενούς με Ρευματοειδή Αρθρίτιδα

- Γίνεται έναρξη anti-TNF-a (Adalimumab) ,συνεχίζει Methotrexate στα 20 mg/week υποδόρια και Prezolon 7.5 mg/day με προσπάθεια σταδιακής μείωσης

- Παρά την έναρξη βιολογικού παράγοντα η ασθενής τρείς μήνες μετά έχει ακόμη υψηλό DAS 28 (ESR) =4.8 ενώ δεν μπορεί να μειώσει τα στεροειδή σε δόση κάτω από 5 mg/day

- Η ασθενής αλλάζει τάξη βιολογικού παράγοντα καθώς θεωρείται προτωπαθής αστοχία και γίνεται έναρξη JAK αναστολέα (Tofacitinib) 5 mg x2 , ενώ γίνεται αύξηση της Methotrexate σε 25 mg/week (SC)

Περίπτωση ασθενούς με Ρευματοειδή Αρθρίτιδα

- Τρείς μήνες μετά υπάρχει σημαντική ανταπόκριση με μείωση του DAS28(ESR)=3.1, Δ(DAS)=1.7 – LDA, με σταθερή δόση Methotrexate και δόση Prezolon από 7.5-5 mg/day

- Δίνεται στην ασθενή πρόγραμμα σταδιακής μείωσης των στεροειδών με πλάνο διακοπής τους σε 2 μήνες

- Στην επανεκτίμηση η ασθενής είναι στα ίδια επίπεδα ενεργότητας-LDA- αλλά εξακολουθεί και λαμβάνει στεροειδή σε δόση 5 mg/day -8 μήνες μετά την αρχική διάγνωση γιατί όπως αναφέρεί δεν μπορεί να τα διακόψει καθώς όταν τα διέκοψε πονούσε αρκετά, είχε πρωινή δυσκαμψία διάρκειας περίπου 40 λεπτών ενώ αρκετές αρθρώσεις των άκρων χειρών ήταν επώδυνες και διογκωμένες

- Η ασθενής θεωρεί ότι τα στεροειδή την βοηθάνε πολύ και θα ήθελε να τα συνεχίσει

Τι κάνουμε στην συνέχεια ;

- Εξηγούμε στην ασθενή τις ανεπιθύμητες επιδράσεις της μακροχρόνιας χρήσης στεροειδών , ιδίως με το ιστορικό της Οστεοπόρωσης και κάνουμε νέα προσπάθεια μείωσης, ίσως με πιο αργό σχήμα ;

- Θεωρούμε ότι παρότι η ασθενής είχε καλή ανταπόκριση-LDA- στην αγωγή με Tofacitinib+MTX εφόσον χρειάζεται ακόμη στεροειδή θα χρειαστεί τελικά αλλαγή βιολογικού παράγοντα με στόχο την πλήρη διακοπή των στεροειδών;

- Θα τις πούμε ότι αν παραμείνει σε χαμηλή δόση μακροχρόνια γύρω στα 5 mg/day αυτό δεν είναι πρόβλημα και ίσως να έχει και ώφελος όσον αφορά τον έλεγχο της ενεργότητας της νόσου;

- Η μακροχρόνια χρήση στεροειδών σχετίζεται με :

1. μείωση της οστικής πυκνότητας
2. αντοχή στην ινσουλίνη
3. δημιουργία καταρράκτη
4. αυξημένο κίνδυνο λοιμώξεων
5. αυξημένη επίπτωση καρδιαγγειακών συμβαμάτων.

Smolen JS, et al.. *Ann Rheum Dis* 2017.

Overman RA, et al . *Arthritis Care Res* 2013.

- Πάνω από το 1/3 των ασθενών με Ρευματοειδή Αρθρίτιδα συνεχίζουν να χρησιμοποιούν χαμηλές δόσεις στεροειδών για περισσότερους από 6 μήνες

- Η μείωση των στεροειδών πρέπει να γίνει αργά και με προσοχή προκειμένου να αποφευχθούν ανεπιθύμητα συμβάματα όπως είναι:

1. Η υποτροπή της νόσου
2. Η φλοιοεπινεφριδιακή ανεπάρκεια

- Evidence- based στρατηγικές απόσυρσης δεν υπάρχουν ενώ και τα βιβλιογραφικά δεδομένα από μελέτες είναι ανεπαρκή

Volkmann ER, et al . *J Rheumatol* 2013

Caporali R, et al. *Neuroimmunomodulation* 2015

ΚΑΤΕΥΘΗΝΤΗΡΙΕΣ ΟΔΗΓΙΕΣ

6. Short-term glucocorticoids should be considered when initiating or changing csDMARDs, in different dose regimens and routes of administration, but should be tapered as rapidly as clinically feasible.

Initiation of a csDMARD without short-term(<3 months) glucocorticoids is **conditionally** recommended over initiation of a csDMARD with short-term glucocorticoids.

Initiation of a csDMARD without longer-term (≥3 months) glucocorticoids is **strongly** recommended over initiation of a csDMARD with longer-term glucocorticoids.

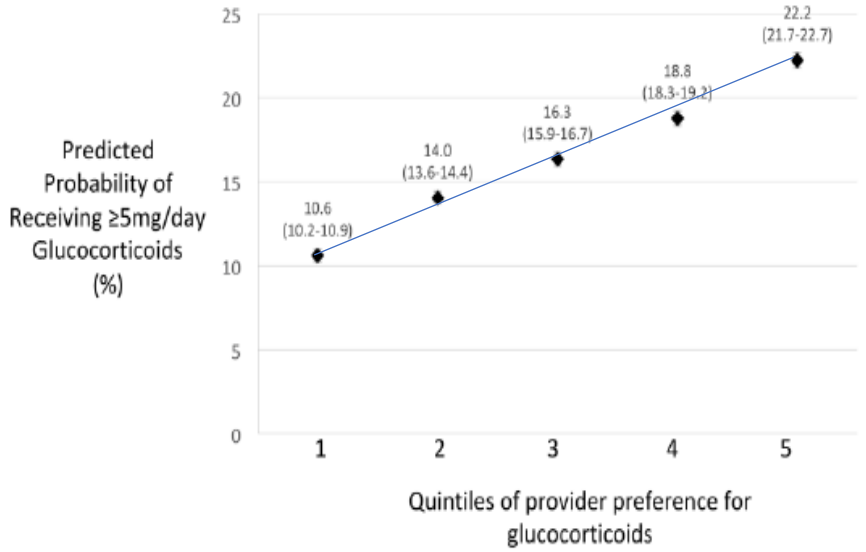
Smolen JS, *et al*. *Ann Rheum Dis* 2020

Fraenken et al. ACR GUIDELINE FOR TREATMENT OF RA 2021

Variability in glucocorticoid prescribing for rheumatoid arthritis and the influence of provider preference on long-term use

Medicare data 2006-2015.

Evaluation whether provider preference for glucocorticoids could independently predict use of ≥5mg/day of glucocorticoids 6-9 months after DMARD initiation.



- Glucocorticoid prescribing for patients with rheumatoid arthritis varied widely among rheumatologists, even when considering differences in case mix.
- Patients who saw a rheumatologist who was a high glucocorticoid prescriber were substantially more likely to receive long-term glucocorticoids.
- Compared to other patient factors, provider preference for glucocorticoids was one of the strongest predictors of long-term glucocorticoid use.

MD, George et al. Arthritis Care & Research 2020

Evidence to support or guide glucocorticoid tapering in rheumatoid arthritis is lacking

Beth I Wallace,[1,2] David M Wallace,[3] Akbar K Waljee,[1,4] Daniel J Clauw[2,5]

In sum, although long-term GC use is common in RA and GC tapering is explicitly supported by current RA management guidelines, there are few data to guide clinicians attempting to taper long-term GCs in RA, particularly among patients with established RA.

Table 1 Characteristics of included studies

Identifier	Acronym	Subjects	RA population	Duration (weeks)	Primary outcome	GC used	Initial GC dose* (mg/day)	Taper length (weeks)	Goal GC dose* (mg/day)	Additional taper instructions
NCT02466581 NCT01491815	NORD-STAR	812	Early	24	CDAI remission	Prednisone	20	9	5	Stop after 9 months
NCT02930343		150	Early	12	EULAR good response	Prednisolone	7.5	6	0	
NCT02997605	STAR	122	LT-GC	52	GC discontinuation	Prednisone	NS	52	0	Reduce 1 mg/ month
						Hydrocorticosone	NS	36	0	20 mg/day for 3 months, 10 mg/ day for 3 months
NCT03649061[13]	CareRA	442	Early	104	Area under DAS-28 curve	Prednisone	30	30	0	
NCT01219933[14]	ACT-ALONE	68	Current GC	20	DAS-28 LDA	Methylprednisolone	1–25	NS	NS	
NCT02644499		186	Early	12	EULAR good response	Prednisolone	15	6	2.5	
NCT02000336	CORRA	386	Early	52	Radiographic progression	Prednisolone	10	12	5	
							60	28	7.5 to 5	
NCT01172639[15]	COBRA	400	Early	104	DAS-28 remission	Prednisone	60	7	6.25	Taper to stop by week 32
							30	32	0	Taper to stop by week 32
NCT00480272	CURE	251	Early	52	DAS-28 remission	Prednisone	50	7	6.25	Stop at week 24
NCT02293590	RICE	43	Established	24	ACR50 response	Prednisone	20	NS	0	Taper every 5 days
NCT02573012 [1617]	SEMIRA	261	Established LT-GC	24	DAS-28 change from baseline	Prednisone	5	24	0	
Tengstrand *et al*[18]		58	Established LT-GC	104	DAS-28 mean	NS	NS	52	0	
Goekoop-Ruiterman *et al*[19]	BEST	508	Early	52	Dutch HAQ mean, Radiographic progression	Prednisolone	60	7	7.5	
Choy *et al*[20]	CARDERA	467	Early	104	New erosions	Prednisolone	60	28	7.5	Taper to stop by week 34
Pincus *et al*[21]		31	LT-GC	NS	Withdrawal for 'lack of efficacy'	Prednisone	5	20	0	
Hickling *et al*[22]		128	Early	156	Radiographic progression	Prednisone	7.5	4	0	7.5 mg/day for 2 years, then taper

Evidence to support or guide GC tapering in rheumatoid arthritis is lacking.
*In prednisone equivalents.
CDAI, clinical disease activity index; DAS-28, disease activity score, 28-joint; EULAR, European League Against Rheumatism; GC, glucocorticoid; LDA, low disease activity; LT-GC, long-term GC; NS, not specified.

Continuing versus tapering glucocorticoids after achievement of low disease activity or remission in rheumatoid arthritis (SEMIRA): a double-blind, multicentre, randomised controlled trial

Gerd R Burmester, Frank Buttgereit*, Corrado Bernasconi, Jose M Álvaro-Gracia, Nidia Castro, Maxime Dougados, Cem Gabay, Jacob M van Laar, Jan Michael Nebesky, Attila Pethoe-Schramm, Carlo Salvarani, Marc Y Donath, Markus R John, on behalf of the SEMIRA collaborators*

Adult patients with rheumatoid arthritis receiving tocilizumab and glucocorticoids 5–15 mg per day for 24 weeks or more were eligible for inclusion if they had received prednisone 5 mg per day for 4 weeks or more and had stable LDA, (DAS28-ESR) of 3·2 or less 4–6 weeks before and on the day of randomisation. Patients were randomly assigned 1:1 to either continue masked prednisone 5 mg per day for 24 weeks or to taper masked prednisone reaching 0 mg per day at week 16.

The primary outcome was the difference in mean DAS28-ESR change from baseline to week 24, with a difference of more than 0,6 defined as clinically relevant between the continued-prednisone group and the tapered-prednisone group.

Lancet 2020; 396: 267–76

	Tapered prednisone (n=131)	Continued prednisone (n=128)	Total population (n=259)
Mean age, years (SD)	54·8 (14·0)	54·0 (12·8)	54·4 (13·4)
Female, n (%)	103 (79%)	97 (76%)	200 (77%)
Race, n (%)			
White	129 (98%)	123 (96%)	252 (97%)
Black	0	0	0
Asian	1 (1%)	2 (2%)	3 (1%)
Other	1 (1%)	3 (2%)	4 (2%)
Region, n (%)			
Germany	65 (50%)	64 (50%)	129 (50%)
Rest of world	66 (50%)	64 (50%)	130 (50%)
Weight, n (%)			
<60 kg	25 (19%)	22 (17%)	47 (18%)
≥60 to <100 kg	95 (73%)	97 (76%)	192 (74%)
≥100 kg	11 (8%)	9 (7%)	20 (8%)
Smoking status, n (%)			
Never	81 (62%)	76 (59%)	157 (61%)
Current	23 (18%)	25 (20%)	48 (19%)
Previous	27 (21%)	27 (21%)	54 (21%)
Disease duration, years			
n (missing)	130 (1)	127 (1)	257 (2)
Mean (SD)	9·6 (8·0)	8·6 (7·4)	9·2 (7·7)
Baseline scores, mean (SD)			
DAS28-ESR	1·88 (0·81)	1·95 (0·93)	1·92 (0·87)
CDAI	5·5 (3·9)	5·7 (4·5)	5·6 (4·2)
SDAI	5·7 (4·3)	5·8 (4·5)	5·7 (4·4)
Swollen joint count at randomisation (66 joints), mean (SD)	1·1 (5·8)	0·8 (1·7)	0·9 (4·3)
Swollen joint count at baseline (28 joints), mean (SD)	0·5 (1·0)	0·7 (1·4)	0·6 (1·2)
Tender joint count at randomisation (68 joints), mean (SD)	2·4 (6·2)	2·4 (3·4)	2·4 (5·0)
Tender joint count at baseline (28 joints), mean (SD)	1·3 (1·7)	1·5 (2·1)	1·4 (1·9)
Rheumatoid arthritis treatment before inclusion, n (%)			
Biological DMARD	50 (38%)	35 (27%)	85 (33%)
Non-biological DMARD	101 (77%)	103 (80%)	204 (79%)
Tocilizumab at randomisation, n (%)			
Monotherapy	47 (36%)	42 (33%)	89 (34%)
Combination with csDMARDs	84 (64%)	86 (67%)	170 (66%)
Tocilizumab formulation at randomisation, n (%)			
Subcutaneous	126 (96%)	127 (99%)	253 (98%)
Intravenous	5 (4%)	1 (1%)	6 (2%)
Concomitant csDMARD during post randomisation phase, n (%)	97 (74%)	99 (77%)	196 (76%)
Concomitant MTX during post-randomisation phase			
Any MTX intake, n (%)	70 (53%)	71 (55%)	141 (54%)
Weekly dose, mg, mean (SD)	14·8 (4·5)	15·5 (12·4)	NA
Concomitant NSAID intake during post-randomisation phase, n (%)	25 (19%)	24 (19%)	49 (19%)

DAS28=Disease Activity Score for 28 joints. ESR=erythrocyte sedimentation rate. CDAI=Clinical Disease Activity Index. SDAI=Simplified Disease Activity Index. DMARD=disease-modifying antirheumatic drug. csDMARD=conventional synthetic disease-modifying antirheumatic drug. MTX=methotrexate. NA=not assessed. NSAID=non-steroidal anti-inflammatory drug.

Table 1: **Patient demographics and baseline characteristics of the intention-to-treat population**

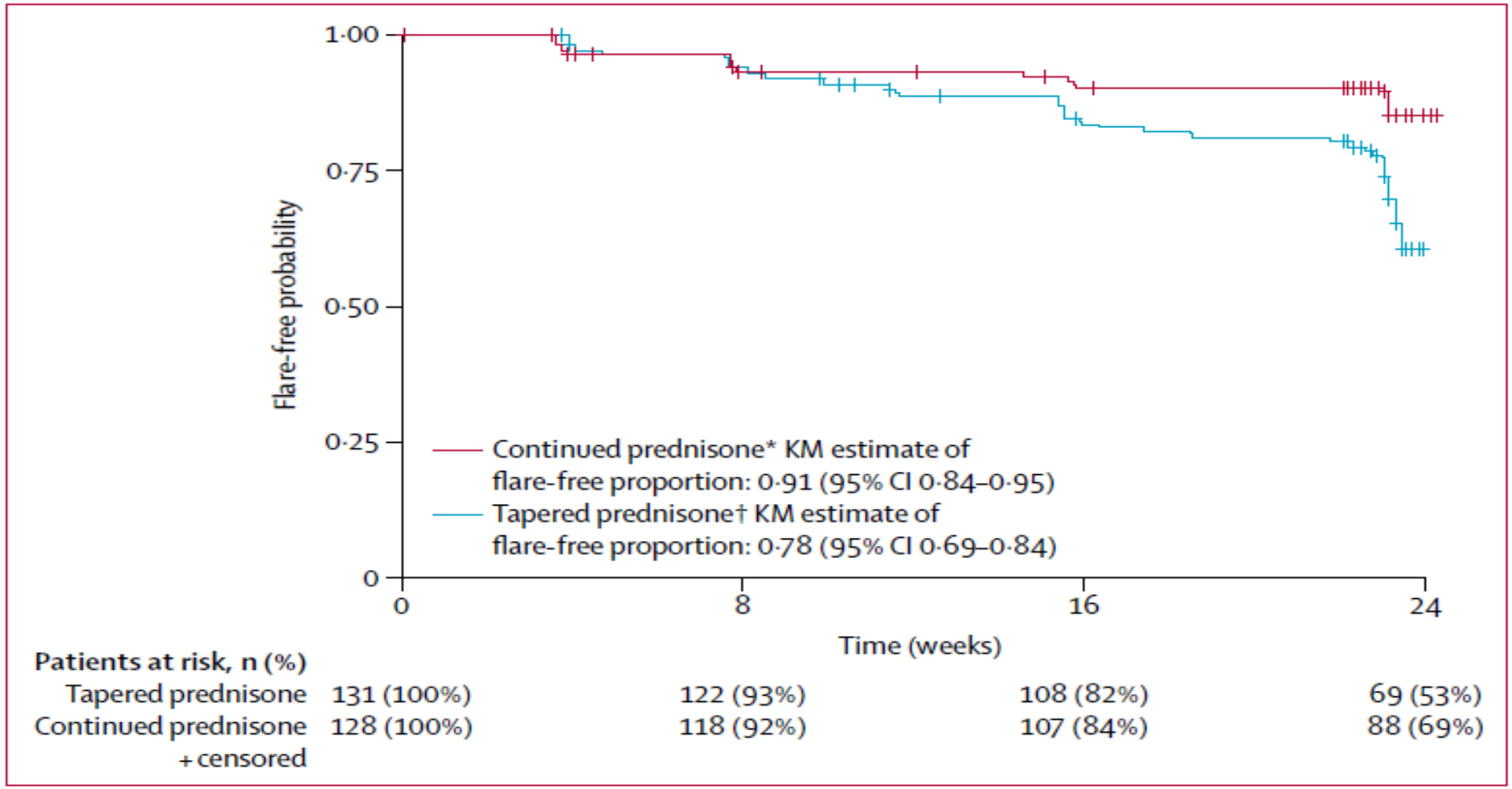


Figure 3: **Time to rheumatoid arthritis flare**

KM=Kaplan-Meier. *14 events (11%) and 114 censored (89%). †34 events (26%) and 97 censored (74%).

	Tapered prednisone (n=131)	Continued prednisone (n=128)	Difference (taper – continuation)
Primary endpoint			
DAS28-ESR change from baseline to week 24	0·538 (0·097; 0·346 to 0·729)	−0·075 (0·099; −0·271 to 0·121)	0·613 (0·135; 0·346 to 0·879) p<0·0001*
LOCF analysis	0·412 (0·090; 0·235 to 0·590)	−0·120 (0·092; −0·301 to 0·062)	0·532 (0·125; 0·285 to 0·779) p<0·0001*
MMRM analysis	0·504 (0·097; 0·313 to 0·696)†	−0·154 (0·099; −0·350 to 0·042)‡	0·658 (0·138; 0·386 to 0·930) p<0·0001*
Secondary endpoints			
CDAI, change from baseline to week 24	2·663 (0·614; 1·454 to 3·872)	0·321 (0·627; −0·914 to 1·556)	2·342 (0·853; 0·661 to 4·023)
Patients who had ≥1 rheumatoid arthritis flare, n (%)	34 (26%)	14 (11%)	NA

Treatment was regarded as successful (defined as low disease activity at week 24,plus absence of rheumatoid arthritis flare for 24 weeks and no confirmed adrenal insufficiency) in 99 (77%) patients in the continued-prednisone group versus 85 (65%) patients in the tapered-prednisone group (relative risk 0·83; 95% CI 0·71–0·97).

Lancet 2020; 396: 267–76

Serious adverse events occurred in seven (5%) patients in the tapered-prednisone group and four (3%) patients in the continued-prednisone group; no patients had symptomatic adrenal insufficiency

Περιορισμοί της μελέτης

1. **Παρακολούθηση μόνο για διάστημα 6 μηνών**
2. **Έλλειψη δεδομένων για την σωρευτική δόση στεροειδών πρίν την ένταξη στην μελέτη**

- **Παρά τα αποτελέσματα της μελέτης μην ξεχνάμε ότι τα 2/3 των ασθενών διέκοψαν χωρίς εξάρσεις της νόσου τα στεροειδή (65%)**

Lancet 2020; 396: 267–76

	Tapered prednisone (n=131)	Continued prednisone (n=128)
Any TEAE	80 (61%)	64 (50%)
CTC grade		
1	37 (28%)	33 (26%)
2	33 (25%)	25 (20%)
3	10 (8%)	5 (4%)
4	0	1 (1)
5	0	0
Blinded treatment-related TEAE	7 (5%)	4 (3%)
Tocilizumab-related TEAE	31 (24%)	19 (15%)
TEAE leading to blinded-treatment discontinuation	4 (3%)	4 (3%)
TEAE leading to tocilizumab discontinuation	5 (4%)	5 (4%)
TEAE resulting in death	0	0
AE of special interest for tocilizumab	5 (4%)	3 (2%)
Confirmed adrenal insufficiency necessitating replacement therapy	0	0
Gastrointestinal perforations	0	0
Serious TEAE	7 (5%)	4 (3%)
Blinded treatment–related serious TEAE	1 (1%)	0
Tocilizumab-related serious TEAE	2 (2%)	1 (1%)
Serious infections or infestations	1 (1%)	1 (1%)
Serious TEAE by preferred term		
Atrial fibrillation	1 (1%)	0
Blood glucose fluctuation	1 (1%)	0
Cerebrovascular accident	1 (1%)	0
Neutropenia	1 (1%)	0
Osteoarthritis	1 (1%)	0
Pneumonia	1 (1%)	1 (1%)
Spinal column stenosis	1 (1%)	0
Asthma	0	1 (1%)
Cellulitis gangrenous	0	1 (1%)
Drug hypersensitivity	0	1 (1%)
Psychotic disorder	0	1 (1%)
Sciatica	0	1 (1%)

Data are n (%). TEAE=treatment-emergent adverse event. CTC=common terminology criteria. AE=adverse event.

Table 3: **Safety and tolerability in the safety population**

POS0470

GLUCOCORTICOID DISCONTINUATION IN EARLY RHEUMATOID AND UNDIFFERENTIATED ARTHRITIS PATIENTS. A SUB-ANALYSIS OF THE BeSt AND IMPROVED STUDIES

J. M. Maassen[1], R. Dos-Santos[2], S. A. Bergstra[1], R. Goekoop[3], T. Huizinga[1], C. Allaart[1]. *[1]Leiden University Medical Center (LUMC), Rheumatology, Leiden, Netherlands; [2]Clinical University Hospital, Rheumatology, Santiago de Compostela, Spain; [3]Haga Hospital, Rheumatology, The Hague, Netherlands*

Conclusion: Primary GCs discontinuation was successful in approximately 60% and secondary in 50% of patients, independent of the treatment target and associated threshold for GC discontinuation. Most baseline characteristics were not predictive of successful GC discontinuation, but ACPA negativity (only in BeSt), baseline DAS (only in IMPROVED) and in both studies DAS prior to GC discontinuation were predictive for successful discontinuation. Based on this data it seems that 'standard' baseline characteristics are insufficient to 'personalize' the duration of temporary GC bridging but the DAS at the moment of GC discontinuation might give guidance.

Table 1. Results logistic regression analyses

	Univariable		Multivariable [a] $R^2 = 0.173$	
BeSt	OR (95% CI)	p-value	OR (95% CI)	p-value
Age, year	1.00 (0.98; 1.03)	0.98		
Gender, female	0.51 (0.24; 1.09)	0.08		
Symptom duration BL, weeks	1.00 (0.99; 1.01)	0.61		
DAS at BL	0.92 (0.61; 1.40)	0.70		
DAS prior to discontinuation	**0.13 (0.05; 0.33)**	**<0.01**	**0.11 (0.04; 0.30)**	**<0.01**
RF, positive	1.28 (0.62; 2.69)	0.50	2.24 (0.81; 6,17)	0.12
ACPA, positive	0.70 (0.34; 1.43)	0.32	**0.32 (0.12; 0.86)**	**0.02**
Erosions, present at BL	0.65 (0.28; 1.49)	0.31		
	Univariable		**Multivariable [a]** $R^2 = 0.065$	
IMPROVED	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
Age, year	1.00 (0.99; 1.02)	0.64		
Gender, female	**0.62 (0.43; 0.89)**	**0.01**	0.75 (0.51; 1.11)	0.15
Symptom duration BL, weeks	1.00 (0.99; 1.00)	0.43	0.99 (0.99; 1.00)	0.08
DAS at BL	**0.80 (0.65; 0.98)**	**0.03**	**0.78 (0.62; 0.98)**	**0.03**
DAS prior to discontinuation	**0.24 (0.15; 0.38)**	**<0.01**	**0.24 (0.14; 0.40)**	**<0.01**
RF, positive	0.82 (0.57; 1.17)	0.27		
ACPA, positive	0.95 (0.66; 1.35)	0.76		
Erosions, present at BL	0.80 (0.49; 1.29)	0.35		

ACPA: anti-citrullinated protein antibodies; BL: baseline; DAS: disease activity score; RF: rheumatoid factor. [α] The final multivariable logistic regression model was based on stepwise forward and backward selection of predictors, both resulting in the same final model.

EXTENDED REPORT

Seven-year tolerability profile of glucocorticoids use in early rheumatoid arthritis: data from the ESPOIR cohort

CONCLUSIONS

This 7-year data analysis of the ESPOIR cohort did not show any significant difference in major safety events among patients with RA with and without GC treatment. These data support the good safety profile of very low-dose GC therapy in early RA. Although our findings need further confirmation, they strongly support the current recommendations[3] that GC should be used for early RA, with DMARDs, for the shortest period and at the lowest possible dose.

Prednisolone (mean 3.1±2.9 mg/day for the entire follow-up)

Table 2 Primary outcome at 7 years (death or cardiovascular disease or severe infection or fracture) in the total sample and patients with and without GC

	Total study population (n=602)	Without GC (n=216)	With GC (n=386)	p Value*
Primary outcome	65 (10.8%)	21 (9.7%)	44 (11.4%)	0.520
Death	7	1	6	0.430
Cardiovascular disease	14	3	11	0.400
Coronary artery disease	8	2	6	–
Stroke	5	1	4	–
Heart failure	1	0	1	–
Severe infections	19	3	16	0.090
Pneumonia	4	2	2	–
Urinary tract infection	7	0	7	–
Digestive	3	1	2	–
Cutaneous	3	0	3	–
Other	2	0	2	–
Fractures	25	14	11	0.150

Data are number or no. (%).
*p Values were assessed by χ^2 test (or Fisher's exact test).
GC, glucocorticoids.

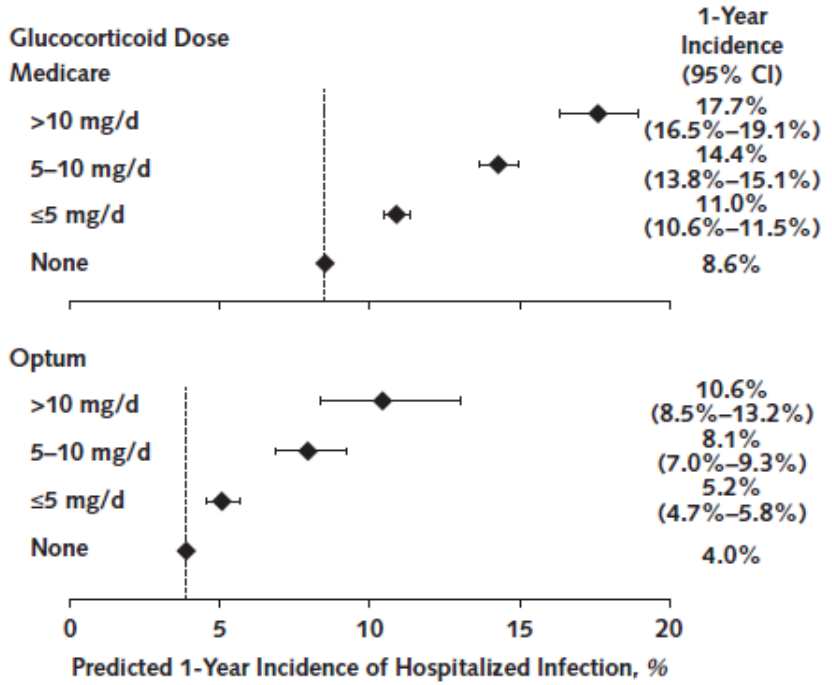
Roubille C, *et al. Ann Rheum Dis* 2017;

Risk for Serious Infection With Low-Dose Glucocorticoids in Patients With Rheumatoid Arthritis

A Cohort Study

Conclusion: In patients with RA receiving stable DMARD therapy, glucocorticoids were associated with a dose-dependent increase in the risk for serious infection, with small but significant risks even at doses of 5 mg or less per day. Clinicians should balance the benefits of low-dose glucocorticoids with this potential risk.

Figure 2. Association between glucocorticoid dose and hospitalized infection (any discharge diagnosis).



Predicted 1-y incidence of hospitalized infection calculated from inverse probability-weighted cause-specific hazards models. Confidence intervals are not available for the reference group, which represents the baseline incidence at 1 y. Variables that were imbalanced across glucocorticoid categories after inverse probability weighting were added as covariates to weighted models (opioid use, outpatient visits, and hospitalizations in both data sets and emergency department visits in Medicare).

MD, George et al. Ann Intern Med 2020

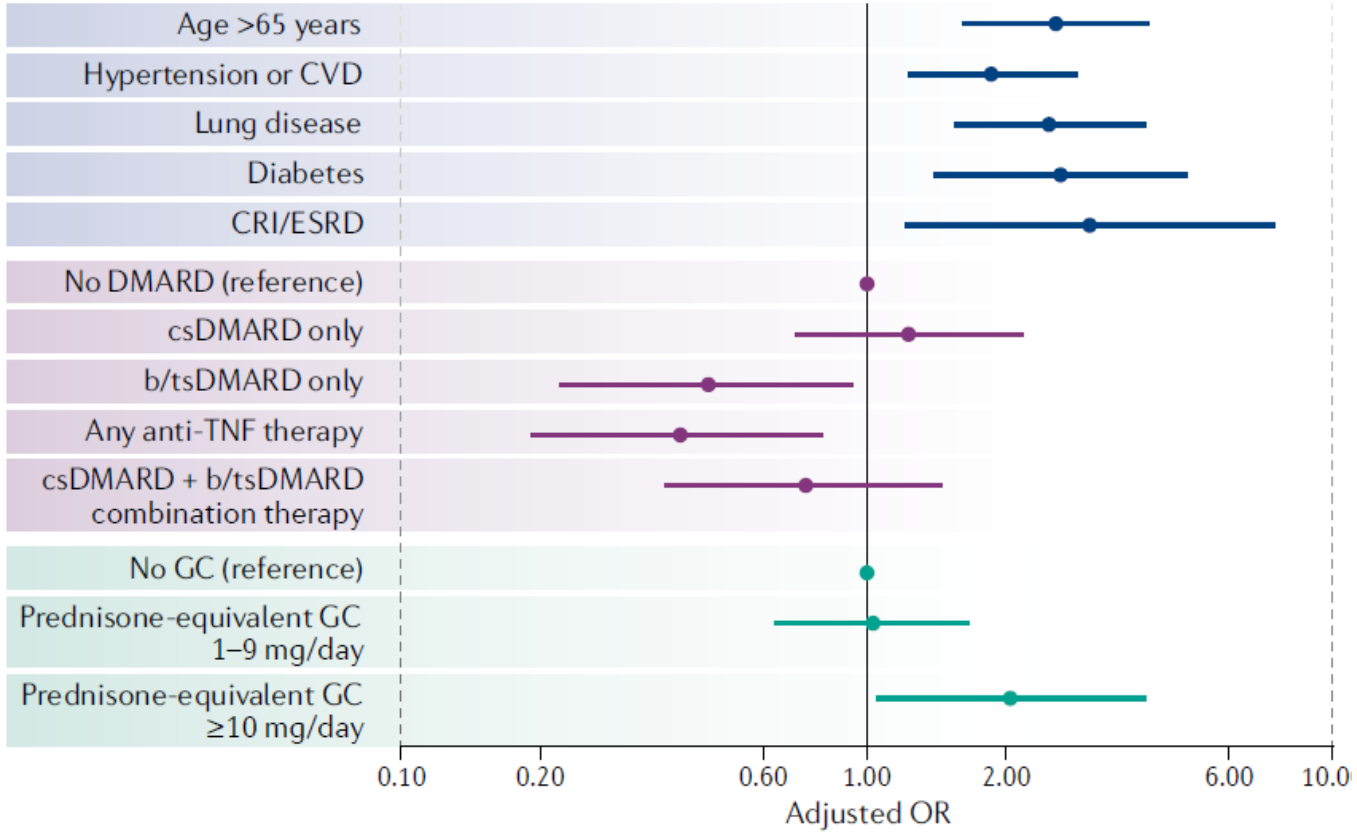


Fig. 1 | **Factors associated with hospitalization for COVID-19 infection.** This graph visualizes data from 600 patients with rheumatic diseases recorded in the COVID-19 Global Rheumatology Alliance international physician registry, reported by Gianfrancesco et al.[4]. Associations between the various factors and odds of hospitalization were estimated using multivariable-adjusted logistic regression and reported as odds ratios (ORs) with 95% confidence intervals. b/tsDMARD, biologic/targeted synthetic DMARD; CRI, chronic renal insufficiency; csDMARD, conventional synthetic DMARD; CVD, cardiovascular disease; ESRD, end-stage renal disease; GC, glucocorticoid.

Rheumatic disease and COVID-19: epidemiology and outcomes

Kimme L. Hyrich and Pedro M. Machado

Adrenal insufficiency is seen in more than one-third of patients during ongoing low-dose prednisolone treatment for rheumatoid arthritis

Stina Willemoes Borresen[1,2], Marianne Klose[1], Bo Baslund[2,3], Åse Krogh Rasmussen[1,2], Linda Hilsted[2,4], Lennart Friis-Hansen[5], Henning Locht[6], Annette Hansen[7], Merete Lund Hetland[2,8], Magnus Christian Lydolph[9] and Ulla Feldt-Rasmussen[1,2]

Distinguishing symptoms of a rheumatoid arthritis flare from subtle signs of adrenal insufficiency is clinically challenging because both phenomena can manifest with worsening fatigue, joint pain, and morning stiffness.

It is conceivable that some patients who experienced worsening of their rheumatoid arthritis were actually experiencing symptoms of adrenal insufficiency.

European Journal of Endocrinology
(2017) **177**, 287–295

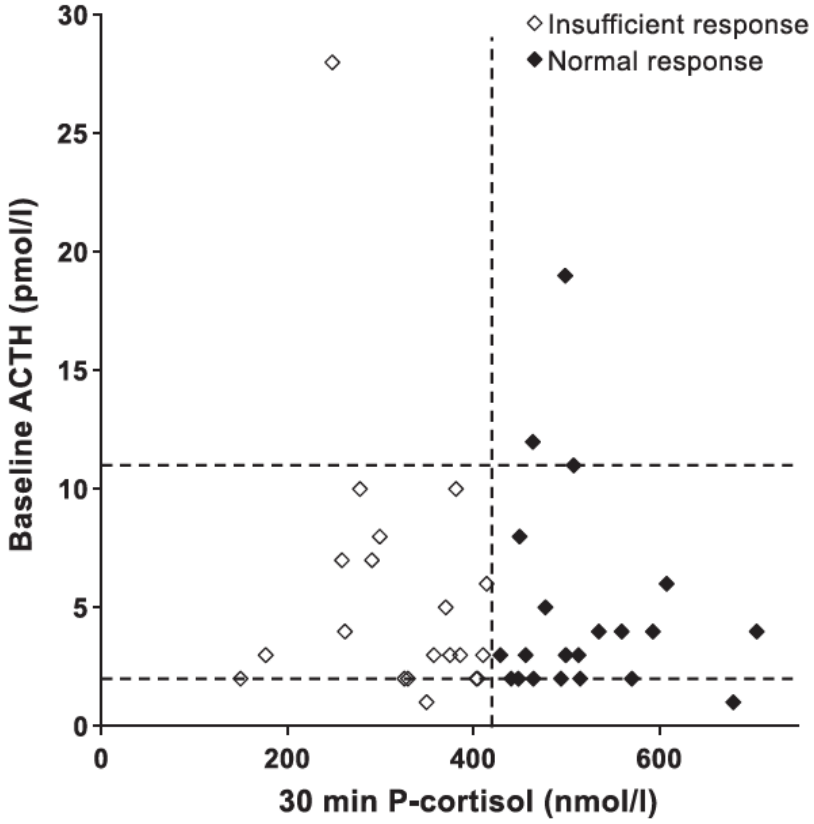


Figure 2
ACTH levels marked on the *y*-axis and P-cortisol 30 min after 250 µg Synacthen injection on the *x*-axis. The ACTH reference range is marked within horizontal dotted lines. ◊ represents patients with insufficient response to the Synacthen test, ♦ represents patients with normal response. Synacthen test cut-off is marked by a vertical dotted line.

Τι κάναμε εμείς

- Νέα προσπάθεια μείωσης των στεροειδών με πιο αργό tapering

- Η ασθενής τελικά κατάφερε και διάκοψε τα στεροειδή 12 μήνες μετά την αρχική διάγνωση

Περίπτωση ασθενούς με Συστηματικό Ερυθηματώδη Λύκο

- Γυναίκα 45 ετών, διάγνωση ΣΕΛ από πενταετία

- Κύριες εκδηλώσεις: αρθρίτιδα μικρών αρθρώσεων, τριχόπτωση , φωτοευαισθησία, εξανθήματα οξέως και υποξέως δερματικού λύκου, λευκοπενία , αιμολυτική αναιμία , θρομβοπενία με αριθμό αιμοπεταλίων μεταξύ 75-120.000, Raynaud, 1 επεισόδιο πλευρίτιδας, ANA : 1/1280 , θετικά anti-Ro και ανοσολογική ενεργότητα με χαμηλά συμπληρώματα και θετικά dsDNA κριθίδια

- Αντιμετωπίστηκε στην αρχή με μέτριες δόσεις στεροειδών 0.5 mg/kg , Hydroxychloroquine 400 mg/day και Azathioprine.

Περιστατικό Συστηματικού Ερυθηματώδους Λύκου

- Στην αύξηση της Azathioprine από 50 σε 100 mg/day η ασθενής παρουσίασε σημαντική λευκοπενία με ολικά λευκά <2000 και ουδετερόφιλα 900 με αποτέλεσμα τη διακοπή της Azathioprine και της αλλαγή της σε Mycophenolate mofetil 2000 mg/day

- Έγινε σταδιακό tapering στεροειδών με την δόση να φτάνει στα 10- 5 mg/day 12 μήνες μετά την διάγνωση. Αλλά λόγω εμμένουσας αρθρίτιδας, εξανθήματος υποξέως δερματικού λύκου, θρομβοπενίας και ανοσολογικής ενεργότητας προστέθηκε Belimumab 200 mg (SC)/week

- Η ασθενής βελτιώθηκε σημαντικά με επίτευξη χαμηλής ενεργότητας νόσου , SLEDAI=4 όμως σε κάθε προσπάθεια (συνολικά 3 μέχρι τώρα) μειώσης των στεροειδών < 5 mg/day ή και διακοπής τους η ασθενής παρουσιάζει υποτροπή του εξανθήματος υποξέως δερματικού λύκου και επιδείνωση της αρθρίτιδας με αποτέλεσμα να λαμβάνει χρονίως Prezolon 5 mg/day

Ερωτήματα

- Ποιό είναι το κατάλληλο χρονικό σημείο σε ασθενή με ΣΕΛ που λαμβάνει χρονίως στεροειδή να γίνει προσπάθεια διακοπής;

- Υπάρχουν ασθενείς που έτσι ή αλλιώς χρειάζονται μικρή δόση στεροειδών για να ελέγχεται καλύτερα ή νόσος τους;

- Είναι τα γενικά συπτώματα και οι αρθραλγίες πάντα έξαρση της νόσου;

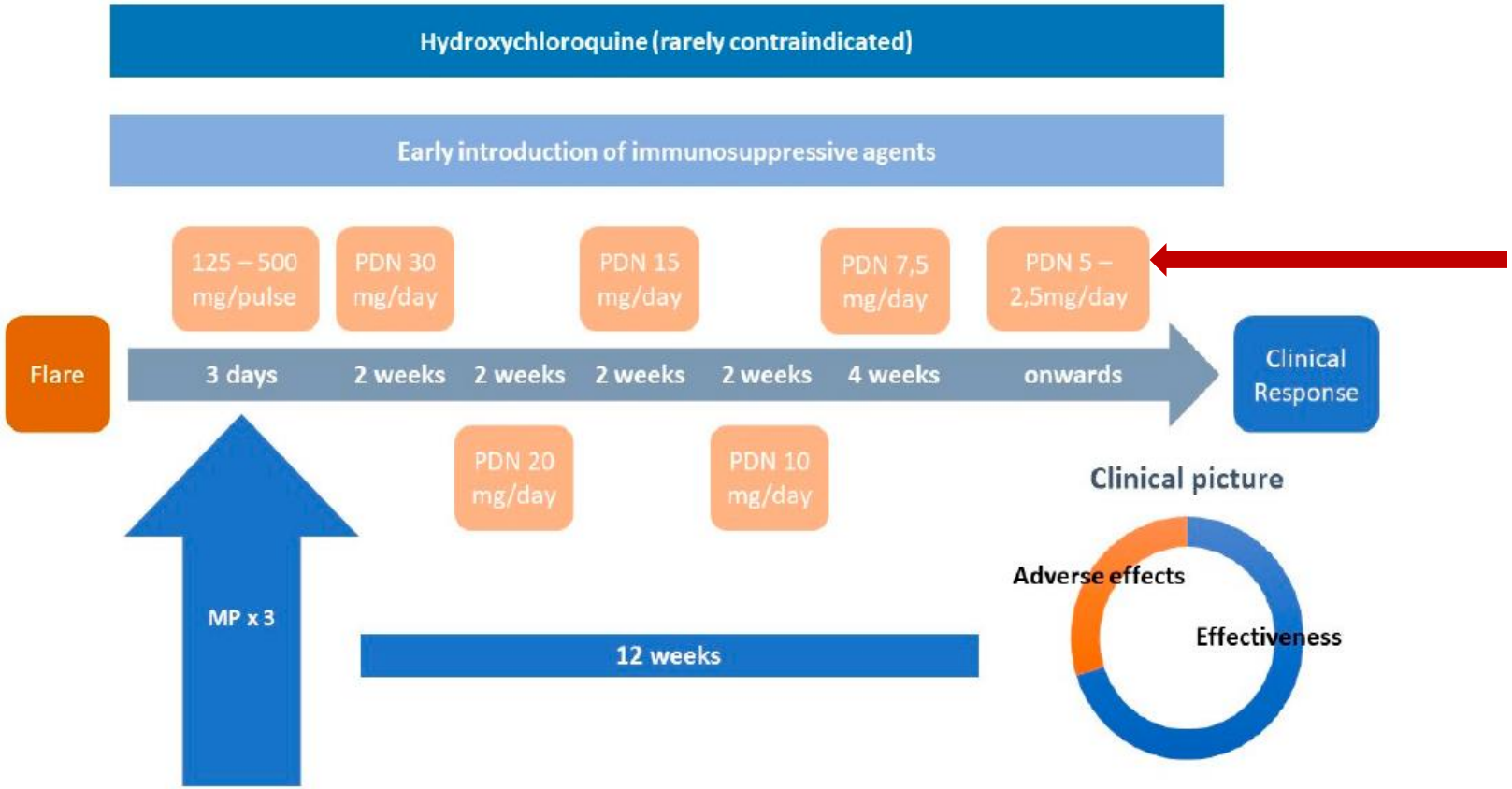


Figure 2. The "new paradigm" in SLE therapy. Note: PDN: prednisone; MP: methylprednisolone pulses; proportions showed in "clinical picture" are merely illustrative.

CLINICAL SCIENCE

Withdrawal of low-dose prednisone in SLE patients with a clinically quiescent disease for more than 1 year: a randomised clinical trial

Alexis Mathian ,[1] Micheline Pha,[1] Julien Haroche,[1] Fleur Cohen-Aubart,[1] Miguel Hié,[1] Marc Pineton de Chambrun,[1] Thi Huong Du Boutin,[1] Makoto Miyara,[2] Guy Gorochov,[2] Hans Yssel,[2] Patrick Cherin,[1] Hervé Devilliers,[3] Zahir Amoura[1]

A monocentric, 12-month, superiority, open-label, randomised (1:1) controlled trial was conducted with 61 patients continuing 5 mg/day prednisone and 63 stopping it. Eligibility criteria were SLE patients who, during the year preceding the inclusion, had a clinically inactive disease and a stable SLE treatment including 5 mg/day prednisone. The primary endpoint was the proportion of patient experiencing a flare defined with the SELENA-SLEDAI flare index (SFI) at 52 weeks

What does this study add?

- In SLE patients with quiescent disease and stable treatment regimen for at least 1 year, withdrawal of 5 mg of prednisone was associated with a fourfold increase in the risk of flare.
- No worsening of Systemic Lupus International Collaborating Clinics damage index and the GC toxicity index were observed during the study.

How might this impact on clinical practice or future developments?

- There is an interest of continuing 5 mg prednisone at long course to avoid relapse in SLE.

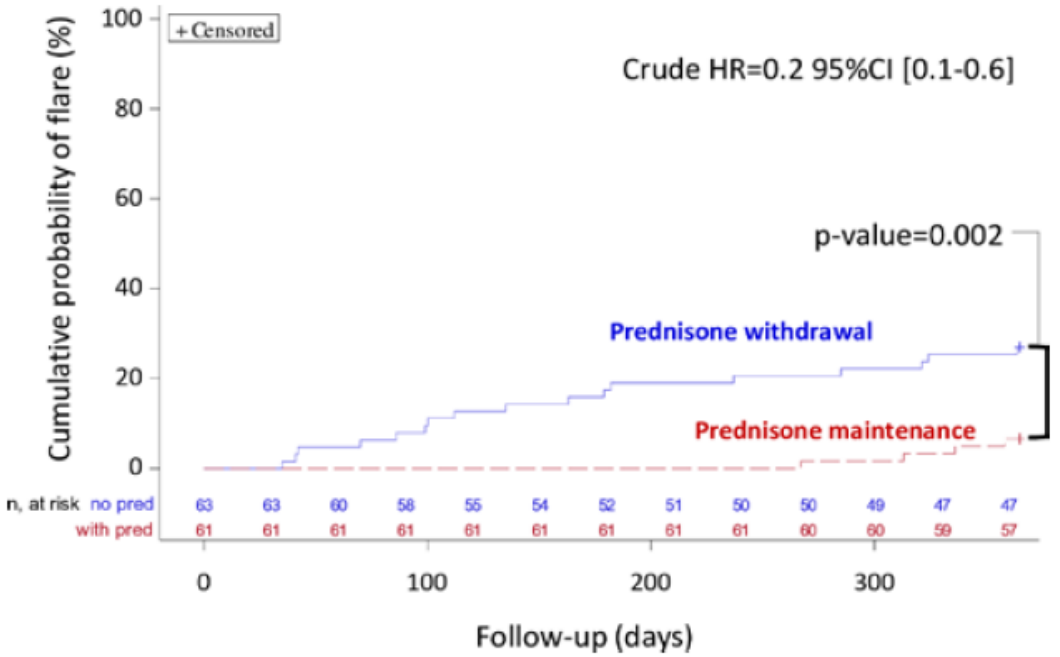


Figure 2 Kaplan-Meier estimates of the cumulative probability of flare for patients in the prednisone maintenance and prednisone withdrawal groups. Clinically quiescent SLE patients were allocated at day 0 to stop (blue line) or to continue (red line) prednisone 5 mg/day and were followed for 52 weeks. Each corner in the curve represents a lupus flare, defined by SELENA-SLEDAI flare index. Patients who had a flare in any organ system were recorded. Kaplan-Meier plots show the percentage of patients who flared in any organ system. All patients had a 52 weeks survey. No patient was censored before the end of the study. Curves were compared using log-rank tests. Crude HR was calculated using a proportional risk COX model. Pred, prednisone; SLE, systemic lupus erythematosus.

Mathian A, *et al*. *Ann Rheum Dis* 2019

RMD Open
Rheumatic & Musculoskeletal Diseases

ORIGINAL ARTICLE

Glucocorticoid withdrawal in systemic lupus erythematosus: are remission and low disease activity reliable starting points for stopping treatment? A real-life experience

Chiara Tani,[1] Elena Elefante,[1] Viola Signorini,[1] Dina Zucchi,[1] Valentina Lorenzoni,[2] Linda Carli,[1] Chiara Stagnaro,[1] Francesco Ferro,[1] Marta Mosca[1]

148 patients were involved in the study; GC withdrawal was attempted in 91 patients (61.5%) with 77 patients (84.6%) successfully stopping GCs. At the beginning of the GC reduction, the majority of patients were in complete or clinical remission (48.9% and 39.6%, respectively).

What does this study add?

- We demonstrated that GCs tapering and complete withdrawal is an achievable goal in patients with SLE.

How might this impact on clinical practice?

- Long-term remission or Lupus Low Disease Activity State can be considered a reliable starting point for GCs tapering.
- Disease flares after GCs withdrawal are not common, and they can occur both early and a long time after stopping GCs.

Table 4 Frequency of GCs-free patients in the cohorts reported in the literature

Author, year	Ref	Study design	Percentage of patients GC free	Note
Ponticelli, 1988	36	Prospective	50	Only LN
Drenkard, 1996	14	Prospective	23	
Formiga, 1999	33	Prospective	24	Remission for at least 1 year
Pons-Estel, 2004	34	Prospective	20.2	
Urowitz, 2005	32	Prospective	6.5	Complete remission for at least 1 year
Moroni, 2006	17	Retrospective	26.6	Only LN
Moroni, 2013	16	Prospective	32	Only LN
Steiman, 2014	15	Prospective	2.4	
Zen, 2017	27	Prospective	7.1	
Petri, 2018	24	Prospective	13	Of follow-up months

GC, glucocorticoid.

Table 3 Univariate and multivariate analysis for predictors of successful GC stopping and flares after GC withdrawal

Successful GC withdrawal	OR	P value	CI
Disease duration	1.00	0.87	0.91 to 1.128
Complete remission	4.25	**0.03**	1.19 to 16.6
Clinical remission	0.36	**0.05**	0.09 to 1.06
LLDAS (not remission)	0.69	0.56	011 to 3.28
SLEDAI	0.70	**0.02**	0.52 to 0.95
Duration from last flare	1.00	0.87	0.90 to 1.12
SLICC	0.63	**0.05**	0.39 to 1.01
Multivariate analysis			
Complete remission	0.40	0.69	0.004 to 38.9
Clinical remission	0.19	0.23	0.009 to 3.84
SLICC	0.59	0.09	0.32 to 1.08
SLEDAI	0.69	0.35	0.31 to 1.51
Flare after GC withdrawal			
Disease duration	1.01	0.76	0.94 to 1.07
Complete remission	0.73	0.58	0.25 to 2.18
Clinical remission	0.53	0.29	0.16 to 1.79
LLDAS (not remission)	4.47	0.07	0.89 to 22.4
SLEDAI	1.43	**0.03**	1.03 to 1.98
Duration from last flare	0.78	**0.03**	0.63 to 1.96
SLICC	0.45	0.27	0.10 to 1.86
Multivariate analysis			
SLEDAI	1.11	0.61	0.72 to 1.0
Duration from last flare	0.8	0.05	0.64 to 1.8

GC, glucocorticoid.

Tani C, *et al. RMD Open* 2019

Τι κάναμε εμείς ;

- Αυξήσαμε την δόση του του Mycophenolate Mofetil στα 2500 mg/day, συνεχίσαμε το Belimumab (SC) και μειώσαμε παιρετέρω τα στεροειδή στα 2.5 mg Prezolon μέρα παρά μέρα

- Με την παραπάνω θεραπεία η ασθενής παραμένεις σε χαμηλή ενεργότητα νόσου

Defining conditions where long-term glucocorticoid treatment has an acceptably low level of harm to facilitate implementation of existing recommendations: viewpoints from an EULAR task force

Cindy Strehl,[1] Johannes W J Bijlsma,[2,3] Maarten de Wit,[4] Maarten Boers,[3,5] Nele Caeyers,[6] Maurizio Cutolo,[7] Bhaskar Dasgupta,[8] William G Dixon,[9] Rinie Geenen,[10] Tom W J Huizinga,[11] Alison Kent,[12] Annette Ladefoged de Thurah,[13] Joachim Listing,[14] Xavier Mariette,[15,16] David W Ray,[17] Hans U Scherer,[11] Raphaèle Seror,[15,16] Cornelia M Spies,[1] Simon Tarp,[18] Dieter Wiek,[19] Kevin L Winthrop,[20] Frank Buttgereit[1]

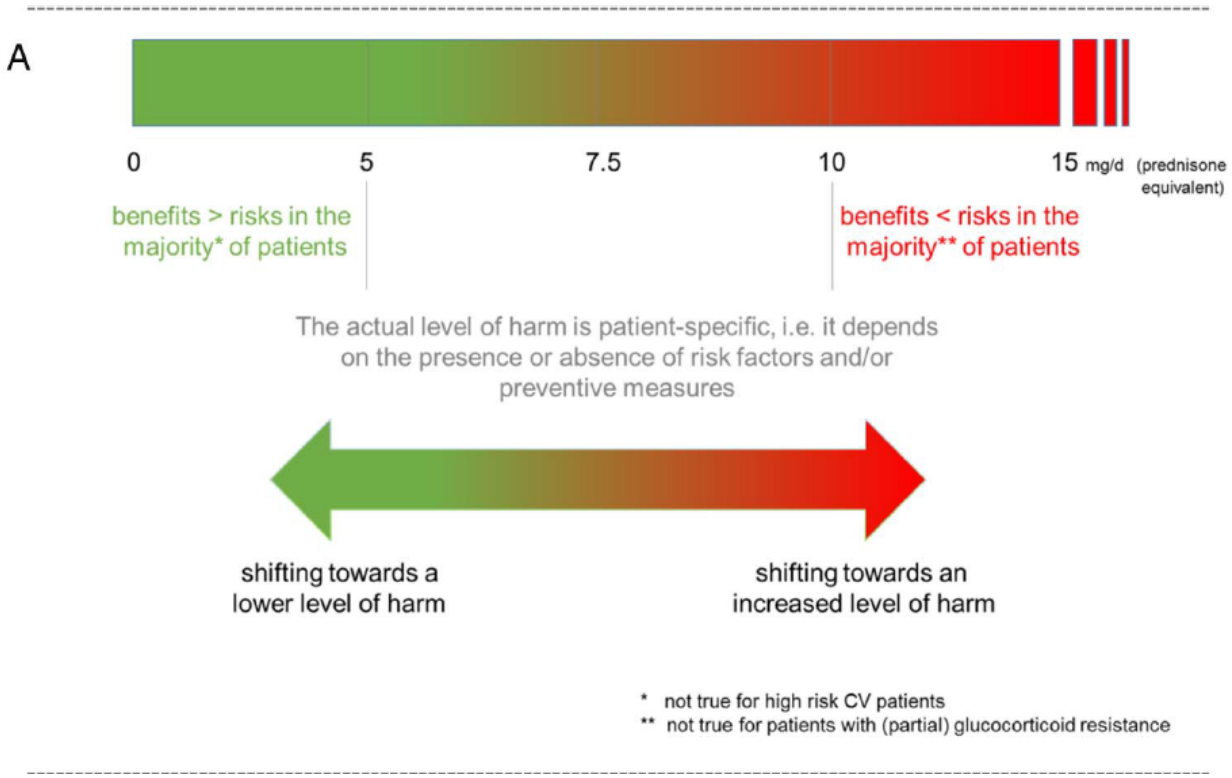


Figure 1 The level of harm of long-term glucocorticoid therapy in rheumatic diseases. Bearing in mind the beneficial effects of glucocorticoids, the Task Force members agreed that (A) at dosages of ≤5 mg/day prednisone equivalent, there is an acceptably low level of harm that is elevated at dosages of >10 mg/day. At dosages between >5 and ≤10 mg/day, there still exists uncertainty and therefore patient-specific characteristics (ie, disease activity, the presence of additional risk factors) need consideration when estimating the risk of harm. These patient-specific factors can shift the level of harm towards the (B) better or (C) worse. ACPA, anti-citrullinated peptide/protein antibodies; CV, cardiovascular; RF, rheumatoid factor.

Strehl C, et al. Ann Rheum Dis 2016

B

Patient specific factors shifting towards a lower level of harm

	Factors	References
General	early diagnosis, low disease activity, low cumulative glucocorticoid dosage, healthy life style (especially cessation of smoking, low alcohol consumption), monitoring and treatment of risk factors and co-morbidities	[1] [21] [37]
Glucocorticoid-induced osteoporosis	sufficient vitamin D & calcium intake, exercise, muscle strengthening, prescription on indication: bisphosphonates, osteoanabolic drugs, selective oestrogen receptor modulators	[36] [39] [40] [41] [42]
Infections	screening for infections, vaccination, usage of risk scores before therapy, follow rules of conduct (avoiding infected persons, appropriate wound care, washing hands, good sleep)	[44] [50] [52]
Carbohydrate metabolism	healthy diet, appropriate exercise, weight loss for obese patients, prescription on indication: hydroxychloroquine, diuretics	[58] [59]
Cardiovascular	diet in low saturated fat & calories, physical activity, weight normalization, sodium restriction, follow the EULAR-recommendations for cardiovascular risk management (including medications like statins or angiotensin-converting enzyme inhibitors on indication)	[2] [60] [70] [75] [76] [77]

These patient-specific factors can shift the level of harm towards the (B) better or (C) worse. ACPA, anti-citrullinated peptide/protein antibodies; CV, cardiovascular; RF, rheumatoid factor.

C

Patient specific factors shifting towards an increased level of harm

	Factors	References
General	high disease activity, high cumulative glucocorticoid dosage, lifestyle (especially bad nutrition, smoking, high alcohol consumption)	[17] [28] [66]
Glucocorticoid-induced osteoporosis	age > 60 years, female sex, low body weight, low bone mineral density, family history of osteoporosis, prevalent fractures, low calcium intake	[23] [35] [36] [37] [38]
Infections	age > 60, male sex, comorbidities (e.g. chronic lung disease, coronary heart disease, heart failure, peripheral vascular diseases, diabetes mellitus, hepatitis C, chronic renal diseases, leukopenia, neurological disease) high number of treatment failures, prior serious infections	[28] [43] [46] [47] [48] [49] [50] [51]
Carbohydrate metabolism	higher age, high body mass index, genetic predisposition, long disease duration	[54] [55]
Cardiovascular	higher age, male sex, severe extra-articular disease manifestation, RF positivity, ACPA positivity, comorbidities (e.g. hypertension, diabetes, dyslipidaemia, obesity, Cushing´s syndrome)	[29] [47] [65] [67] [72] [73] [74]

Strehl C, et al. Ann Rheum Dis

Συμπεράσματα

- Στην Ρευματοειδή Αρθρίτιδα η γενική αρχή η μικρότερη δυνατή δόση για το μικρότερο χρονικό διάστημα πρέπει να εφαρμόζεται καθώς υπάρχουν διαθέσιμες πολλές και αποτελεσματικές θεραπείες

- Υπάρχουν όμως νοσήματα που είναι περισσότερο steroids dependent/responsive (ΣΕΛ, Φλεγμονώδεις μυοσίτιδες) ενώ και οι θεραπευτικές επιλογές δεν είναι πολλές , σε αυτές τις περιπτώσεις η χρήση χαμηλών δόσεων στεροειδών μπορεί να χρειαστεί για περισσότερο χρόνο ή ακόμη και χρονίως, προκειμένου να αποφευχθούν υποτροπές και να ελεγχθεί καλύτερα το νόσημα

- Σε ασθενείς που το νόσημα είναι σε ύφεση ή και χαμηλή ενεργότητα και οι μικρές δόσεις στεροειδών δεν μπορούν να αποσυρθούν ενώ υπάρχουν συννοσηρότητες να μην ξεχνάμε την φλοιοεπινεφριδιακή ανεπάρκεια και να ζητάμε την εκτίμηση από ενδοκρινολόγο

Συμπεράσματα

- Δεν υπάρχουν evidenced-based πρωτόκολλα μείωσης στεροειδών σε κανένα νόσημα και η μείωση-διακοπή τους βασίζεται

1. στην εμπειρία του θεράποντος ιατρού
2. στις διαθέσιμες θεραπευτικές επιλογές
3. στις προτιμήσεις του ασθενούς
4. στις συννοσηρότητες του ασθενούς
5. στην ενεργότητα του υποκείμενου νόσηματος

- Στους ασθενείς που λαμβάνουν χρονίως μικρές δόσεις στεροειδών πρέπει:

1. να παρακολούθουμε στενά για υποκείμενες συννοσηρότητες
2. να λαμβάνουμε μέτρα προφύλαξης (π.χ αντιοστεοπορωτική αγωγή , εμβολιασμοί κτλ)
3. να εκτιμάμε περιοδικά τον καρδιαγγειακό κίνδυνο