Concerns and opportunities related to discontinuation of treatment in rheumatoid arthritis

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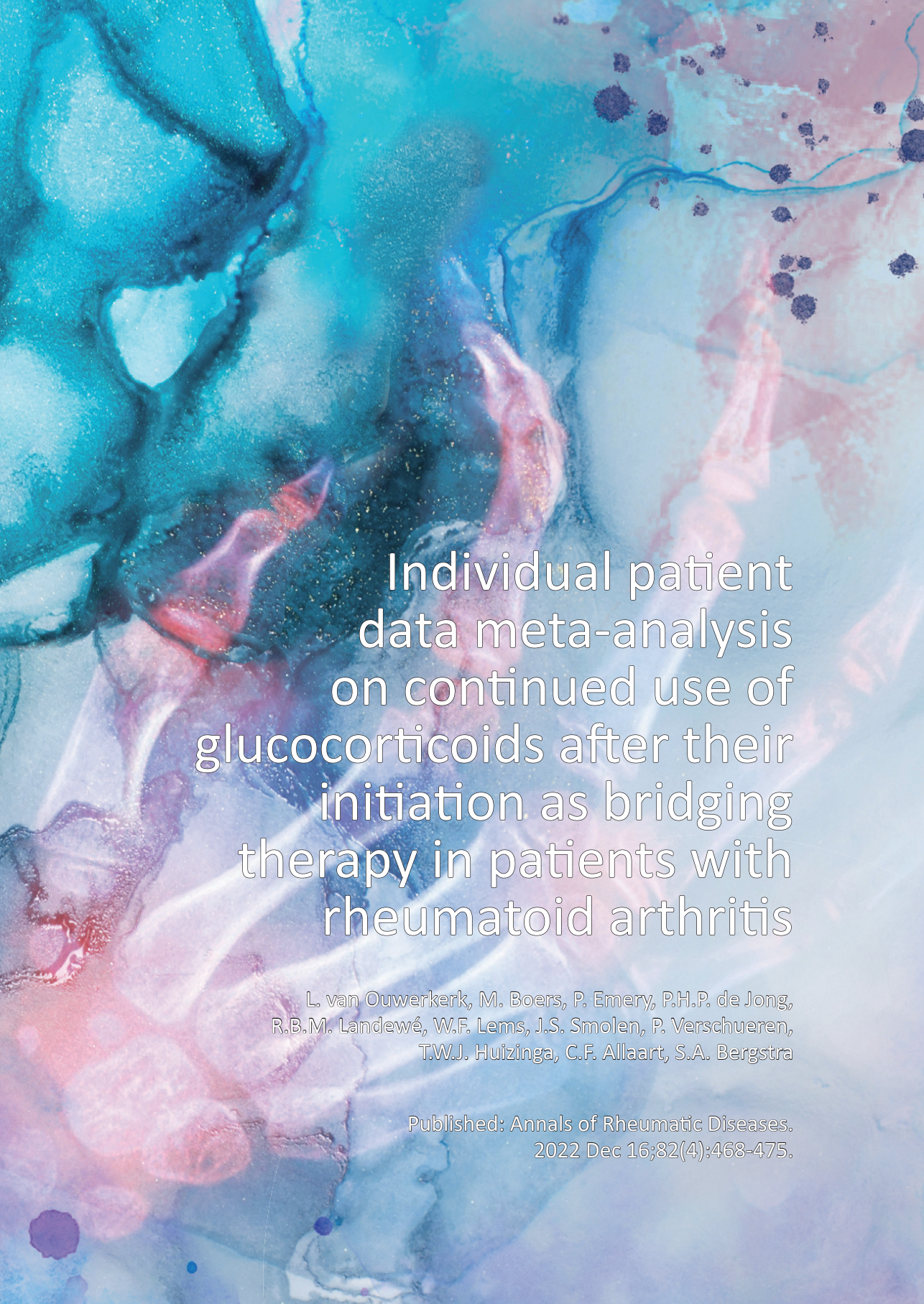

Individual patient data meta-analysis on continued use of glucocorticoids after their initiation as bridging therapy in patients with rheumatoid arthritis

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Published: Annals of Rheumatic Diseases. 2022 Dec 16;82(4):468-475.

ABSTRACT

OBJECTIVES: To investigate whether rheumatoid arthritis patients can discontinue glucocorticoids (GC) after GC 'bridging' in the initial treatment step, and to identify factors that may affect this.

METHODS: Data from 7 clinical trial arms (with 1653 patients) that included a GC bridging schedule, previously identified in a systematic literature search, were combined in an individual patient data meta-analysis. Outcomes were GC use (yes/no) at predefined timepoints (1/3/6/12/18 months after bridging had ended), cumulative GC dose and continuous (≥3 months) GC use after bridging had ended. Age, sex, ACPA status, initial GC dose, duration of bridging schedule, oral versus parenteral GC administration and initial co-treatment were univariably tested with each outcome.

RESULTS: The probability of using GC 1 month after bridging therapy had ended was 0.18, decreasing to 0.07 from 6 until 18 months after bridging had ended. The probability of continuous GC use after bridging had ended was 0.18 at 1 year and 0.30 at 2 years of follow-up. In oral GC bridging studies only, the probabilities of later and continuous GC use, and the cumulative GC doses were higher compared to the combined analyses with also parenteral GC bridging studies. A higher initial dose and a longer GC bridging schedule were associated with higher cumulative GC doses and more patients on GC at 18 months after bridging had ended.

CONCLUSIONS: Based on these RA clinical trial arms with an initial GC bridging schedule, the probability of subsequent ongoing GC use following bridging is low.

Introduction

Glucocorticoids (GC) are often part of the initial treatment of early rheumatoid arthritis (RA).(1, 2) Before slower acting conventional synthetic (cs)DMARDs are effective, GC are used as "bridging" therapy as they rapidly suppress inflammation and symptoms and prevent radiographic damage progression. (3-5) Because long-term use of GC has been associated with serious adverse effects(6-9), the EULAR 2019 recommendations for the management of RA suggest to taper and stop GC as quickly as possible, preferably within 3 months after initiation.(10) The ACR 2021 guidelines for the treatment of RA include a conditional recommendation to avoid GC and only use a csDMARD as initial treatment, based on concerns that patients will not be able to subsequently stop GC.(11)

In our previous systematic literature review (SLR) on continued use of GC after initial "bridging" therapy in patients with RA was shown that there is limited information available on this topic. We identified 10 clinical trials with at least one trial arm applying GC bridging therapy(12), long-term GC use was not among the main outcomes in these trials and details about continued GC use were rarely reported. Due to the insufficient reported data an aggregated meta-analysis could not be performed on all outcomes. Therefore, in the current study, an individual patient data (IPD) meta-analysis was performed on patients in GC bridging arms of the clinical trials that were identified in the aforementioned SLR.(12) With these data, we aimed to establish how often patients continue to use GC after initial GC bridging and we investigated factors that may affect continuation of GC use after bridging.

Methods

Data collection

To acquire details on GC use following bridging therapy in the trials identified in the SLR, the 10 senior researchers of the trials were approached to contribute anonymized individual-level patient data for an IPD meta-analysis. All were invited to participate in an advisory board, composed the statistical analysis plan (unpublished) for an IPD meta-analysis and contributed original data for each patient in a study arm including initial GC bridging. The provided detailed data on GC use over time plus patient characteristics allowed us to study multiple outcome measures and indicators which were not reported earlier on. All analyses were conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analysis of individual participant data (PRISMA-IPD) guidelines and the Cochrane handbook.(13, 14) All trials were approved by the medical ethics committees and all data were collected after patients had given informed consent. The advisory board was consulted in the SLR phase to discuss if potentially suitable trials existed that were not identified by the SLR, they also clarified trial- eligibility and integrity and provided clarity regarding

data uncertainties during the analyzing process (i.e. clarification of missing data in the included trials). Study selection, search strategy and risk of bias of the included trials were described and assessed in the SLR and can be found in those supplementary files.(12) Neither patients nor public representatives were involved in design, conduct, reporting or dissemination of this project.

Outcome measures and indicators

In the workplan standardized outcome definitions were defined and conversion of GC dose into an equivalent oral prednisone dose (milligrams) was agreed. Primary outcomes were: GC status (yes/no still using) at predefined timepoints after bridging had ended, continuous GC use, defined as use for ≥3 months at any time after initial bridging (yes/no), and cumulative GC dose (including the bridging schedule). Secondary outcomes were: occurrence of a disease activity flare (yes/no, flare defined as: DAS28 increase >1.2 or ΔDAS28>0.6 if DAS28 at previous visit was ≥3.2) after stopping GC bridging and after GC were stopped following initial restart ('second flare'), and intensification of DMARD treatment in case of a flare following stopping GC. These outcomes were assessed for the studies separately and also combined with a one stage IPD meta-analysis. Age, sex, anti-citrullinated protein antibodies (ACPA) status, oral or parenteral GC bridging, initial GC dose, duration of GC bridging schedule and the initial csDMARD co-treatment were tested for associations with both the primary and secondary outcomes.

Statistical analysis

IPD from the included study arms (in effect, separate cohorts of patients treated with GC bridging) were analyzed with one stage model mixed-effects regression analyses with study arm as random effect to account for differences between study arms. For dichotomous outcomes this was based on a mixed effects logistic regression model, resulting in odds which were recalculated into probabilities. Such a model can provide the odds that patients who started GC bridging, continue or restart GC (at several time points) after bridging had ended, taking into account differences between the included study arms. Continuous outcomes were combined with mixed effects linear regression models resulting as betas. These models can for example provide cumulative GC doses at certain timepoints, considering differences between studies. Subsequently, in separate univariable models, age, sex, ACPA status, oral or parenteral GC bridging, initial co treatment, initial GC dose and duration of bridging schedule were added as independent variables to the fixed effects parts of the model, to investigate whether the outcomes varied by study characteristics. For all outcomes 95% Confidence Intervals (CI) are presented as an indication of between-study variation. Sensitivity analyses were performed after excluding studies with parenteral administration of GC (the IDEA study and arm 1 of the tREACH study). Given the number of analyses performed in this study, a correction for multiple testing was made with the method of Benjamini-Hochberg taking into

account all models performed.(15, 16) Statistical analyses were performed with Stata V16.1.

Results

The senior researchers of the 10 clinical trials previously identified by the SLR were approached to participate in this study.(12) One declined because the requested data were not yet published for that individual trial.(17) Two others did not respond despite repeated requests.(18, 19) Combining the data of the 7 available trials resulted in 1653 patients with newly diagnosed RA (1987 or 2010 classification criteria) or undifferentiated arthritis (IMPROVED) or a high risk profile for persistent arthritis by the Visser risk model (20) (tREACH) treated with GC bridging therapy (oral, intramuscular or intravenous administration) as part of the initial treatment.(21-27) The baseline characteristics collected for the purpose of this study are presented in table 1. The mean disease activity score based on 28 joints (DAS28) at baseline ranged from 4.8 (tREACH) to 6.5 (COBRA). The majority of the patients in all studies were female, ACPA and/or RF positive and around 50 years of age.

Table 1. Baseline characteristics of the participants with GC bridging therapy from the included trials (N=7)

	COBRA (1997)	BeSt (2005)	IDEA (2014)	COBRA-light (2015)	IMPROVED (2014)	tREACH (2013)	CareRA (2017)
Participants, N	76	133	57	164	610	281*	332
Gender (female, %)	66	66	72	68	68	68	67
Age (baseline)	49 (11.9)	55 (14.1)	53 (12.8)	52 (12.9)	52 (13.9)	53 (14.2)	52 (12.9)
DAS	4.6 (1.0)	4.4 (0.9)	4.0 (1.1)	4.0 (0.8)	3.2 (0.9)	N.D.	N.D.
DAS28	6.5 (1.2)	5.8 (1.0)	5.8 (1.3)	5.4 (1.1)	4.9 (1.3)	4.8 (1.2)	5.2 (1.3)
RF positive (%)	78	65	61	59	56	71	73
ACPA positive (%)	N.D.	55	75	64	56	77	72

Mean (SD) presented, unless specified otherwise.
Abbreviations: ACPA=anti-citrullinated protein antibodies; DAS=disease activity score; N=number; N.D.=no data; prob=probability; pop=population; RF=rheumatoid factor; SJC=swollen joint count; TJC=tender joint count
* High probability population for developing persistent arthritis

Study characteristics

In total, 13 study arms from the 7 trials started with GC bridging therapy. Two study arms (IDEA arm 1 and tREACH arm 1) used single dose intravenous (IDEA) or intramuscular GC (tREACH), the other trial arms started bridging therapy with oral GC, initially with a high dose (30 or 60 mg/day) and rapidly tapered to 5 or 7.5 mg/day as maintenance dose for a fixed duration. An extensive description of the bridging schedules is shown in table 2.

Table 2. Overview of clinical trials.*

Study (publication year)	Type of GC	Initial GC dose	Tapering schedule
COBRA (1997)	Prednisolone	60 mg/day	In 7 weeks to 7.5 mg/day. Stop after 35 weeks.**
BeSt (2005)	Prednisone	60 mg/day	In 7 weeks to 7.5 mg/day. Stop in 8 weeks after week 28 if DAS persistently ≤2.4
IDEA (2014)	Methylprednisolone	250 mg iv once	N.A.
COBRA-light (2015)	Prednisolone	arm 1 60 mg/day arm 2 30 mg/day	arm 1: in 7 weeks to 7.5 mg/day arm 2: in 9 weeks to 7.5 mg/day Stop after 32 weeks if DAS<1.6.
IMPROVED (2014)	Prednisone	60 mg/day	In 7 weeks to 7.5 mg/day. Stop after 20 weeks if DAS <1.6 at 4 months.
tREACH (2013)	Arm 1: methylprednisolone or kenacort arm 2 & 3: prednisone	arm 1: 120 mg or 80 mg im once (single dose) arm 2 & 3: 15 mg/day	In 10 weeks to 0 mg/day.**
CareRA (2017)	Prednisone		
- *COBRA Classic*		- 60mg/day	- in 7 weeks to 7.5 mg/day, further tapered from week 28 and stop after 34 weeks.
- *COBRA Slim*		- 30mg/day	- in 6 weeks to 5 mg/day, further tapered from week 28 and stop after 34 weeks.
- *COBRA Avant garde*		- 30 mg/day	- in 6 weeks to 5 mg/day, further tapered from week 28 and stop after 34 weeks. All if DAS28(CRP) ≤3.2.

Abbreviations: GC=glucocorticoid, im=intramuscular, iv=intravenous, mg=milligram, N.A.=not applicable
* replicated from van Ouwerkerk et al. Ann Rheum Dis(12).
** GC tapered and stopped according to protocol, not depending on disease activity score.

Table 3. Primary and secondary outcomes in patients starting with GC in the included trials

	COBRA (1997)		BeSt (2005)		IDEA (2014)		COBRA light (2015)			IMPROVED (2014)					tREACH (2013)			CareRA (2017)							
							Arm 1 (COBRA)		Arm 2 (COBRA light)	Early remission		Arm 1		Arm 2		Arm 1		Arm 2		Arm 3		Arm 1 (classic)		Arm 2 (slim, high risk)		Arm 3 (avant garde)		Arm 4 (slim, low risk)	
Participants (N)	76		133		57		81		83	387		83		78		91		93		97		98		98		93		43	
GC status several months after bridging (% yes)*																												
	M		M		M		M		M	M		M		M		M		M		M		M		M		M		M	
1 month	-	ND	-	ND	0	0	-	ND	-	ND		-	ND	-	ND	-	ND	-	ND	-	ND	0	9	0	14	0	10	0	21
3 months	0	4	5	32	0	0	0	35	1	37		1	15	11	20	3	3	0	3	0	1	0	7	0	8	0	9	0	10	0	7
6 months	0	5	11	16	0	0	-	ND	-	ND		3	37	36	20	19	4	0	1	0	3	0	6	ND	-	ND	-	ND	-	ND	-
12 months	-	ND	13	17	0	5	-	ND	-	ND		10	24	37	20	23	6	0	1	0	6	0	2	ND	-	ND	-	ND	-	ND	-
18 months	-	ND	-	ND	0	0	-	ND	-	ND		13	19	36	28	26	9	0	3	0	3	0	7	ND	-	ND	-	ND	-	ND	-
Mean cumulative GC dose at predefined time points																														
6 months	ND		2878.7		263.7		2343.7		1678.7	ND		ND		ND		149.6		581.0		629.8		ND		ND		ND		ND	
12 months	2520.0		3571.7		490.5		2950.4		2295.7	2660.1		2935.2		2577.7		183.8		606.4		730.3		2597		1527		1586		1554	
18 months	ND		3934.7		ND		ND		ND	ND		ND		ND		200.1		680.4		754.8		ND		ND		ND		ND	
≥3 months continuous GC use** (% yes) within FU=																														
12 months	4		32		9		57		65	43		21		5		6		4		13		11		12		11		9	
24 months	#		42		#		#		#	64		48		13		11		10		18		22		16		17		12	
Experienced a flare after first attempt to stop GC bridging (% yes) Ω	46.7		17.3		5.6		0		0	5.2		10.8		5.1		1.1		1.1		2.1		19.8		17.3		5.2		11.9	
Experienced a flare after stop attempt second course of GC (% yes) Ω	0		16.7		0		17.9		14.8	1.4		9.7		33.3		0		0		20.0		0		0		0		0	
Having had an extra DMARD after a flare due to first attempt to stop GC bridging (% yes)	2.9		8.7		0		0		0	0		66.7		0		0		100		50		18.8		7.7		0		20	

* months after bridging scheme and oral GC use. ** outside induction scheme
Ω Flare defined as: DAS28 increase > 1.2 or ΔDAS > 0.6 if DAS28 at previous visit was ≥ 3.2
Follow-up shorter than 24 months
Abbreviations: DAS=disease activity score; FU=follow-up M=missings (%); N=number; N.D.=no data; RF=rheumatoid factor; SJC=swollen joint count; TJC=tender joint count

Primary outcomes

Use of GC at various time points after bridging therapy ended, mean cumulative GC dose at 6 and 12 months from baseline (i.e. bridging included) and continuous use of GC for ≥3 months at any point after end of bridging therapy (yes/no) are reported for all 7 studies separately, and by treatment arm, in table 3. The proportions of patients using GC decreased over time or remained low in all trials except for IMPROVED, where GC restart (in arm "early remission", if remission was lost) and or 4 months continuation (arm 1) was required per protocol. The mean cumulative dose was highest in the BeSt study and arm 1 of the COBRA light study whereas in all arms of the tREACH study and the IDEA study it was relatively low. Percentage of patients using continuous GC (for ≥3 months) was higher in the BeSt study, COBRA light study, IMPROVED early remission group and IMPROVED arm 1 than in IMPROVED arm 2, the tREACH, CareRA and the IDEA study.

Table 4. IPD meta-analysis results of GC use after the initial GC bridging schedule in patients starting with GC bridging.

	All included studies intercept only model		**Sensitivity analysis (oral GC use only)**	
Still/again using oral GC xx months after bridging schedule ended:*	odds (95%CI)	Probability	odds (95%CI)	Probability
1 month	0.22 (0.07; 0.72)	0.18	0.42 (0.33; 0.53)	0.30
3 months	0.12 (0.06; 0.23)	0.11	0.16 (0.09; 0.29)	0.14
6 months	0.07 (0.03; 0.19)	0.07	0.13 (0.05; 0.29)	0.12
12 months	0.08 (0.03; 0.21)	0.07	0.14 (0.06; 0.32)	0.12
18 months	0.08 (0.03; 0.25)	0.07	0.16 (0.06; 0.40)	0.14
Mean cumulative GC dose (mg) at predefined time points from baseline:	β (95%CI)		β (95%CI)	
6 months	1218 (415; 2021)		1622 (727; 2518)	
12 months	2118 (1606; 2631)		2373 (1934; 2812)	
*≥3 months continuous GC use** (% yes) at predefined time points from baseline:*	odds (95%CI)	Probability	odds (95%CI)	Probability
12 months	0.22 (0.12; 0.39)	0.18	0.25 (0.14; 0.48)	0.20
24 months	0.43 (0.25; 0.72)	0.30	0.47 (0.28; 0.80)	0.32

Footnote: The β reported for mean cumulative dose should be interpreted as a mean cumulative dose as the intercept only model is presented here. This mean cumulative dose is adjusted for clustering of patients within study arms.
* Induction schedules, stop possible after:
COBRA: 28 weeks (mandatory taper, stop at week 34), BeSt: 36 weeks, IDEA: GC IV once at baseline, COBRA light: 32 weeks, IMPROVED: 4 months
(early remission & arm 2), 8 months (arm 1), tREACH: 10 weeks, CareRA: 34 weeks
** Outside induction schedule and oral GC use
Abbreviations: β=beta, CI=confidence interval, FU=follow-up, GC=glucocorticoids, mg=milligrams.

In table 4 the pooled results for the primary outcomes are shown. The probability of ongoing use or restart of GC 1 month after GC bridging ended is 0.18, decreasing to 0.07 at 6, 12 and 18 months after bridging ended. The probability of continuous GC use for ≥3 months after bridging was 0.18 at 12 months from baseline and 0.30 at 24 months from baseline. In the oral GC bridging studies (i.e excluding IDEA and arm 1 of the tREACH study) the

probabilities of GC use following bridging were higher (0.30 at 1 month and 0.14 at 18 months after GC bridging ended), and to a lesser extent also the probabilities for continuous GC use ≥3 months were higher (*table 4*). The mean cumulative doses were also higher in this sensitivity analysis without parenteral GC bridging.

Secondary outcomes

Based on the combined data of the 7 studies, the probability of a flare was low, both after stopping the initial GC bridging therapy (0.11) and after stopping a second course of GC (0.07) (table 5). In the models including only oral GC use these flare probabilities were higher (0.13 and 0.16 respectively). Also, the probabilities of starting an extra DMARD due to a flare after stopping GC bridging are low, 0.11 in all studies and 0.12 in the studies with oral GC bridging only. The secondary outcomes for each study separately are displayed in table 3. Flares, defined as a DAS28 increase of >1.2 or a DAS28 increase of >0.6 with the DAS28 on the previous visit being ≥3.2, were rare, except in the COBRA study, where in almost 50% of patients a flare occurred after the first attempt to stop GC bridging, and in the BeSt and CareRA study, where in some arms up to 20% of patients had a flare. Across the trials, flares appeared to occur less often after a second course of GC was stopped. However, percentages may have been affected by small numbers. Compared to the other studies, a higher proportion of patients started a new DMARD after a flare following stop of GC bridging therapy in arm 1 of the IMPROVED study and arm 2 and 3 of the tREACH study (all by study protocol design).

Table 5. Secondary outcomes in patients starting with GC bridging (N=1653)

	All included studies intercept only model		**Sensitivity analysis (oral GC use only)**	
Flare after [Ω] *1st GC bridging stop attempt (%)*	odds (95%CI) 0.12 (0.06; 0.23)	Probability 0.11	odds (95%CI) 0.15 (0.08; 0.29)	Probability 0.13
Flare after [Ω] *stop attempt first GC course after bridging had ended*	odds (95%CI) 0.17 (0.07; 0.38)	Probability 0.07	odds (95%CI) 0.19 (0.08; 0.45)	Probability 0.16
DMARD added after flare on stopping GC bridging (%)	odds (95%CI) 0.12 (0.04; 0.36)	Probability 0.11	odds (95%CI) 0.13 (0.04; 0.4)	Probability 0.12

[Ω] Flare defined as: DAS28 increase > 1.2 or ΔDAS28 > 0.6 if DAS28 at previous visit was ≥ 3.2
Abbreviations: CI=confidence interval; DAS=disease activity score; DMARD=disease modifying anti-rheumatic drug; FU=follow-up; GC=glucocorticoids; N=number.

Table 6. Associations of several indicators of patient characteristics and bridging schedules with each outcome measure

(Reference category)	Age at baseline	Being female (male)	ACPA positivity (ACPA negative)	Oral GC bridging (no oral bridging)	Initial co-treatment with multiple csDMARDs (only MTX co-treatment)	Initial GC dose (effect per additional mg)
*GC status after bridging**						
1 month	1.00 (0.99; 1.02)	0.72 (0.44-1.18)	0.93 (0.53; 1.62)	omitted	2.86 (0.35; 23.22)	1.00 (0.99; 1.02)
3 months	1.01 (1.00; 1.02)	1.21 (0.89-1.64)	0.85 (0.63; 1.15)	11.93 (1.63; 87.0)	0.48 (0.13; 1.78)	1.00 (0.99; 1.02)
6 months	1.00 (0.99; 1.02)	1.47 (1.02-2.11)	1.28 (0.89; 1.84)	28.17 (1.88; 421.30)	0.20 (0.04; 1.18)	1.00 (0.97; 1.02)
12 months	1.00 (0.99; 1.02)	1.11 (0.75-1.64)	1.31 (0.89; 1.94)	12.61 (1.62; 97.88)	0.24 (0.03; 1.75)	1.00 (0.97; 1.03)
18 months	1.00 (0.99; 1.02)	1.54 (0.98-2.43)	1.21 (0.78; 1.88)	11.49 (1.37; 96.34)	0.22 (0.03; 1.59)	1.00 (0.98; 1.03)
Mean cumulative GC dose (mg) at						
6 months	-2 (-5; 0.6)	3 (-76; 82)	11 (-69; 92)	1416 (-84; 2916)	-998 (-2745; 749)	-2 (-27; 23)
12 months	0.4 (-2; 2)	29 (-28; 85)	-31 (-91; 29)	**2036 (836; 3236)**	484 (-1633; 666)	4 (-8;16)
18 months	1 (-4;6)	25 (-136;185)	-50 (-217; 116)	1590 (-2616; 5796)	-1905 (-5058; 1247)	-1 (-46; 43)
*Continuous GC use** (%) within*						
12 months	1.00 (0.99; 1.01)	1.32 (1.02; 1.72)	1.07 (0.82; 1.39)	3.72 (0.70; 19.77)	0.29 (0.10; 0.81)	1.00 (0.98; 1.02)
24 months	1.00 (0.99; 1.01)	1.19 (0.93; 1.52)	1.28 (1.00; 1.65)	3.98 (0.60; 26.75)	0.31 (0.12; 0.81)	1.01 (0.99; 1.02)
Flare after $^{\Omega}$						
1st GC bridging stop attempt (%)	1.01 (1.00; 1.03)	1.23 (0.81; 1.88)	0.93 (0.58; 1.47)	7.37 (0.85; 63.90)	0.71 (0.17; 2.90)	1.00 (0.98; 1.03)
Flare after $^{\Omega}$						
stop attempt first GC course after bridging had ended	1.01 (0.97;1.04)	1.26 (0.45; 3.57)	1.36 (0.51; 3.66)	omitted	omitted	0.99 (0.93; 1.05)
DMARD added after flare on stopping GC bridging (%)	0.99 (0.94; 1.04)	0.30 (0.08; 1.15)	0.47 (0.12; 1.81)	omitted	0.79 (0.08; 7.74)	0.94 (0.88; 1.01)

We evaluated associations with mixed effects regression analysis with study arm as random effect: linear mixed models for continuous outcomes, logistic models for dichotomous outcomes. Due to limited variation in the included groups and thereby collinearity, not all analyses provided results and those without results were therefore 'omitted'.
All results reported as OR (95%CI) except mean cumulative GC dose which is reported as coefficient (95%CI). **Bold text** is expressing a significant result after correction for multiple testing.
* months after the induction schedule and oral GC use.
** defined as use for ≥ 3 months outside induction schedule and oral GC use
$^{\Omega}$ Flare defined as: DAS28 increase > 1.2 or ΔDAS28 > 0.6 if DAS28 at previous visit was ≥ 3.2
Abbreviations: CI=confidence interval; csDMARD=conventional synthetic disease modifying antirheumatic drug; GC=glucocorticoids; mg=milligrams; MTX=methotrexate; OR=odds ratio.

Table 7. Associations in database without parenteral GC bridging with primary (upper 3) and secondary (bottom 3) outcomes

	Initial GC dose (effect per additional mg)	**Duration of induction schedule (effect per additional week)**
*GC status after bridging**		
1 month	1.00 (0.99; 1.02)	omitted
3 months	1.02 (0.99; 1.05)	**1.09 (1.04; 1.15)**
6 months	1.03 (1.00; 1.07)	1.06 (0.97; 1.16)
12 months	**1.04 (1.02; 1.06)**	1.08 (1.01; 1.16)
18 months	**1.04 (1.01; 1.06)**	**1.14 (1.05; 1.24)**
Mean cumulative GC dose at (mg)		
6 months	**41 (30; 53)**	**76 (46; 105)**
12 months	**25 (15; 35)**	**73 (35; 111)**
18 months	**67 (63; 71)**	**124 (117; 131)**
*≥3 months continuous GC use** (% yes) within*		
12 months	1.02 (0.99; 1.05)	1.07 (1.00; 1.14)
24 months	1.03 (1.00; 1.05)	1.04 (0.99; 1.10)
Flare after $^{\Omega}$		
1st GC bridging stop attempt (%)	**1.04 (1.01; 1.07)**	**1.09 (1.02; 1.16)**
Flare after $^{\Omega}$		
stop attempt first GC course after bridging had ended	0.99 (0.93;1.05)	0.90 (0.73; 1.12)
DMARD added after flare on stopping GC bridging (%)	0.94 (0.88; 1.01)	0.89 (0.78; 1.02)

Associations were evaluated with mixed effects regression analysis with study arm as random effect. For continuous outcomes we used mixed effects linear regression models (Linear mixed models), for dichotomous outcomes we used mixed effects logistic regression models. This sensitivity analysis was conducted in a dataset without arm 1 of the tREACH study (intramuscular GC bridging) and without the IDEA study (intravenous GC bridging). Due to limited variation in the included groups and thereby collinearity, not all analyses provided results and those without results were therefore 'omitted'.
All results reported as OR (95%CI) except mean cumulative GC dose which is reported as coefficient (95%CI). **Bold text** is expressing a significant result after correction for multiple testing.
* months after the induction schedule and oral GC use.
** outside induction schedule and oral GC use
$^{\Omega}$ Flare defined as: DAS28 increase > 1.2 or ΔDAS28 > 0.6 if DAS28 at previous visit was ≥ 3.2
Abbreviations: CI=confidence interval; GC=glucocorticoids; mg=milligrams; OR=odds ratio.

Associations with bridging schedule and patient characteristics

Oral GC bridging (compared to parenteral bridging) was significantly associated with more patients on GC at all assessments following bridging therapy, before multiple testing correction. The cumulative GC dose was higher for oral than for parenteral GC bridging, with significance reached only at 12 months (table 6) as more studies provided data for this timepoint compared to 18 months. Due to limited variation in the included groups and thereby collinearity, not all analyses provided results and those without results were therefore 'omitted'. In supplementary table 1, the number of patients per analysis is depicted.

A longer duration of the bridging schedule was associated with more patients on GC following bridging at 3 and 18 months and a higher mean cumulative GC dose (all significant after correction for multiple testing) (table 7). At 6 months, this translates for instance to an increase in the mean cumulative dose of 76

mg (95% Confidence interval (CI) 46; 105) with each additional week of GC use in the GC bridging therapy schedule. In the primary analysis initial GC dose was not related to any of the outcomes. However, in the studies with oral GC bridging only, a higher initial oral GC dose was associated with significantly more GC use at 12 and 18 months and a higher mean cumulative dose (table 7). At 6 months, this translates for instance to an increase in the mean cumulative dose of 41 mg (95% CI 30; 53) with each milligram increase in initial GC dose. A higher initial oral GC dose and a longer duration of the bridging schedule were both also associated with higher flare rates after discontinuation of GC bridging therapy (table 6 and 7). Neither initial co-treatment with multiple csDMARDs, nor age, gender or APCA status were associated with the primary or secondary outcomes (table 6).

Discussion

This novel study combining individual patient data from trial-based cohorts showed that most RA patients treated with initial bridging successfully discontinued GC. Additional analyses suggested that lower dosing and shorter schedules were associated with more successful discontinuation.

In both the first EULAR recommendations (2010) as well as the first ACR guidelines (1996) for treatment of RA, GC were considered part of the initial treatment because of their rapid efficacy in suppressing disease activity where a treatment gap exists as csDMARDs are more slow-acting.(28, 29) However, there have always been concerns about the adverse events related to long-term GC use, and therefore it has been stated in every recommendation or guideline since, to taper GC as rapidly as clinically feasible. Unfortunately, we found that published data on the successes of tapering GC after their use as bridging therapy as part of the initial treatment step in patients with RA are scarce.(12) The majority of the clinical trials which used GC bridging therapy focused on presenting data on its rapid efficacy and early safety. We presume that GC use beyond a short course of bridging therapy is triggered by a disease activity relapse after GC are tapered or stopped. This was investigated in the BeSt study and the IMPROVED study, which used GC bridging therapy combined with respectively two and one csDMARD as first treatment step.(30) It was found that 40% of the patients experienced a disease activity flare following GC discontinuation 3 to 4 months after the start of GC bridging therapy, despite continued use of the csDMARD(s). In the BeSt and IMPROVED studies, other treatments were required to avoid restart of GC. An effort to identify predictors of successful discontinuation of GC bridging showed that a lower DAS at both baseline and stop visit and male gender were associated with more successful GC discontinuation but in general both were poor predictors.(30) In the current univariable analysis we did not find an association between sex and GC discontinuation after bridging.

All trials in this analysis used a treatment protocol with fixed rules for GC discontinuation and with alternative treatment steps in case of a disease activity flare, either restarting GC or switching to other DMARDs. In arm 2 of the IMPROVED study, for instance, in case of a flare, restart of GC was prohibited and a switch to a biologic DMARD was required, whereas in arm 1, GC had to be restarted while at the same time sulfasalazine (SSZ) and hydroxychloroquine (HCQ) were added to methotrexate (MTX). In CareRA, patients in the COBRA slim arm received leflunomide on top of MTX in case of insufficient response or a flare, whether this was after stopping GC or not. Also an intramuscular injection of GC or temporary oral GC as bridging was allowed in case of flares after the induction period. The protocolized treatment in the trials may have resulted in more GC discontinuation than in daily practice, where fixed treatment steps and alternative treatments such as biologic DMARD may not always be available. Patients included in trials may differ from patients who were not included in trials or from patients in daily practice, as patients in trials need to fulfill in- and exclusion criteria and are willing to participate in a protocol driven study. The in- and exclusion criteria of the studies selected in our analyses resulted in a selection of patients with early RA, who were DMARD naïve, had active disease at the moment of inclusion and limited comorbidities. One observational study has compared GC use over time in 19 patients who received initial double csDMARD therapy with GC bridging, and 52 who started on MTX monotherapy. Subsequent treatment steps, including tapering and drug discontinuation, were protocolized, aimed at low disease activity and GC discontinuation after initial GC bridging therapy.(31) The initial GC bridging patients did better over time, had fewer DMARD changes, and there was a trend for less GC use in the second year, compared to the initial monotherapy patients.

In our previous SLR and meta-analysis on this subject only information from the publications about the trials instead of raw data were used, therefore we could only focus on two outcomes: GC use at 12 months and GC use at 24 months. The information on these outcomes were available from 4 and 2 trials, respectively, despite the extensive number of publications which are available from the included trials.(12) In this IPD analysis we were able to look into GC use after bridging in more detail. A limitation of using combined data of several trials remains the heterogeneity that exists between the trials, in duration of bridging schedules and concomitant therapy. A sensitivity analysis in only-oral-GC-bridging trials was therefore conducted, showing slightly greater probabilities than in the analysis including also parenteral administration of bridging therapy. Not all studies provided raw data on GC use after 12 months of follow-up which caused a reduction in patient number for analyses at subsequent time points. Also, the bridging schedules of almost all included trials except for the tREACH trial, were longer than the recommended 3 months (in both EULAR recommendations and ACR guidelines), which limits the generalizability

to daily practice. However, in daily practice it may be more difficult to taper and stop GC bridging within these recommended 3 months as protocolized tapering rules are lacking. Furthermore, we did not receive data from 3 eligible trials.(17-19) The study of Hua et al. was a single center randomised double blind clinical trial. They compared MTX combined with HCQ and GC (started at 10mg for 3 months, then 5mg for 2 months and stopped thereafter) with MTX combined with HCQ and placebo. The NORD-STAR trial, a randomised open label (but blind assessor) clinical trial compared 4 study arms. Each arm started with MTX, combined with either GC orally (started at 20mg, tapered to 5mg in 9 weeks and stopped at week 36), HCQ plus SSZ and intra-articular GC, certolizumab pegol, abatacept or tocilizumab. The ARCTIC trial was a randomised controlled strategy trial, primarily focused on the comparison of 2 monitoring strategies within a treat-to-target design, namely ultrasound versus a conventional approach. All patients started with MTX plus GC (15mg at start and tapered in 7 weeks). Since the bridging schedules of these three studies all used lower starting doses compared to the arms included in this analysis and two of them also stopped earlier than most of the included trials, it could have influenced the results if they were involved in this IPD meta-analysis. In the SLR we did not search trial registries to identify unpublished trials and therefore publication bias might have played a role in our study selection.

To conclude, this IPD analysis showed that in the setting of clinical trials with fixed treatment protocols, the chances of long-term GC use after bridging therapy are low and decreasing over time. A shorter bridging schedule and lower initial GC dose decrease the chance of GC use after bridging has ended.

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