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Concerns and opportunities related to discontinuation of treatment in rheumatoid arthritis

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Citation
Ouwerkerk, L. van. (2024, January 18). *Concerns and opportunities related to discontinuation of treatment in rheumatoid arthritis*. Retrieved from https://hdl.handle.net/1887/3713938

Version:	Publisher's Version
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Downloaded from:	https://hdl.handle.net/1887/3713938

Note: To cite this publication please use the final published version (if applicable).


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Initial glucocorticoid bridging in rheumatoid arthritis: does it affect glucocorticoid use over time?

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Published: Annals of Rheumatic Diseases. 2023 Aug 22:ard-2023-224270.

ABSTRACT

OBJECTIVES: To compare the use of glucocorticoids (GC) over time in patients with rheumatoid arthritis (RA) who were or were not treated initially with GC bridging therapy.

METHODS: Data from the BeSt, CareRA and COBRA trials were combined in an individual patient data (IPD) meta-analysis. We compared GC use between bridgers and non-bridgers at 12, 18 and 24 months from baseline with mixed effects regression analysis. Secondary outcomes were mean cumulative GC dose until 24 months after baseline with and without the bridging period, DAS28 over time and number of DMARD changes.

RESULTS: 252/625 patients (40%) were randomized to GC bridging (bridgers). Excluding the period of bridging, later GC use was low in both groups and cumulative doses were similar. Mean DAS28 was similar between the groups, but bridgers improved more rapidly ($p<0.001$) in the first 6 months and the bridgers required significantly fewer changes in DMARDs (incidence rate ratio 0.59 (95%CI 0.38; 0.94)). GC use was higher in the bridgers at t=12 months (OR 3.27 (95% CI 1.06;10.08)) and the bridging schedules resulted in a difference in cumulative GC dose of 2406 mg (95%CI 1403;3408)over 24 months.

CONCLUSIONS: In randomized trials comparing GC bridging and no GC bridging, bridgers had a more rapid clinical improvement, fewer DMARD changes and similar late use of GC compared to non-bridgers. GC bridging per protocol resulted, as could be expected, in a higher cumulative GC dose over 2 years.

Introduction

It has been extensively shown that glucocorticoids (GC) are effective as initial bridging treatment of rheumatoid arthritis (RA) by rapidly suppressing inflammation. This results in early functional improvement assessed by the health assessment questionnaire, HAQ) through relief of clinical symptoms (1-4), but also prevention of joint damage progression in the long term.(5-7) Hence they are now often part of the initial treatment strategy in patients with early RA. However, observational studies suggest GC have significant safety issues if used long term, especially when used in higher doses.(8) Therefore, the 2022 updated EULAR recommendations state that only short-term GC bridging therapy should be considered in the treatment of patients with early RA, without specifying the route or dose.(9) On the other hand, in the 2021 updated ACR guidelines it is stated that the toxicity associated with GC use, may outweigh its known benefits.(10) Consequently, in these guidelines it is advised not to start GC bridging therapy at all, although the advice has a low level of evidence and is 'conditional', as the expert panel acknowledge that GC bridging may often be necessary. Furthermore, the ACR panel state in their discussion that these recommendations against the use of GC, were made in consideration of the difficulty to taper GC once they are started, leading to unwanted prolonged GC use. In our individual patient data (IPD) meta-analysis we showed that in clinical trial patients treated with GC bridging therapy the rates of subsequent ongoing GC use are low and decreasing over time.(11) Thus we did not find evidence that GC bridging is associated with unwanted prolonged use.

It is now of interest to know whether and how initial GC bridging is associated with later GC use and other treatment steps in the disease course, compared to not starting initial GC bridging. In two previous studies it was suggested that patients who had started GC bridging (bridgers) needed less steroids after bridging therapy had ended, to keep their disease activity under control compared to the patients that had not started with GC bridging therapy (non-bridgers).(12, 13) To be able to analyze this in randomized clinical trials (RCTs) with larger numbers, we selected studies with at least one study arm that started initial GC bridging therapy and one that did not start initial GC bridging therapy out of the group of identified clinical trials from our systematic literature review (SLR).(14) We used individual patient data that was collected during the first two years of follow-up in these RCTs.

Methods

Ten clinical trials were identified with the SLR, and we received IPD from 7 of them. We combined IPD from the 3 studies (BeSt, COBRA and CareRA (1, 2, 15)) that had randomized patients to at least one study arm that started with GC bridging next to one or multiple conventional synthetic (cs)DMARD, as

well as one arm that did not start with GC bridging (comparator arms) next to csDMARD therapy. From the CareRA study we only included the patients with a 'low risk for a bad prognosis' as the 'high risk' study population did not have a comparator study arm without GC bridging.

The data collection process is described in the supplementary file. Of the 3 study arms that started with initial GC bridging, one also started with methotrexate (MTX) as initial DMARD and two arms started with MTX plus sulphasalazine (SSZ). In the GC bridging study arms, all patients had had to taper GC, with a protocolized stop 34-36 weeks after baseline (table 1), which was dependent on disease activity levels in BeSt and CareRA. The starting dose of GC bridging in both the BeSt and COBRA bridging arms was 60mg/day, whereas the CareRA bridging arm started with 30mg/day. In the four comparator study arms, DMARD therapy was started without GC bridging, either with SSZ monotherapy (COBRA) or with MTX monotherapy (BeSt and CareRA). In all study arms, different DMARD options were protocolized if the first treatment step failed (supplementary table 1). No study on GC bridging with lower doses of GC than 30mg, a shorter bridging period than 34 weeks or a single intravenous (IV) or intramuscular (IM) application comparing to csDMARD monotherapy with IPD was available. Neither patients nor public representatives were involved in design, conduct, reporting or dissemination of this project.

Outcome measures

As primary outcome we compared oral GC use between the groups (patients starting with GC bridging and patients without initial GC bridging) at selected time points (12, 18 and 24 months from baseline). Secondary outcomes were the mean oral GC cumulative dose from the moment the bridging schedule had ended (this same timepoint was chosen for the comparator arm of that study) until 24 months after baseline (i.e. cumulative dose not including GC bridging), mean oral cumulative GC dose including GC bridging, continuous (≥3 months) use of GC (yes/no) at any time between end of bridging schedule and 24 months of follow-up, number of DMARD changes (adding a DMARD or switching between DMARDs, including csDMARDs and bDMARDs), DAS28 over time and use of ≤5mg/day (yes/no) as oral GC dose (within complete follow-up and during the period after bridging).

Statistical analysis

The outcomes for the individual studies separately are shown in supplementary table 2. The individual data from the included trials were combined with one stage model mixed-effects regression analyses to compare the outcomes between patients who did and did not start GC bridging. Study arm was added as random effect to account for between study arm differences. In case of dichotomous outcomes, mixed effects logistic regression models were used resulting in odds ratios. For continuous outcomes, mixed effects linear

regression models were used resulting in coefficients. These coefficients display for example a difference in GC cumulative dose (mg) between the groups.

For the outcomes 'number of DMARDs' and 'continuous GC use', the time that patients were followed up was included as covariate to account for immortal time bias, as patients who had shorter follow-up time could not receive more or other DMARDs or a continuous GC course anymore after their follow-up time had ended. To investigate DAS28 over time, we included an interaction term between treatment group (started or not started with GC bridging) and time (as categorical variable).

The CareRA study arms included RA patients with a low risk for a bad prognosis (supplementary figure 1). We used the same algorithm to identify low- and high-risk patients in the BeSt and the COBRA studies. The identified high-risk patients were subsequently used in a sensitivity analysis to evaluate if this subgroup showed different results. Missingness in the data was low (<5%) and therefore no data imputation technique was applied.(16) Statistical analyses were performed with Stata SE version 16.1 (StataCorp, College Station, TX, USA).

Table 1. Overview of the included study arms

	BeSt (2)	**COBRA (1)**	**CareRA (15)**
GC bridging study arms	*Arm 3, Initial combination therapy with GC*	*Combined treatment arm*	*Low risk group, COBRA slim arm*
Initial GC dose *Tapering to maintenance* *Planned end*	*60mg/day (prednisone)* *In 7 weeks to 7.5mg/day* *From week 28-36 tapered to zero* *if DAS≤2.4 for at least 6 months*	*60mg/day (prednisone),* *In 6 weeks to 7.5mg/day* *From week 28-34 tapered to zero*	*30mg/day (prednisone),* *In 5 weeks to 5mg/day* *From week 28-34 tapered to zero* *if DAS28(CRP)≤3.2*
DMARD	*MTX 7.5mg/week, increased to 25mg/week if DAS>2.4 after 3 months* *SSZ 2000mg/day*	*MTX 7.5 mg/week* *SSZ 2000mg/day*	*MTX 15mg/week*
Non-GC bridging arms	*Arms 1 (Sequential monotherapy) and Arm 2 (Step up combination therapy)* *MTX 15mg/week (increased to 25 mg/week if DAS>2.4 after 3 months)*	*Monotherapy arm,* *SSZ 2000 mg/day*	*Low risk group,* *MTX tight step up arm* *MTX 15 mg/week*

Abbreviations: GC=glucocorticoids, MTX=methotrexate, SSZ=sulphasalazine.

Results

In total, 625 patients were included for these analyses, of whom 252 (40.3%) were treated in a study arm that started with GC bridging. Baseline characteristics were comparable between the groups with/without initial GC bridging, most patients were female (67%), the mean age was 52 years and the mean baseline DAS and DAS28 (both based on erythrocyte sedimentation rate (ESR)) were high (table 2). Furthermore, the majority of patients had tested positive for rheumatoid factor (RF) and/or anti-citrullinated protein antibodies (ACPA).

Table 2. Baseline characteristics of participants in trials starting oral GC bridging vs. not starting bridging

	Started with GC bridging* (N=252)	**Started without GC bridging** (N=373)**
Age (baseline) mean ±SD	52 (14)	53 (13)
Sex (female) (%)	68	67
DAS mean ±SD	4.5 (0.9)	4.5 (0.9)
DAS28 mean ±SD	5.9 (1.3)	5.9 (1.2)
RF positive (%)	62	61
ACPA positive (%)	48	57

Abbreviations: ACPA=anti-citrullinated protein antibodies; DAS28=disease activity score based on 28 joints and Erythrocyte Sedimentation Rate (ESR); GC=glucocorticoids; MTX=methotrexate; N=number; RF=rheumatoid factor; SJC=swollen joint count; SSZ=sulphasalazine; TJC=tender joint count.
* BeSt arm 3 (methotrexate, sulphasalazine and GC bridging); COBRA arm combination therapy (methotrexate, sulphasalazine and GC bridging); CareRA arm COBRA slim (methotrexate and GC bridging).
** COBRA arm monotherapy (sulphasalazine); BeSt arm 2 (step up combination therapy); BeSt arm 1 (sequential monotherapy)- both starting with methotrexate monotherapy; CareRA arm MTX tight step up (methotrexate monotherapy).

The proportion of patients using oral GC relative to the number of patients in follow-up at that moment is displayed in figure 1. Per protocol, initial GC use was high in the group that started with GC bridging. At the first evaluation point after the planned endings of the bridging schedules (T=12 months), significantly more patients in the GC bridging group (21%) used GC than in the non-GC bridging group (6%) but at the subsequent time points, GC use was not significantly different between the groups, although there were numerical differences.

The end of GC bridging was planned by protocol and in 2 of the 3 studies this was dependent on achieving the treatment target. Of the patients from the GC bridging group who used GC at T=12 months, 77% had restarted GC after bridging had first ended and 23% had not yet stopped but still used GC after the initial planned end of bridging (if disease activity had allowed). When we evaluated the oral GC dose (≤5 mg or >5 mg) related to all visits at which oral GC were used and GC dose was non-missing, it appeared that after the period of bridging until 2 years of follow-up comparable proportions of both groups

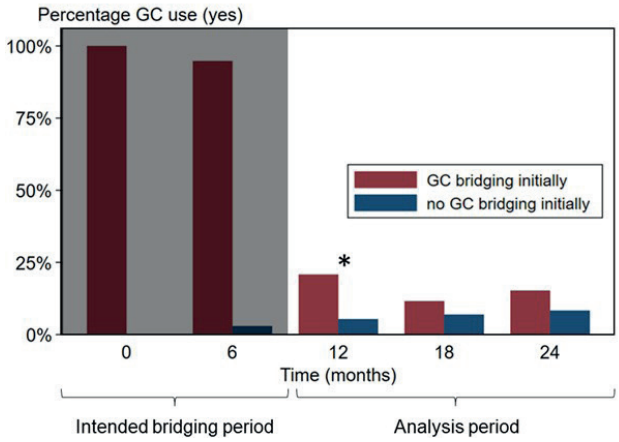

Figure 1. Percentage of patients on GC treatment over time (in months) for the group that started with GC bridging initially (red) and the group that did not (blue). Asterisk (*) indicates significant result from the mixed effects regression analyses performed for 12, 18 and 24 months. Braces below the x-axis indicate the duration of the intended bridging periods and the analysis period, for exact bridging periods see table 1.

were using ≤5 mg as daily dose (p=0.30, supplementary table 3).

The GC bridging group had a significantly higher risk to use GC at the 12 months timepoint (odds ratio (OR) 3.27 (95% confidence interval (CI) 1.06; 10.08)) compared to non-GC bridging group, but it decreased over time and was no longer statistically significant at 18 and 24 months after baseline (OR 1.60 (95%CI 0.46; 5.60) and OR 1.70 (95%CI 0.58; 4.97), respectively). The cumulative dose after the planned bridging schedules did not differ significantly between the two groups (264 mg (95%CI -69; 597)), but of course, when the bridging schedules were included, there was a significantly higher cumulative dose in the GC bridging group (2400 mg (95% CI 1400; 3400). This can be translated to an average difference of 3 mg a day for 2 years compared to the non-GC bridging group.

Furthermore, patients in the GC bridging group had a significantly higher risk of using GC for ≥3 months at any time between the end of bridging schedule and t=24 months (OR 3.11 (95%CI 1.94; 4.98)). The IRR for number of DMARD changes was significantly lower for the GC bridging group (IRR 0.59 (95%CI 0.38; 0.94)).

Mean DAS28 decrease over time was more rapid in the first 6 months in the GC bridging group (interaction term: p<0.001, figure 2). At later timepoints, after the planned end of bridging, there was no statistically significant difference anymore between the groups.

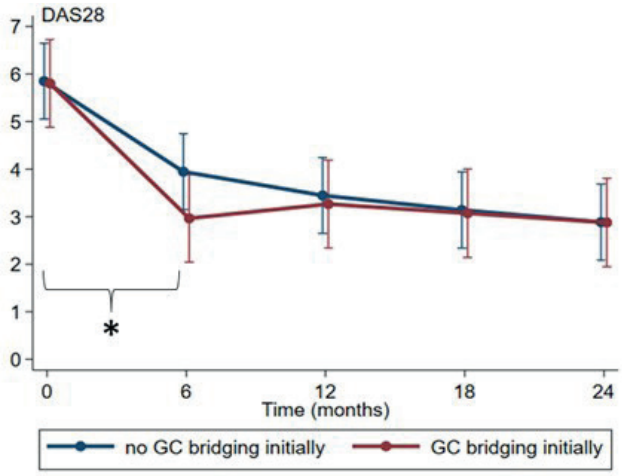

Figure 2. Mean DAS28 (data from linear mixed model) over time, estimated over 24 months. Predictive margins are depicted with 95% confidence intervals (CI) as error bars. An asterisk (*) indicates significant result from the linear mixed model analysis.

Sensitivity analysis

For the sensitivity analysis 478 patients were available after excluding the "low-risk" patients from the CareRA, BeSt and COBRA studies (table 3). The results were comparable with slightly larger effect estimates for the "high-risk" patients only, but the IRR for occurrence of DMARD changes was no longer significantly different, although the IRR remained almost identical.

Table 3. Mixed effects regression analyses (rows indicate outcomes of separate models)

Outcome	Effect estimate and 95% CI	Effect estimate and 95% CI Sensitivity analysis (Patients with a high risk for a bad prognosis from BeSt and COBRA)
GC use at 12 months	**OR 3.3 (1.1; 10.1)**	**OR 3.9 (1.0; 15.0)**
GC use at 18 months	OR 1.6 (0.5; 5.6)	OR 2.0 (0.4; 10.2)
GC use at 24 months	OR 1.7 (0.58; 5.0)	OR 2.32 (1.0; 5.5)
Mean cumulative dose at 24 months, excluding the bridging period	β 264 mg (-69; 597)	β 356 mg (-48; 762)
Mean cumulative dose at 24 months including the bridging period	**β 2406 mg (1403; 3408)**	**β 2935 mg (2348; 3523)**
Using GC ≥3 months*◊	**OR 3.1 (1.9; 5.0)**	**OR 3.5 (2.2; 5.5)**
Occurrence of DMARD changes*◊	**IRR 0.6 (0.4; 0.9)**	IRR 0.6 (0.3; 1.1)

Footnote: reference group: group that did not start GC bridging initially (for all analyses). **Bold** text indicates a significant result.
* in period between bridging had ended and 24 months of follow-up
◊ also corrected for: time in study
Abbreviations: β=coefficient CI=confidence interval; DMARDs=disease modifying anti rheumatic drugs; GC=glucocorticoids; IRR=incidence rate ratio; OR=odds ratio; N=number.

Discussion

In this IPD meta-analysis on 2 years data from 3 randomized clinical trials that compared study arms starting with csDMARDs with or without initial GC bridging, we found that the proportion of patients using GC and the cumulative GC dose after t=12 months were similar between GC bridgers and non-GC bridgers. Also, we confirmed that bridgers achieved low disease activity significantly earlier than non-bridgers. After the end of the initial bridging schemes, bridgers and non-bridgers had similar DAS28 over time, but non-bridgers had more DMARD changes. In these relatively old trials, initially high dosed and long (on average 35 weeks) bridging schedules were used. Patients could by protocol restart or continue GC if the study treatment target was lost during or after tapering. At t=12 months, this resulted in 21% of patients in the bridgers group using GC compared to 6% of the non-bridgers, who had started GC following the allocated first csDMARD treatment. GC bridging resulted in a 2400 mg higher cumulative GC dose in the bridgers compared to the non-bridgers over the total follow-up of 2 years (including the bridging period).

Whether or not to start treatment for patients with RA including GC bridging is the theme of an ongoing international discussion, weighing the balance between benefits and harms. GC use has been associated with adverse effects, particularly in high and/or prolonged doses. However, there are limited data about (long-term) adverse events, particularly medicinally unpreventable or untreatable adverse effects, associated with shorter term GC use (i.e. bridging) in early RA patients. The weighing of the benefits and harms of GC (bridging) in combination with limited evidence on this subject has led to different international recommendations regarding GC bridging. The EULAR recommendations (2022 update) (9) included a recommendation stating that short term GC bridging in the first line of treatment should be considered, but the updated ACR recommendations (2021 update) advised, conditionally, not to use GC bridging at all, on the basis that the benefits of short-term GC do not outweigh the risk that GC initiation will lead to continued use with associated toxicity.(10) In a recent SLR we showed that few trials and no observational cohorts have been published on the successful discontinuation of initial GC bridging therapy in patients with newly diagnosed RA.(14) We subsequently combined the raw data from the identified clinical trials that included an initial GC bridging arm in a previously published IPD meta-analysis, and found that only a minority of patients (with totals decreasing over time) continued GC after the planned initial bridging schedule.(11) Of course, in daily practice GC prescription does not always follow predefined strategies for GC discontinuation or restart that would be comparable to the included clinical trials in this study. In the current study we tested whether initial GC bridging would affect whether patients would be more likely to (re)start GC over time, resulting in differences in cumulative GC dose over time, or more frequent DMARD changes, as it

had been suggested that rapid suppression of disease activity may affect the disease course and later need for treatment changes. Numerical differences in GC use between a GC bridging and non-GC bridging group have been previously reported in a non-randomized prospective study.(12) Furthermore, the CareRA study already reported a numerically lower cumulative GC dose (including intramuscular and intraarticular GC injections) in low risk patients in the GC bridging arm during the second year of follow-up.(13) In the combined trials we did not find a such a difference in later GC use, but non-bridgers did need more DMARD changes and initially more time to achieve a low DAS28 than bridgers. In discussions on risks and benefits of GC bridging, the focus is often on cumulative effects and long-term outcomes. It could be argued that with the introduction of more antirheumatic drugs and embedded in the notion of 'treat-to-target', the opportunities to achieve low disease activity or even remission later in the disease course have greatly increased, which, as we also show here, results in similar control of disease activity after longer follow-up. However, as shown again in this study, for non-bridgers this means prolonged disease activity while sometimes several treatment changes are required, each with their own potential adverse effects. Our studies and numerous RCTs (summarized in SLRs) with newer antirheumatic drugs, have reported that the majority of patients starting treatment on monotherapy csDMARD (methotrexate) do not achieve remission or low disease activity in the first 3-6 months.(1, 2, 17, 18) We have confirmed here again a more rapid decrease in disease activity in the GC bridging arms. The importance of this early clinical response is supported by extensive data from literature as previous research has shown that early suppression of disease activity using GC bridging is associated with less DMARD changes (current study), less radiographic progression (1, 2) and this difference compared to non-bridgers was still statistically significant several years after bridging was stopped.(7) Moreover, GC bridging is associated with less (permanent) productivity loss(19, 20), less analgetic use (21), less long-term fatigue (22) and more long-term self-efficacy.(23) The psychological impact of rapid pain relief and restoration of function on the first treatment has rarely been reported and may require empathic reasoning. Whereas available (observational) studies generally agree on an increased risk of adverse events such as osteoporosis, infections and diabetes associated with GC use, results on a safe daily dose and/or duration are conflicting.(8) Moreover, preventive measures (e.g. anti-osteoporotic treatment) are not always taken into account and the risk of treatment is rarely balanced against the risk of inflammatory RA disease activity.(24, 25) Previous studies that did compare the effects of (suppression of) disease activity and GC use, showed that the least bone mineral density decrease occurred in patients in which disease activity was well suppressed, even with GC, suggesting that well-controlled disease activity may outweigh the potentially detrimental effect on bone mineral density associated with GC use.(25). Most available data on GC toxicity are based on prolonged and/or high dose GC use, in non-RA populations and/

or on observational data with strong risk of confounding (bias) by indication and subject to the risk associated with the condition that was treated.(26-29) Recently, the GLORIA trial demonstrated that the use of lower GC doses (≤5mg/day prednisone equivalent) in elderly patients with established RA was effective in improving disease activity, functional ability and limiting radiographic progression, although associated with an increase of 24% in risk of at least one predefined AE of interest, which were mostly mild to moderate infections.(30) Data on short- as well as long-term adverse events due to initial GC bridging therapy in RA are limited. Randomized controlled trials are in general not sufficiently powered to compare (serious) adverse events, whereas observational studies generally do not focus on bridging schedules specifically and carry the risk of confounding by indication.(8, 31) The BeSt study has reported on the comparison of adverse effects of GC in year 1 between three arms who did not start GC bridging and one arm who did start GC bridging initially. They found slightly more cardiovascular events in the arm with GC bridging compared to the other arms and less bone mineral density loss.(7, 32) The COBRA study reported, for the first 56 weeks after start of treatment, on several expected adverse effects from GC: weight gain was significantly higher in the first 28 weeks in the GC bridging group compared to the SSZ monotherapy group, blood pressure remained stable in both groups and bone mineral density changes were also not significantly different between the bridgers and non-bridgers.(1) In the CareRA study there was a comparable number of adverse events in the bridgers and non-bridgers, not further specified for GC related adverse events.(13) For the current analyses, individual patient data on adverse events were unavailable, which we recognize as a limitation of our study. The principle to 'first do no harm' could be easily translated into not prescribing GC bridging (or in fact any medication). However, treatment decisions always involve weighing benefits and risks, including the benefit of rapid suppression of disease activity versus the risk of unopposed and prolonged high disease activity, but also the risk of potential (long-term) side-effects of initial GC bridging. By design, the planned GC bridging schedules affected the comparison in cumulative GC doses between bridgers and non-bridgers. The initial GC dose used in the BeSt and COBRA studies (both 60 mg) and to a lesser extent the starting dose of the CareRA bridging arm (30 mg) were relatively high and the planned schedules of use relatively long, especially compared to current recommendations to stop within 3 months. The lower starting dose (30 mg) used in CareRA was found equally effective and comparable in terms of safety to the higher dose of 60 mg, in a direct comparison in the COBRA light study.(33) Our previous IPD meta-analysis, which also included trials without a non-bridging treatment arm, showed that a lower initial GC bridging dose was associated with less GC use at 12 and 18 months after the planned end of bridging, and also with lower cumulative GC doses. Furthermore, it was suggested that parenteral GC bridging might be associated with less GC use during follow-up.(11) As yet, the long-term adverse events of these initial higher GC doses are unclear, and a

comparison of the safety profile with shorter GC bridging schedules with lower cumulative GC doses, as proposed in current recommendations, is lacking. Therefore, it seems evident that there is a need for trials comparing lower and shorter GC bridging schedules with a previously tested regimen, such as COBRA slim, and with a treatment arm without GC bridging. Trying to avoid adverse effects of GC could affect achieving the benefits of GC. The recent CORRA trial showed that after a 'COBRA light schedule' that tapered to zero in 3 months, no radiological benefit could be shown.(34) For now, it remains unclear which is the best bridging schedule when balancing both safety and efficacy, and which (cumulative) dose of GC gives an increased risk of adverse events.

Alternatively, bridging with other rapid acting antirheumatic drugs may be considered. In the BeSt study, temporary treatment with infliximab (IFX) was at least as effective and safe as temporary treatment with GC.(2, 35). This is of course associated with higher drug costs, but this might be possibly offset by greater improvement in productivity.(20) The IDEA study compared initial therapy with MTX and 2-monthly IFX to MTX with a single intravenous (IV) 250 mg dose of GC in DMARD naïve early RA patients and found no statistical superiority of the MTX plus IFX group compared to the GC group regarding radiographic progression and DAS remission.(36) Nor was there a statistical significant difference in additional GC requirement between the groups. An earlier RCT that evaluated MRI differences between MTX monotherapy, MTX plus 2-monthly 1000 mg IV GC and MTX plus 2-monthly IFX, after 1 year found less MRI erosion progression in the MTX plus IFX group than in the MTX plus IV IG group, but new erosions in previously undamaged joints were seen more often in the MTX plus IFX group.(37) More studies are needed for this comparison between MTX plus bDMARD and MTX plus GC bridging. For now, in daily practice individual deviations of previously trialed bridging schemes can only be considered per patient.

Patients in the GC bridging group were found to have fewer DMARD changes over time than patients in the non-GC bridging group, which may be cost saving and also more convenient for the individual patient. It is possible that patients in the GC bridging group changed DMARDs less often because the treatment protocols of the BeSt and the COBRA studies required to prolong or restart GC (maintenance) dose before changing the csDMARD if after GC tapering the disease activity relapsed. This would tie in with our finding that at 12 months, patients in the GC bridging group used more GC than patients in the non-GC bridging group. The data showed that this use at 12 months was more often due to a recent restart (77%), than a reflection of a continuous course of GC, indicating a disease flare after the end of bridging while continuing csDMARD treatment. We speculate that GC bridging in general not only acts more rapidly than csDMARD monotherapy, but can mask a lack of efficacy of the csDMARD which becomes apparent only after GC discontinuation and requires a change

of treatment. In patients from the non-GC bridging group with insufficient response, the need for DMARD treatment adaptation (not being masked by effective GC treatment) would have become apparent earlier in the process. In the BeSt study it was shown that after failure on MTX, patients often also did not achieve low disease activity on the next csDMARDs, while in the meantime, radiographic damage progression occurred.(38) This may suggest that rapidly effective alternative treatments should be at hand, if GC use is limited to a short bridging period (e.g. 3 months).

This analysis has several strengths and weaknesses. The combination of individual patient data from clinical trials in an IPD meta-analysis gives the possibility to analyze GC bridging in more detail than with the aggregated published data from the identified clinical trials only (a regular meta-analysis). However, the heterogeneity that exists between the studies can complicate combining these data, although this is partly compensated by adding 'study arm' as random effect. With our previously conducted SLR, 10 clinical trials were identified that included GC bridging.(14) Only 4 of these trials had randomized between initial GC bridging and no initial GC bridging (comparator arms). Subsequently, investigators of 3 of these 4 trials agreed to share data for the current IPD meta-analysis. One (39) did not respond to our requests. As mentioned, individual data on adverse events were unavailable for the current analyses. Another limitation to our efforts to investigate the effects of initial GC bridging, is the lack of available data from observational studies. Only clinical trials were included in this analysis. Clinical trials usually include a more homogeneous RA population than the RA population in clinical practice due to detailed in- and exclusion criteria, and therefore the results of such trials may be less generalizable to a daily practice RA population. As a rule, observational studies do reflect daily practice more (higher generalizability) but these carry the risk of 'confounding by indication'. In contrast to the BeSt and COBRA and perhaps more in resemblance to current daily practice, the CareRA study arms included in this analysis consisted of RA patients with a low risk for a bad prognosis. We therefore have conducted a sensitivity analysis excluding the patients with a low risk for a bad prognosis from the CareRA, the BeSt and COBRA studies, which showed comparable results. However, there was a trend (larger effect estimates for the GC bridging group compared to the non-GC bridging group) towards more GC use when low risk patients were excluded from the analysis, with also higher cumulative GC doses. Future studies, aided by online data collection, could focus on earlier effects of initial treatment and more tailored and responsive treatment adjustments over time. The bridging schedules of the included studies were all relatively long in contrast to the EULAR 2022 updated recommendations, in which 3 months is suggested/ stated as a maximum duration.(9) However, it is possible that the presence of a protocolized tapering schedule and predefined alternative treatment steps actually contributed to the success rates of tapering and stopping GC in the

clinical trials. In daily practice, tapering GCs without such a tapering protocol might be more difficult. Patients often flare or otherwise feel worse after GC discontinuation, when it becomes apparent that csDMARDs are insufficiently effective.(40-42) Switching to a bDMARD may prevent starting or going back to GC treatment. In our selected trials we could not analyze use of biological (b)- and targeted synthetic (ts)DMARD between GC bridgers and non-GC bridgers as the first two years of the COBRA study did not include such medications.

To conclude, this IPD meta-analysis showed that in clinical trials about patients with newly diagnosed RA, initial GC bridging is associated with a more rapid clinical improvement and fewer DMARD changes compared to non-GC bridging, without apparent greater risk to continue GC use beyond 12 months. Future research should focus on finding the optimal bridging strategy in early RA, including the best dose and duration, route of drug administration, and possibly even type of medication, carefully balanced against the risk of adverse events.

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