Is glucocorticoid bridging therapy associated with later use of glucocorticoids and biological DMARDs during the disease course of patients with rheumatoid arthritis in daily practice? A real-world data analysis

Ouwerkerk, L. van; Bergstra, S.A.; Maarseveen, T.D.; Huizinga, T.W.J.; Knevel, R.; Allaart, C.F.

Seminars in Arthritis and Rheumatism 64 (2024) 152305

Contents lists available at ScienceDirect

Seminars in Arthritis and Rheumatism

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

Is glucocorticoid bridging therapy associated with later use of glucocorticoids and biological DMARDs during the disease course of patients with rheumatoid arthritis in daily practice? A real-world data analysis

L. van Ouwerkerk *, S.A. Bergstra, T.D. Maarseveen, T.W.J. Huizinga, R. Knevel, C.F. Allaart

Department of rheumatology, Leiden University Medical Center, Leiden, the Netherlands

ARTICLE INFO

Keywords:
Glucocorticoids
Rheumatoid arthritis
Observational data

ABSTRACT

Objective: To evaluate if initially starting glucocorticoid (GC) bridging leads to a higher probability of long-term GC and biological (b)DMARD use in rheumatoid arthritis (RA)-patients.
Methods: Electronical health records data from newly diagnosed RA-patients from the Leiden University Medical Center were used. Patients who started GC as part of initial treatment (iGC group) and who did not (niGC group) were compared in terms of GC and bDMARD use later in the disease course. Multivariable adjustment was performed to account for confounding by indication.
Results: 465/932 newly diagnosed RA-patients (50 %) were treated with GC as initial treatment step. Patients in the iGC group were older, included fewer females, had a higher disease activity at baseline compared to the niGC group plus a more rapid decrease in DAS28 in the first 6 months. During follow-up, 42 % of the iGC group started a second course of GC and 17 % started a bDMARD, compared to 34 % and 13 % In the niGC group. The hazard to start a bDMARD later in the disease course was not significantly different between the two groups in two time periods (0.34 95 %CI(0.09;1.21) resp. 1.48 95 %CI (0.98;2.22)), but the hazard to (re)start GC later on was higher for the iGC group (aHR 1.37 95 %CI(1.09;1.73)).
Conclusion: In this daily practice cohort of newly diagnosed RA patients, patients in the iGC group had a more rapid DAS28 decrease and an increased probability of starting GC later on compared to the niGC group. The probability of bDMARD use was not significantly increased.

Introduction

Glucocorticoids (GC) are widely used for the treatment of rheumatoid arthritis (RA) but remain a source for discussion and sometimes dispute. It has been proven that temporary 'bridging' therapy with GC, while slower acting conventional synthetic (cs)DMARDs are initiated, results in more rapid suppression of disease activity than with csDMARDs alone [1–3]. This results in earlier clinical improvement and secured work productivity and is also associated with better suppression of radiographic damage progression in the following years [4,5]. According to the 'window of opportunity' theory, rapidly suppressing inflammation may even prevent chronicity and allow drug tapering to drug free remission or ultimately cure of RA [6]. However, besides the benefits of GC bridging, there is also the risk for adverse effects, in particular after long-term and high dose use of GC. The weighing of these benefits and risks of GC bridging is difficult and has even led to conflicting recommendations and guidelines [7,8]. One of the worries of using GC as bridging therapy is the possible difficulty of stopping GC once they are proven effective. Recently, a review of clinical trials using GC as bridging therapy showed that a vast majority successfully discontinued GC after the intended end of bridging [9]. However, the initial csDMARD treatment is often insufficiently effective to further suppress disease activity following the discontinuation of bridging [10]. Furthermore, it has also been suggested that GC as part of the initial treatment of RA may affect the course of RA and necessity for further treatment steps including delayed GC use and/or need to start biologic (b)DMARDs. Data to test this suggestion is mostly derived from clinical trials, which may not reflect daily clinical practice as they use fixed

* Corresponding author.
E-mail address: l.van_ouwerkerk@lumc.nl (L. van Ouwerkerk).

https://doi.org/10.1016/j.semarthrit.2023.152305

Available online 10 November 2023

treatment protocols. Therefore, we used daily practice data from the electronical health records (EHR) of the Leiden University Medical Center (LUMC) to investigate the disease course and use over time of GC and bDMARDs in patients with newly diagnosed RA using initial GC or not.

Methods

Patient selection

Data were extracted from the EHR of the LUMC in the Netherlands from patients who since 2011 (introduction of the EHR) had at least one appointment at the rheumatology department (extraction was done in 2021). The LUMC is a secondary/tertiary medical care center, but in the rheumatology department also patients who are DMARD naive and without a diagnosis are seen. We applied our previously validated machine learning algorithm [11], selecting patients with a probability of RA diagnosis of >0.83. This corresponded to a positive predictive value of 0.85 and sensitivity of 0.85. These selected patients had no visits prior to introduction of the EHR in 2011, no previous treatment in other centers (ruling out second opinions and transition patients from pediatric rheumatology), no treatment decisions based on participation in a clinical trial and at least 3 follow-up visits within 2 years after the first visit (supplementary fig. 1). The selected 932 patients had either started with one or multiple csDMARD(s) without GC during the first 3 months of treatment, or one or multiple csDMARD(s) with GC (including patients who first started GC and started csDMARDs within 4 weeks after that, or vice versa). Data were collected on medication use (prescription data), laboratory test outcomes and disease activity components and composite scores. The baseline visit for every patient in this study was defined as the start of antirheumatic medication. GC cessation was defined as a stop date of prescription plus no new prescription at the following visit. As medication data did not always provide detailed information on the tapering schedule we could not investigate different tapering strategies. Ethical consent for the data collection was obtained from the ethics committee of the LUMC.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Statistical analysis

Based on medication data at baseline (the visit during which the first antirheumatic treatment was initiated), patients were divided into patients who started initial GC (iGC group) and patients who did not start GC initially (niGC group). GC bridging was defined as the start of oral GC next to a csDMARD at the moment that the first antirheumatic medication was started. A 1-month delay in either adding an oral GC to csDMARD or adding csDMARD to an oral GC, was accepted as also representing 'GC bridging'. The two groups (iGC and niGC) were described with descriptive statistics and Kaplan Meier curves to show time to first (in case of the niGC group) or second (in case of the iGC group) GC course and time to first bDMARD course during follow-up (unadjusted). Cox proportional hazards regression models were used to investigate time to start a bDMARD and time to (re)start GC. The proportional hazards (pH) assumption was verified by plotting log minus log survival plots (LML plots) and the performance of the Schoenfeld's global test. For time to start a bDMARD the proportional hazards assumption was violated and therefore the Cox model was divided into two time intervals in which the pH assumption was not violated (stratification). As observational studies carry the risk of confounding by indication, adjustment for multiple (patient) characteristics was performed to account for this type of bias. Analyses were adjusted for: age, sex, year of start medication, DAS28(3) (Disease Activity Score (DAS) based on 28 joints and 3 components (number of swollen joints, number of painful joints and erythrocyte sedimentation rate (ESR)), anti-citrullinated protein antibodies (ACPA) status and physician (from 14 physicians identified) who since 2011 prescribed or authorized the prescription of the initial medication, to account for prescriber preferences. Variables that are time varying were included as time varying. Furthermore, the course of disease activity over time was compared between the two groups using a linear mixed model with as outcome the DAS28(3) over time. An interaction term between group (iGC group or niGC group) and time (as categorical variable) was included to be able to compare the course of DAS28 between two groups during each time period. Based on previous reports, it is known that after start of antirheumatic medication, in particular with GC, the DAS28 decreases more rapidly in the first 6 months [12,13]. Thereafter, the decrease is more gradual. We have therefore added a knot in the model at 6 months to be able to compare both groups (iGC and niGC) during these two different time periods. A random intercept was included to take into account the correlation of different time points within individual patients. Statistical analyses were performed using Stata SE version 16.1 (StataCorp, College Station, TX, USA).

Missing data

Missing data were considered to be at random and imputed using multiple imputation using chained equations (10 imputed databases) with predictive mean matching (with five observations to draw from) for continuous outcomes and logistic regression for binary variables.

Results

932 patients fulfilled the inclusion criteria of this study. There was only one patient who started GC bridging intravenously and one that started GC bridging intramuscularly, these were excluded. The 472 patients who were identified as RA patients by the machine learning algorithm, but were not selected for this analysis because they did not fulfill the inclusion criteria mentioned in the methods, did not differ from the study population in terms of age, sex, DAS28(3), ACPA and RF positivity (supplementary Table 1). Information about ACPA was missing in 10 %, RF in 13 % and DAS28(3) at baseline in 45 %. Missingness was equally prevalent among the groups and patients who had DAS28(3) at baseline present were not different from patients who did not have DAS28(3) present at baseline in terms of medication use (supplementary Table 2).

Of the 932 patients included, 465 (50 %) started with initial GC bridging (iGC group).Within this group, alongside GC, methotrexate (MTX) was the most commonly (87 %) csDMARD prescribed, with as rare alternatives sulfasalazine (SSZ) (5 %) and hydroxychloroquine (HCQ) (3 %). The patients that did not initially start GC bridging (niGC group) also started most frequently with MTX (79 %), or with HCQ monotherapy (11 %). Patients in the iGC group were older, fewer were female, they had a higher disease activity at baseline and more patients were rheumatoid factor (RF) positive (Table 1). There was no significant difference in ACPA positivity between the groups.

The median follow-up time was 4.3 years (interquartile range (IQR) 2.7;6.8) for the iGC group and 5.3 years (IQR 3.0;7.7) for the niGC group. In the iGC group the initial GC course had a median duration of 16 weeks (IQR 6.7;44.7). Of this iGC group, 21 % of the patients continued this first GC course for >1 year and 13 % for >2 years. In 166/394 (42 %) patients who did discontinue the first GC course during follow-up, a second course of GC was started at median 52 weeks (IQR 18;145) after the end of the first GC course. This second course had a median duration of 17 weeks (IQR 6;57). Patients from the iGC group that started a second course of GC were not different from patients that did not start a second course of GC regarding age, sex and DAS28(3) at baseline. However, these patients that needed a second course of GC were significantly more often RF and/or ACPA positive (supplementary

Table 1
Baseline characteristics of participants starting GC as part of the initial treatment (iGC) vs. not starting GC as part of initial treatment (niGC).

	Started with initial GC (iGC group) $N = 465$	Started without initial GC (niGC) $N = 467$	p-value
Age (baseline) mean ±SD	61 (14.8)	57 (15.8)	<0.001
Sex (female) (%)	63	70	0.013
DAS28(3) mean ±SD	4.9 (1.3)	4.3 (1.4)	<0.001
RF positive (%)	63	56	0.04
ACPA positive (%)	58	53	0.112
(Concomitant) medication			
MTX monotherapy	86.9	78.8	0.001
HCQ monotherapy	3.2	11.1	<0.001
LEF monotherapy	1.3	1.3	0.99
SSZ monotherapy	5.4	5.4	0.99
MTX+HCQ	1.9	2.1	0.82
MTX+HCQ+SSZ	0.2	0.4	0.57
HCQ+LEF	0.7	–	n.d
MTX+SSZ	0.4	0.2	0.56
HCQ+SSZ	–	0.7	n.d.

Abbreviations: ACPA = anti-citrullinated protein antibodies; DAS28(3) = disease activity score based on 28 joints, with 3 components (no patient global); GC = glucocorticoids; HCQ=hydroxychloroquine; LEF=leflunomide; MTX=methotrexate; n.d.=not done; N = number; RF = rheumatoid factor; SD = standard deviation; SSZ=sulfasalazine.
Significant results are displayed bold.

Table 3). A third course of GC was started in 68 patients of the iGC group. In the niGC group 157 patients (34 %) eventually started a GC during follow-up, after a median of 60 weeks since start of csDMARDs (IQR 15;168). This first GC course in the niGC group had a median duration of 17 weeks (IQR 9;51). In the niGC group, 24 % of the patients that started this first GC course used it for > 1 year, 15 % used it for > 2 years. A second course of GC was started in 53 patients of the niGC group. During follow-up, 17 % of the iGC group started a bDMARD after a median of 66 weeks, compared to 13 % of the niGC group after a median of 100 weeks. In both groups, adalimumab was started most frequently amongst the bDMARDs.

Modelled mean DAS28(3) decreased significantly more rapidly in the first 6 months for the iGC group (Table 2), which also had a higher mean DAS28(3) at the first visit (0 months) (Fig. 1). In the second part after the knot at 6 months, the decrease was not significantly different between the groups (Table 2).

The cumulative incidence (unadjusted) of GC use steadily increased in both the iGC group (Fig. 2A) and the niGC group (Fig. 2B). In the iGC group, 394/465 patients were available for the Kaplan Meier curve as 71 patients had not discontinued the GC 'bridging' course before the end of follow-up. In both groups there was an initial rapid increase of the cumulative incidence for (re)starting a GC course. In both groups, steadily more patients over time started a GC, but in the niGC group the increase was slower.

For bDMARD use, the unadjusted cumulative incidence of bDMARD

Table 2
Output LMM with interaction term (group * time).

Fixed effects	Beta	95 % CI	p-value
Group (iGC group vs. niGC group (=ref))	0.65	0.40;0.91	<0.001
Group * spline 1 (0–6 months)	−0.11	−0.16;−0.06	<0.001
Group * spline 2 (>6 months)	−0.0001	−0.005;0.005	0.967

Abbreviations: CI=confidence interval; iGC group=group that started with GC bridging; LMM=linear mixed model; niGC group=group that did not start with GC bridging initially.

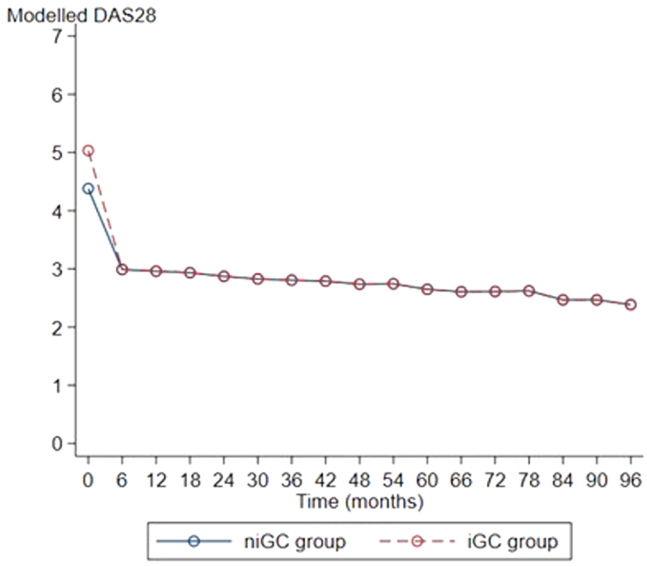

Fig. 1. Mean DAS28(3) (data from linear mixed model with a knot at 6 months) over time for the group that started initial GC bridging (iGC group, red) and the group that did not (niGC group, blue).

start was higher in the iGC group early during follow-up. Slightly more patients in the iGC group started bDMARDs earlier, but at the end of follow-up the cumulative incidences of both groups were similar (Fig. 3).

Taking into account the complete follow-up time, patients in the iGC group had a greater probability to start GC later in the disease course than patients in the niGC group (aHR 1.37 (95 %CI 1.09;1.73), Table 3). Due to violation of the pH assumption, the Cox proportional hazard model for time to start a bDMARD was divided into two time periods (before and after $t = 0.55$ year). The probability to start a bDMARD during complete follow-up time was not significantly different in the two groups, neither during the first time period nor during the second time period (aHR 0.34 (95 % CI 0.09; 1.21) and aHR 1.48 (95 % CI 0.98; 2.22) respectively). We have performed an additional sensitivity analysis in a selected patient group who had DAS28(3) available at baseline only (supplementary Table 5). Regarding the outcome bDMARD use during follow-up, the proportional hazards assumption was violated, similar to the main analysis. We had to exclude the first time period of 0.31 years, during which the number of events was too low to perform multivariable analyses. During the second time period the multivariable adjusted HR was 1.68 (95 % CI 0.99;2.84) for bDMARD use. This was comparable to the HR of the main, although the effect estimate slightly increased. Regarding the outcome 'GC', results were also similar to the main analysis with similar HRs for the relationship between the iGC and niGC group, although the relationship was no longer significant, likely due to a lower power because of a lower number of included patients.

Discussion

This study, based on daily practice data registered in EHRs of newly diagnosed RA patients, provided insights in the treatment differences between patients who initially started with GC bridging and who did not. We found that GC were used as bridging therapy in 50 % of patients starting csDMARD therapy for newly diagnosed RA. These patients had a more rapid decrease in DAS28 than patients who did not start with GC bridging. After the first 6 months, there was no significant difference in the course of the DAS28 over time in both groups. In both groups fewer than 20 % of patients started a bDMARD during follow-up. No statistically significant difference was observed in bDMARD use during follow-up for both groups, although the effect estimate pointed in the same direction as the effect estimate of GC use. The likelihood to use GC later on was higher for the iGC group.

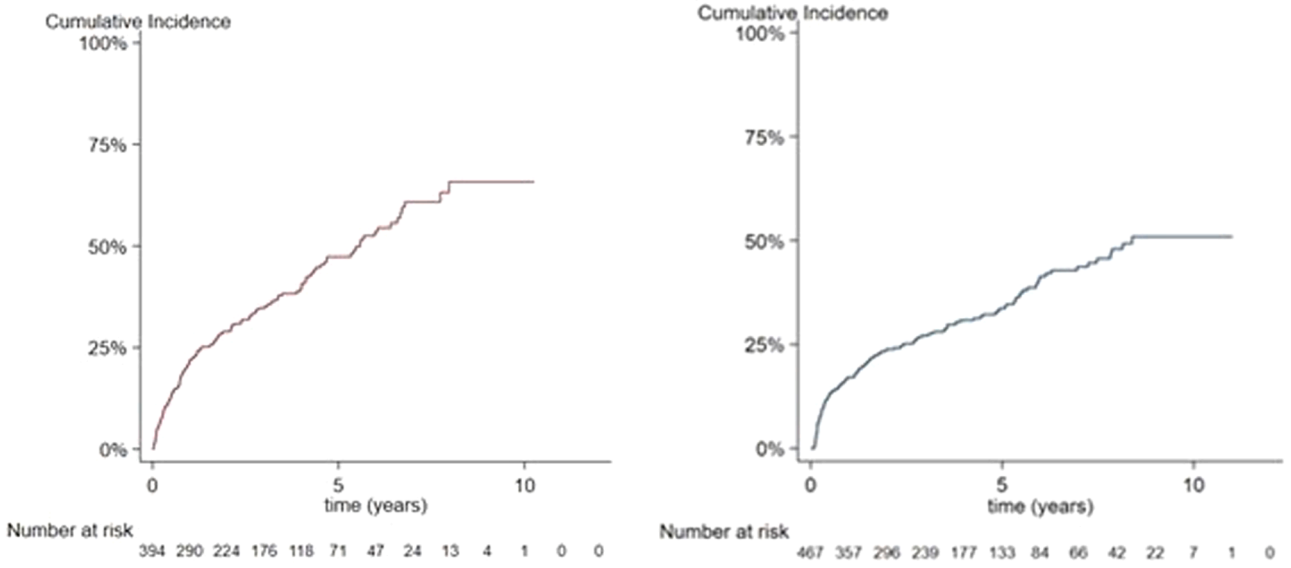

Fig. 2. Percentages of patients starting a course of glucocorticoids during complete follow-up (unadjusted cumulative incidences).
A) iGC group (red): patients starting a second course of glucocorticoids after having completed and discontinued initial glucocorticoid bridging therapy
B) niGC group (blue): patients starting a first course of glucocorticoids who had not started glucocorticoid bridging therapy as part of the first treatment step.
* because of the different courses which are shown here (restart for the iGC group and first start of the niGC group), plots are shown separately.

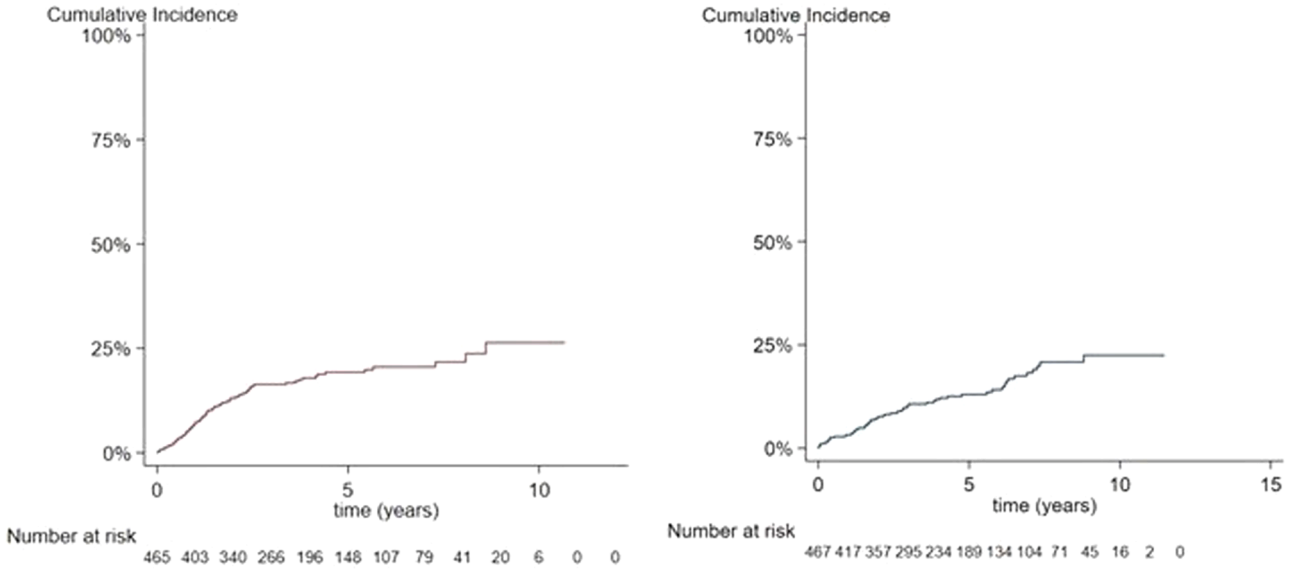

Fig. 3. Start of bDMARD during complete follow-up (unadjusted cumulative incidences)
Abbreviations: bDMARD = biological disease modifying antirheumatic drug.
A) iGC group (red): patients that initially started with glucocorticoids
B) niGC group (blue): patients that did not initially start with glucocorticoids.

To the best of our knowledge, this is the first study based on non-protocolized real-life data studying the relation between starting GC bridging or not and the (re)start of GC and a bDMARD later during the disease course. The reasons why patients start or do not start with GC bridging as initial treatment are important to consider here, as these reasons (patient/disease characteristics but also education, conceptions and preferences of the prescribing physician) possibly also influence treatment decisions later on and thus act as potential confounders. This risk of confounding by indication, which is inherent to using observational (real-life) data, can have a strong influence on the results if not properly adjusted for. We have therefore evaluated whether patient characteristics and prescribing preferences had an influence on differences between the groups. We observed that patients in the iGC group were older, more frequently male, with a higher DAS28 and RF positivity compared to the niGC group. A previous study in the Swiss SCQM registry also found that patients in the iGC group had a significantly higher DAS28 and were older than the niGC group at baseline, but there were no differences regarding female/male distribution and RF positivity proportions between the groups [14]. The German CAPEA cohort also observed a higher DAS28, more males, older patients and more RF positivity in the iGC group, although not significantly tested [15]. Fewer patients in our cohort started with initial GC bridging (50 %) than in the SCQM (61.4 %) and CAPEA (77.4 %) cohorts. Over time, our results show that many patients at some point during their disease course go through a period where temporary treatment with a rapidly active anti-inflammatory drug is required. This may already be at the start of

Table 3
Hazard ratios for GC and bDMARD use.

	Unadjusted HR (95 % CI)		Multivariable adjusted HR (95 % CI)	
GC use (ref group: niGC)	**1.42 (1.14;1.77)**		**1.37 (1.09;1.73)**	
Stratification into two time periods	*First time period*	*Second time period*	*First time period*	*Second time period*
bDMARD use (ref group: niGC)	0.85 (0.39;1.83)	1.31 (0.90;1.93)	0.34 (0.09;1.21)	1.48 (0.98;2.22)

Cox proportional hazards regression with time dependent covariate analyses were performed in a multiple imputed database. In the multivariable analyses, HR were adjusted for: age, sex, year of start medication, DAS28(3) at baseline, ACPA and treating (prescribing or authorizing) physician. For outcome bDMARD use, time was stratified into two time periods as the Cox proportional hazard assumption was violated (supplementary figure 2 and supplementary Table 4).
Abbreviations: ACPA=anti-citrullinated protein antibodies; bDMARDs=biological disease modifying antirheumatic drugs; DAS28(3)=disease activity score based on 28 joints; GC=glucocorticoids; *N*=number.
Significant results are displayed **bold**.

treatment, when the effect of slow acting csDMARDs has to be awaited. The differences in baseline characteristics show that older male patients with higher disease activity are more likely to receive initial GC bridging. Subsequent decisions to start temporary GC treatment may be related to various events during the so-called 'patient journey'. Patients who started with GC may flare after discontinuation of GC when the first csDMARD proofs to be not effective and a second or third csDMARD has to be tried. For many patients the first GC course, or a second course after initial bridging, comes many years after the start of treatment. This later start may suggest no earlier need, withdrawal of earlier limitations or restraints and/or absence of or limitations to use of equal alternatives.

In our analysis we have also evaluated DAS28(3) over time. The iGC group had a higher DAS28(3) at baseline and a significantly greater decrease until 6 months compared to the niGC group. Similar results were reported for DAS28 in the German (CAPEA) and Swiss (SCQM) cohort. Glucocorticoids are known for this rapid acting mechanism in preventing damage and suppressing disease activity in clinical trials [16]. This early clinical improvement is important to avoid damage, productivity loss and may affect the option to achieve clinical remission over time. GC do therefore still fulfill an important role in the initial treatment of RA as long as other rapidly acting DMARDs (e.g. bDMARDs) are not part of the initial treatment step. We hypothesized that initial treatment with GC would be associated with less or delayed treatment with bDMARD later in the disease course. The course of time to bDMARD start (Kaplan Meier curves) showed a similar pattern in our patient selection and the SCQM cohort with overlapping/crossing lines in the first year and subsequently a greater rise of the cumulative incidence for the iGC group. Our Cox proportional hazard models did not show significantly different escalations to bDMARD treatment between the iGC and niGC groups during follow-up, although the effect estimates for both time periods were comparable to the effect estimate of GC use during follow-up. With the lower bound of the 95 % CI being close to 1, it is possible that this is caused by a lack of statistical power. For now, our results seem to hypothesize that the benefit of earlier use of GC did not extend to a lesser need for GC, by whatever motivation, or a lesser need to start bDMARD later in the disease course. However, it is also possible that the increased use of GC and perhaps a numerical increase of bDMARD use during follow-up the result is of confounding by indication, despite our best efforts to correct for it. In this scenario, a worse prognosis of the iGC compared to the niGC patients at baseline would also increase the risk of more intensive treatment during follow-up for the iGC patients and not the GC bridging use itself. In line with this, the SCQM cohort found a significantly higher proportion of bDMARD escalation in the iGC group compared to the niGC group. However, despite of the observational nature of this registry, no correction for confounding was applied which limits the comparability with our study.

Despite the known benefits of GC bridging, there is still an ongoing debate about the balance of the advantages and potential disadvantages of GC bridging therapy [17–19]. It is known from literature that the prescription of GC varies widely amongst rheumatologists [20,21]. In part this may be related to personal worries and preferences; some may feel that even a small chance on a future serious adverse event outweighs the high chance of early reduction in pain and restoration of function, others may feel the reverse. The current discrepancy between the EULAR and ACR guidelines regarding the use of GC bridging therapy may both reflect and stimulate a more pronounced personal preference for initial GC of the prescribing physician in consultation with their patient. In our patient selection from the LUMC, an academic hospital, we did not see a major influence of prescriber's preference but this might be different in other (non-academic) hospitals. In our analysis we could not take into account patient preferences as we did not have any data about this. Furthermore, besides prescriber and/or patient preferences also patient characteristics such as comorbidities and comedication might play a role in the decision to use GC or not. Once GC have been used as bridging therapy initially, the favorable conditions without contraindications to use GC might still be present in the same patients that also had GC bridging therapy, giving them a higher probability to use GC later in the disease course as well compared to patients who did not start GC bridging. For this study at this moment, we did not have high quality data available on standardized registration of comorbidities (that may either affect use or GC, elements of the DAS28, or may have been an adverse event of treatment) or comedication, making it impossible to correct for it. Also, therapy adherence might have played a role in the outcomes as patients might not always take their prescribed medication. Our data set is not equipped to explore this detailed information.

From the 2010 update of the EULAR recommendations onwards, a statement is included that GC should be tapered as rapidly as clinically feasible [22]. This GC 'short term' use is in the latest EULAR update (2022) defined as taper and stop *within* 3 months. The median time of the first GC course in the iGC group in our analysis is 16 weeks, probably because most visits occur 4 months after initial visit instead of 3 months (e.g. because DMARDs are started somewhat later than GC). This is close enough to 3 months to conclude that at least in our Dutch cohort there is no such large gap between clinical practice and the recommendations, as has been previously described in the Chinese TARRA cohort [12]. This can potentially be explained by at least an intention not to prescribe GC too high or too long, a practice of DAS steered treatment adjustments and easy access to multiple DMARDs, including bDMARDs, that are all reimbursed in the Netherlands [23]. However, in order to better adhere to the 3 months GC use advised in the EULAR recommendations, experience in clinical studies suggests that it may be wise to prescribe, taper and discontinue GC using a predefined protocol. Use of other medication such as bDMARDs should be considered to achieve suppression of disease activity at times of a flare in order to avoid repeated courses of GC.

A strength of our study is the use of data from an unselected patient cohort with non-protocolized treatment and non-protocolized control visits. Although, we cannot be certain that our results are generalizable to other hospitals due to our monocenter design. Nevertheless, our data showed comparability with two other cohorts regarding baseline characteristics of the iGC and the niGC groups which argues in the direction of a good reflection of other patient groups. This study also has several limitations that should be addressed. We found that in many cases a DAS could not be found in the baseline clinical records and despite various methods to assemble a retrospective DAS28(3) based on various DAS components, the absence of baseline DAS remains inexplicably high. To account for missing data in several variables (DAS28(3), ACPA and RF), we used multiple imputation. Due to much higher availability of the DAS28 based on 3 components we have chosen to use this disease

activity measure instead of the DAS28 based on 4 components. As observational studies carry a risk for confounding by indication, we have conducted multiple adjusted analyses to correct for this. Nevertheless, despite our efforts to correct for factors potentially affecting the initial treatment decisions, our results may still be affected by residual confounding by indication, as well as by bias concerning treatment choices during follow-up. Therefore causal interpretation should be avoided. However, observational data can still be helpful to provide insights in daily practice treatment patterns. Since the medication data were extracted from the EHR there is some uncertainty in for example tapering schedules because these may not always be reported in full detail. Therefore, we could not study tapering regimens in our analysis.

To conclude, this observational EHR data showed that initial GC bridging was prescribed in 50 % of patients with RA. Patients who started with GC bridging in our center initially had a more rapid decrease in DAS28 than non-bridgers. Over subsequent years, patients who started with GC bridging were more likely to start a GC course as incidental treatment than non-bridgers, but the likelihood to start a bDMARD was not significantly increased.

Contributorship

RK and TDM provided the data. SAB, CFA and LvO analysed the data and drafted the manuscript. All authors revised the drafted manuscript. SAB, CFA and LvO are responsible for the overall content as guarantor (accepting full responsibility for the finished work and the conduct of the study, had access to the data, and controlled the decision to publish).

Funding

this study was not funded.

Declaration of Competing Interest

LO, CFA, TDM, TWJH, RK: have no relevant financial relationship(s) with ineligible companies to disclose. SAB: received an ASPIRE grant from Pfizer.

Data availability

Data are available upon reasonable request.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.semarthrit.2023.152305.

References

[1] Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, van Zeben D, Kerstens PJ, Hazes JM, et al. Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): a randomized, controlled trial. Arthritis Rheum 2008;58(2 Suppl):S126–35.
[2] Cutolo M, Spies CM, Buttgereit F, Paolino S, Pizzorni C. The supplementary therapeutic DMARD role of low-dose glucocorticoids in rheumatoid arthritis. Arthritis Res Ther 2014;16(Suppl 2):S1.
[3] Boers M, Verhoeven AC, Markusse HM, van de Laar MA, Westhovens R, van Denderen JC, et al. Randomised comparison of combined step-down prednisolone, methotrexate and sulphasalazine with sulphasalazine alone in early rheumatoid arthritis. Lancet 1997;350(9074):309–18.
[4] Klarenbeek NB, Güler-Yüksel M, van der Kooij SM, Han KH, Ronday HK, Kerstens PJ, et al. The impact of four dynamic, goal-steered treatment strategies on the 5-year outcomes of rheumatoid arthritis patients in the BeSt study. Ann Rheum Dis 2011;70(6):1039–46.
[5] Stouten V, Westhovens R, Pazmino S, De Cock D, Van der Elst K, Joly J, et al. Five-year treat-to-target outcomes after methotrexate induction therapy with or without other csDMARDs and temporary glucocorticoids for rheumatoid arthritis in the CareRA trial. Ann Rheum Dis 2021.
[6] Burgers LE, Raza K, van der Helm-van Mil AH. Window of opportunity in rheumatoid arthritis - definitions and supporting evidence: from old to new perspectives. RMD Open 2019;5(1):e000870.
[7] Smolen JS, Landewé RBM, Bergstra SA, Kerschbaumer A, Sepriano A, Aletaha D, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2022 update. Ann Rheum Dis 2022.
[8] Fraenkel L, Bathon JM, England BR, St Clair EW, Arayssi T, Carandang K, et al. 2021 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis Rheumatol 2021;73(7):1108–23.
[9] van Ouwerkerk L, Boers M, Emery P, de Jong PH, Landewé RB, Lems W, et al. Individual patient data meta-analysis on continued use of glucocorticoids after their initiation as bridging therapy in patients with rheumatoid arthritis. Ann Rheum Dis 2022.
[10] Maassen JM, Dos Santos Sobrín R, Bergstra SA, Goekoop R, Huizinga TWJ, Allaart CF. Glucocorticoid discontinuation in patients with early rheumatoid and undifferentiated arthritis: a post-hoc analysis of the BeSt and IMPROVED studies. Ann Rheum Dis 2021;80(9):1124–9.
[11] Maarseveen TD, Meinderink T, Reinders MJT, Knitza J, Huizinga TWJ, Kleyer A, et al. Machine learning electronic health record identification of patients with rheumatoid arthritis: algorithm pipeline development and validation study. JMIR Med Inform 2020;8(11):e23930.
[12] Xie W, Huang H, Li G, Hao Y, Gui Y, Wang Y, et al. Dynamical trajectory of glucocorticoids tapering and discontinuation in patients with rheumatoid arthritis commencing glucocorticoids with csDMARDs: a real-world data from 2009 to 2020. Ann Rheum Dis 2021.
[13] Verschueren P, De Cock D, Corluy L, Joos R, Langenaken C, Taelman V, et al. Effectiveness of methotrexate with step-down glucocorticoid remission induction (COBRA Slim) versus other intensive treatment strategies for early rheumatoid arthritis in a treat-to-target approach: 1-year results of CareRA, a randomised pragmatic open-label superiority trial. Ann Rheum Dis 2017;76(3):511–20.
[14] Mueller RB, Reshiti N, Kaegi T, Finckh A, Haile SR, Schulze-Koops H, et al. Does addition of glucocorticoids to the initial therapy influence the later course of the disease in patients with early RA? Results from the Swiss prospective observational registry (SCQM). Clin Rheumatol 2017;36(1):59–66.
[15] Albrecht K, Callhoff J, Schneider M, Zink A. High variability in glucocorticoid starting doses in patients with rheumatoid arthritis: observational data from an early arthritis cohort. Rheumatol Int 2015;35(8):1377–84.
[16] Bergstra SA, Sepriano A, Kerschbaumer A, van der Heijde D, Caporali R, Edwards CJ, et al. Efficacy, duration of use and safety of glucocorticoids: a systematic literature review informing the 2022 update of the EULAR recommendations for the management of rheumatoid arthritis. Ann Rheum Dis 2022.
[17] Moore MN, Wallace BI. Glucocorticoid and opioid use in rheumatoid arthritis management. Curr Opin Rheumatol 2021;33(3):277–83.
[18] Buttgereit F. Views on glucocorticoid therapy in rheumatology: the age of convergence. Nat Rev Rheumatol 2020;16(4):239–46.
[19] Boers M. Three Months of Glucocorticoids in Rheumatoid Arthritis: a Bridge Too Short? Arthritis Rheumatol 2022.
[20] Wallace BI, Lin P, Kamdar N, Noureldin M, Hayward R, Fox DA, et al. Patterns of glucocorticoid prescribing and provider-level variation in a commercially insured incident rheumatoid arthritis population: a retrospective cohort study. Semin. Arthritis Rheum. 2020;50(2):228–36.
[21] George MD, Baker JF, Wallace B, Chen L, Wu Q, Xie F, et al. Variability in Glucocorticoid Prescribing for Rheumatoid Arthritis and the Influence of Provider Preference on Long-Term Use of Glucocorticoids. Arthritis Care Res (Hoboken) 2021;73(11):1597–605.
[22] Smolen JS, Landewé R, Breedveld FC, Dougados M, Emery P, Gaujoux-Viala C, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. Ann Rheum Dis 2010;69(6):964–75.
[23] Putrik P, Ramiro S, Kvien TK, Sokka T, Pavlova M, Uhlig T, et al. Inequities in access to biologic and synthetic DMARDs across 46 European countries. Ann Rheum Dis 2014;73(1):198–206.