RMD Open
Rheumatic & Musculoskeletal Diseases

ORIGINAL RESEARCH

Glucocorticoid trajectories over 2 years in patients with rheumatoid arthritis in a real-life setting

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To cite: Delteil A, Lambert C, Pereira B, *et al*. Glucocorticoid trajectories over 2 years in patients with rheumatoid arthritis in a real-life setting. *RMD Open* 2023;**9**:e003366. doi:10.1136/rmdopen-2023-003366

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/rmdopen-2023-003366).

Received 5 June 2023
Accepted 18 September 2023

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ABSTRACT

Objectives To analyse glucocorticoid (GC) use and trajectories in a real-life cohort of rheumatoid arthritis (RA).

Methods Patients with RA included in the longitudinal RCVRIC cohort for initiating or changing biological disease-modifying antirheumatic drugs, were compared for the use of GCs at baseline. Among the GC users, the GC dose was analysed over 2 years of follow-up by group-based trajectory models. Characteristics and outcomes were compared between the trajectories.

Results Among the 184 patients (RA duration 4.2 years (1.3; 12.6), Disease Activity Scores (DAS)28-C reactive protein (CRP) 4.24±2.14), 81 (44%) were on GCs. The GC users were significantly older, had higher CRP and Health Assessment Questionnaire (HAQ), more hypertension and lower lumbar T-score, but similar activity and erosive scores. Among the GC users, two trajectories were identified: trajectory 1 (n=20, 25%) with GC discontinuation in the first year and trajectory 2 (n=61, 75%) with maintenance of low-dose GCs at 2 years. Trajectory 2 was significantly associated with higher HAQ, a longer GC duration and a less frequent methotrexate association. After adjustment for HAQ, GC duration and MTX use, good EULAR responses were less frequent at 6 months and 1 year in the GC maintenance trajectory (38.3% vs 81.3%, p=0.03; 42.0% vs 82.4%, p=0.02). Diabetes, fractures and increased body mass index were noted in trajectory 2.

Conclusion GCs were used in almost half of patients with established RA in real-world practice. For the majority of GC users, a long-term low dose of GCs is maintained over 2 years. These results highlight the difficulties with stopping GCs, the lack of consensus for the efficacy–safety balance of GCs, and the need to individualise the best GC tapering.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The most recent guidelines specify use of glucocorticoids (GCs) for no more than 3 months as a bridging therapy in the management of patients with rheumatoid arthritis (RA). Use of GCs is not warranted when initiating or changing biological (b) disease-modifying antirheumatic drugs (bDMARDs). However, there are concerns regarding the ability to stop GC use in clinical practice.

⇒ Limited data are available on the use of GC as bridging or maintenance therapy in real-life settings, and, in particular, no data on the trajectory of GC therapy are available in established RA.

WHAT THIS STUDY ADDS

⇒ GCs were used in 44% of patients with established RA initiating or changing bDMARDs. Among the patients treated with GCs, discontinuation of GCs was not possible for the majority of patients with long-term use of low-dose GCs (<5 mg/day) after 2 years of follow-up. In the GC discontinuation trajectory, 80% of patients could stop GCs at 6 months, and all patients could do so at 1 year. In long-term GC trajectory, good EULAR responses at 6 months and 1 year were less frequent, and adverse events (diabetes, fractures and increased body mass index) were reported consistent with treatment-associated harm, but also with the fact that the most severe patients are also those with the most comorbidities, and are most often treated with GCs. This indication bias influences the interpretation of efficacy–safety balance of low-dose GCs during observational studies.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ In established RA and clinical practice, a long-term low dose of GCs is maintained over 2 years in the majority of patients. This discrepancy between the recommendations and clinical practice highlights the need to identify barriers and facilitators and to individualise the tapering strategy.

INTRODUCTION

Since 2010, the EULAR has provided guidelines for the management of rheumatoid arthritis (RA). The use of short-term glucocorticoids (GCs) as a bridging therapy in combination with methotrexate (MTX) is recommended as the first-line treatment strategy because of the delayed action of MTX as well as a structural effect.[1 2] Due to the dose-dependent side effects of GCs on mortality, cardiovascular diseases, infections and osteoporosis, it is recommended that

they are used for a short time only (less than 6 months) and at the lowest cumulative dose possible.[1 2] More recent recommendations specify short-term use as no more than 3 months and a low dose as no more than 7.5 mg/day of prednisone equivalent.[3] Moreover, the use of GCs is not warranted when initiating or changing biological disease-modifying anti-rheumatic drugs (bDMARDs) or targeted synthetic DMARDs. Although GCs have been used for decades in the treatment of RA, few data are available on their use as bridging or maintenance therapies in real life,[4 5] but they suggest that there may be difficulties with stopping GCs after initial bridging treatment in clinical practice. Although a prespecified protocol involving GC tapering was used, data from clinical trials in early RA report 22% of patients were still on GCs at 12 months and 10% at 24 months.[4] In the 10-year analysis of the French ESPOIR cohort, the mean duration of GCs was 45 months and 55% of patients were treated with GCs for more than 2 years.[6] Similarly, data from the German Early Arthritis Cohort (CAPEA) showed that 47% of patients remained on GCs after 2 years.[7] In a recent observational study in MTX-naive patients with RA, the cumulative likelihood of discontinuing GCs was only 30% at 12 months and 54% at 24 months.[8] The trajectory of GC therapy during RA management has been studied little to date in real-life settings. A traditional approach of longitudinal studies is to analyse mean GC dose over time. However, this type of analysis does not take into account the heterogeneity of the data and individual variability, which are furthermore too complex to be analysed by individual trajectories. Group-based trajectory modelling accounts for individual variability around an average population trend.[9] It makes it possible to identify, from individual trajectories, homogeneous groups of patients following approximately the same developmental course on the outcome of interest to distinguish different trajectories. Differences for baseline characteristics or outcomes can then be identified within these distinct trajectories or subgroups of patients.

We hence analysed the use of GCs in combination with conventional synthetic (cs) DMARDs or bDMARDs in a real-life cohort of established RA and identified the different GC trajectories (using the group-based trajectory modelling) and associated factors.

METHODS

Patients

Patients over 18 years of age with active RA who attended the Rheumatology Department of Clermont-Ferrand University Hospital for initiating or changing bDMARDs were invited to participate in the longitudinal observational cohort RCVRIC analysing the evolution of cardiovascular risk with bDMARDs in chronic inflammatory rheumatism (PHRC RCVRIC AOI 2014 N° ID-RCB-A01847-40). The patients fulfilled the 2010 RA classification criteria.[10] Patients starting a first TNF inhibitor (TNFi) or a non-TNF-targeted bDMARD either in first-line or after a first TNFi failure were included from 2014 to 2020 in the longitudinal cohort. All patients had a longitudinal follow-up every 6 months in the first year and then once every year. Only patients with at least two visits, including a baseline visit were analysed. There was no predefined therapeutic intervention strategy concerning GC therapy. The treatment decisions at each visit was made at the discretion of the treating rheumatologists. The study was approved by the local ethics committee of Clermont-Ferrand (Institutional Review Boards: AU 1161) and all the patients provided informed consent for their participation.

Clinical assessments and data collection

The collected data included demographic data (age, sex), clinical features of RA (disease duration, rheumatoid factor (RF) and/or anti-CCP antibodies, the erythrocyte sedimentation rate (ESR), C reactive protein (CRP) levels, radiographic erosions). Disease activity was evaluated by the Disease Activity Scores (DAS)28 ESR/CRP, Simple Disease Activity Index (SDAI) and Clinical Disease Activity Index (CDAI). The remission rate defined as a DAS28 <2.6 and the percentage of good EULAR response according to the EULAR criteria were specified. Functional disability was evaluated with the Health Assessment Questionnaire (HAQ) and the Rheumatoid Arthritis Impact of Disease (RAID) Score. Pain was assessed with the first question of the RAID and fatigue with the third question. Comorbidities including diabetes, hypertension, obesity and smoking (past or current), as well as the use of cholesterol-lowering, antihypertensive and/or antidiabetic drugs were recorded. The cardiovascular risk was estimated with the systematic coronary risk estimation (SCORE) equation. Anxiety and depression were evaluated with the Hospital Anxiety and Depression (HAD) Scale. Bone mineral density (BMD) was measured with dual-energy X-ray absorptiometry (DXA) at the lumbar spine and hip. The fracture risk was estimated using the Fracture Risk Assessment Tool (FRAX).

For the treatments, GC use (current or initiated within 2 months of inclusion), duration before inclusion, dose at inclusion, percentage of patients with a GC dose greater than 7.5 mg/day, non-steroidal anti-inflammatory drugs (NSAIDs) use (current or initiated within 2 months of inclusion), csDMARDs use (current or initiated within 3 months of inclusion), bDMARDs use (current or initiated within 3 months of inclusion) and the line of therapy, antiosteoporotic treatment (current or initiated within 3 months of inclusion) were collected.

Statistical analysis

Sample size estimation was determined according to Cohen's recommendations who has defined effect size (ES) bounds as small (ES=0.2), medium (ES=0.5) and large (ES=0.8).[11] So, with 54 patients evaluated at baseline and 6 months, an ES greater than 0.5 can be highlighted for GC dose change, with a two-sided alpha level of 5%,

a statistical power of 95% and an intraindividual correlation coefficient equals 0.5.[12] Considering the inclusion of 80 patients in order to take into account the lost to follow-up and incomplete data, a between-group (trajectories) dose change difference higher than 0.8 effect-size can be highlighted with a statistical power greater than 90% and at least 0.65 effect-size for a statistical power greater than 80%.

Statistical analyses were performed using Stata software (V.15; StataCorp, College Station, Texas, USA). All tests were two-sided, with an alpha level set at 5%. Categorical data are presented as the number of patients and associated percentages, and continuous data as mean±SD or median (25th; 75th percentiles), depending on the statistical distribution. The rate of GC use is presented with a 95% CI estimated by a binomial distribution. Baseline comparisons between patients treated or not with GCs at baseline or within the next 2 months were made by the χ^2 test or the Fisher's exact test for categorical variables, and by the Student's t test or the Mann-Whitney test for continuous variables.

To analyse longitudinal data (GC dose over 2 years), linear mixed models for repeated data were used, with time as a fixed effect and patient as a random effect, to account for between-patient and within-patient variability. ES and 95% CI were calculated between baseline and 6 months, and interpreted according to Cohen's recommendations aforementioned.

To identify subgroups of patients sharing distinct trajectory of GC dose over 2 years, group-based trajectory models were used. The patients were assigned to the trajectory group to which they most likely belonged based on the evolution of their GC dose. Several models were tested with different numbers of trajectories and shapes (linear, quadratic and cubic). The selected model was the one with the smallest Bayesian and Akaike information criteria accompanied by higher average posterior probability (≥0.7) and odds of correct classification.[13]

The baseline characteristics of the patients were then compared according to the trajectories, as described previously, as well as the changes in disease activity, comorbidities, treatment response and retention over 2 years. Usual statistical tests were used, given the absence of a physician effect (tested with linear mixed models). Adjusted analyses were also performed for the remission (DAS28 <2.6) and EULAR response using logistic regressions, with covariates determined according to univariate results and clinical relevance. Due to the small sample size, the number of covariates included in the models was limited. In order to guaranty the robustness of our results, two distinct adjustments were performed: one with age, sex and disease duration, and another with HAQ, duration of prior steroids and baseline MTX therapy. In addition, we tested the adjustment for each of the parameters separately. Furthermore, longitudinal analysis of DXA BMD according to GC trajectories were made with linear mixed models with the patient as random effect and the interaction 'time × trajectory' as fixed effect.

Finally, censored data (bDMARD and MTX retention) were estimated using the Kaplan-Meier method. The comparisons between trajectories were realised using log-rank test. The causes of discontinuation of treatment were not specified.

RESULTS

Baseline characteristics of the patients according to the GC treatment

A flow chart of the enrolment is shown in figure 1. Of the 209 patients with RA included in the cohort, data from 184 patients were available for at least two visits including the baseline visit. The baseline characteristics of the 184 patients are presented in table 1. The mean age of the patients was 58±11 years, with a median disease duration of 4.2 years (1.3; 12.6). Most patients were female (74.5%). The presence of RF and anti-CCP antibodies

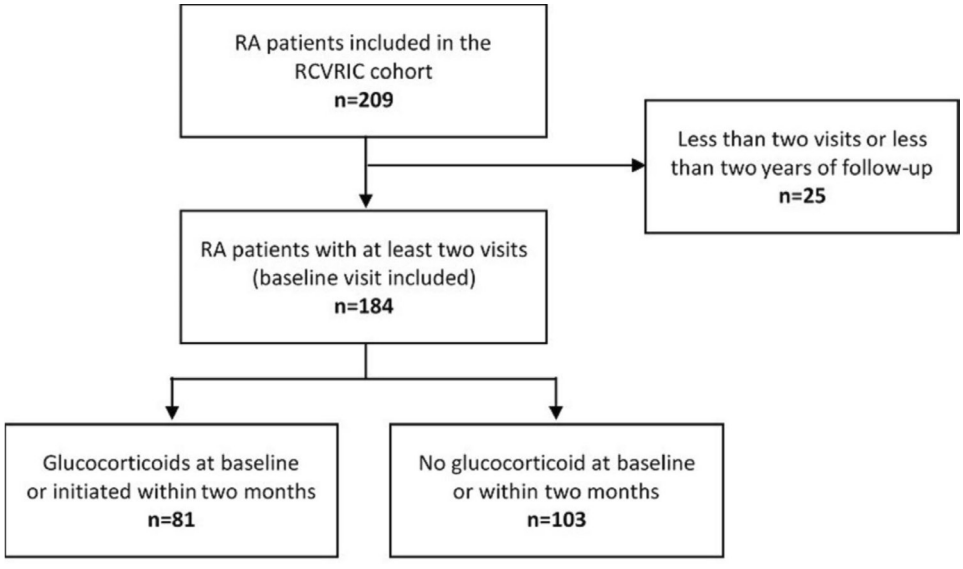

Figure 1 Flow chart of the study. RA, rheumatoid arthritis.

Table 1 Baseline characteristics of the patients according to GC treatment and GC trajectories

	No GCs (n=103)	GCs (n=81)	P	Trajectory 1 (n=20)	Trajectory 2 (n=61)	P
Age (years)	55.7±11.1	60.9±10.1	0.001	62.2±11.1	60.5±9.9	0.56
Female gender	77 (74.8)	60 (74.1)	0.92	17 (85.0)	43 (70.5)	0.20
Duration of disease (years)	4.8 (1.3; 14.7)	3.7 (1.0; 11.3)	0.50	1.9 (0.5; 8.4)	3.8 (1.3; 12.6)	0.10
Rheumatoid factor	86 (83.5)	69 (85.2)	0.76	15 (75.0)	54 (88.5)	0.16
Anti-CCP	85 (82.5)	69 (85.2)	0.63	15 (75.0)	54 (88.5)	0.16
Radiographic erosions	53/97 (54.6)	35/77 (45.5)	0.23	9/20 (45.0)	26/57 (45.6)	0.96
Past or current smoking	56/101 (55.4)	44 (54.3)	0.88	10 (50.0)	34 (55.7)	0.66
Body mass index (kg/m^2)	25.9±5.7	26.4±5.0	0.53	26.3±4.9	26.5±5.1	0.91
<25 25 to 30 ≥30	53 (51.5) 33 (32.0) 17 (16.5)	35 (43.2) 32 (39.5) 14 (17.3)	0.50	10 (50.0) 5 (25.0) 5 (25.0)	25 (41.0) 27 (44.3) 9 (14.7)	0.29
CRP (mg/L) (*n=101/79/19/60*)	6 (3; 15)	12 (3; 26)	0.03	12 (3; 23)	12 (3; 30)	0.58
ESR (mm) (*n=100/77/19/58*)	16 (8; 27)	17 (9; 28)	0.53	24 (9; 43)	15 (8; 28)	0.08
DAS28-VS (*n=100/75/18/57*)	4.17±1.16	4.33±1.26	0.42	4.64±1.23	4.23±1.26	0.20
DAS28-CRP (*n=99/77/19/58*)	4.25±2.66	4.22±1.21	0.40	4.21±1.01	4.23±1.27	0.87
CDAI (*n=95/75/18/57*)	19 (13; 24)	19 (13; 28)	0.14	23 (16; 27)	19 (13; 28)	0.68
SDAI (*n=94/75/18/57*)	20 (13; 26)	22 (14; 31)	0.09	24 (16; 28)	22 (13; 35)	0.91
HAQ (*n=69/59/14/45*)	0.75 (0.50; 1.25)	1.00 (0.75; 1.50)	0.008	0.75 (0.50; 1.00)	1.25 (0.75; 1.63)	0.01
RAID (*n=68/55/13/42*)	5.8 (4.4; 6.3)	5.9 (5.1; 6.8)	0.18	5.6 (4.0; 6.7)	5.9 (5.3; 6.9)	0.26
Pain (RAID1) (*n=68/54/13/41*)	6.0 (4.5; 7.0)	6.5 (5.0; 8.0)	0.17	6.0 (4.0; 7.0)	7.0 (5.0; 8.0)	0.15
Function (RAID2) (n=68/55/13/42)	6.0 (4.0; 7.0)	6.0 (5.0; 7.0)	0.07	6.0 (4.0; 7.0)	6.0 (5.0; 8.0)	0.16
Fatigue (RAID3) (*n=68/56/14/42*)	6.0 (4.0; 8.0)	6.0 (5.0; 8.0)	0.70	6.0 (4.0; 8.0)	6.0 (5.0; 8.0)	0.22
csDMARD	98 (95.1)	74 (91.4)	0.30	20 (100)	54 (88.5)	0.18
First line of csDMARD	79/98 (80.6)	64/74 (86.5)	0.31	19/20 (95.0)	45/54 (83.3)	0.27
Methotrexate	82 (79.6)	63 (77.8)	0.76	19 (95.0)	44 (72.1)	0.03
bDMARD	75 (72.8)	66 (81.5)	0.17	14 (70.0)	52 (85.2)	0.18
First line of bDMARD	67/75 (89.3)	59/66 (89.4)	0.99	14/14 (100)	45/52 (86.5)	0.33
NSAIDs	39 (37.9)	10 (12.3)	<0.001	2 (10.0)	8 (13.1)	1.00
Antiosteoporotic treatment*	1 (1.0)	17 (21.0)	<0.001	5 (25.0)	12 (19.7)	0.75
GC duration (months)	–	22 (5; 68)	–	8 (0; 24)	33 (7; 99)	0.008
GC dose (mg/day)	–	7 (5; 10)	–	8 (5; 10)	7 (5; 10)	0.65
GC dose >7.5 mg/day	–	30 (37.0)	–	11 (55.0)	19 (31.1)	0.06

Continued

Table 1 Continued

	No GCs (n=103)	GCs (n=81)	P	Trajectory 1 (n=20)	Trajectory 2 (n=61)	P
GC cumulative dose (mg)	–	3780 (492; 15165)		1190 (0; 3755)	5580 (1630; 18385)	0.005
HAD anxiety (*n=64/53/11/42*)	10 (8; 12)	10 (5; 12)	0.52	5 (2; 12)	10 (6; 12)	0.07
HAD depression (*n=66/52/12/40*)	7 (4; 9)	7 (6; 11)	0.14	7 (5; 10)	7 (6; 11)	0.27
Diabetes	3 (2.9)	4 (4.9)	0.70	1 (5.0)	3 (4.9)	1.00
Hypertension	26 (25.2)	35 (43.2)	0.01	9 (45.0)	26 (42.6)	0.85
SCORE (*n=81/71/16/55*)	1.0 (0.0; 1.5)	1.0 (0.0; 2.0)	0.01	1.5 (0.5; 2.5)	1.0 (0.0; 2.0)	0.97
DXA lumbar T-score (*n=84/66/17/49*)	0.5 (–1.8; 0.5)	1.2 (–2.3; 0.1)	0.04	1.6 (–2.3; 0.5)	1.1 (–2.3; 0.0)	0.83
DXA femoral T-score (*n=82/66/17/49*)	0.7 (–1.4; 0.3)	0.9 (–1.5; –0.3)	0.16	1.4 (–1.9; 0.3)	0.8 (–1.4; –0.3)	0.26
DXA femoral neck T-score (*n=80/63/17/46*)	1.2 (–1.7; –0.4)	1.3 (–2.2; –0.3)	0.33	1.6 (–2.2; –0.1)	1.3 (–2.1; –0.3)	0.85
FRAX (*n=70/58/13/45*)	5 (4; 8)	8 (5; 13)	<0.001	12 (9; 15)	8 (5; 11)	0.06

Data are presented as number of patients (percentages), mean±SD or median (25th; 75th percentiles). When there are missing data, the numbers in each group are indicated in parentheses in the first column of the table in the following order: no GCs/GCs/trajectory 1/trajectory 2.
*Bisphosphonates, denosumab, teriparatide.
bDMARDs, biological disease-modifying antirheumatic drugs; CCP, Cyclic Citrullinated Peptide; CDAI, Clinical Disease Activity Index; CRP, C reactive protein; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; DAS, Disease Activity Scores; DXA, dual-energy X-ray absorptiometry; ESR, erythrocyte sedimentation rate; FRAX, Fracture Risk Assessment Tool; GCs, glucocorticoids; HAQ, Health Assessment Questionnaire; NSAIDs, non-steroidal anti-inflammatory drugs; RAID, Rheumatoid Arthritis Impact of Disease; SCORE, systematic coronary risk estimation; SDAI, Simple Disease Activity Index.

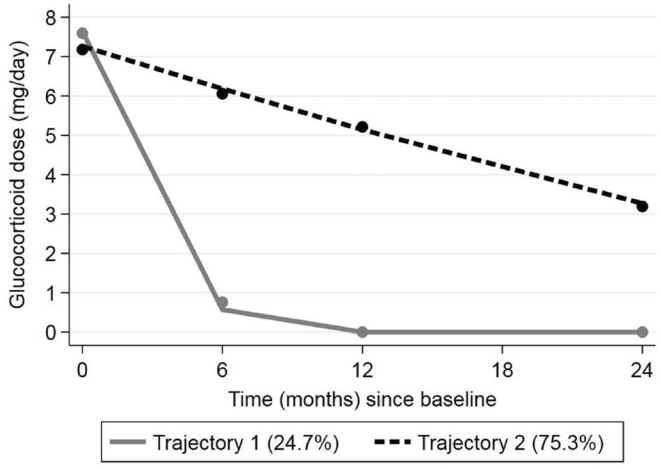

Figure 2 Trajectories of glucocorticoid dose in patients with rheumatoid arthritis.

was reported in 84.2% and 83.7%, respectively, and radiographic erosions in 50.6%. Treatment with csDMARDs was provided to 93.5% of patients, with MTX being the most frequently prescribed (78.8%). bDMARDs were prescribed in 76.6% of patients and were used as first-line therapy in 89.4% of patients.

GC use was reported in 81 patients (44.0%, 95% CI: 36.7% to 51.5%) at inclusion (table 1). GCs were used for a median of 22 months (5; 68), with a median dosage of 7 mg/day (5; 10) and a dose greater than 7.5 mg/day in 30/81 patients (37.0%). No differences in DMARD use were noted between patients with or without GCs. More frequent use of NSAIDs was observed in GC-naive patients (37.9% vs 12.3%, p<0.001).

Compared with the patients without GCs, the GC-treated patients were older (61±10 vs 56±11 years, p=0.001), had higher CRP levels (12 mg/L (3; 26) vs 6 (3; 15) p=0.03) and disability (HAQ 1.00 (0.75; 1.50) vs 0.75 (0.50; 1.25), p=0.008). However, the Disease Activity Scores (DAS28-VS, DAS28-CRP, CDAI and SDAI) and the radiographic erosions were not different. There were no significant differences in the total score, pain, fatigue or function with the RAID Questionnaire. Hypertension was more frequent in the GC group (43.2% vs 25.2%, p=0.01). No difference in smoking, diabetes or body mass index (BMI) were noted. A higher 10-year FRAX, lower lumbar T-score and more frequent use of antiosteoporotic treatments were observed in the GC group.

GC trajectories

The GC dose decreased from 7.3±3.5 mg/day at baseline (n=81) to 4.8±4.2 at 6 months (n=81), 3.9±4.4 at 1 year (n=76) and 2.4±3.3 at 2 years. The ES of the main endpoint (6 months vs baseline) was −0.60 (95%CI: −0.81 to −0.37, p<0.001).

Two distinctive trajectories of GC doses during the 2 years of follow-up were identified (figure 2). Trajectory 1 (n=20, 24.7%, 'GC discontinuation') was characterised by a significant reduction in GC dosages at 6 months from 7.5±4.0 to 0.7±1.4 mg/day (ES: −2.24, 95% CI: −2.68 to −1.81), with discontinuation in the first year for all patients that was maintained at 2 years. Trajectory 2 (n=61, 75.3%, 'Maintenance GCs') was characterised by a more progressive tapering in GCs, from 7.2±3.4 to 6.1±3.9 mg/day at 6 months (ES: −0.27, 95% CI: −0.52 to −0.01), and by maintaining a low dose of GCs (3.2±3.4 mg/day) at 2 years. There was a significant interaction between GC dose trajectories and time, especially between baseline and 6 months (ES: 0.65, 95% CI: 0.43 to 0.87).

Discontinuation of GCs within 6 months as recommended by the EULAR guidelines was observed for 16 patients in trajectory 1 and for only 1 patient in trajectory 2 (80.0% vs 1.6%, p<0.001). A majority of trajectory 1 patients (65.0%) were included after the date of publication of the EULAR guidelines (June 2017) compared with 29.5% of the patients from trajectory 2 (p=0.005).

Over the inclusion and follow-up period, 11 physicians were involved in patient follow-up with 1–35 patients per physician. Among physicians with the most patients (at least 8), the rate of patients belonging to trajectory 2 was quite similar (4/8=50%, 6/8=75%, 28/35=80% and 13/16=81%). We did not find any significant difference according to the gender of the physician (55% of patients in trajectory 1 were followed by a male physician compared with 72% in trajectory 2, p=0.15), or to the physician age (mean age: 49±12 years in trajectory 1 vs 52±11 years in trajectory 2, p=0.56).

Baseline characteristics of the patients according to the GCs trajectories

There were no differences in gender, age, BMI or smoking status between the two trajectories (table 1). The median disease duration was shorter in trajectory 1 than in trajectory 2 (1.9 years (0.5; 8.4) vs 3.8 years (1.3; 12.6), p=0.10). The Disease Activity Scores, CRP levels and radiographic erosions were not different. More severe disability (HAQ) was noted in trajectory 2 (1.25 (0.75; 1.63) vs 0.75 (0.50; 1.00), p=0.01).

The GC dose at baseline was not different between the two trajectories although 55.0% of patients from trajectory 1 used more than 7.5 mg/day compared with 31.1% in trajectory 2 (p=0.06). The duration of GC use was longer in trajectory 2 (33 months (7; 99) vs 8 (0; 24), p=0.008). The use of MTX was more frequent in trajectory 1 (95.0% vs 72.1%, p=0.03), whereas no differences were observed for bDMARDs and antiosteoporotic treatments. For patients treated with GCs and MTX at inclusion, the median dose of MTX was not different between the two trajectories (15 mg/week (15; 20) in both trajectories, p=0.42). The proportion of patients on first-line biological therapy was not different in trajectory 1 and trajectory 2 (100% and 86.5%, respectively, p=0.33).

Concerning comorbidities, no associations between GC trajectories and the presence of diabetes, hypertension or cardiovascular risk score were noted.

Table 2 Outcomes associated with the glucocorticoid trajectories

	Total		Trajectory 1		Trajectory 2				
	n	n (%) or median (IQR)	n	n (%) or median (IQR)	n	n (%) or median (IQR)	P[1]	P[2]	P[3]
DAS28-ESR <2.6									
At M6	66	23 (34.8)	18	9 (50.0)	48	14 (29.2)	0.11	0.15	0.49
At M12	72	36 (50.0)	18	13 (72.2)	54	23 (42.6)	0.03	0.02	0.07
At M24	54	27 (50.0)	14	9 (64.3)	40	18 (45.0)	0.21	0.43	0.76
At M6 and M12	60	16 (26.7)	17	7 (41.2)	43	9 (20.9)	0.19	0.15	0.65
At M6, M12 and M24	46	9 (19.6)	14	5 (35.7)	32	4 (12.5)	0.11	0.16	0.57
DAS28-CRP <2.6									
At M6	67	26 (38.8)	17	11 (64.7)	50	15 (30.0)	0.01	0.02	0.16
At M12	70	41 (58.6)	18	15 (83.3)	52	26 (50.0)	0.01	0.01	0.38
At M24	56	28 (50.0)	14	11 (78.6)	42	17 (40.5)	0.01	0.07	0.23
At M6 and M12	59	21 (35.6)	16	10 (62.5)	43	11 (25.6)	0.008	0.01	0.24
At M6, M12 and M24	46	10 (21.7)	12	7 (58.3)	34	3 (8.8)	0.001	0.007	–
Good EULAR response									
At M6	63	31 (49.2)	16	13 (81.3)	47	18 (38.3)	0.003	0.006	0.03
At M12	67	35 (52.2)	17	14 (82.4)	50	21 (42.0)	0.004	0.004	0.02
At M24	54	28 (51.9)	13	9 (69.2)	41	19 (46.3)	0.15	0.3	0.53
Occurrence of erosion*	32	6 (18.8)	10	1 (10.0)	22	5 (22.7)	0.64		
HAQ ≤0.5									
At M6	53	22 (41.5)	13	6 (46.2)	40	16 (40.0)	0.7		
At M12	51	24 (47.1)	10	5 (50.0)	41	19 (46.3)	1		
At M24	32	18 (56.3)	5	4 (80.0)	27	14 (51.9)	0.36		
Change in RAID									
Between baseline and M6	40	1.6 (–3.5; –0.2)	9	2.2 (–3.4; –0.4)	31	1.4 (–3.5; –0.2)	0.72		
Between baseline and M12	39	1.8 (–2.8; –0.8)	8	1.7 (–2.6; –1.0)	31	1.8 (–2.8; –0.8)	0.93		
Between baseline and M24	23	1.6 (–2.7; 0.0)	3	2.2 (–2.3; 0.0)	20	1.3 (–2.7; 0.0)	0.93		
Change in fatigue (RAID3)									
Between baseline and M6	41	0 (–1; 1)	10	1 (–2; 0)	31	0 (–1; 2)	0.35		
Between baseline and M12	39	1 (–2; 0)	9	4 (–4; –2)	30	1 (–2; 0)	0.046		
Between baseline and M24	24	0 (–2; 0.5)	4	1 (–2; 0.5)	20	0 (–2; 0.5)	0.81		
Change in anxiety (HAD)									
Between baseline and M6	35	1 (–3; 0)	6	1 (–3; –1)	29	1 (–2; 0)	0.51		
Between baseline and M12	36	1 (–3; 0)	7	1 (–1; 0)	29	2 (–3; 0)	0.5		
Between baseline and M24	21	1 (–3; 0)	3	0 (0; 3)	18	2 (–4; 0)	0.04		
Change in BMI (%)									
Between baseline and M6	73	0.0 (–2.0; 1.3)	20	0.0 (–4.0; 0.0)	53	0.0 (–1.3; 1.8)	0.08		
Between baseline and M12	75	0.7 (–2.6; 4.2)	19	2.0 (–4.5; 1.4)	56	1.5 (0.0; 4.7)	0.02		
Between baseline and M24	60	0.0 (–4.0; 3.8)	14	3.0 (–6.7; 1.2)	46	1.1 (–3.3; 4.2)	0.053		
Occurrence of diabetes*	77	2 (2.6)	19	0 (0.0)	58	2 (3.5)	1		
Occurrence of a fracture*	67	5 (7.5)	18	0 (0.0)	49	5 (10.2)	0.31		
Occurrence of severe infection*	79	9 (11.4)	20	3 (15.0)	59	6 (10.2)	0.69		

Data are presented as number of patients (percentages) or median (25th; 75th percentiles). P[1]: non-adjusted analyses; P[2]: analyses adjusted for age, sex and disease duration; P[3]: analyses adjusted for HAQ, duration of prior steroids and baseline methotrexate therapy.
*Between baseline and month 24.
BMI, body mass index; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; HAD, Hospital Anxiety and Depression; HAQ, Health Assessment Questionnaire; M6, 6 months; M12, 12 months; M24, 24 months; RAID, Rheumatoid Arthritis Impact of Disease.

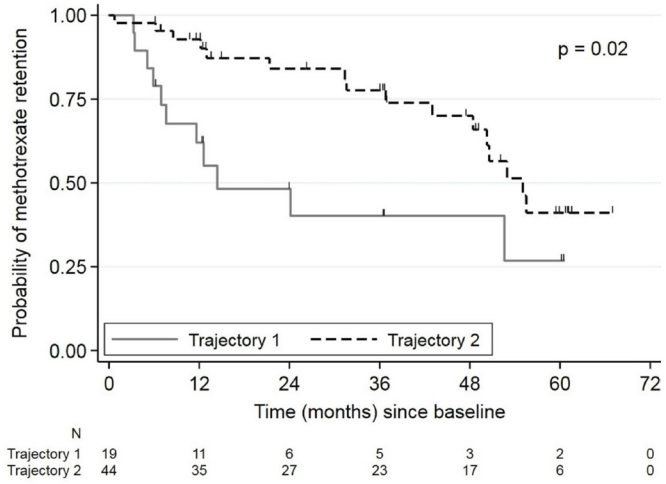

Figure 3 Retention of methotrexate treatment in patients using glucocorticoids (n=63).

Outcomes associated with trajectories

Non-adjusted and adjusted analyses are presented in table 2 and in online supplemental table 1 for each parameters separately. DAS28-CRP remission was more frequent in trajectory 1 'GC discontinuation' than trajectory 2 at six months (64.7% vs 30.0%, p=0.01), 1 year (83.3% vs 50.0%, p=0.01) and 2 years (78.6% vs 40.5%, p=0.01). Sustained remission, defined by a DAS28 <2.6 on at least two successive visits, was also more frequent in trajectory 1 than in trajectory 2 at 1 year (62.5% vs 25.6%, p=0.008) and 2 years (58.3% vs 8.8%, p=0.001). In adjusted analyses the difference between the two trajectories for remission was independent of age, sex, disease duration and time of inclusion but not of HAQ and to a lesser extent of baseline MTX therapy (online supplemental table 1). Similarly, a good EULAR response was more frequent at 6 months and 1 year in trajectory 1 (81.3% and 82.4%, respectively) compared with trajectory 2 (38.3% and 42.0%, respectively, p=0.003 and p=0.004). This difference persisted after adjustment for HAQ, prior GC duration, and MTX treatment at baseline. There were no differences in the occurrence of radiographic erosion, HAQ or RAID variation between the two trajectories.

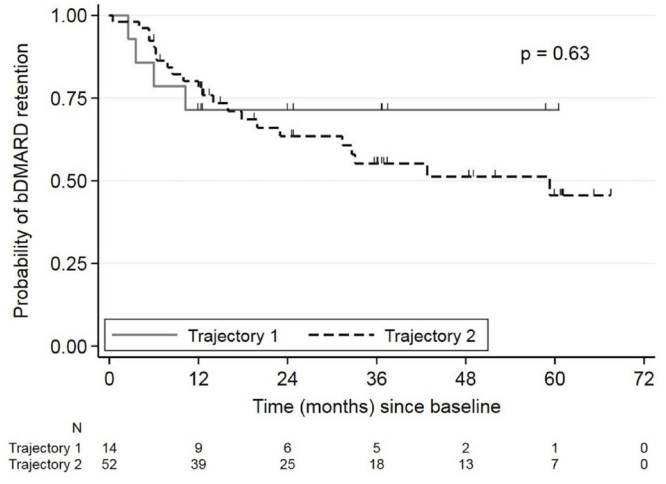

Figure 4 Retention of bDMARDs in patients using glucocorticoids (n=66). bDMARDs, biological disease-modifying antirheumatic drugs.

Although the occurrence of adverse events under GCs may be confounded by the indication and the disease activity, the occurrence of two cases of diabetes and five fractures, as well as a significant increase in the BMI at 1 year were observed in trajectory 2. The fractures occurred at spine (n=2), ribs (n=1), pelvis (n=1) and ankle (n=1). Change in BMD was analysed during the follow-up (online supplemental table 1). A significant decrease in trajectory 2 compared with trajectory 1 was noted for femoral neck BMD at 1 and 2 years. No change was noted for hypertension, cardiovascular risk (SCORE) or FRAX (data not shown). Combining the 'occurrence of diabetes', 'occurrence of fracture', 'occurrence of a severe infection' and 'increase in BMI class', 3/18 (16.7%) patients in trajectory 1 had at least one adverse events compared with 20/60 (33.3%) in trajectory 2 (p=0.17 and p=0.10 after adjustment for the baseline DAS28-CRP).

Trajectory 2 was associated with higher retention of MTX (HR: 2.55, 95% CI: 1.17 to 5.55, p=0.02), while no difference was observed for bDMARDs (figures 3 and 4).

DISCUSSION

In this real-life setting cohort of established patients with RA initiating or changing bDMARD, GCs were used in 44% of patients despite more comorbidities (age, hypertension and higher fracture risk), similar disease activity scores and lack of recommendations for this situation. Among GC users, two GC trajectories were identified. A first trajectory (25% of GC-use patients) was characterised by a rapid decrease in GC dose which could subsequently be stopped for 16 patients (80% of patients in trajectory 1) at 6 months, and for all patients at 1 year of follow-up. Second GC trajectory which concerned the majority of GC-users (75%) was characterised by a long-term use of low-dose GCs (<5 mg/day), confirming the difficulties with stopping GCs reported in early arthritis after bridging therapy.[6–8 14] Trajectory 2 was characterised by a lower initial dosage (<7.5 mg/day) but for a longer time. The majority of the patients from the GC discontinuation trajectory were included after the 2017 EULAR guidelines unlike for the GC maintenance trajectory suggesting that the publication of the EULAR guidelines may have changed the prescribing patterns of corticosteroid. In our cohort of established RA, no difference in Disease Activity Scores or structural damage were observed at inclusion for the GC users despite a long history of GC use and more disability. MTX was prescribed more in the GC discontinuation trajectory which may have contributed to GC tapering. After 24 months of follow-up, the remission rate, EULAR response and the quality of life were not better in long-term GC use than in the tapering GC trajectory. No difference in bDMARD retention was

noted. The MTX retention rate was lower in the GC discontinuation trajectory, possibly due to better disease control and sustained remission with bDMARDs leading to csDMARD tapering. Our study does not allow us to conclude that there is no benefit from GCs nor to determine whether the occurrence of comorbidities is linked to the consequences of the disease itself or to GCs. The continuation of GCs during RA can be explained by beneficial effects on disease activity, responsible for an alteration in the quality of life, disability and the occurrence of comorbidities. Higher disability (HAQ) associated with GCs use and maintenance trajectory might explain GC prescription in our study. Several data from the literature show a dissociation between improvement in disease activity, decreased structural progression and the absence of improvement in functional disability despite more active treatment.[15] Furthermore, the strong collinearity between Disease Activity Scores and HAQ makes it difficult to differentiate between these two parameters. Recent randomised trials suggest that long-term low-dose GCs could be safe and better for controlling the disease.[16 17] In the SEMIRA trial, patients with established RA treated with tocilizumab and prednisone at 5–15 mg/day for at least 6 months were randomised to continue prednisone at 5 mg/day or to taper prednisone reaching 0 mg/day at week 16.[16] More patients maintained low disease activity and had no flare ups by week 24 in the continued-prednisone regimen (77%) than in the tapered-prednisone regimen (65%). In patients with established RA and aged 65 or above, adding prednisolone at 5 mg/day to standard care for 2 years was associated with a better response in terms of disease activity and less damage progression at 2 years.[17] Adverse effects, mostly mild to moderate infections and bone loss, were more frequent in GC users over the 2 years of follow-up.[17] In our study, numerical increases in BMI, fractures and diabetes were observed in the maintenance GC trajectory consistent with treatment-associated harm, but also with the fact that patients with the more active and severe RA and with more comorbidities are more often treated with GCs. Besides this bias by indication, GC use toxicity is now well established, increasing with the dose and/or time of exposure. A meta-analysis of controlled studies reported an increase of 47% for all cardiovascular events with corticosteroids in RA.[18] GC use in RA is associated with a dose-dependent increase in mortality rates, with a daily threshold dose of 8 mg.[19] Data from observational studies have also reported an increased risk of serious infections with GCs even at low dose.[20 21] However, while the risk of cardiovascular events, serious infections, diabetes and osteoporotic fractures is increased for patients treated with GCs in the majority of studies, the safe daily dose and duration are still debated.[5] Maintenance therapy with low-dose GCs has also been reported in early arthritis cohorts showing that approximately half of the patients were still on GCs after 2 years of follow-up.[6 7 14] In patients who started GCs and concomitant csDMARD, the calculated median time to GC stop was 27 months.[22] The current use of GCs in the management of RA therefore remains heterogeneous and controversial whether in early or established RA.

The present study has several strengths. First, it provides evidence regarding GC use in patients with established RA initiating bDMARDs in a real-world setting. The second strength of the study is the longitudinal evaluation of GC use over 2 years through a trajectory methodology. This methodology has allowed us to define distinct trajectories of GC tapering ranging from GC discontinuation to very low doses, and the corresponding disease activity, comorbidities and outcomes. We acknowledge several limitations of this study. First, the findings of a single-centre cohort may limit the external generalisability. Other limitations include the relatively small sample size and the lack of power to detect small, but possibly nonetheless relevant differences. The missing data at the end of the study and the 2-year follow-up period may not be sufficient to identify all the predictive factors and adverse events associated with each GC prescription trajectory. Finally, confounding by indication can be a major limitation that can influence the interpretation of efficacy–safety balance of low-dose GCs in observational studies. Nevertheless, no study identifying different trajectories of GC use in patients with established RA has been published to date.

CONCLUSION

In patients with established RA, GCs were used in almost half of patients. For the majority of patients, a long-term low dose of GCs will be maintained over 2 years. In real-world practice, these results highlight the difficulties with stopping GCs despite clear EULAR recommendations, the lack of consensus for the efficacy–safety balance of GCs, and the need to individualise the best GC tapering with the identification of barriers and facilitators.

Acknowledgements The authors thank the patients who participated in this study, the clinical research associates (Cathy Chen Wa, Angélique Fan) and research nurses (Françoise Fayet, Mallory Rodere) associated with the study.

Contributors BP, CL, MS and AT contributed to this study by substantially participating in the study conception and design. All the coauthors of this manuscript participated at the elaboration of the protocol and the CRF. AD, MC, SM, SM-G, MEP, MV, MS and AT contributed to investigation and data collection. AD, CL, BP and AT contributed to the study by analysing data, drafting the article and revising it critically for important intellectual content, by giving a final approval of the version of the article to be published. All the coauthors of this manuscript have revised the manuscript critically and agree with its content. AT acts as guarantor.

Funding This study has been conducted thanks to a grant from the French Minister of health (PHRC AOI-RCVRIC).

Competing interests None declared.

Patient consent for publication Consent obtained directly from patient(s)

Ethics approval This study involves human participants and was approved by Institutional Review Boards: AU 1161.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

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