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# **Comparison of two strategies of glucocorticoid withdrawal in patients with rheumatoid arthritis in low disease activity (STAR): a randomised, placebo-controlled, double-blind trial**

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**Keywords:**

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# Abstract

## Objectives:

To compare two strategies—a hydrocortisone replacement strategy and a prednisone tapering strategy—for their success in glucocorticoid discontinuation in patients with rheumatoid arthritis (RA) with low disease activity (LDA).

## Methods:

The Strategies for glucocorticoid Tapering in Rheumatoid arthritis (STAR) study was a double-blind, double-placebo randomised controlled trial including patients with RA receiving a stable dose of glucocorticoid 5 mg/day for  $\geq 3$  months and were in LDA for  $\geq 3$  months. Patients were randomly assigned in a 1:1 ratio to either replace prednisone with 20 mg/day of hydrocortisone for 3 months, then reduce to 10 mg/day for 3 months before discontinuation or to taper prednisone by 1 mg/day every month until complete discontinuation, contingent on maintaining LDA. The primary outcome was the percentage of patients achieving glucocorticoid discontinuation at 12 months. Other secondary outcomes were proportion of flares, need for additional glucocorticoid use, disease activity, patient-reported outcomes and the results of adrenocorticotrophic hormone (ACTH) stimulation tests.

## Results:

Of the 102 patients randomised in the trial (mean age 62.4 years, 70.6% females), 53 had hydrocortisone replacement and 49 tapered prednisone. At 12 months, 29 patients (55%) in the hydrocortisone replacement group and 23 patients (47%) in the prednisone tapering group achieved glucocorticoid discontinuation ( $p=0.4$ ). No difference was observed between groups in the secondary outcomes. No cases of acute adrenal insufficiency were observed; however, 17 patients still had an abnormal ACTH stimulation test at 12 months, with no differences between arms.

## Conclusion:

A hydrocortisone replacement strategy was not superior to a prednisone tapering strategy for achieving glucocorticoid discontinuation success in patients with RA in LDA.

## Trial registration number:

NCT02997605.

Glucocorticoids are commonly prescribed for rheumatoid arthritis (RA), alongside disease-modifying antirheumatic drugs (DMARDs), as a bridging therapy to control pain and symptoms.<sup>1</sup> However, 70 years of data have shown the long-term effects of glucocorticoid exposure,<sup>2</sup> and nowadays experts recommend tapering and discontinuing glucocorticoids as rapidly as clinically feasible.<sup>1</sup> However, real-life studies have demonstrated that long-term glucocorticoid therapy is used in about half of patients with RA,<sup>3</sup> indicating that complete cessation is still a challenge for many of them.

Beside the risk of flare when discontinuing glucocorticoids, long-term glucocorticoid-treated patients can have complete hypothalamic-pituitary- adrenal axis suppression, characterised by functional adrenal gland atrophy and, uncommonly, a risk of adrenal insufficiency.<sup>4</sup> Furthermore, after a glucocorticoid dose reduction, patients often describe depression, fatigue weakness, nausea and arthralgias related to glucocorticoid withdrawal symptoms.<sup>5</sup>

To date, there is no consensus about the best approach for glucocorticoid tapering after long-term exposure. Two tapering strategies are usually proposed when the glucocorticoid dose reaches 5 mg/day of prednisone.<sup>6</sup> Some experts propose to systematically replace a low dose of 5 mg/day of prednisone or prednisolone by 15–25 mg/day of hydrocortisone (the hydrocortisone replacement strategy).<sup>7–9</sup> After a delay of 6–12 weeks, an adrenocorticotropic hormone (ACTH) stimulation test is performed. If the test is normal, hydrocortisone can be interrupted. If the test is abnormal, hydrocortisone is prolonged for 3–6 months and another ACTH stimulation test is then prescribed, with the cycle repeated until normal response.<sup>4 7–9</sup> The second commonly used strategy is to slowly taper glucocorticoids by decreasing the daily dose by 1 mg/day every month until complete discontinuation.<sup>7 10</sup> Experts do not always recommend the use of an ACTH stimulation test in this scenario as, unlike in Addison's disease, it might not reflect the risk of acute adrenal insufficiency.<sup>11</sup> This late strategy is widely used in routine. These two schemes have never been compared. We hypothesised that a hydrocortisone replacement strategy might increase the success rate of glucocorticoid discontinuation by decreasing glucocorticoid withdrawal syndrome effects and by limiting the risk of adrenal insufficiency.

The aim of this study was to compare the success rates of glucocorticoid discontinuation between a hydrocortisone replacement strategy and a glucocorticoid tapering strategy at 1 year in patients with RA with low disease activity (LDA) treated with 5 mg/day of glucocorticoids on top of DMARDs.

## METHODS

### Study design and participants

The Strategies for glucocorticoid Tapering in Rheumatoid arthritis (STAR) study was a double-blind, double-dummy, randomised parallel-group trial conducted at 16 sites in France, with a 1:1 randomisation ratio.

The study enrolled patients with RA aged at least 18 years who fulfilled the 2010 American College of Rheumatology-EULAR classification criteria for RA.<sup>12</sup> To be eligible, patients must have been treated with a stable dose of conventional synthetic DMARD (csDMARD) or targeted DMARD for at least 3 months, treated with oral glucocorticoids for at least 6 months with a stable dose of prednisone or prednisolone of 5 mg/day for at least 3 months and had to

be in remission or LDA, defined by a Disease Activity Score based on 28 joints and erythrocyte sedimentation rate (DAS28-ESR)  $\leq 3.213$  for at least 3 months. Full inclusion and exclusion criteria are listed in the online supplemental file.

The study was registered under NCT02997605.

### **Randomisation and masking**

Patients were randomly assigned to either a hydrocortisone replacement strategy including hydrocortisone and a placebo of prednisone, or a prednisone tapering strategy including prednisone and a placebo of hydrocortisone, for a blinded period of 6 months and a total study duration of 12 months after randomisation.

Randomisation was stratified on clinical centre and on prior glucocorticoid exposure duration ( $\leq 2$  years or  $> 2$  years). A randomisation list was established by the Unité de Soutien Méthodologique à la Recherche at Toulouse University Hospital (France) before the start of the study. In each stratum, a design based on randomised blocks of two patients was applied, according to the 1:1 ratio. The randomisation list was provided electronically.

### **Procedures**

Patients eligible for the study were included in a first period of 1 month during which they all received 5 mg/day of prednisone (branded). This period was designed to homogenise glucocorticoid therapy since patients could be eligible if they were taking 5 mg/day of prednisone or prednisolone, with branded or generic drug. After 1 month of follow-up, patients still in LDA defined by a DAS28-ESR  $\leq 3.213$  were randomly assigned, at month 1, to a hydrocortisone replacement strategy or a prednisone tapering strategy for a double-blinded period of 6 months from month 1 to month 7 (see online supplemental appendix for the design scheme).

At month 1, patients assigned to the hydrocortisone replacement strategy received 20 mg/day of hydrocortisone for 3 months until month 4, then 10 mg/day of hydrocortisone for 3 months until month 7. This group also received a placebo of prednisone that was prescribed with the same tapering scheme as in the prednisone tapering group for 4 months (placebo of prednisone 4 mg/day for 1 month, then placebo of prednisone 3 mg/day for 1 month, then placebo of prednisone 2 mg/day for 1 month and finally placebo of prednisone 1 mg/day for 1 month).

Patients assigned to the prednisone tapering group received a tapering scheme of prednisone over 4 months with prednisone 4 mg/day for 1 month, then prednisone 3 mg/day for 1 month, then prednisone 2 mg/day for 1 month and finally prednisone 1 mg/day for 1 month. During this period, they also received a placebo of hydrocortisone (20 mg/day for 3 months, then 10 mg/day for 3 months until month 7).

After the double-blinded period of 6 months, patients were followed until the end of the study with a visit at month 9 and the last visit at month 12.

In the event of flare, defined by a DAS28-ESR > 3.2 at any visit despite the use of non-steroidal anti-inflammatory drugs and analgesic drugs, patients received an additional standardised rescue treatment with 30 mg/day of prednisone for 2 days, then 20 mg/day for 2 days, then finally 10 mg/day for 2 days. Physicians were allowed to prescribe two courses of prednisone rescue therapy during the study.

Patients could also receive a maximum of two glucocorticoid joint injections for RA during the study. Patients systematically underwent a short 250 µg ACTH stimulation test at month 4 (3 months after randomisation) and month 7 (6 months after randomisation). In the event of an abnormal ACTH stimulation test as defined by a serum cortisol concentration under 20 µg/100 mL 1 hour after the ACTH injection, patients received open-label 20 mg/day of hydrocortisone in addition to the prednisone or placebo of prednisone received in the randomisation arm. Patients having an abnormal ACTH stimulation test at month 7 had another ACTH stimulation test performed at the end of the study. In the event of symptoms suggesting an adrenal insufficiency at month 9 or month 12, additional ACTH stimulation tests were performed. Patients with an abnormal ACTH stimulation test at month 12 were classified as strategy failures.

Prednisone, hydrocortisone and placebo capsules were packaged and supplied by the Coordinating Hospital Pharmacy of Toulouse. Two different packages were prepared: one for prednisone or placebo of prednisone and another for hydrocortisone or placebo of hydrocortisone. Capsules of hydrocortisone or prednisone and their placebos were indistinguishable. Patients received one package containing three boxes of each product or placebo for 3 months of treatment at visits at 1 month and 4 months. Only the pharmacist of the Coordinating Hospital Pharmacy of Toulouse was aware of the content (product or placebo) of each package. Patients, investigators and pharmacists from other centres were blinded to the treatment received.

## Outcomes

The primary outcome was the proportion of patients who had discontinued glucocorticoids at 12 months. Furthermore, the strategy was considered a failure if one of the following conditions were met: if a patient required more than two courses of glucocorticoids or more than two glucocorticoid joint injections to control disease activity; if the standardised rescue treatment was not followed; if the patient was still receiving prednisone and/or hydrocortisone at the end of the study or if a patient had received >2 weeks of oral glucocorticoids for a reason other than their disease.

The secondary outcomes included the proportion of patients who could discontinue prednisone only (keeping or not keeping hydrocortisone) at 1 year; the proportion of patients who needed extra oral glucocorticoid courses or joint injections to control disease activity during the study; the proportion of patients who experienced a flare as determined a physician during the study; the proportion of patients in remission or LDA at each visit; the variation of the DAS28-ESR during the study and the variation in patient-reported outcomes during the study, including patient-reported flares assessed by the Flare Assessment in RA (FLARE-RA) questionnaire,<sup>14</sup> disability assessed by the Health Assessment Questionnaire-Disability Index (HAQ-DI),<sup>15</sup> fatigue assessed by the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) questionnaire,<sup>16</sup> quality of life assessed by the Rheumatoid Arthritis Impact of Disease (RAID)<sup>17</sup> and EuroQuol Group Questionnaire five dimensions (EQ-5D)<sup>18</sup>

questionnaires. Safety was assessed by the number of adverse events, the number of severe adverse events, the proportion of patients with an abnormal ACTH stimulation test and the number of patients with acute adrenal insufficiency. An independent, external adjudication committee blindly adjudicated all suspected severe adverse events, including acute adrenal insufficiency events.

	Hydrocortisone replacement (n=53)	Prednisone tapering (n=49)	Total (n=102)
<b>Sex</b>			
Female	38 (72%)	34 (69%)	72 (71%)
Male	15 (28%)	15 (31%)	30 (29%)
Missing	0	0	0
<b>Age (years)</b>			
	63.0 (13.1)	61.8 (13.8)	62.4 (13.4)
Missing	0	0	0
<b>BMI (kg/m<sup>2</sup>)</b>			
	26.3 (5.6)	26.0 (4.3)	26.1 (5.0)
Missing	0	0	0
<b>Duration since rheumatoid arthritis diagnosis (years)</b>			
	13.7 (11.5)	13.5 (12.7)	13.6 (12.1)
Missing	0	0	0
<b>Autoantibodies</b>			
Rheumatoid factor positive	47 (89%)	45 (92%)	92 (90%)
Anticyclic citrullinated protein positive	44 (83%)	47 (96%)	91 (89%)
Missing	0	0	0
<b>Patients with erosions</b>			
	24 (45%)	27 (55%)	51 (50%)
Missing	0	1	0
<b>Charlson Comorbidity Index</b>			
	3.6 (2.1)	3.4 (1.8)	3.5 (2.0)
Missing	0	0	0
<b>Duration of low disease activity</b>			
	1.4 (2.1)	1.1 (1.7)	1.2 (1.9)
Missing	0	0	0
<b>Duration of prior glucocorticoids (years)</b>			
	10.5 (11.8)	7.6 (10.6)	9.1 (11.2)
Missing	0	0	0
<b>Patients with csDMARDs</b>			
	40 (75%)	39 (80%)	79 (77%)
Missing	0	0	0
<b>Patients with targeted DMARDs</b>			
	33 (62%)	28 (57%)	61 (60%)
Missing	0	0	0
<b>TJC28</b>			
	0.6 (1.2)	0.7 (1.2)	0.7 (1.2)
Missing	0	0	0
<b>SJC28</b>			
	0.4 (0.9)	0.4 (1.0)	0.4 (0.9)
Missing	0	0	0
<b>PatGA (100 mm VAS)</b>			
	21.7 (17.2)	20.2 (17.0)	21.0 (17.0)
Missing	0	0	0
<b>Pain (100 mm VAS)</b>			
	22.3 (18.1)	21.0 (17.0)	21.7 (17.5)
Missing	1	1	2
<b>Fatigue (100 mm VAS)</b>			
	36.2 (28.4)	32.9 (24.5)	34.6 (26.5)
Missing	1	1	2
<b>DAS28-ESR</b>			
	2.1 (0.8)	2.3 (0.7)	2.2 (0.8)
Missing	2	3	5
<b>CRP (mg/L)</b>			
	3.1 (3.7)	3.3 (5.0)	3.2 (4.3)
Missing	0	0	0

Data are expressed in number (percentage) or mean (SD).  
 BMI, body mass index; CRP, C reactive protein; csDMARD, conventional synthetic DMARD; DAS28-ESR, Disease Activity Score on 28 joints based on ESR; DMARDs, disease-modifying antirheumatic drugs; PatGA, patient global Disease Activity Score; SJC28, swollen joint count on 28 joints; targeted DMARD, included biological and targeted synthetic DMARDs; TJC28, tender joint count on 28 joints; VAS, Visual Analogue Scale.



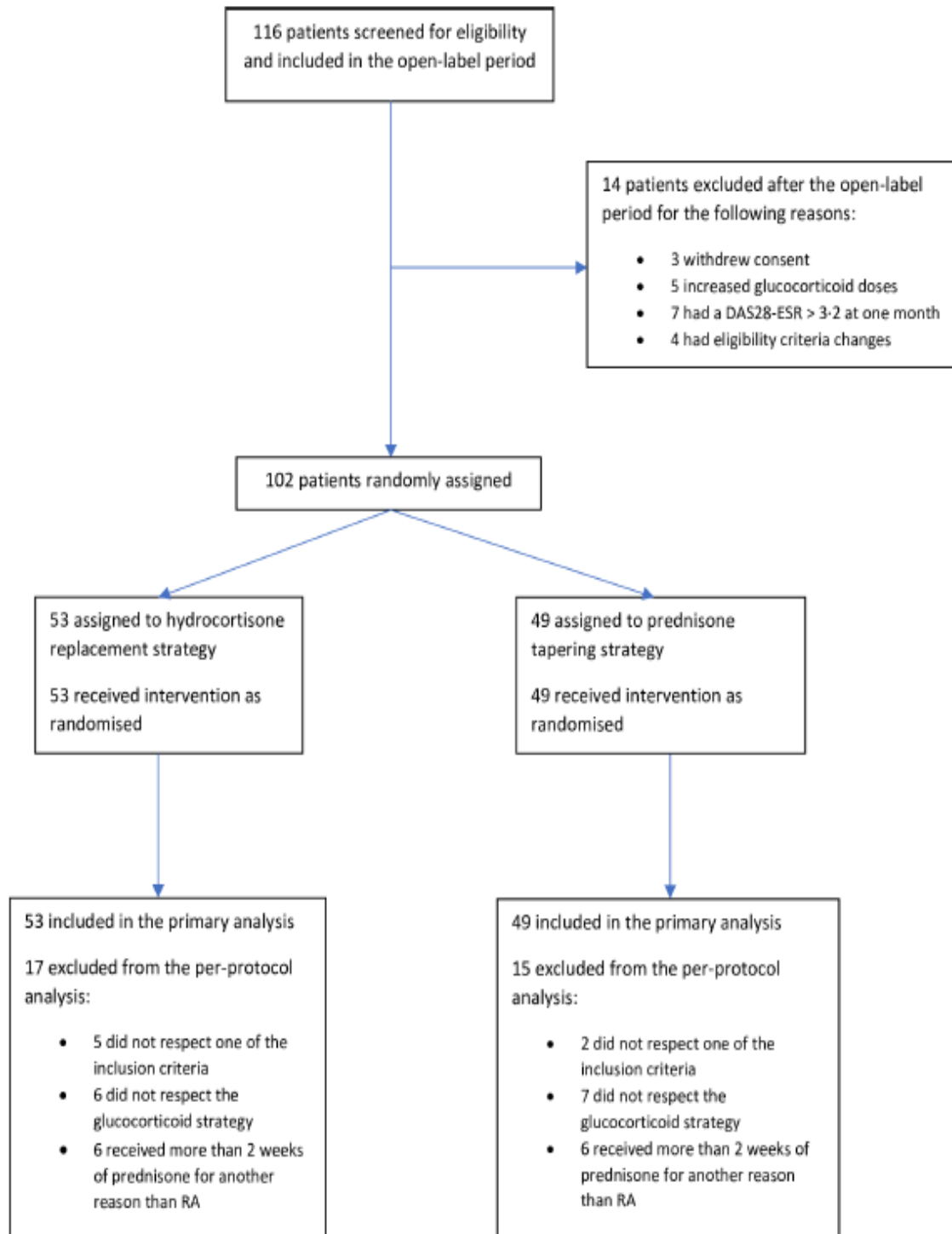
## Statistical analyses

We hypothesised that in the tapering group, the proportion of patients who would discontinue glucocorticoid (success) would be about 30%.<sup>10</sup> We assumed that replacing prednisone with hydrocortisone, which is considered a safe regimen in glucocorticoid discontinuation,<sup>4</sup> could increase the success rate to 60% in the intervention group. Given these hypotheses, 42 patients per group were necessary to assess a significant difference between groups, with a 5% type 1 error rate, 80% power and a two-sided comparison. Given that we anticipated that 20% of patients would be lost to follow-up, the study planned to include 102 randomised patients (51 in each group). It was also expected that about 20% of patients would not fulfil the inclusion criteria after the first open-label period of the study, until the randomisation visit, at month 1. Thus, we needed to include 122 patients at baseline to provide 102 randomised patients at month 1. All efficacy analyses were performed on the intention-to treat population, meaning on all randomised patients at month 1. The primary outcome analysis was the comparison of the proportion of patients achieving glucocorticoid discontinuation at 1 year between the groups and was analysed using a two-sided  $\chi^2$  test with the significance level set at 0.05. Patients with missing data for the primary outcome were analysed as strategy failures. A two-sided  $\chi^2$  test was also used to analyse categorical secondary end points, while continuous end points were compared using a Student's t-test if the application conditions were met, or a Mann-Whitney Wilcoxon test otherwise. The analysis was also performed on the per-protocol population. In addition, an analysis adjusted on clinical factors was provided. Factors associated with glucocorticoid discontinuation success were first tested using logistic regression models systematically adjusted for the randomization arm. The variables tested included age, sex, disease duration, rheumatoid factor, anticitrullinated protein antibodies, erosions, baseline DAS28-ESR, remission/ LDA duration before inclusion in the study, baseline HAQ-DI, baseline fatigue, Charlson Comorbidity Index, csDMARD intake, targeted DMARD intake (including biologic and targeted synthetic DMARDs) and prior glucocorticoid exposure duration. Variables associated with a p value of  $\leq 0.2$  were then included in a full multivariate model. Only significant ( $p < 0.05$ ) confounders were maintained in the final model after a backward step-by-step procedure, adjusted for the randomisation arm. The log-linearity of the relationship between the dependent and each independent continuous variable was tested. All analyses were performed blindly using STATA V.18. Missing data for all outcomes were reported (table 1 and online supplemental table S1).

## RESULTS

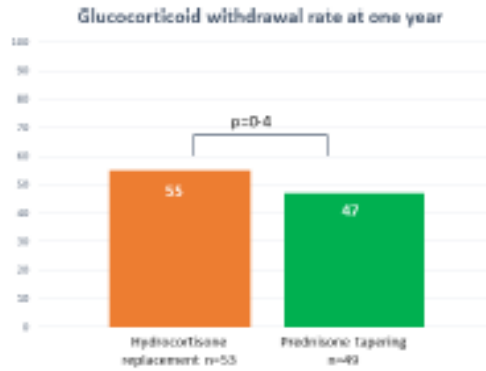
Between January 2017 and February 2021, 116 patients were screened, of whom 102 were randomly assigned to either the hydrocortisone replacement strategy ( $n=53$ ) or the prednisone tapering strategy ( $n=49$ ), which constituted the intention-to-treat population (figure 1). Among these patients, 17 in the hydrocortisone group and 15 in the prednisone group had at least one change in the glucocorticoid tapering scheme and were excluded from the per protocol population (figure 1).

Patient demographics and disease activity were balanced across the treatment arms (table 1). Most of the patients were female (71%), with an overall mean age of 62.4 years (SD 13.4) and a mean duration since RA diagnosis of 13.6 years (SD 12.1). The mean duration of LDA was 1.2 years (SD 1.9), and the mean glucocorticoid exposure duration was 9.1 years (SD 11.2). The majority of patients (77%) were treated with a csDMARD, while 60% received a targeted DMARD (either as monotherapy or in combination with a csDMARD).



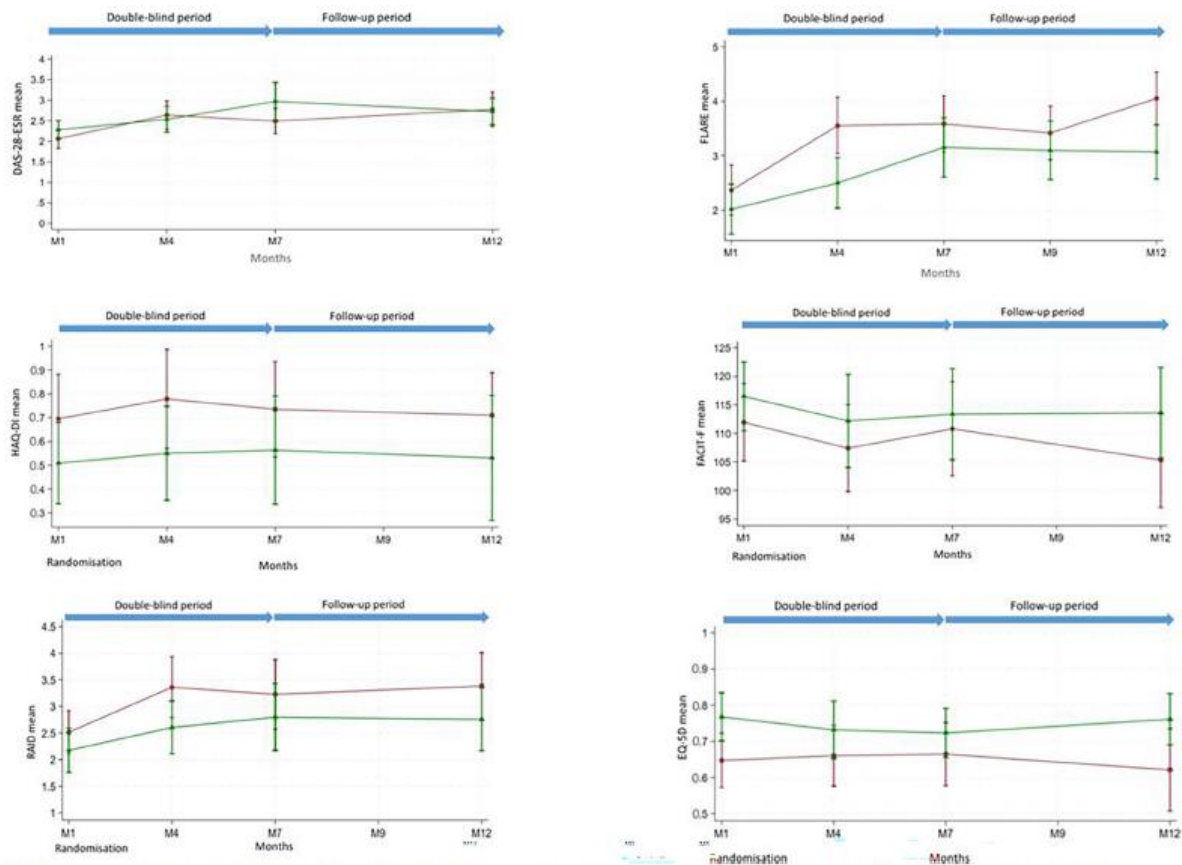
**Figure 1** Flow diagram. DAS28-ESR, Disease Activity Score based on 28 joints and erythrocyte sedimentation rate; RA, rheumatoid arthritis.

At 1 year, the proportion of patients who succeeded in the primary outcome was similar in the two groups (figure 2): 29 patients (55%) in the hydrocortisone replacement group and 23 patients (47%) in the prednisone tapering group had discontinued glucocorticoids ( $p=0.4$ ). The per-protocol analysis showed consistent results: 22 patients (61%) achieved the primary outcome in the hydrocortisone replacement group vs 22 patients (65%) in the prednisone tapering group ( $p=0.8$ ).



**Figure 2** Glucocorticoid withdrawal rate at 1 year.

The proportion of patients who could discontinue prednisone only (keeping or not keeping hydrocortisone) at 1 year was numerically higher in the hydrocortisone replacement group (n=32 patients, 71%) than in prednisone tapering group (n=23 patients, 61%), but the difference was not significant (p=0.3). Sixteen patients (30%) in the hydrocortisone replacement group and 18 patients (37%) in the prednisone tapering group (p value for difference=0.5) needed one short course of oral glucocorticoid supplementation, while two patients in the prednisone tapering group needed glucocorticoid joint injections to control disease activity during the follow-up.



**Figure 3** Evolution of DAS28-ESR and patient-reported outcomes means and 95% CIs over 1 year in both groups. (a) Evolution of DAS28-ESR over 1 year. (b) Evolution of FLARE-RA over 1 year. (c) Evolution of HAQ-DI over 1 year. (d) Evolution of FACIT-F over 1 year. (e) Evolution of RAID over 1 year. (f) Evolution of EQ-5D over 1 year. DAS28-ESR, Disease Activity Score based on 28 joints and erythrocyte sedimentation rate; EQ-5D, EuroQuol group questionnaire five dimensions; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; FLARE-RA, Flare Assessment in RA; HAQ-DI, Health Assessment Questionnaire-Disability Index; RAID, Rheumatoid Arthritis Impact of Disease.

There was no significant difference in the proportion of patients who flared up during the follow-up (in the hydrocortisone replacement group: n=17 (33%)) compared with the prednisone tapering group: n=19 (42%), p=0.4). Seventy-eight per cent of patients in the hydrocortisone replacement group were still in DAS28-ESR LDA at month 7, compared with 66% of patients in the prednisone tapering group (p=0.2). At the end of the study, the proportion of patients still in LDA was similar in both groups (n=29 (74%) in the hydrocortisone replacement group compared with n=26 (79%) in the prednisone group, p=0.7). The DAS28-ESR variation during follow-up was comparable between groups for the duration of the study (figure 3).

Patient-reported outcomes including FLARE, HAQ-DI, RAID, FACIT-F and EQ-5D varied similarly between the two groups during follow-up (figure 3). However, at 1 year, the median HAQ-DI was slightly higher in the hydrocortisone replacement group (0.75 (IQR 0.06–1.13)) in comparison with the prednisone tapering group (0.13 (IQR 0.00–0.75), p value for difference: 0.049). All other comparisons revealed no statistically significant differences.

**Table 2** Variables associated with glucocorticoid withdrawal success

	Adjusted analyses for randomisation group and covariate only		Adjusted multivariate analyses	
	OR (95% CI)	P value	OR (95% CI)	P value
Age: ref ≤50 years	–	–		
50–60 years	1.25 (0.33 to 4.66)	0.7		
60–70 years	0.99 (0.31 to 3.14)	0.9		
70–80 years	1.18 (0.34 to 4.03)	0.8		
80–90 years	0.40 (0.06 to 2.64)	0.3		
Sex: female versus male	0.87 (0.36 to 2.04)	0.7		
Disease duration (years)	<b>0.95 (0.91 to 0.99)</b>	<b>0.007</b>	<b>0.95 (0.91 to 0.98)</b>	<b>0.004</b>
Rheumatoid factor positive	1.47 (0.57 to 3.82)	0.4		
Anticitrullinated protein antibody positive	1.46 (0.52 to 4.09)	0.5		
Patients with erosions	<b>0.37 (0.16 to 0.83)</b>	<b>0.016</b>		
DAS28-CRP: <2.6 (yes/no)	2.11 (0.81 to 5.49)	0.1		
Remission/Low disease activity duration prior randomisation: >0.5 years (yes/no)	1.09 (0.49 to 2.39)	0.8		
HAQ-DI: >0.5 (yes/no)	1.21 (0.54 to 2.69)	0.6		
Fatigue VAS: >3 (yes/no)	0.723 (0.328 to 1.594)	0.4		
Charlson Comorbidity Index	0.91 (0.74 to 1.12)	0.4		
csDMARD intake	<b>0.30 (0.10 to 0.91)</b>	<b>0.03</b>		
Targeted DMARD intake	<b>0.23 (0.06 to 0.91)</b>	<b>0.04</b>	<b>0.20 (0.05 to 0.80)</b>	<b>0.02</b>
Prior prednisone duration: >2 years (yes/no)	<b>0.41 (0.17 to 0.94)</b>	<b>0.04</b>		
Hydrocortisone replacement versus prednisone tapering*	0.73 (0.33 to 1.60)	0.4	0.69 (0.30 to 1.61)	0.4

Univariate and multivariate analyses were systematically adjusted on randomisation arm.  
 \*Data obtained by univariate analysis.  
 csDMARD, conventional synthetic DMARD; DAS28-CRP, Disease Activity Score based on 28 joints and C reactive protein; DMARDs, disease-modifying antirheumatic drugs; HAQ-DI, Health Assessment Questionnaire-Disability Index; targeted DMARD, included biological and targeted synthetic DMARD; VAS, Visual Analogue Scale.

Univariate analyses and a multivariate model systematically adjusted on randomisation arm were conducted to assess the impact of other variables on discontinuation success. Longer disease duration, erosion presence at baseline, csDMARD and targeted DMARD intake (including biologic DMARDs and targeted synthetic DMARDs) and prior glucocorticoid exposure >2 years were negatively associated with glucocorticoid discontinuation success after adjustment for treatment arm (table 2). The multivariate analysis identified only two factors independently associated with glucocorticoid discontinuation failure after the backward step-by-step procedure: disease duration (per year, OR (95% CI)=0.95 (0.91 to 0.98), p=0.004) and targeted DMARDs (including biologic and targeted synthetic DMARDs) intake (OR (95% CI)=0.20 (0.04 to 0.81), p=0.02) (table 2) after adjustment for treatment arm.

The number of patients with an abnormal ACTH stimulation test at month 4 was higher in the hydrocortisone replacement group than in the prednisone tapering group (23 vs 14), but the difference was not significant at other follow-up visits (online supplemental figure S2). At the end of the study, 17 patients still had a pathological ACTH stimulation test leading to the continuation of hydrocortisone therapy.

Safety analyses identified adverse events in 43 patients (81%) in the hydrocortisone replacement group, of whom 3 patients (4 adverse events) had severe adverse events (1 patient with pericardial effusion and aortic dissection, 1 patient with pleural effusion and 1 patient with a tibia fracture) and in 33 patients (67%) in the prednisone tapering group, of whom 3 patients (3 adverse events) had severe adverse events (2 lung neoplasia, 1 severe atopic dermatitis). None of the severe adverse events was considered related to the treatment strategy. None of the patients had an acute adrenal insufficiency during follow-up.

## DISCUSSION

The STAR trial aimed to compare a hydrocortisone replacement strategy with a prednisone tapering strategy in RA in LDA or remission, with patients still receiving 5 mg/day of prednisone or prednisolone. At the end of the study, one patient out of two could discontinue glucocorticoids, with a similar success rate of glucocorticoid discontinuation between groups, indicating that both strategies performed similarly to achieve glucocorticoid discontinuation. At the end of the study, the proportion of patients in LDA or remission was similar in both groups. There was no difference in the proportion of flares during follow-up, and a similar number of patients in both arms needed additional glucocorticoids during follow-up because of flares. Neither of the two strategies had a better impact on patient-reported outcomes such as fatigue, disability, patient-reported flares or quality of life. Longer disease duration and targeted DMARD intake decreased the chances of achieving glucocorticoid discontinuation. No acute adrenal insufficiency was observed in the whole population, but an abnormal ACTH stimulation test was still observed in 17 patients at the end of the study. The number of adverse events and severe adverse events was similar between groups.

About 50% of patients had discontinued glucocorticoid at the end of the study. Only a few clinical trials have specifically investigated glucocorticoid discontinuation regimens in RA. A first trial, published in 1998, showed that a quick tapering of prednisolone from 7.5 mg/day to alternate-day treatment for 2 weeks, followed by treatment every third day for 2 weeks before discontinuation, resulted in greater joint damage over 1 year compared with abrupt prednisolone discontinuation.<sup>19</sup> A second trial showed that a slow tapering of prednisolone from 5 to 7.5 mg/day, with a 2.5 mg reduction in the total weekly dose once a week, allowed an effective discontinuation of prednisolone in only 11/26 patients randomised to discontinue glucocorticoid treatment within 1 year.<sup>20</sup> A third trial showed that a slow tapering of prednisone from 1 to 4 mg/day, with a 1 mg reduction every 4 weeks before discontinuation, allowed an effective discontinuation of prednisone in only 4/15 participants within 24 weeks.<sup>10</sup> In the recent Steroid EliMination In Rheumatoid Arthritis (SEMIRA) trial, the authors aimed to compare the same glucocorticoid tapering scheme used in this trial with a glucocorticoid continuous treatment at 5 mg/day of prednisone in patients with RA treated with tocilizumab. In the tapering arm, 13% of patients withdrew from the study, mostly because of flare, and 26% of patients experienced a flare during the follow-up.<sup>21</sup> Finally, a

recent trial<sup>22</sup> investigated the feasibility of glucocorticoid discontinuation in 96 patients with RA aged >65 years who had been treated with 5 mg/day of glucocorticoids for 2 years, with a tapering scheme consisting of skipping one additional prednisone 5 mg/day intake per week every 2 weeks until complete discontinuation after 3 months. In this group, 45% experienced a flare during follow-up, compared with 33% in a control group without long-term glucocorticoid treatment.

To our knowledge, this is the first study comparing a hydrocortisone replacement strategy with a conventional prednisone tapering strategy. Although some experts recommend systematically replacing prednisone with hydrocortisone,<sup>6</sup> the efficacy of this strategy has never been investigated in rheumatic diseases. Many studies have shown that patients exposed to long-term glucocorticoid therapy have alterations of the hypothalamic-pituitary-adrenal axis,<sup>23</sup> with prednisone doses of >7.5 mg/day prescribed for >3 weeks.<sup>1 6</sup> Although acute adrenal insufficiency seems to be very uncommon, with an overall prevalence about 0.015%–0.1%, mostly in the perioperative context,<sup>24–26</sup> the rate of glucocorticoid discontinuation failure is high because of RA flare-up risk and also because of glucocorticoid discontinuation syndrome, which patients and physicians might confound with RA activity symptoms. Elevated concentrations of circulating interleukin-6 may cause many of the symptoms of glucocorticoid withdrawal.<sup>27</sup> Furthermore, glucocorticoid discontinuation after long-term exposure may lead to a neuropsychiatric disorder such as depression or confusion,<sup>28 29</sup> probably linked to the neurological effects of glucocorticoids. The hydrocortisone replacement strategy might reduce these symptoms and potentially benefit patient-reported outcomes such as pain, fatigue, patient-reported flare-up, disability or quality of life. However, in this study we could not identify significant differences between groups in these patient-reported outcomes, and thus we can assume that glucocorticoid withdrawal symptoms have a marginal impact and the majority of the glucocorticoid discontinuation failures are related to flares in RA. Furthermore, the hydrocortisone replacement strategy exposed patients to higher cumulative glucocorticoid doses than did the prednisone tapering strategy. However, the duration of hydrocortisone exposure in the trial was designed to have glucocorticoids in both parallel arms in the blinded part of the study, and shorter hydrocortisone duration could also have been designed. Interestingly, patients with targeted DMARD (biologic and targeted synthetic DMARDs) were less likely to achieve glucocorticoid cessation at 12 months, although the glucocorticoid-sparing effect by biologic DMARDs have been proved.<sup>30–32</sup> However, this trial was not designed to assess the sparing effect of treatments and this result probably reflected the association between active disease and/or severity and the low chances of glucocorticoid discontinuation.

At the end of the study, 17 patients still had an abnormal ACTH stimulation test requiring additional long-term hydrocortisone therapy, with no difference between the two arms. In 1967, Daly *et al*<sup>33</sup> revealed that median plasma cortisol levels only remained in normal ranges in patients receiving <5 mg of glucocorticoids per day. In fact, the suppression of the hypothalamic-pituitary-adrenal axis by glucocorticoids has interindividual variations and cannot be predicted.<sup>33</sup> The high proportion of patients with abnormal ACTH stimulation test results in this study is consistent with other studies. A meta-analysis of studies on various chronic conditions<sup>34</sup> showed that almost 40% of patients with rheumatic conditions taking long-term oral glucocorticoids had abnormal ACTH stimulation tests. In studies investigating ACTH stimulation retesting strategies, about 25% of patients still had abnormal tests 6 months after a first abnormal test.<sup>34</sup> Consistently with previous studies,<sup>34</sup> none of the patients included in the STAR trial had an acute adrenal insufficiency during the follow-up. However, since all patients with an abnormal ACTH stimulation test in the STAR trial

systematically received a supplementation of 20 mg/day of hydrocortisone until their next ACTH stimulation test, we cannot exclude the possibility that some of these patients might have experienced clinical symptoms of adrenal insufficiency had they not received such supplementation. In SEMIRA trial,<sup>21</sup> patients did not have systematically ACTH stimulation tests and no adrenal insufficiency was observed, raising the issue of systematically conducting these tests in routine. Interestingly, a difference was observed between groups at the 4-month end point (23 patients in the hydrocortisone group vs 14 patients in the prednisone group). At this time point, patients in the hydrocortisone group were still receiving 20 mg/day of prednisone (equivalent to 5 mg/day of prednisone), while patients in the prednisone group were receiving only 2 mg/day of prednisone. No difference was observed at other end points while patients had interrupted glucocorticoids. The difference observed at the 4-month end point might be explained by a higher suppressive effect on adrenal function in the hydrocortisone group.

This study has several limitations. First, the trial investigated only 102 patients. The sample size was calculated based on a 30% absolute difference in discontinuation rate, assuming a success discontinuation rate of 30% in the prednisone tapering group, as previously demonstrated in the study by Pincus *et al.*<sup>10</sup> However, in this study, the success rate of prednisone discontinuation was higher, approximately 47%, which is consistent with most recent studies.<sup>21 22</sup> As no study has investigated the efficacy of a hydrocortisone replacement strategy, we could not formulate hypotheses regarding the success rate of this approach. A difference of 30% was anticipated, which might be considered high. However, we assumed that such a difference, if present, would be sufficiently convincing to change clinical practice. A larger sample size would have increased the power to identify significant differences between groups. Furthermore, some numerical differences may have been observed between groups in secondary outcomes, particularly in patient-reported outcomes over time. The large CIs were overlapping for most timepoints, indicating that the differences were not significant, which may be related to a lack of power. It is possible that the relatively small sample size could have led to the non-detection of a difference between groups. However, the numeric differences observed across the various outcomes were mostly below 10% and, therefore, not clinically relevant. The authors believe that a larger sample size would likely not have changed the main results of this study. Furthermore, this study involved only patients taking a stable dose of 5 mg/day of prednisone and in sustained LDA. Thus, these results cannot be extrapolated to other populations with higher disease activity or taking higher or lower doses of prednisone. Finally, the study included patients with long-standing disease, with a mean disease duration of 13 years. Therefore, the findings cannot be extrapolated to early stages of the disease, where glucocorticoids may be used as bridging therapy when initiating a first DMARD with the objective of rapidly achieving remission and glucocorticoid cessation.<sup>1</sup>

In summary, this study aimed to compare two glucocorticoid discontinuation strategies—a hydrocortisone replacement strategy and a prednisone tapering strategy—and did not find any significant differences in the success rate of glucocorticoid discontinuation in patients with RA in LDA. Both strategies allowed glucocorticoid discontinuation in half of the patients at 12 months, with a moderate risk of RA flare-up. Although no cases of acute adrenal insufficiency were observed, a significant number of patients still had abnormal ACTH stimulation tests at the end of the study. These findings support the EULAR recommendations,<sup>1</sup> suggesting a prednisone tapering strategy until complete discontinuation. Additionally, this study did not identify an advantage in systematically replacing prednisone with hydrocortisone. Further studies are needed to assess the consequences of an abnormal ACTH stimulation test in asymptomatic patients after glucocorticoid discontinuation. The

relevance and cost-effectiveness of systematic ACTH testing and hydrocortisone replacement in cases of abnormal tests while patients remain asymptomatic also require investigation.

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## **Contributors**

AR-W is the guarantor of this work. AR-W was in charge of the design of the study, protocol writing, conducting the trial, inclusion of patients, data interpretation and manuscript writing. VB was involved in the design of the study, protocol reviewing and data analyses. She directly accessed and verified the underlying data reported in the manuscript. CB was in charge of the statistical analyses. She directly accessed and verified the underlying data reported in the manuscript. AC was involved in the design of the study, protocol preparation and data interpretation and contributed to the draft manuscript. MM, CS, LP, MN, CHR, CR, AS, PV-S, JM, RMF, MP, J-EG, HM, MS, LG, PD, SL, LZ, GC, JFB, BJ and YD were involved in patient recruitment and patient follow-up in the study and made substantial contributions to the draft manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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## **Disclaimer**

The sponsor was not involved in conducting the trial, interpreting the data or writing the manuscript.

## **Competing interests**

AR-W, CB, MM, VB, MN, Ch R, AS, PV-S, RMF, MP, J-EG, MS, PD, SL, LZ, GC, JFB, BJ, YD and AC declare no competing interests. HM declared to have received grants from Celltrion, Healthcare, Lilly, Nordic Pharma, Medac, consulting fees from AbbVie, Accord,



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### **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.

### **Patient consent for publication**

Consent obtained directly from patient(s).

### **Ethics approval**

Study-related documents were reviewed and approved by an independent ethics committee (CPP Sud-Ouest et Outre-Mer 4 CCP-16-028a EudraCT: 2016-001618-18). The study was conducted in accordance with the International Conference on Harmonisation guidelines, applicable regulations, guidelines governing clinical study conduct and the Declaration of Helsinki. All patients provided written informed consent before participating in the study.

### **Provenance and peer review**

Not commissioned; externally peer reviewed.

## Data availability statement

Data are available on reasonable request. The study protocol and statistical analysis plan are provided as online supplemental files 3 and 4. Informed consent form, clinical study report and analytic code will be available on demand. The database will be available for investigators whose proposed use of the database has been approved by an independent review committee, beginning 3 months and ending 5 years following article publication with a purpose of achieving aims in the approved proposal. Proposals may be submitted to the corresponding author up to 36 months following article publication.

## Author note

The lead author (AR-W) affirms that the manuscript is an honest, accurate and transparent account of the study being reported; no important aspects of the study have been omitted; there is no discrepancies from the study as originally planned and registered.

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