



ORIGINAL RESEARCH

Tapering glucocorticoids and risk of flare in rheumatoid arthritis on biological disease-modifying antirheumatic drugs (bDMARDs)

Giovanni Adami , Angelo Fassio, Maurizio Rossini, Davide Bertelle, Francesca Pistillo, Camilla Benini, Ombretta Viapiana , Davide Gatti

To cite: Adami G, Fassio A, Rossini M, *et al.* Tapering glucocorticoids and risk of flare in rheumatoid arthritis on biological disease-modifying antirheumatic drugs (bDMARDs). *RMD Open* 2023;**9**:e002792. doi:10.1136/rmdopen-2022-002792

Received 12 October 2022
Accepted 21 December 2022

ABSTRACT

Introduction Glucocorticoids are still a mainstream of rheumatoid arthritis (RA) treatment. Reducing glucocorticoids should be attempted in all patients. However, choosing the right tapering strategy is challenging. The primary aim of our study is to determine the dose–response association between glucocorticoid tapering and risk of flare in RA.

Methods We conducted a case-crossover study to determine the factors associated to higher risk of flare in patients with RA. In case-crossover studies time-varying factors are assessed before events (hazard periods) and before control periods. We defined hazard periods as the 6 months immediately preceding flares of RA. Control periods were the 6 months prior to visits without flare. Exposure of interest was the tapering of glucocorticoids to various doses.

Results 508 patients with RA were included in the study and 267 (52.5%) had at least a flare and served as the case-crossover study population. 1545 visits were available for analysis and 345 (22.3%) flares were recorded. Discontinuation of glucocorticoids (ie, tapering to doses of 0 mg/day) and tapering to 0–2.5 mg/day was associated with higher risk of flare (adjusted OR (aOR) of 1.45, 95% CI: 1.13 to 2.24 and aOR of 1.37; 95% CI: 1.06 to 2.01, respectively). Tapering to doses >2.5 mg/day was not associated with significantly higher risk of flare.

Conclusions We found that tapering to doses of >2.5 mg/day was generally effective in terms of risk of flare. Flare risk was higher when glucocorticoids were tapered to doses ≤2.5 mg/day. Our study might help design new tapering strategies in patients with RA on biological disease-modifying antirheumatic drugs.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic condition characterised by periods of remission alternated with disease reactivations (ie, flares). Many factors have been associated with flares, including infections, treatment discontinuation and other environmental factors, including air pollution exposure.^{1–4}

WHAT IS ALREADY KNOWN ON THIS TOPIC

- ⇒ Chronic glucocorticoids are associated with significant adverse events.
- ⇒ Tapering strategies are largely based on personal experience and many patients experience a flare after tapering or discontinuing glucocorticoids.

WHAT THIS STUDY ADDS

- ⇒ We found that tapering to doses above 2.5 mg/day was not associated to a higher risk of flare in patients with rheumatoid arthritis receiving biological disease-modifying antirheumatic drugs (bDMARDs).

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- ⇒ Patients with rheumatoid arthritis on bDMARDs tapering glucocorticoids to doses ≤2.5 mg/day might incur a higher risk of flare.

Treatment options for RA are rapidly expanding but glucocorticoids are still largely prescribed to reduce inflammation and control disease activity.⁵ Tapering glucocorticoids to the lowest dose possible is strongly encouraged by the 2019 European League Against Rheumatism (EULAR) recommendations for the management of RA.⁶ Moreover, the need for rapid glucocorticoid dose reduction and possibly discontinuation is even more clearly stressed in the recent update of the recommendations.⁷ Yet, tapering strategies are mostly based on expert opinion or personal belief and it is unclear whether chronic low-dose glucocorticoid treatment can provide substantial benefits that overcome the harms of such approach.^{8–10} Approximately 50% of patients with early RA attain glucocorticoids discontinuation at 3 years but about 30% of them will have a flare within the next 6 months from discontinuation.¹¹ Indeed, tapering and discontinuing



© Author(s) (or their employer(s)) 2023. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

Rheumatology Unit, Department of Medicine, University of Verona, Verona, Italy

Correspondence to
Dr Giovanni Adami;
adami.g@yahoo.com

glucocorticoids has been associated with higher risk of flare but the dosage at which the flare happens is unpredictable and mostly not known.⁹ In addition, the EULAR definition for low-dose glucocorticoids (ie, ≤ 7.5 mg/day) is arbitrary and based on questionable assumptions, which are not related to efficacy on disease activity but mostly on common sense and frequency of adverse events.¹² The primary objective of the present study is to describe and determine the dose–response association between glucocorticoid tapering and risk of flare in RA.

METHODS

We collected demographic, clinical and laboratoristic data on patients with RA from the outpatient service of the Rheumatology Unit of the University of Verona between January 2016 and January 2020. Patients were seen, as per clinical practice, every 3–4 months. We included patients with: (1) diagnosis of RA according to ACR/EULAR 2010 classification criteria¹³ and (2) initiating treatment biological disease-modifying antirheumatic drugs (bDMARDs). The following clinical, radiological and demographic parameters were collected: gender, age, weight, height, Disease Activity Score on 28 joints (DAS28), C reactive protein (CRP) serum levels, X-ray of hands and feet (at baseline and every 6–12 months), disease duration prior to bDMARD initiation, glucocorticoids and treatment with conventional and biological therapies including methotrexate, leflunomide, infliximab, etanercept, adalimumab, golimumab, certolizumab pegol, rituximab, abatacept, tocilizumab, baricitinib and tofacitinib.

We conducted a case-crossover study in which every patient serves as its own control. In case-crossover study time-varying factors are assessed in hazard periods (before an ‘event’) and in control periods. In such scheme every patient could have multiple hazard periods and control periods. Case-crossover design permits to control for time-invariant and between patients’ factors (figure 1). We defined hazard periods as the 6 months (and 3-month periods in sensitivity analysis) immediately preceding a flare of disease. Flare was defined as DAS28–CRP increase >1.2 and current DAS28–CRP ≥ 3.2 (OMERACT definition).¹⁴ Other definitions of flare were employed in sensitivity analyses. The time-variant independent variable of interest (exposure) was the tapering of glucocorticoids during the hazard periods



Figure 1 Case-crossover study design. In case-crossover study each patient provides one or multiple hazard periods and control periods. Hazard period was the 6-month period immediately preceding a flare, control period was the 6-month period preceding a visit in which Disease Activity Score on 28 joints–C reactive protein was <3.2 .

versus control periods. Tapering of glucocorticoids was defined as the reduction of glucocorticoids dose from prior visit. Glucocorticoid tapering was further categorised into (1) tapering to 0 mg/day (ie, discontinuation), (2) tapering to 0–2.5 mg/day, (3) tapering to 2.5–5 mg/day, (4) tapering to 5–7.5 mg/day and (5) tapering to ≥ 7.5 mg/day. Conditional logistic regression analysis was employed to determine the association between tapering of glucocorticoids with flare risk. We adjusted, as per case-crossover design, for relevant time-varying confounders (ie, biological Disease Modifying Anti-Rheumatic Drug (bDMARD) use, conventional synthetic (cs)DMARD use, Non-Steroidal Anti-Inflammatory Drugs (NSAID) use and disease activity). Indeed, patients were allowed to switch bDMARD or csDMARD during the study and can use NSAID medications for pain control. Smoothed curve with restricted cubic splines with knots at each glucocorticoid tapering dose was employed to describe the dose–response association between glucocorticoid tapering and risk of flare. Differences were considered significant at $p < 0.05$. All statistical analyses were performed using SPSS V.26 (SPSS, Chicago, Illinois, USA) and GraphPad Prism V.9.3.1 (GraphPad Software, San Diego, California, USA). The study was conducted according to the protocol BIOREVE 534CESC approved by the University of Verona local Ethic Committee, in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

RESULTS

A total of 508 patients were included in the study. Among the cohort, 267 (52.5%) patients had at least a flare (DAS28–CRP increase >1.2 and current DAS28–CRP ≥ 3.2 between two consecutive visits) during the follow-up and served as the case-crossover study population. A total of 1545 visits were available for analysis and 345 (22.3%) flares were recorded. Two hundred and sixteen (80.9%) patients were on glucocorticoids at baseline. Tapering of glucocorticoids was done in 176 (81.5% of 216) patients and discontinuation was attained, at least once, in 125 (57.8% of 216) patients. Definitive discontinuation was achieved in 101 (46.7%) patients at a median follow-up of 884 days (IQR: 700–976 days). Among the overall cohort 320 (62.9%) patients switched bDMARD at least once and 102 (20.1%) switched bDMARD more than once. General characteristics of the overall and flare cohorts are presented in table 1.

The adjusted ORs (aORs) for flare compared with no tapering were as follows: for tapering to 0 mg/day (ie, discontinuation) 1.45 (95% CI: 1.13 to 2.24), for tapering to 0–2.5 mg/day 1.37 (95% CI: 1.06 to 2.01), for tapering to 2.5–5 mg/day 1.29 (95% CI: 0.98 to 1.90), for tapering to 5–7.5 mg/day 0.98 (95% CI: 0.68 to 1.61) and for tapering to ≥ 7.5 mg/day 0.89 (95% CI: 0.39 to 2.10). Figure 2 depicts the smoothed line for dose–response association between glucocorticoid tapering and risk of flare. Apparently, tapering the doses to >2.5 mg/day did

Table 1 Baseline characteristics of the cohort and outcomes

Characteristic	Overall cohort (n=508)	Flare cohort (n=267)
Age, years (±SD)	58.3 (12.9)	55.4 (14.6)
Sex, female (%)	472 (81.6)	218 (81.6)
Weight, kg (±SD)	67.7 (13.9)	69.1 (14.8)
Height, cm (±SD)	164 (8)	165 (9)
Median follow-up, days (IQR)	806 (559–974)	884 (700–1005)
First bDMARD prescribed		
Abatacept, n (%)	139 (24.0)	105 (39.3)*
Adalimumab, n (%)	89 (15.4)	46 (17.2)
Baricitinib (%), n	25 (4.3)	14 (5.2)
Certolizumab Pegol, n (%)	27 (4.6)	20 (7.4)
Etanercept, n (%)	151 (26.1)	42 (15.7)*
Golimumab, n (%)	34 (5.9)	11 (4.1)
Infliximab, n (%)	13 (2.2)	5 (1.9)
Rituximab, n (%)	27 (4.6)	3 (1.1)*
Tocilizumab, n (%)	73 (12.6)	21 (7.8)*
Seropositive, n (%)	344 (59.5)	158 (59.2)
Erosive disease, n (%)	296 (51.2)	228 (85.4)*
Disease duration, years (IQR)	12 (6–21)	8 (4–16)*
Treatment with cDMARD, n (%)	543 (93.9)	240 (89.9)
Outcomes		
Treatment with glucocorticoids any dose any time, n (%)	382 (75.2)	216 (80.9)
Tapering of glucocorticoids any dose, n (%)	297 (77.7 of 382)	176 (81.5 of 216)
Glucocorticoid dose at baseline, mg/day of prednisone equivalent (IQR)	2.5 (0–5)	5 (1–7.5)*
Glucocorticoid dose before tapering, mg/day of prednisone equivalent (IQR)	2.0 (0–5)	4.5 (1.5–15)
Median glucocorticoid cumulative dose during follow-up, mg of prednisone equivalent (IQR)	2300 (400–3400)	3900 (700–4400)*
Average DAS28–CRP, (IQR)	2.69 (1.82–3.63)	2.81 (1.92–4.90)*
Average VAS pain, (IQR)	30 (10–60)	34 (15–70)*
Average swelling joint count (IQR)	1 (0–2)	1.5 (0–3)
Average tender joint count (IQR)	2.9 (1–5)	2.6 (1–6)

Patients were allowed to switch or swap bDMARD during follow-up.

*P<0.05.

bDMARD, biological disease-modifying antirheumatic drug; cDMARD, conventional disease modifying antirheumatic drug; CRP, C reactive protein; DAS28, Disease Activity Score on 28 joints; VAS, visual analogue scale.

not result in an increased risk of flare. Similar results were found when we applied a different flare definition (DAS28–CRP increase >1 and current DAS28–CRP ≥3.2), data not shown.

DISCUSSION

Herein, we conducted a case-crossover study design aimed to determine the dose–response association between glucocorticoids tapering and risk of flare in patients with RA on biologics. In aggregate, we found that tapering to doses above 2.5 mg/day of prednisone

was generally effective in terms of flare risk in patients receiving bDMARDs. We found an apparent threshold at above 2.5 mg/day for an increased risk of flares despite CIs were somehow wide and no definitive conclusion can be drawn. The vast majority of patients in our study were on glucocorticoids at baseline and most of these tried tapering the dose through the follow-up, reflecting a good application of EULAR recommendations.⁶ However, less than half of the cohort initially treated with glucocorticoids achieved definitive discontinuation. These findings are in line with the modern literature on

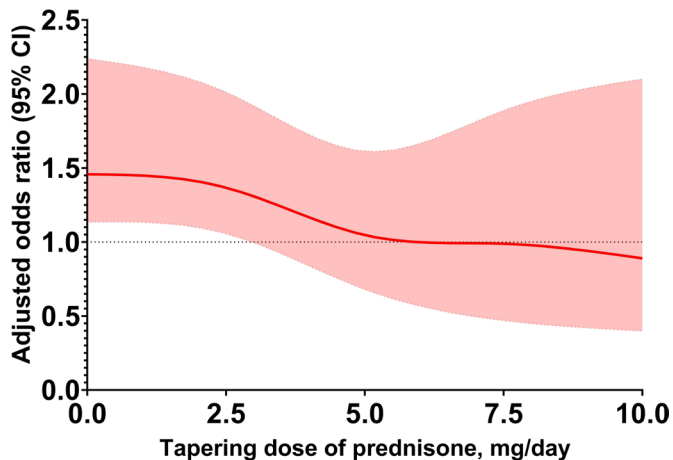


Figure 2 Dose–response association between tapering of glucocorticoids and risk of flare the curve was interpolated using the conditional logistic regression model. The curve was smoothed with restricted cubic splines with knots at 0–2.5 mg/day, 2.5–5 mg/day, 5–7.5 mg/day and ≥ 7.5 mg/day. The reference was not tapering.

patients with RA,¹¹ further highlighting the generalisability of our results. Indeed, glucocorticoids withdrawal might be challenging in many patients due to recurrent disease flares.¹⁵

Reducing glucocorticoids to doses ≤ 2.5 mg/day was associated with higher risk of flare. Such finding is somehow in line with other studies. As an example, in the Steroid ELiMiNation In Rheumatoid Arthritis (SEMIRA) study patients with RA were randomised to receive tocilizumab and fixed dose of glucocorticoids or tocilizumab with glucocorticoids tapered until discontinuation over 6 months.⁹ Interestingly, most of the flares in the tapering group of the SEMIRA study were reported at doses between 2 mg/day and 0 mg/day. The authors speculated that the latter finding might be due either to a delayed effect of tapering higher doses or that some patients still respond to lower glucocorticoid doses but do not tolerate discontinuation. Our finding might point towards the second hypothesis.

Our results might have immediate clinical fallouts. Glucocorticoids are associated with relevant adverse events, which strictly depends on dose.^{16–18} Treating chronically with < 2.5 mg/day of prednisone equivalent might not result in better disease control, as we demonstrated, but might pose patients at greater risk of adverse events.⁸ In the Glucocorticoid LOw-dose in Rheumatoid Arthritis (GLORIA) trial patients with RA over the age of 65 years were randomised to receive 5 mg/day of prednisone or placebo. After 2 years of treatment disease activity was 0.37 points lower on prednisolone with trade-off of 24% increase in patients with mostly non-severe adverse events, which lead the authors to conclude that the harm/benefit balance of treating chronically with glucocorticoids in such population was overall positive. We have drawn a somehow similar conclusion from our analysis as regard effectiveness of chronic glucocorticoid

treatment, despite our study is largely different in design and population from the GLORIA trial.

The EULAR set the threshold for low-dose glucocorticoids at 7.5 mg/day and many authors proposed to lower such threshold to 5 mg/day.^{12,19} Both definitions are arbitrary and, arguably, based on debatable assumption. Our results might suggest to slightly lower this threshold in patients with RA receiving bDMARDs.

Our study has strengths and limitations. To explore the causative and temporal association between glucocorticoid tapering and risk of flare, we applied a case-crossover design, which effectively controls for between-patients and time-invariant within-patients confounders. Such study design can reduce confounding by indication bias, a type of channelling bias, that commonly affects observational studies. However, our population might not be generalisable to the entire population with RA (not on bDMARDs or early RA). Indeed, patients with early disease are commonly treated with glucocorticoids and tapering of glucocorticoids towards discontinuation might be easier in such population. In addition, non-measured time-varying confounders (such as infections) might have affected our results. Indeed, it is reasonable to think that few patients might have reduced glucocorticoids in the fear of adverse events and some others might not have reduced glucocorticoids in the fear of disease relapse. In addition, we did not collect information regarding the rapidity of tapering, which might have affected the flare rate. The monocentric nature of the study might have induced some type of systematic bias related to center-specific attitudes towards tapering glucocorticoids. Multicentric studies or similar studies replicated in other cohorts are warranted to assess reproducibility of our results.

In conclusion we found that tapering glucocorticoids to doses above 2.5 mg/day was generally effective in a population of patients with RA treated with bDMARDs. Our study might help define new glucocorticoid reducing strategies, which should aim to doses between 5 and 2.5 mg/day of prednisone equivalent.

Contributors Conceptualisation, data curation and formal analysis: GA. Investigation: GA, AF, MR, DB, FP, CB, OV and DG. Project administration and supervision: MR. Validation: GA and MR. Writing—original draft: GA and FP. Writing—review and editing: GA, AF, MR, DB, FP, CB, OV and DG. GA is the guarantor of the work. GA accepts full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

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

Ethics approval The study was conducted according to the protocol BIOREVE 534CESC approved by the University of Verona local Ethic Committee, in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

ORCID iDs

Giovanni Adami <http://orcid.org/0000-0002-8915-0755>

Ombretta Viapiana <http://orcid.org/0000-0003-1917-5655>

REFERENCES

- Adami G, Viapiana O, Rossini M, *et al.* Association between environmental air pollution and rheumatoid arthritis flares. *Rheumatology* 2021;60:4591–7.
- Adami G, Rossini M, Viapiana O, *et al.* Environmental air pollution is a predictor of poor response to biological drugs in chronic inflammatory arthritides. *ACR Open Rheumatol* 2021;3:451–6.
- van der Leeuw MS, Messelink MA, Tekstra J, *et al.* Using real-world data to dynamically predict flares during tapering of biological DMARDs in rheumatoid arthritis: development, validation, and potential impact of prediction-aided decisions. *Arthritis Res Ther* 2022;24:74.
- Kashiwado Y, Kiyohara C, Kimoto Y, *et al.* Clinical course of patients with rheumatoid arthritis who continue or discontinue biologic therapy after hospitalization for infection: a retrospective observational study. *Arthritis Res Ther* 2022;24:131.
- Albrecht K, Callhoff J, Schneider M, *et al.* High variability in glucocorticoid starting doses in patients with rheumatoid arthritis: observational data from an early arthritis cohort. *Rheumatol Int* 2015;35:1377–84.
- Smolen JS, Landewé RBM, Bijlsma JWJ, *et al.* EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. *Ann Rheum Dis* 2020;79:685–99.
- Smolen JS, Landewé RBM, Bergstra SA. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2022 update. *Ann Rheum Dis* 2022. [Epub ahead of print: 10 Nov 2022].
- Boers M, Hartman L, Opris-Belinski D, *et al.* Low dose, add-on prednisolone in patients with rheumatoid arthritis aged 65+: the pragmatic randomised, double-blind placebo-controlled GLORIA trial. *Ann Rheum Dis* 2022;81:925–36.
- Burmester GR, Buttgerit F, Bernasconi C, *et al.* Continuing versus tapering glucocorticoids after achievement of low disease activity or remission in rheumatoid arthritis (SEMIRA): a double-blind, multicentre, randomised controlled trial. *Lancet* 2020;396:267–76.
- Volkman ER, Rezai S, Tarp S, *et al.* We still don't know how to taper glucocorticoids in rheumatoid arthritis, and we can do better. *J Rheumatol* 2013;40:1646–9.
- Xie W, Huang H, Li G, *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;80:997–1003.
- Buttgerit F, da Silva JAP, Boers M, *et al.* Standardised Nomenclature for glucocorticoid dosages and glucocorticoid treatment regimens: current questions and tentative answers in rheumatology. *Ann Rheum Dis* 2002;61:718–22.
- Aletaha D, Neogi T, Silman AJ, *et al.* 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League against rheumatism collaborative initiative. *Ann Rheum Dis* 2010;69:1580–8.
- van der Maas A, Lie E, Christensen R, *et al.* Construct and criterion validity of several proposed DAS28-based rheumatoid arthritis flare criteria: an OMERACT cohort validation study. *Ann Rheum Dis* 2013;72:1800–5.
- Maassen JM, Dos Santos Sobrin R, Bergstra SA, *et al.* Glucocorticoid discontinuation in patients with early rheumatoid and undifferentiated arthritis: a post-hoc analysis of the best and improved studies. *Ann Rheum Dis* 2021;80:1124–9.
- Wilson JC, Sarsour K, Gale S, *et al.* Incidence and risk of Glucocorticoid-Associated adverse effects in patients with rheumatoid arthritis. *Arthritis Care Res* 2019;71:498–511.
- Saag KG, Koehnke R, Caldwell JR, *et al.* Low dose long-term corticosteroid therapy in rheumatoid arthritis: an analysis of serious adverse events. *Am J Med* 1994;96:115–23.
- Adami G, Saag KG. Glucocorticoid-Induced osteoporosis: 2019 Concise clinical review. *Osteoporos Int* 2019;30:1145–56.
- Strehl C, Bijlsma JWJ, de Wit M, *et al.* Defining conditions where long-term glucocorticoid treatment has an acceptably low level of harm to facilitate implementation of existing recommendations: viewpoints from an EULAR Task force. *Ann Rheum Dis* 2016;75:952–7.