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Risk of flare after tapering or withdrawal of biologic/targeted synthetic disease-modifying anti-rheumatic drugs in patients with rheumatoid arthritis or axial spondyloarthritis

A systematic review and meta-analysis

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Risk of flare after tapering or withdrawal of b-/tsDMARDs in patients with RA or axSpA: *A systematic review and meta-analysis*

Running header: SLR on tapering/withdrawal of b-/tsDMARDs in RA and axSpA

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ABSTRACT

Objective: To evaluate flare risk when tapering or withdrawing biological or targeted synthetic disease-modifying antirheumatic drugs (b-/tsDMARDs) compared to continuation in patients with inflammatory arthritis (IA) in sustained remission or low disease activity.

Methods: Articles were identified in Cochrane Library, PubMed, EMBASE and Web of Science. Eligible trials were randomised, controlled trials comparing tapering and/or withdrawal of b- and/or tsDMARDs with standard dose in IA. Random-effects meta-analysis was performed with risk ratio (RR), or Peto's Odds Ratio (POR) for sparse events, and 95% confidence intervals (95%CI).

Results: The meta-analysis comprised 22 trials: 11 assessed tapering and 7 addressed withdrawal (4 assessed both). Only trials with an rheumatoid arthritis (RA) or axial spondyloarthritis (axSpA) population were identified. An increased flare risk was demonstrated when b-/tsDMARD tapering was compared to continuation, RR = 1.45 (95%CI: 1.19 to 1.77, I^2 = 42.5%), and potentially increased for persistent flare, POR = 1.56 (95%CI: 0.97 to 2.52, I^2 = 0%). Comparing tumour necrosis factor inhibitor (TNFi) withdrawal to continuation, a highly increased flare risk (RR = 2.28, 95%CI: 1.78 to 2.93, I^2 = 78%) and increased odds of persistent flare (POR = 3.41, 95%CI: 1.91 to 6.09, I^2 = 49%) was observed. No clear difference in flare risk between RA or axSpA was observed.

Conclusion: A high risk for flare and persistent flare was demonstrated for TNFi withdrawal whereas an increased risk for flare but not for persistent flare was observed for b-/tsDMARD tapering. Thus, tapering seems to be the more favourable approach.

Registration: PROSPERO (CRD42019136905).

Keywords: Biological therapies, Rheumatoid arthritis, Spondylarthropathies (including psoriatic arthritis), Systematic review, Metaanalysis.

KEY MESSAGES

- Tapering b-/tsDMARDs in RA and axSpA results in an increased risk of flare but not persistent flare
- Withdrawing TNFis in RA and axSpA results in both an increased risk of flare and persistent flare
- Tapering seems to be the more favourable choice for a dose reduction strategy in RA and axSpA

INTRODUCTION

In recent years, a topic of great interest has been whether biologic or targeted synthetic disease-modifying antirheumatic drugs (bDMARDs or tsDMARDs, respectively) should be continued indefinitely in patients with inflammatory arthritis (IA) [i.e. rheumatoid arthritis (RA), psoriatic arthritis (PsA) and axial spondyloarthritis (axSpA)] in sustained remission or low disease activity (LDA). Lifelong continuation of standard dose can potentially lead to overtreatment; thereby, putting the individual patient at an unnecessary risk of adverse events e.g. serious infections (1). In addition to cost-savings (as b-/tsDMARDs are expensive), dose reduction by interval prolonging or complete drug withdrawal would result in fewer visits to the outpatient clinic for intravenous infusions or for medicine pick-up. Previous research has shown, that patient quality of life and patient satisfaction improve when the disease is controlled with fewer drug doses as the patients feel less dependent on their medication (2). A recent qualitative study in RA observed fear of arthritis flare and joint damage when discussing tapering of bDMARDs; however, as tapering would minimise the inconvenience of taking bDMARDs regularly, patients were willing to taper but not to completely withdraw (3).

Currently, several international guidelines recommend tapering of b- or tsDMARDs in patients with IA in sustained remission, whereas complete withdrawal is generally not recommended due to an increased flare risk (4–6). In the existing literature, various flare criteria have been used to evaluate patients with IA as validated flare criteria only was developed in 2013 for RA (DAS28crp increase >1.2 or >0.6 if current DAS28crp ≥3.2) (7) and in 2018 for axSpA (ASDAS increase ≥0.9) (8) whereas none exist for PsA. The heterogeneity in flare criteria must be taken into consideration when comparing trial results.

Previously, evidence from meta-analyses found tapering of bDMARDs in patients with RA in sustained remission/LDA to be comparable to continuation of standard dose (9–11) whereas

complete withdrawal was potentially inferior (9,10,12). To our knowledge, no meta-analyses have assessed flare risk when tapering or withdrawing b- or tsDMARDs compared to continuation of standard dose across all main forms of IA (spanning RA, axSpA, and PsA). However, recent reviews found tapering but not withdrawal of bDMARDs to be comparable to continuation of standard dose in axSpA and PsA (13–15).

This systematic literature review (SLR) aims to assess the risk for flare in patients with IA in sustained remission/LDA randomised to either tapering or withdrawal of various b- or tsDMARDs compared to continuation of the treatments.

MATHERIALS AND METHODS

Patient and public involvement

The conduct of this SLR was discussed with and acknowledged by patients treated with b- or tsDMARDs in sustained remission/LDA from the Department of Rheumatology, Aalborg University Hospital. Results were discussed at an informal meeting prior to submission.

Protocol and registration

This SLR was performed in accordance with the pre-specified protocol (**Supplementary Data S1**) as recommended in the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) protocol guideline (16,17) and registered at the International Prospective Register of Systematic Reviews (PROSPERO) on 2019-05-27 (CRD42019136905). Furthermore, the review was performed and reported in accordance with the recommendations of the 'Methodological Expectations of Cochrane Intervention Reviews' (18) and the PRISMA statement (19).

Search strategy

A systematic literature search was performed to identify randomised, controlled trials (RCTs) comparing tapering or withdrawal of b- or tsDMARDs with continuation of standard dose in adults with RA, PsA, or axSpA. The minimum required follow-up period was pre-specified as 24 weeks. The search strategy (**Supplementary Data S2**) was developed in collaboration with a trained medical research librarian (CS). On 2019/06/13-14, Cochrane Library, PubMed, EMBASE and Web of Science were searched. The search period was from the inception of the database up until the search date (rerun: 2021-01-11). Moreover, congress abstracts from EULAR and ACR after 2017-01-01 and reference lists of included articles/excluded reviews were reviewed for eligibility.

Study selection process

All identified records were uploaded in Endnote to remove duplicates; thereafter, imported to the Covidence Technology Platform (Covidence). The screening process was divided into three phases; all assessors were trained with a calibration exercise to ensure reviewer consistency. In phase one, LU, WKHD, CHL and SSA assessed titles and abstracts for relevance (yes, no or unclear); thereafter, LU and SK independently evaluated the abstracts for eligibility. In phase three, LU and SK reviewed full-texts articles for inclusion. Disagreement was resolved by discussion and if necessary, by consultation of a third independent assessor (LD).

Data collection process

A unique data extraction sheet was developed in Covidence based on the Cochrane Systematic Review Data Collection Form. Data extraction was done independently by LU and SK who resolved any disagreements by discussion and if necessary, by consultation of a third assessor

(LD/RC). Multiple reports of the same study was collated as recommended by Cochrane (18) . Extracted data included: journal, publication year, first author, study design, eligibility criteria, disease duration, duration of remission/LDA before inclusion, assessed b- or tsDMARDs, intervention and comparator details, risk of flare and persistent flare, risk of adverse events such as serious infections and identification of possible prognostic factors.

Study risk of bias assessment

For each eligible trial, the internal validity was evaluated using the Revised Cochrane risk-of-bias tool for randomised trials (RoB 2.0) template (20); thus, the following six domains were assessed: 1) Risk of bias arising from the randomisation process; 2) Risk of bias due to deviations from the intended interventions; 3) Missing outcome data; 4) Risk of bias in measurement of the outcome; 5) Risk of bias in selection of the reported result, and 6) The overall risk of bias. The domains were assessed as either "low risk of bias", "some concerns", or "high risk of bias". LU performed the risk of bias assessment; thereafter, SK checked the assessment for agreement. Differences was resolved by discussion and consensus. Corresponding authors of 16 studies were contacted by e-mail (a maximum of three emails) to gain access to the trial protocol and statistical analysis plan for the risk of bias assessment. Seven authors did not respond to the e-mails.

Effect measures

The primary statistical effect measure was the risk ratio (RR) with 95% confidence interval (95%CI) for flares (21). Secondary outcomes were due to anticipated sparse events analysed with Peto's Odds Ratio (POR) (22): (*i*) Persistent flare (i.e. flares with no improvement despite

dose escalation or glucocorticoids) and (*ii*) Serious adverse events (SAE) incl. serious infections.

Synthesis methods

Meta-analyses were performed based on restricted maximum likelihood (REML) mixed-effects models with trials applied as random effects. I^2 statistics was used to evaluate inconsistency among studies and prediction intervals were added to facilitate interpretation of the impact of between study heterogeneity (23,24). Two trials had more than one tapering strategy (25,26); therefore, data from the two tapering groups in each study was pooled. For the purpose of sensitivity, stratified meta-analyses were performed for the outcomes of flare and persistent flare. Further, in order to evaluate the robustness of the findings in the primary analyses, an arm-based Generalized Linear Mixed model (empirical Bayes) was used to evaluate the odds for flare and persistent flare for the tapering-, withdrawal- and continuation group. All analyses were performed in STATA (version 16) or SAS studio software (version 9.4).

Grading the certainty of the evidence

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to assess the overall quality of the evidence for risk of bias, imprecision, inconsistency, indirectness, and publication bias (27). The GRADE ratings of very low–, low-, moderate-, or high quality evidence was applied (28).

RESULTS

Study selection

The systematic literature search identified 14,861 references. **Figure 1** provides a detailed overview of study selection. From 163 papers assessed in full text, twenty-three studies were found

eligible and included in the qualitative synthesis; however, only 22 studies were included in the meta-analyses as one study did not provide sufficient data on the control group (29).

Study characteristics and risk of bias in individual trials

Study characteristics of the 23 included trials published between 2012 and 2021 are presented in **Table 1.** The study population based on data from the 22 trials included in the meta-analyses comprised 4,082 patients with RA from 17 trials and 831 patients with axSpA from 5 trials. The axSpA population were: ankylosing spondylitis (AS) in three studies (30–32), axSpA including AS in one study (33) and non-radiographic axSpA in one study (34). No studies were identified for patients with PsA or a mixed population of IA. Of the included trials, 64% were funded by the drug manufacture (29,30,33–45) with no difference between RA or axSpA (12/18 trials [67%] vs. 3/5 trials [60%], respectively). However, significantly more withdrawal studies (10/11 trials [91%]) were funded by the manufacture compared to tapering trials (8/16 trials [50%]).

Mean age across trials was 49 years with a younger axSpA population (39 years) compared to the RA population (52 years). As expected, a higher proportion of females were observed in the RA population (71%) compared to the axSpA population (22%). Disease duration was between 10 months (40) and 16.9 years (25).

Risk of bias assessment of the 23 included studies according to the RoB 2.0 are presented in Table 1. Only one study was evaluated corresponding to a low risk of bias in all items (24).

Synthesis of results

Risk for flare

Fifteen studies were included in a meta-analysis of the risk for flare after tapering b- or tsDMARDs compared to continuation of standard dose. Eight trials assessed etanercept (26,30–

32,35,37,46,47), five adalimumab (26,31,46–48), two certolizumab pegol (33,36) and one trial abatacept (41), baricitinib (43), golimumab (31), infliximab (31), rituximab (25), or tocilizumab (39). Across the fifteen trials, the observed flare rate was 32.7% (431/1,319) for tapering and 22.2% (254/1,146) for continuation. As presented in **Figure 2**, the meta-analysis of these data demonstrated an increased risk of flares, RR = 1.45 (95%CI: 1.19 to 1.77); corresponding to an absolute number needed to treat in order to harm (NNH) of 10 patients.

In a meta-analysis assessing flare risk after withdrawal compared to continuation of standard dose only data on TNFi were available. Among 11 included studies, six evaluated etanercept (35,37,38,44,45,49), four adalimumab (34,40,42,49) three certolizumab pegol (33,36,49) and one study golimumab (49), and infliximab (49). The observed flare rate was 55.3% (830/1,500) for withdrawal and 24.1% (293/1,217) for continuation. In the meta-analysis, a highly increased flare risk (Figure 2) was observed, RR = 2.28 (95%CI: 1.78 to 2.93), NNH was 3 patients.

As presented in **Supplementary Table S1**, a network meta-analysis confirmed the highly increased odds for flare when b- or tsDMARDs was withdrawn compared to tapered, OR = 5.62 (95%CI: 3.44 to 9.17).

Risk for persistent flare

Eight trials assessing a tapering strategy to continuation of standard dose had data on persistent flare and were included in the meta-analysis. Four trials assessed etanercept (35,37,46,47), two adalimumab (46,47), two certolizumab pegol (33,36), and one trial baricitinib (43), or rituximab (25). The observed persistent flare rate was 4.8% (50/1,035) for tapering and 2.9% (25/854) for continuation. The meta-analysis, however, only indicated potentially increased odds for persistent flare, Peto's OR = 1.56 (95%CI: 0.97 to 2.52) (**Figure 3**) with NNH of 64 patients.

Seven trials evaluating a withdrawal strategy of TNFi to continuation of standard dose had data on persistent flare. Four trials evaluated etanercept (39,41,43,44) two certolizumab pegol (33,36), and one study adalimumab (34). The observed persistent flare rate was 15.3% (108/707) for withdrawal and 4.2% (28/664) for continuation. The meta-analysis demonstrated a significant increase in odds for persistent flare (Figure 3), Peto's OR = 3.41 (95%CI: 1.91 to 6.09), with NNH corresponding to 11 patients.

The network meta-analysis confirmed the increased odds for persistent flare when comparing withdrawal of b- or tsDMARDs to tapering, OR = 3.16 (95%CI: 1.49 to 6.67) (Supplementary Table S1).

No statistically significant difference in odds for serious adverse events (SAE), serious infections or death was observed between the tapering group and the continuation group nor between the withdrawal group and the continuation group (**Supplementary Figures S1-S3**).

Sensitivity analyses

Stratified meta-analyses on the risk for flare, showed no significant difference between patients with RA or axSpA tapering or withdrawing b- or tsDMARDs compared to continuation of standard dose (**Supplementary Figure S4**). However, when comparing withdrawal of TNFi to continuation, the risk for persistent flare in patients with RA appeared to be higher than for patients with axSpA (**Supplementary Figure S5**).

When stratifying for b- or tsDMARD therapy, a sub-group meta-analysis demonstrated an increased flare risk when baricitinib, tocilizumab or a combined group of TNFis (i.e. studies with ≥ 2 different TNFi) were tapered compared to continuation of standard dose (**Supplementary Figure S6**) but not when tapering abatacept, adalimumab, certolizumab pegol, etanercept, or

rituximab. When assessing withdrawal, an increased risk for flare was demonstrated for adalimumab, etanercept and a combined group of TNFi but not for certolizumab pegol (Supplementary Figure S6). However, as data were sparse for the individual drugs for both tapering and withdrawal, these sub-analyses are limited by uncertainties.

When the risk for flare in the tapering group compared to the continuation group was stratified by dose reduction strategy, the flare risk appeared to be highest for the disease-activity guided dose reduction strategy, followed by the one-step fixed 50-65% dose reduction strategy and lowest for the one-step fixed 25% dose reduction strategy (**Supplementary Figure S7**).

Stratifying for time since arthritis diagnosis, a trend towards a higher flare risk for patients with established disease (i.e. diagnosis ≥ 3 years) compared to recently diagnosed (i.e. < 3 years) was observed when b- or tsDMARDs was tapered compared to continued (**Supplementary Figure S8**). No significant difference in flare risk stratified by length of arthritis diagnosis was found when comparing TNFi withdrawal to continuation. Moreover, subgroup meta-analyses found no significant difference in flare risk when tapering or withdrawing b- or tsDMARDs compared to continuation of standard dose were stratified by length of prior remission/LDA (i.e. < 26 weeks versus ≥ 26 weeks) before the start of the intervention period (**Supplementary Figure S9**). However, a significantly increased flare risk when withdrawing TNFi compared to continuation was observed in studies with longer follow-up (i.e. a longer intervention period) compared to studies with a shorter follow-up period (**Supplementary Figure S10**). No significant difference in flare risk was observed between the tapering group and the continuation group when stratifying for length of the intervention period. Lastly, a list of potential prognostic factors are presented in **Supplementary Table S2**.

Certainty of the evidence

Quality assessment of the evidence was performed in accordance with the GRADE approach (27) and presented in Table 2. Visual assessment in a funnel plot did not reveal any publication bias for the primary outcome flare (**Supplementary Figure S11**). Nor did an Eggers test for small-study effects. A large difference in studies funded by the manufacture was observed (withdrawal trials: 91%, tapering trials: 50%); however, a stratified meta-analysis did not reveal any difference in flare risk between studies that were funded by the manufacture or not (**Supplementary Figure S12**).

Withdrawing bDMARDs compared to continuation of standard dose stratified by the overall risk of bias showed a significant difference as studies with a high overall risk of bias had a higher flare risk and persistent flare risk compared to studies with an unclear overall risk of bias (**Supplementary Figure S13-14**). The meta-analyses did not reveal any significant group differences for tapering compared to continuation; however, a trend towards a higher flare risk for studies with less overall risk of bias and a trend towards a higher persistent flare risk for studies with higher overall bias was observed.

DISCUSSION

To our knowledge, this SLR is the first to evaluate tapering and withdrawal of various b- or tsDMARDs in patients with RA and axSpA. An increased flare risk for patients who taper or withdraw b- or tsDMARDs compared to continuation of standard dose was observed; however, the odds for persistent flare was only significantly increased for withdrawal compared to continuation. Moreover, a network meta-analysis demonstrated a highly significant increased odds for flare and persistent flare when withdrawal of b- or tsDMARDs was compared to tapering.

The findings in this SLR support current international treatment guidelines in RA and axSpA as tapering, but not withdrawal, is judged to be feasible and safe (4,5). Moreover, the findings

are in line with previous evidence as a recent Cochrane SLR demonstrated that withdrawal of TNFi in patients with RA may be inferior to continuation but that tapering was comparable (9). Similarly, *Henaux et al.* found an increased risk among patients with RA for losing LDA when withdrawing bDMARDs compared to continuation of standard dose but no increased risk when tapering (10). A recent review by *Vasconcelos et al.* supports these findings as no significant difference in LDA in patients with RA was observed between the tapering group and the continuation group (11). Furthermore, *Schlager et al.* reported a very high odds for flare after withdrawal of bDMARDs compared to continuation in patients with RA (12). The effect of tapering or withdrawal of b- or tsDMARDs on disease activity in patients with axSpA have not yet been evaluated in a meta-analysis. However, the observed flare rate in this SLR of 63.8% for patients with axSpA withdrawing TNFi lies within the range of previously reported flare rates of 11-53% (15) and 76-100% (13). Three studies that were excluded in this review after full-text screening have previously been included in other reviews; however, these studies had only a small proportion of patients in treatment with bDMARDs (50,51) or the follow-up period was very short (< 24 weeks) (52).

This SLR demonstrated no significant difference in odds for SAE, serious infections or death when tapering or withdrawing b- or tsDMARDs compared to continuation of standard dose. Similarly, a recent meta-analysis by *Vinson et al.* found no significant difference in the risk for serious infection, SAE, death, malignancies or adverse events among patients with RA or axSpA who tapered or continued b- or tsDMARDs (53).

There are limitations to this work as the majority of studies had data on patients with RA (17 studies), only five studies on axSpA and none on PsA. However, no significant difference in flare risk was observed between patients with RA or axSpA tapering or withdrawing b- or tsDMARDs compared to continuation of standard dose. No conclusion can be drawn from this

work on the flare risk among patients with PsA due to the absence of available studies; future research is needed. Another important limitation to discuss is the heterogenous flare definition in the included trials as validated flare criteria first was published in 2013 for RA (7) and 2018 for axSpA (8). However, the two independent assessors, LU and SK, judged the flare definitions to be adequate and reasonable for measuring flare, thereby, allowing combination of trial data. Important differences in tapering strategies e.g. one-step fixed dose reduction versus disease-activity guided dose reduction was observed among the included studies. However, these differences were taken into consideration in a subgroup meta-analysis where a tendency towards a higher flare risk (as expected) was observed for the disease-activity guided dose reduction strategy (step-wise reduction of b- or tsDMARDs until flare or complete withdrawal) compared to a one-step fixed dose reduction strategy.

Data on b- or tsDMARDs with different modes of actions was combined in the meta-analyses as data on the individual drugs are sparse; however, a subgroup meta-analyses was performed to explore potential differences in flare risk. The subgroup analyses revealed that some drugs seem to have a greater flare risk than others. However, conclusions must be made with caution as data are sparse; especially for abatacept, baricitinib, rituximab and tocilizumab where only one study exists.

Another limitation to discuss regards the heterogeneity in study designs: newly diagnosed or established disease, duration of remission/LDA before start of the intervention period and duration of follow-up. Subgroup meta-analyses were performed to explore these differences and revealed a trend towards a higher flare risk in patients with established disease when tapering b- or tsDMARDs compared to continuation and a higher flare risk in studies with a longer follow-up period when TNFi was withdrawn compared to continued. Thus, the observed risk differences are important to have in mind when discussing dose reduction in clinical practice.

The overall certainty of evidence was judged to be low for the following outcomes: flare when withdrawing, persistent flare when tapering, and death for both tapering and withdrawal. Thus, this limits the confidence of these findings and highlights the need for future research.

CONCLUSION

To our knowledge, this meta-analysis is the first to evaluate the risk of flare among patients with RA and axSpA tapering or withdrawing various b- or tsDMARDs compared to continuation of standard dose. A significantly and noteworthy high risk for flare and, moreover, for persistent flare was observed when withdrawing TNFi. Furthermore, an increased risk for flare but not for persistent flare was demonstrated when b- or tsDMARDs was tapered. Thus, for clinical practise tapering should be considered the more favourable approach (compared to withdrawal) when dose reduction of b- or tsDMARDs is considered feasible.

DATA SHARING

This review contain data that are available in the included published papers; however, access to (not publicly available) study protocols and statistical analysis plans was obtained from authors.

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DISCLOSURE STATEMENT

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AUTHORS' CONTRIBUTIONS

LU drafted this manuscript. LU, SK, LD, RC, AS and EMH contributed to development of the review design. LU and CS developed the search strategy and CS performed the database searches. RC provided specialist statistic knowledge and drafted the data analysis plan. WKHD, CL and SSA performed the phase 1 screening. SK and LU performed phase 2 and 3 screening, data extraction and risk of bias assessment. LU and RC conducted the quality assessment in accordance with GRADE. All authors contributed to refinement of this systematic review and approved the final manuscript.

REFERENCE LIST

1. Singh JA, Cameron C, Noorbaloochi S, Cullis T, Tucker M, Christensen R, et al. Risk of serious infection in biological treatment of patients with rheumatoid arthritis: A systematic review and meta-analysis. *Lancet* 2015;386:258–65.
2. Richter A, Anton SF, Koch P, Dennett SL. The impact of reducing dose frequency on health outcomes. *Clin Ther* 2003;25:2307–35.
3. Chan SJ, Stamp LK, Liebergreen N, Ndukwe H, Marra C, Treharne GJ. Tapering Biologic Therapy for Rheumatoid Arthritis: A Qualitative Study of Patient Perspectives. *Patient* 2020;13:225–34.
4. Smolen JS, Landewé RBM, Bijlsma JWJ, Burmester GR, Dougados M, Kerschbaumer A, 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.
5. van der Heijde D, Ramiro S, Landewé R, Baraliakos X, Van den Bosch F, Sepriano A, et al. 2016 update of the ASAS-EULAR management recommendations for axial spondyloarthritis. *Ann Rheum Dis* 2017;76:978–91.
6. Gossec L, Baraliakos X, Kerschbaumer A, de Wit M, McInnes I, Dougados M, et al. EULAR recommendations for the management of psoriatic arthritis with pharmacological therapies: 2019 update. *Ann Rheum Dis* 2020;79:700–12.
7. van der Maas A, Lie E, Christensen R, Choy E, de Man YA, van Riel P, 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.
8. Molto A, Gossec L, Meghnathi B, Landewé RBM, van der Heijde D, Atagunduz P, et al. An Assessment in SpondyloArthritis International Society (ASAS)-endorsed

definition of clinically important worsening in axial spondyloarthritis based on ASDAS. *Ann Rheum Dis* 2018 Jan;77:124–7.

9. Verhoef LM, van den Bemt BJF, van der Maas A, Vriezekolk JE, Hulscher ME, van den Hoogen FHJ, et al. Down-titration and discontinuation strategies of tumour necrosis factor-blocking agents for rheumatoid arthritis in patients with low disease activity. *Cochrane Database Syst Rev* 2019;5:CD010455.
10. Henaux S, Ruyssen-Witrand A, Cantagrel A, Barnetche T, Fautrel B, Filippi N, et al. Risk of losing remission, low disease activity or radiographic progression in case of bDMARD discontinuation or tapering in rheumatoid arthritis: Systematic analysis of the literature and meta-analysis. *Ann Rheum Dis* 2018;77:515–22.
11. Vasconcelos LB, Silva MT, Galvao TF. Reduction of biologics in rheumatoid arthritis: A systematic review and meta-analysis. *Rheumatol Int* 2020;40:1949–59.
12. Schlager L, Loiskandl M, Aletaha D, Radner H. Predictors of successful discontinuation of biologic and targeted synthetic DMARDs in patients with rheumatoid arthritis in remission or low disease activity: A systematic literature review. *Rheumatology* 2020;59:324–34.
13. Navarro-Compán V, Plasencia-Rodríguez C, de Miguel E, Balsa A, Martín-Mola E, Seoane-Mato D, et al. Anti-TNF discontinuation and tapering strategies in patients with axial spondyloarthritis: A systematic literature review. *Rheumatology* 2016;55:1188–94.
14. Ye W, Tucker LJ, Coates LC. Tapering and Discontinuation of Biologics in Patients with Psoriatic Arthritis with Low Disease Activity. *Drugs* 2018;78:1705–15.
15. Edwards CJ, Fautrel B, Schulze-Koops H, Huizinga TWJ, Kruger K. Dosing down with biologic therapies: A systematic review and clinicians' perspective. *Rheumatology*

2017;56:1847–56.

16. Moher D, Shamseer L, Clarke M, Ghersi D, Liberato A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis (PRISMA-P) 2015 statement. *Syst Rev* 2015;4:1.

17. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: Elaboration and explanation. *BMJ* 2016;354:g7647.

18. Higgins JPJ, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al. Cochrane Handbook for Systematic Reviews of Interventions. *Cochrane* 2020, version 6.2 (updated February 2021). Available from www.training.cochrane.org/handbook.

19. Page MJ, Moher D, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. PRISMA 2020 explanation and elaboration: Updated guidance and exemplars for reporting systematic reviews. *BMJ* 2021;372:n160.

20. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: A revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;366:l4898.

21. Guyatt GH, Oxman AD, Santesso N, Helfand M, Vist G, Kunz R, et al. GRADE guidelines: 12. Preparing Summary of Findings tables - Binary outcomes. *J Clin Epidemiol* 2013;66:158–72.

22. Bradburn MJ, Deeks JJ, Berlin JA, Localio AR. Much ado about nothing: A comparison of the performance of meta-analytical methods with rare events. *Stat Med* 2007;26:53–77.

23. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557–60.

24. Riley RD, Higgins JPT, Deeks JJ. Interpretation of random effects meta-analyses. *BMJ*

2011;342:d549.

25. Verhoef LM, den Broeder N, Thurlings RM, van der Laan WH, van der Weele W, Kok MR, et al. Ultra-low doses of rituximab for continued treatment of rheumatoid arthritis (REDO study): A randomised controlled non-inferiority trial. *Lancet Rheumatol* 2019;1:e145–53.

26. Ibrahim F, Lorente-Cánovas B, Doré CJ, Bosworth A, Ma MH, Galloway JB, et al. Optimizing treatment with tumour necrosis factor inhibitors in rheumatoid arthritis-A proof of principle and exploratory trial: Is dose tapering practical in good responders? *Rheumatology* 2017;56:2004–14.

27. Balshem H, Helfand M, Schünemann HJ Oxman AD, Kunz R, Brozek J, et al. GRADE guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol* 2011;64:401–6.

28. Mustafa RA, Santesso N, Brozek J, Akl EA, Walter SD, Norman G, et al. The GRADE approach is reproducible in assessing the quality of evidence of quantitative evidence syntheses. *J Clin Epidemiol* 2013;66:736–42.

29. Raffeiner B, Botsios C, Ometto F, Bernardi L, Stramare R, Todesco S, et al. Effects of half dose etanercept (25 mg once a week) on clinical remission and radiographic progression in patients with rheumatoid arthritis in clinical remission achieved with standard dose. *Clin Exp Rheumatol* 2015;33:63–8.

30. Yates M, Hamilton LE, Elender F, Dean L, Doll H, MacGregor AJ, et al. Is etanercept 25 mg once weekly as effective as 50 mg at maintaining response in patients with ankylosing spondylitis? a randomized control trial. *J Rheumatol* 2015;42:1177–85.

31. Gratacós J, Pontes C, Juanola X, Sanz J, Torres F, Avendaño C, et al. Non-inferiority of dose reduction versus standard dosing of TNF-inhibitors in axial spondyloarthritis. *Arthritis Res Ther* 2019;21:11.

32. Cantini F, Niccoli L, Cassará E, Kaloudi O, Nannini C. Duration of remission after halving of the etanercept dose in patients with ankylosing spondylitis : A randomized, prospective, long-term, follow-up study. *Biol Targets Ther* 2013;7:1–6.

33. Landewé RBM, van der Heijde D, Dougados M, Baraliakos X, van den Bosch FE, Gaffney K, et al. Maintenance of clinical remission in early axial spondyloarthritis following certolizumab pegol dose reduction. *Ann Rheum Dis* 2020;79:920–8.

34. Landewé R, Sieper J, Mease P, Inman RD, Lambert RG, Deodhar A, et al. Efficacy and safety of continuing versus withdrawing adalimumab therapy in maintaining remission in patients with non-radiographic axial spondyloarthritis (ABILITY-3): A multicentre, randomised, double-blind study. *Lancet* 2018;392:134–44.

35. van Vollenhoven RF, Østergaard M, Leirisalo-Repo M, Uhlig T, Jansson M, Larsson E, et al. Full dose, reduced dose or discontinuation of etanercept in rheumatoid arthritis. *Ann Rheum Dis* 2016;75:52–8.

36. Weinblatt ME, Bingham CO, Burmester GR, Bykerk VP, Furst DE, Mariette X, et al. A Phase III Study Evaluating Continuation, Tapering, and Withdrawal of Certolizumab Pegol After One Year of Therapy in Patients With Early Rheumatoid Arthritis. *Arthritis Rheumatol* 2017;69:1937–48.

37. Smolen JS, Nash P, Durez P, Hall S, Ilivanova E, Irazoque-Palazuelos F, et al. Maintenance, reduction, or withdrawal of etanercept after treatment with etanercept and methotrexate in patients with moderate rheumatoid arthritis (PRESERVE): A randomised controlled trial. *Lancet* 2013;381:918–29.

38. Yamanaka H, Nagaoka S, Lee SK, Bae SC, Kasama T, Kobayashi H, et al. Discontinuation of etanercept after achievement of sustained remission in patients with rheumatoid arthritis who initially had moderate disease activity - results from the

ENCOURAGE study, a prospective, international, multicenter randomized study. *Mod Rheumatol* 2016;26:651–61.

39. Sanmarti R, Veale DJ, Martin-Mola E, Escudero-Contreras A, González C, Ercole L, et al. Reducing or Maintaining the Dose of Subcutaneous Tocilizumab in Patients With Rheumatoid Arthritis in Clinical Remission: A Randomized, Open-Label Trial. *Arthritis Rheumatol* 2019;71:1616–25.
40. Smolen JS, Emery P, Fleischmann R, van Vollenhoven RF, Pavelka K, Durez P, et al. Adjustment of therapy in rheumatoid arthritis on the basis of achievement of stable low disease activity with adalimumab plus methotrexate or methotrexate alone: The randomised controlled OPTIMA trial. *Lancet* 2014;383:321–32.
41. Westhovens R, Robles M, Ximenes AC, Wollenhaupt J, Durez P, Gomez-Reino J, et al. Maintenance of remission following 2 years of standard treatment then dose reduction with abatacept in patients with early rheumatoid arthritis and poor prognosis. *Ann Rheum Dis* 2015;74:564–8.
42. Chatzidionysiou K, Turesson C, Teleman A, Knight A, Lindqvist E, Larsson P, et al. A multicentre, randomised, controlled, open-label pilot study on the feasibility of discontinuation of adalimumab in established patients with rheumatoid arthritis in stable clinical remission. *RMD Open* 2016;2:e000133.
43. Takeuchi T, Genovese MC, Haraoui B, Li Z, Xie L, Klar R, et al. Dose reduction of baricitinib in patients with rheumatoid arthritis achieving sustained disease control: Results of a prospective study. *Ann Rheum Dis* 2019;78:171–8.
44. Curtis JR, Emery P, Karis E, Haraoui B, Bykerk V, Yen PK, et al. Etanercept or Methotrexate Withdrawal in Rheumatoid Arthritis Patients in Sustained Remission. *Arthritis Rheumatol* 2021;73:759-768.

45. Pavelka K, Akkoç N, Al-Maini M, Zerbini CAF, Karateev DE, Nasonov EL, et al. Maintenance of remission with combination etanercept–DMARD therapy versus DMARDs alone in active rheumatoid arthritis: Results of an international treat-to-target study conducted in regions with limited biologic access. *Rheumatol Int* 2017;37:1469–79.

46. Fautrel B, Pham T, Alfaiate T, Gandjbakhch F, Foltz V, Morel J, et al. Step-down strategy of spacing TNF-blocker injections for established rheumatoid arthritis in remission: Results of the multicentre non-inferiority randomised open-label controlled trial. *Ann Rheum Dis* 2016;75:59–67.

47. van Herwaarden N, van der Maas A, Minten MJM, van den Hoogen FHJ, Kievit W, van Vollenhoven RF, et al. Disease activity guided dose reduction and withdrawal of adalimumab or etanercept compared with usual care in rheumatoid arthritis: open label, randomised controlled, non-inferiority trial. *BMJ* 2015;350:h1389.

48. L'ami MJ, Krieckaert CLM, Nurmohamed MT, van Vollenhoven RF, Rispens T, Boers M, et al. Successful reduction of overexposure in patients with rheumatoid arthritis with high serum adalimumab concentrations: An open-label, non-inferiority, randomised clinical trial. *Ann Rheum Dis* 2018;77:484–7.

49. Ghiti Moghadam M, Vonkeman HE, ten Klooster PM, Tekstra J, van Schaardenburg D, Starmans-Kool M, et al. Stopping Tumor Necrosis Factor inhibitor Treatment in Patients with Established Rheumatoid Arthritis in Remission or with Stable Low Disease Activity: A Pragmatic Randomized Multicenter Open-Label Controlled Trial. *Arthritis Rheumatol* 2016;68:1810–7.

50. El Miedany Y, El Gaafary M, Youssef S, Ahmed I, Bahlas S, Hegazi M, et al. Optimizing therapy in inflammatory arthritis: Prediction of relapse after tapering or

stopping treatment for rheumatoid arthritis patients achieving clinical and radiological remission. *Clin Rheumatol* 2016;35:2915–23.

51. Haschka J, Englbrecht M, Hueber AJ, Manger B, Kleyer A, Reiser M, et al. Relapse rates in patients with rheumatoid arthritis in stable remission tapering or stopping antirheumatic therapy: Interim results from the prospective randomised controlled RETRO study. *Ann Rheum Dis* 2016;75:45–51.

52. Kaine J, Gladstein G, Strusberg I, Robles M, Louw I, Gujrathi S, et al. Evaluation of abatacept administered subcutaneously in adults with active rheumatoid arthritis: Impact of withdrawal and reintroduction on immunogenicity, efficacy and safety (Phase IIIb ALLOW study). *Ann Rheum Dis* 2012;71:38–44.

53. Vinson D, Molet-Benhamou L, Degboé Y, den Broeder A, Ibrahim F, Pontes C, et al. Impact of tapering targeted therapies (bDMARDs or JAKis) on the risk of serious infections and adverse events of special interest in patients with rheumatoid arthritis or spondyloarthritis: A systematic analysis of the literature and meta-analysis. *Arthritis Res Ther* 2020;22:97.

Figure 1: Flow diagram of study selection

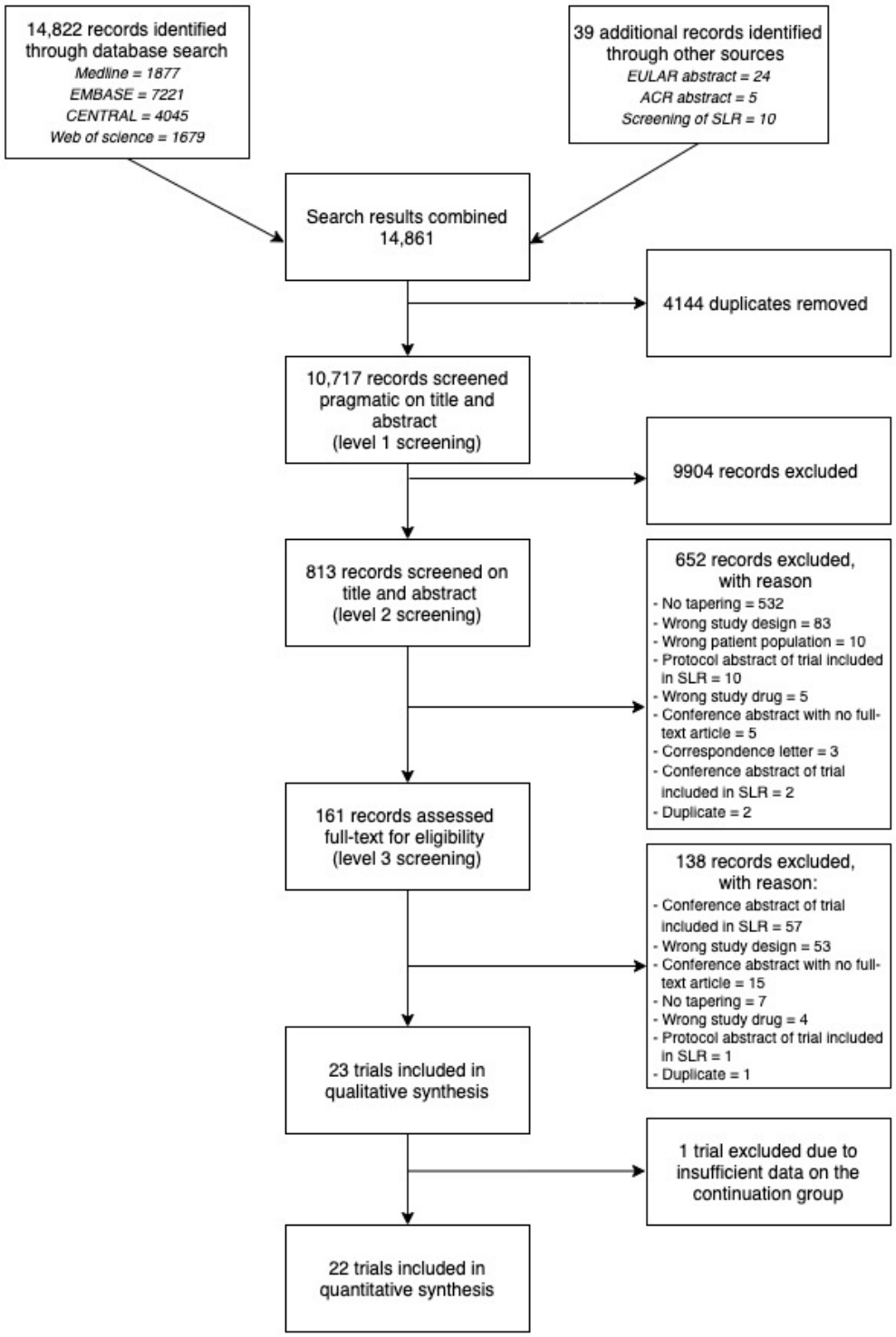

Table 1: Study characteristics and risk of bias assessment of trials eligible for qualitative synthesis

First author (Acronym) Year	Disease duration, years	Inclusion criteria before tapering/ withdrawal	Strategy	Rando-mised, N	Primary endpoint assessment	Definition of flare	Risk of bias[a] 1 2 3 4 5 6
Axial spondyloarthritis trials							
Landewé (C-OPTIMISE) 2020 (33)	***TG:*** 2.0 ***WG:*** 2.1 ***CG:*** 2.5	ASDAS < 1.3 at week 32 or 36 AND week 48 in period 1	***TG:*** CZP 200 mg/E4W ***WG:*** CZP stop ***CG:*** CZP 200 mg/E2W	***TG:*** 105 ***WG:*** 104 ***CG:*** 104	48 weeks	ASDAS ≥ 2.1 at two consecutive visits OR ASDAS > 3.5 at any visit	
Gratacos (REDES-TNF) 2019 (31)	***TG:*** 9.3 ***CG:*** 10.4	BASDAI ≤ 2, no arthritis or enthesitis and no CRP ≥ URL ≥ 6 months	***TG:*** ADA 40 mg/E3W, ETN 50 mg/E10D, GOL 50 mg/E6W or IFX 3 mg/kg/E8W ***CG:*** standard dose TNFi continued	***TG:*** 61 ***CG:*** 62	52 weeks	ASDAS ≥ 2.1 OR BASDAI AND physician GA ≥ 4 AND: 1) Patient GA ≥ 4 or 2) Nocturnal axial pain ≥ 4 or 3) Increased CRP/ESR	
Landewé (ABILITY-3) 2018 (34)	***WG:*** 1.8 ***CG:*** 1.9	Sustained remission (ASDAS score < 1.3) at weeks 16, 20, 24, and 28 in period 1	***WG:*** ADA stop CG***:*** ADA 40 mg/E2W	***WG:*** 153 ***CG:*** 152	40 weeks	ASDAS ≥ 2.1 on two consecutive visits	
Yates (ANSWERS) 2015 (30)	***TG:*** NA ***CG:*** NA	Responders (50% reduction or ≥ 2 units fall in BASDAI and spinal pain. Duration not specified.	***TG:*** ETN 25 mg/W ***CG:*** ETN 50 mg/W	***TG:*** 23 ***CG:*** 24	26 weeks	ΔBASDAI ≥ 2 or 50% increase to baseline on ≥ 2 visits AND Δspinal pain ≥ 2 AND re-instatement of therapy needed	
Cantini 2013 (32)	***TG:*** 13 ***CG:*** 12	BASDAI < 4, no arthritis, dactylitis, tenosynovitis or uveitis and normal ESR/CRP. Duration not specified.	***TG:*** ETN 50 mg/E2W ***CG:*** ETN 50 mg/W	***TG:*** 22 ***CG:*** 21	Mean: TG: 22 ±1 months CG: 21 ±1.6 months	BASDAI > 4 or extra-articular manifestations	
Rheumatoid arthritis trials							
Curtis (SEAM-RA) 2020 (44)	***WG:*** 9.7 ***CG:*** 10.3	SDAI ≤ 3.3 through 24 weeks	***WG:*** ETN stop ***CG:*** ETN 50 mg/W	***WG:*** 101 ***CG:*** 51	48 weeks	ΔSDAI 3.4-11.0 on two visits ≥ 2 weeks apart OR SDAI 3.4-11.0 at any time on ≥ 3 separate visits OR any SDAI > 11	
Sanmarti (TO-SPACE) 2019 (39)	***TG:*** 6.4 ***CG:*** 6.5	DAS28-ESR < 2.6 between week 20 and 24 in period 1	***TG:*** TCZ 162 mg/E2W ***CG:*** TCZ 162 mg/W	***TG:*** 90 ***CG:*** 89	24 weeks	DAS28-ESR score ≥ 2.6	
Takeuchi (RA-BEYOND) 2019 (43)	***TG:*** 9.3 ***CG:*** 9.5	≥ 3 months: CDAI ≤ 10 for RA-BEAM, -BUILD, -BEACON OR CDAI ≤ 2.8 for RA-BEGIN	***TG:*** BCN 2 mg/D ***CG:*** BCN 4 mg/D	***TG:*** 278 ***CG:*** 281	48 weeks	Failure to maintain CDAI LDA or remission	
Verhoef (REDO) 2019 (25)	***TG:*** 14.0 ***CG:*** 16.9	≥ 6 months LDA after last RTX (DAS28-CRP < 2.9 or LDA judged by rheumatologist) and DAS28-CRP ≤ 3.5 at baseline	***TG:*** RTX 500 mg x 1 or RTX 200 mg x 1 ***CG:*** RTX 1000 mg x 1	***TG:*** 113 ***CG:*** 29	26 weeks	ΔDAS28-CRP > 1.2 from baseline, or ΔDAS28-CRP > 0.6 from baseline AND DAS28-CRP ≥ 2.9 at month 6	
L'Ami 2018 (48)	***TG:*** 11 ***CG:*** 11	ADA serum trough concentration > 8 µg/mL after at least 28 weeks of treatment	***TG:*** ADA 40 mg/E3W ***CG:*** ADA 40 mg/E2W	***TG:*** 27 ***CG:*** 28	28 weeks	DAS28-ESR ≥ 0.6	
Ibrahim (OPTTIRA) 2017 (26)	***TG:*** 11.6 ***CG:*** 10.6	Sustained DAS28-ESR < 3.2 without increase of > 0.6 during last 3 months	***TG:*** ADA/ETN tapered by 33% or ADA/ETN tapered by 66% ***CG:*** ADA 40 mg/E2W or ETN 50 mg/W	***TG:*** 47 ***CG:*** 50	26 weeks	ΔDAS28-ESR ≥ 0.6 with DAS28 > 3.2 AND increased swollen joint on two visits ≥ 1 week apart OR ΔDAS28-ESR ≥ 1.2 with DAS28 > 3.2	
Pavelka 2017 (45)	***WG:*** 8.3 ***CG:*** 8.0	LDA (DAS28-ESR < 3.2) at week 24 in period 1	***WG:*** ETN stop ***CG:*** ETN 50 mg/W	***WG:*** 177 ***CG:*** 169	28 weeks	DAS28-ESR ≥ 3.2 AND ΔDAS28-ESR ≥ 0.6 from the week 24	
Weinblatt (C-EARLY) 2017 (36)	***TG:*** 2.6 ***WG:*** 2.5 ***CG:*** 2.9	Sustained DAS28-ESR ≤ 3.2 at weeks 40 and 52 in period 1	***TG:*** CZP 200mg/E4W ***WG:*** CZP stop ***CG:*** CZP 200 mg/E2W	***TG:*** 127 ***WG:*** 82 ***CG:*** 84	52 weeks	Self-reported flare AND at 2 visits 2 weeks apart: ΔDAS28-ESR ≥ 0.6 from period 2 baseline AND DAS28-ESR > 3.2 AND investigator judged RA activity	

Fautrel (STRASS) 2016 (46)	***TG:*** 8.3 ***CG:*** 11.0	DAS28-ESR ≤ 2.6 for 6 months AND no progression on X-rays during last year	***TG:*** stepwise increased ADA/ETN injection interval every 3 month[b] ***CG:*** ADA 40 mg/E2W or ETN 50 mg/W	***TG:*** 64 ***CG:*** 74	78 weeks	DAS28-ESR > 2.6 AND ΔDAS28-ESR > 0.6 since last visit	
Ghiti Moghadam (POET) 2016 (49)	***WG:*** 12.0 ***CG:*** 11.1	In last 6 months: 1) DAS28-CRP < 3.2 OR 2) LDA judged by rheumatologist + DAS28-CRP < 3.2 at baseline and ≥ one CRP < 10 mg/L	***WG:*** stop TNFi ***CG:*** standard dose TNFi continued	***WG:*** 531 ***CG:*** 286	52 weeks	DAS28 ≥ 3.2 and ΔDAS28 ≥ 0.6 compared to the baseline	
Van Vollenhoven (DOSERA) 2016 (35)	***TG:*** 16.6 ***WG:*** 11.5 ***CG:*** 12.3	DAS28-ESR ≤ 3.2 on ≥ 11 months prior to baseline	***TG:*** ETN 25 mg/W ***WG:*** ETN stop ***CG:*** ETN 50 mg/W	***TG:*** 27 ***WG:*** 23 ***CG:*** 23	48 weeks	1) DAS28-ESR > 5.1, 2) DAS28-ESR > 3.2 and ΔDAS28 ≥ 1.2 from baseline, 3) DAS28-ESR > 3.2 and ΔDAS28 ≥ 0.6 from baseline on two visits 1–3 weeks apart 4) Disease flare judged by investigator or patient	
Yamanaka (ENCOURAGE) 2016 (38)	***WG:*** 2.4 ***CG:*** 1.9	DAS28 < 2.6 at both month 6 and 12 in period 1	***WG:*** ETN stop ***CG:*** ETN 50 mg/W	***WG:*** 50 ***CG:*** 49	52 weeks	DAS28 ≥ 3.2	
Raffeiner 2015 (29)	***TG:*** 14.3 ***CG:*** 13.4	DAS28-ESR < 2.6 for at least 12 months	***TG:*** ETN 25 mg/W ***CG:*** ETN 25 mg/BW	***TG:*** 159 ***CG:*** 164	Mean: 3.6 ± 1.5 years	DAS28-ESR > 2.6	
Van Herwaarden (DRESS) 2015 (47)	***TG:*** 10 ***CG:*** 10	DAS28-CRP < 3.2 or LDA judged by rheumatologist at two visits ≥ 3 months apart	***TG***: stepwise increased ADA/ETN injection interval every 3 month[c] ***CG:*** ADA 40 mg/E2W or ETN 50 mg/W	***TG:*** 121 ***CG:*** 59	78 weeks	ΔDAS28-CRP > 1.2 from baseline OR ΔDAS28-CRP > 0.6 from baseline and current DAS28 ≥ 3.2	
Westhovens (AGREE) 2015 (41)	***TG:*** 2.4 ***CG:*** 2.4	DAS28-ESR < 2.6 on day 701 i.e. year 2 of phase 1	***TG:*** ABA 5 mg/kg/E4W ***CG:*** ABA 10 mg/kg/E4W	***TG:*** 50 ***CG:*** 58	52 weeks	Additional DMARD required, or ≥ 2 courses of high-dose steroids, or require open-label ABA 10 mg/kg, or DAS28-CRP ≥ 3.2 at two consecutive visits	
Smolen (OPTIMA) 2014 (40)	***WG:*** 0.8 ***CG:*** 0.8	DAS28-CRP ≤ 3.2 at week 22 and 26 in period 1	***WG:*** ADA stop ***CG:*** ADA 40 mg/E2W	***WG:*** 102 ***CG:*** 105	52 weeks	Not defined	
Smolen (PRESERVE) 2013 (37)	***TG:*** 6.4 ***WG:*** 6.8 ***CG:*** 7.3	DAS28-ESR ≤ 3.2 from weeks 12 to 36 in period 1 and DAS28-ESR ≤ 3.2 at week 36	***TG:*** ETN 25 mg/W ***WG:*** ETN stop ***CG:*** ETN 50 mg/W	***TG:*** 202 ***WG:*** 200 ***CG:*** 202	52 weeks	DAS28-ESR > 3.2 AND ΔDAS28 ≥ 0.6 or discontinuation due to poor efficacy, protocol violation,or other	
Chatzidionysiou (ADMIRE) 2012 (42)	***WG:*** 10.4 ***CG:*** 7.6	Sustained remission (DAS28 < 2.6) ≥ 3 months	***WG:*** ADA stop ***CG:*** ADA 40 mg/E2W	***WG:*** 16 ***CG:*** 17	28 weeks	DAS28 ≥ 2.6 or ΔDAS28 > 1.2 from baseline	

N: number, b-/tsDMARD: biological or targeted synthetic disease-modifying antirheumatic drug, TG: tapering group, WG: withdrawal group, CG: continuation group, ASDAS: Ankylosing Spondylitis Disease Activity Score, mg: milligram, E: every, W: week, CZP: certolizumab pegol, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, CRP: C-reactive protein, URL: upper reference limit, ADA: adalimumab, ETN: etanercept, D: days, GOL: golimumab, IFX: infliximab, kg: kilogram, GA: global assessment, NA: not assessed, ESR: erythrocyte sedimentation rate, RA: rheumatoid arthritis, SDAI: Simplified Disease Activity Index, TCZ: tocilizumab, DAS28: disease Activity Score28, LDA: low disease activity, CDAI: Clinical Disease Activity Index, BCN: baricitinib, RTX: rituximab, µg: microgram, mL: millilitre, TNFi: tumour necrosis factor inhibitors, L: litre, BW: biweekly, ABA: abatacept, DMARD: disease-modifying antirheumatic drug.

[a]: Risk of bias assessment 2.0 consists of the following assessments represented by a coloured bullet: 1) Risk of bias arising from the randomisation process, 2) Risk of bias due to deviations from the intended interventions, 3) Missing outcome data, 4) Risk of bias in measurement of the outcome, 5) Risk of bias in selection of the reported result, 6) Overall risk of bias. The bullet colour represents the following risk of bias assessment: Green = low risk of bias, Yellow = unclear risk of bias, and Red = high risk of bias.

[b]: ETA 50 mg every 10 days (step 1), 14 days (step 2), 3 weeks (step 3) or stopped (step 4); ADA 40 mg every 21 days (step 1), 28 days (step 2), 6 weeks (step 3) or stopped (step 4).

[c]: ADA: (1) 40 mg every 21 days, (2) 40 mg every 28 days, and (3) stop. ETN: (1) 50 mg every 10 days, (2) 50 mg every 14 days, and (3) stop.

Figure 2: Random-effects meta-analysis of flare risk after either tapering or withdrawal of b-/tsDMARDs compared to continuation.

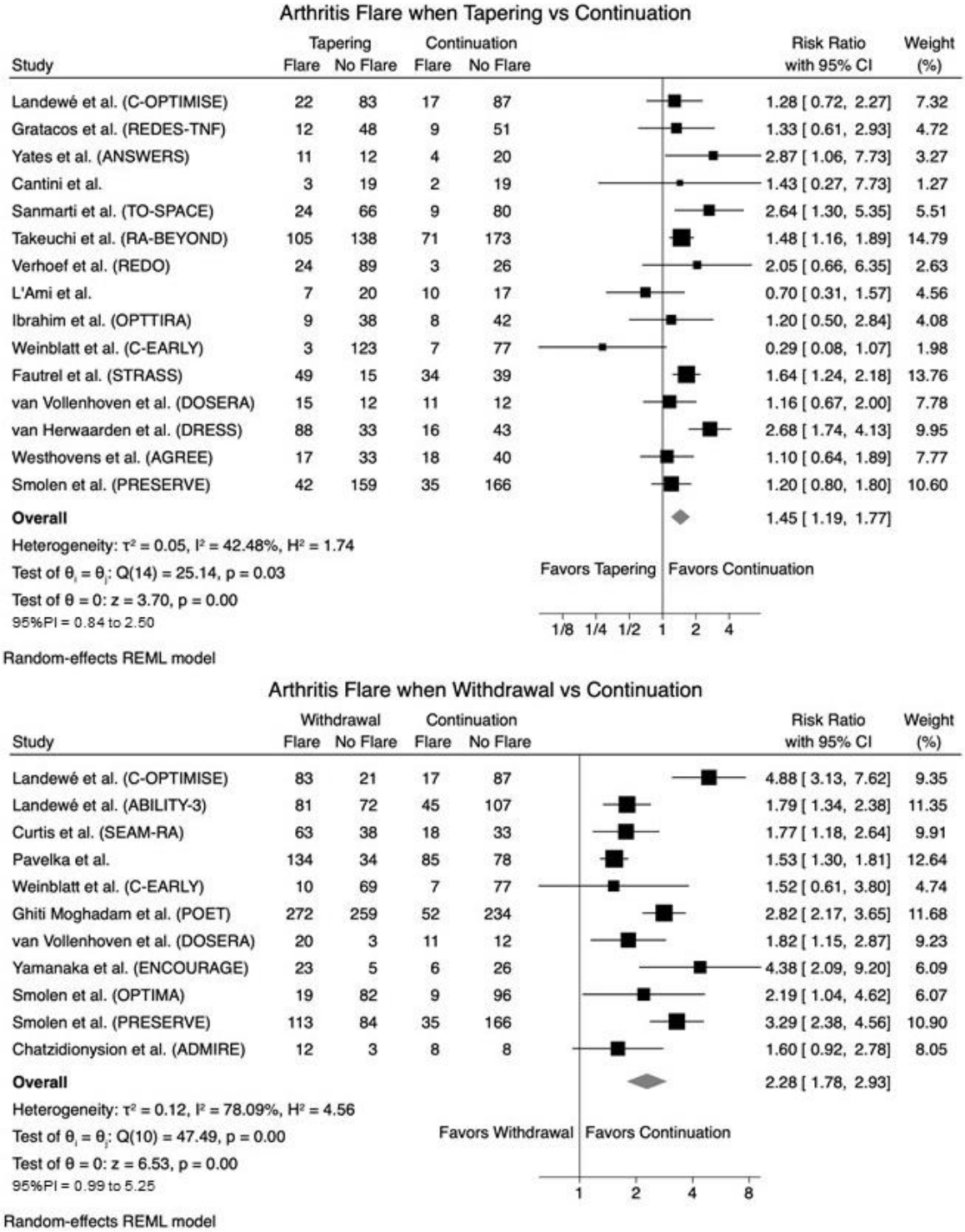

Figure 3: Random-effects meta-analysis of persistent flare odds after either b-/tsDMARDs tapering or withdrawal compared to continuation.

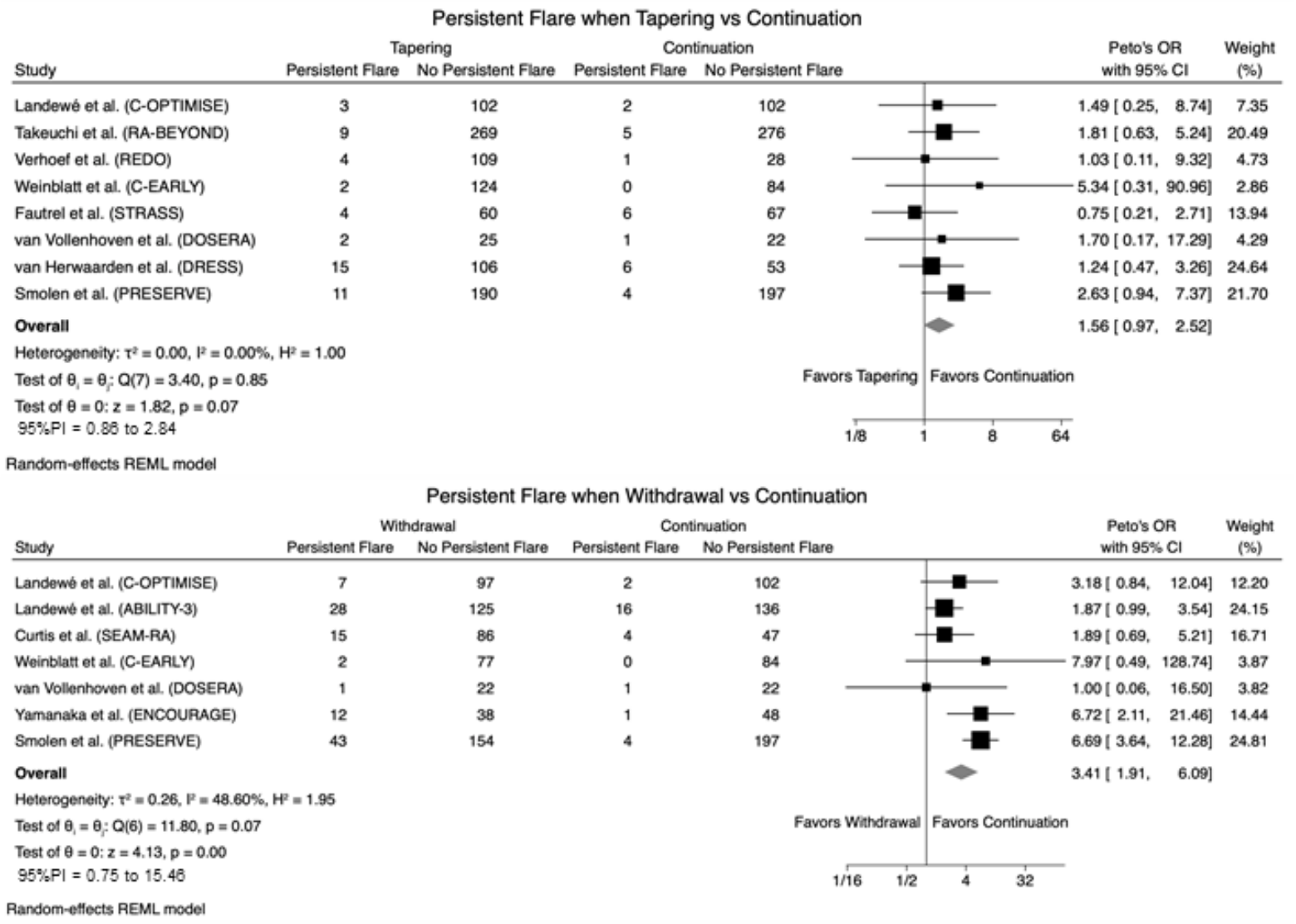

Table 2: Summary of evidence synthesis: Tapering/Withdrawal group versus Continuation group

	Summary of findings					Quality assessment					
Outcome (N studies)	**Reduction group, n/N (%)**	**Continuation group, n/N (%)**	**Relative measure (95%CI)**	**Absolute measure (95%CI)**	**NNH**	**Overall risk of bias[a]**	**Inconsistency[b] I^2**	**Indirectness**	**Imprecision[c]**	**Publication bias[d]**	**GRADE quality**
Tapering versus Continuation group											
Flare (15 studies)	431/1,319 (32.7%)	254/1,146 (22.2%)	RR 1.45 (1.19 to 1.77)	99.2 per 1,000 (46.8 to 151.7)	10	Serious	Not serious I^2 = 42.5%	Not serious	Not serious	Undetected	Moderate ⨁⨁⨁◯
Persistent flare (8 studies)	50/1,035 (4.8%)	25/854 (2.9%)	POR 1.56 (0.97 to 2.52)	15.6 per 1,000 (-1.2 to 32.3)	64	Serious	Not serious I^2 = 0.0%	Not serious	Serious	Undetected	Low ⨁⨁◯◯
Serious infection (11 studies)	12/1,121 (1.1%)	16/945 (1.7%)	POR 0.51 (0.24 to 1.10)	-8.3 per 1,000 (-17.7 to 1.1)	-121	Not serious	Not serious I^2 = 0.0%	Not serious	Not serious	Undetected	High ⨁⨁⨁⨁
SAE (14 studies)	95/1,334 (7.1%)	80/1,161 (6.9%)	POR 0.91 (0.61 to 1.35)	-6.0 per 1,000 (-30.6 to 18.6)	-166	Not serious	Not serious I^2 = 23.2%	Not serious	Serious	Undetected	Moderate ⨁⨁⨁◯
Death (9 studies)	1/862 (0.1%)	2/674 (0.3%)	POR 0.58 (0.09 to 3.84)	-1.3 per 1,000 (-5.6 to 3.1)	-793	Not serious	Not serious I^2 = 0.0%	Not serious	Very serious	Undetected	Low ⨁⨁◯◯
Flare in axSpA (4 studies)	48/210 (22.9%)	32/209 (15.3%)	RR 1.49 (0.99 to 2.24)	75.4 per 1,000 (-1.15 to 152.0)	13	Not serious	Not serious I^2 = 0.0%	Not serious	Serious	Undetected	Moderate ⨁⨁⨁◯
Flare in RA (11 trials)	383/1,109 (34.5%)	222/937 (23.7%)	RR 1.42 (1.11 to 1.81)	98.6 per 1,000 (28.8 to 168.4)	10	Serious	Not serious I^2 = 59.1%	Not serious	Not serious	Undetected	Moderate ⨁⨁⨁◯
Withdrawal versus Continuation group											
Flare (11 studies)	830/1,500 (55.3%)	293/1,217 (24.1%)	RR 2.28 (1.78 to 2.93)	309.4 per 1,000 (216.6 to 402.4)	3	Serious	Serious I^2 = 78.1%	Not serious	Not serious	Undetected	Low ⨁⨁◯◯
Persistent flare (7 studies)	108/707 (15.3%)	28/664 (4.2%)	POR 3.41 (1.91 to 6.09)	88.0 per 1,000 (46.3 to 129.7)	11	Serious	Not serious I^2 = 48.6%	Not serious	Not serious	Undetected	Moderate ⨁⨁⨁◯
Serious infection (8 studies)	25/1,282 (2%)	14/1,035 (1.4%)	POR 1.43 (0.75 to 2.71)	5.9 per 1,000 (-4.7 to 16.5)	170	Not serious	Not serious I^2 = 0.0%	Not serious	Serious	Undetected	Moderate ⨁⨁⨁◯
SAE (10 studies)	90/1,486 (6.1%)	47/1,192 (3.9%)	POR 1.49 (0.79 to 2.83)	18.1 per 1,000 (-10.9 to 47.1)	55	Not serious	Not serious I^2 = 62.3%	Not serious	Serious	Undetected	Moderate ⨁⨁⨁◯
Death (10 studies)	0/1486 (0%)	3/1192 (0.3%)	POR 0.23 (0.04 to 1.43)	-2.3 per 1,000 (-5.2 to 0.6)	-431	Not serious	Not serious I^2 = 0.0%	Not serious	Very serious	Undetected	Low ⨁⨁◯◯
Flare in axSpA (2 studies)	164/257 (63.8%)	62/256 (24.2%)	RR 2.91 (1.09 to 7.79)	462.5 per 1,000 (36.6 to 888.3)	2	Not serious	Serious I^2 = 92.8%	Not serious	Not serious	Undetected	Moderate ⨁⨁⨁◯
Flare in RA (9 studies)	666/1,243 (53.6%)	231/961 (24.0%)	RR 2.16 (1.69 to 2.75)	277.9 per 1,000 (189.7 to 366.1)	4	Serious	Not serious I^2 = 69.6%	Not serious	Not serious	Undetected	Moderate ⨁⨁⨁◯

N: total number, n: number of patients with event, 95%CI: 95% confidence interval, NNH: number needed to harm, I^2: I^2 test, RR: relative risk, POR: Peto's odds ratio

[a]: Evaluated using subgroup meta-analysis stratified for the overall risk of bias assessment for the primary outcome flare and the secondary outcome persistent flare. The overall risk of bias for adverse events was judged not to be serious based on expert opinion.

[b]: I^2 test was evaluated as: <25% = not serious and > 75% = serious. For I^2 test between 25%-75% was evaluated as serious if the relative estimate from the fixed effect meta-analysis were within the limits of the 95%CI from the random-effects meta-analysis.

[c]: Evaluated as serious if the 95%CI of the relative measure was inconclusive.

[d]: Evaluated for the primary outcome flare by funnel plots, an Egger's test and subgroup meta-analyses stratified by funding by manufacture. Publication bias for adverse events was judged not to be serious based on expert opinion.