Can Patients with Controlled Rheumatoid Arthritis Taper Methotrexate from Targeted Therapy and Sustain Remission? A Systematic Review and Meta-analysis

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ABSTRACT (247/250 words)

Objective. To determine the risk of not being able to sustain remission after tapering MTX from targeted therapy in patients with controlled RA.

Methods. A systematic literature search was conducted in Medline, Embase and Cochrane Library for studies reporting remission outcomes after tapering MTX from targeted therapies in RA. Full-text articles and abstracts reported in English were included. Meta-analyses were conducted using random effects models. Forest and funnel plots were created.

Results. Ten articles were included. Studies evaluated MTX being tapered from combination treatment with TNF-inhibitors, tocilizumab, abatacept and tofacitinib. Nine studies were randomized and one was observational. Three out of 10 studies focused on early RA (<1 year). The MTX tapering strategy was gradual in 2 and rapid in 8 studies. Follow-up ranged from 3-18 months in randomized trials, and up to 3 years in the observational study. Our meta-analysis conducted in 2000 RA participants from 10 studies showed that patients who tapered MTX from targeted therapy had a 10% reduction in ability to sustain remission, an overall pooled RR 0.90 (95% CI 0.84, 0.97). There was no heterogeneity, (I^2=0.0%, p=0.938). Our funnel plot indicated minimal publication bias.

Conclusion. Patients with controlled RA may taper MTX from targeted therapy with a 10% reduction in ability to sustain remission, for up to 18 months. Longer follow-up studies with

attention to radiographic, functional and patient-reported outcomes are needed. The risk of disease worsening should be discussed with the patient with careful follow-up and prompt re-treatment of disease worsening.

INTRODUCTION

Methotrexate (MTX) is recommended to be used in combination with biologic (b)DMARDs in the treatment of rheumatoid arthritis (RA) because of its additive therapeutic benefits and its mitigation of immunogenicity[1]. In clinical practice however, up to 30% of patients are on bDMARD monotherapy[2-4], in part due to intolerance of MTX and other csDMARDs. Adverse effects from MTX has been cited to be the most common reason for its discontinuation, particularly from gastrointestinal intolerance, cytopenias and abnormal liver function tests[5]. MTX adherence has been observed to be highly variable[6], and inferior to that with bDMARDs[7]. In addition, several RA studies have shown the effectiveness of monotherapy with IL6-inhibitors(i) and JAK-i[4,8-10]. Going forward, we refer to both bDMARDs and JAK-i as targeted therapies.

Tapering DMARD therapy is a desirable goal for many patients with chronic diseases such as rheumatoid arthritis. Patients wish to reduce adverse effects, reduce risk of future adverse effects and maintain control over their own health[11]. However, the clinical benefits of tapering treatment in RA are less clear, and many studies have shown a high risk of disease worsening when stopping DMARDs[12,13]. What is not known is how feasible it is for patients who are taking a combination of targeted therapy with MTX to taper their MTX and continue to be controlled. Observational studies have reported 34-62% of RA patients using TNF-i later tapered their MTX[14,15]. The 2021 ACR guidelines conditionally recommend 1) continuation of all DMARDs at their current dose over a dose reduction due to risk of flare and 2) in patients

who are taking both MTX and a targeted therapy, the tapering of MTX before tapering the targeted therapy, but acknowledge there is an absence of direct evidence[16].

Prior reviews have focused on tapering of MTX from combination treatment with either csDMARDs or TNF-i[17]. A 2015 systematic review of tapering of synthetic or biologic DMARDs reported a flare rate after tapering MTX ranging from 8% at 24 weeks (patients remained on HCQ and corticosteroid) to 42% at 32 weeks (patients on infliximab)[12]. According to our literature search, there have no updated reviews addressing MTX tapering from other targeted therapies such as IL6-i or JAK-i, nor has there been a systematic review with meta-analysis addressing this question. Factors associated with successful tapering such as disease duration (early versus established RA) or the tapering scheme itself (gradual versus brisk) remain unknown[18].

We therefore conducted a systematic literature review to evaluate whether remission can be sustained after the tapering (dose reduction, gradual dose reduction before stopping or withdrawal) of MTX in RA patients taking it in combination with targeted therapy. We also aim to evaluate the factors associated with successful tapering such as disease duration and tapering schemes. Our hypothesis is that patients with controlled RA may taper MTX from targeted therapy with low risk of not being able to sustain remission.

METHODS

We searched for tapering studies in which patients received any targeted therapy, including all classes of bDMARDs (abatacept (ABA), certolizumab pegol (CZP), etanercept (ETA), golimumab, infliximab (IFX), rituximab, tocilizumab (TCZ), sarilumab) or JAK-i (tofacitinib

(TOFA), baricitinib, upadacitinib) in combination with MTX, in which the study evaluated the proportion of patients in remission after the dosage of MTX was tapered

Search strategy: The search strategy was initially developed in MEDLINE (PubMed) by a medical librarian. It was then adapted for the other databases searched – EMBASE and the Cochrane Library, including the Cochrane Central Register of Controlled Trials, Health Technology Assessment database, and NHS Economic Evaluation Database (see Supplementary Data 1 for full search strategy and search terms). The search period was limited to January 1, 2014 – August 30, 2021, with the last updated search run in all databases on 8/30/21. Additional studies were identified through manually searching reference lists and gray literature references. Studies were excluded if they were not published in English.

Studies were imported into the Covidence platform (Veritas Health Innovation Ltd; Melbourne, Australia), allowing duplicates to be removed. The screening process was completed by two authors CM and DR. Title/abstract screening was conducted first, followed by full-text screening. Any issues were resolved through consensus with VB. This review was conducted and reported according to the procedures outlined in the PRISMA statement[19].

Study selection: Inclusion criteria: 1) Prospective comparative studies including randomized controlled trials (RCTs), pragmatic trials and observational studies of RA patients 2) Subjects were taking MTX and targeted therapy (TNF-i, IL6-i, ABA, rituximab, or JAK-i. 3) Study design included an intervention group who underwent tapering of MTX from combination with targeted therapy and a comparator group who continued combination therapy. 4) The study reported those subjects who remained in or achieved remission as measured by composite score. Exclusion criteria: 1) Retrospective studies 2) No reporting of proportion of remission outcomes after tapering treatment.

Data extraction: CM and DR selected potential manuscripts for retrieval, and upon retrieval, established study eligibility by applying the selection criteria. Studies in doubt were discussed with VB until consensus was reached. If trial data relevant to the review was found in a secondary publication or abstract, it was included and noted in the tables. The original publication of the COMET trial[20] was used to extract study information and baseline data, but remission data were obtained from an updated publication[21] that was analyzed according to low disease activity/remission before tapering, consistent with our inclusion criteria. A standardized data collection form was used to extract the following: study design, patient inclusion/exclusion criteria, prior and baseline treatment, whether patients were MTX-naïve or inadequate responders, RA duration dichotomized as either early (diagnosis < 1 year) or established. Included was the implementation information for tapering, including criteria for tapering of therapy, tapering strategy, frequency of assessment, follow-up interval after tapering, as well as the reported outcome measure(s), including that of remission, disease worsening, duration of remission, retreatment outcomes, radiographic outcomes, patient reported outcomes, and predictors of remaining in disease control or losing disease control.

Quality assessment: The methodological quality of each randomized study was assessed using the Revised Cochrane risk of bias tool for randomized trials[22] by CM and DR, discussed with DJ, and where clarification was needed, with VB. The criteria for evaluation included randomization, deviations from intended interventions, missing outcome data, measurement of outcome and selection of reported result. Studies were judged to be overall low risk of bias if found to have low risk of bias for all domains. Studies were judged overall to have some concerns, if found to have some concerns in at least one domain. Studies are judged overall to have high risk of bias if found to have high risk of bias in at least one domain or some concerns

for multiple domains that substantially lowered confidence in results[22]. Non-randomized studies were assessed using the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool[23], which used similar criteria to judge overall risk of bias (Supplementary Table 1).

Statistical analysis: Random effects models were used to calculate pooled risk ratios[24]. Heterogeneity was assessed by calculating the I^2 index using the Cochran-Mantel-Haenszel technique[25]. Additionally, forest plots were generated for each analysis. A funnel plot was created and the Egger and Harbord tests were calculated[26,27] to aid in the assessment of bias. All analyses were performed in Stata version 14.2

RESULTS

Literature search: Our search identified 5762 citations using the prespecified search terms. After removal of duplicates and articles not pertaining to the study question using the COVIDENCE platform, 504 full-text articles were reviewed (Figure 1, Supplementary data 1). Of these, 10 articles addressed our research question and met our inclusion criteria.

Characteristics of included studies: Ten studies of tapering MTX from combined treatment with targeted therapy were reviewed. Three studies tapered MTX from combined treatment with ETA[20,21,28,29], three studies tapered MTX from TCZ[30-32], one study each tapered MTX from TOFA[33,34], CZP[35], ADA[36] and ABA[37,38] (Table 1). No studies tapering MTX from rituximab met our inclusion criteria. Seven articles studied established RA (6-11 years) and three studied early RA (1-9 months). Use of prior DMARDs ranged from 11-30%, but was not specified in five studies. MTX-naïve patients were evaluated in the three early RA trials and the remaining trials studied patients who were MTX-inadequate responders. Seropositivity ranged from 58%-88% in seven studies. Nine were RCTs, seven of which studied withdrawal as the second phase

of their study, and one was a long-term extension study (LTE). Two RCTs used a run-in period. (Table 1, Supplementary Table 2). Seven RCTs were placebo-controlled during tapering (Supplementary Table 2).

Eight studies stopped MTX in their tapering strategy and two gradually reduced the dose of MTX. Criteria for taper was DAS-based LDA in three studies, change in DAS28 in one study, SDAI remission in two studies, both DAS remission and LDA in 2 studies and EULAR response-based in one study (Table 1, Supplementary Table 2). Eight studies used as their outcome measure the proportion with DAS-based remission, with two studies using SDAI remission (Table 1, Supplementary Table 2).

Follow-up ranged from 28 weeks to 18 months in nine RCTs, up to three years in the LTE (Table 1). The three-year LTE [36] did not specify time of withdrawal, so duration of remission after taper was not explicitly reported.

Quality Assessment: In the RCTs, the overall risk of bias was judged to be low in one study, some concerns in six studies, and high in two open-label studies (Figure 2). The LTE study was judged to have serious risk of bias (Supplementary Table 1).

Tapering scheme: Two studies tapered off MTX gradually, whereas eight studies stopped MTX (Table 1). COMET tapered MTX from ETA+MTX over 4 weeks and was among the studies reporting a higher remission rate of 70%[21], compared to a remission rate ranging 16-76% in the studies who stopped MTX abruptly[28-31,33,36,37]. However, ACT-TAPER tapered the dose of MTX more slowly over 24 weeks from TCZ+MTX, and reported a lower remission rate of 50%[32].

Duration of remission/follow-up: Remission outcomes after MTX withdrawal were obtained at varying timepoints, ranging from 12 weeks to 18 months in randomized studies (Table 2).

Studies reporting outcomes up to 1 year after tapering had remission rates ranging 48-76%, but this dropped to 40% in one study reporting 18-month remission outcomes[29]. When persistent remission, defined as consistent remission at weeks 12, 24, 36 and 48, after tapering MTX to tofacitinib monotherapy was used, remission rates dropped to 4%[33].

Mean disease activity scores after tapering: Eight studies reported on changes in mean disease activity scores after tapering MTX (Table 2). Curtis found disease worsening defined as SDAI > 11 was similarly high in those who stopped MTX (75%) compared to those who continued ETA+MTX (78%). Two studies COMP-ACT and JUST-ACT demonstrated non-inferiority of change in DAS28 scores in withdrawing MTX from TCZ compared to combination therapy. Pope did not demonstrate noninferiority of maintaining change in DAS28 scores in the group withdrawing MTX from CZP compared to continuing therapy (Table 2). AVERT-2, ACT-TAPER and CAMEO did not find a significant difference in mean scores between groups.

Functional outcomes: Seven studies reported on functional or other patient reported outcomes (Table 2). AVERT-2 found an adjusted mean change in HAQ-DI of +0.16 in those who stopped MTX vs -0.04 in those who continued ABA+MTX[38]. SF-36 PFS scores were also worse in the stop MTX group -1.45 vs 1.68 in the combination group. Pope found significantly longer AM stiffness in the CZP monotherapy vs CZP+MTX groups (39.9 minutes vs 21.7, p=0.026). Patient global, pain, fatigue, work loss and TJC scores trended worse with CZP monotherapy but did not reach significance (Table 2).

Radiographic outcomes: Two randomized trials and one observational study assessed radiographic outcomes after tapering MTX. No significant differences in radiographic progression after tapering MTX to targeted therapy alone was observed.

Predictors of maintaining disease control: Two RCTs[28,34] and one LTE study[36] examined predictors of maintaining remission after tapering MTX from targeted therapy. Higher baseline disease activity scores, and rheumatoid factor positivity were found to be associated with lower likelihood of maintaining remission (Table 2). Higher physician global scores were associated with restarting MTX during the open-label LTE ($p<0.01$) (Table 2).

Recapture of remission: Two studies reported on re-treatment outcomes[28,36]. Curtis reported remission was recaptured with re-treatment in 75% of the ETA monotherapy group by week 48. The LTE study reported that patients who restarted MTX later than 4 weeks after entering the LTE had worse disease activity scores compared to those who restarted MTX earlier (Table 2).

Safety: Safety was reported by all studies, and overall there were no significant differences between groups in number of AEs, SAEs and discontinuations of treatment from AEs. Three studies (SEAM, COMP-ACT, Keystone 2018) noted a numerical increase in frequency of AEs in the MTX-treated patients compared to other arms (Table 2). JUST-ACT reported higher AEs in the TCZ monotherapy group compared to the MTX-treated group (Table 2).

Meta-analysis: The meta-analysis, conducted in 2000 RA participants from 10 studies, showed a pooled risk ratio for maintaining remission after tapering methotrexate from targeted therapy of 0.90 (95% CI: 0.84, 0.97) (Figure 3). There was no heterogeneity among the studies in this group ($I^2=0.0\%$, $p=0.938$). Among the studies that enrolled patients with early RA, the risk ratio was 0.84 (95% CI 0.73, 0.98) and the heterogeneity was 0.0% ($p=0.392$). Among studies with patients with established RA, the risk ratio was 0.92 (0.85, 1.01) and there was 0% heterogeneity present ($p=0.996$) (Supplementary Figure 1). We specifically evaluated remission outcomes, rather than LDA, after tapering. Since some studies used LDA in their criteria to taper MTX, we performed a separate meta-analysis on the risk ratios of maintaining LDA after tapering MTX.

We found similar results to the ones reported above [RR 0.92 (CI 0.86, 0.98)] (Supplementary Figure 2). Additionally, we did a sensitivity analysis, where we omitted the 2018 LTE study as it had a higher bias. Again, we found similar results [RR 0.90 (CI 0.83, 0.97)] (Supplementary Figure 3). Figure 4 shows our funnel plot for all included studies, along with a fitted line representing Egger's test for asymmetry, and indicates minimal publication bias. Results from both the Egger's and Harbord's modified test for small study effects were found to be not statistically significant indicating weak evidence of small study effects. Risk differences were calculated with an overall pooled RD of -0.05 (95% CI -0.10, -0.01). Using the pooled estimate, if one were to taper MTX from targeted therapy in 20 patients, 2 (10%) patients would not be able to sustain remission. (Supplementary Figure 4).

DISCUSSION

This is the first study and systematic review with meta-analysis to examine the impact of tapering MTX in RA patients who combine MTX with a broad range of targeted therapies. Our meta-analysis showed that patients who tapered MTX from targeted therapy had a 10% reduction in ability to sustain remission compared to not tapering therapy [RR 0.90 (CI 0.84, 0.97)] for up to 18 months. There was no heterogeneity, and our confidence intervals were narrow.

These data extend those from Subesinghe et al. who published a narrative review[17] on tapering MTX which included two trials of MTX with IFX (iRAMT) and ETA (COMET, included in present review). In the 2005 iRAMT trial, MTX was tapered in patients who had achieved 40% reduction in tender and swollen joint counts from baseline with combination IFX/MTX therapy. Seventy-five percent of patients were able to taper MTX to a minimum dose of 5mg/week without loss of efficacy, suggesting low doses of MTX may help protect against loss of efficacy of IFX. Other classes of targeted therapies were not evaluated. To our

knowledge, this is the first systematic review and meta-analysis to address tapering of MTX from a range of targeted therapies, including IL6-i and JAK-i. Both these targeted therapies have also been shown to be effective as monotherapy in RA[4,8-10,39,40]. Several of our reviewed studies showed numerically increased AEs in patients treated with MTX compared to those on targeted therapies alone. Our patients who may now be taking any of a wide range of targeted therapies often wish to taper their MTX due to intolerance. This review helps inform patients and their physicians as to whether this is a good decision.

Longer follow-up times were associated with lower remission rates, underscoring the importance of including longer follow-up times in tapering studies in RA. Loss of remission over time is common even without changes in treatment[41]. Three of the 5 TNF-i studies were of ETA, which is not associated with anti-drug antibodies, and may not benefit as much from concomitant treatment with MTX. It is possible if the other TNF-i's were more broadly represented, the data may have been different. Although the development of anti-drug antibodies could occur if patients remain on monotherapy with bDMARDs and specifically TNF-inhibitors after MTX tapering, there is little evidence to support this. An observational study found that the long-term drug survival of the TNF-inhibitor was not significantly different between those who discontinued MTX and those who continued it (HR 1.046, CI 0.76-1.44), though how long patients remained off MTX was not explicitly reported[14].

We expected that patients who tapered MTX gradually or allowed a dose reduction without stopping would maintain remission more so than abrupt withdrawal. There was no clear association of tapering schemes with remission outcomes; however, only two studies performed a gradual dose reduction, one of which tapered MTX off within 4 weeks[21]. The other study tapered MTX over 24 weeks and stopped the taper in event of flare[32], allowing subjects to

remain in the taper group if retreatment recaptured disease control at a dose that was not higher than at randomization. This was the only study we reviewed that allowed dose reduction of MTX without stopping in their protocol; the mean dose of MTX in tapering group was not reported.

We analyzed both early and established RA and found both groups had increased risk of not being able to sustain remission but it did not reach significance in established RA. Prior studies have shown that those with early RA may more successfully taper bDMARDs[18,42,43]. Only three studies on early RA were analyzed in our review, and more studies are needed to address this question.

Patient- reported physical function was reported to worsen when MTX was tapered; although it was not statistically significant, it could become significant with longer follow-up. Only three studies reported on predictors of maintaining disease control after tapering MTX[28,33,36]. Higher baseline disease activity and RF seropositivity were associated with reduced likelihood of maintaining remission, similar to prior studies[44]. Higher physical global score was associated with restarting MTX in the LTE. A systematic review of biomarkers for successful tapering of bDMARDs found shorter symptom duration, lower erosion scores and higher ADA drug levels were significant predictors for successful tapering, but evidence was limited by low-quality studies and reporting bias[18]. Understanding the subset of patients who can successfully taper RA therapies will help prevent disease worsening and avoid the undesirable scenario of not being able to recapture disease control with re-treatment.

One study looked at re-treatment after tapering MTX and reported a 75% rate of recapture of remission[28], similar to that reported by prior studies tapering bDMARDs[45,46]. However, these results should be interpreted with caution, as only one study reported on

retreatment outcomes. One trial, not eligible for the meta-analysis, evaluated outcomes of patients tapering both csDMARDs and bDMARDs, and reported recapture of DAS remission by 65% of patients tapering csDMARDs[47]. More research on recapture of remission after tapering MTX from targeted therapy is indicated.

Several limitations of our review should be considered. Studies differed with respect to whether patients had early or established RA, were MTX-naïve or inadequate responders, the tapering strategy used, and the criteria used to taper (Table 1). MTX-naïve patients were studied, not surprisingly, in the three early RA studies which we analyzed separately as previously mentioned (Supplementary Figure 1). The current guidelines recommend gradual tapering of MTX if this is necessary for the care of a given patient, however most available evidence for MTX tapering is based on studies in which MTX is either abruptly or rapidly withdrawn. It is possible that more gradual tapering studies of MTX may have allowed each patient to determine the optimal dose of MTX needed to maintain remission after tapering. Overall, our studies had no heterogeneity with an I squared of 0.0%, p=0.938. This could limit the external validity of this study, but more likely reflects the similarity of the populations being studied.

We included pragmatic studies to increase generalizability to patients seen in routine practice but due to their open-label design, they scored higher on the risk of bias assessment tool. These studies also provided longer follow-up data which we felt was important in addressing our study question. Our one observational LTE study was judged to have serious risk of bias. We included it because it met our inclusion criteria, reported remission outcomes including an adjusted analysis with propensity scoring and evaluated MTX tapering in the real-world setting. Our sensitivity analysis excluding the LTE showed similar results.

One strength of this study is that we were able to estimate the proportion of people who could sustain remission when withdrawing MTX from therapy combined with multiple classes of advanced therapies. Although there were too few studies to draw conclusions about specific classes of drugs, the pooled data were consistent and could inform a broader group of RA patients needing to stop MTX regardless of which targeted therapy was currently in use, be it a TNF-i, IL6-i or JAK-i. Of note, we found no randomized MTX tapering study for patients using it in combination with rituximab which met our criteria.

We evaluated specifically remission outcomes rather than LDA after tapering. Only two studies in our review used remission alone as their tapering criteria, with the other studies using less stringent criteria to taper. It is possible if we looked at LDA as our outcome after tapering, our results may have been shown higher proportions of maintaining disease control. We further evaluated this by performing a meta-analysis of the RR of maintaining LDA after tapering MTX, and found similar results [OR 0.92 (CI 0.86, 0.98) (Supplementary Figure 2). Current guidelines recommend achieving sustained remission prior to tapering therapy; thus, this stricter criterion was applied to inform tapering of MTX from targeted therapy.

In summary, the results of our systematic review and meta-analysis supported our hypothesis that patients with controlled RA have low risk of not being able to sustain remission when tapering MTX from targeted therapy up to 18 months. This review adds to the body of evidence to help inform ACR guidelines regarding tapering of MTX from combination therapy. It can also help inform discussions with patients who have controlled RA, are struggling with common MTX-related intolerances such as hair loss, stomatitis, nausea, diarrhea and elevated liver enzymes and wish to taper it. Our data may aid discussion for female patients of childbearing age, who are concerned about the teratogenicity of MTX. The authors of this

review advocate for the continuing of MTX with targeted therapy when it is well tolerated, as the long-term effects of tapering beyond 18 months requires further study and there were indicators of potential worsening of functional outcomes in some studies. Patients need to be informed that disease control may be lost over time if they remain on targeted monotherapy and that the recapture of remission may not be possible with retreatment. Most importantly patients need to continue careful follow-up over time as prompt re-treatment to recapture disease control is essential.

Further research is needed that include studies with longer follow-up, that also address predictors of successful tapering, long term consequences of treatment withdrawal including worsening of function, measures of joint damage, safety outcomes and whether or not there is an advantage to gradual tapering regimens. Whether targeted therapy used as monotherapy in RA can also tapered is an important sequitur to this study.

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ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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Figure 1: PRISMA Flowchart for identification of studies

Figure 2: Risk of bias assessment of randomized trials using revised Cochrane risk of bias assessment tool for randomized trials

Figure 3: Meta-analysis of studies tapering methotrexate from targeted therapy

Author (study year)

Favors loss of remission

Favors remission

RR (95% CI)

Events,

Treatment

arm

Events, Control arm

% Weight

Figure 4: Funnel plot with pseudo 95% CI for studies tapering methotrexate from targeted therapy

Table 1: Summary characteristics of included studies tapering methotrexate from targeted therapy
caption

* - refers to population subject to tapering ** - good/moderate EULAR response: DAS28<3.2 and decrease >1.2, DAS28<3.2 and decrease >0.6-<1.2 or DAS28>3.2-<5.1 and decrease>0.6-<1.2 or >1.2 or DAS28>5.1 and decrease>1.2, ABS abstract, IR inadequate responder, RCT randomized controlled trial, MTX methotrexate, OLE open-label extension, LTE long-term extension, ETA etanercept, ABA abatacept, ADA adalimumab, CZP certolizumab pegol, TCZ tocilizumab, TNFi TNF-inhibitor, TOFA tofacitinib, early RA (<= 1 year) (eRA), established RA (estRA), NR not reported, WD withdrawal, LDA low disease activity, REM remission, Wk week, Mo months.

Table 2: Outcomes of studies tapering methotrexate from targeted therapy
caption

Δ change in, ABA abatacept, ABS abstract, ADA adalimumab, AE adverse events, bDMARDs biologic DMARDs, CDAI Clinical disease activity index, CI, confidence interval (where available, point estimates reported with 95% CI), CRP C-Reactive Protein, csDMARDS conventional synthetic DMARDs, CZP certolizumab, DAS28 Disease Activity Score 28, DAS28-ESR Disease Activity Score 28 (using ESR), both DAS28 which uses the ESR and DAS28-CRP REM defined as score < 2.6, Diff difference, DMARD Disease Modifying Anti-Rheumatic Drug, ESR erythrocyte sedimentation rate, ETA etanercept, HAQ Health assessment questionnaire, Health HAQ-DI assessment questionnaire-disability index, IQR interquartile range, JAK-i Janus Kinase inhibitor, LSM least squares mean, LDA low disease activity, MCS mental component score, MDGA physician's global assessment of disease, Mono

monotherapy, mo month, mTSS modified total Sharp score, MTX methotrexate, NI noninferiority, NR not reported, n.s. not significant, OLE open label extension, OR odds ratio, PCS physical component score, PDGA Patient's global assessment, PFS Physical functioning scale, PGA Physician global assessment, PtGA Patient global assessment, Prop proportion, REM remission, RF rheumatoid factor, RCT randomized controlled trial, SD standard deviation, SAE serious adverse events, SDAI Simplified disease activity index, SF-36 Short Form Survey 36, Sig significant, SJC swollen joint count, TJC tender joint count, TCZ tocilizumab, TOFA tofacitinib, targeted therapy bDMARDs and JAK-i, WD withdrawal, wk week.

Table 1: Summary characteristics of included studies tapering methotrexate from targeted therapy

Study name/ Author/ Year	n *	RA Early or Established	Age	Number & Type of prior DMARDs	MTX-naïve or IR	Seropositive (%)	Baseline treatment	MTX Taper Strategy	Criteria for taper/ duration of REM or LDA prior to taper	REM outcome measure	Frequency of assessment	Follow-up	Study design/WD 2nd phase or LTE
SEAM Curtis et al 2020	253	estRA (10 -11 years)	55-56	NR	IR	58-69	ETA+MTX	Stop MTX	SDAI ≤ 3.3 REM/ 24 wk run-in	SDAI ≤ 3.3	Every 12 wks	48 wks	RCT/no
AVERT 2 Emery et al 2019 (ABS)[37]	147	eRA (1-1.5 mos)	46-48	DMARD naïve	Naive	NR	ABA+MTX	Stop MTX	SDAI<3.3 REM/ NR	SDAI ≤ 3.3	Wk 24 (WD), 40, 48	48 wks	RCT/2nd phase
ORAL shift Cohen et al 2019	533	estRA (9 years)	56	csDMARD: excluded MTX: 26% Prior TNFi: 30%	IR	62-68	Tofa+MTX	Stop MTX	CDAI<10 LDA/ 24 wk run-in	DAS28-CRP < 2.6	Wk 12, 24 (WD), 36, 48	48 wks	RCT/2nd phase
COMET Emery et al 2010/2019 (ABS) [21]	411	eRA (9 mos)	52	NR	Naive	68	ETA+MTX	Taper MTX over 4 wks	DAS28<2.6 REM or <3.2 LDA/ NR	DAS28 < 2.6	Wk 52 (WD), wk 104	52 wks	RCT/2nd phase
JUST-ACT Pablos et al 2019	165	estRA (6 years)	50-51	NR	IR	NR	TCZ+MTX	Stop MTX	DAS≤3.2/ NR	DAS28 < 2.6	Baseline, wk 16, (WD wk 24), wk 28	28 wks	RCT/2nd phase
Pope et al 2019	88	estRA (8-10 years)	54-58	11-14% prior targeted therapy	IR	60-62	CZP+DMARD (64% on MTX)	Stop DMARDs	change in DAS28 > 1.2 after adding CZP/ NR	DAS28 <2.6	Baseline, 18 mos (WD time varied)	18 mos	RCT/no
COMP-ACT Kremer et al 2018	296	estRA (7 years)	54-56	Prior csDMARDs:1.2 No. prior TNFi: 0.2	IR	70-74	TCZ+MTX	Stop MTX	DAS≤3.2/ NR	DAS28 <2.6	Wk 24 (WD), 40, 52	52 wks	RCT/2nd phase
ACT-TAPER Edwards et al 2017	272	estRA (7 years)	54-56	NR	IR	NR	TCZ+MTX	Taper MTX over 24 wks	good/moderate EULAR response**/ NR	DAS28 <2.6	Wk 24 (WD), every 4 wks to wk 72	48 wks	RCT/2nd phase
CAMEO Keystone et al 2016	205	estRA (9 years)	54	1 prior DMARD (mean)	IR	65-67	ETA+MTX	Stop MTX	Subgroup analysis: pts in LDA/REM DAS28-ESR<3.2/ NR	DAS28 <2.6	Mo 6 (WD), mo 12, 18, 24	18 mos	RCT/2nd phase
Keystone et al 2018	140	eRA (0.7-0.8 years)	50-51	27-32% prior DMARD	Naive	84-88	ADA+MTX	Stop MTX	DAS28-CRP<3.2 LDA/ NR	DAS28-CRP < 2.6	Baseline WD (varied), every 12 wks in OLE 1, every 16 wks during OLE years 2-3	3 years	Pooled post-hoc analysis of OLE/LTE

* - refers to population subject to tapering ** - good/moderate EULAR response: DAS28<3.2 and decrease >1.2, DAS28<3.2 and decrease >0.6-<1.2 or DAS28>3.2-<5.1 and decrease>0.6-<1.2 or >1.2 or DAS28>5.1 and decrease>1.2, ABS abstract, IR inadequate responder, RCT randomized controlled trial, MTX methotrexate, OLE open-label extension, LTE long-term extension, ETA etanercept, ABA abatacept, ADA adalimumab, CZP certolizumab pegol, TCZ tocilizumab, TNFi TNF-inhibitor, TOFA tofacitinib, early RA (<= 1 year) (eRA), established RA (estRA), NR not reported, WD withdrawal, LDA low disease activity, REM remission, Wk week, Mo months.

Table 2: Outcomes of studies tapering methotrexate from targeted therapy

Study/year/author/ design	Proportion (%) Maintaining REM	Time of REM assessment after taper	Mean disease activity scores	Functional outcomes	Patient Reported Outcomes	Radiographic Outcomes	Predictors	Proportion (%) recapture of REM with retreatment	Safety (%) AEs/SAEs/ withdrawn due to AEs
SEAM 2021 Curtis et al RCT	**SDAI REM:** ETA+MTX: 53 ETA mono 50	48 wks	% with SDAI>11: ETA+MTX: 78 ETA mono: 75	NR	NR	NR	Higher baseline SDAI, RF positivity less likely to maintain REM	At 12 wks/48wks ETA+MTX: 47/80 ETA mono: 42/75	ETA+MTX:62/6/0 ETA mono: 56/4/2
AVERT 2 2019 (ABS) Emery et al RCT	**SDAI REM:** ABA+MTX: 74 ABA mono: 57	24 wks	Adjusted mean diff in SDAI score from ABA+MTX [97.5% CI]: stop MTX: 1.12 [-1.08, 3.32]	Adjusted mean diff in HAQ-DI: ABA+MTX: - 0.04 ABA mono + 0.16 (ABS 2020)[38]	Adjusted mean diff in SF-36 PFS: ABA+MTX: + 1.68 ABA mono: -1.45 (ABS 2020)[38]	% with non-progression (95% CI): ABA+MTX: 87 (77, 97) Stop MTX: 87 (77, 98)	NR	NR	ABA+MTX:44/6/0 ABA mono:51/0/0
ORAL Shift 2019 Cohen et al RCT	**DAS28-CRP REM:** Tofa+MTX: 55 Tofa mono: 50	24 wks % persistent REM wks 12, 24, 36, 48 (36 wks) Tofa + MTX: 8 Tofa mono: 4	LSM Δ DAS28-4 ESR: 0.30 [95% CI 0.12-0.48] n.s. NI met	Similar LSM Δ in HAQ-DI	LSM Δ in SF-36 PCS similar	NR	Baseline CDAI OR 0.32 (0.24, 0.43); p<0.0001 (multivariable analysis, ABS 2019)[34]	NR	Tofa+MTX: 41/2/2 Tofa: 41/4/2 n.s.
COMET 2010/2019 (ABS)[21] Emery et al	**DAS28 REM:** ETA+MTX: 85 ETA mono: 70	52 wks	NR	% normal HAQ-DI: ETA+MTX: 81.5% ETA:77.8%	NR	NR in 2019 ABS	NR	NR	ETA+MTX:82/7/NR ETA mono:80/9/NR n.s.
JUST-ACT 2019 Pablos et al RCT	**DAS28 REM:** TCZ+MTX: 82 TCZ mono: 76	12 wks	Δ DAS28 with treatment diff: -0.06 [-0.40, 0.27; p=0.007] NI met	No diff in HAQ scores, p=0.674	Δ SF-12 PCS: TCZ+MTX: 44.9, MTX: 40.2 (p=0.15) No diff in SF-12 MCS, PDGA, MDGA	NR	NR	NR	TCZ+MTX: 49/1/NR TCZ: 55/5/NR
2019 Pope et al RCT	**DAS28 REM:** CZP+MTX: 41 CZP: 41 p=1.0	Not specified (WD time NR)	Maintenance of Δ DAS28 > 1.2 with absolute risk diff: 2.6% [90% CI: 19%; one sided] p=0.402 NI not met	ΔHAQ-DI ≥ 0.22: CZP+MTX: 44% CZP: 54% p=0.377	CZP+MTX vs CZP: AM stiffness: 21.7 vs 39.9 (p=0.026) PtGA: 32.3 vs 34.8 Pain: 35.0 vs 38.2 Fatigue: 43.7 vs 43.4 %work loss:7.4 vs 5.4 TJC: 2.1 vs 3.1	NR	NR	NR	CZP+MTX: 72/5/0 CZP: 69/4/2
COMP-ACT 2018 Kremer et al RCT	**DAS28 REM:** TCZ+MTX: 55 TCZ: 48 Between-group diff (%) -7 [-18, 5]	28 wks	Adjusted mean D DAS28-ESR (95%CI): TCZ+MTX: 0.14 (-0.11, 0.39) TCZ mono: 0.46 (0.22, 0.70) Adjusted diff: 0.318 (0.45, 0.592) NI met	NR	NR	NR	NR	NR	TCZ+MTX: 68/6/NR TCZ mono: 62/4/NR Higher in TCZ+MTX 1.5% developed anti-TCZ antibodies (while on MTX)
ACT-TAPER 2017 Edwards et al RCT	**DAS28 REM:** TCZ+stable MTX: 51 TCZ+ taper MTX: 50 p=0.902	48 wks	Mean Δ DAS28 n.s.	NR	NR	NR	NR	NR	% AEs/withdraw TCZ+stable MTX: 72/1 TCZ+taper MTX: 72/12 % SAEs: TCZ-related:5 MTX-related:3
CAMEO 2016 Keystone et al RCT	**DAS28 REM:** ETA+MTX: 51 [37, 65] ETA: 40 [26, 54]	18 mos	DAS28-ESR mean (SD) Δ n.s.	HAQ-DI, Δ mean score (SD): ETA+MTX: 0.1[0.5] ETA: 0.2[0.4]	NR	% progression in mTSS: ETA+MTX:13 ETA:14 n.s.	No	NR	ETA+MTX:86/16/NR ETA mono:88/11/NR n.s.
PREMIER OLE 2018 Keystone et al Observational	**DAS28-CRP REM:** MTX use: 48 MTX non-use: 50	Up to 3 years after MTX WD; MTX restarted varying timepoints	none	% normal function (HAQ-DI<0.5): MTX use: 45% MTX non-use: 58%	NR	% with no progression: MTX use: 46 MTX non-use: 50	Higher PGA associated with MTX use during OLE (p<0.01)	Median (IQR) time to 1st MTX restart: 5.1 (0.1-31.4) wks; Higher DAS28 if patients restarted later	MTX use group: 93/29/9 MTX non-use: 89/30/8 Infectious AEs higher in MTX use vs non-use:73 vs 67

Δ change in, ABA abatacept, ABS abstract, ADA adalimumab, AE adverse events, bDMARDs biologic DMARDs, CDAI Clinical disease activity index, CI, confidence interval (where available, point estimates reported with 95% CI), CRP C-Reactive Protein, csDMARDS conventional synthetic DMARDs, CZP certolizumab, DAS28 Disease Activity Score 28, DAS28-ESR Disease Activity Score 28 (using ESR), both DAS28 which uses the ESR and DAS28-CRP REM defined as score < 2.6, Diff difference, DMARD Disease Modifying Anti-Rheumatic Drug, ESR erythrocyte sedimentation rate, ETA etanercept, HAQ Health assessment questionnaire, Health HAQ-DI assessment questionnaire-disability index, IQR interquartile range, JAK-i Janus Kinase inhibitor, LSM least squares mean, LDA low disease activity, MCS mental component score, MDGA physician's global assessment of disease, Mono monotherapy, mo month, mTSS modified total Sharp score, MTX methotrexate, NI noninferiority, NR not reported, n.s. not significant, OLE open label extension, OR odds ratio, PCS physical component score, PDGA Patient's global assessment, PFS Physical functioning scale, PGA Physician global assessment, PtGA Patient global assessment, Prop proportion, REM remission, RF rheumatoid factor, RCT randomized controlled trial, SD standard deviation, SAE serious adverse events, SDAI Simplified disease activity index, SF-36 Short Form Survey 36, Sig significant, SJC swollen joint count, TJC tender joint count, TCZ tocilizumab, TOFA tofacitinib, targeted therapy bDMARDs and JAK-i, WD withdrawal, wk week.

Figure 1 PRISMA Flowchart for identification of studies

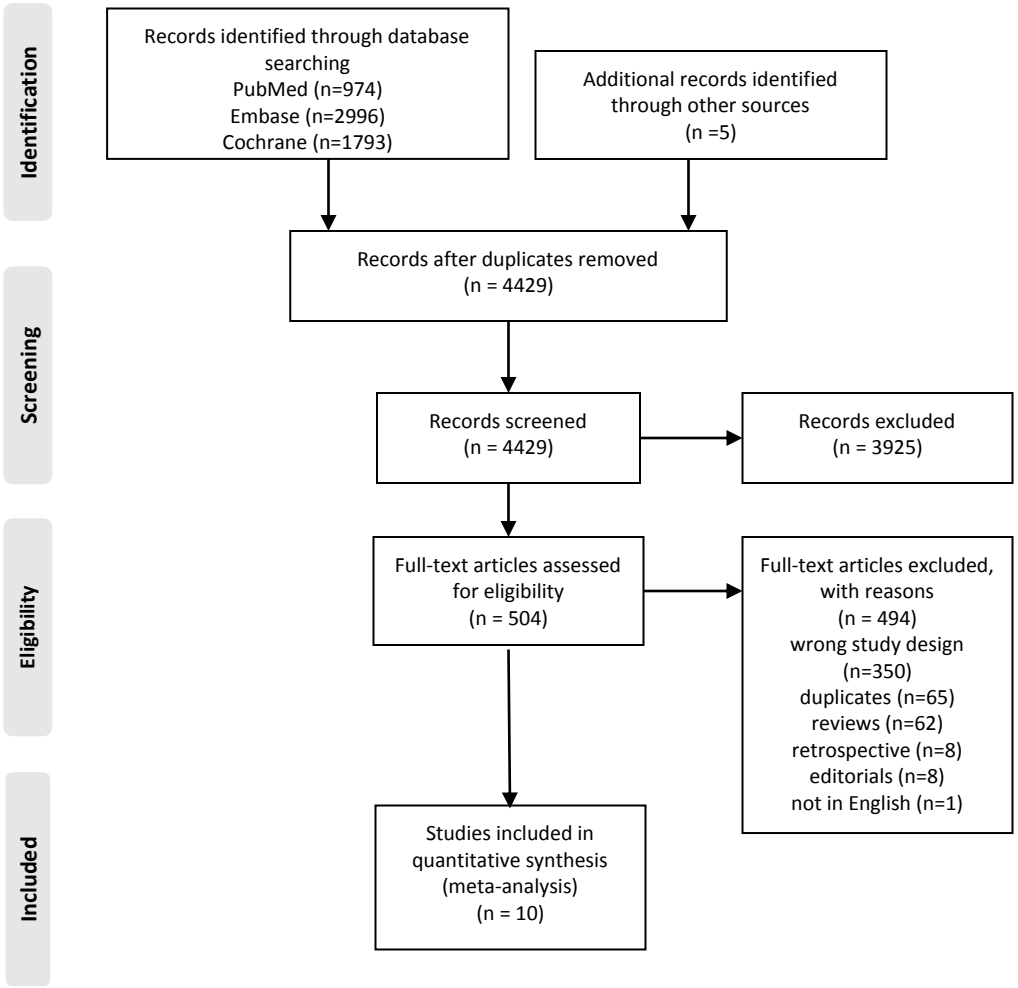

Figure 2: Risk of bias assessment of randomized trials using revised Cochrane risk of bias assessment tool for randomized trials