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Can Patients With Controlled Rheumatoid Arthritis Taper Methotrexate From Targeted Therapy and Sustain Remission? A Systematic Review and Metaanalysis

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ABSTRACT. ***Objective.*** To determine the risk of not being able to sustain remission after tapering methotrexate (MTX) from targeted therapy in patients with controlled rheumatoid arthritis (RA).

Methods. A systematic literature search was conducted in MEDLINE, Embase, and the 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. Metaanalyses were conducted using random-effects models. Forest and funnel plots were created.

Results. A total of 10 articles were included. Studies evaluated MTX being tapered from combination treatment with tumor necrosis factor inhibitors, tocilizumab, abatacept, and tofacitinib. A total of 9 studies used a randomized design and 1 was observational. Out of 10 studies, 3 focused on early RA (ie, < 1 yr). The MTX-tapering strategy was gradual in 2 studies and rapid in 8 studies. Follow-up ranged from 3 to 18 months in randomized trials and up to 3 years in the observational study. Our metaanalysis, which included 2000 participants with RA from 10 studies, showed that patients who tapered MTX from targeted therapy had a 10% reduction in the ability to sustain remission and an overall pooled risk ratio of 0.90 (95% CI 0.84-0.97). There was no heterogeneity ($I^2 = 0\%$, $P = 0.94$). Our funnel plot indicated minimal publication bias.

Conclusion. Patients with controlled RA may taper MTX from targeted therapy with a 10% reduction in the 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 retreatment of disease worsening.

Key Indexing Terms: methotrexate, remission, rheumatoid arthritis

Methotrexate (MTX) is recommended to be used in combination with biologic disease-modifying antirheumatic drugs (bDMARDs) 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 because of their intolerance to MTX and other conventional synthetic disease-modifying antirheumatic drugs (csDMARDs). Adverse effects from MTX have been cited to be the most common reason for its discontinuation, particularly from gastrointestinal intolerance, cytopenia, and abnormal liver function tests.[5] MTX adherence has been observed to be highly variable[6] and inferior to that of bDMARDs.[7] In addition, several RA studies have shown the effectiveness of monotherapy with interleukin 6 inhibitors (IL-6i) and Janus kinase inhibitors (JAKi).[4,8-10] Going forward, we refer to both bDMARDs and JAKi as targeted therapies.

Tapering disease-modifying antirheumatic drugs (DMARD) therapy is a desirable goal for many patients with chronic diseases such as RA. 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

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that 34% to 62% of patients with RA using tumor necrosis factor inhibitors (TNFi) later tapered their MTX.[14,15] The 2021 American College of Rheumatology (ACR) guidelines conditionally recommend (1) continuation of all DMARDs at their current dose over a dose reduction because of a 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. However, the ACR acknowledge there is an absence of direct evidence.[16]

Prior reviews have focused on tapering of MTX from combination treatment with either csDMARDs or TNFi.[17] A 2015 systematic review of tapering of csDMARDs or bDMARDs reported a flare rate after tapering MTX ranging from 8% at 24 weeks (patients remained on hydroxychloroquine and corticosteroids) to 42% at 32 weeks (patients on infliximab).[12] According to our literature search, there have been no updated reviews addressing MTX tapering from other targeted therapies, such as IL-6i or JAKi, nor has there been a systematic review with a metaanalysis addressing this question. Factors associated with successful tapering, such as disease duration (ie, early vs established RA) or the tapering scheme itself (ie, gradual vs brisk), remain unknown.[18]

Therefore, we conducted a systematic literature review to evaluate whether remission can be sustained after the tapering (ie, dose reduction, gradual dose reduction before stopping, or withdrawal) of MTX in patients with RA who are taking MTX in combination with targeted therapy. We also aimed to evaluate the factors associated with successful tapering, such as disease duration and tapering schemes. Our hypothesis was 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 (ie, abatacept [ABA], certolizumab pegol [CZP], etanercept [ETN], golimumab, infliximab [IFX], rituximab [RTX], tocilizumab [TCZ], and sarilumab) or JAKi (ie, tofacitinib [TOF], baricitinib, and 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 (ie, PubMed) by a medical librarian. It was then adapted for other databases that were searched: Embase; the Cochrane Library, including the Cochrane Central Register of Controlled Trials; the Health Technology Assessment database; and the NHS (National Health Service) Economic Evaluation Database (for full search strategy and search terms, see Supplementary Data S1, available with the online version of this article). We searched for articles published between January 1, 2014, and August 30, 2021, and ran the last updated search in all databases on August 30, 2021. 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), allowing duplicates to be removed. The screening process was completed by 2 authors (CFM and DAR). Title and abstract screening were conducted first, followed by full-text screening. Any issues were resolved through consensus with VPB. This review was conducted and reported according to the procedures outlined in the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) statement.[19]

Study selection. Inclusion criteria for articles comprised the following: (1) prospective comparative studies, including randomized controlled trials (RCTs), pragmatic trials, and observational studies of patients with RA; (2) subjects were taking MTX and targeted therapy (ie, TNFi, IL-6i, ABA, RTX, or JAKi); (3) the study design included an intervention group who underwent tapering of MTX from a combination with targeted therapy and a comparator group who continued combination therapy; and (4) reporting of subjects who remained in or achieved remission as measured by a composite score. Exclusion criteria comprised the following: (1) retrospective studies and (2) no reporting of the proportion of remission outcomes after tapering treatment.

Data extraction. CFM and DAR selected potential manuscripts for retrieval and, upon retrieval, established study eligibility by applying the selection criteria. Studies in doubt were discussed with VPB until consensus was reached. If trial data relevant to the review were found in a secondary publication or abstract, they were included and noted in the tables. The original publication of the Combination of Methotrexate and Etanercept in Active Early Rheumatoid Arthritis (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 (LDA)/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, and RA duration dichotomized as either early (diagnosis < 1 yr) 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 measures, including that of remission, disease worsening, duration of remission, retreatment outcomes, radiographic outcomes, patient-reported outcomes, and predictors of either 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 CFM and DAR, discussed with DPJK and, where clarification was needed, with VPB. The criteria for evaluation included randomization, deviations from intended interventions, missing outcome data, measurement of outcomes, and selection of reported results. Studies were judged to have an overall low risk of bias if they were found to have a low risk of bias for all domains. Studies were judged to have some concerns overall if they were found to have some concerns in at least 1 domain. Studies were judged to have an overall high risk of bias if they were found to have a high risk of bias in at least 1 domain or some concerns for multiple domains that substantially lowered the confidence in the results.[22] Nonrandomized 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 S1, available with the online version of this article).

Statistical analysis. Random-effects models were used to calculate pooled risk ratios (RRs).[24,25] Heterogeneity was assessed by calculating the I^2 index using the Cochran-Mantel-Haenszel technique.[26] Additionally, forest plots were generated for each analysis. A funnel plot was created, and the Egger and Harbord tests were calculated[27,28] to aid in the assessment of bias. All analyses were performed in Stata (version 14.2; StataCorp).

RESULTS

Literature search. Our search identified 5763 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 and Supplementary Data S1, available with the online version of this article). Of these, 10 articles addressed our research question and met our inclusion criteria.

Characteristics of included studies. A total of 10 studies examining

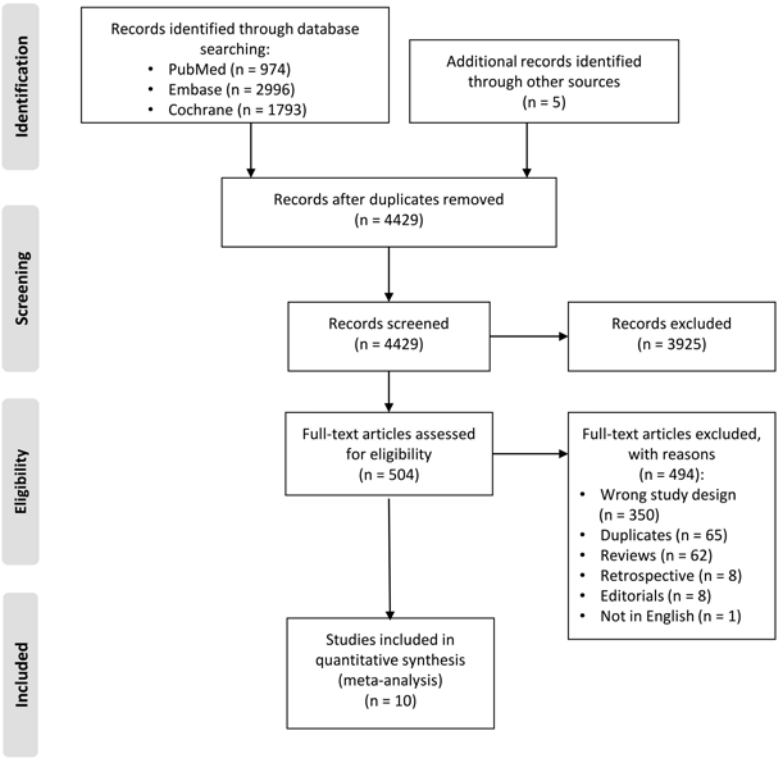

Figure 1. PRISMA flowchart for identification of studies. PRISMA: Preferred Reporting Items for Systematic reviews and Meta-Analyses.

the tapering of MTX from combined treatment with targeted therapy were reviewed. In total, 3 studies tapered MTX from combined treatment with ETN,[20,21,29-31] 3 studies tapered MTX from TCZ,[32-34] and 1 trial each tapered MTX from TOF,[35,36] CZP,[37] adalimumab (ADA),[38] and ABA[39,40] (Table 1). No studies tapering MTX from RTX met our inclusion criteria. In total, 7 articles studied established RA[29,30,32-35,37] (ie, 6-11 yrs) and 3 studied early RA[21,38,39] (ie, 1-9 months). Use of prior DMARDs ranged from 11% to 32%[31,35,37,38] but was not specified in the remaining studies.[20,29,32,34] Patients who were MTX-naïve were evaluated in the early RA trials,[20,38,39] and the remaining trials[29,30,32-35,37] studied patients who were MTX-inadequate responders. Seropositivity ranged from 58% to 88% in 7 studies.[20,29,30,33,35,37,38] There were 9 RCTs,[20,29,30,32-35,37,39] 7 of which studied withdrawal as the second phase of their study, and 1 was a long-term extension (LTE) study.[38] In total, 2 RCTs used a run-in period[29,35] (Table 1 and Supplementary Table S2, available with the online version of this article). In total, 7 RCTs[20,29,32-35,39] were placebo-controlled during tapering (Supplementary Table S2).

Criteria for tapering was LDA based on Disease Activity Score in 28 joints (DAS28) in 4 studies,[31,32,33,38] Clinical Disease Activity Index LDA in 1 study,[35] change in DAS28 in 1 study,[37] Simplified Disease Activity Index (SDAI) remission in 2 studies,[29,39] both DAS28 remission and LDA in 1 study,[21] and based on the European Alliance of Associations for Rheumatology (EULAR) response in 1 study[34] (Table 1 and Supplementary Table S2, available with the online version of this article). As their outcome measure, a total of 8 studies[21,31,32-35,37,38] used the proportion of patients with DAS28-based remission, with 2 studies[29,39] using SDAI remission (Table 1 and Supplementary Table S2).

Follow-up ranged from 28 weeks to 18 months in 9 RCTs[20,21,29,30,32-35,37,39] but was up to 3 years in the LTE study[38] (Table 1). The 3-year LTE study[38] 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 1 study,[29] have some concerns in 6 studies,[21,32-35,39] and be high in 2 open-label studies[30,37] (Figure 2). The LTE study[38] was judged to have a serious risk of bias (Supplementary Table S1, available with the online version of this article).

Tapering scheme. Eight studies[29,30,32,33,35,37-39] stopped MTX in their tapering strategy and 2 studies[20,21,34] gradually reduced the dose of MTX. The COMET trial tapered MTX from ETN+MTX over 4 weeks and was among the studies reporting a higher remission rate of 70%,[21] compared to a remission rate ranging from 16% to 76% in the studies that stopped MTX abruptly.[29,30,32,33,35,37-39] However, the study by Edwards et al (ACT-TAPER) tapered the dose of MTX more slowly over 24 weeks from TCZ+MTX and reported a lower remission rate of 50%.[34]

Duration of remission and follow-up. Remission outcomes after MTX withdrawal were obtained at varying timepoints, ranging

Table 1. Summary characteristics of included studies tapering MTX from targeted therapy.

Study, Author, Year	n[a]	Early or Established RA (duration)	Age, yrs	Type and Number 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[29], Curtis, 2021	253	estRA (10 -11 yrs)	55-56	NR	IR	58-69	ETN+MTX	Stop MTX	SDAI ≤ 3.3 REM; 24-wk run-in	SDAI ≤ 3.3	Every 12 wks	48 wks	RCT; no
AVERT-2[39], Emery, 2019 (ABS)	147	eRA (1-1.5 mos)	46-48	DMARD naïve	Naïve	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[35], Cohen, 2019	533	estRA (9 yrs)	56	csDMARD: excluded MTX: 26% Prior TNFi: 30%	IR	62-68	TOF+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, 2010[20] / 2019 (ABS)[21]	411	eRA (9 mos)	52	NR	Naïve	68	ETN+MTX	Taper MTX over 4 wks	DAS28 < 2.6 REM or < 3.2 LDA; NR	DAS28 < 2.6	Wk 52 (WD), 104	52 wks	RCT; 2nd phase
JUST-ACT[32], Pablos, 2019	165	estRA (6 yrs)	50-51	NR	IR	NR	TCZ+MTX	Stop MTX	DAS28 ≤ 3.2; NR	DAS28 < 2.6	Baseline, wk 16, wk 24 (WD), 28	28 wks	RCT; 2nd phase
Pope[37], 2020	88	estRA (8-10 yrs)	54-58	Prior targeted therapy: 11-14%	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[33], Kremer, 2018	296	estRA (7 yrs)	54-56	No. of prior csDMARD: 1.2 No. of prior TNFi: 0.2	IR	70-74	TCZ+MTX	Stop MTX	DAS28 ≤ 3.2; NR	DAS28 < 2.6	Wk 24 (WD), 40, 52	52 wks	RCT; 2nd phase
ACT-TAPER[34], Edwards, 2018	272	estRA (7 yrs)	54-56	NR	IR	NR	TCZ+MTX	Taper MTX over 24 wks	Good/moderate EULAR response[b]; NR	DAS28 < 2.6	Wk 24 (WD), every 4 wks to wk 72	48 wks	RCT; 2nd phase
CAMEO, Keystone, 2016[30] / Pope 2014[31]	205	estRA (9 yrs)	54	No. prior DMARD (median): 1	IR	65-67	ETN+MTX	Stop MTX	Subgroup analysis: DAS28-ESR < 3.2 LDA; NR	DAS28 < 2.6	Mo 6 (WD), 12, 18, 24	18 mos	RCT; 2nd phase
PREMIER OLE, Keystone[38], 2018	140	eRA (0.7-0.8 yrs)	50-51	Prior DMARD: 27-32%	Naïve	84-88	ADA+MTX	Stop MTX	DAS28-CRP < 3.2 LDA; NR	DAS28-CRP < 2.6	Baseline WD2018 (varied), every 12 wks in OLE 1, every 16 wks during OLE yrs 2-3	3 yrs	Pooled post hoc analysis of OLE; LTE

[a] This refers to the population subject to tapering. [b] Good/moderate EULAR response: DAS28 < 3.2 and decrease > 1.2, DAS28 < 3.2 and decrease > 0.6 to < 1.2, DAS28 > 3.2 to < 5.1 and decrease > 0.6 to < 1.2 or > 1.2, or DAS28 > 5.1 and decrease > 1.2. ABA: abatacept; ABS: abstract; ADA: adalimumab; AVERT-2: Assessing Very Early Rheumatoid Arthritis Treatment-2; CAMEO: Canadian Methotrexate and Etanercept Outcome Study; COMET: Combination of Methotrexate and Etanercept in Active Early Rheumatoid Arthritis: CRP: C-reactive protein; csDMARD: conventional synthetic disease-modifying antirheumatic drug; CZP: certolizumab pegol; DAS28: Disease Activity Score in 28 joints; DMARD: disease-modifying antirheumatic drug; eRA: early rheumatoid arthritis (≤ 1 yr); ESR: erythrocyte sedimentation rate; estRA: established rheumatoid arthritis; ETN: etanercept; EULAR: European Alliance of Associations for Rheumatology; IR: inadequate responder; LDA: low disease activity; LTE: long-term extension; MTX: methotrexate; NR: not reported; OLE: open-label extension; RA: rheumatoid arthritis; RCT: randomized controlled trial; REM: remission; SDAI: simplified disease activity index; SEAM: Study of Etanercept and Methotrexate in Combination or as Monotherapy; TCZ: tocilizumab; TNFi: TNF inhibitor; TOF: tofacitinib; WD: withdrawal.

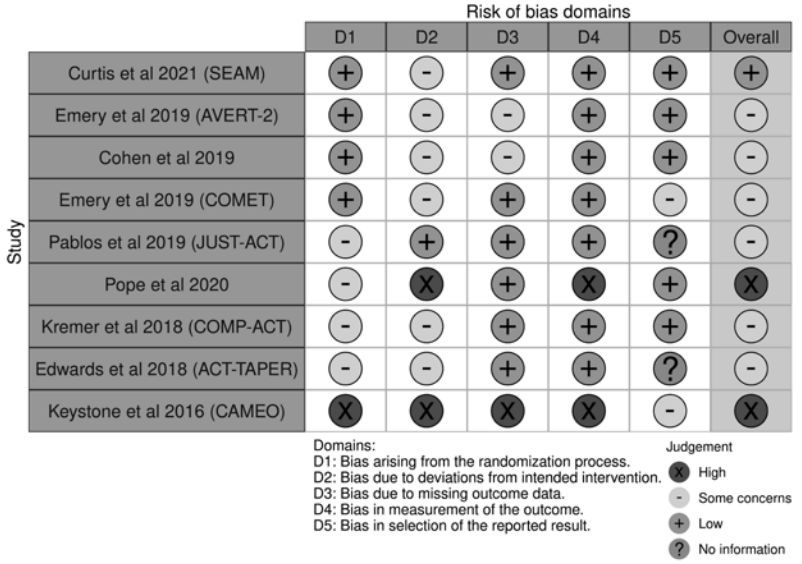

Figure 2. Risk-of-bias assessment of randomized trials using the revised Cochrane risk of bias assessment tool for randomized trials. AVERT-2: Assessing Very Early Rheumatoid Arthritis Treatment-2; COMET: Combination of Methotrexate and Etanercept in Active Early Rheumatoid Arthritis.

from 12 weeks to 18 months in randomized studies[21,29,30,32-35,37,39] (Table 2). Studies that reported outcomes up to 1 year[21,29,32-35,37,39] after tapering had remission rates ranging from 48% to 76%, but this dropped to 40% in 1 study that reported 18-month remission outcomes.[30] When persistent remission—defined as consistent remission at weeks 12, 24, 36, and 48—after tapering MTX to TOF monotherapy was used, remission rates dropped to 4%.[35]

Mean disease activity scores after tapering. In total, 8 studies[29,30,32-35,37,39] reported on changes in mean disease activity scores after tapering MTX (Table 2). Curtis et al[29] found that disease worsening defined as SDAI > 11 was similarly high in those who stopped MTX (75%) compared to those who continued ETN+MTX (78%). In total, 2 studies[32,33]—COMP-ACT and JUST-ACT—demonstrated noninferiority of change in DAS28 scores in withdrawing MTX from TCZ compared to combination therapy. Pope et al[37] did not demonstrate noninferiority of maintaining change in DAS28 scores in the group withdrawing MTX from CZP compared to continuing therapy (Table 2). The Assessing Very Early Rheumatoid Arthritis Treatment-2 (AVERT-2), and Canadian Methotrexate and Etanercept Outcome (CAMEO) trials and study by Edwards et al (ACT-TAPER) did not find a significant difference in mean scores between groups.

Functional outcomes. In total, 7 studies[20,30,32,35,37-39] reported on functional or other patient-reported outcomes (Table 2). The AVERT-2 trial found an adjusted mean change in the Health Assessment Questionnaire–Disability Index of 0.16 in those who stopped MTX vs −0.04 in those who continued ABA+MTX.[40] The physical functioning scale scores from the 36-item Short Form Health Survey were also worse in the group that stopped MTX (−1.45 vs 1.68 in the combination group). Pope et al[37] found significantly longer morning stiffness in the CZP monotherapy group (39.9 min) compared to the CZP+MTX group (21.7 min; $P = 0.026$). Patient global pain, fatigue, work loss, and tender joint count scores trended worse with CZP monotherapy but did not reach significance (Table 2).

Radiographic outcomes. In total, 2 randomized trials[30,39] and 1 observational study[38] 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. In total, 2 RCTs[29,35,36] and 1 LTE study[38] examined predictors of maintaining remission after tapering MTX from targeted therapy. Higher baseline disease activity scores and rheumatoid factor (RF) positivity were found to be associated with lower likelihood of maintaining remission (Table 2). Higher physician global assessment scores were associated with restarting MTX during the open-label LTE[38] ($P < 0.01$; Table 2).

Recapture of remission. In total, 2 studies reported on retreatment outcomes.[29,38] Curtis et al[29] reported that remission was recaptured with retreatment in 75% of patients in the ETN monotherapy group by week 48. The LTE study[38] 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 the number of adverse events (AEs), serious AEs, and discontinuations of treatment as a result of AEs. In total, 3 studies—SEAM, COMP-ACT, and Keystone et al[36]—noted a numerical increase in the frequency of AEs in the patients treated with MTX compared to other arms (Table 2). The study by Pablos et al (JUST-ACT)[32] reported higher AEs in the TCZ monotherapy group compared to the MTX-treated group (Table 2).

Metaanalysis. The metaanalysis, conducted among 2000

Table 2. Outcomes of studies tapering MTX from targeted[a] 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	Proportion Safety AEs/SAEs/ withdrawn because of AEs
SEAM[29], 2021, Curtis, RCT	SDAI REM: ETN+MTX: 53% ETN mono: 50%	48 wks	Proportion with SDAI > 11: ETN+MTX: 78% ETN mono: 75%	NR	NR	NR	Higher baseline SDAI, RF positivity less likely to maintain REM	At 12 wks/48wks ETN+MTX: 47%/80% ETN mono: 42%/75%	ETN+MTX: 62%/6%/0% ETN mono: 56%/4%/2%
AVERT-2[39], 2019 (ABS), Emery, RCT	SDAI REM: ABA+MTX: 74% ABA mono: 57%	24 wks	Adjusted mean diff in SDAI score from ABA+MTX: Stop MTX: 1.12 (97.5% CI −1.08 to 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]	Proportion with nonprogression: ABA+MTX: 87% (95% CI 77-97) Stop MTX: 87% (95% CI 77-98)	NR	NR	ABA+MTX: 44%/6%/0% ABA mono: 51%/0%/0%
ORAL Shift[35], 2019, Cohen, RCT	DAS28-4(CRP) REM[b]: TOF+MTX: 55% TOF mono: 50% Persistent REM: TOF+MTX: 8% TOF mono: 4%	24 wks Persistent REM wks 12, 24, 36, 48	LSM Δ DAS28-4(ESR)[b]: 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 (95% CI 0.24-0.43) $P < 0.0001$ (multivariable analysis, ABS 2019)[36]	NR	TOF+MTX: 41%/2%/2% TOF: 41%/4%/2% n.s.
COMET, 2010[20]/2019 (ABS)[21], Emery RCT	DAS28 REM: ETN+MTX: 85% ETN mono: 70%	52 wks	NR	Proportion normal HAQ-DI: ETN+MTX: 81.5% ETN: 77.8%	NR	NR in 2019 ABS	NR	NR	ETN+MTX: 82%/7%/NR ETN mono: 80%/9%/NR n.s.
JUST-ACT[32], 2019, Pablos, RCT	DAS28 REM: TCZ+MTX: 82% TCZ mono: 76%	12 wks	Δ DAS28 with treatment diff: −0.06 (95% CI−0.40 to 0.27) $P = 0.007$ NI met	No diff in HAQ scores $P = 0.674$	Δ SF-12 PCS: TCZ+MTX: 0.80 (95% CI −1.1 to 2.7); MTX: −2.58 (95% CI −4.48 to −0.67) $P = 0.015$ No diff in SF-12 MCS, PtGA, MDGA	NR	NR	NR	TCZ+MTX: 49%/1%/NR TCZ: 55%/5%/NR
Pope[37], 2020 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% (upper limit of 90% CI: 19%[c]; 1-sided $P = 0.402$) NI not met	Δ HAQ-DI ≥ 0.22: CZP+MTX: 44% CZP: 54% $P = 0.377$	CZP+MTX vs CZP: Morning stiffness (VAS mm): 21.7 vs 39.9 ($P = 0.026$) PtGA (VAS mm): 32.3 vs 34.8 Pain (VAS mm): 35.0 vs 38.2 Fatigue (VAS mm): 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%

Table 2. Continued.

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	Proportion Safety AEs/SAEs/ withdrawn because of AEs
COMP-ACT[33], 2018, Kremer, RCT	DAS28 REM: TCZ+MTX: 55% TCZ: 48% Between-group diff: −7% (95% CI −18% to 5%)	28 wks	Adjusted mean Δ in DAS28-ESR: TCZ+MTX: 0.14 (95% CI −0.11 to 0.39) TCZ mono: 0.46 (95% CI 0.22 to 0.70) Adjusted diff: 0.318 (95% CI 0.45 to 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[34], 2018, Edwards, 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	Proportion AEs/withdrawn: TCZ+stable MTX: 72%/13 TCZ+taper MTX: 72%/12% Proportion SAEs: TCZ-related: 5% MTX-related: 3%
CAMEO, 2016, Keystone[30]/ 2014, Pope[31] RCT	DAS28 REM: ETN+MTX: 51% (95% CI 37-65) ETN: 40% (95% CI 26-54)	18 mos	DAS28-ESR mean (SD) Δ n.s.	HAQ-DI, Δ mean score (SD): ETN+MTX: 0.1 (0.5) ETN: 0.2 (0.4)	NR	Proportion progression in mTSS: ETN+MTX: 13% ETN: 14% n.s.	No	NR	ETN+MTX: 86%/16%/NR ETN mono: 88%/11%/NR n.s.
PREMIER OLE, 2018, Keystone[38], observational	DAS28-CRP REM: MTX use: 48% MTX nonuse: 50%	Up to 3 yrs after MTX WD; MTX restarted at varying timepoints	None	Proportion normal function (HAQ-DI < 0.5): MTX use: 45% MTX nonuse: 58%	NR	Proportion with no progression: MTX use: 46% MTX nonuse: 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 nonuse: 89%/30%/8% Infectious AEs higher in MTX use vs nonuse: 73% vs 67%

[a] Where available, point estimates are reported. [b] Both DAS28-ESR and DAS28-CRP REM defined as score < 2.6; [c] Targeted therapy includes biologic disease-modifying antirheumatic drugs and Janus kinase inhibitor. ABA: abatacept; ABS: abstract; ADA: adalimumab; AE: adverse event; AVERT-2: Assessing Very Early Rheumatoid Arthritis Treatment-2; CAMEO: Canadian Methotrexate and Etanercept Outcome Study; CDAI: Clinical Disease Activity Index; COMET: Combination of Methotrexate and Etanercept in Active Early Rheumatoid Arthritis; CRP: C-reactive protein; CZP: certolizumab; DAS28: Disease Activity Score in 28 joints; diff: difference; Δ: change in; ESR: erythrocyte sedimentation rate; DAS28-4(CRP): Disease Activity Score in 28 joints with four variables including C-reactive protein; DAS28-4(ESR):Disease Activity Score in 28 joints with four variables including ESR; ETN: etanercept; HAQ: Health Assessment Questionnaire; HAQ-DI: Health Assessment Questionnaire–Disability Index; LSM: least squares mean; MCS: mental component score; MDGA: physician global assessment of disease; mono: monotherapy; 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; PFS: physical functioning scale; PGA: physician global assessment; PtGA: patient global assessment; RCT: randomized controlled trial; REM: remission; RF: rheumatoid factor; SAE: serious adverse event;; SDAI: simplified disease activity index; SEAM: Study of Etanercept and Methotrexate in Combination or as Monotherapy; SF-12: 12-Item Short Form Health Survey; SF-36: 36-Item Short Form Health Survey; TCZ: tocilizumab; TJC: tender joint count; TOF: tofacitinib; WD: withdrawal.

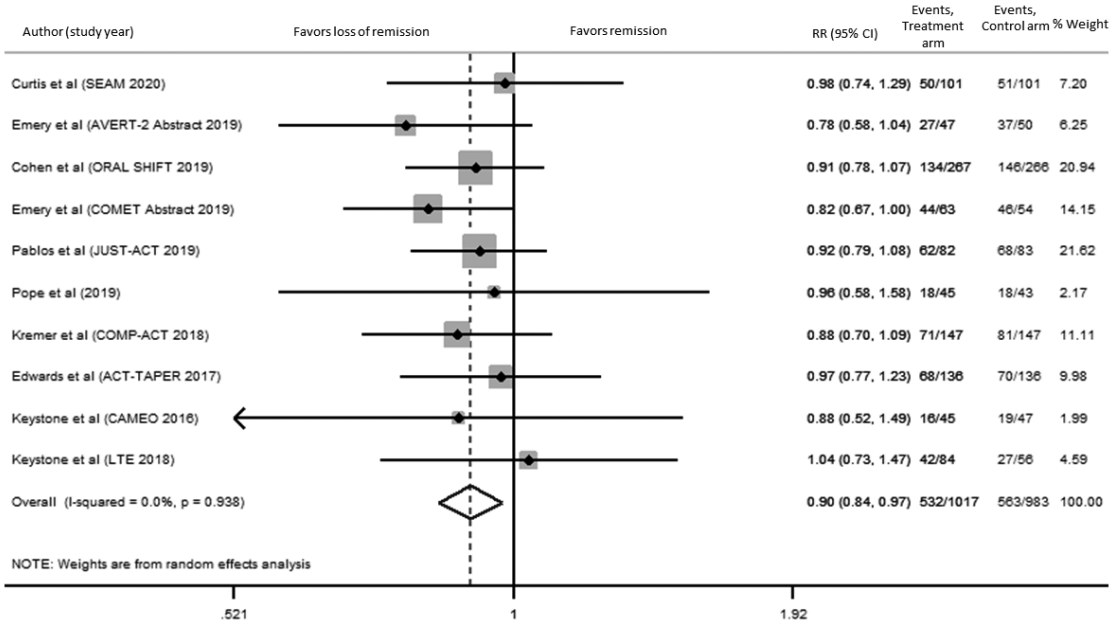

Figure 3. Metaanalysis of studies tapering methotrexate from targeted therapy. AVERT-2: Assessing Very Early Rheumatoid Arthritis Treatment-2; CAMEO: Canadian Methotrexate and Etanercept Outcome; COMET: Combination of Methotrexate and Etanercept in Active Early Rheumatoid Arthritis; LTE: long-term extension; RR: risk ratio; SEAM: Study of Etanercept and Methotrexate in Combination or as Monotherapy

participants with RA from 10 studies, showed a pooled RR for maintaining remission after tapering MTX from targeted therapy of 0.90 (95% CI 0.84-0.97; Figure 3). There was no heterogeneity among the studies in this group ($I^2 = 0\%, P = 0.94$). Among the studies that enrolled patients with early RA, the RR was 0.84 (95% CI 0.73-0.98) and the heterogeneity was 0% ($P = 0.39$). Among studies with patients with established RA, the RR was 0.92 (95% CI 0.85-1.01) and there was 0% heterogeneity present ($P > 0.99$; Supplementary Figure S1, available with the online version of this article). 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 metaanalysis on the RRs of maintaining LDA after tapering MTX. We found similar results to the ones reported above (RR 0.92, 95% CI 0.86-0.98; Supplementary Figure S2, available with the online version of this article). Additionally, we performed a sensitivity analysis, where we omitted the 2018 LTE study[38] as it had a higher bias. Again, we found similar results (RR 0.90, 95% CI 0.83-0.97; Supplementary Figure S3, available with the online version of this article). Figure 4 shows our funnel plot for all included studies, along with a fitted line representing the Egger test for asymmetry; the results indicate minimal publication bias. Results from both the Egger test and the Harbord 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 risk difference of –0.05 (95% CI –0.10 to –0.01; Supplementary Figure S4, available with the online version of this article). 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.

DISCUSSION

To our knowledge, this is the first study and systematic review with metaanalysis to examine the effects of tapering MTX in patients with RA who combined MTX with a broad range of targeted therapies. Our metaanalysis showed that patients who tapered MTX from targeted therapy had a 10% reduction in the ability to sustain remission compared to not tapering therapy (RR 0.90, 95% CI 0.84-0.97) for up to 18 months. There was no heterogeneity, and our CIs were narrow.

These data extend those from Subesinghe et al[17] who published a narrative review on tapering MTX, which included 2 trials of MTX, one with IFX in Infliximab Rheumatoid Arthritis Methotrexate Tapering (iRAMT) trial and ETN (COMET trial,[21] included in the present review). In the 2005 iRAMT trial, MTX was tapered in patients who had achieved a 40% reduction in tender and swollen joint counts from baseline with combination IFX/MTX therapy. In total, 75% of patients were able to taper MTX to a minimum dose of 5 mg/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 metaanalysis to address tapering of MTX from a range of targeted therapies, including IL-6i and JAKi. Both of these targeted therapies have also been shown to be effective as monotherapies in RA.[4,8-10,41,42] Several of our reviewed studies showed numerically increased AEs in patients treated with

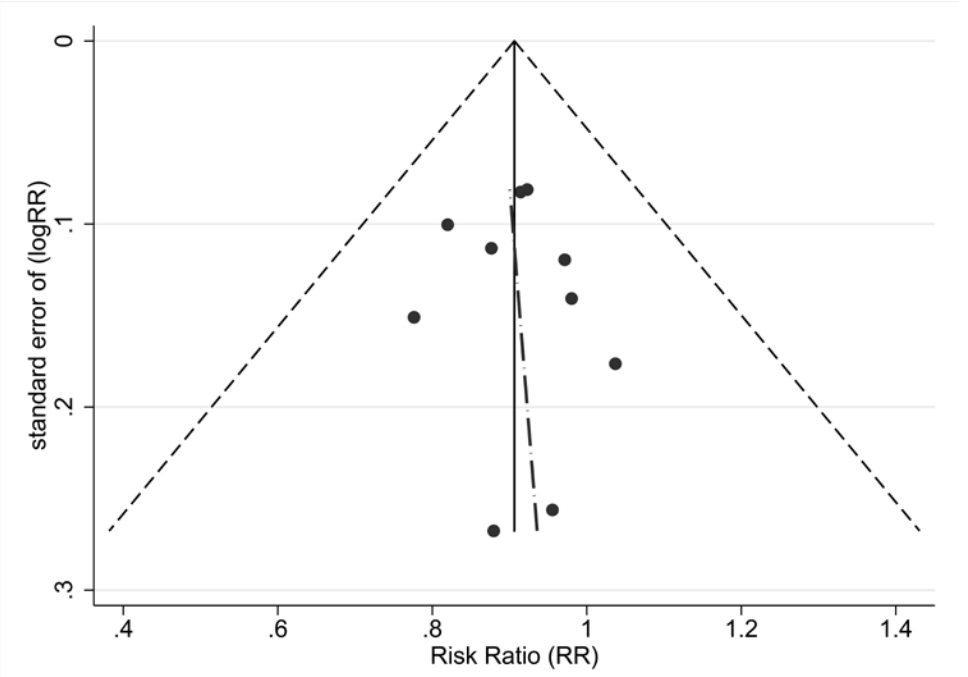

Figure 4. Funnel plot with pseudo 95% CIs for studies tapering methotrexate from targeted therapy. The fitted line represents the Egger test for asymmetry.

MTX compared to those on targeted therapies alone.[29,33,38] Our patients who may now be taking any of a wide range of targeted therapies often wish to taper their MTX because of 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.[43] Three[21,29,30] of the 5 TNFi studies examined ETN, which is not associated with antidrug antibodies and may not benefit as much from concomitant treatment with MTX. It is possible that if the other TNFi drugs were more broadly represented, the data may have been different. Although the development of antidrug antibodies could occur if patients remain on monotherapy with bDMARDs and specifically TNFi after MTX tapering, there is little evidence to support this. An observational study found that the long-term drug survival of TNFi was not significantly different between those who discontinued MTX and those who continued it (hazard ratio 1.046, 95% 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 with abrupt withdrawal. There was no clear association of tapering schemes with remission outcomes; however, only 2 studies[21,34] 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 tapering in the event of flare,[34] 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 the tapering group was not reported.

We analyzed both early and established RA and found that both groups had an 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 be more successful in tapering bDMARDs.[18,44,45] Only 3 studies on early RA[21,38,39] 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 periods. Only 3 studies reported on predictors of maintaining disease control after tapering MTX.[29,35,38] Higher baseline disease activity and RF seropositivity were associated with reduced likelihood of maintaining remission, similar to prior studies.[46] A higher physician global score was associated with restarting MTX in the LTE study. A systematic review of biomarkers for successful tapering of bDMARDs found that 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 retreatment.

Only 1 study looked at retreatment after tapering MTX and reported a 75% rate of recapture of remission,[29] similar to that reported by prior studies tapering bDMARDs.[47,48] However, these results should be interpreted with caution, as only 1 study

reported on retreatment outcomes. Only 1 trial, not eligible for the metaanalysis, evaluated outcomes of patients tapering both csDMARDs and bDMARDs and reported recapture of DAS28 remission by 65% of patients tapering csDMARDs.[49] More research on the recapture of remission after tapering MTX from targeted therapy is needed.

Several limitations of our review should be considered. Studies differed with respect to whether patients had early or established RA, whether patients were MTX-naïve or inadequate responders, the tapering strategy used, and the criteria used to taper (Table 1). Patients who were MTX-naïve were studied, not surprisingly, in the 3 early RA studies[20,38,39] that we analyzed separately as previously mentioned (Supplementary Figure S1, available with the online version of this article). 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 of MTX, as examined in some studies, 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^2 of 0% ($P = 0.94$). This could limit the external validity of this study, but it more likely reflects the similarity of the populations being studied.

We included pragmatic studies to increase generalizability to patients seen in routine practice; however, because of 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 1 observational LTE study was judged to have serious risk of bias.[38] We included it because it met our inclusion criteria; reported remission outcomes, including an adjusted analysis with propensity scoring; and evaluated MTX tapering in a real-world setting. Our sensitivity analysis excluding the LTE study 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 TNFi, IL-6i, or JAKi. Of note, we found no randomized MTX-tapering study for patients using it in combination with RTX that met our criteria.

We specifically evaluated remission outcomes rather than LDA after tapering. Only 2 studies[29,39] in our review used remission alone as their tapering criteria, with the other studies[21,30,32-35,37,38] using less stringent criteria to taper. It is possible that if we looked at LDA as our outcome after tapering, our results may have shown higher proportions of maintaining disease control. We further evaluated this by performing a metaanalysis of the RR of maintaining LDA after tapering MTX, and we found similar results (RR 0.92, 95% CI 0.86-0.98; Supplementary Figure S2, available with the online version of this article). 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 a 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 and who 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 in the discussion among female patients of childbearing age, who are concerned about the teratogenicity of MTX. The authors of this review advocate for the continuation 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 retreatment to recapture disease control is essential.

Further research is needed that includes studies with longer follow-up periods that also address predictors of successful tapering and long-term consequences of treatment withdrawal, including worsening of function, measures of joint damage, whether drug immunogenicity develops, and whether there is an advantage to gradual tapering regimens. Whether targeted therapy used as monotherapy in RA can also be 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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