Flare Rate in Patients with Rheumatoid Arthritis in Low Disease Activity or Remission When Tapering or Stopping Synthetic or Biologic DMARD: A Systematic Review

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ABSTRACT. ***Objective.*** To evaluate the risk of having a disease flare in patients with rheumatoid arthritis (RA) with low disease activity (LDA) or in remission when deescalating (tapering or stopping) disease-modifying antirheumatic drug (DMARD) therapy.

Methods. A search in medical databases including publications from January 1950 to February 2015 was performed. Included were trials and observational studies in adults with RA who were in LDA or remission, evaluating ≥ 20 patients tapering or stopping DMARD. Flare rates had to have been reported. A metaanalysis was performed on studies deescalating tumor necrosis factor (TNF) blockers.

Results. Four studies evaluated synthetic DMARD. Flare rates ranged from 8% at 24 weeks to 63% at 4 months after deescalation. Fifteen studies reported on TNF blockers. Estimated flare rates by metaanalysis on studies tapering or stopping TNF blockers were 0.26 (95% CI 0.17–0.39) and 0.49 (95% CI 0.27–0.73) for good-quality and moderate-quality studies, respectively. Flare rates in 3 studies stopping tocilizumab were 41% after 6 months, 55% at 1 year, and 87% at 1 year. Flare rates in 3 studies deescalating abatacept were 34% at 1 year, 41% at 1 year, and 72% at 6 months. Five studies evaluating radiographic progression in patients deescalating treatment all found limited to no progression.

Conclusion. Results suggest that more than one-third of patients with RA with LDA or in remission may taper or stop DMARD treatment without experiencing a disease flare within the first year. Dose reduction of TNF blockers results in lower flare rates than stopping and may be noninferior to continuing full dose. Radiological progression after treatment deescalation remains low, but may increase slightly. (First Release October 1 2015; J Rheumatol 2015;42:2012–22; doi:10.3899/jrheum.141520)

Key Indexing Terms:

RHEUMATOID ARTHRITIS | SYNTHETIC DMARD | BIOLOGIC DMARD
REMISSION | TREATMENT DEESCALATION | SYSTEMATIC REVIEW

The treatment of rheumatoid arthritis (RA) has advanced greatly. Combination therapy with disease-modifying antirheumatic drugs (DMARD), early tight-controlled treatment, and biologic agents improve outcomes in patients[1]. Increasing numbers of patients reach and maintain a state of low disease activity (LDA) or remission. The issue arises whether DMARD therapy should be continued unchanged (indefinitely) to keep the disease under control. Deescalation (tapering or stopping) of 1 or more antirheumatic agents could yield several benefits, such as less drug toxicity, fewer adverse reactions, and lower medical costs. However, it would then be important to know the risk of flare, radiographic progression, and whether disease control can be easily regained after flare.

The objective of our review was to assess the course of disease after tapering or stopping synthetic DMARD (sDMARD) or biologic DMARD (bDMARD) therapy in patients with RA in remission or LDA. To do this, we set out the following goals:

(1) To assess the risk of having a disease flare after tapering or stopping DMARD.

(2) To evaluate the mean or median time to flare (time to flare) after tapering or stopping DMARD.

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(3) To evaluate the rate of radiographic progression after tapering or stopping DMARD.

(4) To assess how much time is needed to regain a state of LDA or remission (time to remission) after a disease flare has occurred.

MATERIALS AND METHODS

Search strategy and selection criteria. This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines[2].

The search strategy was developed and performed in collaboration with 2 medical librarians, and was performed in the digital databases of Ovid-SP, Embase, PubMed, and the Cochrane library for articles published up to February 2015. Keywords included terms and synonyms for RA, specific types of DMARD [e.g., methotrexate (MTX), etanercept (ETN)], and stopping/tapering. One investigator (TMK) manually searched through cited references of published reviews of deescalation of DMARD in RA. The complete search strategy is available online (Supplementary Data 1, available online at jrheum.org).

We included both clinical trials and observational studies on adult patients with RA in LDA or in remission (as defined by any available criteria or on clinical grounds), tapering or stopping DMARD, and reporting a flare rate at ≤ 1 year of followup. A minimum sample size of 20 patients deescalating DMARD was required to be included. Patients needed to have equal duration of followup in studies that reported flare rates as percentages or alternatively reported flares per person-years in cases where patients had unequal followup duration. Studies were excluded if published only in the form of congress abstracts, and if they reported only combined flare rates for DMARD with different modes of action [e.g., tumor necrosis factor (TNF) inhibitors and tocilizumab (TCZ)]. Because most disease flares would be expected to occur within the first 3–6 months after treatment deescalation, we considered a followup time of up to 1 year to be adequate.

Data extraction. One investigator (TMK) reviewed titles and abstracts, and selected potential manuscripts for retrieval. After retrieval of potential manuscripts, the same investigator established study eligibility by applying the selection criteria specified above. In case of doubt, studies were discussed with the coinvestigators (FBGL, JWGJ, JMWH) until consensus was reached. We used a standardized data collection form to extract the following information: type of study, patient definition, number of patients tapering or stopping medication, the DMARD that was tapered or stopped, comedication, definition of LDA/remission used, manner in which medication was tapered or stopped, definition of flare, number of flares per followup time, mean/median time to flare, radiological progression, and time to regain disease control after a flare.

Risk of bias assessment. We used a modification of Downs and Black's list to perform a quality assessment on observational studies[3]. The original list contained 27 items distributed over 5 subscales: reporting, external validity, bias, confounding, and power. Some minor modifications were made to the original list to suit treatment deescalation studies: items 6, 10, 16, and 25 from the original list were omitted, while item 17 was extended with 2 subitems addressing the adequacy of followup for the outcomes flare rate and radiographic progression. Item 27 was modified to: "Was the sample size used to calculate the flare rate larger than n = 100?" This ensured an adequate precision (95% CI < 0.2). The modified list is available from the authors on request (Supplementary Data 2). Two investigators (FBGL and JJL) independently rated each study. Disagreements were resolved by consensus. A table with item scores for each study was generated (Supplementary Data 3, available online at jrheum.org), so that readers can easily identify design flaws introducing a potential for bias among studies.

Pooling of data. Because of the small numbers and differences in the study design, metaanalysis was deemed inappropriate for studies on abatacept (ABA), TCZ, and sDMARD. A metaanalysis was performed on studies deescalating TNF blockers, reporting a flare rate at 1 year of followup.

The software Comprehensive Meta-Analysis version 2.2 (Biostat Inc.) was used. A random effects model was chosen based on the assumption that there were 2 sources of variability in effects observed in the various studies, i.e., sampling error and variability introduced by doing studies in different populations. Subgroup analyses by study quality were performed using a moderator variable. First, a quality score was generated using the item scores from the quality assessment as follows:

$$\text{Quality score} = (\#\text{items "yes"} + 0.5 \times \#\text{items "partly"}) \div \text{total \#items}$$

Then, based on the median score of the studies selected for metaanalysis, a dichotomous moderator variable was created to compare the results of studies according to their quality.

RESULTS

The search in electronic databases yielded 8147 publications, of which 7909 articles were excluded based on titles and abstracts (Figure 1). After full text assessment of the remaining 238 publications, 25 studies remained that were eligible for inclusion (Figure 1).

Included studies showed a large heterogeneity in the specific DMARD, the concomitant treatment with other DMARD, the remission criteria used to initiate tapering, and followup time (Table 1)[4–14,15–25,26,27,28]. Sample sizes were relatively small (median 65, range 22–717).

Risk of disease flare with sDMARD. Four studies [2 randomized controlled trials (RCT), 2 single-arm trials] evaluated the deescalation of sDMARD (Table 1)[4,5,6,7]. Reported flare rates after tapering MTX ranged from 8% at 24 weeks (flare defined on clinical criteria)[6] to 42% at 32 weeks (loss of 40% reduction in swollen and tender joint counts compared with baseline)[4]. In patients receiving triple DMARD therapy with prednisone (PRED), tapering of subsequent DMARD (PRED, sulfasalazine, and hydroxychloroquine) to MTX monotherapy was evaluated[5]. Sixty-three percent of patients lost response to therapy [defined as 44-joint Disease Activity Score (DAS44) > 1.6] after 4 months[5]. The study by ten Wolde, *et al*[7] defined flare as having ≥ 3 swollen joints while fulfilling ≥ 2 additional criteria[7], and found an overall flare rate of 37% at Year 1 (Table 1).

None of the included studies evaluated radiographic progression for sDMARD, and none evaluated time to flare for sDMARD. No data on time to remission were available. The study by ten Wolde, *et al* found that 47% of patients retreated with the same sDMARD achieved the American College of Rheumatology 20 response within 3 months[7].

Risk of disease flare with TNF inhibitors. Fifteen studies (5 single-arm trials, 2 retrospective cohort studies, 4 prospective cohort studies, and 4 RCT) evaluated the tapering or stopping of TNF blockers (Table 1)[5,8-17,19-22], 4 of which involved early RA[5,9,16,20]. A metaanalysis was performed on the 10 studies (11 study arms) deescalating TNF blockers and reporting a flare rate at 1 year (Figure 2). Overall heterogeneity was high ($I^2 = 93.1$) with respect to patients (early vs established RA), deescalation strategy, type of TNF blocker,

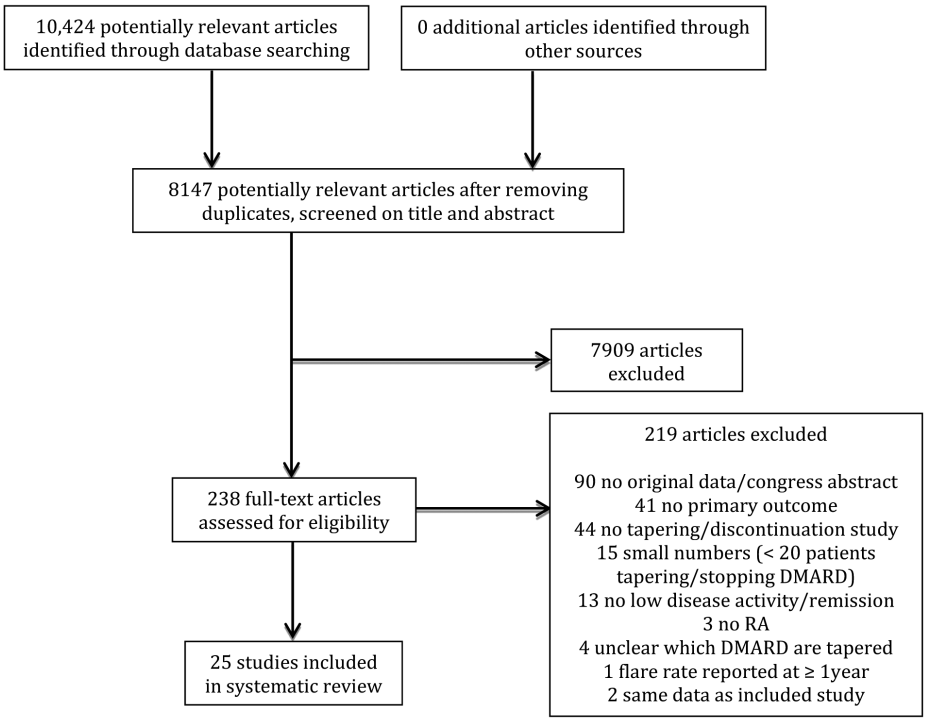

Figure 1. Flow diagram of study selection. DMARD: disease-modifying antirheumatic drug; RA: rheumatoid arthritis.

and comedication with sDMARD. Pooled flare rates for the studies with good[12,15,16,17,20,22] and moderate[8,10,13,21] quality scores were 0.26 (95% CI 0.17–0.39) and 0.49 (95% CI 0.27–0.73), respectively, and the overall flare rate was 0.33 (95% CI 0.23–0.45). Pooling studies on tapering versus stopping of TNF blockers did not lead to different flare rates (Supplementary Data 4, available online at jrheum.org).

Three studies evaluated radiological progression by directly comparing groups of patients continuing and stopping treatment[16,17] or deescalating treatment to various extents[9]. The PRESERVE study (a randomized, double-blind study comparing the safety and efficacy of once-weekly ETN 50 mg, ETN 25 mg, and placebo in combination with MTX in subjects with active RA) compared radiological progression between groups of patients continuing full-dose ETN with patients switching to half-dose or stopping of ETN[17]. Change in the modified total Sharp score (ΔmTSS) was significantly higher in the group stopping ETN (0.60 units/yr) compared with the group continuing ETN 50 mg/week (–0.06 units/yr, p = 0.026). However, no significant difference was found between the group receiving ETN 25 mg/week (0.05 units/yr) compared with the full-dose or placebo groups[17]. In the Optimal Protocol for Treatment Initiation with MTX and Adalimumab (ADA; OPTIMA) trial, patients with early RA were randomized to stop or continue ADA. After 1 year, there was no significant difference in the percentage of nonprogressors (ΔTSS ≤ 0.05) between groups (stop 81%, continue 89%, p = 0.06)[16]. Emery, *et al* compared 3 deescalation strategies in patients with early RA treated with MTX and ETN: reducing ETN to half-dose, stopping ETN, and stopping both ETN and MTX[9]. After 39 weeks, mean ΔmTSS (± SE) were similar for all groups: 0.1 (0.1), –0.0 (0.2), and 0.4 (0.2), respectively.

Three studies[19,20,22] evaluated radiographic progression by comparing patients experiencing a flare with those with sustained LDA/remission after stopping infliximab (IFX)[20,22] or ADA[19]. The Behandel Strategieën, i.e., Treatment Strategies (BeSt) study reported a median damage progression of 0 units/year at 1 year in both groups[20], while the Remission induction by Remicade in RA (RRR) study reported similar progression for the flare group (1.6 units/yr) and the nonflare group (0.3 units/yr, p = 0.11) at 28 weeks[22]. The Humira discontinuation without functional and radiographic damage progression following sustained remission (HONOR) study found that ΔmTSS increased from –0.74 to 0.85/year in patients with a flare. Those with sustained LDA had equal ΔmTSS regardless of whether ADA was continued[19].

Eight studies involving deescalation of TNF blockers[8,11,12,13,14,20,21,22] reported on the mean or median time to flare. Reported times to flare ranged from 14.7 weeks (mean)[8] to ≥ 20 months (median; gentle tapering scheme)[12].

Three studies that involved stopping TNF blockers evaluated time to remission[8,19,22]. In the RRR study, the restart of IFX was effective in 70% of patients, of whom the majority reached DAS28 < 3.2 within 24 weeks[22]. Brocq, *et al* found that all 15 patients regained remission after

Table 1. Overview of included studies.

Study	Study Design	Disease Duration	Patients	Criteria Used to Initiate Tapering/ discontinuation	Medication Tapered/ stopped	Comedication	No. Patients Tapered/ stopped	Flare Definition	Flare, % (n)/ followup	Median/mean Time to Flare	Time to Remission After Flare	Radiological Progression	Study Limitations, Items[#]
bDMARD: TNFi													
Smolen, *et al*[17] (PRESERVE)	RCT	Mean 6.9 yrs	RA, 18–70 yrs old; ETN + MTX 36 weeks	DAS28 ≤ 3.2 for 24 weeks	ETN 50 mg/week + MTX, randomized 1:1:1 to A) ETN 50 mg/week + MTX, B) ETN 25 mg/week +MTX, C) PBO + MTX	MTX ± GCS	202 full-dose ETN, 202 half-dose ETN, 200 PBO	DAS28 > 3.2 at 52 weeks	50 mg: 17.4 (35), 25 mg: 20.9 (42), PBO: 57.4 (113)/1 yr	—	—	Group A: –0.06 u/yr, B: 0.05 u/yr, C: 0.60 u/yr; A vs C was significant	9, 11, 12, 26; partly: 1
van der Maas, *et al*[21]	Single-arm trial	Median 12 yrs	RA, 1987 ACR	DAS28 < 3.2 for 6 mos	IFX, down titration 3 mg/kg every 8–12 weeks	± sDMARD	51	Reversed EULAR response criteria*	54 (28)/ 1 yr	Median 200 days	—	—	9, 12,15, 19, 26
Heimans, *et al*[5] (IMPROVED)	Single-arm trial	8 mos	Early RA, ACR 2010; or undifferentiated arthritis	DAS44 < 1.6 for 4 mos	ADA 40 mg/ 2 weeks, MTX 25 mg/week, tapered† to MTX monotherapy	MTX	26	DAS44 > 1.6 4 mos	35 (9)/	—	—	—	9, 12, 14, 19, 27
Maneiro, *et al*[13]	Retrospective observational study	Median 10.6 yrs	Early and established RA, ≤ and > 2 yrs of diagnosis, respectively	Early RA: sustained‡ DAS28 < 2.6, established RA: sustained‡ DAS28 < 3.2	IFX 5 to 3 mg/kg and/or 6 to 8 weeks, ETN 7 to 10 days, ADA 2 to 3 weeks, CTZ 2 to 3 weeks	± sDMARD ± GCS	54: ADA 9, CTZ 7, ETN 28, IFX 10	DAS28 increase > 20% or increase in dose or frequency of bDMARD, sDMARD, or GCS	All 19.1 (ADA 30.8, CTZ 50.0, ETN 11.1, IFX 25.0)/ 1 yr	ADA 19 mos, ETN 15.5 mos, IFX 16.5 mos, CTZ not reported	—	—	1, 5, 11–15, 19, 27
Tanaka, *et al*[22] (RRR)	Single-arm trial	Mean 5.9 yrs	RA, 1987 ACR	DAS28 < 3.2 for > 24 weeks, PRED < 5 mg/day	IFX, stop	MTX	114	IFX restarted within 1 yr, DAS28 ≥ 3.2 at Yr 1	40 (46)/1 yr	Mean 6.4 mos	Majority within 24 weeks	—	11, 12, 19, 26; partly: 3, 9, 15
van den Broek, *et al*[20] (BeSt)	Single-arm trial	Median 23 mos	RA, 1987 ACR	DAS44 < 2.4 for 6 mos	IFX, stop	MTX	104	DAS44 > 2.4	20 (21) /1 yr	Median 17 mos	—	—	9, 12,15,19, 26; partly: 1
Brocq, *et al*[8]	Single-arm trial	Mean 11.3 yrs	Inflammatory joint disease, 304/442 fulfilling 1987ACR criteria	DAS28 < 2.6 for 6 mos, DMARD stable for 6 mos, no NSAID, PRED < 5 mg	TNF blocker (IFX, ETN, ADA), stop	sDMARD	24	DAS28 > 3.2	63 (15)/1 yr	Mean 14.7 weeks	Mean 5.6 weeks	—	9, 12, 15, 19, 26, 27; partly: 11
Harigai, *et al*[10] (BRIGHT)	Retrospective cohort study	Mean 10.3 yrs	RA	DAS28-CRP ≤ 2.7	ADA, stop	MTX ± GCS	22	DAS28-CRP > 2.7 or restart of bDMARD	54 (12)/ 1 yr	—	—	—	8, 9, 12, 15, 19, 23, 26, 27; partly: 5
Tanaka, *et al*[19] (HONOR)	Observational cohort with control group	Mean 7.5 yrs, SD 10.2 yrs	RA, 1987 ACR; inadequate response to MTX; and/or sDMARD	DAS28 < 2.6 for 6 mos, stable MTX dose ≥ 12 weeks, no GCS, no NSAID	ADA 40 mg/ 2 weeks, stop	MTX	A) 52, B) 23 control	DAS28 ≥ 3.2	A) 40 (21), B) 9 (2)/1 yr	—	Restart ADA ± MTX: 90% LDA within 6 mos, 100% LDA within 9 mos	—	9,14, 15, 19, 23, 27
Smolen, *et al*[16] (OPTIMA)	RCT	< 1 yr	Early RA, 1987 ACR	DAS28-CRP < 3.2 at weeks 22 and 26	ADA 40 mg/ 2 weeks: A) stop, B) continue	MTX 20 mg/ week ± NSAID ± GCS	A) 102, B) 105	DAS28-CRP ≥ 3.2	A) 19 (19), B) 9 (9)/1 yr	—	—	Radiographic non-progression, ΔTSS ≤ 0.05, from baseline to Week 78: A) 81%, B) 89%, p = 0.06	9, 12, 19

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Table 1. Continued

Study	Study Design	Disease Duration	Patients	Criteria Used to Initiate Tapering/ discontinuation	Medication Tapered/ stopped	Comedication	No. Patients Tapered/ stopped	Flare Definition	Flare, % (n)/ followup	Median/mean Time to Flare	Time to Remission After Flare	Radiological Progression	Study Limitations, Items[#]
Iwamoto, *et al*[11]	Observational cohort	8.2 yrs	RA, 1987 ACR OR 2010 ACR/ EULAR	DAS28 < 2.6	TNFi (IFX, ETN, ADA, GOL, CTZ), stop	± MTX ± GCS	32	DAS28 > 3.2 and escalation of antirheumatic treatment	38 (12)/ 6 mos	Mean 14.8 weeks	—	—	9, 11, 12, 14, 19, 26, 27; partly: 5, 15
Emery, *et al*[9]	RCT	6.8 mos	Early active disease; RA, 1987 ACR; MTX + biological-naive; ETN + MTX for 52 weeks	DAS28 ≤ 3.2 at Week 39 and DAS28 < 2.6 at Week 52	ETN 50 mg/week + MTX 10–25 mg/ week, randomized to: A) ETN 25 mg/week + MTX, B) MTX + PBO, C) PBO + PBO for 39 weeks. hereafter if DAS28 ≤ 3.2, all treatment was withdrawn	± GCS	A) 63, B) 65, C) 65	DAS28 ≥ 2.6	A) 21 (13), B) 46 (30), C) 62 (40)/ 39 weeks	—	—	ΔmTSS, mean ± SE: A) 0.1 ± 0.1, B) –0.0 ± 0.2, C) 0.4 ±0.2/39 weeks; p A vs B = 0.79, p A vs C = 0.48, p B vs C = 0.34	9, 17C, 19
Marks, *et al*[14]	Prospective cohort	129.5 mos	RA, 2010 ACR/ EULAR; TNFi >1 yr	DAS28 ≤ 2.6 + PDUS = 0 > 6 mos, no oral GCS	TNFi, tapered 1/3 (increased interval)	± sDMARD	69	DAS28 ≥ 2.6 or PDUS ≥ 1 or according to patient	63 (43) /9 mos	Median 6–9 mos	—	—	9, 12, 14, 15, 17A, 18, 19, 26, 27; partly: 3
Raffeiner, *et al*[15]	RCT	14.3 yrs	RA, 1987 ACR; failure traditional DMARD; ETN 25 mg 2 ×/week	DAS28 < 2.6 for ≥ 12 weeks	A) ETN 25 mg/week, B) ETN 25 mg 2×/ week	± sDMARD ± NSAID ± GCS	A) 159, B) 164	DAS28 > 2.6	A) 11 (18), B) not reported/1 yr	—	—	ΔTSS = 0, > 0, ≥ 5 at 1 yr: A) 82%, 18%, 1%; B) 82%, 18%, 1%. At 2 yrs: A) 85%, 16%, 1%; B) 80%, 20%, 1%	12, 15, 19, 9, 24, 26
Kavanaugh, *et al*[12]	Observational cohort	Median 8 yrs	RA, discontinued first TNFi, no other previous bDMARD	CDAI ≤ 10	TNFi, stop	± sDMARD ± GCS	717	CDAI > 10 or bDMARD initiation or sDMARD initiation/ dose escalation or GCS initiation/dose escalation	26.6 (191)/1 yr	Median ≥ 20 mos	—	—	8, 9, 15, 19, 26
bDMARD: TCZ													
Nishimoto, *et al*[24,26] (DREAM/ RESTORE)	Single-arm trial	Median 7.8 yrs	RA, 1987 ACR; ≥ 20 yrs old	DAS28 ≤ 3.2 at 2–3 consecutive timepoints	TCZ	± NSAIDs ± oral GCS	187	DAS28 > 3.2 at 2 consecutive observations	86.6 (162)/1 yr	—	139 of 157 (88.5%) retreated with TCZ achieved DAS28 < 2.6 within 12 weeks	—	12–15, 19
Aguilar, *et al*[23]	Prospective cohort	Mean 13.7 yrs	RA, MTX + TCZ for 5 yrs	DAS28 < 2.6 and SJC = 0	TCZ 8 mg/kg/ 4 weeks, stop	MTX	45	SJC ≥ 1	55 (25)/1 yr	Median 3 mos	—	—	9, 12–15, 26, 27; partly: 3, 5
van Herwaarden, *et al*[25]	Retrospective cohort	Median 10 yrs	RA, 1987 ACR or 2010 ACR/EULAR or clinical diagnosis	DAS28 < 3.2 or rheumatologist's judgement	TCZ 8 mg/kg/ 4 weeks to 4 mg/ kg/4 weeks	± MTX ± sDMARD ± GCS	22	DAS28 > 3.2 or rheumatologist's judgement	41 (9)/ 6 mos	7/9 (78%) within first 16 weeks	After dose-escalation, 8/9 achieved LDA (clinical judgement) within 6 mos; 1/9 LDA after 6 mos		9, 12, 15, 26, 27

Table 1. Continued

Study	Study Design	Disease Duration	Patients	Criteria Used to Initiate Tapering/ discontinuation	Medication Tapered/ stopped	Comedication	No. Patients Tapered/ stopped	Flare Definition	Flare, % (n)/ followup	Median/mean Time to Flare	Time to Remission After Flare	Radiological Progression	Study Limitations, Items[#]
bDMARD: ABA													
Emery, *et al*[27] (AVERT)	Single-arm trial	≤ 2 yrs, symptoms	Clinical synovitis ≥ 2 joints for ≥ 8 weeks; ACPA-positive; MTX-naive; ≥ 18 yrs	DAS28-CRP < 3.2 at Mo 12	A) ABA 125 mg/ week + MTX 15–20 mg/week, B) ABA 125 mg/week, C) MTX 15-20 mg/week, ABA stopped immediately, MTX + steroids tapered over 1 mo	± GCS	A) 84, B) 66, C) 73	DAS28-CRP ≥ 3.2	A) 75 (55), B) 72 (36), C) 83 (44)/ 6 mos	—	—	—	9, 12, 14, 15, 17C, 19, 23, 26, 27; partly: 5, 8
Westhovens, *et al*[28] (AGREE)	RCT	≤ 2 yrs	Early RA, seropositive, erosive	DAS28-ESR < 2.6 at 1 yr	ABA 10 mg/kg IV: A) 5 mg/kg IV, B) 10 mg/kg IV	± sDMARD ± GCS	A) 50, B) 58	DAS28-CRP ≥ 3.2 at 2 visits or additional DMARD required or ABA 10 mg required or ≥ 2 courses of GCS	A) 34 (17), B) 31 (18) /1 yr	—	Restart ABA 10 mg/kg: 3/4 remission within 1 yr	—	9, 27
Takeuchi, *et al*[18]	Prospective cohort with control	A) 9.6 yrs, B) 15.3 yrs	RA, 1987 ACR; age ≥ 20 yrs; ABA > 2 yrs	DAS28-CRP < 2.3	ABA 10 mg/kg/ 4 weeks: A) stop, B) continue	± sDMARD ± NSAID ± GCS	A) 34, B) 17	DAS28-CRP > 2.7	A) 41 (14), B) 6 (1)/ 1 yr	—	—	ΔmTSS: A) 0.80/yr, B) 0.32/yr, p = 0.37	9, 12, 14, 15, 23, 27
sDMARD													
Fleischmann, *et al*[4] (iRAMT)	Single-arm trial	Mean 10.4 yrs	RA, 1987 ACR	40% reduction in TJC + SJC	MTX, tapering 5 mg/ 8 weeks to minimum of 5 mg/week	IFX ± GCS	159	Loss of response; response defined as 40% reduction in TJC + SJC compared with baseline	42 (67)/ 32 weeks	—	—	—	9, 12, 15, 19; partly: 1, 5
Heimans, *et al*[5] (IMPROVED)	Single-arm trial	8 mos	Early RA, ACR 2010; or undifferentiated arthritis	DAS44 < 1.6 for 4 mos	PRED 7.5 mg/day, SSZ 2000 mg/day, HCQ 400 mg/day, MTX 25 mg/week; tapered in above order to MTX monotherapy	MTX	30	DAS44 > 1.6	63 (19)/ 4 mos	—	—	—	9, 12, 14, 19, 27
Luis, *et al*[6]	RCT	Mean 2.8 yrs	RA, 1987 ACR; functional class I or II; disease duration < 15 yrs	Clinical remission ACR criteria ≥ 6 mos, stable dose weekly MTX ≥ 9 mos	MTX, weekly to 2-weekly	± HCQ ± GCS	25	Loss of remission; clinical criteria	8 (2)/ 24 weeks	—	—	—	2, 12, 14, 19, 27; partly: 3, 5, 24

Table 1. Continued

Study	Study Design	Disease Duration	Patients	Criteria Used to Initiate Tapering/ discontinuation	Medication Tapered/ stopped	Comedication	No. Patients Tapered/ stopped	Flare Definition	Flare, % (n)/ followup	Median/mean Time to Flare	Time to Remission After Flare	Radiological Progression	Study Limitations, Items[#]
ten Wolde, *et al*[7]	RCT	Median 9 yrs	RA, 1987 ACR; age 18–85 yrs	Good therapeutic response ARA criteria (5/6), stable disease for 1 yr, RX second-line drugs for 2 yrs, no previous unsuccessful attempt to discontinue second line drugs	sDMARD (CHL, HCQ, PG, DPEN, SSZ, AZA, MTX), stop	± NSAID	143	SJC ≥ 3 and ≥ 2 additional criteria; clear clinical recurrence of synovitis	Overall: 37 (53), HCQ/CHL: 33 (26), PG: 33 (11), SSZ: 47 (8), PEN: 40 (4), AZA: 67 (2), MTX 100 (2)/1 yr	—	24/51 (47%) patients retreated with same cDMARD achieved ACR20 response within 3 mos	—	12, 19; partly: 3

*DAS28 increase ≥ 1.2 compared with baseline at 2 consecutive visits with at least 2 weeks in between or DAS28 increase ≥ 0.6 if DAS28 > 3.2. [†]Mode of tapering was not described. [‡]Remission duration was not further specified. [#]Study limitations (Supplementary Data 3, available online at jrheum.org): reporting items 1–9, external validity items 11–13, internal validity/bias items 14–20, internal validity/confounding items 21–26, and power item 27. DMARD: disease-modifying antirheumatic drugs; bDMARD: biologic DMARD; sDMARD: synthetic DMARD; TNFi: tumor necrosis factor inhibitor; TCZ: tocilizumab; ABA: abatacept; RCT: randomized controlled trial; RA: rheumatoid arthritis; ETN: etanercept; MTX: methotrexate; ACR: American College of Rheumatology; EULAR: European League Against Rheumatism; ACPA: anticitrullinated protein antibodies; DAS28: Disease Activity Score at 28 joints; DAS44: DAS at 44 joints; PRED: prednisone; NSAID: nonsteroidal antiinflammatory drug; CRP: C-reactive protein; GCS: glucocorticoids; PDUS: power Doppler ultrasound; SJC: swollen joint count; TJC: tender joint count; ESR: erythrocyte sedimentation rate; ARA: American Rheumatism Association; RX: treatment; PBO: placebo; IFX: infliximab; ADA: adalimumab; CTZ: certolizumab pegol; GOL: golimumab; IV: intravenous; SSZ: sulfasalazine; HCQ: hydroxychloroquine; CHL: chloroquine; PG: parenteral gold; DPEN: d-penicillamine; AZA: azathioprine; CDAI: Clinical Disease Activity Index; PEN: penicillamine; LDA: low disease activity; cDMARD: conventional DMARD; TSS: Total Sharp score; mTSS: modified TSS; PRESERVE: a randomized, double-blind study comparing the safety and efficacy of once-weekly ETN 50 mg, ETN 25 mg, and placebo in combination with MTX in subjects with active RA; IMPROVED: remission induction therapy with methotrexate and prednisone in patients with early rheumatoid and undifferentiated arthritis; RRR: Remission induction by Remicade in RA; BeSt: Behandel Strategieën, i.e., Treatment Strategies Study; BRIGHT: Biologics-free remission and low disease activity after stopping adalimumab in Japanese patients with rheumatoid arthritis; HONOR: Humira discontinuation without functional and radiographic damage progression following sustained remission; OPTIMA: Optimal Protocol for Treatment Initiation with MTX and ADA; DREAM: Drug-free REmission/low disease activity after cessation of TCZ (Actemra) Monotherapy; RESTORE: Retreatment Efficacy and Safety of TOcilizumab in patients with RA in Recurrence; AVERT: Assessing Very Early Rheumatoid arthritis Treatment; AGREE: ABA trial to Gauge Remission and joint damage progression in MTX-naive patients with Early Erosive RA; iRAMT: IFX RA MTX Tapering.

Study Arms	Medication	Characteristics	Followup	n	Flare Rate (95% CI)
Good quality					
Smolen, *et al*[17], half dose	ETN	r[1], p	1 yr	202	0.19 (0.14–0.25)
Smolen, *et al*[17], stop	ETN	s, p	1 yr	200	0.57 (0.51–0.64)
Tanaka, *et al*[22]	IFX	s, a	1 yr	114	0.45 (0.36–0.54)
van den Broek, *et al*[20]	IFX	s, a, e	1 yr	104	0.20 (0.13–0.29)
Smolen, *et al*[16], stop	ADA	s, a, e	1 yr	102	0.19 (0.12–0.27)
Raffeiner, *et al*[15]	ETN	r[2], p	1 yr	159	0.11 (0.07–0.17)
Kavanaugh, *et al*[12]	TNFi	s, p	1 yr	717	0.27 (0.24–0.30)
Pooled estimate				**1598**	**0.26 (0.17–0.39)[h1]**
Moderate quality					
van der Maas, *et al*[21]	IFX	r[3], p	1 yr	51	0.55 (0.41–0.68)
Maneiro, *et al*[13]	ADA, CTZ, ETN, IFX	s, p	1 yr	52	0.19 (0.11–0.32)
Brocq, *et al*[8]	IFX, ETN, ADA	s, a	1 yr	21	0.75 (0.53–0.89)
Harigai, *et al*[10]	ADA	s, a	1 yr	22	0.55 (0.34–0.74)
Pooled estimate				**146**	**0.49 (0.27–0.73)[h2]**
Overall				**1744**	**0.33 (0.23–0.45)[h3]**
Not included in pooled analysis					
Smolen, *et al*[17], full dose	ETN	c, p	1 yr	202	0.17 (0.12–0.23)
Harigai, *et al*[10], full dose	ADA	c, a	1 yr	24	0.08 (0.01–0.27)
Heimans, *et al*[5]*	ADA	r[4], e	4 mos	26	0.35 (0.17–0.56)
Smolen, *et al*[16], full dose	ADA	c, a, e	1 yr	105	0.09 (0.03–0.16)
Tanaka, *et al*[19]*	ADA	s, a	24 weeks	52	0.40 (0.27–0.55)
Tanaka, *et al*[19], full dose	ADA	c, a	24 weeks	23	0.09 (0.01–0.28)
Iwamoto, *et al*[11]*	TNFi	s, p	6 mos	32	0.38 (0.21–0.56)
Emery, *et al*[9], ETN half dose*	ETN	r[1], a, e	39 weeks	63	0.21 (0.12–0.33)
Emery, *et al*[9], ETN stop*	ETN	s, a, e	39 weeks	65	0.46 (0.34–0.59)
Emery, *et al*[9], stop + MTX	ETN	s, a, e	39 weeks	65	0.62 (0.49–0.73)
Marks, *et al*[14]*	TNFi	r[5], p	9 mos	69	0.62 (0.50–0.74)

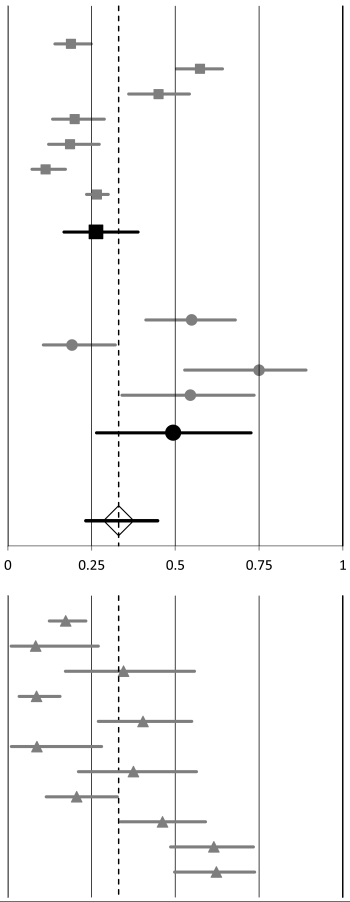

Figure 2. Reported flare rates among studies deescalating TNF blockers. Pooled estimates were calculated for studies categorized as having good- and moderate-quality separately and overall. Flare rates for study arms that were not included in the pooled analysis are shown as well. *Not pooled because flare rate was not estimated at 1 year. h: heterogeneity ($^{h1} = I^2$: 94.4, $^{h2} = I^2$: 86.1, $^{h3} = I^2$: 93.1). a: comedication with sDMARD in all patients; c: continued treatment (control arm); e: early RA; n: no comedication with sDMARD; p: comedication with sDMARD in selected patients; s: stop; r^1: dose reduction: ETN 50 mg/week, dose reduced to ETN 25 mg/week; r^2: dose reduction: ETN 2× 25 mg/week, dose reduced to ETN 25 mg/week; r^3: dose reduction: IFX 3 mg/kg, tapered down 0.75 mg/kg every 8–12 weeks; r^4: dose reduction: ADA 40 mg/2 weeks, tapered down to MTX monotherapy; r^5: dose reduction with 1/3 (by increasing interval *1.5); TNF: tumor necrosis factor; TNFi: TNF inhibitors; DMARD: disease-modifying antirheumatic drugs; bDMARD: biological DMARD; sDMARD: synthetic DMARD; RA: rheumatoid arthritis; ETN: etanercept; IFX: infliximab; ADA: adalimumab; MTX: methotrexate; CTZ: certolizumab.

restarting the same TNF blocker, 87% within 2 months[8]. In the HONOR study, MTX dose escalation was not effective in 75% of patients experiencing a flare, but after readministration of ADA, those patients regained LDA with 90% within 6 months[19].

Risk of disease flare with TCZ. Three studies reported on the deescalation of TCZ[23,24,25]. The Drug-free REmission/low disease activity after cessation of TCZ (Actemra) Monotherapy (DREAM) study reported a flare rate of 87% at 1 year for patients with LDA stopping TCZ and not receiving any concurrent DMARD[24]. Aguilar, *et al* found a flare rate of 55% one year after stopping TCZ in patients in remission with a combination therapy of TCZ and MTX[23]. van Herwaarden, *et al* reported that after 6 months, 41% of patients lost LDA status after a dose reduction of TCZ from 8 mg/kg to 4 mg/kg every 4 weeks[25].

None of the included studies evaluated radiographic progression for TCZ. Two studies that focused on deescalating TCZ[23,25] reported on time to flare. After stopping TCZ, 50% of flares occurred within 3 months[23], while in another study 78% of flares occurred within the first 4 months after dose reduction of TCZ[25]. As far as time to remission, in the DREAM/Retreatment Efficacy and Safety of TOcilizumab in patients with rheumatoid arthritis in Recurrence (RESTORE) study, 88% of patients achieved DAS28 remission within 12 weeks after restarting TCZ[24,26]. In the

dose reduction study by van Herwaarden, *et al*, all patients who experienced a flare achieved LDA after dose escalation, with 89% within 6 months[25].

Risk of disease flare with ABA. The deescalation of ABA was evaluated in 3 studies[18,27,28]. In the Assessing Very Early Rheumatoid arthritis Treatment (AVERT) study, patients with early initially active RA with LDA at 1 year entered the treatment withdrawal period in which all treatment was stopped. After 6 months, flare rates were 75% and 72% in the ABA + MTX and the ABA monotherapy arms, respectively[27]. Dose reduction of ABA to half-dose in patients with early RA was evaluated in the ABA trial to Gauge Remission and joint damage progression in methotrexate-naive patients with Early Erosive RA (AGREE) study[28]. At 1 year, 34% (half-dose) and 31% (full-dose) of patients experienced a flare[28]. In a cohort of patients with established RA, Takeuchi, *et al* compared stopping with continuing ABA[18]. Flare rates at 1 year were 41% (stop) versus 6% (continuation)[18].

Only 1 study of ABA presented radiological data. Takeuchi, *et al* found no difference in radiographic progression after 1 year between the groups stopping (ΔmTSS = 0.80) and continuing ABA (ΔmTSS = 0.32, p = 0.37)[18].

None of the included studies evaluated time to flare for ABA. As far as time to remission, increasing ABA from half-dose to full-dose after flare resulted in 75% of patients regaining remission within 1 year[28].

DISCUSSION

Despite a large heterogeneity in primary studies, tapering down or stopping sDMARD or bDMARD therapy without experiencing an immediate flare of disease is possible in more than one-third of patients with LDA or in remission. Deescalation of TNF blockers suggest even better results with flare rates at 1 year of 0.26 (95% CI 0.17–0.39) for good-quality studies and 0.49 (95% CI 0.27–0.73) for moderate-quality studies in the pooled analysis. Further, evidence from 2 well-executed RCT suggests that reducing TNFi to half-dose results in a lower risk of flare (≈ 20%) compared with stopping (≈ 50%)[9,17], and is possibly noninferior to full-dose continuation[17]. Precaution should be taken in the decision to taper medication because evidence on radiographic progression is limited. Only 5 studies presented radiographic data comparing patients continuing and stopping bDMARD, of which the PRESERVE study found a significantly higher rate of radiographic progression in the stop group versus the continuation group[17]. In 3 other studies[9,16,18], a trend for slightly more progression was found for the discontinuation versus the continuation arms, but differences were not significant. However, it should be emphasized that included studies were not powered to detect differences in radiographic progression.

Time needed to regain remission after the occurrence of a flare was evaluated in 6 studies stopping bDMARD[8,19,22,24,25,28]. The majority of patients regained a state of LDA within 2–6 months after reinitiating therapy with the same bDMARD. No data were available for sDMARD. Whether deescalation of TNF blockers leads to increased immunogenicity and the formation of antidrug antibodies remains unclear and should be the subject of further study because the formation of such antibodies could lead to treatment inefficacy on reintroducing the TNF blocker after a flare[29].

Two RCT found a lower risk of flare for dose reduction versus a complete stop of ETN[9,17]. This was less clear when we pooled the flare rates among study arms tapering versus immediately stopping TNF blockers. Pooling resulted in a small but insignificant difference (flare rate of 0.31 vs 0.38, respectively), but a difference may well have been missed because of heterogeneity among studies. Among included studies in patients with early RA, flare rates for bDMARD[9,16,20,27,28] are not consistently lower compared with those in studies in patients with established RA. A discussion on risk factors for flare that were addressed in the primary studies is provided in Supplementary Data 5 (available online at jrheum.org).

Time to flare was assessed in studies deescalating bDMARD only and ranged widely (mean 14.7 weeks, median ≥ 20 mos) across studies[8,11,12,13,14,20,22,23,25]. No relationship could be observed between the use of concomitant DMARD or the deescalation strategy and time to flare.

A risk of bias assessment was performed[3] (Supplementary Data available online at jrheum.org) to assess the internal validity of the primary studies and to see whether this would influence the observed flare rate. In the metaanalysis of TNF deescalation, good-quality studies showed lower flare rates compared with moderate-quality studies. No single quality assessment item discriminated well between good- and moderate-quality studies, except for sample size, which was consistently larger in good-quality studies. Higher study quality was observed in the more recent studies because they were more often RCT compared with earlier cohort studies that were using existing data not necessarily collected with the aim to evaluate deescalation strategies.

Three systematic[30,31,32] and 2 narrative[33,34] reviews have previously been published on the deescalation of both bDMARD[30,32,34] and sDMARD[31,33]. While overlap exists between our review and those previously published, to our knowledge, we are the first systematic review with quality assessment addressing both sDMARD and bDMARD performing a pooled analysis on TNFi. Regarding sDMARD, the authors were reluctant to state that some of the patients could deescalate treatment, given the higher flare rates compared with treatment continuation[31,33]. Considering bDMARD, in line with our findings, Yoshida, *et al*[32] reported that studies showed large heterogeneity, and Tanaka, *et al*[34] and Navarro-Millán, *et al*[30] concluded that discontinuation is possible in patients with RA.

Our review has several strengths and weaknesses. We

synthesized all available data to answer clinically relevant questions regarding the deescalation of DMARD, despite the underlying heterogeneity in the primary studies. For the deescalation of TNF blockers, data was metaanalyzed, resulting in a different flare rate between good- and moderate-quality studies. This should be interpreted with caution because of the underlying differences in the study designs. Relevant publications could have been missed, although we performed an extensive systematic search in various databases without the use of language restrictions. Regarding radiographic progression, a major limitation of the primary studies is that they were not powered to detect differences in progression rates among groups. To address this, data from adequately powered cohort studies and RCT, using uniform definitions for initiation of deescalation and flare, is needed.

Despite a large heterogeneity between studies, our overall results suggest that more than one-third of patients with LDA or in remission may taper or stop DMARD treatment without experiencing a flare within the first year. Limited radiological data suggest progression after treatment deescalation remains low, but data are needed from adequately powered cohorts or RCT.

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ONLINE SUPPLEMENT

Supplementary data for this article are available online at jrheum.org.

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