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. 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.
(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. 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. 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 JLL) 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:

Quality score = (#items “yes” + 0.5 × #items “partly”) ÷ 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). Reported flare rates after tapering MTX ranged from 8% at 24 weeks (flare defined on clinical criteria) to 42% at 32 weeks (loss of 40% reduction in swollen and tender joint counts compared with baseline). In patients receiving triple DMARD therapy with prednisone (PRED), tapering of subsequent DMARD (PRED, sulfasalazine, and hydroxychloroquine) to MTX monotherapy was evaluated. Sixty-three percent of patients lost response to therapy [defined as 44-joint Disease Activity Score (DAS44) > 1.6] after 4 months. The study by ten Wolde et al defined flare as having ≥ 3 swollen joints while fulfilling ≥ 2 additional criteria, 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.

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). Of which involved early RA, 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 (I² = 93.1%) with respect to patients (early vs established RA), deescalation strategy, type of TNF blocker,
and comedication with sDMARD. Pooled flare rates for the studies with good\textsuperscript{12,15,16,17,20,22} and moderate\textsuperscript{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\textsuperscript{16,17} or deescalating treatment to various extents\textsuperscript{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\textsuperscript{17}. Change in the modified total Sharp score ($\Delta$mTSS) 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\textsuperscript{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 ($\Delta$TSS $\leq$ 0.05) between groups (stop 81%, continue 89%, $p = 0.06$)\textsuperscript{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\textsuperscript{9}. After 39 weeks, mean $\Delta$mTSS (± SE) were similar for all groups: 0.1 (0.1), –0.0 (0.2), and 0.4 (0.2), respectively.

Three studies\textsuperscript{19,20,22} evaluated radiographic progression by comparing patients experiencing a flare with those with sustained LDA/remission after stopping infliximab (IFX)\textsuperscript{20,22} or ADA\textsuperscript{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\textsuperscript{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\textsuperscript{22}. The Humira discontinuation without functional and radiographic damage progression following sustained remission (HONOR) study found that $\Delta$mTSS increased from –0.74 to 0.85/year in patients with a flare. Those with sustained LDA had equal $\Delta$mTSS regardless of whether ADA was continued\textsuperscript{19}.

Eight studies involving deescalation of TNF blockers\textsuperscript{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)\textsuperscript{8} to $\geq$ 20 months (median; gentle tapering scheme)\textsuperscript{12}. Three studies that involved stopping TNF blockers evaluated time to remission\textsuperscript{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\textsuperscript{22}. Brocq, et al found that all 15 patients regained remission after
<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design</th>
<th>Disease Duration</th>
<th>Patients</th>
<th>Criteria Used to Initiate Tapering/Discontinuation</th>
<th>Medication Tapered/Stopped</th>
<th>Comorbidities</th>
<th>No. Patients Tapered/Stopped</th>
<th>Flare Definition</th>
<th>Flare, % (n)/Time to Flare</th>
<th>Median/mean Time to Remission</th>
<th>Time to Remission After Flare</th>
<th>Radiological Progression</th>
<th>Study Limitations, Items</th>
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<td><strong>bDMARD: TNFi</strong></td>
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<tr>
<td>Smolen, et al (PRESERVE)</td>
<td>RCT</td>
<td>Mean 6.9 yrs RA, 18–70 yrs old; ETN + MTX 36 weeks</td>
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<td>DAS28 ≤ 3.2 for 24 weeks</td>
<td>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</td>
<td>MTX ± GCS</td>
<td>202 full-dose ETN, 202 half-dose ETN, 200 PBO</td>
<td>DAS28 &gt; 3.2 at 52 weeks</td>
<td>17.4 (35.0), 25 mg, 20.9 (42), PBO: 57.4 (113/11 yr)</td>
<td>80 mg: Group A: -0.06 u/yr, B: 0.05 u/yr, C: 0.60 u/yr; A vs C was significant</td>
<td>9, 11, 12, 19, 26</td>
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<td>Smolen, et al (IMPROVED)</td>
<td>Single-arm trial</td>
<td>Median 12 yrs RA, 1987 ACR</td>
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<td>DAS28 &lt; 3.2 for 6 mos</td>
<td>IFX, down titration 3 mg/kg every 8–12 weeks</td>
<td>± sDMARD</td>
<td>51</td>
<td>Reversed EULAR response criteria*</td>
<td>54 (28)/1 yr</td>
<td>26</td>
<td>19, 26</td>
<td>9, 12, 14, 19, 27</td>
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<td>Heimans, et al (IMPROVED)</td>
<td>Single-arm trial</td>
<td>Median 8 mos Early RA, ACR 2010; or undifferentiated arthritis</td>
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<td>DAS44 &lt; 1.6 for 4 mos</td>
<td>ADA 40 mg/2 weeks, MTX 25 mg/week, tapered to MTX monotherapy</td>
<td>MTX</td>
<td>26</td>
<td>Majority</td>
<td>35 (9)/4 mos</td>
<td>19, 26</td>
<td>9, 12, 14, 19, 27</td>
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<td>Maneiro, et al (RRR)</td>
<td>Retrospective observational study</td>
<td>Median 10.0 yrs RA, ≤ and &gt; 2 yrs of diagnosis, respectively</td>
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<td>Early RA: sustained DAS28 &lt; 2.6, established RA: sustained DAS28 &lt; 3.2</td>
<td>IFX, stop</td>
<td>MTX</td>
<td>114</td>
<td>Mean 6.4 mos</td>
<td>Majority within 24 weeks</td>
<td>19, 26</td>
<td>11, 12, 19, 26; partly: 3, 9, 15</td>
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<td>Tanaka, et al (HONOR)</td>
<td>Observational cohort study</td>
<td>Median 10.3 yrs RA</td>
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<td>DAS28-CRP ≥ 2.7</td>
<td>ADA, stop</td>
<td>MTX ± GCS</td>
<td>22</td>
<td>DA28-CRP ≥ 2.7 or restart of bDMARD</td>
<td>54 (12)/1 yr</td>
<td>19 (19)/1 yr</td>
<td>9, 12, 15, 19, 26; partly: 5</td>
<td>9, 14, 15, 19, 23, 26; 27; partly: 5</td>
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<td>Harigai, et al (BRIGHT)</td>
<td>Retrospective cohort study</td>
<td>Median 7.5 yrs RA</td>
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<td>DAS28-CRP ≥ 2.6</td>
<td>ADA 40 mg/2 weeks, stop</td>
<td>MTX</td>
<td>A) 52, B) 23 control</td>
<td>DAS28 ≥ 3.2</td>
<td>19 (19)/1 yr</td>
<td>8, 9, 12, 15, 19, 23, 26, 27; partly: 5</td>
<td>9, 14, 15, 19, 23, 27</td>
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<td>Tanaka, et al (OPTIMA)</td>
<td>RCT</td>
<td>&lt;1 yr RA, 1987 ACR</td>
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<td>DAS28-CRP ≥ 3.2 at weeks 22 and 26</td>
<td>ADA 40 mg/2 weeks: A) stop, B) continue</td>
<td>MTX 20 mg/week ± NSAID ± GCS</td>
<td>A) 102, B) 105</td>
<td>9 (9)/1 yr</td>
<td>9, 12, 19</td>
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<td><strong>sDMARD</strong></td>
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<td>Brocq, et al (BeSt)</td>
<td>Single-arm trial</td>
<td>Median 22 mos RA, 1987 ACR</td>
<td></td>
<td>DAS44 &lt; 2.4 for 6 mos</td>
<td>IFX, stop</td>
<td>MTX</td>
<td>104</td>
<td>Median 17 mos</td>
<td>Majority</td>
<td>9, 12, 15, 19, 26; partly: 1</td>
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<td>Smolen, et al (OPTIMA)</td>
<td>Single-arm trial</td>
<td>Median 11.3 yrs Inflammatory joint disease, 304/142 fulfilling 1987 ACR criteria</td>
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<td>DAS28 &lt; 2.6 for 6 mos, DMDAR stable for 6 mos, PRED &lt; 5 mg</td>
<td>TNF blocker (IFX, ETN, ADA, sDMARD)</td>
<td>sDMARD</td>
<td>24</td>
<td>Mean 6 weeks</td>
<td>Mean 14.7 weeks</td>
<td>9, 12, 15, 19, 26, 27</td>
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<td><strong>sDMARD</strong></td>
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<td>DA28-CRP ≥ 2.7 or restart of bDMARD</td>
<td>54 (12)/1 yr</td>
<td>19 (19)/1 yr</td>
<td>9, 12, 15, 19, 26; partly: 5</td>
<td>9, 14, 15, 19, 23, 26; 27; partly: 5</td>
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<tr>
<td>Tanaka, et al (HONOR)</td>
<td>Observational cohort study</td>
<td>Median 7.5 yrs RA, ACR inadequately responsive to MTX; and/or sDMARD</td>
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<td>DAS28 &lt; 2.6 for 6 mos, stable MTX dose ≥ 12 weeks, no GCS, no NSAID</td>
<td>ADA 40 mg/2 weeks, stop</td>
<td>MTX</td>
<td>A) 52, B) 23 control</td>
<td>DAS28 ≥ 3.2</td>
<td>19 (19)/1 yr</td>
<td>8, 9, 12, 15, 19, 23, 26, 27; partly: 5</td>
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<td>A) 102, B) 105</td>
<td>9 (9)/1 yr</td>
<td>9, 12, 19</td>
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<td>Study</td>
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<td>No. Patients Tapered/Stopped</td>
<td>Flare Definition</td>
<td>Flare, % (n)/Followup</td>
<td>Median/mean Time to Remission After Flare</td>
<td>Time to Remission After Flare</td>
<td>Radiological Progression Limitations, Items</td>
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<td>Iwamoto, et al&lt;sup&gt;11&lt;/sup&gt;</td>
<td>Observational cohort</td>
<td>8.2 yrs RA, 1987 ACR OR 2010 ACR/ EULAR</td>
<td>DAS28 &lt; 2.6</td>
<td>TNFi (IFX, ETN, ADA, GOL, CTZ), stop</td>
<td>± MTX ± GCS</td>
<td>32</td>
<td>DAS28 &gt; 3.2 and escalation of antirheumatic treatment</td>
<td>38 (12)/6 mos</td>
<td>Mean</td>
<td>14.8 weeks</td>
<td>—</td>
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<td>9, 11, 12, 14, 19, 26, 27, partly: 5, 15</td>
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<tr>
<td>Emery, et al&lt;sup&gt;6&lt;/sup&gt;</td>
<td>RCT</td>
<td>6.8 mos Early active disease; RA, 1987 ACR; MTX + biological-naive; ETN + MTX for 52 weeks</td>
<td>DAS28 ≤ 3.2 at Week 39 and DAS28 &lt; 2.6 at Week 52</td>
<td>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</td>
<td>± GCS</td>
<td>A) 63, B) 65, C) 65</td>
<td>DAS28 ≥ 2.6</td>
<td>A) 21 (13), B) 46 (30), C) 62 (40)/39 weeks</td>
<td>—</td>
<td>—</td>
<td>ΔmTSS, mean SE: A) 0.1 ± 0.1, B) −0.0 ± 0.2, C) 0.4 ± 0.2/29 weeks; pA vs B = 0.79, pA vs C = 0.48, pB vs C = 0.34</td>
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<tr>
<td>Marks, et al&lt;sup&gt;14&lt;/sup&gt;</td>
<td>Prospective cohort</td>
<td>129.5 mos RA, 2010 ACR/ EULAR; TNFi, tapered 1/3 ± sDMARD ± A) 63, B) 65, DAS28 ≥ 2.6 or C) 62 (40)/9 mos</td>
<td>DAS28 ≤ 2.6 + PDUS = 0 or 6 mos, no oral GCS</td>
<td>TNFi, tapered 1/3 (increased interval)</td>
<td>± sDMARD</td>
<td>69</td>
<td>DAS28 ≥ 2.6 or PDUS ≥ 1 or according to patient</td>
<td>63 (43)/9 mos</td>
<td>Median</td>
<td>6–9 mos</td>
<td>—</td>
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<td>9, 12, 14, 15, 17, 18, 19, 26, 27, partly: 3</td>
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<tr>
<td>Raffeiner, et al&lt;sup&gt;15&lt;/sup&gt;</td>
<td>RCT</td>
<td>14.3 yrs RA, 1987 ACR; failure traditional DMARD; ETN 25 mg 2 ×/week</td>
<td>DAS28 ≤ 2.6 for ≥ 12 weeks</td>
<td>A) ETN 25 mg/week, B) ETN 25 mg 2 ×/week</td>
<td>± sDMARD ± NSAID ± GCS</td>
<td>A) 159, B) 164</td>
<td>DAS28 &gt; 2.6</td>
<td>A) 11 (18), B) not reported/1 yr</td>
<td>—</td>
<td>—</td>
<td>ΔTSS = 0, &gt; 0, ≥ 5 at 1 y, A) 82%, 18%, 1%, B) 82%, 18%, 1%, C) 85%, 16%, 1%; B) 80%, 20%, 1%</td>
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<tr>
<td>Kavanaugh, et al&lt;sup&gt;12&lt;/sup&gt;</td>
<td>Observational cohort</td>
<td>Median 8 yrs RA, discontinued first TNFi, no other previous bDMARD</td>
<td>CDAI ≤ 10</td>
<td>TNFi, stop</td>
<td>± sDMARD ± GCS</td>
<td>717</td>
<td>CDAI &gt; 10 or bDMARD initiation or sDMARD initiation/dose escalation or GCS initiation/dose escalation</td>
<td>26.6 (191)/1 yr</td>
<td>Median</td>
<td>≥ 20 mos</td>
<td>—</td>
<td>—</td>
<td>8, 9, 15, 19, 26</td>
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<td>Nishimoto, et al&lt;sup&gt;24–26&lt;/sup&gt;</td>
<td>Single-arm trial</td>
<td>Median 7.8 yrs RA, 1987 ACR; ≥ 20 yrs old</td>
<td>DAS28 ≤ 3.2 at 2–3 consecutive timepoints</td>
<td>TCZ</td>
<td>± NSAIDs ± oral GCS</td>
<td>187</td>
<td>DAS28 &gt; 3.2 at 2 consecutive observations</td>
<td>86.6 (162)/1 yr</td>
<td>—</td>
<td>—</td>
<td>139 of 157 (88.5%) retreated with TCZ achieved DAS28 ≤ 2.6 within 12 weeks</td>
<td>12–15, 19</td>
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<td>Aguilar, et al&lt;sup&gt;23&lt;/sup&gt;</td>
<td>Prospective cohort</td>
<td>Mean 13.7 yrs RA, MTX + TCZ for 5 yrs</td>
<td>DAS28 &lt; 2.6 and SJC = 0</td>
<td>TCZ 8 mg/kg/4 weeks, stop</td>
<td>MTX</td>
<td>45</td>
<td>SJC ≥ 1</td>
<td>55 (25)/1 yr</td>
<td>Median</td>
<td>3 mos</td>
<td>—</td>
<td>—</td>
<td>9, 12–15, 19, 26, 27, partly: 3, 5</td>
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<td>van Herven, Retrospective cohort</td>
<td>Median 10 yrs RA, 1987 ACR or 2010 ACR/EULAR or clinical diagnosis</td>
<td>DAS28 ≥ 3.2 or rheumatologist’s judgement</td>
<td>TCZ 8 mg/kg/4 weeks, stop</td>
<td>± MTX ± sDMARD ± GCS</td>
<td>22</td>
<td>DAS28 &gt; 3.2 or rheumatologist’s judgement</td>
<td>41 (9)/6 mos</td>
<td>7/9 (78%) within first 16 weeks</td>
<td>After dose-escalation, 8/9 achieved LDA (clinical judgement) within 6 mos; 1/9 LDA after 6 mos</td>
<td>9, 12, 15, 26, 27</td>
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<td>Study</td>
<td>Study Design</td>
<td>Disease Duration</td>
<td>Patients Criteria</td>
<td>Medication Comedication</td>
<td>Comedication</td>
<td>No. Patients Flare</td>
<td>Flare, Median/mean Time to Flare (n)/ Remission Progression Limitations, Items#</td>
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<td>bDMARD: ABA</td>
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<tr>
<td>Emery, et al&lt;sup&gt;27&lt;/sup&gt; (AVERT)</td>
<td>Single-arm trial</td>
<td>2 yrs, symptoms</td>
<td>Clinical synovitis ≥ 2 joints for ≥ 8 weeks; ACPA-positive; MTX-naive; ≥ 18 yrs</td>
<td>DAS28-CRP &lt; 3.2 at Mo 12</td>
<td>± GCS</td>
<td>A) 84, B) 66, C) 73</td>
<td>DAS28-CRP ≥ 3.2</td>
<td>A) 75 (55), B) 72 (36), C) 83 (44)/ 6 mos</td>
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<td>Westhovens, et al&lt;sup&gt;28&lt;/sup&gt; (AGREE)</td>
<td>RCT</td>
<td>≤ 2 yrs</td>
<td>Early RA, seropositive, erosive</td>
<td>DAS28-ESR &lt; 2.6 at 1 yr</td>
<td>± sDMARD ± GCS</td>
<td>A) 50, B) 58</td>
<td>DAS28-CRP ≥ 3.2 at 2 visits or additional DMARD required or ABA 10 mg required or ≥ 2 courses of GCS</td>
<td>A) 34 (17), B) 31 (18)/ 1 yr</td>
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<td>Takeuchi, et al&lt;sup&gt;18&lt;/sup&gt;</td>
<td>Prospective cohort with control</td>
<td>9.6 yrs, RA, ACR; DAS28-CRP ABA 10 mg/kg/ ± sDMARD</td>
<td>A) 9.6 yrs, B) 15.3 yrs</td>
<td>ABA 10 mg/kg/ 4 weeks: A) stop, B) continue</td>
<td>± sDMARD ± NSAID ± GCS</td>
<td>A) 34, B) 17</td>
<td>DAS28-CRP &gt; 2.7</td>
<td>A) 41 (14), B) 6 (1)/ 1 yr</td>
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<td>Fleischmann, et al&lt;sup&gt;4&lt;/sup&gt; (iRAMT)</td>
<td>Single-arm trial</td>
<td>Mean 10.4 yrs</td>
<td>RA, 1987 ACR; MTX, tapering 5 mg/8 weeks to minimum 5 mg/week</td>
<td>MTX, tapering 5 mg/8 weeks to minimum 5 mg/week</td>
<td>IFX ± GCS</td>
<td>159</td>
<td>Loss of response; response defined as 40% reduction in TJC + SJC compared with baseline</td>
<td>42 (67)/ 32 weeks</td>
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<td>Heimans, et al&lt;sup&gt;6&lt;/sup&gt; (IMPROVED)</td>
<td>Single-arm trial</td>
<td>8 mos</td>
<td>Early RA, ACR 2010; or undifferentiated arthritis</td>
<td>DAS44 &lt; 1.6 for 4 mos</td>
<td>MTX</td>
<td>30</td>
<td>DAS44 &gt; 1.6</td>
<td>63 (19)/ 4 mos</td>
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<td>Luis, et al&lt;sup&gt;6&lt;/sup&gt;</td>
<td>RCT</td>
<td>Mean 2.8 yrs</td>
<td>RA, 1987 ACR; functional class I or II; disease duration &lt; 15 yrs</td>
<td>Clinical remission ACR criteria ≥ 6 mos, stable dose weekly MTX ≥ 9 mos</td>
<td>MTX, weekly to 2-weekly</td>
<td>± HCQ ± GCS</td>
<td>25</td>
<td>Loss of remission; clinical criteria</td>
<td>8 (2)/ 24 weeks</td>
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<td>Study</td>
<td>Study Design</td>
<td>Disease Duration</td>
<td>Patients Criteria</td>
<td>Medication Used</td>
<td>Comedication No.</td>
<td>Flare Definition</td>
<td>Time to Flare Remission Progression Limitations Items</td>
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<td>ten Wolde, et al</td>
<td>RCT</td>
<td>Median 9 yrs</td>
<td>RA, 1987 ACR; age 18–85 yrs</td>
<td>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</td>
<td>± NSAID</td>
<td>SI ≥ 3 and ≥ 2 additional criteria; clear clinical recurrence of synovitis</td>
<td>Overall: 37 (55), HCQ/CHL: 33 (26), PG: 33 (11), SSZ: 47 (8), PEN: 40 (4), AZA: 67 (2), MTX: 100 (2)/1 yr</td>
<td>— 24/51 (47%) patients retreated with same cDMARD achieved ACR20 response within 3 mos — 12, 19; partly: 3</td>
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*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; PEN: 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.
restarting the same TNF blocker, 87% within 2 months. 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. Risk of disease flare with TCZ. Three studies reported on the deescalation of TCZ. 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. 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. 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.

None of the included studies evaluated radiographic progression for TCZ. Two studies that focused on deescalating TCZ reported on time to flare. After stopping TCZ, 50% of flares occurred within 3 months, while in another study 78% of flares occurred within the first 4 months after dose reduction of TCZ. 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. 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 months25.

**Risk of disease flare with ABA.** The deescalation of ABA was evaluated in 3 studies18,27,28. 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, respectively27. 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) study28. At 1 year, 34% (half-dose) and 31% (full-dose) of patients experienced a flare28. In a cohort of patients with established RA, Takeuchi, et al compared stopping with continuing ABA18. 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 (AmTSS = 0.80) and continuing ABA (AmTSS = 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 year28.

**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 TNF to half-dose results in a lower risk of flare (≈ 20%) compared with stopping (≈ 50%)9,17, and is possibly noninferior to full-dose continuation17. 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 group17. In 3 other studies9,16,18, 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 bDMARD8,19,22,24,25,28. 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 flare29.

Two RCT found a lower risk of flare for dose reduction versus a complete stop of ETN9,17. 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 bDMARD9,16,20,27,28 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 deesclalating bDMARD only and ranged widely (mean 14.7 weeks, median ≥ 20 mos) across studies8,11,12,13,14,20,22,23,25. 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 performed3 (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 systematic30,31,32 and 2 narrative33,34 reviews have previously been published on the deescalation of both bDMARD30,32,34 and sDMARD31,33. 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 continuation31,33. Considering bDMARD, in line with our findings, Yoshida, et al32 reported that studies showed large heterogeneity, and Tanaka, et al34 and Navarro-Millán, et al30 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 metanalyzed, 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.

ACKNOWLEDGMENT

We thank Gerdien de Jonge and Wichor Bramer, librarians at the Erasmus Medical Center, for their assistance in performing our search strategy.

ONLINE SUPPLEMENT

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

REFERENCES


