International Journal of
Rheumatic Diseases

*International Journal of Rheumatic Diseases* 2017

REVIEW ARTICLE

# Dosing down and then discontinuing biologic therapy in rheumatoid arthritis: a review of the literature

Der-Yuan CHEN,[1,2] Chak Sing LAU,[3] Bassel ELZORKANY,[4] Ping-Ning HSU,[5] Sonja PRAPROTNIK,[6] Radu VASILESCU,[7] Lisa MARSHALL[8] and Lyndon LLAMADO[9]

[1]*Division of Allergy, Immunology and Rheumatology, Department of Medical Education and Research, Taichung Veterans General Hospital, Taichung,* [2]*Institute of Biomedical Science and Rong Hsing Research Center for Translational Medicine, National Chung Hsing University, Taichung, Taiwan,* [3]*Division of Rheumatology and Clinical Immunology, The University of Hong Kong, Pokfulam, Hong Kong,* [4]*Department of Rheumatology, Cairo University, Cairo, Egypt,* [5]*National Taiwan University, Taipei, Taiwan,* [6]*University Medical Center, Ljubljana, Slovenia,* [7]*Regional Medical Affairs, Pfizer, Brussels, Belgium,* [8]*Global Medical Affairs, Pfizer, Collegeville, Pennsylvania, USA, and* [9]*Medical and Regulatory Affairs, Pfizer, Inc., Makati City, Philippines*

## Abstract

**Aim:**
To review the published studies that dose down and then discontinue biologic therapy in patients with rheumatoid arthritis (RA), particularly concerning the criteria for such dosing and the impact on clinical outcomes.

**Methods:**
Published studies conducted in patients with RA that sequentially decreased the dose and then discontinued therapy were included if one or more of the following biologic disease modifying antirheumatic drugs (bDMARDs) was evaluated: abatacept, adalimumab, certolizumab, etanercept, golimumab, infliximab, rituximab or tocilizumab.

**Results:**
Five studies qualified for inclusion. The populations of patients with RA were heterogeneous among the studies; patients were required to have low disease activity (LDA) or to be in remission prior to dose titration. Approximately 25–65% of patients successfully decreased and in some cases, discontinued the bDMARD. However, the flare rate was higher than for the patients who remained on a standard dose. The only variable that predicted relapse in more than one study was down-titration of the bDMARD dose.

**Conclusion:**
In patients who have achieved LDA or remission, down-titration and discontinuation of bDMARD therapy may be attempted, with careful monitoring. However, it is likely that some patients will flare, and it is not known how to predict these patients.

**Key words:** biologic, discontinuation, down-titration, rheumatoid arthritis.

## INTRODUCTION

Rheumatoid arthritis (RA) is a chronic disease with systemic inflammation that leads to progressive destruction of the synovial joints[1] and the accompanying symptoms of pain, stiffness and swelling, as well as systemic symptoms such as fatigue.[2] This may lead to disability and can impact quality of life (QoL).[3] To limit the potential for complications, current guidelines recommend early treatment with potent therapy, in a 'treat to target' strategy, in order to inhibit the systemic inflammation and suppress the joint destruction before permanent damage takes place.[4–7]

*Correspondence:* Professor Der-Yuan Chen, Division of Allergy, Immunology and Rheumatology, Department of Medical Education and Research, Taichung Veterans General Hospital, 1650 Taiwan Boulevard Sect. 4, Taichung, Taiwan 40705, ROC. Email: dychen@vghtc.gov.tw

As a result, biologic disease-modifying antirheumatic drugs (bDMARDs) have become more commonly used, either alone or in combination with traditional synthetic DMARDs (tsDMARDs).[8,9] Biologic therapies include the tumor necrosis factor (TNF) inhibitors, consisting of adalimumab, certolizumab, etanercept, golimumab and infliximab, as well as an interleukin (IL)-6 receptor antagonist (tocilizumab), a B-cell inhibitor (rituximab) and a T-cell activation inhibitor (abatacept). With the introduction and use of these therapies, the RA landscape has drastically changed; treatment expectations are the induction of low disease activity (LDA) or remission.[10] Physicians may consider biologic dose reduction or discontinuation for some patients once they have achieved LDA or remission.[11] This option may be considered as a result of concerns such as dose-dependent adverse events, risk of infection, including re-activation of latent tuberculosis,[5] and the economic burden of these agents.[10,11]

The number of published studies evaluating dosing down or discontinuing bDMARDs has steadily increased.[12] Many studies evaluate the tapering of the bDMARD dose, either by reducing the administered dose or lengthening the dosing interval of the original dose.[10–13] Other studies evaluate discontinuation of the bDMARD following full-dose therapy.[11,14] A related dosing strategy is to gradually dose down the bDMARD and then discontinue it. Fewer studies have evaluated this practice. The aim of this report is to analyze the published studies that dose down and then discontinue bDMARDs in RA, concerning: (i) the type of RA patient included in the studies and the criteria for dosing down and discontinuing bDMARD therapy; and (ii) the impact of this dosing strategy on clinical outcomes and cost.

**Table 1** Search strategy

| Topic | Terms for electronic search |
|---|---|
| Indication | • Rheumatoid Arthritis |
| Dosing | • Dose reduction, dosage reduction, dose reduc*, dosage reduc*<br>• Dose decreas*, dosage decreas*<br>• Dose adjust*, dosage adjust*<br>• Dose titration, dosage titration, dose titrat*, dosage titrat*<br>• Dose down, dosage down<br>• Dose withdrawal, dosage withdrawal<br>• Dose modification, dosage modification<br>• Dose decrement, dosage decrement<br>• Dose de-escalation, dosage de-escalation<br>• Step down<br>• Taper, tapering |
| Limits | • Humans<br>• English |
| | **Terms for manual search** |
| Biologic therapies | • Abatacept<br>• Adalimumab<br>• Certolizumab pegol<br>• Etanercept<br>• Golimumab<br>• Infliximab<br>• Rituximab<br>• Tocilizumab<br>• Biologic<br>• Tumor necrosis factor inhibitor, TNF inhibitor, anti-tumor necrosis factor, anti-TNF<br>• IL-1 receptor antagonist<br>• IL-6 receptor antagonist<br>• B-cell inhibitor<br>• T-cell activation inhibitor |

IL, interleukin; TNF, tumor necrosis factor.

## METHODS

An electronic search of PubMed, the biomedical library of the US National Library of Medicine within the National Institutes of Health, was conducted on March 4, 2015 to search for articles published any time up to that date. The search was repeated on September 9, 2016 to look for recently published articles. The PubMed database indexes published manuscripts; it does not include congress abstracts. The search strategy is provided in Table 1. The electronic search combined the term rheumatoid arthritis and a term for dosing down, i.e., rheumatoid arthritis and (dose decreas* or dosage decreas*). This was repeated for each dosing down term. The search was limited to articles written in English. The titles and abstracts were reviewed for bDMARDs approved for use in RA: abatacept, adalimumab, certolizumab, etanercept, golimumab, infliximab, rituximab and tocilizumab. Studies meeting these criteria underwent a full-text review to determine if the down-titration of the bDMARD was followed by discontinuation of the bDMARD. There was no limit to the publication timeframe. Only studies in humans were included. Case reports were excluded; review articles and meta-analyses were read to identify any references that were not located in the literature search.

# RESULTS

## Literature search

The electronic search identified 1284 articles, some of which were duplicates. Initial review of the titles and published abstracts, and removal of articles with duplicate PubMed identification numbers yielded 129 articles that qualified for further review. Examination of the full study publications and the review articles determined that most studies down-titrated the bDMARD but did not discontinue it. A few studies had parallel down-titration and discontinuation arms; they did not sequentially down-titrate and then discontinue the same patients. These studies were not included in the review. Evaluation of the publications determined that in five studies bDMARDs were sequentially down-titrated and then discontinued in the same patients, and provided details on these patients at study entry and in the results, thus qualifying for inclusion.[15–19] A comparison of the studies is provided in Table 2.

## Study summaries

*PRIZE*[15]

The PRIZE study was a randomized, controlled trial that took place in Europe and Asia. The study included patients with early active disease who had not previously received methotrexate (MTX) or a bDMARD. At study start, patients received etanercept (ETN) 50 mg plus MTX 10 mg weekly (QW) for 52 weeks as open-label therapy. During the first 8 weeks of the study, the MTX dose could be adjusted by the investigator; the maximum allowable dose was 25 mg QW. Patients were permitted to receive other DMARDs, and corticosteroids were allowed at a daily dose of ≤ 10 mg prednisone equivalent until week 26. Then, all corticosteroids were tapered and completely discontinued by week 39.

Patients with LDA at week 39 (disease activity score in 28 joints [DAS28] ≤ 3.2) and remission at week 52 (DAS28 < 2.6) were randomized to receive double-blind ETN 25 mg + MTX, or MTX only, or placebo (PBO) beginning at week 52. At weeks 4 and 12 of the double-blind phase, patients who did not have LDA received corticosteroids. After receiving double-blind treatment for 39 weeks, therapy was discontinued for patients with DAS28 ≤ 3.2. Patients were withdrawn from ETN and the PBO injection at week 39, and MTX and the PBO capsules were tapered over 2–4 weeks. The primary endpoint was maintenance of remission during the double-blind phase at weeks 24 and 39, without any corticosteroids from weeks 0 to 12.

More patients in the ETN+MTX group versus the MTX only or PBO group achieved the primary endpoint: 40/63 (63%) versus 26/65 (40%) and 15/65 (23%), respectively; $P = 0.009$ for ETN+MTX versus MTX only; $P < 0.001$ for ETN+MTX versus PBO. The mean DAS28 scores after all treatment was withdrawn were significantly lower in the ETN+MTX group than in the PBO group at week 52 ($P = 0.002$) and week 65 ($P = 0.003$). The percentage of patients achieving remission at the end of phase 3 was 28/63 (44%) for the patients who received ETN 25 mg + MTX QW in phase 2, 19/65 (29%) for the patients who received MTX QW in phase 2, and 15/65 (23%) for patients on PBO in phase 2. Adverse events (AEs) leading to discontinuation occurred in 4/63 (6%) patients in the ETN+MTX group, 1/65 (2%) in the MTX only group and 1/65 (2%) in the PBO group in the double-blind phase, and 4/53 (8%), 0/46 (0%) and 1/32 (3%), respectively, in the withdrawal phase.

According to the authors, patients who achieve remission or LDA after early, aggressive management of RA may be candidates for reducing the dose or withdrawing the bDMARD. Close monitoring of all patients is recommended. A predictor analysis was not provided, and it is not clear how to identify which patients are most appropriate for this treatment strategy. Additionally, no information was provided on how patients were managed if they were unable to maintain remission following dose reduction/withdrawal, and whether they were able to regain remission.

*STRASS*[16]

This randomized, controlled, open-label non-inferiority trial took place in France and Monaco. Patients included in the study had established RA, had received adalimumab (ADA) or ETN monotherapy at a stable dose for ≥ 1 year, or had received ADA or ETN combined with a stable dose of MTX or leflunomide for ≥ 6 months. Patients taking prednisone were allowed into the study if the dose was stable at ≤ 5 mg daily for ≥ 6 months. Patients were in DAS28 remission for ≥ 6 months, and had no structural progression on X-ray for the past year. In this 18-month study, patients were randomized to receive either standard dose ADA or ETN, or injections spaced by 50% every 3 months and then discontinued. Patients could continue tsDMARDs and/or prednisone ≤ 5 mg daily at a stable dose. The primary endpoint was the standardized difference of the DAS28 slopes. A secondary endpoint was the proportion of patients who relapsed over the 18 months; this was defined as having DAS28 > 2.6

**Table 2** Summary of published studies in RA that evaluated dosing down and then discontinuing biologic DMARD therapy

| Study citation (Study name) bDMARD | Type of RA patient | Study design | Criteria for dosing down and discontinuing bDMARD | Clinical result | Comments |
|---|---|---|---|---|---|
| Emery, *et al.* 2014[15] (PRIZE) ETN | Early active disease; MTX and bDMARD naïve | *Standard dose for 52 weeks (P1):*<br>ETN 50 mg + MTX QW, $N = 306$<br>*Taper for 39 weeks (P2):*<br>ETN 25 mg + MTX QW, $n = 63$<br>or<br>MTX QW, $n = 65$<br>or<br>PBO, $n = 65$<br>*Discontinue for 26 weeks (P3):*<br>No treatment. | *Criteria to taper:*<br>LDA (DAS28 ≤ 3.2) at week 39 and remission (DAS28 < 2.6) at week 52 of P1<br>*Criteria to discontinue:*<br>LDA at week 39 of P2. | *Sustained remission at end of P2:*<br>ETN 25 mg + MTX QW: 40/63 (63%), $P = 0.009$ *vs.* MTX; $P < 0.001$ *vs.* PBO<br>MTX QW: 26/65 (40%)<br>PBO: 15/65 (23%)<br>*Remission at end of P3:*<br>Previously ETN 25 mg + MTX QW: 28/63 (44%), $P$ = ns *vs.* MTX; $P = 0.02$ *vs.* PBO.<br>Previously MTX QW: 19/65 (29%)<br>Previously PBO: 15/65 (23%)<br>Radiographic progression did not differ significantly between the groups. | No information was provided on how patients were managed if unable to maintain remission, and whether they were able to regain remission.<br>According to the authors, in early RA, some patients in remission or LDA after full-dose therapy may be considered for reduction or withdrawal of the bDMARD. |
| Fautrel, *et al.* 2016[16] (STRASS) ADA, ETN | Established RA | Standard dose, $N = 73$<br>Dose spaced by 50% every 3 months until discontinued, $N = 64$. | Stable dose of ETN or ADA for ≥ 1 year as monotherapy or combined with a stable tsDMARD for ≥ 6 months.<br>DAS28 remission for ≥ 6 months.<br>No structural damage progression on hand and foot X-rays for 1 year before inclusion. | Spacing arm: ADA and ETN were successfully tapered 3 times for 10 (16%) patients, tapered 2 times for 7 (11%), tapered once for 6 (9%), discontinued for 25 (39%), and continued on full dose for 13 (20%).<br>Progression of structural damage did not differ significantly between the groups.<br>Relapse:<br>49 (77%) in the spacing arm *vs.* 34 (47%) in standard dose arm, $P = 0.0004$.<br>Median time to relapse:<br>Spacing arm: 9 months<br>Standard dose arm: 18 months.<br>Patients in spacing arm who relapsed received an increased dose of bDMARD: 20 of 49 | Non-inferiority could not be demonstrated. The authors stated that since nearly 25% of the patients in the spacing arm did not relapse, additional studies are needed to determine which patients can be down-titrated. |

**Table 2** (continued)

| Study citation (Study name) bDMARD | Type of RA patient | Study design | Criteria for dosing down and discontinuing bDMARD | Clinical result | Comments |
|---|---|---|---|---|---|
| | | | | (41%) achieved remission again; 19 (39%) achieved LDA; 4 (8%) experienced MDA and continued the bDMARD.<br>Factors significantly associated with relapse:<br>**1** spacing the dose rather than giving standard dose<br>**2** baseline HAQ score<br>**3** immunoglobulin M rheumatoid factor+ | |
| Hashka, *et al.* 2014[17] (RETRO) Anti-TNFs and TOC | Median (IQR) disease duration: 5.0 (7) years; duration of remission: 12.0 (12) months before study entry. | Patients are receiving tsDMARDs and/or bDMARDs.<br>Arm 1: Continue DMARDs, $n = 38$.<br>16 (42%) patients are on bDMARD.<br>Arm 2: Taper all DMARDs by 50%, $n = 36$.<br>18 (50%) patients are on bDMARD.<br>Arm 3: Taper all DMARDs for 6 months then discontinue, $n = 27$.<br>7 (26%) patients are on bDMARD. | DAS28 < 2.6 for ≥ 6 months.<br>77% were also in ACR/EULAR Boolean remission. | Incidence of relapse:<br>Arm 1:16%<br>Arm 2:39%, $P = 0.036$ *vs.* arm 1<br>Arm 3:52%, $P = 0.003$ *vs.* arm 1<br>Most relapses occurred within 6 months of taper start.<br>Predictors of relapse:<br>ACPA positivity ($P = 0.038$), reducing rather than continuing treatment (Arm 2: $P = 0.012$; Arm 3: $P = 0.003$). | No information was provided on how patients were managed following flare, and whether they were able to regain remission.<br>The authors noted that more than half of the patients maintained remission for 1 year after tapering or stopping tsDMARDs and/or bDMARDs. |
| Van der Maas, *et al.* 2012[18] INF | Disease duration: median (25th, 75th percentile): 12 (9, 18) years. | Standard dose of INF (3 mg/kg) decreased by 25% every 8–12 weeks until discontinuation or flare, $N = 51$. | LDA based on DAS28 and stable treatment ≥ 6 months. | Over 1 year, INF was discontinued in 16% of patients, decreased in 45%, and 39% of patients were put back on original dose.<br>No patient demographics or | No information was provided on how patients were managed following flare, and whether they were able to regain remission.<br>According to the authors, in |

**Table 2** (continued)

| Study citation (Study name) bDMARD | Type of RA patient | Study design | Criteria for dosing down and discontinuing bDMARD | Clinical result | Comments |
|---|---|---|---|---|---|
| | | | | clinical characteristics predicted successful down-titration. | most cases, patients with stable DAS28 LDA can successfully decrease the dose of INF or discontinue it. Research is needed to find predictors of successful dose-titration. |
| van Herwaarden, *et al.* 2015[19] (DRESS) ETN, ADA | RA of any duration. May have attempted dosing down > 6 months prior. Median disease duration was 10 years. | Injection interval increased every 3 months until discontinuation or flare, $n = 121$. Standard dose, $n = 59$. | LDA based on DAS28-CRP or rheumatologist judgment. Stable dose of ETN or ADA for ≥ 6 months. | Primary endpoint: cumulative proportion of patients with major flare over 18 months: 14/119 (12%) in the dose reduction group and 5/50 (10%) in usual care group. Dose reduction was determined to be non-inferior to the standard dose. Short-lived flares: dose reduction group: 88/121 (73%); usual care group: 16/59 (27%), $P < 0.001$. Low level radiographic progression was more common in dose reduction group than usual care group: 37/116 (32%) *vs.* 9/59 (15%). 24/121 (20%) successfully discontinued ETN or ADA, 52/121 (43%) successfully increased dosing interval, 45/121 (37%) could not increase dosing interval. | No information was provided on whether patients were able to regain remission following flare. The authors concluded that dose reduction of ADA or ETN guided by disease activity was non-inferior to usual care when measuring major flares. |

ACPA, anti-citrullinated protein antibodies; ACR/EULAR, American College of Rheumatology/European League Against Rheumatism; ADA, adalimumab; bDMARD, biologic disease modifying antirheumatic drug; CRP, C-reactive protein; DAS28, disease activity score in 28 joints; ETN, etanercept; HAQ, health assessment questionnaire; INF, infliximab; LDA, low disease activity; MDA, moderate disease activity; MTX, methotrexate; P1-3, periods 1, 2, and 3; PBO, placebo; QW, weekly; RA, rheumatoid arthritis; TNF, tumor necrosis factor; TOC, tocilizumab; tsDMARDs, traditional synthetic DMARDs.

and a DAS28 increase of > 0.6 since the prior measurement.

The spacing arm and the standard dose arm included 64 and 73 patients, respectively. Due to recruitment difficulties, the study was underpowered to demonstrate non-inferiority. In the spacing arm, TNF inhibitors were stopped for 39%, only tapered for 36% and kept at full dose for 20% of patients. More patients relapsed in the spacing arm than in the standard dose arm (77% *vs.* 47%, $P = 0.0004$). However, structural damage progression did not differ between the groups. The patients in the spacing arm who relapsed were given an increased dose of bDMARD, and of the 49 patients who relapsed, 20 (41%) were able to achieve remission again, 19 (39%) achieved LDA and 4 (8%) experienced moderate disease activity and continued the bDMARD. Sixteen serious AEs were reported by 6 (9%) patients in the spacing arm, and 14 serious AEs were reported by 10 (14%) in the standard dose arm.

The authors determined that factors significantly associated with relapse included the dose spacing strategy, the health assessment questionnaire (HAQ) score at baseline, and being positive for immunoglobulin M rheumatoid factor. The authors concluded that since approximately 25% of the patients on the decreased dose did not relapse, more studies are needed in order to determine in which patients tapered therapy may be appropriate.

*RETRO*[17]

This was a randomized, controlled, parallel-group study that enrolled patients with RA who were receiving a stable dose of tsDMARDs (MTX, leflunomide, sulfasalazine, hydroxychloroquine) and/or bDMARDs. Treatment with rituximab, abatacept or corticosteroids > 5 mg daily was not allowed. Patients with DAS28 < 2.6 (remission) for least 6 months were randomized to either arm 1: continue DMARDs at standard dose; arm 2: taper all DMARDs by 50%; or arm 3: taper all DMARDs for 6 months and then discontinue. Tocilizumab, tsDMARDs and corticosteroids were tapered by decreasing the dose by 50%; TNF inhibitors were tapered by doubling the time between dose administration. Throughout the study, nonsteroidal anti-inflammatory drugs (NSAIDs) were allowed as needed. The primary endpoint was sustained remission during 12 months; DAS28 > 2.6 was considered to be a relapse.

All patients were in DAS28 remission at baseline and 77% were in American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) remission. MTX was taken by 82% of patients; other tsDMARDs and bDMARDs were taken by 10% and 41% of patients, respectively. Of the patients taking bDMARDS, 76% were taking TNF inhibitors. A total of 101 patients reached the 12-month endpoint (38 in arm 1, 36 in arm 2 and 27 in arm 3) and 67 (66%) remained in remission. Relapses occurred as follows: arm 1, 16%; arm 2, 39%; arm 3, 52%; $P = 0.007$ across arms. AE details were not provided.

According to multivariate logistic regression, anti-citrullinated protein antibodies (ACPA) positivity ($P = 0.038$) predicted relapse, as did reducing rather than continuing treatment (arm 2: $P = 0.012$; arm 3: $P = 0.003$). A greater percentage of the patients who relapsed were women (74%); however, female sex was not a statistically significant predictor of relapse. Longer disease duration also did not predict relapse. Additionally, even though 77% of patients met the ACR/EULAR Boolean remission criteria at the study start, indicating they were in 'deep' remission, deep remission was not a predictor of maintaining remission following dose titration. Most relapses occurred within 6 months of the start of tapering. The authors concluded that tapering and/or stopping DMARD therapy is possible, since more than half of the patients in the combined group maintained remission for 1 year.

*van der Maas*, et al.[18]

Van der Maas, *et al.*[18] conducted an observational study of a cohort of clinic patients in the Netherlands. Out of 94 patients with RA, 51 met the criteria for dosing down: stable LDA (DAS28 < 3.2) and a stable treatment regimen for ≥ 6 months. The original dose of infliximab (INF, 3 mg/kg) was down-titrated by 25% every 8–12 weeks until patients flared or it was discontinued. Patients were considered to have a flare if two subsequent visits ≥ 2 weeks apart demonstrated an increase in DAS28 of ≥ 1.2 from baseline. Once patients reached DAS28 > 3.2, then an increase ≥ 0.6 was considered to be a flare. Patients were allowed to continue tsDMARDs, NSAIDs and corticosteroids, and investigators could adjust the doses throughout the study. The primary endpoint was the percentage of patients whose INF dose could be successfully down-titrated and the percentage that could be successfully discontinued after 1 year.

At baseline, 35 (68%) patients were receiving concomitant MTX; 12% were receiving concomitant leflunomide or azathioprine, and 20% were receiving INF monotherapy. Additionally, 4% and 53% of patients were receiving concomitant corticosteroids and

NSAIDs, respectively. Over a period of 1 year, INF could be discontinued in 16% of patients and down-titrated in 45% of patients. INF was returned to the original dose in 39% of patients. After 1 year, the mean dose of INF had decreased from 224 to 130 mg and the median DAS28 increased from 2.5 to 2.8, $P = 0.002$. Out of a total of 421 clinic visits, additional corticosteroids were administered during 8% of visits; DMARDs and NSAIDs were adjusted during 3.5% and 10% of visits, respectively.

No patient demographics or clinical characteristics were found to predict which patients could be successfully down-titrated. Following down-titration, there was no statistically significant change in QoL as measured by the EuroQoL 5-dimensions. No INF infusion reactions were reported; information about other AEs was not given. The mean decrease in cost per patient was €3474 over the 1-year period. The authors concluded that most patients with a stable treatment regimen and stable LDA can be successfully down-titrated or discontinued from INF for 1 year, resulting in considerable cost savings. Longer studies are needed in order to understand all of the consequences of this treatment practice. Predictors of successful down-titration should also be investigated.

*DRESS*[19]

Van Herwaarden *et al.*[19] conducted a randomized, controlled, open-label, non-inferiority dose-titration study in the Netherlands. The study included 180 patients with RA of any duration who had LDA (DAS28 < 3.2 or judgment of the rheumatologist at two subsequent visits), and who had also been receiving a stable dose of ADA or ETN for ≥ 6 months.[19,20] Patients were allowed to have down-titrated the TNF inhibitor previously, if it was > 6 months prior to study start. Patients could continue NSAIDs or stable DMARD or prednisone (≤ 5 mg) therapy throughout the study, and doses could be adjusted to treat flares. Flare was considered an increase in DAS28 > 1.2, or an increase > 0.6 and a current DAS28 score ≥ 3.2 at two timepoints.[20] If flare occurred, the TNF inhibitor was restarted or the dose was increased. The primary endpoint was the difference between treatment groups in the proportion of patients with major flare (DAS28-C-reactive protein [CRP] based flare > 3 months) at 18 months, and a comparison of this with the non-inferiority margin of 20%.

A total of 121 patients attempted dose reduction (increase in the dosing interval every 3 months until discontinuation or flare) and 59 patients received usual care.[19] At baseline, 60% and 80% of patients in the dose reduction and usual care groups, respectively, were taking a DMARD; 48% and 69% were taking MTX at a mean dose of 16 mg; 54% and 59% were taking NSAIDs, and 5% in each treatment group were taking corticosteroids. The bDMARD could be stopped in 24/121 (20%) patients, and the dosing interval was successfully increased in 52/121 (43%) patients; however, 45/121 (37%) patients could not decrease the dose.[19] Over 18 months, the cumulative proportion of patients with major flare was 14/119 (12%) in the dose reduction group and 5/50 (10%) in the group receiving usual care. The 95% confidence interval (CI) of the difference was within the non-inferiority margin, so dose reduction of ADA or ETN was determined to be non-inferior to usual care. Short-lived flares were significantly more frequent in the dose reduction group than the usual care group (88/121 [73%] *vs.* 16/59 [27%], respectively, $P < 0.001$). No patients in either group experienced a radiographic progression score (modified Sharp-van der Heijde [SvdH]) over the minimally clinically significant change of 8 units. However, more patients in the dose reduction group than the usual care group experienced a low degree of radiographic progression (> 0.5 units on SvdH score): 37/116 (32%) *vs.* 9/59 (15%), respectively; difference (95% CI): 17% (2–29%). There were no significant differences between the groups in QoL. Adverse events were reported by 79% of patients in the dose reduction group and 76% in the usual care group. The authors concluded that dose reduction of ADA or ETN guided by disease activity was non-inferior to usual care when measuring major flares.

*Cost-effectiveness of dose titration and discontinuation*

Only one study included in this report provided cost-effectiveness data for dosing down the bDMARD. In their observational cohort study, van der Maas, *et al.*[18] determined the mean decrease in direct costs per patient following INF dose reduction was €3474 (95% CI: €2457 to €4492) over a 1-year period. The authors found that costs decreased gradually every 4 months. If cost savings are calculated based on the last 4 months of the dose-titration period, then the savings are €5689 per patient per year in subsequent years. The authors concluded that substantial cost savings are possible by decreasing or discontinuing the dose of INF.

## DISCUSSION

This report summarizes the published studies that sequentially dosed down and then discontinued bDMARD therapy in patients with RA. Most of the

bDMARDs evaluated in the studies were TNF inhibitors; only one study included tocilizumab in addition to TNF inhibitors. In these publications, a proportion of patients ranging from approximately 25% to 65% was able to successfully decrease and, in some cases, discontinue the bDMARD dose. The authors of the studies concluded that in patients with LDA or in remission, it is acceptable to attempt to dose down and then possibly discontinue therapy, with careful monitoring. However, the authors also acknowledged that the percentage of patients with disease relapse/flare was higher in the groups that decreased or discontinued the bDMARD dose than in the groups that continued the standard dose.

Currently, there is no mechanism for determining in which patients dosing down and discontinuing bDMARD therapy are appropriate.[10] Several studies evaluated whether particular clinical characteristics will predict which patients are likely to flare with down-titration and discontinuation, and the results were varied. In the STRASS study, factors significantly associated with relapse included the HAQ score at baseline, immunoglobulin M rheumatoid factor positivity, and extending the time between doses rather than using standard dosing.[16] In the RETRO study, ACPA positivity predicted relapse, as did reducing rather than continuing treatment.[17] The DRESS study did not identify any clinical characteristics, laboratory values or concomitant treatment variables that were associated with successful dose reduction or discontinuation of the bDMARD.[19]

Van der Maas, *et al.*[18] stated that immunogenicity may have played a role in disease relapse during down-titration. Over 1 year, INF was successfully discontinued in 16% of patients and the dose was successfully decreased in 45% of patients; however, 39% of patients were returned to the original dose. Published studies with the monoclonal antibodies ADA and INF have demonstrated an association between anti-drug antibodies to the biologic and decreased serum levels, decreased treatment response and the occurrence of infusion reactions.[21,22] In addition, studies in the gastroenterology literature have shown an association between low dose/long dosing intervals of the biologic, and the presence of anti-drug antibodies.[23–25] Van der Maas, *et al.*[18] noted that although they did not see any infusion reactions, it was necessary to switch three patients to a different bDMARD due to treatment failure. Also, 20% of the patients in the study did not receive an immune modulator in addition to INF. This is also a risk for antibody formation.[22,23,26] In contrast, the PRIZE study evaluated tapering and discontinuing ETN, and found that 44% of patients who tapered therapy for 39 weeks and then discontinued for 39 weeks were able to maintain remission.[15] Anti-drug antibodies with ETN have not been linked to a decrease in clinical response;[27] however, this was not specifically evaluated in the PRIZE study.

It is important to note that the inclusion criteria for the studies in this report were heterogeneous. The PRIZE study included patients with early RA who were naïve to MTX and bDMARD therapy, the STRASS study included patients with established RA, and RETRO, DRESS and van der Maas did not limit inclusion to one or other.[15–19] Additionally, the requirement for DAS28 LDA or DAS28 remission varied; PRIZE required LDA at week 39 and remission at week 52, STRASS and RETRO required remission $\geq$ 6 months, van der Maas required LDA > 6 months and DRESS required LDA per DAS28 or rheumatologist judgment. This variability in patient status may have had an effect on the success rates of down-titration and discontinuation. In the PRIZE study (early RA), 63% were able to dose down for 39 weeks and 44% of patients were able to dose down and then discontinue for 26 weeks. This is compared to the STRASS study (established RA), in which 36% were able to dose down and 39% were able to dose down and then discontinue. In a published study that discontinued the biologic but did not taper, patients with early RA and DAS28 < 2.6 for $\geq$ 6 months after treatment with ETN 50 mg QW + MTX were discontinued from ETN and followed for 1 year.[28] Remission was maintained by 15/28 (54%) patients who discontinued ETN, a result similar to that in the PRIZE study.

Only the STRASS study provided details of whether patients with flare could regain remission by increasing the bDMARD dose. Of the 49 patients who relapsed, 20 (41%) patients were able to achieve remission again, 19 (39%) achieved LDA and 4 (8%) experienced acceptable moderate disease activity following a dose increase.[16] There is a need for additional studies that evaluate whether patients can return to remission following down-titration and discontinuation of a bDMARD.

Some published studies in the literature have evaluated dose titration and discontinuation of a bDMARD in parallel treatment groups, not sequentially in the same treatment group. Two examples include the PRESERVE study in patients with moderate RA[29] and the DOSERA[30] study in moderate to severe RA. In both studies, patients initially received ETN 50 mg + MTX QW; then in phase 2, patients with DAS28 LDA received ETN 25 mg + MTX QW or MTX QW only for

52 weeks (PRESERVE) or 48 weeks (DOSERA). The proportion of patients maintaining LDA ranged from 44% to 79% in the ETN 25 mg + MTX groups, and from 13% to 43% in the MTX only groups, similar to the values in this report. In the DOSERA study, patients who lost LDA during phase 2 were retreated with ETN 50 mg + MTX QW, and 91% of patients were able to regain remission or LDA.[30] This is similar to the 80% of patients who regained remission or LDA in the STRASS study. The median times to regain remission or LDA were 6.0, 5.9 and 3.9 weeks for the ETN 50 mg + MTX, ETN 25 mg + MTX, and MTX only groups, respectively.[30]

In summary, in RA studies that sequentially dosed down and then discontinued the bDMARD, approximately 25% to 65% of patients could successfully decrease, and in some cases, discontinue the bDMARD. The only variable that predicted relapse in more than one study was decreasing the bDMARD dose/increasing the dosing interval. It appears reasonable to attempt down-titration and discontinuation of the bDMARD. However, additional research is needed to determine predictors for success or failure and to establish the disease status (DAS28 LDA or remission or something else) that is necessary for successful down-titration. Future studies should include bDMARDs with varied mechanisms of action, not just TNF inhibitors.

## AUTHOR CONTRIBUTIONS

All authors made substantial contributions to the conception or design of the work; or the acquisition, analysis or interpretation of data. All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. All authors agree to be accountable for all aspects of the work.

## ACKNOWLEDGEMENTS

Medical writing support was provided by Jennica Lewis, PharmD, CMPP of Engage Scientific Solutions and was funded by Pfizer.

## CONFLICT OF INTEREST

Dr Chen, Dr Lau, Dr Elzorkany, Dr Hsu and Dr Praprotnik have no conflict of interest to declare. Dr Vasilescu, Dr Marshall and Dr Llamado are employees of and own stock in Pfizer.

## REFERENCES

1 Choy EHS, Panayi GS (2001) Cytokine pathways and joint inflammation in rheumatoid arthritis. *N Engl J Med* **344**, 907–16.
2 Nikolaus S, Bode C, Taal E, van de Laar MAFJ (2013) Fatigue and factors related to fatigue in rheumatoid arthritis: a systematic review. *Arthritis Care Res* **65**, 1128–46.
3 Chiu Y, Lai M, Lin H, Lang H, Lee L, Wang J (2014) Disease activity affects all domains of quality of life in patients with rheumatoid arthritis and is modified by disease duration. *Clin Exp Rheumatol* **32**, 898–903.
4 Singh JA, Saag KG, Bridges SL *et al.* (2016) 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. *Arthritis Rheumatol* **68**, 1–26.
5 Lau CS, Chia F, Harrison A *et al.* (2015) APLAR rheumatoid arthritis treatment recommendations. *Int J Rheum Dis* **18**, 685–713.
6 Smolen JS, Landewé R, Breedveld FC *et al.* (2014) EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. *Ann Rheum Dis* **73**, 492–509.
7 Smolen JS, Breedveld FC, Burmester GR *et al.* (2016) Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international task force. *Ann Rheum Dis* **75**, 3–15.
8 Furst DE, Emery P (2014) Rheumatoid arthritis pathophysiology: update on emerging cytokine and cytokine-associated cell targets. *Rheumatology (Oxford)* **53**, 1560–9.
9 Kievit W, Fransen J, Adang EMM *et al.* (2011) Long-term effectiveness and safety of TNF-blocking agents in daily clinical practice: results from the Dutch Rheumatoid Arthritis Monitoring register. *Rheumatology (Oxford)* **50**, 196–203.
10 Schett G, Emery P, Tanaka Y *et al.* (2016) Tapering biologic and conventional DMARD therapy in rheumatoid arthritis: current evidence and future directions. *Ann Rheum Dis* **75**, 1428–37.
11 Kuijper TM, Lamers-Karnebeek FBG, Jacobs JWG, Hazes JMW, Luime JJ (2015) Flare rate in patients with rheumatoid arthritis in low disease activity or remission when tapering or stopping synthetic or biologic DMARD: a systematic review. *J Rheumatol* **42**, 2012–22.
12 van Herwaarden N, den Broeder AA, Jacobs W *et al.* (2014) Down-titration and discontinuation strategies of tumor necrosis factor–blocking agents for rheumatoid arthritis in patients with low disease activity. *Cochrane Database of Syst Rev* **9**, CD010455.
13 Lau CS, Gibofsky A, Damjanov N *et al.* (2017) Down-titration of biologics for the treatment of rheumatoid arthritis: a systematic literature review. *Rheumatol Int* **37**, 1789–98.
14 Tanaka Y, Hirata S, Saleem B, Emery P (2013) Discontinuation of biologics in patients with rheumatoid arthritis. *Clin Exp Rheumatol* **31**, S22–7.

15 Emery P, Hammoudeh M, FitzGerald O *et al.* (2014) Sustained remission with etanercept tapering in early rheumatoid arthritis. *N Engl J Med* **371**, 1781–92.
16 Fautrel B, Pham T, Alfaiate T *et al.* (2016) Step-down strategy of spacing TNF-blocker injections for established rheumatoid arthritis in remission: results of the multicentre non-inferiority randomised open-label controlled trial (STRASS: Spacing of TNF-blocker injections in Rheumatoid ArthritiS Study). *Ann Rheum Dis* **75**, 59–67.
17 Haschka J, Englbrecht M, Hueber AJ *et al.* (2016) Relapse rates in patients with rheumatoid arthritis in stable remission tapering or stopping antirheumatic therapy: interim results from the prospective randomised controlled RETRO study. *Ann Rheum Dis* **75**, 45–51.
18 van der Maas A, Kievit W, van den Bemt BJF, van den Hoogen FHJ, van Riel PL, den Broeder AA (2012) Down-titration and discontinuation of infliximab in rheumatoid arthritis patients with stable low disease activity and stable treatment: an observational cohort study. *Ann Rheum Dis* **71**, 1849–54.
19 van Herwaarden N, van der Maas A, Minten MJM *et al.* (2015) Disease activity guided dose reduction and withdrawal of adalimumab or etanercept compared with usual care in rheumatoid arthritis: open label, randomised controlled, non-inferiority trial. *BMJ* **350**, h1389.
20 den Broeder AA, van Herwaarden N, van der Maas A *et al.* (2013) Dose REduction strategy of subcutaneous TNF inhibitors in rheumatoid arthritis: design of a pragmatic randomised non inferiority trial, the DRESS study. *BMC Musculoskelet Disord* **14**, 299.
21 Bartelds GM, Krieckaert CM, Nurmohamed MT *et al.* (2011) Development of antidrug antibodies against adalimumab and association with disease activity and treatment failure during long-term follow-up. *JAMA* **305**, 1460–8.
22 Baert F, Noman M, Vermeire S *et al.* (2003) Influence of immunogenicity on the long-term efficacy of infliximab in Crohn's disease. *N Engl J Med* **348**, 601–8.
23 Vermeire S, Noman M, Van Assche G, Baert F, D'Haens G, Rutgeerts P (2007) Effectiveness of concomitant immunosuppressive therapy in suppressing the formation of antibodies to infliximab in Crohn's disease. *Gut* **56**, 1226–31.
24 Maser EA, Villela R, Silverberg MS, Greenberg GR (2006) Association of trough serum infliximab to clinical outcome after scheduled maintenance treatment for Crohn's disease. *Clin Gastroenterol Hepatol* **4**, 1248–54.
25 Hanauer SB, Wagner CL, Bala M *et al.* (2004) Incidence and importance of antibody responses to infliximab after maintenance or episodic treatment in Crohn's disease. *Clin Gastroenterol Hepatol* **2**, 542–53.
26 Krieckaert CLM, Bartelds GM, Lems WF, Wolbink GJ (2010) The effect of immunomodulators on the immunogenicity of TNF-blocking therapeutic monoclonal antibodies: a review. *Arthritis Res Ther* **12**, 217.
27 van Schouwenburg PA, Rispens T, Wolbink GJ (2013) Immunogenicity of anti-TNF biologic therapies for rheumatoid arthritis. *Nat Rev Rheumatol* **9**, 164–72.
28 Yamanaka H, Nagaoka S, Lee S-K *et al.* (2016) Discontinuation of etanercept after achievement of sustained remission in patients with rheumatoid arthritis who initially had moderate disease activity—results from the ENCOURAGE study, a prospective, international, multicenter randomized study. *Mod Rheumatol* **26**, 651–61.
29 Smolen JS, Nash P, Durez P *et al.* (2013) Maintenance, reduction, or withdrawal of etanercept after treatment with etanercept and methotrexate in patients with moderate rheumatoid arthritis (PRESERVE): a randomised controlled trial. *Lancet* **381**, 918–29.
30 van Vollenhoven RF, Østergaard M, Leirisalo-Repo M *et al.* (2016) Full dose, reduced dose or discontinuation of etanercept in rheumatoid arthritis. *Ann Rheum Dis* **75**, 52–8.