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Down-titration and discontinuation strategies of tumour necrosis factor–blocking agents for rheumatoid arthritis in patients with low disease activity (Review)

Verhoef LM, van den Bemt BJF, van der Maas A, Vrizekolk JE, Hulscher ME, van den Hoogen FHJ, Jacobs WCH, van Herwaarden N, den Broeder AA

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[Intervention Review]

Down-titration and discontinuation strategies of tumour necrosis factor–blocking agents for rheumatoid arthritis in patients with low disease activity

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ABSTRACT

Background

Anti–tumour necrosis factor (TNF) agents are effective in treating people with rheumatoid arthritis (RA), but are associated with (dose-dependent) adverse effects and high costs. To prevent overtreatment, several trials have assessed the effectiveness of down-titration compared with continuation of the standard dose. This is an update of a Cochrane Review published in 2014.

Objectives

To evaluate the benefits and harms of down-titration (dose reduction, discontinuation, or disease activity-guided dose tapering) of anti-TNF agents on disease activity, functioning, costs, safety, and radiographic damage compared with usual care in people with RA and low disease activity.

Search methods

We searched MEDLINE, Embase, Web of Science and CENTRAL (29 March 2018) and four trial registries (11 April 2018) together with reference checking, citation searching, and contact with study authors to identify additional studies. We screened conference proceedings (American College of Rheumatology and European League Against Rheumatism 2005–2017).

Selection criteria

Randomised controlled trials (RCTs) and controlled clinical trials (CCTs) comparing down-titration (dose reduction, discontinuation, disease activity-guided dose tapering) of anti-TNF agents (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab) to usual care/no down-titration in people with RA and low disease activity.

Data collection and analysis

We used standard Cochrane methodology.

Main results

One previously included trial was excluded retrospectively in this update because it was not an RCT/CCT. We included eight additional trials, for a total of 14 studies (13 RCTs and one CCT, 3315 participants in total) reporting anti-TNF down-titration. Six studies (1148 participants) reported anti-TNF dose reduction compared with anti-TNF continuation. Eight studies (2111 participants) reported anti-TNF discontinuation compared with anti-TNF continuation (three studies assessed both anti-TNF discontinuation and dose reduction), and three studies assessed disease activity-guided anti-TNF dose tapering (365 participants). These studies included data on all anti-TNF agents, but primarily adalimumab and etanercept. Thirteen studies were available in full text, one was available as abstract. We assessed the included studies generally at low to moderate risk of bias; our main concerns were bias due to open-label treatment and unblinded outcome assessment. Clinical heterogeneity between the trials was high. The included studies were performed at clinical centres around the world and included people with early as well as established RA, the majority of whom were female with mean ages between 47 and 60. Study durations ranged from 6 months to 3.5 years.

We found that anti-TNF dose reduction leads to little or no difference in mean disease activity score (DAS28) after 26 to 52 weeks (high-certainty evidence, mean difference (MD) 0.06, 95% confidence interval (CI) -0.11 to 0.24, absolute risk difference (ARD) 1%) compared with continuation. Also, anti-TNF dose reduction does not result in an important deterioration in function after 26 to 52 weeks (Health Assessment Questionnaire Disability Index (HAQ-DI)) (high-certainty evidence, MD 0.09, 95% CI 0.00 to 0.19, ARD 3%). Next to this, anti-TNF dose reduction may slightly reduce the proportion of participants switched to another biologic (low-certainty evidence), but probably slightly increases the proportion of participants with minimal radiographic progression after 52 weeks (moderate-certainty evidence, risk ratio (RR) 1.22, 95% CI 0.76 to 1.95, ARD 2% higher). Anti-TNF dose reduction may cause little or no difference in serious adverse events, withdrawals due to adverse events and proportion of participants with persistent remission (low-certainty evidence).

Results show that anti-TNF discontinuation probably slightly increases the mean disease activity score (DAS28) after 28 to 52 weeks (moderate-certainty evidence, MD 0.96, 95% CI 0.67 to 1.25, ARD 14%), and that the RR of persistent remission lies between 0.16 and 0.77 (low-certainty evidence). Anti-TNF discontinuation increases the proportion participants with minimal radiographic progression after 52 weeks (high-certainty evidence, RR 1.69, 95% CI 1.10 to 2.59, ARD 7%) and may lead to a slight deterioration in function (HAQ-DI) (low-certainty evidence). It is uncertain whether anti-TNF discontinuation influences the number of serious adverse events (due to very low-certainty evidence) and the number of withdrawals due to adverse events after 28 to 52 weeks probably increases slightly (moderate-certainty evidence, RR 1.46, 95% CI 0.75 to 2.84, ARD 1% higher).

Anti-TNF disease activity-guided dose tapering may result in little or no difference in mean disease activity score (DAS28) after 72 to 78 weeks (low-certainty evidence). Furthermore, anti-TNF disease activity-guided dose tapering results in little or no difference in the proportion of participants with persistent remission after 18 months (high-certainty evidence, RR 0.89, 95% CI 0.75 to 1.06, ARD -9%) and may result in little or no difference in switching to another biologic (low-certainty evidence). Anti-TNF disease activity-guided dose tapering may slightly increase proportion of participants with minimal radiographic progression (low-certainty evidence) and probably leads to a slight deterioration of function after 18 months (moderate-certainty evidence, MD 0.2 higher, 0.02 lower to 0.42 higher, ARD 7% higher). It is uncertain whether anti-TNF disease activity-guided dose tapering influences the number of serious adverse events due to very low-certainty evidence.

Authors' conclusions

We found that fixed-dose reduction of anti-TNF, after at least three to 12 months of low disease activity, is comparable to continuation of the standard dose regarding disease activity and function, and may be comparable with regards to the proportion of participants with persistent remission. Discontinuation (also without disease activity-guided adaptation) of anti-TNF is probably inferior to continuation of treatment with respect to disease activity, the proportion of participants with persistent remission, function, and minimal radiographic damage. Disease activity-guided dose tapering of anti-TNF is comparable to continuation of treatment with respect to the proportion of participants with persistent remission and may be comparable regarding disease activity.

Caveats of this review are that available data are mainly limited to etanercept and adalimumab, the heterogeneity between studies, and the use of superiority instead of non-inferiority designs.

Future research should focus on the anti-TNF agents infliximab and golimumab; assessment of disease activity, function, and radiographic outcomes after longer follow-up; and assessment of long-term safety, cost-effectiveness, and predictors for successful down-titration. Also, use of a validated flare criterion, non-inferiority designs, and disease activity-guided tapering instead of fixed-dose reduction or discontinuation would allow researchers to better interpret study findings and generalise to clinical practice.

PLAIN LANGUAGE SUMMARY

Lowering the dose of or stopping anti-tumour necrosis factor drugs in people with rheumatoid arthritis who are doing well (low disease activity)

We conducted an updated review of studies in which treatment with anti-tumour necrosis factor (anti-TNF) drugs (adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab) was lowered or stopped in people with rheumatoid arthritis (RA) who use anti-TNF drugs and are doing well (low disease activity). Our systematic search up to March 2018 identified 14 studies (3315 participants).

The included studies were performed at clinical centres around the world and included people with early as well as established RA, the majority of whom were female with mean ages varying between 47 and 60. Study durations ranged from 6 months to 3.5 years.

What is rheumatoid arthritis? What is stopping or lowering the dose of anti-TNF drugs?

When you have RA, your immune system, which normally fights infection, attacks the lining of your joints. This makes your joints swollen, stiff, and painful. There is no cure for RA, so treatments aim to relieve pain and stiffness, improve ability to move, and prevent damage to the joints.

Anti-TNF agents are biological drugs for RA. They lessen complaints by reducing inflammation in the joints, and they reduce radiographic joint damage. Reducing or stopping anti-TNF treatment when disease activity is low might reduce dose-dependent side effects (mainly infections) and costs.

Key results

Data were available for all anti-TNF agents, but mostly for adalimumab and etanercept.

Disease activity

- People who lowered the dose of anti-TNF showed little or no increase in disease activity compared with people who continued anti-TNF (high-certainty evidence).
- People who stopped anti-TNF had a 0.96 unit increase in disease activity on a scale from 0.9 to 8 compared with people who continued anti-TNF (absolute difference 14%, moderate-certainty evidence).
- People who gradually lowered the dose of anti-TNF showed little or no increase in disease activity compared with people who continued anti-TNF (low-certainty evidence).

Persistent remission

- There was little or no difference in the number of people who had persistent remission between those who lowered the dose of anti-TNF compared with continuation of anti-TNF (low-certainty evidence).
- Data on how stopping anti-TNF affects persistent remission were not pooled because results were not similar across studies (low-certainty evidence). The absolute difference varied between 15% and 68% fewer people that remained in remission when stopping anti-TNF compared to continuation of anti-TNF.
- There was little or no difference in the number of people who had persistent remission between those who gradually lowered the dose of anti-TNF compared with continuation of anti-TNF (high-certainty evidence).

X-ray progression

- 24 more people per 1000 had a greater than 0.5 point progression of joint damage after a year when lowering the dose of anti-TNF (scale 0 to 448) (absolute difference 2%, moderate-certainty evidence).
- 73 more people per 1000 who stopped anti-TNF had a greater than 0.5 point progression of joint damage after a year than people who continued anti-TNF (absolute difference 7%, high-certainty evidence).
- 110 more people per 1000 had greater than 0.5 or greater than 1.0 point progression of joint damage after 1.5 years when gradually lowering the dose of anti-TNF (low-certainty evidence).

Function

- People who lowered the dose of anti-TNF had a 0.09 unit worsening of function (scale 0 to 3) compared with people who continued anti-TNF (absolute difference 3%, high-certainty evidence).
- People stopping anti-TNF had a 0.18 unit worsening of function compared with people who continued anti-TNF (absolute difference 6%, low-certainty evidence).
- People gradually lowering the dose of anti-TNF had a 0.2 unit worsening in function compared with people who continued anti-TNF (absolute difference 7%, moderate-certainty evidence).

Side effects

- There was little or no difference in number of serious adverse events in people lowering the dose of anti-TNF compared to continuation anti-TNF (low-certainty evidence).

- It is uncertain whether gradually lowering the dose of or stopping anti-TNF influences the number of serious adverse events (very low-certainty evidence).

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Anti-TNF dose reduction versus anti-TNF continuation

Anti-TNF dose reduction compared to anti-TNF continuation for rheumatoid arthritis in patients with low disease activity

Patient or population: people with rheumatoid arthritis with low disease activity using a standard dose of anti-TNF agents

Setting: clinical research centres

Intervention: anti-TNF dose reduction

Comparison: anti-TNF continuation

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	N° of participants (studies)	Certainty of the evidence (GRADE)	Comments	What happens
	Risk with anti-TNF continuation	Risk with anti-TNF dose reduction					
Disease activity score Assessed with: DAS28 Scale from 0.9 to 8; higher scores indicate worse disease activity Follow-up: range 26 weeks to 52 weeks	The mean disease activity score was 2.34	MD 0.06 higher (0.11 lower to 0.24 higher)	-	501 (2 RCTs)	⊕⊕⊕⊕ HIGH	Absolute risk difference: 1% higher (95% CI 2% lower to 3% higher) Relative percentage change: 2% higher (95% CI 5% lower to 10% higher)	Anti-TNF dose reduction results in little or no difference in disease activity score (DAS28).
Proportion of participants with persistent remission Assessed with: DAS28 < 2.6 (remission) Follow-up: 52 weeks	653 per 1000	659 per 1000 (522 to 835)	RR 1.01 (0.80 to 1.28)	612 (2 RCTs)	⊕⊕⊕⊖ LOW ¹	Absolute risk difference: 1% higher (95% CI 13% lower to 18% higher) Relative percentage change: 1% higher (95% CI 20% lower to 28% higher) NNTB: not applicable (not statistically significant)	Anti-TNF dose reduction may result in little or no difference in the proportion of participants with persistent remission (DAS28 < 2.6).
Proportion of participants switched to another biologic Mean follow-up of 3.5 ± 1.5 years	110 per 1000	44 per 1000 (19 to 102)	RR 0.40 (0.17 to 0.93)	323 (1 RCT)	⊕⊕⊖⊖ LOW ²	Absolute risk difference: 7% lower (95% CI 9% lower to 1% lower) Relative percentage change: 60% (95% CI 83% lower to 7% lower) NNTB: 15 (95% CI 12 to 100)	Anti-TNF dose reduction may slightly reduce the proportion of participants switched to another biologic.

Proportion of participants with minimal radiographic progression Assessed with: mSvdH score > 0.5 Follow-up: 52 weeks	105 per 1000	129 per 1000 (80 to 206)	RR 1.22 (0.76 to 1.95)	553 (2 RCTs)	⊕⊕⊕⊖ MODERATE ³	Absolute risk difference: 2% higher (95% CI 3% lower to 10% higher) Relative percentage change: 22% higher (95% CI 34% lower to 95% higher) NNTH: not applicable (not statistically significant)	Anti-TNF dose reduction probably slightly increases the proportion of participants with minimal radiographic progression (mSvdH > 0.5) .
Function Assessed with: Health Assessment Questionnaire Scale from 0 to 3; higher scores indicate worse function Follow-up: range 26 weeks to 52 weeks	The mean function was 0.52	MD 0.09 higher (0 to 0.19 higher)	-	501 (2 RCTs)	⊕⊕⊕⊕ HIGH	Absolute risk difference: 3% higher (95% CI 0% higher to 6% higher) Relative percentage change: 15% higher (95% CI 0% higher to 31% higher)	Anti-TNF dose reduction does not result in an important deterioration in function.
Number of serious adverse events Follow-up: range 26 weeks to 52 weeks (mean follow-up for Raffeiner 2015 3.5 ± 1.5 years)	52 per 1000	56 per 1000 (34 to 94)	RR 1.09 (0.65 to 1.82)	1084 (5 RCTs)	⊕⊕⊕⊖ LOW ^{3 4}	Absolute risk difference: 0% (95% CI 2% lower to 4% higher) Relative percentage change: 9% higher (95% CI 35% lower to 82% higher) NNTH: not applicable (not statistically significant)	Anti-TNF dose reduction may cause little or no difference in the number of serious adverse events..
Withdrawals due to adverse events Follow-up: 52 weeks (mean follow-up for Raffeiner 2015 3.5 ± 1.5 years)	31 per 1000	33 per 1000 (16 to 70)	RR 1.07 (0.51 to 2.24)	937 (3 RCTs)	⊕⊕⊕⊖ LOW ^{3 4}	Absolute risk difference: 0% (95% CI 2% lower to 4% higher) Relative percentage change: 7% higher (95% CI 49% lower to 124% higher) NNTH: not applicable (not statistically significant)	Anti-TNF dose reduction may cause little or no difference in the number of withdrawals due to adverse events .

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **DAS28:** disease activity score in 28 joints; **MD:** mean difference; **mSvdH:** modified Sharp van der Heijde; **NNTB:** number needed to treat for an additional beneficial outcome; **NNTH:** number needed to treat for an additional harmful outcome; **RCT:** randomised controlled trial; **RR:** risk ratio; **TNF:** tumour necrosis factor

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

¹Downgraded two levels due to heterogeneity ($I^2=73\%$)

²Downgraded two levels due to concerns about study risk of bias (high risk of selection bias, performance bias, detection bias and other bias).

³Downgraded one level due to imprecision (insufficient sample size/low number of events).

⁴Downgraded one level due to concerns about study risk of bias (mainly due to high risk of attrition bias in [Smolen 2013 \(PRESERVE\)](#) and high risk of bias on several domains in [Raffaener 2015](#)).

Summary of findings 2. Anti-TNF discontinuation versus anti-TNF continuation

Anti-TNF discontinuation compared to anti-TNF continuation for rheumatoid arthritis in patients with low disease activity

Patient or population: people with rheumatoid arthritis with low disease activity using a standard dose of anti-TNF agents

Setting: clinical research centres

Intervention: anti-TNF discontinuation

Comparison: anti-TNF continuation

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments	What happens
	Risk with anti-TNF continuation	Risk with anti-TNF discontinuation					
Disease activity score - assessed with: DAS28 Scale from: 0.9 to 8; higher scores indicate worse disease activity follow up: range 28 weeks to 52 weeks	Discontinuation without restarting, or with restarting and LOCF analysis Mean disease activity score was 2.82	MD 0.96 higher (0.67 higher to 1.25 higher)	-	733 (2 RCTs)	⊕⊕⊕⊖ MODERATE ¹	Absolute risk difference: 14% higher (95% CI 9% higher to 18% higher) Relative percentage change: 25% (95% CI 18% higher to 33% higher)	Anti-TNF discontinuation probably increases the disease activity score slightly
Proportion of participants with persistent remission	RR values range from 0.16 to 0.77. Absolute risk differences range from 15% lower to 68% lower.			1188 (6 RCTs)	⊕⊕⊖⊖ LOW ²	Data not pooled due to heterogeneity.	Anti-TNF discontinuation may reduce the proportion of participants with persistent remission

Assessed with: DAS28 < 2.6 (remission) Follow-up: range 28 weeks to 52 weeks						pants with persistent remission	
Proportion participants that switched to another biologic due to loss of response - not measured	-	-	-	-	-	No studies were found that evaluated the proportion of participants that switched to another biologic due to persistent loss of response.	
Proportion participants with minimal radiographic progression Assessed with: mSvdH > 0.5 Follow-up: mean 52 weeks	105 per 1000	178 per 1000 (116 to 273)	RR 1.69 (1.10 to 2.59)	549 (3 RCTs)	⊕⊕⊕⊕ HIGH	Absolute risk difference: 7% higher (95% CI 1% higher to 17% higher) Relative percentage change: 69% higher (95% CI 10% higher to 159% higher) NNTH: 15 (95% CI 6 to 100)	Anti-TNF discontinuation increases the proportion participants with minimal radiographic progression > 0.5 mSvdH point.
Function Assessed with: Health Assessment Questionnaire Scale from 0 to 3; higher scores indicate worse functioning Follow-up: range 28 weeks to 52 weeks	The mean function was 0.52	MD 0.18 higher (0.05 higher to 0.31 higher)	-	1498 (4 RCTs)	⊕⊕⊕⊖ LOW ²	Absolute risk difference: 6% higher (95% CI 2% higher to 17% higher) Relative percentage change: 26% higher (95% CI 7% higher to 44% higher)	Anti-TNF discontinuation may lead to a slight deterioration in function.
Number of serious adverse events Follow-up: range 28 weeks to 52 weeks	57 per 1000	74 per 1000 (47 to 116)	RR 1.29 (0.82 to 2.03)	2095 (8 RCTs)	⊕⊕⊕⊖ VERY LOW ^{1 3 4}	Absolute risk difference: 2% higher (95% CI 1% lower to 6% higher) Relative percentage change: 29% higher (95% CI 18% lower to 103% higher) NNTH: not applicable (not statistically significant)	It is uncertain whether anti-TNF discontinuation influences the number of serious adverse events because the certainty of the evidence is very low and because of imprecision.
Withdrawals due to adverse events Follow-up: range 28 weeks to 52 weeks	27 per 1000	39 per 1000 (20 to 76)	RR 1.46 (0.75 to 2.84)	1116 (4 RCTs)	⊕⊕⊕⊖ MODERATE ³	Absolute risk difference: 1% higher (95% CI 1% lower to 5% higher)	Anti-TNF discontinuation probably slightly increases the number of with-

Relative percentage change:
46% (95% CI 25% lower to
184% higher)

NNTH: not applicable (not sta-
tistically significant)

drawals due to ad-
verse events.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **DAS28:** disease activity score in 28 joints; **LOCF:** last observation carried forward; **MD:** mean difference; **mSvdH:** modified Sharp van der Heijde; **NNTH:** number needed to treat for an additional harmful outcome; **RCT:** randomised controlled trial; **RR:** risk ratio; **TNF:** tumour necrosis factor

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

¹Downgraded one level due to heterogeneity ($I^2=61\%$ for disease activity score and $I^2=31\%$ for number of serious adverse events).

²Downgraded two levels due to heterogeneity ($I^2=80\%$ for proportion of participants with remission and $I^2=79\%$ for function).

³Downgraded one level due to imprecision (low number of events).

⁴Downgraded one level due to concerns about study risk of bias (high risk of selection bias, detection bias, attrition bias and other bias).

Summary of findings 3. Anti-TNF disease activity-guided dose tapering versus anti-TNF continuation

Anti-TNF disease activity-guided dose tapering compared to anti-TNF continuation for rheumatoid arthritis in patients with low disease activity

Patient or population: people with rheumatoid arthritis with low disease activity using a standard dose of anti-TNF agents

Setting: clinical research centres

Intervention: anti-TNF disease activity-guided dose tapering

Comparison: anti-TNF continuation

Outcomes	Anticipated absolute effects* (95% CI)		Relative ef- fect (95% CI)	N° of partici- pants (studies)	Certainty of the evidence (GRADE)	Comments	What happens
	Risk with an- ti-TNF con- tinuation	Risk with an- ti-TNF dis- ease activ- ity-guided dose taper- ing					

Disease activity score Assessed with: DAS28 Scale from 0.9 to 8; higher scores indicate worse disease activity Follow-up: range 72 weeks to 78 weeks	The mean disease activity score was 2.34	MD 0.25 higher (0.17 lower to 0.67 higher)	-	357 (3 RCTs)	⊕⊕○○ LOW ¹	Absolute risk difference: 4% higher (95% CI 2% lower to 9% higher) Relative percentage change: 10% higher (95% CI 7% lower to 26% higher)	Anti-TNF disease activity-guided dose tapering may result in little or no difference in disease activity score.
Proportion of participants with persistent remission Assessed with: DAS28 < 2.6 (remission) Follow-up: 18 months	797 per 1000	709 per 1000 (597 to 844)	RR 0.89 (0.75 to 1.06)	180 (1 RCT)	⊕⊕⊕⊕ HIGH	Absolute risk difference: 9% lower (95% CI 20% lower to 5% higher) Relative percentage change: 10% higher (95% CI 7% lower to 26% higher) NNTH: not applicable (not statistically significant)	Anti-TNF disease activity-guided dose tapering results in little or no difference in the proportion of participants with persistent remission.
Proportion of participants switched to another biologic due to loss of response Follow-up: 18 months	76 per 1000	47 per 1000 (19 to 117)	RR 0.62 (0.25 to 1.54)	317 (2 RCTs)	⊕⊕○○ LOW ²	Absolute risk difference: 3% lower (95% CI 6% lower to 4% higher) Relative percentage change: 38% higher (95% CI 75% lower to 54% higher) NNTH: not applicable (not statistically significant)	Anti-TNF disease activity-guided dose tapering may result in little or no difference in the proportion of participants that switch to another biologic.
Proportion of participants with minimal radiographic progression Assessed with: mSvdH score > 0.5 or > 1.0 Follow-up: mean 18 months	242 per 1000	352 per 1000 (187 to 662)	RR 1.45 (0.77 to 2.73)	312 (2 RCTs)	⊕⊕○○ LOW ^{3 4}	Absolute risk difference: 11% higher (95% CI 6% lower to 42% higher) Relative percentage change: 45% higher (95% CI 23% lower to 173% higher) NNTH: not applicable (not statistically significant)	Anti-TNF disease activity-guided dose tapering may slightly increase the proportion of participants with minimal radiographic progression (mSvdH > 0.5 or > 1.0).
Function	The mean function was 0.4	MD 0.2 higher (0.02 lower to 0.42 higher)	-	123 (1 RCT)	⊕⊕⊕○ MODERATE ⁴	Absolute risk difference: 7% higher (95% CI 1% lower to 14% higher)	Anti-TNF disease activity-guided dose tapering probably leads to a

Assessed with: Health Assessment Questionnaire Scale from 0 to 3; higher scores indi- cate worse function Follow-up: mean 18 months						Relative percentage change: 33% higher (95% CI 3% lower to 70% higher)	slight deterioration of function.
Number of serious adverse events Follow-up: 18 months	129 per 1000	160 per 1000 (54 to 477)	RR 1.24 (0.42 to 3.70)	317 (2 RCTs)	⊕⊕⊕⊕ VERY LOW ^{1 2}	Absolute risk difference: 3% high- er (95% CI 8% lower to 35% high- er) Relative percentage change: 24% higher (95% CI 58% lower to 270% higher) NNTH: not applicable (not statis- tically significant)	It is uncertain whether anti-TNF disease ac- tivity-guided dose ta- pering influences the number of serious ad- verse events because the certainty of the ev- idence is very low and because of impreci- sion.
Withdrawals due to adverse events - not measured	-	-	-	-	-	No studies were found that eval- uated the number of withdrawals due to adverse events.	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **DAS28:** disease activity score in 28 joints; **MD:** mean difference; **mSvdH:** modified Sharp van der Heijde; **NNTH:** number needed to treat for an addi-
tional harmful outcome; **RCT:** randomised controlled trial; **RR:** risk ratio; **TNF:** tumour necrosis factor

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

¹Downgraded two levels due to heterogeneity ($I^2=70\%$ for disease activity score and $I^2=69\%$ for number of serious adverse events).

²Downgraded two levels due to imprecision (insufficient sample size/low number of events).

³Downgraded one level due to heterogeneity ($I^2=59\%$).

⁴Downgraded one level due to imprecision (insufficient sample size).

BACKGROUND

Description of the condition

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease characterised by symmetrical joint inflammation that often leads to joint damage. Tumour necrosis factor–blocking (anti-TNF) agents have proved effective as therapies for RA ([Blumenauer 2002](#); [Blumenauer 2003](#); [Navarro-Sarabia 2005](#); [Ruiz Garcia 2014](#); [Singh 2009](#); [Singh 2010](#)). They improve clinical symptoms and functioning and inhibit joint destruction, and have become an important part of treatment prescribed for RA.

Description of the intervention

Treatment of individuals with RA has been evolving from traditional step-up regimens to more aggressive step-down strategies. Pivotal to these changes are the early start of treatment (hit early), the use of combination therapy including steroids with rapid escalation to biologics (hit-hard), and, most important, frequent assessment of disease activity and treatment modification based on assessment (tight control). Strategies incorporating these concepts lead to the swift achievement of low disease activity or remission in most patients, which prevents joint damage and improves function and quality of life ([Schipper 2010](#)). An important disadvantage of the hit-hard approach compared with the traditional step-up approach, however, is that the former method does not allow for individual titration of the minimal effective treatment. Indeed, the traditional step-up approach largely prevents overtreatment, but high(er) disease activity at the beginning of the disease has to be accepted. To prevent overtreatment when high-dose or multidrug strategies are used, treatment must be tapered down when low disease activity is reached up to the point that disease activity increases again or medication can be stopped. In this way, the minimal effective dose is found and overtreatment is prevented. Optimal dosing of biologics is especially important because of the risk of dose-dependent adverse effects and the risk of low cost-effectiveness due to high cost ([den Broeder 2010](#); [Ramiro 2017](#); [Singh 2011](#)). The concept of dose reduction has been incorporated into current guidelines for the treatment of RA ([Singh 2016](#); [Smolen 2017](#)).

The intervention that is the subject of this review is therefore dose reduction of anti-TNF agents (by adaptation of dose or dosing interval) or discontinuation or both in people with RA and low disease activity status.

How the intervention might work

Successful dose reduction or discontinuation of anti-TNF agents can be expected for several reasons. First, amongst patients who seem to respond to treatment with anti-TNF agents are those who show spontaneous improvement (regression to the mean) ([den Broeder 2010](#); [van Vollenhoven 2004](#)); this phenomenon applies to 10% to 30% of all patients, as was shown by proportions of placebo group response ([Doherty 2009](#); [St Clair 2004](#)). Second, often concomitant medication is given that might induce a response. Both mechanisms are supported by the fact that a proportion of patients who seem to do well while taking the drug have (neutralising) antibodies (less than 5% to 43%) ([Bartelds 2007](#); [Klareskog 2011](#); [Wolbink 2006](#)). Finally, a substantial proportion of patients might need a lower than standard dose for a clinical response ([Fautrel 2015](#); [Verhoef 2017](#)). Anti-TNF agents are registered at the dose that shows the best response for the

most patients (top of group level dose-response curve). However, individual patients might respond to a lower dose as well, which is reflected in response percentages of lower doses in these initial trials ([Genovese 2002](#); [Maini 1998](#); [Weinblatt 2003](#)).

Uncontrolled research has shown that down-titration of anti-TNF agents can be successful in a relevant proportion of patients. Most data are available for infliximab, adalimumab, and etanercept, and most are derived from discontinuation studies ([Brocq 2009](#); [den Broeder 2002](#); [Kavanaugh 2012](#); [Nawata 2008](#); [Saleem 2010](#); [Tanaka 2010](#); [Tanaka 2012](#); [van den Bemt 2008](#); [van der Bijl 2007](#); [van der Maas 2012](#)).

Why it is important to do this review

Although the adverse effects of anti-TNF agents reported in clinical trials were generally mild in severity, these drugs are associated with unintended effects including increased risk of infection and perhaps a dose-dependent increased risk of malignancy and rare severe adverse events ([Bongartz 2006](#)). The introduction of anti-TNF agents - and other biological drugs - has also led to an increase in cost because they are much more expensive than traditional disease-modifying antirheumatic drugs (DMARDs) ([van Vollenhoven 2009](#)).

It was appropriate at this time to conduct an update of this Cochrane Review of randomised controlled trials (RCTs) of anti-TNF down-titration as well as discontinuation studies, because several new RCTs on this topic are emerging, and additional information on the already included studies has been published.

OBJECTIVES

To evaluate the benefits and harms of down-titration (dose reduction, discontinuation, or disease activity-guided dose tapering) of anti-TNF agents (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab) on disease activity, functioning, costs, safety, and radiographic damage compared with usual care in people with RA and low disease activity.

METHODS

Criteria for considering studies for this review

Types of studies

We considered all randomised controlled trials (RCTs) and controlled clinical trials (CCTs) (including cluster randomised and cross-over trials) according to the Cochrane definition comparing down-titration of tumour necrosis factor–blocking (anti-TNF) agents versus usual care/no down-titration for inclusion. The minimal required follow-up was six months. Both superiority and non-inferiority trials were included.

Types of participants

People with RA (1987, [Arnett 1988](#), or 2010, [Aletaha 2010 RA criteria](#), or both) American College of Rheumatology (ACR) criteria) using anti-TNF agents in a standard (or lower) dosing regimen (adalimumab 40 mg every other week, etanercept 50 mg every week or 25 mg twice a week, infliximab 3 mg/kg every eight weeks, golimumab 50 mg every month, certolizumab pegol 200 mg every other week) for longer than six months and with a low disease activity state (clinical judgement of rheumatologist or disease activity score in 28 joints (DAS28) < 3.2; DAS < 2.4; Clinical Disease

Activity Index (CDAI) < 10; Simplified Disease Activity Index (SDAI) < 11 or DAS28 < 2.6; DAS < 1.6; CDAI < 2.8; SDAI < 3.3, [Aletaha 2005](#); [Fransen 2005](#), or 2011 ACR/European League Against Rheumatism (EULAR) remission ([Felson 2011](#))).

Types of interventions

Protocolised down-titration or discontinuation of the anti-TNF agent for optimal dose finding (not for other reasons, including reduction of side effects, availability, planned surgery, pregnancy). Non-protocolised change in medication (DMARDs, non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids) was allowed. Comparison was usual care/no down-titration/continuation of anti-TNF.

Types of outcome measures

Major outcomes

- Mean disease activity score; DAS28/DAS/CDAI/SDAI at six, 12, 18, and 24 months ([Aletaha 2005](#); [Prevoo 1995](#); [Smolen 2003](#); [van der Heijde 1990](#)).
- Proportion of participants with persistent remission (as specified above) after six, 12, 18, and 24 months.
- Proportion of participants that switched to another biologic due to persistent loss of response, refractory to re-instatement of the tapered anti-TNF in the intervention group.
- Proportion of participants with minimal radiographic progression, as measured by Larsen ([Larsen 1973](#)), Sharp ([Sharp 1971](#)), or modified Sharp-van der Heijde score (mSvdH score) ([van der Heijde 2000](#)).
- Function (as measured by Health Assessment Questionnaire (HAQ)/Arthritis Impact Measurement Scale (AIMS)).
- Number of serious adverse events.
- Withdrawals due to adverse events.

Minor outcomes

- Proportion of participants with a flare (or loss of response) (defined as any composite disease activity index-based flare criteria) during follow-up time.
- Quality of life as measured by Short Form (SF) Health Survey-12/36, Health Utilities Index (HUI), or EuroQoL Quality of Life Scale (EQ-5D).
- Costs (direct (e.g. medication, consultations, travel costs) and indirect (e.g. health-related absenteeism)).
- Incremental cost-effectiveness ratio (difference in costs divided by difference in quality of life expressed as utility, thus the potential savings when accepting the loss of one quality-adjusted life year (QALY)).
- Time to flare.
- Change in other medication (including DMARDs, NSAIDs, corticosteroids).

Search methods for identification of studies

Electronic searches

We searched the following electronic databases: MEDLINE (1946 to 29 March 2018), Embase (1974 to 29 March 2018), Web of Science (1945 to 2018) and the Cochrane Central Register of Controlled Trials (CENTRAL) 2018 issue 3. The specific search strategy for each of the databases is shown in the appendices ([Appendix 1](#); [Appendix](#)

[2](#); [Appendix 3](#); [Appendix 4](#)). Our search was not limited by language, year of publication, or publication type. The search period for all databases extended from inception to September 2013 for the original review, and from 2013 to 29 March 2018 for the update.

Searching other resources

We searched proceedings of conferences from 2005 to 2017 of the ACR and from 2005 to 2017 of the European League Against Rheumatism (EULAR) for abstracts of RCTs and CCTs. We searched reference lists of identified clinical trials and performed citation tracking of the included trials in the ISI Web of Knowledge citation index. We searched trial registries for completed and ongoing trials ([Appendix 5](#)). We contacted experts (first authors of included studies) to ask about additional trials.

Data collection and analysis

Selection of studies

We selected studies based on the inclusion criteria outlined in the [Criteria for considering studies for this review](#) section. Two review authors (NvH and BJFvdB for the original review; LMV and BJFvdB for the update) independently screened titles and abstracts for inclusion, obtaining full articles if necessary. Any differences were resolved by discussion and consensus or by consultation with a third review author (AAdB) if needed. In case the same study population was described in more than one publication, all publications were used, but for the analysis, all were grouped, with the most informative publication as the primary reference and with other publications as secondary references. We recorded reasons for exclusion of studies.

Data extraction and management

Two review authors (NvH and BJFvdB for the original review; LMV and BJFvdB for the update) independently abstracted data from each study using a data extraction form. Any differences were resolved by discussion and consensus or by consultation with a third review author (AAdB) if needed. We pilot-tested the data extraction form on a selection of trials. If necessary, we contacted the authors of a given study to ask for missing data.

We extracted the following data.

- General study information: first author, author affiliation, publication source, publication year, and source of funding.
- Study characteristics: design, setting, participant selection, method of randomisation, allocation procedure, blinding, inclusion/exclusion criteria, and study duration.
- Population characteristics: age, sex, diagnostic criteria, disease duration, DMARD comedication, previous DMARD use, previous anti-TNF use, rheumatoid factor status, anti-cyclic citrullinated peptide (CCP) status, disease activity state, total number of participants screened, total number of participants recruited, total number of participants randomly assigned, total number of participants followed, and numbers in each group.
- Intervention characteristics: anti-TNF agent, type of intervention (dose reduction/interval widening/discontinuation), treatment comparators.
- Outcome measures as noted above.
- Analysis: statistical technique used, intention-to-treat analyses and/or per-protocol analyses used.

- Results with number, mean and standard deviation.

Assessment of risk of bias in included studies

Two review authors (NvH and BJFvdB for the original review; LMV and BJFvdB for the update) assessed risk of bias in the included studies in accordance with the recommendations in the *Cochrane Handbook for Systematic Reviews of Interventions* (Appendix 6) (Higgins 2011).

We assessed the following 'Risk of bias' domains.

- Random sequence generation.
- Allocation concealment.
- Blinding of participants and personnel.
- Blinding of outcome assessment.
- Incomplete outcome data.
- Selective reporting.
- Other sources of bias (baseline imbalance in possible prognostic variables: DMARD comedication, duration of anti-TNF use, and disease duration).

We judged each of these domains as having low, high, or unclear risk of bias.

Measures of treatment effect

We analysed the results of the included studies using [Review Manager 2014](#). Continuous data were expressed as mean differences (MDs) or standardised mean differences (SMDs). Dichotomous data were expressed as risk ratios (RRs). Rates were expressed as rate ratios (RaRs). We summarised data in meta-analyses if the studies were sufficiently homogeneous, both clinically and statistically.

Unit of analysis issues

The participant was the unit of analysis. Post-hoc, it was chosen to pool the data from the two dose reduction arms in the study by [Ibrahim 2017 \(OPTTIRA\)](#) for outcomes in which data from multiple studies could be pooled because this facilitated comparison with the 50% dose reduction applied in all other included dose reduction studies (mean dose reduction of 33% and 66% being 50%).

Dealing with missing data

We accepted missing clinical data in trials when they represented less than 20% of findings. We planned to perform a sensitivity analysis if more than 20% of the data from a given study were missing in order to explore the impact of including or excluding such studies. We attempted to obtain missing information on parameter variability by contacting the authors of the trial. In the event that study authors were not able or were unwilling to provide this information, it was estimated from ranges if provided or from comparable trials.

Assessment of heterogeneity

We evaluated heterogeneity first clinically by considering comparability across trials on the following variables: type of intervention (dose reduction/discontinuation/disease activity-guided dose tapering), type of anti-TNF agent, duration of anti-TNF use, baseline disease activity (low disease activity versus remission), disease duration, DMARD comedication, and presence of anti-TNF rescue strategy. We examined forest plots and tested

for heterogeneity using the Chi² test with a $P < 0.10$ indicating significant heterogeneity. We used the I^2 statistic to describe the percentage of variability in effect estimates that is due to heterogeneity rather than to chance (Higgins 2003). A value greater than 50% may indicate substantial heterogeneity (Higgins 2011). If we detected significant heterogeneity ($I^2 > 80\%$), we did not pool data but performed subgroup analyses in an attempt to explain the heterogeneity.

Assessment of reporting biases

Publication bias implies that studies that report favourable results are more likely to be published than those describing negative or inconclusive (non-significant) results, leading to a bias in the overall published literature. To minimise the effect of selective reporting of results, we searched trial registries for completed but unpublished studies. We planned to use a funnel plot to assess potential publication bias. However, due to the small number of studies, the funnel plot was not informative. We also searched the trial registries for ongoing studies that are potentially interesting for a future update of this review (see [Characteristics of ongoing studies](#) for details), and for additional data on included studies.

We assessed reporting bias at the outcome level by using published protocols of the studies along with published results of the study to compare outcomes intended to be analysed with those actually analysed.

Data synthesis

When possible, we analysed data using an intention-to-treat model and, for non-inferiority studies, by also using a per-protocol model. Our reason for this was that intention-to-treat analyses can lead to false conclusions of non-inferiority in non-inferiority trials. We analysed outcomes of included studies using a random-effects model.

Subgroup analysis and investigation of heterogeneity

We planned that if sufficient data were available we would perform subgroup analyses for the following candidate effect modifiers: type of intervention (dose reduction/discontinuation/disease activity-guided dose tapering), type of anti-TNF agent, duration of anti-TNF use, baseline disease activity (low disease activity versus remission), disease duration, DMARD comedication, and presence of anti-TNF rescue strategy.

Sensitivity analysis

We planned to perform the following sensitivity analyses when possible.

- Effect of risk of bias of included studies.
- Effect of imputation of missing data or statistical transformations.

'Summary of findings' tables

We completed three separate 'Summary of findings' tables included in [Review Manager 2014](#) to improve the readability of the review. We examined seven outcomes in a table for each of the three subgroups of down-titration: (1) dose reduction, (2) discontinuation, and (3) disease activity-guided dose tapering. The study population consisted of people with RA with low disease activity using a standard dose of anti-TNF. The intervention

provided was down-titration (dose reduction, discontinuation, or disease activity-guided dose tapering). The intervention was compared with usual care (continuation or no formalised dose reduction of anti-TNF). In addition to the absolute and relative magnitude of effect, the number needed to treat for an additional beneficial outcome (NNTB) and number needed to treat for an additional harmful outcome (NNTH) were calculated by comparing the intervention group with the control group. We used [GRADEpro 2015](#) to conduct an overall grading of the quality of evidence.

The GRADE approach specifies four levels of certainty (high, moderate, low, and very low). The highest certainty rating is given for randomised trial evidence. Randomised trial evidence can be downgraded to moderate, low, or very low depending on the presence of five factors.

- Limitations in the design and implementation of available studies suggesting high likelihood of bias.
- Indirectness of evidence.
- Unexplained heterogeneity or inconsistency of results.
- Imprecision of results.
- High probability of publication bias.

RESULTS

Description of studies

The results of the search are presented in [Figure 1](#) and are described in detail in the following sections of the review.

Figure 1. Flow chart of study selection.

Results of the search

The previous version of this review included seven studies. Database searches for this update (2013 to March 2018) resulted in 2352 records, and after de-duplication 1565 search results. Reference checking, contact with experts, and performing additional searches in congress abstract databases and trial registers resulted in 42 additional records. After title and abstract screening of these 1607 records, 21 studies remained. After assessing these 21 studies for eligibility, we identified eight new studies for inclusion in the review. One of the previously included studies, [Harigai 2012 \(BRIGHT\)](#), was retrospectively excluded for this updated version of the review because we considered their

method of allocation (at the discretion of the physician) as not random or quasi-random, which is a prerequisite for the classification as RCT or CCT. Newly found studies that used allocation based on physician or patient preference were also not included in this updated version ([Tanaka 2013 \(HONOR\)](#); [Tanaka 2014 \(HOPEFUL-2\)](#)). Finally, a total of 14 studies were included in this update of the systematic review, consisting of six old studies and eight new studies. All of the old studies were now available as full text. Of the eight new studies, one was published as abstract and seven as full text.

We contacted the authors of 11 studies to obtain missing data or to clarify methods/results. We received a response from authors of 10 studies.

The total number of participants in the studies included in this review was 3315. Most participants (2111) were included in the eight studies comparing anti-TNF discontinuation versus anti-TNF continuation. Six studies (1148 participants) compared anti-TNF dose reduction versus continuation. Three studies (365 participants) compared disease activity-guided anti-TNF dose tapering versus continuation. Eleven studies used a superiority design; two studies used a non-inferiority design; and one study reported an equivalence design.

Included studies

Anti-TNF dose reduction versus anti-TNF continuation studies

Design

Six studies compared anti-TNF fixed-dose reduction versus anti-TNF continuation (El Miedany 2016; Ibrahim 2017 (OPTTIRA); Raffeiner 2015; Smolen 2013 (PRESERVE); van Vollenhoven 2016 (DOSERA); Weinblatt 2017 (C-EARLY)). Weinblatt 2017 (C-EARLY), Smolen 2013 (PRESERVE), and van Vollenhoven 2016 (DOSERA) were randomised, blinded, placebo-controlled, superiority studies that reported three arms (discontinuation, dose reduction, and continuation). The randomisation ratio was 1:1:1 for Smolen 2013 (PRESERVE) and van Vollenhoven 2016 (DOSERA); for Weinblatt 2017 (C-EARLY) this was 2:3:2 (stop; dose reduction; continuation). El Miedany 2016, Raffeiner 2015, and Ibrahim 2017 (OPTTIRA) were open-label superiority studies. The study by Raffeiner 2015 was reported as a prospective long-term follow-up study; randomisation was done in a consecutive manner (alternation) in a ratio 1:1, which we defined as quasi-random, making the study a CCT. The randomisation ratio for Ibrahim 2017 (OPTTIRA) was 1:1:2, and for El Miedany 2016 it was 1:1:1:1:1 (only group 1 and group 5 were relevant for this review).

The duration of the included studies was 6 months in Ibrahim 2017 (OPTTIRA); 40 weeks in van Vollenhoven 2016 (DOSERA); 52 weeks in Smolen 2013 (PRESERVE), El Miedany 2016, and Weinblatt 2017 (C-EARLY); and a mean follow-up of 3.5 ± 1.5 years in Raffeiner 2015. The study by Smolen 2013 (PRESERVE) had a total follow-up of 88 weeks, however 52 weeks of follow-up were provided after randomisation for dose reduction or continuation of etanercept. The total follow-up for van Vollenhoven 2016 (DOSERA) was 48 weeks, and 40 weeks of follow-up were provided after randomisation for dose reduction or continuation of etanercept. The study by Weinblatt 2017 (C-EARLY) describes period 2 of the C-EARLY study with a duration of 52 weeks, which was a re-randomisation of participants from the first period, which also lasted 52 weeks.

Sample size

The sample size for this comparison varied from 50 participants in the study by van Vollenhoven 2016 (DOSERA) (73 participants in total study due to multiple intervention arms) to 404 participants in Smolen 2013 (PRESERVE) (604 participants in total study due to multiple intervention arms).

Setting

Ibrahim 2017 (OPTTIRA) reported that participants were screened at 20 centres in the United Kingdom. The study by Raffeiner 2015 was reported as a single-centre study in Italy. Smolen 2013 (PRESERVE) was reported to have been conducted in 80 centres in Europe, Latin America, Asia, and Australia. The study by van Vollenhoven 2016 (DOSERA) was performed in 16 rheumatology units in Sweden (5), Denmark (2), Finland (2), Norway (3), Hungary (3), and Iceland (1). Weinblatt 2017 (C-EARLY) reported that it recruited participants at 103 centres in Europe, Australia, North America, and Latin America. El Miedany 2016 did not report a specific setting.

Participants

El Miedany 2016 did not provide information on participant characteristics. Most participants were female in the studies by van Vollenhoven 2016 (DOSERA), Smolen 2013 (PRESERVE), Weinblatt 2017 (C-EARLY), and Raffeiner 2015. Mean age was approximately 47 years in Smolen 2013 (PRESERVE); 49 years in Weinblatt 2017 (C-EARLY); 56 years in Raffeiner 2015; and 57 years in van Vollenhoven 2016 (DOSERA) and Ibrahim 2017 (OPTTIRA). Disease duration ranged from around 2.6 months in Weinblatt 2017 (C-EARLY) (median disease duration at baseline of C-EARLY period 1) to 14 years in Raffeiner 2015 and van Vollenhoven 2016 (DOSERA). Duration of anti-TNF agents had to be > 3 months in Ibrahim 2017 (OPTTIRA); ≥ 6 months in El Miedany 2016; ≥ 12 months in Raffeiner 2015; and ≥ 14 months in van Vollenhoven 2016 (DOSERA). Smolen 2013 (PRESERVE) started the anti-TNF agent at study start 36 weeks before randomisation for dose reduction or discontinuation. In the study by Weinblatt 2017 (C-EARLY), all participants had started certolizumab pegol treatment one year earlier (period 1 of C-EARLY). El Miedany 2016 and Ibrahim 2017 (OPTTIRA) did not report previous use of DMARDs. Participants in Raffeiner 2015 and Smolen 2013 (PRESERVE) were biologic disease-modifying antirheumatic drug (bDMARD) naive before the study. Raffeiner 2015 reported a mean (standard deviation (SD)) of 2.4 (1.1) previously used DMARDs in the dose reduction group and 2.4 (1.3) in the continuation group. Participants in Weinblatt 2017 (C-EARLY) were bDMARD and conventional synthetic disease-modifying antirheumatic drug (csDMARD) naive. van Vollenhoven 2016 (DOSERA) described that 66% of the participants had used a DMARD other than methotrexate (MTX) before the study.

In all included studies, participants had to have low disease activity, Ibrahim 2017 (OPTTIRA); Smolen 2013 (PRESERVE); van Vollenhoven 2016 (DOSERA); Weinblatt 2017 (C-EARLY), or remission, El Miedany 2016; Raffeiner 2015. Duration of low disease activity/remission had to be > 3 months in Ibrahim 2017 (OPTTIRA); ≥ 6 months in El Miedany 2016; ≥ 12 months in Raffeiner 2015; or ≥ 11 months in van Vollenhoven 2016 (DOSERA). Participants in the study by Smolen 2013 (PRESERVE) had to have a mean DAS28 ≤ 3.2 in the 24-week period before randomisation and a DAS28 ≤ 3.2 at the moment of randomisation. In the study by Weinblatt 2017 (C-EARLY), participants needed to have a DAS28 ≤ 3.2 12 weeks before randomisation and at the moment of randomisation. All included studies used a DAS28-based criterion to define low disease activity or remission.

Intervention and comedication

Raffeiner 2015 reported etanercept dose reduction by comparing etanercept 25 mg twice a week versus etanercept 25 mg

once a week. [Smolen 2013 \(PRESERVE\)](#) and [van Vollenhoven 2016 \(DOSERA\)](#) reported etanercept dose reduction (25 mg/week) compared with etanercept continuation (50 mg/week). [Ibrahim 2017 \(OPTTIRA\)](#) reported 33% and 66% dose reduction of adalimumab and etanercept versus 100%. [El Miedany 2016](#) reported 50% dose reduction of bDMARDs versus continuation. [Weinblatt 2017 \(C-EARLY\)](#) reported 50% dose reduction of certolizumab pegol (200 mg/4 weeks) versus continuation (200 mg/2 weeks). Participants were required to use MTX comedication (dose ranged from 7.5 to 25 mg/week) in [Smolen 2013 \(PRESERVE\)](#) and [van Vollenhoven 2016 \(DOSERA\)](#). In [Raffaeiner 2015](#), steroids, NSAIDs, and DMARDs were continued at the same dosages. No intra-articular steroids were permitted during the study period. [Smolen 2013 \(PRESERVE\)](#) allowed up to three intra-articular corticosteroid injections during the study. In the study by [van Vollenhoven 2016 \(DOSERA\)](#), participants continued MTX and other medications at the same dose. Participants in [Weinblatt 2017 \(C-EARLY\)](#) used MTX in the maximum tolerated ("optimised") dose throughout the study. Use of intra-articular, intramuscular, or intravenous corticosteroids at any dose was prohibited. The maximum allowed dose of oral corticosteroids during the study was ≥ 10 mg/day prednisone or equivalent, and no changes in dose were allowed during the study period. In the study of [El Miedany 2016](#), participants in the relevant study arms used a stable dose of a csDMARD during the trial. No intramuscular or local steroid joint injections were allowed. In five studies ([El Miedany 2016](#); [Ibrahim 2017 \(OPTTIRA\)](#); [Raffaeiner 2015](#); [van Vollenhoven 2016 \(DOSERA\)](#); [Weinblatt 2017 \(C-EARLY\)](#)), participants could return to their initial dose of anti-TNF after disease flare. In [Smolen 2013 \(PRESERVE\)](#), no attempt was made to recapture low disease activity by reintroducing etanercept in participants whose condition had deteriorated after etanercept withdrawal.

Outcomes

All studies reported a primary outcome measure. Three studies reported proportion of participants with low disease activity or remission as the primary outcome. [Raffaeiner 2015](#) and [El Miedany 2016](#) used $\text{DAS28} \leq 2.6$, and [Smolen 2013 \(PRESERVE\)](#) used $\text{DAS28} \leq 3.2$. The primary outcome in the study by [van Vollenhoven 2016 \(DOSERA\)](#) was proportion of non-failures for etanercept 50 mg/week versus placebo. The primary outcome for [Ibrahim 2017 \(OPTTIRA\)](#) was reported to be time to flare. [Weinblatt 2017 \(C-EARLY\)](#) reported maintenance of low disease activity (disease activity score in 28 joints using erythrocyte sedimentation rate (DAS28-ESR) of ≤ 3.2) for all 5 consecutive study visits to week 52 without flares as the primary outcome measure. Secondary outcomes reported in the included studies were very different. None of the included studies provided data on costs or change in comedication. All studies were analysed with a (modified) intention-to-treat approach.

Anti-TNF discontinuation versus anti-TNF continuation studies

Design

Eight of the included studies reported anti-TNF discontinuation compared with anti-TNF continuation ([Chatzidionysiou 2016 \(ADMIRE\)](#); [Ghiti Moghadam 2016 \(POEET\)](#); [Pavelka 2017](#); [Smolen 2013 \(PRESERVE\)](#); [Smolen 2014 \(OPTIMA\)](#); [van Vollenhoven 2016 \(DOSERA\)](#); [Weinblatt 2017 \(C-EARLY\)](#); [Yamanaka 2016 \(ENCOURAGE\)](#)). All included studies were randomised controlled superiority studies comparing anti-TNF discontinuation versus continuation. [Smolen 2014 \(OPTIMA\)](#), [Smolen 2013 \(PRESERVE\)](#),

[van Vollenhoven 2016 \(DOSERA\)](#), [Pavelka 2017](#), and [Weinblatt 2017 \(C-EARLY\)](#) were blinded placebo-controlled studies. The other studies were open-label studies ([Chatzidionysiou 2016 \(ADMIRE\)](#); [Ghiti Moghadam 2016 \(POEET\)](#); [Yamanaka 2016 \(ENCOURAGE\)](#)). [Chatzidionysiou 2016 \(ADMIRE\)](#) was reported to be a pilot study. [Smolen 2013 \(PRESERVE\)](#), [van Vollenhoven 2016 \(DOSERA\)](#), and [Weinblatt 2017 \(C-EARLY\)](#) reported three arms (both discontinuation and dose reduction compared with continuation).

[Smolen 2013 \(PRESERVE\)](#) and [van Vollenhoven 2016 \(DOSERA\)](#) reported a 1:1:1 randomisation ratio, and [Weinblatt 2017 \(C-EARLY\)](#) a randomisation ratio of 2:3:2. [Chatzidionysiou 2016 \(ADMIRE\)](#), [Pavelka 2017](#), [Smolen 2014 \(OPTIMA\)](#), and [Yamanaka 2016 \(ENCOURAGE\)](#) reported a 1:1 randomisation ratio. [Ghiti Moghadam 2016 \(POEET\)](#) randomised in a ratio of 2:1 (discontinuation versus continuation). [Smolen 2013 \(PRESERVE\)](#), [Smolen 2014 \(OPTIMA\)](#), [Pavelka 2017](#), and [van Vollenhoven 2016 \(DOSERA\)](#) reported a "run-in" period in which anti-TNF treatment was given open-label, before randomisation was provided for anti-TNF continuation, discontinuation, or dose reduction in a double-blind phase.

The duration of the included studies was 48 weeks for [van Vollenhoven 2016 \(DOSERA\)](#) (40 weeks double-blind period); 52 weeks for [Chatzidionysiou 2016 \(ADMIRE\)](#), [Ghiti Moghadam 2016 \(POEET\)](#), and [Pavelka 2017](#) (28 weeks double-blind period). [Weinblatt 2017 \(C-EARLY\)](#) reported a total follow-up of 104 weeks, in which the second 52-week double blind period was of interest for this review. [Smolen 2014 \(OPTIMA\)](#) and [Smolen 2013 \(PRESERVE\)](#) reported a total follow-up of 78 weeks and 88 weeks, respectively; however, both described 52-week follow-up after randomisation for discontinuation or continuation of the anti-TNF agent. [Yamanaka 2016 \(ENCOURAGE\)](#) described a period of one year in which participants were treated with open-label etanercept and MTX before they were randomised to open-label continuation or discontinuation.

Sample size

The sample size varied from 31 participants in [Chatzidionysiou 2016 \(ADMIRE\)](#) to 817 in [Ghiti Moghadam 2016 \(POEET\)](#).

Setting

All eight studies were reported as multicentre studies. [Chatzidionysiou 2016 \(ADMIRE\)](#) was performed in several hospitals in Sweden, and [Ghiti Moghadam 2016 \(POEET\)](#) in 47 rheumatology centres throughout the Netherlands. [Smolen 2013 \(PRESERVE\)](#) reported that the study was conducted in 80 centres in Europe, Latin America, Asia, and Australia. [van Vollenhoven 2016 \(DOSERA\)](#) recruited participants at 16 rheumatology units in Sweden (5), Denmark (2), Finland (2), Norway (3), Hungary (3), and Iceland (1). [Pavelka 2017](#) was conducted at 61 centres in 19 countries in Africa, Asia, Central and Eastern Europe, Latin America, and the Middle East. [Smolen 2014 \(OPTIMA\)](#) reported 161 sites around the world. [Weinblatt 2017 \(C-EARLY\)](#) was conducted at 103 participating sites in Europe, Australia, North America, and Latin America. [Yamanaka 2016 \(ENCOURAGE\)](#) was a co-operation of rheumatology institutes/departments in Japan and Korea.

Participants

Six studies reported a minimum age of 18 years for inclusion ([Chatzidionysiou 2016 \(ADMIRE\)](#); [Pavelka 2017](#); [Smolen 2013 \(PRESERVE\)](#); [Smolen 2014 \(OPTIMA\)](#); [van Vollenhoven 2016 \(DOSERA\)](#); [Weinblatt 2017 \(C-EARLY\)](#)). [Ghiti Moghadam 2016](#)

(POEET) was reported to include people 18 years of age or older. Smolen 2013 (PRESERVE) reported an upper age limit (70 years) for inclusion. Yamanaka 2016 (ENCOURAGE) did not report any age criteria. The mean age of participants varied from around 47 in Pavelka 2017 and Smolen 2013 (PRESERVE) to early 60s in Chatzidionysiou 2016 (ADMIRE) and Ghiti Moghadam 2016 (POEET). Most participants in the included studies were female. Mean disease duration ranged from seven to 14 years, except in Smolen 2014 (OPTIMA), in which the mean disease duration was only 3.9 months; Weinblatt 2017 (C-EARLY), in which median disease duration was around 2.7 months (measured one year before randomisation); and Yamanaka 2016 (ENCOURAGE), in which mean disease duration was two years. Duration of the anti-TNF agent had to be ≥ 6 months in Chatzidionysiou 2016 (ADMIRE); ≥ 1 year in Ghiti Moghadam 2016 (POEET); and ≥ 14 months in van Vollenhoven 2016 (DOSERA). Pavelka 2017, Smolen 2014 (OPTIMA), Smolen 2013 (PRESERVE), and Yamanaka 2016 (ENCOURAGE) started the anti-TNF agent at study start, 24 weeks, 26 weeks, 36 weeks, and 1 year, respectively before randomisation for dose reduction or discontinuation. In the study by Weinblatt 2017 (C-EARLY), participants were treated with certolizumab pegol (blinded) one year before randomisation for dose reduction or discontinuation. Participants in Smolen 2013 (PRESERVE), Smolen 2014 (OPTIMA), and Weinblatt 2017 (C-EARLY) were bDMARD naive before study start. Smolen 2014 (OPTIMA) reported that 8.8% of participants in the discontinuation group and 9.5% in the continuation group had used ≥ 1 DMARD. Chatzidionysiou 2016 (ADMIRE) reported a median of 1 (interquartile range (IQR) 0 to 1) number of previous bDMARDs and 2 (IQR 1 to 3) previous csDMARDs. In the study by Ghiti Moghadam 2016 (POEET), 13.4% of participants in the discontinuation group and 15% in the continuation group had previously used a bDMARD. In Pavelka 2017, 34% of participants in the discontinuation group had previously used a csDMARD versus 38% in the continuation group. van Vollenhoven 2016 (DOSERA) reported that 66% of all participants had used a DMARD other than MTX before study start. Yamanaka 2016 (ENCOURAGE) did not report on prior DMARD use.

Participants in all included studies had to have low disease activity, Ghiti Moghadam 2016 (POEET); Pavelka 2017; Smolen 2013 (PRESERVE); Smolen 2014 (OPTIMA); van Vollenhoven 2016 (DOSERA); Weinblatt 2017 (C-EARLY), or remission, Chatzidionysiou 2016 (ADMIRE); Yamanaka 2016 (ENCOURAGE). The duration of low disease activity had to be 4 weeks in Smolen 2014 (OPTIMA); ≥ 3 months in Chatzidionysiou 2016 (ADMIRE); ≥ 6 months in Ghiti Moghadam 2016 (POEET); or ≥ 11 months in van Vollenhoven 2016 (DOSERA). Participants in the study by Smolen 2013 (PRESERVE) had to have a mean DAS28 ≤ 3.2 in the 24-week period before randomisation and a DAS28 ≤ 3.2 at the moment of randomisation. In the study by Weinblatt 2017 (C-EARLY), participants needed to have a DAS28 ≤ 3.2 12 weeks before randomisation and at the moment of randomisation. In Yamanaka 2016 (ENCOURAGE), participants had to have a DAS < 2.6 at 6 and 12 months after study start. Pavelka 2017 reported that participants had to have low disease activity after period 1 (24 weeks after study start). All included studies used a DAS28-based criterion to define low disease activity or remission.

Intervention and comedication

Smolen 2013 (PRESERVE), van Vollenhoven 2016 (DOSERA), Yamanaka 2016 (ENCOURAGE), and Pavelka 2017 reported etanercept discontinuation compared with etanercept

continuation. The studies by Chatzidionysiou 2016 (ADMIRE) and Smolen 2014 (OPTIMA) reported adalimumab discontinuation compared with adalimumab continuation. Ghiti Moghadam 2016 (POEET) reported discontinuation of all anti-TNF agents versus anti-TNF continuation. Weinblatt 2017 (C-EARLY) reported discontinuation of certolizumab pegol compared to continuation of the standard dose.

Participants in most included studies were required to use MTX comedication (dose ranged from 6 to 25 mg/week). Ghiti Moghadam 2016 (POEET) included participants using any csDMARD comedication. Participants included in Smolen 2014 (OPTIMA) were MTX naive at the start of the study (26 weeks before randomisation for discontinuation or continuation of adalimumab). Seven studies stated that participants could restart the anti-TNF after disease flare (Chatzidionysiou 2016 (ADMIRE); Ghiti Moghadam 2016 (POEET); Pavelka 2017; Smolen 2014 (OPTIMA); van Vollenhoven 2016 (DOSERA); Weinblatt 2017 (C-EARLY); Yamanaka 2016 (ENCOURAGE)). The study by Smolen 2013 (PRESERVE) allowed up to three intra-articular corticosteroid injections during the study; however, no attempt was made to recapture low disease activity by reintroducing etanercept in participants whose condition had deteriorated after etanercept withdrawal.

Outcomes

All studies reported a primary outcome measure; for most studies this was proportion of participants with low disease activity or remission. All studies used DAS28-based criteria, but different definitions were employed. Chatzidionysiou 2016 (ADMIRE) and Yamanaka 2016 (ENCOURAGE) used DAS28 remission (< 2.6). Smolen 2013 (PRESERVE) and Pavelka 2017 used DAS28 low disease activity (≤ 3.2 for Smolen 2013 (PRESERVE) and < 3.2 for Pavelka 2017). Weinblatt 2017 (C-EARLY) reported maintenance of low disease activity (DAS28-ESR of ≤ 3.2) for all 5 consecutive study visits to week 52 without flares as the primary outcome measure. Ghiti Moghadam 2016 (POEET) reported proportion of participants with a flare (DAS28 ≥ 3.2 plus an increase > 0.6) as the primary outcome. The primary outcome in the study by van Vollenhoven 2016 (DOSERA) was proportion of non-failure. The primary outcome in Smolen 2014 (OPTIMA) was the proportion of participants with both low disease activity and radiographic non-progression; however, this concerned a comparison of study groups that was not of interest for this review (adalimumab continuation versus methotrexate monotherapy). Secondary outcomes reported in the included studies concerned many different domains, including participant-reported outcomes (function, quality of life), radiographic outcomes, number of flares, relapse-free survival, and safety outcomes. None of the included studies provided data on costs or change in comedication. All studies were analysed with a (modified) intention-to-treat approach.

Disease activity-guided dose tapering until stop versus anti-TNF continuation studies

Design

Three studies compared disease activity-guided anti-TNF dose tapering with anti-TNF continuation (Bejerano 2016 (OPTIBIO) (abstract only); Fautrel 2016 (STRASS); van Herwaarden 2015 (DRESS)). All studies were open-label RCTs. van Herwaarden 2015 (DRESS) and Bejerano 2016 (OPTIBIO) were reported to be non-inferiority studies. Fautrel 2016 (STRASS) reported an

equivalence design. Randomisation ratio was 2:1 (dose tapering versus continuation) in [van Herwaarden 2015 \(DRESS\)](#) and 1:1 in [Fautrel 2016 \(STRASS\)](#) and [Bejerano 2016 \(OPTIBIO\)](#). Study duration was 1 year for [Bejerano 2016 \(OPTIBIO\)](#) and 18 months for [van Herwaarden 2015 \(DRESS\)](#) and [Fautrel 2016 \(STRASS\)](#).

Sample size

The sample size varied from 48 in [Bejerano 2016 \(OPTIBIO\)](#) (66 in the total study, which also included other biologics besides anti-TNF) to 180 in [van Herwaarden 2015 \(DRESS\)](#). The projected sample size for the study by [Fautrel 2016 \(STRASS\)](#) was 250 participants; however, only 137 participants were included. The abstract on [Bejerano 2016 \(OPTIBIO\)](#) reported preliminary data.

Setting

[van Herwaarden 2015 \(DRESS\)](#) and [Fautrel 2016 \(STRASS\)](#) were reported to be multicentre studies. [van Herwaarden 2015 \(DRESS\)](#) included patients from two hospitals in the Netherlands, and [Fautrel 2016 \(STRASS\)](#) recruited participants at 22 rheumatology departments in France and one department in Monaco. [Bejerano 2016 \(OPTIBIO\)](#) was a monocentre study conducted in a hospital in Spain.

Participants

The abstract by [Bejerano 2016 \(OPTIBIO\)](#) provided no information on participant characteristics of anti-TNF users only. The mean age of participants was 56 years in the study by [Fautrel 2016 \(STRASS\)](#) and 59 years in the study by [van Herwaarden 2015 \(DRESS\)](#). Most participants were female in [Fautrel 2016 \(STRASS\)](#) and [van Herwaarden 2015 \(DRESS\)](#). Mean disease duration at baseline was about 10 years for both [Fautrel 2016 \(STRASS\)](#) and [van Herwaarden 2015 \(DRESS\)](#). Participants in [van Herwaarden 2015 \(DRESS\)](#) had a median of 2 (IQR 1 to 3) previous DMARDs and 0 (IQR 0 to 1) previous anti-TNF agents. [Fautrel 2016 \(STRASS\)](#) reported a mean (SD) of 2.7 (1.7) previous DMARDs, and 24% of participants had previously used a bDMARD.

The duration of anti-TNF agents had to be ≥ 6 months in [van Herwaarden 2015 \(DRESS\)](#) and > 1 year in [Fautrel 2016 \(STRASS\)](#). [Bejerano 2016 \(OPTIBIO\)](#) reported no minimal duration of anti-TNF use. Participants in [Bejerano 2016 \(OPTIBIO\)](#) had to have clinical remission (DAS < 2.6 , SDAI < 5 , or ACR/EULAR 2011 criteria) for ≥ 6 months. Participants in [Fautrel 2016 \(STRASS\)](#) needed to have a DAS28 ≤ 2.6 for ≥ 6 months with no structural damage progression. Participants in [van Herwaarden 2015 \(DRESS\)](#) had to have stable low disease activity (DAS28 < 3.2) at two subsequent visits.

Intervention and comedication

All three studies reported disease activity-guided dose tapering. [Bejerano 2016 \(OPTIBIO\)](#) included all anti-TNF agents, while [Fautrel 2016 \(STRASS\)](#) and [van Herwaarden 2015 \(DRESS\)](#) included adalimumab and etanercept. Dose tapering in [Fautrel 2016 \(STRASS\)](#) was done by increasing the interval between two subcutaneous injections by 50% every three months up to a complete stop in the fourth step; if DAS28 remission (DAS28 ≤ 2.6) was not maintained, dose tapering was suspended or was reversed to the previous interval based on DAS28 level. The dose reduction strategy in [van Herwaarden 2015 \(DRESS\)](#) consisted of stepwise increases of the time interval between injections every three months until complete stop in the third step. In the instance

of a flare (Δ DAS28-CRP score > 1.2 , or Δ DAS28-CRP > 0.6 , and a current score of ≥ 3.2), the last effective interval was reinstated. The dose reduction strategy in [Bejerano 2016 \(OPTIBIO\)](#) consisted of a stepwise increase in interval every year with withdrawal as the third step. In case of flare (DAS28 > 2.6 or SDAI > 5 or ACR/EULAR criteria not fulfilled), participants returned to the standard dose. In all studies, the dose-tapering intervention was compared with unchanged continuation of the anti-TNF agents.

Outcomes

All studies reported a primary outcome measure that was based on the DAS28 score. [Fautrel 2016 \(STRASS\)](#) reported standardised difference of DAS28 slopes based on a linear mixed-effects model as the primary outcome compared to an equivalence margin of $\pm 30\%$. For [van Herwaarden 2015 \(DRESS\)](#), this was difference in proportions of participants with major flare (DAS28-CRP-based flare longer than three months) compared with a non-inferiority margin of 20%. The primary outcome measure in [Bejerano 2016 \(OPTIBIO\)](#) was the proportion of participants that maintained clinical remission after one year. The abstract for this study did not report on secondary outcome measures. Several secondary measures were reported in [Fautrel 2016 \(STRASS\)](#) and [van Herwaarden 2015 \(DRESS\)](#), including function, radiographic progression, and adverse events. [Fautrel 2016 \(STRASS\)](#) and [van Herwaarden 2015 \(DRESS\)](#) primarily performed a per-protocol analysis and additionally performed an intention-to-treat analysis. [Bejerano 2016 \(OPTIBIO\)](#) did not specify their analysis approach, which was therefore labelled as intention-to-treat.

Excluded studies

We excluded 29 articles from this review (15 for the original publication and 14 from the updated version). Fourteen articles (concerning 13 studies) reported anti-TNF down-titration without an anti-TNF continuation control arm ([Awan 2011](#); [Bejerano 2010](#); [Detert 2013 \(HIT-HARD\)](#); [Emery 2013 \(PRIZE\)](#); [Heimans 2016 \(IMPROVED\)](#); [Klarenbeek 2011](#); [Oba 2017 \(RRRR study\)](#); [Quinn 2005](#); [Seddighzadeh 2014 \(NORD-STAR\)](#); [Smolen 2012 \(CERTAIN\)](#); [van den Broek 2011](#); [van der Kooij 2009](#); [Villeneuve 2012](#); [Wiland 2016 \(PRIZE\)](#)). In four studies, allocation to anti-TNF continuation or discontinuation was based on patient or physician preference ([Harigai 2012 \(BRIGHT\)](#); [Rakieh 2013](#); [Tanaka 2013 \(HONOR\)](#); [Tanaka 2014 \(HOPEFUL-2\)](#)), therefore these study were not classified as RCT or CCT. [Tada 2012 \(PRECEPT\)](#) reported low-dose versus standard-dose etanercept from study start. In the study by [Haschka 2016 \(RETRO\)](#), participants were randomised to dose reduction or discontinuation of all DMARDs, therefore the intervention was too broad for this review. The studies by [Kobelt 2011](#) and [Kobelt 2014](#) provided data from a Markov model. [Aletaha 2010](#), [Ichikawa 2007](#), and [Keystone 2003](#) were overview articles. [Ramírez-Herráiz 2013](#) was a retrospective study; [CADTH Report 2014](#) described a literature study; and [Greenberg 2014](#) was a cohort study. In the study by [Haraoui 2014](#), no doses below standard dose were investigated.

See [Characteristics of excluded studies](#) for more information.

Risk of bias in included studies

See [Characteristics of included studies](#) for 'Risk of bias' tables with information on all aspects of risk of bias. Graphic summaries of the risk of bias in included studies are shown in [Figure 2](#) and [Figure 3](#).

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias): Subjective outcomes	Blinding of participants and personnel (performance bias): Objective outcomes	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Bejerano 2016 (OPTIBIO)	?	?	-	+	-	?	?	?
Chatzidionysiou 2016 (ADMIRE)	?	+	-	+	-	+	+	+
El Miedany 2016	?	?	-	+	-	+	?	+
Fautrel 2016 (STRASS)	+	+	-	+	+	+	+	-
Ghiti Moghadam 2016 (POEET)	+	?	-	+	-	+	+	-
Ibrahim 2017 (OPTTIRA)	+	+	-	+	-	+	+	+
Pavelka 2017	+	+	+	+	+	+	+	+
Raffener 2015	-	-	-	+	-	+	?	-
Smolen 2013 (PRESERVE)	+	+	+	+	+	-	+	+
Smolen 2014 (OPTIMA)	?	+	+	+	+	+	+	+
van Herwaarden 2015 (DRESS)	+	+	-	+	-	+	+	+
van Vollenhoven 2016 (DOSERA)	+	+	+	+	+	+	+	+
Weinblatt 2017 (C-EARLY)	+	+	+	+	+	+	+	-
Yamanaka 2016 (ENCOURAGE)	?	+	-	+	-	-	+	-

Allocation

Seven included studies described an adequate random sequence generation and allocation concealment procedure, resulting in an assessment of low risk of selection bias (Fautrel 2016 (STRASS); Ibrahim 2017 (OPTTIRA); Pavelka 2017; Smolen 2013 (PRESERVE); van Herwaarden 2015 (DRESS); van Vollenhoven 2016 (DOSERA); Weinblatt 2017 (C-EARLY)). The precise method of random sequence generation was not described in three studies (Chatzidionysiou 2016 (ADMIRE); Smolen 2014 (OPTIMA); Yamanaka 2016 (ENCOURAGE)). Ghiti Moghadam 2016 (POEET) did not describe allocation concealment. The methods of randomisation and allocation concealment were not described in the abstract by Bejerano 2016 (OPTIBIO) and the study by El Miedany 2016. The study by Raffeiner 2015 described alternation as the method of randomisation, which resulted in a judgement of high risk of selection bias.

Blinding

Five studies were reported to be placebo controlled (Pavelka 2017; Smolen 2013 (PRESERVE); Smolen 2014 (OPTIMA); van Vollenhoven 2016 (DOSERA); Weinblatt 2017 (C-EARLY)). The remaining nine studies were open-label (Bejerano 2016 (OPTIBIO); Chatzidionysiou 2016 (ADMIRE); El Miedany 2016; Fautrel 2016 (STRASS); Ghiti Moghadam 2016 (POEET); Ibrahim 2017 (OPTTIRA); Raffeiner 2015; van Herwaarden 2015 (DRESS); Yamanaka 2016 (ENCOURAGE)); five of these described blinding of X-ray reading (Fautrel 2016 (STRASS); Ibrahim 2017 (OPTTIRA); Raffeiner 2015; van Herwaarden 2015 (DRESS); Yamanaka 2016 (ENCOURAGE)), and the study by Fautrel 2016 (STRASS) also reported blinded DAS28 measurements, which resulted in an assessment of low risk of detection bias.

Incomplete outcome data

We used three criteria for judging this item: intention-to-treat analyses, imputation of missing data, and attrition rate.

Most studies performed an intention-to-treat analysis (Chatzidionysiou 2016 (ADMIRE); Fautrel 2016 (STRASS); Ghiti Moghadam 2016 (POEET); Ibrahim 2017 (OPTTIRA); Pavelka 2017; Smolen 2013 (PRESERVE); Smolen 2014 (OPTIMA); van Herwaarden 2015 (DRESS); van Vollenhoven 2016 (DOSERA); Weinblatt 2017 (C-EARLY); Yamanaka 2016 (ENCOURAGE)). The abstract by Bejerano 2016 (OPTIBIO) and the studies by Raffeiner 2015 and El Miedany 2016 did not report on the type of analysis. Five studies did not report any imputation of missing data (El Miedany 2016; Fautrel 2016 (STRASS); Ibrahim 2017 (OPTTIRA); Raffeiner 2015; van Herwaarden 2015 (DRESS)). Smolen 2013 (PRESERVE) reported a modified non-responder imputation analysis in which participants who discontinued early due to poor efficacy were imputed as non-responders for all time points; all other participants were analysed by the last observation carried forward (LOCF) method. All other postbaseline analyses were based on the LOCF method (except radiographic endpoints). Chatzidionysiou 2016 (ADMIRE) used non-responder imputation for participants with no available DAS28 at the time of the primary outcome (this included most participants who had a flare in the adalimumab discontinuation group). Ghiti Moghadam 2016 (POEET) reported imputation of DAS28 components based on the expectation-maximisation algorithm using the participant's values of the remaining components of the DAS28. Pavelka 2017 reported that efficacy analyses were conducted in the full analysis set population in each period using the last observation before rescue carried forward approach. The

study by Smolen 2014 (OPTIMA) used non-responder imputation for the primary endpoint, and non-responder imputation and LOCF, or both, for additional clinical outcomes; LOCF was used for functional outcomes. Markov chain Monte Carlo method was used to impute missing radiographic data 10 times (multiple imputation). Weinblatt 2017 (C-EARLY) reported that missing data from participants who entered period 2 but withdrew before the end of the study were imputed using non-responder imputation for the primary and key secondary endpoints. Radiographic analyses used linear extrapolation. In post hoc analyses, LOCF imputation was used for the proportions of participants achieving low disease activity, remission, and normative physical function. The study by Yamanaka 2016 (ENCOURAGE) described LOCF to impute missing data. van Vollenhoven 2016 (DOSERA) reported that a non-responder imputation was applied for dichotomous clinical outcomes. The abstract by Bejerano 2016 (OPTIBIO) did not describe the procedure for handling missing data. Most studies reported some participants that were lost to follow-up (Chatzidionysiou 2016 (ADMIRE); El Miedany 2016; Fautrel 2016 (STRASS); Ghiti Moghadam 2016 (POEET); Ibrahim 2017 (OPTTIRA); Pavelka 2017; Raffeiner 2015; Smolen 2014 (OPTIMA); van Herwaarden 2015 (DRESS); van Vollenhoven 2016 (DOSERA); Weinblatt 2017 (C-EARLY)). The study by Smolen 2013 (PRESERVE) reported that fewer participants completed the study in the placebo group than in the etanercept 50 mg and 25 mg groups (141 versus 181 and 175 participants). Yamanaka 2016 (ENCOURAGE) reported high dropout rates in both groups (16/49 in the continuation group and 16/50 in the discontinuation group). The abstract by Bejerano 2016 (OPTIBIO) did not describe completion rate.

Selective reporting

Most studies, with the exception of Raffeiner 2015 and El Miedany 2016, had a study protocol that was available. Bejerano 2016 (OPTIBIO) was published as abstract only, and therefore did not report all prespecified outcomes. All other studies reported the prespecified outcomes (Chatzidionysiou 2016 (ADMIRE); Fautrel 2016 (STRASS); Ghiti Moghadam 2016 (POEET); Ibrahim 2017 (OPTTIRA); Pavelka 2017; Smolen 2013 (PRESERVE); Smolen 2014 (OPTIMA); van Herwaarden 2015 (DRESS); van Vollenhoven 2016 (DOSERA); Weinblatt 2017 (C-EARLY); Yamanaka 2016 (ENCOURAGE)).

Other potential sources of bias

Eight studies appeared to be free of other potential sources of bias (Chatzidionysiou 2016 (ADMIRE); El Miedany 2016; Ibrahim 2017 (OPTTIRA); Pavelka 2017; Smolen 2013 (PRESERVE); Smolen 2014 (OPTIMA); van Herwaarden 2015 (DRESS); van Vollenhoven 2016 (DOSERA)). There was insufficient information in the abstract by Bejerano 2016 (OPTIBIO) to assess this domain. The study by Ghiti Moghadam 2016 (POEET) reported a different flare criterion in their final publication compared to the information in the trial register. No study protocol was present for Raffeiner 2015, but information from an earlier abstract indicated that the inclusion criteria, outcome measures, and duration of follow-up had changed over time. A lower than anticipated number of participants was included in Yamanaka 2016 (ENCOURAGE), Weinblatt 2017 (C-EARLY), and Fautrel 2016 (STRASS).

Effects of interventions

See: [Summary of findings for the main comparison](#) Anti-TNF dose reduction versus anti-TNF continuation; [Summary of findings 2](#) Anti-TNF discontinuation versus anti-TNF continuation; [Summary of findings 3](#) Anti-TNF disease activity-guided dose tapering versus anti-TNF continuation

We have presented study results by type of intervention: (1) dose reduction, (2) discontinuation, and (3) disease activity-guided dose tapering.

Anti-TNF dose reduction versus anti-TNF continuation

Major outcomes

See [Summary of findings for the main comparison](#).

- Mean disease activity: Of the six studies included for this comparison (1148 participants), two studies, [Smolen 2013 \(PRESERVE\)](#) and [Ibrahim 2017 \(OPTTIRA\)](#), with 501 participants provided data on mean disease activity (DAS28). Anti-TNF dose reduction resulted in little or no difference in mean disease activity score after 26 to 52 weeks' follow-up (mean difference (MD) 0.06, 95% confidence interval (CI) -0.11 to 0.24). We pooled data from the two dose reduction arms in the study by [Ibrahim 2017 \(OPTTIRA\)](#) for this outcome. [Analysis 1.1](#)
- Proportion persistent remission: Of the six studies included for this comparison (1148 participants), two studies, [Smolen 2013 \(PRESERVE\)](#) and [Weinblatt 2017 \(C-EARLY\)](#), with 612 participants provided data on persistent remission. Anti-TNF dose reduction may result in little or no difference in the proportion of participants with persistent remission (DAS28 < 2.6) after 52 weeks (risk ratio (RR) 1.01, 95% CI 0.80 to 1.28). [Analysis 1.2](#)
- Proportion of participants that switched to another biologic: Of the six studies included for this comparison (1148 participants), only one study with 323 participants provided data on this outcome ([Raffaener 2015](#)). The data showed that anti-TNF dose reduction may slightly reduce the proportion of participants who are switched to another biologic (RR 0.40, 95% CI 0.17 to 0.93; mean follow-up period 3.5 ± 1.5 years). This result might be explained by a difference in treatment strategy after flare in the two treatment groups. In the continuation group, a flare resulted in a switch of biologic treatment, while in the dose reduction group the standard dose of etanercept was reinstated first ([Raffaener 2015](#)). [Analysis 1.3](#)
- Proportion of participants with minimal radiographic progression: Of the six studies included for this comparison (1148 participants), two studies provided data on radiographic progression, [Smolen 2013 \(PRESERVE\)](#) and [Weinblatt 2017 \(C-EARLY\)](#), with 553 participants. Anti-TNF dose reduction probably slightly increases the proportion of participants with minimal radiographic progression (mSvdH > 0.5) after 52 weeks (RR 1.22, 95% CI 0.76 to 1.95). [Analysis 1.4](#)
- Function: Of the six studies included for this comparison (1148 participants), two studies, [Smolen 2013 \(PRESERVE\)](#) and [Ibrahim 2017 \(OPTTIRA\)](#), with 501 participants provided data on this outcome. Anti-TNF dose reduction does not result in an important deterioration in function (HAQ Disability Index (HAQ-DI)) after 26 to 52 weeks' follow-up (MD 0.09, 95% CI 0.00 to 0.19). We pooled data from the two dose reduction arms in the study by [Ibrahim 2017 \(OPTTIRA\)](#) for this outcome. [Analysis 1.5](#)

- Number of serious adverse events: Of the six studies included for this comparison (1148 participants), five studies with 1084 participants provided data on this outcome ([Ibrahim 2017 \(OPTTIRA\)](#); [Raffaener 2015](#); [Smolen 2013 \(PRESERVE\)](#); [van Vollenhoven 2016 \(DOSERA\)](#); [Weinblatt 2017 \(C-EARLY\)](#)). Anti-TNF dose reduction may cause little or no difference in the number of serious adverse events after 26 to 52 weeks' follow-up (RR 1.09, 95% CI 0.65 to 1.82). We pooled data from the two dose reduction arms in the study by [Ibrahim 2017 \(OPTTIRA\)](#) for this outcome. [Analysis 1.6](#)
- Withdrawals due to adverse events: Of the six studies included for this comparison (1148 participants), three studies with 937 participants provided data on this outcome ([Raffaener 2015](#); [Smolen 2013 \(PRESERVE\)](#); [Weinblatt 2017 \(C-EARLY\)](#)). Anti-TNF dose reduction may cause little or no difference in the number of withdrawals due to adverse events after 52 weeks (RR 1.07, 95% CI 0.51 to 2.24). [Analysis 1.7](#)

Minor outcomes

- Proportion of participants with a flare: Of the six included studies for this comparison (1148 participants), three studies with 357 participants provided data on this outcome ([Ibrahim 2017 \(OPTTIRA\)](#); [van Vollenhoven 2016 \(DOSERA\)](#); [Weinblatt 2017 \(C-EARLY\)](#)). The three studies used different criteria for flare. [Ibrahim 2017 \(OPTTIRA\)](#) defined a flare as an increase in DAS28 scores ≥ 0.6 resulting in a DAS28 > 3.2 together with an increase in the swollen joint count; both had to be present on two occasions at least one week apart. An increase in DAS28 score ≥ 1.2 resulting in DAS28 > 3.2 was defined as flare irrespective of changes in swollen joints. [van Vollenhoven 2016 \(DOSERA\)](#) defined a flare as (a) a DAS28-ESR > 5.1; (b) a DAS28-ESR > 3.2 and an increase ≥ 1.2 from baseline; (c) DAS28-ESR > 3.2 and an increase in DAS28 ≥ 0.6 from baseline on two consecutive visits at least one to three weeks apart; or (d) disease progression as determined by either the investigator or disease flare as experienced by the participant. [Weinblatt 2017 \(C-EARLY\)](#) stated that participants reporting a flare also had to meet the following three criteria at two consecutive visits two weeks apart: 1) an increase in the DAS28-ESR of ≥ 0.6 above the DAS28-ESR at week 52; 2) a DAS28-ESR of > 3.2; and 3) in the investigator's judgement, an increase in the participant's RA activity. Furthermore, [Ibrahim 2017 \(OPTTIRA\)](#) included two intervention groups: 33% and 66% dose reduction. Due to this heterogeneity data were not pooled. The studies did not show a difference between the anti-TNF dose reduction group(s) and the continuation group; risk ratios were found between 0.29 and 1.79.
- Quality of life: Of the six studies included for this comparison (1148 participants), two studies, [Smolen 2013 \(PRESERVE\)](#) and [Ibrahim 2017 \(OPTTIRA\)](#), with 501 participants provided data on this outcome. Anti-TNF dose reduction resulted in little or no difference in mean EQ-5D after 26 to 52 weeks' follow-up (MD 0.00, 95% CI -0.04 to 0.03). We pooled data from the two dose reduction arms in the study by [Ibrahim 2017 \(OPTTIRA\)](#) for this outcome.
- Costs: None of the six included studies provided data on this outcome.
- Incremental cost-effectiveness ratio: None of the six included studies provided data on this outcome.

- Time to flare: Of the six studies included for this comparison (1148 participants), one study with 50 participants provided data on this outcome ([van Vollenhoven 2016 \(DOSERA\)](#)). Median time to failure was 48 weeks in the etanercept 50 mg/week continuation group and 36 weeks in the etanercept 25 mg/week dose reduction group, but no SDs were available.
- Change in other medication: None of the six included studies reported data on this outcome.

Anti-TNF discontinuation versus anti-TNF continuation

See [Summary of findings 2](#).

Major outcomes

- Mean disease activity: Of the eight studies (2111 participants) included for this comparison, three studies, [Smolen 2013 \(PRESERVE\)](#), [Ghiti Moghadam 2016 \(POEET\)](#), and [Pavelka 2017](#), with 402, 692, and 331 participants, respectively, provided data on mean disease activity. We pooled data from [Pavelka 2017](#) and [Smolen 2013 \(PRESERVE\)](#). Anti-TNF discontinuation probably increases the mean disease activity score (DAS28) slightly after 28 to 52 weeks' follow-up (MD 0.96, 95% CI 0.67 to 1.25). We considered the study by [Ghiti Moghadam 2016 \(POEET\)](#) to be different since participants could return to standard dose in case of flare, and no LOCF was described, therefore the results will reflect the effect of a discontinuation and restarting strategy. This strategy resulted in a small, possibly unimportant increase in mean disease activity score after 52 weeks (MD 0.29, 95% CI 0.14 to 0.44). [Analysis 2.1](#)
- Proportion persistent remission: Of the eight studies reporting on this comparison (2111 participants), six studies with 1188 participants provided data on the proportion of participants with persistent remission ([Chatzidionysiou 2016 \(ADMIRE\)](#); [Pavelka 2017](#); [Smolen 2013 \(PRESERVE\)](#); [Smolen 2014 \(OPTIMA\)](#); [Weinblatt 2017 \(C-EARLY\)](#); [Yamanaka 2016 \(ENCOURAGE\)](#)). We were unable to pool data due to heterogeneity. The RR after 28 to 52 weeks varied between 0.16 in [Chatzidionysiou 2016 \(ADMIRE\)](#) and 0.77 in [Smolen 2014 \(OPTIMA\)](#) and [Weinblatt 2017 \(C-EARLY\)](#). The absolute risk difference varied between 15% fewer in [Weinblatt 2017 \(C-EARLY\)](#) and 68% fewer in [Chatzidionysiou 2016 \(ADMIRE\)](#). [Analysis 2.2](#)
- Proportion of participants that switched to another biologic due to persistent loss of response (refractory to re-installment of the tapered anti-TNF in the intervention group): None of the eight included studies provided data on this outcome. [Smolen 2013 \(PRESERVE\)](#) reported that no attempt was made to recapture low disease activity by reintroducing etanercept in participants whose condition had deteriorated after etanercept withdrawal, raising some ethical issues in our view.
- Proportion of participants with minimal radiographic progression: Of the eight studies (2111 participants) included for this comparison, three studies, [Smolen 2013 \(PRESERVE\)](#), [Weinblatt 2017 \(C-EARLY\)](#), and [Yamanaka 2016 \(ENCOURAGE\)](#), with 549 participants provided data on this outcome. The meta-analysis showed that anti-TNF discontinuation increases the proportion of participants with minimal radiographic progression > 0.5 mSvdH point after 52 weeks (RR 1.69, 95% CI 1.10 to 2.59). [Analysis 2.3](#)
- Function: Of the eight studies (2111 participants) included for this comparison, four studies with 1498 participants provided data on this outcome ([Ghiti Moghadam 2016 \(POEET\)](#); [Pavelka](#)

[2017](#); [Smolen 2013 \(PRESERVE\)](#); [Smolen 2014 \(OPTIMA\)](#)). The results showed that anti-TNF discontinuation may lead to a slight deterioration in function after 28 to 52 weeks' follow-up (MD 0.18, 95% CI 0.05 to 0.31). [Analysis 2.4](#)

- Number of serious adverse events: All eight studies included for this comparison provided data on this outcome, with 2095 participants. Due to the very low certainty of the evidence and imprecision of the results, it is uncertain whether anti-TNF discontinuation influences the number of serious adverse events after 28 to 52 weeks (RR 1.29, 95% CI 0.82 to 2.03). [Analysis 2.5](#)
- Withdrawals due to adverse events: Of the eight studies (2111 participants) included for this comparison, four studies with 1116 participants provided data on this outcome ([Pavelka 2017](#); [Smolen 2013 \(PRESERVE\)](#); [Smolen 2014 \(OPTIMA\)](#); [Weinblatt 2017 \(C-EARLY\)](#)). Anti-TNF discontinuation probably slightly increases the number of withdrawals due to adverse events after 28 to 52 weeks (RR 1.46, 95% CI 0.75 to 2.84). [Analysis 2.6](#)

Minor outcomes

- Proportion of participants with a flare: Of the eight studies (2111 participants) included for this comparison, five studies provided data on this outcome ([Chatzidionysiou 2016 \(ADMIRE\)](#); [Ghiti Moghadam 2016 \(POEET\)](#); [Pavelka 2017](#); [van Vollenhoven 2016 \(DOSERA\)](#); [Weinblatt 2017 \(C-EARLY\)](#)), with 31, 46, 331, 817, and 163 participants, respectively. We did not pool data because of clinical and statistical heterogeneity. The study by [Chatzidionysiou 2016 \(ADMIRE\)](#) defined flare as DAS28 $\geq$ 2.6 or an increase of more than 1.2 from baseline. After 28 weeks, proportion of flare in the adalimumab discontinuation group was not statistically significantly different from that in the adalimumab continuation group (RR 1.6, 95% CI 0.92 to 2.78). [van Vollenhoven 2016 \(DOSERA\)](#) defined flare as (a) a DAS28-ESR > 5.1; (b) a DAS28-ESR > 3.2 and an increase $\geq$ 1.2 from baseline; (c) DAS28-ESR > 3.2 and an increase in DAS28 $\geq$ 0.6 from baseline on two consecutive visits at least one to three weeks apart; or (d) disease progression as determined by either the investigator or disease flare as experienced by the participant. After 48 weeks' follow-up, the proportion of participants with flare was higher in the discontinuation group compared to the continuation group (RR 1.82, 95% CI 1.15 to 2.87). [Ghiti Moghadam 2016 \(POEET\)](#), [Pavelka 2017](#), and [Weinblatt 2017 \(C-EARLY\)](#) used the same criterion for flare: DAS28 $\geq$ 3.2 and an increase of 0.6 or more. [Ghiti Moghadam 2016 \(POEET\)](#) found that the proportion of participants with flare was higher in the anti-TNF discontinuation group than in the continuation group (after 24 weeks RR 3.37, 95% CI 2.42 to 4.70; after 52 weeks RR 2.82, 95% CI 2.17 to 3.65). [Pavelka 2017](#) found a higher proportion of flare in the participants that stopped anti-TNF after 28 weeks (RR 1.53, 95% CI 1.30 to 1.81). [Weinblatt 2017 \(C-EARLY\)](#) found no difference in the proportion of participants with flare between the anti-TNF discontinuation group and the continuation group (RR 1.52, 95% CI 0.61 to 3.80).
- Quality of life: Of the eight studies (2111 participants) included for this comparison, two studies, [Smolen 2013 \(PRESERVE\)](#) and [Pavelka 2017](#), with 733 participants provided data on this outcome. Anti-TNF discontinuation led to a deterioration in quality of life after 28 to 52 weeks (MD -0.10, 95% CI -0.13 to -0.07).
- Costs: None of the eight included studies provided data on direct or indirect costs.

- Incremental cost-effectiveness ratio: None of the eight included studies provided data on this outcome.
- Time to flare: Of the eight studies included for this comparison (2111 participants), two studies, [Chatzidionysiou 2016 \(ADMIRE\)](#) and [van Vollenhoven 2016 \(DOSERA\)](#), provided data on this outcome, with 31 and 46 participants, respectively. These two studies used different flare/failure criteria. [Chatzidionysiou 2016 \(ADMIRE\)](#) reported that survival curves suggested higher flare-free survival over time in participants randomised to continue treatment with adalimumab, but that the difference did not reach statistical significance ($P = 0.07$). The study by [van Vollenhoven 2016 \(DOSERA\)](#) reported a median time to failure of 48 weeks in the etanercept 50 mg/week continuation group and six weeks in the etanercept discontinuation (placebo) group, but no SDs were available.
- Change in other medication: None of the eight included studies provided data on change in other medication.

Anti-TNF disease activity-guided dose tapering versus anti-TNF continuation

See [Summary of findings 3](#).

Primary outcomes

- Mean disease activity: All three studies included in this comparison reported on this outcome, with 357 participants ([Bejerano 2016 \(OPTIBIO\)](#) (abstract only); [Fautrel 2016 \(STRASS\)](#); [van Herwaarden 2015 \(DRESS\)](#)). Anti-TNF disease activity-guided dose tapering may result in little or no difference in mean disease activity score (MD 0.25, 95% CI -0.17 to 0.67). [Analysis 3.1](#)
- Proportion persistent remission: Of the three studies included in this comparison (365 participants), one study with 180 participants reported on this outcome ([van Herwaarden 2015 \(DRESS\)](#)). Anti-TNF disease activity-guided dose tapering resulted in little or no difference in the proportion of participants with persistent remission ($\text{DAS28} < 2.6$) after 18 months (RR 0.89, 95% CI 0.75 to 1.06). [Analysis 3.2](#)
- Proportion of participants that switched to another biologic due to persistent loss of response (refractory to re-instatement of the tapered anti-TNF in the intervention group): Of the three studies included in this comparison (365 participants), two studies, [Fautrel 2016 \(STRASS\)](#) and [van Herwaarden 2015 \(DRESS\)](#), with 317 participants reported on this outcome. Anti-TNF disease activity-guided dose tapering may result in little or no difference in the proportion of participants that switch to another biologic after 18 months (RR 0.62, 95% CI 0.25 to 1.54). [Analysis 3.3](#)
- Proportion of participants with minimal radiographic progression: Of the three studies included in this comparison (365 participants), two studies, [Fautrel 2016 \(STRASS\)](#) and [van Herwaarden 2015 \(DRESS\)](#), with 312 participants reported on this outcome. Although [Fautrel 2016 \(STRASS\)](#) used a cut-off value of 1 point and [van Herwaarden 2015 \(DRESS\)](#) a cut-off value of 0.5 point mSvdH score, data could be pooled. Anti-TNF disease activity-guided dose tapering may slightly increase the proportion of participants with minimal radiographic progression ($\text{mSvdH} > 0.5$ or > 1.0) after 18 months (RR 1.45, 95% CI 0.77 to 2.73). [Analysis 3.4](#)
- Function: Of the three studies included in this comparison (365 participants), one study with 123 participants reported on this outcome ([Fautrel 2016 \(STRASS\)](#)). Anti-TNF disease activity-guided dose tapering probably leads to a slight deterioration in

function after 18 months (MD 0.20, 95% CI -0.02 to 0.42). [Analysis 3.5](#)

- Number of serious adverse events: Of the three studies included in this comparison (365 participants), two studies, [Fautrel 2016 \(STRASS\)](#) and [van Herwaarden 2015 \(DRESS\)](#), reported on this outcome, with 137 and 180 participants, respectively. Due to the very low certainty of the evidence and imprecision, it is uncertain whether anti-TNF disease activity-guided dose tapering influences the number of serious adverse events after 18 months. [Analysis 3.6](#)
- Withdrawals due to adverse events: None of the three included studies provided data on this outcome.

Minor outcomes

- Proportion of participants with a flare: All three studies (365 participants) included in this comparison reported on this outcome. The studies used different criteria for flare. In [Bejerano 2016 \(OPTIBIO\)](#) (abstract only), participants had a flare if $\text{DAS28} > 2.6$; $\text{SDAI} > 5$; or when ACR/EULAR criteria were not fulfilled. [Bejerano 2016 \(OPTIBIO\)](#) (abstract only) found no difference in the proportion of participants with a flare between the anti-TNF disease activity-guided dose tapering group and the anti-TNF continuation group after 24, 48, 72, and 96 weeks' follow-up (24 weeks: RR 3.25, 95% CI 0.14 to 76.01; 48 weeks: RR 1.09, 95% CI 0.24 to 4.86; 72 weeks: RR 1.09, 95% CI 0.36 to 3.27; 96 weeks: RR 1.27, 95% CI 0.50 to 3.22). [Fautrel 2016 \(STRASS\)](#) defined flare as $\text{DAS28} > 2.6$ with an increase in DAS28 of > 0.6 . They reported a higher proportion of participants with flare in the anti-TNF disease activity-guided dose tapering group compared to the anti-TNF continuation group after 18 months' follow-up (RR 1.64, 95% CI 1.24 to 2.18). In [van Herwaarden 2015 \(DRESS\)](#), participants had a flare if DAS28 increased > 1.2 , or if DAS28 increased > 0.6 and current DAS28 was ≥ 3.2 . The authors reported a higher proportion of participants with flare in the anti-TNF disease activity-guided dose tapering group compared to the anti-TNF continuation group after 9 and 18 months (9 months: RR 2.68, 95% CI 1.58 to 4.56; 18 months: RR 2.68, 95% CI 1.74 to 4.13). [van Herwaarden 2015 \(DRESS\)](#) found no difference in major flares (duration > 3 months) after 9 and 18 months (9 months: RR 1.71, 95% CI 0.37 to 7.96; 18 months: RR 1.22, 95% CI 0.50 to 2.98).
- Quality of life: Of the three studies included in this comparison (365 participants), two studies, [Fautrel 2016 \(STRASS\)](#) and [van Herwaarden 2015 \(DRESS\)](#), reported on this outcome, with 98 and 180 participants, respectively. Both studies reported mean quality-adjusted life years (QALYs) of the 18-month study period. [Fautrel 2016 \(STRASS\)](#) found that the anti-TNF disease activity-guided dose tapering group gained fewer QALYs during the 18-month study period than the anti-TNF continuation group (MD -0.158). No confidence intervals were available. [van Herwaarden 2015 \(DRESS\)](#) reported no difference between the anti-TNF disease activity-guided dose tapering group versus the anti-TNF continuation group (MD -0.02, 95% percentiles -0.06 to 0.02).
- Costs: Of the three studies included in this comparison (365 participants), two studies, [Fautrel 2016 \(STRASS\)](#) and [van Herwaarden 2015 \(DRESS\)](#), reported on this outcome, with 98 and 180 participants, respectively. Both studies reported lower costs in the anti-TNF disease activity-guided dose tapering group compared to the anti-TNF continuation group after 18 months' follow-up ([Fautrel 2016 \(STRASS\)](#): MD EUR -8440.

No confidence intervals were available. [van Herwaarden 2015 \(DRESS\)](#): MD EUR -9051, 95% percentiles -10,278 to -7731 (rectification submitted)).

- **Decremental cost-effectiveness ratio:** Of the three studies included in this comparison (365 participants), two studies, [Fautrel 2016 \(STRASS\)](#) and [van Herwaarden 2015 \(DRESS\)](#), reported on this outcome, with 98 and 180 participants, respectively. [Fautrel 2016 \(STRASS\)](#) reported a decremental cost-effectiveness ratio (DCER) of EUR 53,417 per QALY loss. [van Herwaarden 2015 \(DRESS\)](#) reported a DCER of EUR 379,433 per QALY loss (rectification submitted).
- **Time to flare:** None of the three included studies reported data on this outcome.
- **Change in other medication:** Of the three studies included in this comparison (365 participants), one study with 180 participants reported on this outcome ([van Herwaarden 2015 \(DRESS\)](#)). No difference was found between the anti-TNF disease activity-guided dose tapering group and the anti-TNF continuation group after 18 months concerning use of intramuscular or intra-articular glucocorticosteroids (RR 1.50, 95% CI 0.89 to 2.51); use of oral glucocorticosteroids (RR 0.65, 95% CI 0.24 to 1.79); DMARD initiation or dose escalation (RR 3.90, 95% CI 0.93 to 16.41); and use of a DMARD (RR 0.88, 95% CI 0.71 to 1.10). The proportion of participants that reduced the dose of their DMARD or discontinued the DMARD after 18 months' follow-up was lower in the anti-TNF disease activity-guided dose tapering group compared to the anti-TNF continuation group (RR 0.37, 95% CI 0.19 to 0.72).

Subgroup and sensitivity analyses

We planned to perform a subgroup analysis as described in the [Subgroup analysis and investigation of heterogeneity](#) section. However, because of the small number of included studies, analyses were not informative.

We also planned to perform sensitivity analyses as described in the [Sensitivity analysis](#) section. However, because of the small number of included studies, analyses were not informative.

DISCUSSION

This is the first update of the original Cochrane Review first published in 2014. We identified eight new studies for inclusion in this update and additional data on old studies, which changed some results. We retrospectively excluded one study that had been included in the original review. Our main conclusions remained largely the same.

Summary of main results

This systematic review summarises evidence from 14 studies (13 RCTs and one CCT) of down-titration of anti-TNF agents in people with RA with low disease activity. We considered three down-titration strategies to be sufficiently different to warrant separate reviewing: (1) anti-TNF dose reduction, (2) anti-TNF discontinuation, and (3) anti-TNF disease activity-guided dose tapering. We presented the available data on these strategies separately.

Anti-TNF dose reduction compared with anti-TNF continuation

Six studies (three on etanercept, one on etanercept and adalimumab, one on certolizumab pegol, and one on all anti-

TNF agents) reported data on fixed anti-TNF dose reduction compared with anti-TNF continuation. After pooling of data where possible, we can conclude that anti-TNF dose reduction leads to little or no difference in mean disease activity, the proportion of participants with persistent remission, number of serious adverse events and withdrawals due to adverse events compared to continuation. Also, anti-TNF dose reduction does not result in an important deterioration in function but probably slightly increases the proportion of participants with minimal radiographic damage. Next to this, anti-TNF dose reduction may slightly reduce the proportion of participants switched to another biologic. We found no data on important outcomes like cost-effectiveness.

Anti-TNF discontinuation compared with anti-TNF continuation

Eight RCTs reported data on anti-TNF discontinuation compared with anti-TNF continuation for all anti-TNF agents, but mainly adalimumab and etanercept. Different types of outcome measures were reported, and marked heterogeneity was present. The results showed that anti-TNF discontinuation probably increases the mean disease activity score slightly, and that the risk ratio of persistent remission lies between 0.16 and 0.77 (data not pooled). Anti-TNF discontinuation increases the proportion participants with minimal radiographic progression of > 0.5 mSvdH point per year and may lead to a slight deterioration in function and probably slightly increases the number of withdrawals due to adverse events. It is uncertain whether anti-TNF discontinuation influences the number of serious adverse events due to very low-certainty evidence. Again, we found no data on cost-effectiveness.

Anti-TNF disease activity-guided dose tapering compared with anti-TNF continuation

Three studies (all anti-TNF agents, but again mostly etanercept and adalimumab) compared disease activity-guided anti-TNF dose tapering with anti-TNF continuation. Anti-TNF disease activity-guided dose tapering may result in little or no difference in mean disease activity score and the proportion of participants switched to another biologic. Furthermore, anti-TNF disease activity-guided dose tapering results in little or no difference in the proportion of participants with persistent remission. Next to this, tapering may result in a slight increase in the proportion of participants with minimal radiographic progression and probably causes a slight deterioration in function. It is uncertain whether anti-TNF disease activity-guided dose tapering influences the number of serious adverse events due to very low-certainty evidence. No data were available on withdrawals due to adverse events. In the two studies that reported on cost-effectiveness, costs were significantly lower, and decremental cost-effectiveness ratios were found to be between EUR 53,000 and EUR 379,000 per QALY lost.

Overall completeness and applicability of evidence

The number of controlled studies on this matter is increasing, although they are mostly limited to adalimumab and etanercept. Data were available on all three strategies, although discontinuation was studied most extensively. We considered the included studies to be quite comparable clinically and decided to accept some clinical heterogeneity in order to obtain more precision. One study was reported as abstract only ([Bejerano 2016 \(OPTIBIO\)](#)). Excluding the results reported in this abstract did not change our conclusions.

An important issue remains that the superiority design of the fixed-dose reduction or discontinuation studies hampers interpretability and generalisability to clinical practice. With regard to the first issue, these studies do provide point estimates about between-group differences in important outcomes between the strategies, but they do not compare these point estimates and their confidence intervals with a prespecified relevant non-inferiority margin. Consequently, independent of whether superiority tests demonstrate a significant difference, the interpretation has to be made post hoc whether this (non-)significant difference is relevant compared to a non-inferiority claim, although this issue might become less important in meta-analyses where sample sizes are large. Next to this, the preferred method of analysis for non-inferiority trials is per protocol, while an intention-to-treat analysis is favoured for superiority trials. This hampers comparison of studies with different approaches. With regard to generalisability, it seems important to mention that for patients and clinicians alike, the outcome of fixed-dose reduction or discontinuation is valuable to know. However, it would be much more valuable to know whether disease activity-guided dose reduction and discontinuation is non-inferior with regard to important outcomes, as this supports shared decision making with patients.

The participants included in these studies vary from early RA with short treatment duration and no prior DMARD treatment to longstanding, established RA patients who have been treated for a long time with several other DMARDs, and also include patients with and without concomitant DMARD. This increases generalisability, although it also has been shown that no clinical patient-, disease-, or treatment-related variable is clearly an effect modifier for the chance of successful dose reduction or discontinuation (Tweehuysen 2017).

With regard to outcome measures, we noted that domains are often missing, such as functioning, radiographic damage progression, or cost (effectiveness). Also, when a domain is included as an outcome, there is marked heterogeneity in the way the outcome is assessed, leaving much room for improvement of outcome standardisation.

Quality of the evidence

Anti-TNF dose reduction compared with anti-TNF continuation

Using the GRADE approach, we assessed the overall certainty of evidence as high for two of the seven 'Summary of findings' outcomes in the anti-TNF dose reduction versus continuation comparison: mean disease activity and function. We assessed the certainty of the evidence for the proportion of participants with minimal radiographic progression as moderate because of imprecision. We assessed the certainty of the evidence for the remaining four main outcomes as low. For the proportion of participants with persistent remission, this was the result of heterogeneity (downgraded two times). For the proportion of participants that switched to another biologic, this was due to concern about risk of bias in the reporting study (downgraded two times). We downgraded the evidence on the number of serious adverse events and the number of withdrawals due to adverse events one level for risk of bias and one level for imprecision.

Anti-TNF discontinuation compared with anti-TNF continuation

The overall certainty of the evidence was high for one of the seven 'Summary of findings' outcomes in the anti-TNF discontinuation versus continuation comparison: proportion of participants with minimal radiographic progression. We assessed the certainty of the evidence for the outcomes mean disease activity and withdrawals due to adverse events as moderate. We performed a subanalysis for the outcome mean disease activity, since heterogeneity was present between the studies that could be explained by the study characteristics. We downgraded the evidence on mean disease activity for discontinuation without restarting or with restarting and with LOCF analysis one level because of imprecision. We downgraded the evidence for mean disease activity with restarting and without LOCF analysis one level due to concerns about risk of bias. We downgraded the evidence on withdrawals one level because of imprecision. We assessed the certainty of the evidence on the proportion of participants with persistent remission and function as low because of substantial heterogeneity (downgraded two levels). Lastly, we assessed the certainty of the evidence on the number of serious adverse events as very low because of (1) concerns about risk of bias, (2) moderate heterogeneity between effect estimates, and (3) imprecision. The included anti-TNF discontinuation studies did not report the proportion of participants that switched to another biologic.

Anti-TNF disease activity-guided dose tapering compared with anti-TNF continuation

The certainty of the evidence for the outcome proportion of participants with persistent remission was high in the anti-TNF disease activity-guided dose tapering versus continuation comparison. The data came from one study with a low risk of bias, and there were no other reasons to downgrade the certainty of the evidence. We assessed the certainty of the evidence on function as moderate because of imprecision. We assessed the certainty of the evidence on mean disease activity as low because of heterogeneity (downgraded two levels). We graded the certainty of the evidence on the proportion of participants that switched to another biologic as low because of imprecision (downgraded two levels). We graded the certainty of the evidence on the proportion of participants with minimal radiographic progression as low due to heterogeneity and imprecision. We assessed the certainty of the evidence for serious adverse events as very low because of substantial heterogeneity (downgraded two levels) and imprecision (downgraded two levels). The included studies for this comparison did not report on withdrawals due to adverse events.

Potential biases in the review process

Two review authors independently reviewed all titles and abstracts, extracted data, and performed bias and quality assessment. Consequently, errors in extraction have been minimised. Risk of bias could not be completely assessed for some studies due to restricted information despite efforts to obtain additional information from study authors. Post-hoc decisions had to be made regarding the presentation and pooling of outcomes (e.g. time of follow-up, threshold values) which could have had implications on the results. The authors have tried to be as transparent as possible about choices that have been made, although they remain subjective.

Agreements and disagreements with other studies or reviews

A few other systematic reviews have examined anti-TNF down-titration, although the focus differed to some extent (Galvão 2016; Kuijper 2015; Navarro-Millán 2013; Yoshida 2014). Galvão 2016 focused on discontinuation of biological DMARDs, and Kuijper 2015 on discontinuation of biologic and synthetic DMARDs. Navarro-Millán 2013 investigated discontinuation of anti-TNF agents specifically. The results of these reviews are comparable to the findings in our review. The systematic review by Yoshida 2014 looked into the design and failure definitions in anti-TNF discontinuation studies. The review authors concluded that heterogeneity can be seen across studies in both study design and failure definition. This is consistent with the findings reported in our review.

AUTHORS' CONCLUSIONS

Implications for practice

This review of the data has several implications for clinical practice with regard to the three different strategies studied: dose reduction, discontinuation, and disease activity-guided tapering of anti-tumour necrosis factor (anti-TNF).

Firstly, fixed-dose reduction of anti-TNF (especially etanercept) in people with rheumatoid arthritis (RA) with at least three to 12 months of low disease activity is comparable with continuing the standard dose with regard to mean disease activity, the proportion of participants remaining in remission, and mean function. Consequently, an attempt to reduce the dose (or increase the dosage interval) in people with low disease activity with RA on full-dose anti-TNF seems sensible in clinical practice. It should be mentioned, however, that all treatment changes in RA should be done carefully on a background of 'treat to target', that is guided by disease activity. Dose reduction probably slightly increases the proportion of participants with minimal radiographic progression. Anti-TNF dose reduction may cause little or no difference in number of serious adverse events and withdrawals due to adverse events, although certainty of evidence was low. This review showed that slightly fewer participants undergoing anti-TNF dose reduction may switch to another biologic disease-modifying antirheumatic drug (bDMARD) compared to continuation. An explanation for this might be that temporary disease flares (inherent to the disease) are treated in the dose reduction group by increasing the dose, while in the continuation group patients are switched to another biologic.

Secondly, this review shows that anti-TNF discontinuation (without disease activity-guided restarting of treatment) is an inferior strategy compared with continuation of anti-TNF in terms of disease control (mean disease activity and the proportion of participants remaining in remission), minimal radiographic damage, function and the number of withdrawals due to adverse events. Although a sizeable proportion of patients can stop the anti-TNF without deterioration, the large majority of patients who cannot discontinue the drug are harmed if the treatment is not reinstated. The effect of discontinuation on the number of serious adverse events remains uncertain. However, given the current evidence, discontinuation should not be attempted without regular assessment of disease activity, setting a treatment goal, and reinstatement of treatment when necessary.

The abovementioned findings converge finally in the evidence on the disease activity-guided dose tapering strategy. This review shows that disease activity-guided tapering is comparable to continuation with regard to mean disease activity, the proportion of participants remaining in remission and the proportion of participants switched to another biologic. Tapering may result in a slight increase in the proportion of participants with radiographic progression and probably leads to a slight deterioration in function. The effect of disease activity-guided dose tapering of anti-TNF on the number of serious adverse events and withdrawals due to adverse events could not be determined with certainty. This evidence is similar to that for fixed-dose reduction. Because disease activity-guided dose tapering provides the opportunity to find the lowest effective dose for each individual patient and to discontinue treatment as the final step of the tapering process, this may be the most cost-effective and feasible approach in clinical practice. Since uncertainty remains on several important outcome measures, more data on, for example, radiographic damage progression, function, (serious) adverse events, and costs are warranted.

With respect to interpretation, it should be noted that the burden of proof in this case does not lie solely with dose reduction or stopping compared with continued use. To our knowledge, no controlled data are available on anti-TNF continued use after week 52, including all registration studies. Consequently, there remains equipoise on what is the best strategy after one year of treatment with anti-TNF.

Implications for research

Our review highlights what is already known about anti-TNF down-titration in people with low RA disease activity, and on the other hand identifies gaps in our knowledge. Here we would like to mention a number of aspects that could be targeted in future studies. Of note, most of these points are currently being addressed in several ongoing studies.

- The design selected for studies comparing an anti-TNF down-titration strategy versus an anti-TNF continuation strategy should include a non-inferiority approach instead of the classical superiority analyses, as the aim is to maintain and not improve clinical outcomes, while minimising the amount of treatment that is needed. Superiority analyses can be reserved for domains where superiority can be expected, such as drug use, infections, and costs. As guidelines for performing a systematic review on non-inferiority studies are absent, development of such guidelines would be helpful.
- The intervention should include disease activity-guided dose tapering or stopping of the anti-TNF agent using tight control/treat to target instead of fixed-dose adaptation or stopping, as the former is more compatible with clinical practice.
- The domain in which an intervention should be non-inferior is long-term RA disease control. Although temporary flaring will inevitably be seen more often in the trial-and-error dose-tapering arm, both the incidence of more severe or prolonged flaring and mean disease activity at study end should be comparable.
- Consequently, in addition to mean disease activity at study end, cumulative incidence of a validated RA flare criterion could be used. Use of (one of) validated Outcome Measures in Rheumatology Clinical Trials (OMERACT) disease activity score in 28 joints (DAS28)-based flare criteria should be considered

(van der Maas 2013 Flare). Use of a validated flare criterion also increases standardisation for future meta-analyses.

- Other outcomes besides disease activity that should be included are cost, quality of life, cost-effectiveness, and (long-term) safety, because these constitute the reason why down-titration is contemplated in the first place.
- The drugs that are studied should preferably also include other anti-TNF agents like certolizumab pegol, golimumab, and infliximab.
- Prediction of (un)successful dose tapering would perhaps further improve outcomes of individualised disease activity-guided dose tapering, and prediction modelling should be considered, using, for example, genetics, imaging, biomarkers, and drug levels. Possible gains when using a good prediction rule include (1) prevention of unnecessary flaring in patients

that cannot be dose reduced; and (2) prevention of months of slow dose tapering in patients that can be stopped directly.

- Finally, although outside the scope of this review, efforts should be (and already are) directed toward other non-anti-TNF biologicals (abatacept, tocilizumab) and toward other inflammatory diseases in which biologicals are used, both within rheumatology (ankylosing spondylitis, psoriatic arthritis) and within other medical specialties (gastroenterology, dermatology).

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Bejerano 2016 (OPTIBIO)

Methods	Open, randomised and controlled study in a hospital in Spain
Participants	Inclusion criteria: <ul style="list-style-type: none"> RA treated with anti-TNF therapies (etanercept, infliximab, adalimumab, certolizumab, golimumab), tocilizumab and abatacept

Down-titration and discontinuation strategies of tumour necrosis factor-blocking agents for rheumatoid arthritis in patients with low disease activity (Review)

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Bejerano 2016 (OPTIBIO) (Continued)

- in clinical remission (DAS28 < 2.6 or SDAI < 5 or ACR/EULAR 2011 criteria) at least 6 months followed in Third level Hospital Rheumatology Department

Exclusion criteria: none described

Baseline characteristics: not reported

Interventions	<p>Participants are assigned to 2 groups randomly:</p> <ul style="list-style-type: none"> • Intervention group: according to a standardised protocol of dose reduction of biological therapies (n = 32, n = 23 for anti-TNF) • Control group: according to standard dose regimen (n = 34, n = 25 for anti-TNF)
Outcomes	<p>Primary endpoint is to evaluate the proportion of patients that after 1 year are maintained in clinical remission with a dose reduction treatment regimen of biological therapy in people with RA, and to evaluate if the proportion of participants in remission with new regimen dose of treatment is not inferior to participants in remission with standard dose regimen.</p> <p>Analyses: ITT</p>
Notes	<p>Acronym: OPTIBIO</p> <p>At time of review, study presented in abstract form only (preliminary results).</p> <p>EudraCT: 2012-004482-40</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described in this abstract
Allocation concealment (selection bias)	Unclear risk	Not described in this abstract
Blinding of participants and personnel (performance bias) Subjective outcomes	High risk	"Open-label study"
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	Open-label study, but outcome not likely to be influenced
Blinding of outcome assessment (detection bias) All outcomes	High risk	"Open-label study"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient reporting of attrition/exclusions to permit judgement of 'low risk' or 'high risk'
Selective reporting (reporting bias)	Unclear risk	Study protocol available. Not all outcome measures described in this abstract.
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists

Chatzidionysiou 2016 (ADMIRE)

Methods	52-week, multicentre, randomised, controlled, open-label pilot study in Sweden
Participants	<p>Inclusion criteria:</p> <ul style="list-style-type: none"> age ≥ 18 years diagnosis of RA based on the 1987 revised ACR classification criteria, positive RF or at least 1 erosion on the radiograph of hands or feet treatment with adalimumab in the approved dose of 40 mg every other week for at least 6 months; concomitant treatment with methotrexate at a dose of at least 10 mg/week for a minimum of 6 months (stable dose for a minimum of 2 months) stable remission according to the DAS28 (DAS28 < 2.6) for at least 3 months based on assessments at study entry = baseline and on at least 1 more occasion 3 to 6 months prior to baseline, documented in patient record or registry concomitant corticosteroids were allowed if the dose was 10 mg/day or less (prednisolone or equivalent) and had been stable for at least 3 months at baseline <p>Baseline characteristics: median age 61 (IQR 53 to 65) years, 65% female, median disease duration 8 (IQR 5 to 16) years, median DAS28 1.9 (IQR 1.55 to 2.39), median number of previous DMARDs 2 (IQR 1 to 3), median number of previous bDMARDs 0 (IQR 0 to 1)</p>
Interventions	<p>People fulfilling the inclusion criteria were randomised in a 1:1 ratio to arm AM (continue with adalimumab and methotrexate) or to arm M (discontinue adalimumab and continue with methotrexate monotherapy) for 52 weeks. Any participant experiencing disease "flare" at any visit could continue in the rescue arm, where adalimumab would be re-instituted. Disease flare was defined as DAS28 ≥ 2.6 or a change in DAS28 (ΔDAS28) > 1.2 from baseline at any time.</p> <ul style="list-style-type: none"> M arm: discontinue adalimumab and continue methotrexate (n = 15) AM arm: continue both adalimumab and methotrexate (n = 16)
Outcomes	<p>Primary outcome: proportion of participants in remission (DAS28 < 2.6) at week 28 in both arms</p> <p>Secondary outcomes:</p> <ul style="list-style-type: none"> Incidence of disease flare (DAS28 ≥ 2.6 or a ΔDAS28 > 1.2 from baseline at any time) Incidence of at least 1 DAS28 ≥ 2.6 from baseline to week 28 Incidence of at least 1 ΔDAS28 > 1.2 from baseline to week 28 Proportion of participants with at least 1 of the following from baseline to week 28: ΔDAS28 > 0.6, DAS28 ≥ 2.6 AND ΔDAS28 > 1.2, DAS28 ≥ 2.6 AND ΔDAS28 > 0.6 Proportion of participants in DAS28 remission at week 52 Flare-free survival during the first 28 weeks Change in functional status (assessed by HAQ) at week 28 Change in radiological status (analysis of radiographic data at week 52) Frequency of remission according to the EULAR/ACR Boolean remission criteria Adverse events <p>Analyses: ITT; non-responder imputation (i.e. "flare" imputed) was performed for participants with no available DAS28 score at week 28 (this included most participants who had a flare in the M arm and who restarted treatment with adalimumab)</p>
Notes	<p>Acronym: ADMIRE</p> <p>Pilot study</p> <p>Funding: AbbVie</p> <p>Disclosures: KC has received consultancy fees and/or speaker honoraria from Pfizer and Roche. CT has received consultancy fees and/or speaker honoraria from AbbVie, Bristol-Myers Squibb, Janssen,</p>

Chatzidionysiou 2016 (ADMIRE) (Continued)

MSD, Pfizer, Roche, Novartis, and UCB, and has received unrestricted research grants from AbbVie, Pfizer, and Roche. KF has received consultancy fees and/or speaker honoraria from AbbVie, Bristol-Myers Squibb, MSD, and Pfizer. RvV has received research support and/or honoraria from AbbVie, Biotest, BMS, GSK, Lilly, Merck, Pfizer, Roche, UCB, and Vertex. MH is an employee of AbbVie.

EudraCT: 2008-004398-16

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described; "The randomization was 4 patients in each block"
Allocation concealment (selection bias)	Low risk	"Use of an independent person and a sealed, opaque envelope system"
Blinding of participants and personnel (performance bias) Subjective outcomes	High risk	"Open-label study"
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	Open-label study, but outcome not likely to be influenced
Blinding of outcome assessment (detection bias) All outcomes	High risk	"Open-label study"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups.
Selective reporting (reporting bias)	Low risk	The study protocol is available, and all of the study's prespecified (primary and secondary) outcomes that are of interest in the review have been reported in the prespecified way.
Other bias	Low risk	The study appears to be free of other sources of bias.

El Miedany 2016

Methods	12-month randomised controlled trial
Participants	<p>Inclusion criteria:</p> <ul style="list-style-type: none"> RA for at least 18 months sustained clinical remission with a DAS28 based on ESR of < 2.6 for at least 6 months. Remission had to be assessed clinically and documented at least at 3 sequential visits covering a screening period of 6 months. stable treatment with csDMARDs (methotrexate, leflunomide, hydroxychloroquine, and sulfasalazine) as well as bDMARD therapy (infliximab, adalimumab, etanercept, golimumab, certolizumab, tocilizumab, or abatacept) without alteration in dose for at least 6 months <p>Exclusion criteria:</p>

El Miedany 2016 (Continued)

- patients receiving rituximab or those taking oral steroids within 12 months prior to screening were excluded from the study

Baseline characteristics: mean (SD) DAS28 group 1: 1.97 (0.4), group 5: 2.2 (0.5); RF+ group 1: 55%, group 5: 56%; ACPA+ group 1: 61%, group 5: 59%

Interventions	<p>Participants were randomised 1:1:1:1:1 to 5 groups (group 1 and 5 of interest for this review):</p> <ul style="list-style-type: none"> Group 1 (n = 32): (tapering) reduced the bDMARDs by 50% whilst continuing to take the full csDMARD(s) therapy dose Group 2 (n = 32): (tapering) reduced the dose of both csDMARD and bDMARD therapy by 50% Group 3 (n = 32): (stop) stop bDMARD therapy whilst reducing csDMARD(s) dose by 50 Group 4 (n = 32): stop both csDMARD and bDMARD therapy Group 5 (n = 32): (control group continuation) kept existing bDMARD as well as csDMARD
Outcomes	<p>Primary endpoint was the maintenance of remission for 12 months. Secondary endpoint was identifying the potential predictors, whether ultrasonographic, clinical, or lab measures, for relapses in patients tapering and/or stopping DMARD(s) and/or biologic therapy.</p> <p>Analyses: ITT</p>
Notes	<p>This study included participants using anti-TNF as well as non-anti-TNF. The authors provided data for the participants using anti-TNF only for this review.</p> <p>Disclosures: none</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) Subjective outcomes	High risk	Blinding not described, however very unlikely due to the absence of a description of placebo treatment
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	Open-label study, but outcome not likely to be influenced
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcome measure assessment was unblinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 1 participant lost to follow-up, in group 1.
Selective reporting (reporting bias)	Unclear risk	No study protocol present, therefore insufficient information to permit judgement of 'low risk' or 'high risk'
Other bias	Low risk	The study appears to be free of other sources of bias.

Fautrel 2016 (STRASS)

Methods	18-month, multicentre randomised controlled equivalence trial in France
Participants	<p>Inclusion criteria:</p> <ul style="list-style-type: none"> • ≥ 18 years old • diagnosis of RA according to the 1987 ACR classification criteria • received subcutaneous injections of etanercept or adalimumab at a standard and stable dosage (i.e. 50 mg weekly for etanercept or 40 mg every other week for adalimumab) for at least 1 year as monotherapy or combined with a stable csDMARD (methotrexate or leflunomide) for at least 6 months • prednisone was allowed if daily doses were stable and at ≤ 5 mg for at least 6 months • patients needed to be in clinical remission according to the DAS28 (i.e. $\text{DAS28} \leq 2.6$) for at least 6 months with no structural damage progression seen on hand and foot X-rays in the year before inclusion according to the treating rheumatologist <p>Exclusion criteria</p> <ul style="list-style-type: none"> • contraindications to TNF-blocker therapy maintenance • prednisone use > 5 mg/day • planned surgical intervention or pregnancy within the 18-month study period • women of childbearing age without efficacious contraception • history of cancer • diagnosis of an autoimmune disorder other than RA • non-affiliation with the French social security system • presence of factors preventing informed consent or protocol adherence (e.g. inability to communicate in the French language, mental incapacity, guardianship) <p>Baseline characteristics: age (mean, SD) 55.6 (11.2) years, female 78%, disease duration 9.5 (8.0) years, 69% rheumatoid factor positive, 78% anti-CCP positive, DAS28 1.8 (0.6), 54% etanercept, 46% adalimumab, number of previous DMARDs 2.7 (1.7), percentage of participants with previous bDMARD treatment 24%</p>
Interventions	<p>Participants were randomised into 1 of 2 arms: maintenance of the subcutaneous injections at the standard full regimen (M-arm) or injections spacing by 50% every 3 months up to complete stop (S-arm). Spacing was reversed to the previous interval in case of relapse, and eventually reattempted after remission was re-achieved.</p> <ul style="list-style-type: none"> • Spacing arm: $n = 64$ • Maintenance arm: $n = 73$
Outcomes	<p>Primary outcome: evolution in RA inflammatory activity over 18 months as measured by the DAS28 every 3 months</p> <p>Secondary outcomes:</p> <ul style="list-style-type: none"> • Evolution of RA inflammatory activity during the 18 months as measured by the DAS44 every 3 months • Evolution of functional ability over 18 months as measured by the HAQ score • Relapse during the 18 months defined as $\text{DAS28} > 2.6$ with DAS28 increase > 0.6 since the previous study visit • X-ray damage progression assessed by mSvdH (progression defined as change in mSvdH score > 1) • Safety of the 2 strategies: rate of non-serious and serious adverse events <p>Analyses: primary analysis PP, supplemented by an ITT analysis</p>
Notes	<p>Acronym: STRASS</p> <p>Funding: the trial was conducted under the auspices of the CRI-IMIDIATE clinical research FCRIN network. Institutional support by a grant from the Ministry of Health (PHRC national 2007, AOM 07 127/P</p>

Fautrel 2016 (STRASS) (Continued)

070120), France. The sponsor was the Département à la Recherche Clinique et au Développement, Assistance Publique–Hôpitaux de Paris.

Disclosures: none declared

EudraCT: 2007-004483-41

ClinicalTrials.gov: NCT00780793

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The randomisation list was generated by use of a computer-generated sequence with blocks of variable (2–6) and undisclosed size stratified by centre and TNF-blocker (ie, ETA or ADA)"
Allocation concealment (selection bias)	Low risk	"Treatment allocation was concealed to patients, research staff and clinical staff until randomisation by use of an internet-based randomisation module (Cleanweb, Telemedecine technologies S.A.S, Boulogne-Billancourt, France)."
Blinding of participants and personnel (performance bias) Subjective outcomes	High risk	Open study
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	Open-label study, but outcome not likely to be influenced
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Most important outcome assessments (DAS28 and X-ray) blinded. Other outcomes likely to be influenced.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons for missing outcome data unlikely to be related to true outcome
Selective reporting (reporting bias)	Low risk	The study protocol is available, and all of the study's prespecified (primary and secondary) outcomes that are of interest in the review have been reported in the prespecified way.
Other bias	High risk	Number of included participants was lower than anticipated in the sample size calculation.

Ghiti Moghadam 2016 (POEET)

Methods	12-month, open-label randomised controlled study in the Netherlands
Participants	Inclusion criteria: <ul style="list-style-type: none"> age > 18 years RA diagnosis according to the ACR 1987 criteria, anti-TNF treatment for at least 1 year with stable concomitant csDMARDs use for at least 6 months prior to inclusion patients were in remission or had stable low disease activity for at least 6 months, defined as either DAS28 < 3.2 or the rheumatologist's clinical impression of remission or stable low disease activity in

Ghiti Moghadam 2016 (POEET) (Continued)

combination with a baseline DAS28 < 3.2 and at least 1 CRP level < 10 mg/L in the 6 months prior to inclusion

There were no exclusion criteria.

Participant characteristics: mean (SD): age intervention 60.0 (11.8), control 59.7 (10.6); female: intervention 68%, control 66%; disease duration: intervention 12.0 (8.8), control 11.1 (8.4); previous bDMARD: intervention 13.4%, control 15%

Interventions	<p>Participants were randomised 2:1 to either stop or continue their anti-TNF. All other medications, including csDMARDs, glucocorticoids, and NSAIDs, were left at the discretion of the treating rheumatologist and were continued unchanged as much as possible. In case of flare, defined as a DAS28 $\geq$ 3.2 plus an increase $\geq$ 0.6 compared to the baseline DAS28, anti-TNF treatment could be restarted in the stop group or switched in the continuation group.</p> <ul style="list-style-type: none"> 531 participants stopped their anti-TNF therapy. 286 continued their anti-TNF therapy.
Outcomes	<p>Primary outcome: percentage of participants who experienced a flare (DAS28 $\geq$ 3.2 and DAS28 increase $\geq$ 0.6) of RA during the first year</p> <p>Secondary outcomes:</p> <ul style="list-style-type: none"> Time to flare Change in DAS28 from baseline Change in functional status Number of participants and time to regain remission (DAS28 < 2.6) or low disease activity (DAS28 < 3.2) after restarting anti-TNF (only in stop group) Proportion of participants with (serious) adverse events <p>Analyses: ITT with participants that were correctly included</p>
Notes	<p>Acronym: POEET</p> <p>Dutch trial register: NTR3112</p> <p>Funding: The Netherlands Organization for Health Research and Development (ZonMw)/Government of the Netherlands, Ministry of Health, Welfare and Sport (VWS)</p> <p>Disclosures: none</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Computer block randomization was used to achieve balance in allocation per center."
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) Subjective outcomes	High risk	"Open-label study"
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	Open-label study, but outcome not likely to be influenced

Ghiti Moghadam 2016 (POEET) *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	High risk	"Open-label study"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups.
Selective reporting (reporting bias)	Low risk	The study protocol is available, and all of the study's prespecified (primary and secondary) outcomes that are of interest in the review have been reported in the prespecified way.
Other bias	High risk	The flare criterion differs between the trial register and the final publication, which might have introduced risk of bias.

Ibrahim 2017 (OPTTIRA)

Methods	Open-label, 6-month, multicentre randomised controlled proof-of-principle trial in the United Kingdom
Participants	<p>103 RA patients receiving etanercept or adalimumab plus a DMARD who achieved sustained good responses with DAS28 scores of ≤ 3.2 without increases of > 0.6 during the previous 3 months</p> <p>Baseline characteristics: mean (SD): age 57 (11), female 74%, median disease duration 11.3 (IQR 7.3 to 16.7)</p>
Interventions	<p>Participants were randomised 1:1:2 to:</p> <ul style="list-style-type: none"> dose reduction of 66% ($n = 21$); dose reduction of 33% ($n = 26$); continuation ($n = 50$). <p>Note: in months 6 to 12, controls tapered anti-TNF and experimental groups discontinued anti-TNF (data not included in review).</p>
Outcomes	<p>Primary outcome: time to first flare, defined as an increase in DAS28 scores ≥ 0.6 resulting in a DAS28 > 3.2 together with an increase in the swollen joint count; both had to be present on 2 occasions at least 1 week apart. An increase in DAS28 score ≥ 1.2 resulting in DAS28 > 3.2 was defined as flare irrespective of changes in swollen joints.</p> <p>Secondary outcomes:</p> <ul style="list-style-type: none"> Function: HAQ Quality of life: EQ-5D, SF-36, FACIT Radiographic damage: X-ray, modified Larsen scores DAS28-ESR <p>Analyses: ITT, participants without flares who withdrew or were lost to follow-up were censored at the time of their last visit.</p>
Notes	<p>Acronym: OPTTIRA</p> <p>The trial was funded by Arthritis Research UK (grant reference number 18813).</p> <p>Disclosures: JBG has received honoraria for speaking from UCB, Pfizer, Celgene, and Bristol-Myers Squibb. All other authors declared no conflicts of interest.</p> <p>EudraCT: 2010-020738-24</p>

Ibrahim 2017 (OPTTIRA) (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomisation by online electronic data capture system using minimization protocol with randomly permuted blocks"
Allocation concealment (selection bias)	Low risk	"Trial team were blinded to allocation process and sequences"
Blinding of participants and personnel (performance bias) Subjective outcomes	High risk	Open-label study
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	Open-label study, but outcome not likely to be influenced
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label study, and most outcomes likely to be influenced. "X-ray reading was blinded"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Numbers of participants included in different analysis sets clearly described. 100% of participants included in ITT analyses.
Selective reporting (reporting bias)	Low risk	Study protocol available; similar outcome measures in the paper compared to the protocol
Other bias	Low risk	The study appears to be free of other sources of bias.

Pavelka 2017

Methods	52-week, double-blind, multicentre randomised controlled study in locations around the world Period 1: 24 weeks open-label; period 2: 28 weeks double-blind
Participants	Inclusion criteria (period 1): <ul style="list-style-type: none"> individual has a minimum 1-year history/diagnosis of rheumatoid arthritis based on the 1987 ACR Revised criteria for RA individual must have active moderate to severe rheumatoid arthritis despite methotrexate therapy of ≥ 10 mg/week for at least 12 weeks. The methotrexate dose must be stable for at least 4 weeks immediately prior to screening. age 18 to 70 years Exclusion criteria (period 1):

Pavelka 2017 (Continued)

- individuals who used any of the following systemic treatments during the washout periods given below:
 - * oral corticosteroid dose of prednisone > 7.5 mg/day (or equivalent) or a change in dose within 28 days of baseline
 - * treatment with more than 1 NSAID within 14 days of baseline
 - * methotrexate dose greater than 25 mg/week, or change in the dose of methotrexate within 28 days of baseline
 - * participants will be allowed to continue the following non-biologic DMARDs: sulfasalazine, hydroxychloroquine, and leflunomide. All other non-biologic DMARDs (including but not limited to gold, penicillamine, azathioprine, cyclophosphamide) and biologic DMARDs must have been discontinued at least 2 months prior to week 1.
 - * any biologic B cell depleting agent (e.g. rituximab) within 2 years of week 1
- receipt of any live (attenuated) vaccine within 4 weeks prior to baseline

Inclusion criteria (period 2):

- individuals achieving low disease activity (DAS28 < 3.2) after period 1

Baseline characteristics: mean (SD): age: intervention 47.2 (11.8), control 46.1 (12.9); female: intervention 85%, control 83%; symptom duration in years: intervention 8.3 (6.8), control 8.0 (7.4); prior csD-MARD (not MTX): intervention 34%, control 38%

Interventions	<p>Period 1:</p> <ul style="list-style-type: none"> • Etanercept 50 mg once weekly + methotrexate with or without other DMARDs (n = 489) <p>Period 2:</p> <ul style="list-style-type: none"> • Group A: etanercept 50 mg once weekly + methotrexate with or without other DMARDs (n = 169) • Group B: etanercept placebo once weekly + methotrexate with or without other DMARDs (n = 177)
Outcomes	<p>Primary outcome measure: proportion of participants who remained in LDA (DAS28 < 3.2) at week 52 without rescue medication</p> <p>Secondary outcome measures:</p> <ul style="list-style-type: none"> • Proportion of remission and LDA • Proportion of flare • Change in DAS28, CDAI, SDAI • Adverse events • HAQ-DI • EQ-5D <p>Analyses: ITT with LOCF approach on the full analysis set, which included participants who had taken at least 1 dose of study medication and had at least 1 DAS28-ESR evaluation</p>
Notes	<p>EudraCT: 2011-005448-87</p> <p>ClinicalTrials.gov: NCT01578850</p> <p>Funding: Pfizer</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Screening, enrollment, and randomization were accomplished using an automated internet/telephone randomization system (i.e., the Interactive Web Response System)."

Pavelka 2017 (Continued)

Allocation concealment (selection bias)	Low risk	"Screening, enrollment, and randomization were accomplished using an automated internet/telephone randomization system (i.e., the Interactive Web Response System)."
Blinding of participants and personnel (performance bias) Subjective outcomes	Low risk	The study was participant-, investigator-, and sponsor-blinded. Prefilled syringes were labelled in such a way that participants' treatment assignment could not be determined.
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	"Double-blind trial"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Double-blind trial"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data < 10% and balanced in numbers across intervention groups, with similar reasons for missing data across groups.
Selective reporting (reporting bias)	Low risk	The study protocol is available, and all of the study's prespecified (primary and secondary) outcomes that are of interest in the review have been reported in the prespecified way.
Other bias	Low risk	The study appears to be free of other sources of bias.

Raffaener 2015

Methods	Open-label quasi-randomised controlled study in a hospital in Italy
Participants	<p>Inclusion criteria:</p> <ul style="list-style-type: none"> • individuals with RA as defined by 1987 ACR treated with etanercept 25 mg biweekly after the failure of traditional synthetic DMARDs • among this cohort, individuals with DAS28-ESR < 2.6 for at least 12 months <p>Baseline characteristics: mean (SD): age: intervention 55.7 (13.5), control 55.6 (12.8); female: intervention 85%, control 81%; disease duration: intervention 14.3 (9), control 13.4 (5.9); number of previous DMARDs: intervention 2.4 (1.1), control 2.4 (1.3)</p>
Interventions	<p>Participants were randomised to 1 of the following 2 subcutaneous dose regimens: etanercept 25 mg weekly (group A) or etanercept 25 mg biweekly (group B). The randomisation was done in a consecutive manner, 1:1, and treatment was continued until disease flare-up.</p> <ul style="list-style-type: none"> • Group A, half dose etanercept: n = 159 • Group B, standard dose etanercept: n = 164
Outcomes	<p>Primary outcome: maintained DAS28 remission (DAS28 < 2.6)</p> <p>Secondary outcomes:</p> <ul style="list-style-type: none"> • Clinical and laboratory evidence of adverse events • Joint damage <p>Analyses: ITT</p>

Raffaener 2015 (Continued)

Notes

Funding: This study was supported in part by AIFA (Agenzia Italiana del Farmaco).

Disclosures: none declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	"The randomisation was done according to the order of the recruitment. The first patient recruited was allocated to group A, the second one to group B, and so on." Comment: semi-randomisation
Allocation concealment (selection bias)	High risk	Predictability of allocation due to consecutive randomisation
Blinding of participants and personnel (performance bias) Subjective outcomes	High risk	"Patients, physicians and study nurses were not blinded."
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	Open-label study, but outcome not likely to be influenced
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label study, and most outcomes likely to be influenced; "the radiologist was blinded"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons for missing outcome data unlikely to be related to true outcome
Selective reporting (reporting bias)	Unclear risk	No study protocol present, therefore insufficient information to permit judgement of 'low risk' or 'high risk'
Other bias	High risk	No study protocol present, but information from earlier abstract indicates that inclusion criteria, outcome measures, and duration of follow-up have changed over time.

Smolen 2013 (PRESERVE)

Methods	88-week, randomised, placebo-controlled trial in 80 centres in Europe, Latin America, Asia, and Australia Open-label period: weeks 0 through 36. Randomisation at week 36. Double-blind period: weeks 36 through 88
Participants	Open-label period: <ul style="list-style-type: none"> Inclusion criteria: rheumatoid arthritis, aged between 18 and 70 years, moderate disease activity at screening and at baseline (DAS28 > 3.2 and ≤ 5.1), stable methotrexate (15 to 25 mg/week) for at least 8 weeks before screening Exclusion criteria: previous/current biologicals, DMARD other than methotrexate within 28 days of baseline, more than 1 NSAID at baseline, prednisone > 10 mg/d or a dose that was changed within 14 days of screening, IA or IV or IM or SC glucocorticoids within 28 days of screening, live vaccine within

Smolen 2013 (PRESERVE) (Continued)

28 days of baseline, tuberculosis in the previous 2 years, latent tuberculosis infection and not treated according to local guidelines or not started before etanercept

Double-blind period:

- Inclusion criteria: completed the open-label stage, sustained low disease activity (mean DAS28 $\leq$ 3.2 from weeks 12 to 36 and DAS28 $\leq$ 3.2 at week 36)
- Exclusion criteria: dose of NSAID or prednisone changed within 14 days of randomisation, prednisone > 10 mg/d, methotrexate dose changed within 8 weeks of randomisation (except for reducing dose because of adverse events)

Baseline characteristics:

- Etanercept 50 mg/week (n = 202): age (mean, SD) 48.1 (12.0) years, 164 (81%) female, disease duration 6.8 (7.2) years, 147 (73%) RF positive, 161 (80%) anti-CCP positive, DAS28 at week 36: 2.0 (0.6)
- Etanercept 25 mg/week (n = 202): age (mean, SD) 46.4 (12.2) years, 157 (78%) female, disease duration 6.4 (7.1) years, 142 (71%) RF positive, 156 (78%) anti-CCP positive, DAS28 at week 36: 2.1 (0.6)
- Placebo (n = 200): age (mean, SD) 48.3 (12.2) years, 167 (84%) female, disease duration 7.3 (6.7) years, 147 (74%) RF positive, 156 (79%) anti-CCP positive, DAS28 at week 36: 2.1 (0.6)

Interventions	<p>Open-label period:</p> <ul style="list-style-type: none"> • Etanercept 50 mg/week + MTX (n = 834) <p>Double-blind period:</p> <ul style="list-style-type: none"> • Etanercept 50 mg/week + MTX (n = 202), etanercept 25 mg/week + MTX (n = 202), placebo + MTX (n = 200) • Methotrexate dose maximum 25 mg/week
Outcomes	<p>Primary outcome (double-blind period): proportion of participants with DAS28 $\leq$ 3.2 in the etanercept 50 mg/week versus placebo group at week 88 (52 weeks after randomisation)</p> <p>In case of significantly more low disease activity in the etanercept 50 mg/week group compared with the placebo group, the conditional primary endpoint was proportion of participants receiving etanercept 25 mg/week who achieved DAS28 $\leq$ 3.2.</p> <p>Secondary outcomes:</p> <ul style="list-style-type: none"> • Remission (DAS28 < 2.6, SDAI $\leq$ 3.3, ACR/EULAR Boolean-based definition) • LDA (SDAI $\leq$ 11) • ACR20, ACR50, or ACR70 response • EULAR good or moderate response • Physical function HAQ-DI • Change from baseline in DAS28, CDAI, SDAI • Change from baseline in TJ counts, SJ counts, CRP, ESR • Change from baseline in morning stiffness • Change from baseline in participant global, GH and pain • Change from baseline in physician global • Time to loss of efficacy (loss of DAS28 LDA and change in DAS28 $\geq$ 0.6; discontinuation due to poor efficacy, protocol violation, or other reason) • Participant-reported outcomes: HAQ-DI, EQ-5D total, medical outcomes, study sleep scale, functional assessment of chronic illness, therapy measurement, brief pain inventory, work productivity and activity impairment scale for RA • Radiographic outcome (proportion of participants - non-progressors - achieving an mSvdH score progression rate of up to 0.5 units per year or up to 2.0 units per year (smallest detectable difference)) • Adverse events <p>Analyses: modified ITT population made up of participants who had received at least 1 dose of study drug and had 1 or more DAS28 evaluations. A modified non-responder analysis was done in which par-</p>

Smolen 2013 (PRESERVE) (Continued)

Participants who discontinued early because of poor efficacy were imputed as non-responders for all time points; all other participants were analysed with the LOCF method.

Notes

Acronym: PRESERVE

Funding: "PRESERVE was sponsored by Wyeth, which was acquired by Pfizer in October 2009. Pfizer was responsible for data collection and analyses. The academic authors and sponsors representatives were involved in the study design, data analyses, data interpretation, writing of the report, and the final decision to submit for publication. Biostatisticians at Pfizer did and verified all data analyses. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication."

Disclosures: JSS has received honoraria for consultations or speaking engagements, or grant support, or both, from Abbott, Amgen, AstraZeneca, Bristol-Myers Squibb, Celgene, GlaxoSmithKline, MSD, Novo Nordisk, Pfizer, Roche, Sandoz, Sanofi, and UCB. PN has received grant support and honoraria for consultations from Pfizer. FI-P has received grant support and honoraria for consultations or speaking engagements from Bristol-Myers Squibb, Janssen, Pfizer, and Roche. PM has received grant support from Abbott, Bristol-Myers Squibb, Celltrion, Centocor, GlaxoSmithKline, Human Genome Sciences, Merck, Neovacs, and Pfizer. KP has received honoraria for lectures from Abbott, Fidia, MSD, Pfizer, Roche, and UCB. RP, CH, ASK, and BV are employees of Pfizer and own Pfizer stock. AS is an employee of Inventive Health, who are paid contractors for Pfizer, providing statistical support for the PRESERVE study and the development of this report. The other authors declare that they have no conflicts of interest.

EudraCT: 2007-000896-41

ClinicalTrials.gov: NCT00565409

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"randomly assigned by a centralised system"
Allocation concealment (selection bias)	Low risk	"allocation of patients to treatment groups was done with the ICOPhone interactive voice response system on the basis of information supplied by the investigator or the study staff"
Blinding of participants and personnel (performance bias) Subjective outcomes	Low risk	"patients, investigators, data-analysts and study staff were all masked to treatment allocation" "etanercept packages for each patient were identical"
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	"Double-blind trial"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"patients, investigators, data-analysts and study staff were all masked to treatment allocation"
Incomplete outcome data (attrition bias) All outcomes	High risk	"Patients who discontinued early because of poor efficacy were imputed as non-responders for all time points" "Significantly more patients discontinued in group given placebo than in 50 mg and 25 mg groups"
Selective reporting (reporting bias)	Low risk	Study protocol available; similar outcome measures in the paper compared to the protocol

Smolen 2013 (PRESERVE) (Continued)

Other bias	Low risk	The study appears to be free of other sources of bias.
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Smolen 2014 (OPTIMA)

Methods	<p>78-week, multicentre, randomised, double-blind, placebo-controlled trial in 161 sites across Europe (n = 71), North America (n = 73), South America (n = 5), Africa (n = 6), Australia (n = 3), and New Zealand (n = 3)</p> <p>Period 1: weeks 0 through 26, re-randomisation at week 26; period 2: weeks 26 through 78</p>
Participants	<p>Period 1:</p> <ul style="list-style-type: none"> Inclusion criteria: eligible patients were aged 18 years or older with active RA (< 1-year duration) according to 1987-revised ACR classification criteria Exclusion criteria: we excluded patients if they had previously received anti-TNF therapy, methotrexate, or more than 2 DMARDs, or if they were immunocompromised, pregnant, or planning to become pregnant. Cotherapy with NSAIDs or prednisone or a prednisone equivalent (≤ 10 mg/day) could continue if maintained at a stable dose for 4 weeks or more before baseline. <p>Period 2:</p> <ul style="list-style-type: none"> adalimumab + methotrexate during period 1 of the study, stable low disease activity (DAS28-CRP < 3.2) at weeks 22 and 26 <p>Baseline characteristics: mean (SD): age: intervention 50.1 (14.9), control 49.5 (15.3); female: intervention 73%, control 73%; RF+: intervention 95%, control 89%; ACPA+: intervention 90%, control 90%; disease duration in months: intervention 3.9 (3.3), control 3.9 (2.9); percentage with ≥ 1 previous DMARDs: intervention 8.8%, control 9.5%</p>
Interventions	<p>Period 1: participants were randomised in a ratio 1:1 to:</p> <ul style="list-style-type: none"> adalimumab (40 mg every other week) + MTX (n = 515); placebo + MTX (n = 517). <p>Period 2: participants in the adalimumab plus methotrexate group reaching DAS28-CRP < 3.2 at weeks 22 and 26 were re-randomised in a 1:1 ratio to:</p> <ul style="list-style-type: none"> continuation group: adalimumab + MTX (n = 105); withdrawal group: placebo + MTX (n = 102).
Outcomes	<p>Primary outcome (period 2): not described</p> <p>Outcomes:</p> <ul style="list-style-type: none"> Proportion of participants with ACR20/50/70 Proportion of participants with DAS28-CRP < 3.2 Proportion of participants with DAS28-CRP < 2.6 Proportion of participants with SDAI < 11.0 Proportion of participants with SDAI ≤ 3.3 Proportion of participants with CDAI < 10.0 Proportion of participants with CDAI ≤ 2.8 Proportion of participants with ΔmTSS ≤ 0.5 (from baseline to 78 weeks) Mean HAQ Adverse events <p>Analyses: ITT including all participants who had received at least 1 dose of study drug in period 2. The primary endpoint was assessed using non-responder imputation (NRI). NRI or LOCF, or both, was used</p>

Smolen 2014 (OPTIMA) (Continued)

for additional clinical outcomes; LOCF was used for functional outcomes. Markov chain Monte Carlo method was used to impute missing radiographic data 10 times (multiple imputation).

Notes	<p>Acronym: OPTIMA</p> <p>Funding: AbbVie</p> <p>Disclosures: JSS has received grant fees, research fees, consulting fees, or other remuneration from AbbVie, Amgen, AstraZeneca, Bristol-Myers Squibb, Celgene, Centocor-Janssen, GlaxoSmithKline, Lilly, Pfizer (Wyeth), MSD (Schering-Plough), Novo Nordisk, Roche, Sandoz, and UCB. PE has provided paid expert advice and has done trials for AbbVie, Merck, Pfizer, UCB, Roche, and Bristol-Myers Squibb. RF has received research grants and consulting fees or other remuneration from AbbVie, Pfizer, Merck, Roche, UCB, Celgene, Centocor-Janssen, Amgen, AstraZeneca, Bristol-Myers Squibb, Lilly, and Novartis. RFvV has served as a consultant for, or received grant or research support from, AbbVie, GlaxoSmithKline, Merck, Pfizer, Roche, and UCB. KP has received consulting fees or other remuneration and speaker honoraria from AbbVie, Pfizer, MSD, Roche, Amgen, and Bristol-Myers Squibb. PD has served on speaker's bureaus for BMS. BG, HK, and VA are shareholders and employees of AbbVie. LR is a former employee of AbbVie. AK has received grant fees, research fees, or provided paid expert advice to AbbVie, Amgen, AstraZeneca, Bristol-Myers Squibb, Celgene, Centocor-Janssen, Pfizer, Roche, and UCB.</p> <p>EudraCT: 2006-004139-31</p> <p>ClinicalTrials.gov: NCT00420927</p>
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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised trial, method not described
Allocation concealment (selection bias)	Low risk	"Patients were centrally randomised in blocks of four by interactive voice response system on the basis of information supplied by the investigator"
Blinding of participants and personnel (performance bias) Subjective outcomes	Low risk	"During period 2, treatment reallocation of patients who achieved the target was also masked to patients and investigators"
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	"During period 2, treatment reallocation of patients who achieved the target was also masked to patients and investigators"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind trial
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons for missing outcome data unlikely to be related to true outcome
Selective reporting (reporting bias)	Low risk	The study protocol is available, and all of the study's prespecified (primary and secondary) outcomes that are of interest in the review have been reported in the prespecified way.
Other bias	Low risk	The study appears to be free of other sources of bias.

van Herwaarden 2015 (DRESS)

Methods	Pragmatic, multicentre, open-label, randomised, controlled, cost-effectiveness non-inferiority strategy trial, stratified for anti-TNF agent in 2 hospitals in the Netherlands
Participants	<p>Inclusion criteria: we enrolled consenting patients with rheumatoid arthritis (based on 2010 or 1987 ACR criteria, or clinical diagnosis by the treating rheumatologist) using adalimumab or etanercept at any stable dose and interval for at least 6 months, with stable low disease activity at 2 subsequent visits</p> <p>Exclusion criteria: none described</p> <p>Baseline characteristics: mean (SD): age: intervention 59 (10.5), control 58 (9.3); female: intervention 62%, control 69%; median disease duration: intervention 10 (IQR 6 to 17), control 10 (IQR 6 to 16), median number of previous DMARD treatment: intervention 2 (IQR 1 to 3), control 2 (IQR 1 to 3); median number of previous TNFi treatment: intervention 0 (IQR 0 to 1), control 0 (IQR 0 to 1)</p>
Interventions	<p>Participants were randomised (stratified by anti-TNF) in a ratio of 2:1.</p> <ul style="list-style-type: none"> Control group (n = 59): usual care with tight control (visit every 3 months, DAS28 measurement on day of visit, aiming for DAS28 < 3.2) Intervention group (n = 121): tight control and dose reduction (increase in the interval every 3 months until stop and withdrawal strategy advice to the treating rheumatologist. Only 1 attempt at dose reduction was done, and in the case of flare and treatment escalation, no further attempts at reduction were made. <p>Increase in interval for adalimumab: start 14, 21, 28 days and stop, etanercept start 7, 10, 14 days and stop</p>
Outcomes	<p>Primary outcome is to assess whether the difference in cumulative incidence in persistent RA flares (DAS28 increase > 1.2 or DAS28 increase > 0.6 with a current DAS28 ≥ 3.2) and a duration of > 3 months between the intervention group and the usual care group does not exceed the non-inferiority margin of 20% after 18 months' follow-up.</p> <p>Secondary outcomes include cost-effectiveness ratio between intervention and usual care groups. Other secondary outcomes are predictive factors for successful dose reduction and progression of radiological joint damage.</p> <p>Analyses: primary analyses were done PP by including only participants who (1) completed follow-up, (2) actually started dose reduction of TNF inhibitors in the dose reduction arm, and (3) had not stopped or reduced TNF inhibitor use at 18 months' follow-up in the usual care arm. Additional ITT analyses were also done. No multiple imputation was deemed necessary since almost no data were missing.</p>
Notes	<p>Dutch trial register: NTR3216</p> <p>Acronym: DRESS</p> <p>Funding: The study received no external funding.</p> <p>Disclosures: JB received grants and personal fees from Pfizer and AbbVie during the conduct of the study, and grants and personal fees from Roche, Bristol-Myers Squibb, and Union Chimique Belge outside the submitted work. RvV received grants from AbbVie, BMS, GlaxoSmithKline, Pfizer, Roche, and UCB, and personal fees from AbbVie, Biotest, BMS, GlaxoSmithKline, Janssen, Lilly, Merck, Pfizer, Roche, UCB, and Vertex outside the submitted work. The other authors declare no conflicts of interest.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
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van Herwaarden 2015 (DRESS) (Continued)

Random sequence generation (selection bias)	Low risk	"A randomisation list generated by computer"
Allocation concealment (selection bias)	Low risk	"To conceal the sequence until treatment strategy was assigned, sequentially numbered sealed opaque envelopes that contained the randomly assigned allocations were used."
Blinding of participants and personnel (performance bias) Subjective outcomes	High risk	"Open-label study"
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	Open-label study, but outcome not likely to be influenced
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label study, and most outcomes likely to be influenced. X-ray reading was blinded: "Radiographs of hands and feet (at baseline and 18 months) were assessed in chronological order by two blinded, trained readers"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data < 10% and balanced in numbers across intervention groups, with similar reasons for missing data across groups
Selective reporting (reporting bias)	Low risk	The study protocol is available, and all of the study's prespecified (primary and secondary) outcomes that are of interest in the review have been reported in the prespecified way.
Other bias	Low risk	Lack of DMARD cotreatment and a higher level of radiological damage at baseline were more prevalent in the dose reduction group than in the usual care group, but there was a low chance of inducing bias.

van Vollenhoven 2016 (DOSERA)

Methods	48-week, double-blind, randomised, placebo-controlled trial in 16 rheumatology units in Sweden (n = 5), Denmark (n = 2), Finland (n = 2), Norway (n = 3), Hungary (n = 3), and Iceland (n = 1) Period 1: 8-week run-in period; period 2: RCT period
Participants	Inclusion criteria for period 1: <ul style="list-style-type: none"> adult patients diagnosed with RA (1987 ACR criteria) etanercept 50 mg + methotrexate weekly (in 1 single or 2 divided doses) for at least 14 months in combination with methotrexate at a stable dose of 7.5 to 25 mg/week for at least 4 months before baseline LDA (DAS28-ESR $\leq$ 3.2) at the time of screening evidence of LDA at least 11 months prior to the screening visit had to be documented in either the clinical chart or a clinical registry, with no contrary data in the interim no other concurrent antirheumatic therapy stable (for at least 4 weeks) low-dose ($\leq$ 7.5 mg/day) prednisolone (or equivalent) therapy was allowed <p>Exclusion criteria for period 1: key exclusions were: prior therapy with biologics except anti-TNFs and a prior attempt at etanercept discontinuation or dose reduction for the purpose of maintaining a good clinical result (i.e. for the same purpose to be assessed in this study)</p>

van Vollenhoven 2016 (DOSERA) (Continued)

Inclusion criteria for period 2:

- maintaining a DAS $\leq$ 3.2 during period 1

Baseline characteristics: mean (SD): age 56.7 (11.0), female 70%, disease duration 13.6 (8.8), RF+ 69%, prior treatment with DMARDs other than MTX 66%

Interventions	<p>Period 1: run-in period with etanercept + methotrexate. Methotrexate dose was kept unchanged throughout the study, etanercept was provided in a once-weekly 50 mg dose in the form of the lyophilised product. (n = 91)</p> <p>Period 2: participants were randomised in a ratio 1:1:1</p> <ul style="list-style-type: none"> • ETN50: etanercept 50 mg weekly (unchanged) + methotrexate (n = 23) • ETN25: etanercept 25 mg weekly (reduced dose) + methotrexate (n = 27) • PBO: placebo + methotrexate (n = 23) <p>If a flare occurred during period 2, the participant was withdrawn from this phase. Participants who discontinued period 2 were designated as failures in the primary analysis, transferred to the third phase (period 3), and received etanercept 50 mg weekly plus methotrexate.</p>
Outcomes	<p>Primary outcome: proportion of non-failures for ETN50 versus PBO</p> <p>Secondary outcomes:</p> <ul style="list-style-type: none"> • Comparison of non-failures between ETN25 and PBO • Time to failure in period 2 • Time from failure to LDA/remission • Predictors for failure • Adverse events <p>Analyses: modified ITT consisting of the participants who had received a randomised treatment assignment and who had at least 1 available evaluation after the first dose of study medication at randomisation. For dichotomous clinical outcomes, a non-responder imputation was applied, designating a participant as a 'failure' if he/she had discontinued double-blinded treatment for any reason. The primary analysis was performed on LOCF data.</p>
Notes	<p>Acronym: DOSERA</p> <p>Funding: This study was sponsored by Wyeth, which was acquired by Pfizer in October 2009.</p> <p>Disclosures: RFvV has received research support and honoraria from AbbVie (Abbott), BMS, GSK, Lilly, MSD, Pfizer, Roche, and UCB Pharma. MØ has received research support or honoraria, or both from AbbVie (Abbott), BMS, Centocor, GSK, Janssen, Merck, Mundipharma, Novo, Pfizer, Schering-Plough, Roche, UCB, and Wyeth. TU has received research support and honoraria from AbbVie (Abbott), BMS, MSD, Pfizer, Roche, and UCB Pharma. ML-R has been a consultant for Abbott, Pfizer, MSD, Roche, and BMS. EL and MJ were employees of Pfizer Sweden at the time of the study; EL is currently an employee of Eli Lilly. FB is an employee of Quanticate, who were paid consultants to Pfizer in connection with statistical support for the development of this manuscript. KF-L was an employee of Wyeth/Pfizer at the time of the conduct of the study and is currently employed by the Swedish Medical Products Agency.</p> <p>EudraCT: 2007-006657-63</p> <p>ClinicalTrials.gov: NCT00858780</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Pfizer generated a randomization schedule. Allocation of subjects to treatment groups proceeded through the use of the Clinical Operations Random-

van Vollenhoven 2016 (DOSERA) *(Continued)*

		ization Environment II (CORE II) system /Impala system that was accessible 24 hours a day, 365 days a year."
Allocation concealment (selection bias)	Low risk	"Pfizer generated a randomization schedule. Allocation of subjects to treatment groups proceeded through the use of the Clinical Operations Randomization Environment II (CORE II) system /Impala system that was accessible 24 hours a day, 365 days a year."
Blinding of participants and personnel (performance bias) Subjective outcomes	Low risk	"Double-blind trial"
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	"Double-blind trial"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Double-blind trial"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups
Selective reporting (reporting bias)	Low risk	The study protocol is available, and all of the study's prespecified (primary and secondary) outcomes that are of interest in the review have been reported in the prespecified way.
Other bias	Low risk	The study appears to be free of other sources of bias.

Weinblatt 2017 (C-EARLY)

Methods	Multicentre, double-blind randomised controlled trial conducted at 103 study centres in Europe, Australia, North America, and Latin America (of the 181 that participated in C-EARLY period 1) Period 1: 52 weeks, double-blind. Period 2: week 52 to 104, double-blind (period of interest)
Participants	Inclusion for period 1: <ul style="list-style-type: none"> • active RA according to the 2010 ACR/EULAR classification criteria • DMARD-naïve with early disease (diagnosis 1 year prior to randomisation, with 76% of patients randomised within 4 months of their diagnosis) • poor prognostic factors for severe disease progression (positive at screening for rheumatoid factor or anti-citrullinated protein antibody) Exclusion period 1: <ul style="list-style-type: none"> • use of intra-articular, intramuscular, or intravenous corticosteroids at any dose was prohibited in the C-EARLY study Inclusion for period 2: <ul style="list-style-type: none"> • participants in C-EARLY period 1 who had achieved sustained low disease activity at weeks 40 and 52 after 52 weeks of certolizumab pegol plus optimised methotrexate treatment were eligible for enrolment into C-EARLY period 2

Weinblatt 2017 (C-EARLY) (Continued)

Exclusion period 2:

- patients who had used intra-articular corticosteroids within 28 days of baseline (in C-EARLY period 1) were excluded from study enrolment. The maximum allowed dose of oral corticosteroids during the study was ≤ 10 mg/day prednisone or equivalent, with changes in dose allowed only between weeks 4 and 14 and between weeks 24 and 34 in period 1 of the study. Participants taking oral corticosteroids were therefore to maintain their dosage during period 2.

Baseline characteristics:

CZP standard dose: mean (SD): age 49.1 (13.1), female 79%, RF+ 98%, ACPA+ 92%, time since diagnosis in months 2.5 (2.5)

CZP reduced dose: age 49.2 (12.5), female 68%, RF+ 95%, ACPA+ 89%, time since diagnosis in months 2.6 (2.8)

CZP stopped: age 47.6 (14.0), female 73%, RF+ 100%, ACPA+ 86%, time since diagnosis in months 2.9 (3.1)

Interventions	<p>Period 2: participants were randomised into 1 of 3 groups in ratio 2:3:2.</p> <ul style="list-style-type: none"> CZP standard group: 200 mg certolizumab pegol every 2 weeks plus methotrexate Reduced-frequency group: 200 mg certolizumab pegol every 4 weeks plus methotrexate CZP stopped group: placebo every 2 weeks plus methotrexate <p>In the event of a confirmed disease flare, participants received a loading dose of certolizumab pegol (400 mg at 3 subsequent visits) followed by the standard dose (200 mg every 2 weeks) until the end of the study.</p>
Outcomes	<p>Primary: proportion of participants with sustained low disease activity (DAS28-ESR of ≤ 3.2 at both week 40 and week 52) who maintained low disease activity (DAS28-ESR of ≤ 3.2) for all 5 consecutive study visits to week 104 without flares</p> <p>Secondary outcome measures:</p> <ul style="list-style-type: none"> Proportion participants in sustained remission Proportion low disease activity and normal physical function Radiographic non-progression during period 2 Time to flare <p>Analyses: ITT. Missing data from participants who entered period 2 but withdrew before the end of the study were imputed using non-responder imputation for the primary and key secondary endpoints. Radiographic analyses used linear extrapolation. In post hoc analyses, LOCF imputation was used for the proportions of participants achieving low disease activity, remission, and normative physical function.</p>
Notes	<p>Acronym: C-EARLY period 2</p> <p>Funding: supported by UCB Pharma</p> <p>Disclosures: Dr Weinblatt has received consulting fees, speaking fees, and/or honoraria from AbbVie, Amgen, Bristol-Myers Squibb, Roche (less than USD 10,000 each), Lilly, Pfizer, UCB Pharma, AstraZeneca, Merck, Novartis, Crescendo Bioscience, and MedImmune (more than USD 10,000 each). Dr Bingham has received consulting fees, speaking fees, and/or honoraria from UCB Pharma (less than USD 10,000). Dr Burmester has received consulting fees, speaking fees, and/or honoraria from AbbVie, Bristol-Myers Squibb, Celgene, MSD, UCB Pharma, Roche, Pfizer, and Lilly (less than USD 10,000 each). Dr Bykerk has received consulting fees, speaking fees, and/or honoraria from Pfizer, AbbVie, Bristol-Myers Squibb, Sanofi, and UCB Pharma (less than USD 10,000 each). Dr Furst has received consulting fees, speaking fees, and/or honoraria from Abbott, AbbVie, Amgen, Biogen, Bristol-Myers Squibb, Cytos, Gilead, GlaxoSmithKline, Janssen, NIH, Novartis, Pfizer, Roche/Genentech, and UCB Pharma (less than USD 10,000 each) and research grants from Abbott, Actelion, Amgen, Biogen, Bristol-Myers Squibb, GlaxoSmithKline, Novartis, Pfizer, Roche/Genentech, and UCB Pharma. Dr Mariette has received consulting fees, speaking fees, and/or honoraria from Bristol-Myers Squibb, GlaxoSmithKline, Pfizer, and</p>

Weinblatt 2017 (C-EARLY) (Continued)

UCB Pharma (less than USD 10,000 each). Dr van der Heijde has received consulting fees, speaking fees, and/or honoraria from AbbVie, Amgen, Astellas, AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Celgene, Daiichi, Eli Lilly and Company, Galapagos, Gilead, Janssen, Merck, Novartis, Pfizer, Regeneron, Roche, Sanofi, and UCB Pharma (less than USD 10,000 each). Dr van Vollenhoven has received consulting fees and/or honoraria from AbbVie, Biotest, Bristol-Myers Squibb, Celgene, Crescendo Bioscience, GlaxoSmithKline, Janssen, Lilly, Merck, Novartis, Pfizer, Roche, UCB Pharma, and Vertex (less than USD 10,000 each) and research grants from AbbVie, Amgen, Bristol-Myers Squibb, GlaxoSmithKline, Pfizer, Roche, and UCB Pharma. Ms VanLunen and Drs Ecoffet and Cioffi own stock or stock options in UCB Pharma. Dr Emery has received consulting fees and/or honoraria from Pfizer, MSD, AbbVie, Bristol-Myers Squibb, UCB Pharma, Roche, Novartis, Samsung, Sandoz, and Lilly (more than USD 10,000 each).

EudraCT: 2011-001729-25

ClinicalTrials.gov: NCT01521923

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Re-randomisation at week 52 was performed centrally using an interactive voice/web response system (IXRS).
Allocation concealment (selection bias)	Low risk	Re-randomisation at week 52 was performed centrally using an interactive voice/web response system (IXRS).
Blinding of participants and personnel (performance bias) Subjective outcomes	Low risk	Double-blind study. Placebo was supplied as 0.9% saline, and certolizumab pegol was supplied as a 200 mg solution. Both were in prefilled syringes for subcutaneous injection and were administered up to week 102.
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All study personnel were blinded with respect to treatment, except for a separate group who supervised and administered the study medication and determined ESR but who otherwise had no involvement in the study.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups
Selective reporting (reporting bias)	Low risk	The study protocol is available, and all of the study's prespecified (primary and secondary) outcomes that are of interest in the review have been reported in the prespecified way.
Other bias	High risk	The number of included participants was lower than anticipated in the sample size calculation. "The primary end point of the present study was not achieved. Fewer patients than projected from period 1 were eligible to enter period 2 (i.e., achieved sustained low disease activity), which may have resulted in an underpowered study."

Yamanaka 2016 (ENCOURAGE)

Methods Multicentre, open-label randomised controlled study in Japan and Korea

Down-titration and discontinuation strategies of tumour necrosis factor-blocking agents for rheumatoid arthritis in patients with low disease activity (Review)

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Yamanaka 2016 (ENCOURAGE) (Continued)

Period 1: first year. Period 2: second year (period of interest for review)

Participants	<p>Period 1:</p> <ul style="list-style-type: none"> Inclusion criteria: individuals with early-stage RA who had been diagnosed according to the 1987 classification criteria for RA, whose disease duration from the onset of symptoms was < 5 years, and whose disease activity was $3.2 \leq \text{DAS28} \leq 5.1$, despite treatment with csDMARDs, including MTX for no less than 3 months. Patients who had received any bDMARDs prior to the start of the study had to stop using these agents for the following amounts of time prior to participation in this study: no less than 8 weeks for infliximab, no less than 2 weeks for adalimumab, and no less than 4 weeks for tocilizumab. Exclusion criteria: individuals who did not meet the guidelines for anti-TNF therapy were excluded from the study. Other exclusion criteria included serious infection, tuberculosis, pregnancy, and others, as in the clinical trials of anti-TNF agents. <p>Period 2:</p> <ul style="list-style-type: none"> Inclusion criteria: those participants in the etanercept + methotrexate group who were in clinical remission, defined as $\text{DAS28} < 2.6$ at both 6 months and 12 months. <p>Baseline characteristics: mean (SD): age: intervention 52.9 (14.9), control 49.8 (13.0); female: intervention 88%, control 88%; RF+: intervention 71%, control 70%; DAS28: intervention 1.8 (0.5), control 1.7 (0.5); disease duration in years: intervention 2.4 (1.4), control 1.9 (1.4)</p>
Interventions	<p>Period 1: participants were randomised into 1 of 2 groups at a ratio of 1:4</p> <ul style="list-style-type: none"> MTX group: methotrexate 6 mg/week (n = 43) ETN + MTX group: methotrexate 6 mg/week and etanercept subcutaneous twice a week (n = 179) <p>Period 2: participants were randomised at a ratio of 1:1</p> <ul style="list-style-type: none"> ETN discontinuation (n = 50) ETN continuation (n = 49)
Outcomes	<p>Primary outcome period 2: maintenance of remission rates, including clinical remission, structural remission, and functional remission rates at 12 months after the second randomisation</p> <p>Secondary outcomes:</p> <ul style="list-style-type: none"> Resumption of remission in discontinuation group Changes in total Sharp score <p>Analyses: ITT and PP. Missing data were imputed using the LOCF strategy.</p>
Notes	<p>Acronym: ENCOURAGE</p> <p>Funding: This investigator-initiated study was supported by a grant from Pfizer Inc through the non-profit corporation Advanced Clinical Research Organization (www.npo-acro.jp/), due to an international multicentre co-operative study led by the Institute of Rheumatology, Tokyo Women's Medical University.</p> <p>Disclosures: HY has received research grants from AbbVie, Asahi Kasei Pharma, Astellas, Bristol-Myers Squibb, Chugai, Daiichi-Sankyo, Eisai, GlaxoSmithKline, Janssen, Mitsubishi-Tanabe, MSD, Nippon Kayaku, Pfizer, Santen, Taisho-Toyama, Takeda, and Teijin Pharma, and has received honorarium for lectures or consultancy from Teijin Pharma, Chugai, Astellas, Bristol-Myers Squibb, AbbVie, Daiichi-Sankyo, Nippon Kayaku, Mitsubishi-Tanabe, Pfizer, Takeda, and UCB. SN has received research grants from AbbVie, Bristol-Myers Squibb, and Pfizer, and honorarium for lectures or consultancy from Bristol-Myers Squibb and Pfizer. TK has received research grants from AbbVie, Astellas, Bristol-Myers Squibb, Chugai, Eisai, Mitsubishi-Tanabe, Pfizer, and Takeda, and honorarium for lectures from Chugai, Astellas, AbbVie, and Mitsubishi-Tanabe. YU has received speaking fees from Pfizer, Mitsubishi-Tanabe, Chugai, Bristol-Myers Squibb, and Astellas. YS has received speaking fees from AbbVie and Pfizer. NT has received research grant or speaking fee, or both from Mitsubishi-Tanabe Pharma, Chugai, Takeda, Astellas, and Eisai. KS has received speaking fees from Mitsubishi-Tanabe, Chugai, Eisai, AbbVie, Bris-</p>

Yamanaka 2016 (ENCOURAGE) (Continued)

tol-Myers Squibb, Takeda, and Astellas. YI has received speaking fees from Eisai and Pfizer. YM has received research grants from Mitsubishi-Tanabe, Astellas, Pfizer, and Eisai. YT has received consulting fees, speaking fees, and/or honoraria from AbbVie, Chugai, Astellas, Takeda, Santen, Mitsubishi-Tanabe, Pfizer, Janssen, Eisai, Daiichi-Sankyo, UCB, GlaxoSmithKline, and Bristol-Myers Squibb, and research grants from Mitsubishi-Tanabe, Chugai, MSD, Astellas, and Novartis. TTa has received research grants from Astellas, Bristol-Myers Squibb, Chugai, Daiichi-Sankyo, Eisai, Mitsubishi-Tanabe, Pfizer, Santen, Takeda, Teijin Pharma, AbbVie, Asahikasei Pharma, Taisho-Toyama, and SymBio Pharmaceuticals; speaking fees from AbbVie, Bristol-Myers Squibb, Chugai, Eisai, Janssen, Mitsubishi-Tanabe, Pfizer, Takeda, Astellas, and Daiichi-Sankyo; and consultant fees from AstraZeneca, Eli Lilly, Novartis, Mitsubishi-Tanabe, Asahi Kasei Pharma, AbbVie, Daiichi-Sankyo, and Bristol-Myers Squibb.

UMIN Clinical Trials Registry Japan: UMIN000002687

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process to permit judgement of 'low risk' or 'high risk'
Allocation concealment (selection bias)	Low risk	"Randomization of ENCOURAGE study was conducted by the sealed envelope method in central study secretariat"
Blinding of participants and personnel (performance bias) Subjective outcomes	High risk	"Open-label study"
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	Open-label study, but outcome not likely to be influenced
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label study, and most outcomes likely to be influenced. X-ray reading was blinded: "Assessment of outcome was mostly conducted by the investigators without blinding, but only radiological scores (Total Sharp score) was assessed centrally by experts of evaluating scores, thus radiological score was assessed by blinding manner."
Incomplete outcome data (attrition bias) All outcomes	High risk	Proportion of missing data is likely to induce clinically relevant bias.
Selective reporting (reporting bias)	Low risk	The study protocol is available, and all of the study's prespecified (primary and secondary) outcomes that are of interest in the review have been reported in the prespecified way.
Other bias	High risk	The number of included participants was lower than anticipated in the sample size calculation.

ACPA: Anti-Citrullinated Protein Antibody
ACR: American College of Rheumatology
bDMARD: biological DMARD
CCP: cyclic citrullinated peptide
CDAI: Clinical Disease Activity Index
CRP: C-reactive protein
csDMARD: conventional synthetic DMARD
CZP: certolizumab pegol
DAS28: disease activity score in 28 joints

DAS28-ESR: disease activity score in 28 joints using erythrocyte sedimentation rate
 DAS44: disease activity score in 44 joints
 DMARD: disease-modifying antirheumatic drug
 ESR: erythrocyte sedimentation rate
 ETN: etanercept
 EULAR: European League Against Rheumatism
 EQ-5D: European Quality of Life-5 Dimensions (a standardised measure of health-related quality of life)
 FACIT: Functional Assessment of Chronic Illness Therapy
 GH: growth hormone
 HAQ-DI: Health Assessment Questionnaire-Disability Index
 IA: intra-articular
 IM: intramuscular
 IV: intravenous
 IQR: interquartile range
 ITT: intention-to-treat
 LDA: low disease activity
 LOCF: last observation carried forward
 mSvdH score: modified Sharp-van der Heijde score
 mTSS: modified total Sharp score
 MTX: methotrexate
 NSAID: non-steroidal anti-inflammatory drug
 PP: per protocol
 RA: rheumatoid arthritis
 RCT: randomised controlled trial
 RF: rheumatoid factor
 SC: subcutaneous
 SD: standard deviation
 SDAI: Simplified Disease Activity Index
 SF-36: 36-item short-form health survey
 SJ: swollen joint
 TJ: tender joint
 TNF: tumour necrosis factor

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Aletaha 2010	Overview article
Awan 2011	No anti-TNF continuation comparison group. No separate RA data
Bejarano 2010	After 1 year, all participants receiving infliximab plus methotrexate discontinued infliximab. No comparison with infliximab continuation arm
CADTH Report 2014	Literature study
Detert 2013 (HIT-HARD)	HIT-HARD study After 24 weeks, all participants receiving adalimumab plus methotrexate discontinued adalimumab. No comparison with adalimumab continuation arm
Emery 2013 (PRIZE)	PRIZE study Etanercept reduced or discontinued, no continuation comparison arm.
Greenberg 2014	Cohort study
Haraoui 2014	No certolizumab pegol dose below standard dose
Harigai 2012 (BRIGHT)	BRIGHT study

Down-titration and discontinuation strategies of tumour necrosis factor-blocking agents for rheumatoid arthritis in patients with low disease activity (Review)

Study	Reason for exclusion
	Not an RCT or CCT according to the Cochrane definition; randomisation based on physician preference
Haschka 2016 (RETRO)	RETRO study Dose reduction of bDMARDs and sDMARDs at the same time
Heimans 2016 (IMPROVED)	IMPROVED study No comparison with an adalimumab continuation arm
Ichikawa 2007	Overview article
Keystone 2003	Overview article
Klarenbeek 2011	BeSt study In the combination therapy with infliximab arm, infliximab dose could be reduced and stopped. No comparison with infliximab continuation arm
Kobelt 2011	No real participant data. Markov model
Kobelt 2014	No real participant data. Markov model
Oba 2017 (RRRR study)	RRRR study No comparison with a continuation arm
Quinn 2005	After 1 year, all participants receiving infliximab plus methotrexate discontinued infliximab. No comparison with infliximab continuation arm
Rakieh 2013	Not an RCT or CCT according to the Cochrane definition; allocation based on patient decision
Ramírez-Herráiz 2013	Retrospective study
Seddighzadeh 2014 (NORD-STAR)	NORD-STAR study No comparison with a continuation arm
Smolen 2012 (CERTAIN)	CERTAIN study No certolizumab pegol continuation comparison arm
Tada 2012 (PRECEPT)	PRECEPT study Participants who required biological therapy were randomly assigned to receive low-dose versus standard-dose etanercept. Participants had not used etanercept before study start. No dose reduction protocol
Tanaka 2013 (HONOR)	HONOR study Not an RCT or CCT according to the Cochrane definition
Tanaka 2014 (HOPEFUL-2)	HOPEFUL-2 Not an RCT or CCT according to the Cochrane definition; allocation based on patient/investigator decision
van den Broek 2011	BeSt study

Study	Reason for exclusion
	In the combination therapy with infliximab arm, infliximab dose could be reduced and stopped. No comparison with infliximab continuation arm
van der Kooij 2009	BeSt study In the combination therapy with infliximab arm, infliximab dose could be reduced and stopped. No comparison with infliximab continuation arm
Villeneuve 2012	No etanercept continuation control arm, and no data after etanercept withdrawal
Wiland 2016 (PRIZE)	PRIZE study No comparison with etanercept continuation arm

bDMARD: biological DMARD

CCT: controlled clinical trial

DMARD: disease-modifying antirheumatic drug

RA: rheumatoid arthritis

RCT: randomised controlled trial

sDMARD: synthetic DMARD

TNF: tumour necrosis factor

Characteristics of ongoing studies [ordered by study ID]

2012-004631-22

Trial name or title	TapERA: Maintaining remission in RA while tapering Etanercept
Methods	Open-label randomised controlled trial
Participants	People with established RA in remission for ≥ 6 months, treated with etanercept ≥ 1 year
Interventions	<ul style="list-style-type: none"> 50 mg etanercept every 2 weeks 50 mg etanercept every week (control)
Outcomes	<p>Primary outcome: the proportion of participants maintaining remission 6 months after decreasing the dose of etanercept to 50 mg every 2 weeks compared to the proportion of participants maintaining remission while continuing the established dose of 50 mg weekly</p> <p>Secondary outcomes: baseline predictors, maintenance of remission, regaining remission after re-treatment, FLARE questionnaire, adverse events</p>
Starting date	2012
Contact information	Rene Westhovens, University Hospitals Leuven
Notes	EudraCT Number: 2012-004631-22

2017-001970-41

Trial name or title	The BIODOPT trial (BIological Dose OPTimisation). Dose reduction and discontinuation of biological therapy in patients with rheumatoid arthritis, psoriatic arthritis and axial spondyloarthritis: protocol for a 18 months randomised, open label, parallel-group, multi-centre trial
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2017-001970-41 (Continued)

Methods	Randomised, open-label, parallel group, multicentre
Participants	People with RA, PsA, or SpA treated with a bDMARD in stable dose in sustained clinical remission
Interventions	Dose optimisation tapering strategy for biological therapy
Outcomes	The co-primary endpoint is: 1A Superiority: the proportion of participants who at 18 months are reduced to 50% or less of their inclusion dose of biological therapy. 1B Equivalence: disease activity assessed 18 months from baseline
Starting date	December 2017
Contact information	MD Line Uhrenholt, The Department of Rheumatology, Aalborg University Hospital
Notes	EudraCT: 2017-001970-41

NCT01793519

Trial name or title	Stopping tumor necrosis factor-alpha inhibitors in rheumatoid arthritis
Methods	Multicentre, randomised, double-blind, placebo-controlled, non-inferiority trial
Participants	People with RA, remission for > 6 months while taking etanercept, adalimumab, or infliximab and at least 1 DMARD
Interventions	Randomisation 2:1 Matching placebo OR current anti-TNF agent (etanercept/adalimumab/infliximab)
Outcomes	Primary outcome: 48-week relapse-free status Secondary outcomes: difference in progression of joint damage on radiographs, differences in physical function and predictors of relapse
Starting date	January 2013
Contact information	Arthur Weinstein, MD/Michael M Ward, MD
Notes	ClinicalTrials.gov: NCT01793519

NCT01881308

Trial name or title	Remission in rheumatoid arthritis - assessing withdrawal of disease-modifying antirheumatic drugs in a non-inferiority design
Methods	Randomised, open, controlled, parallel-group, multicentre, phase 4, non-inferiority strategy study in Norway
Participants	People with RA with disease duration < 5 years, stable DAS28 remission > 12 months and unchanged treatment with anti-TNF and/or sDMARDs > 12 months
Interventions	Stable dose anti-TNF OR stepdown and withdrawal of anti-TNF (half-dose anti-TNF first 4 months, thereafter withdrawal) OR stable dose sDMARD OR sDMARD dose reduction (half-dose sDMARD for

NCT01881308 (Continued)

	first 12 months, after 12 months re-randomisation, continue half-dose or withdraw DMARD) OR ARCTIC follow-up
Outcomes	<p>Primary endpoint is the proportion of participants who are non-failures (have not experienced a flare) at 12 months' follow-up.</p> <p>Secondary endpoints include composite disease activity scores and remission criteria, joint damage and inflammation assessed by various imaging modalities, work participation, healthcare resource use, and health-related quality of life.</p>
Starting date	June 2013
Contact information	Siri Lillegraven, MD, MPH/Espen A Haavardsholm, MD, PhD
Notes	ClinicalTrials.gov: NCT01881308

NCT02198651

Trial name or title	PREDICTRA: A Phase 4 Trial Assessing the ImPact of Residual Inflammation Detected Via Imaging TEchniques, Drug Levels and Patient Characteristics on the Outcome of Dose Tapering of Adalimumab in Clinical Remission Rheumatoid ArThritis (RA) Subjects
Methods	Randomised, double-blind, phase 4 trial
Participants	People with RA treated with adalimumab and methotrexate who are in sustained clinical remission
Interventions	<ul style="list-style-type: none"> Adalimumab continuation Placebo
Outcomes	<p>Primary outcome measures: hand and wrist synovitis RAMRIS score, bone marrow oedema RAMRIS score, flare occurrence</p> <p>Secondary outcome measures: time to flare, flare severity, DAS28, CDAI, SDAI, HAQ-DI, RAPID-3, TSQM, WPAI, SF-36</p>
Starting date	December 2014
Contact information	AbbVie
Notes	ClinicalTrials.gov: NCT02198651

NCT02373813

Trial name or title	Study of etanercept monotherapy vs methotrexate monotherapy for maintenance of rheumatoid arthritis remission
Methods	Multicentre, double-blind randomised controlled study
Participants	People with RA on etanercept plus methotrexate therapy in very good disease control for 6 months prior to study entry
Interventions	<ul style="list-style-type: none"> Etanercept monotherapy Methotrexate monotherapy

NCT02373813 (Continued)

- Etanercept plus methotrexate

Outcomes	Primary outcome measure: SDAI remission at week 48 Secondary outcome measures: DAS28, CDAI, adverse events
Starting date	February 2015
Contact information	Amgen
Notes	ClinicalTrials.gov: NCT02373813

NTR3903

Trial name or title	Dose-to-target of etanercept treatment: a dose-tapering randomised controlled trial in patients with rheumatoid arthritis, ankylosing spondylitis or psoriatic arthritis
Methods	Open randomised controlled study of a dose-to-target step-down treatment strategy in the Netherlands
Participants	People with RA, PsA, and AS, etanercept treatment 50 mg/week > 6 months and minimal disease activity
Interventions	Continuation of etanercept 50 mg/week OR etanercept 50 mg/2 weeks After 6 months among participants still in a state of minimal disease activity, etanercept 50 mg/2 weeks in the original continuation group and etanercept discontinuation in the original etanercept 50 mg/2 weeks
Outcomes	Primary outcome: proportion of participants with RA, AS, PsA maintaining minimal disease activity after dose interval prolongation of etanercept Secondary outcomes: cost-effectiveness of tapering down etanercept treatment, whether the lowest effective etanercept dose will reduce the risk of adverse events, predictive value of serum etanercept through levels and other participant-related factors for successful down-titration
Starting date	May 2013
Contact information	Dr GJ Wolbink
Notes	Dutch trial register: NTR3903

AS: ankylosing spondylitis

bDMARD: biological DMARD

CDAI: Clinical Disease Activity Index

DAS28: disease activity score in 28 joints

DMARD: disease-modifying antirheumatic drug

HAQ-DI: Health Assessment Questionnaire-Disability Index

PsA: psoriatic arthritis

RA: rheumatoid arthritis

RAMRIS: Rheumatoid Arthritis Magnetic Resonance Imaging Score

RAPID-3: Routine Assessment of Patient Index Data 3

SDAI: Simplified Disease Activity Index

sDMARD: synthetic DMARD

SF-36: 36-item Short Form Health Survey

SpA: spondyloarthritis

TNF: tumour necrosis factor
TSQM: Treatment Satisfaction Questionnaire for Medication
WPAI: Work Productivity and Activity Impairment

DATA AND ANALYSES

Comparison 1. Anti-TNF dose reduction versus anti-TNF continuation

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean disease activity score (DAS28)	2	501	Mean Difference (IV, Random, 95% CI)	0.06 [-0.11, 0.24]
2 Proportion persistent remission (DAS28)	2	612	Risk Ratio (IV, Random, 95% CI)	1.01 [0.80, 1.28]
3 Proportion switched to another biologic	1	323	Risk Ratio (IV, Random, 95% CI)	0.40 [0.17, 0.93]
4 Proportion radiographic progression (mSvdH > 0.5)	2	553	Risk Ratio (IV, Random, 95% CI)	1.22 [0.76, 1.95]
5 Function (Health Assessment Questionnaire)	2	501	Mean Difference (IV, Random, 95% CI)	0.09 [-0.00, 0.19]
6 Number of serious adverse events	5	1084	Risk Ratio (IV, Random, 95% CI)	1.09 [0.65, 1.82]
7 Withdrawals due to adverse events	3	937	Risk Ratio (IV, Random, 95% CI)	1.07 [0.51, 2.24]
8 Proportion of participants with a flare	3		Risk Ratio (IV, Random, 95% CI)	Subtotals only
9 Quality of life	2	501	Mean Difference (IV, Random, 95% CI)	-0.00 [-0.04, 0.03]

Analysis 1.1. Comparison 1 Anti-TNF dose reduction versus anti-TNF continuation, Outcome 1 Mean disease activity score (DAS28).

Analysis 1.2. Comparison 1 Anti-TNF dose reduction versus anti-TNF continuation, Outcome 2 Proportion persistent remission (DAS28).

Analysis 1.3. Comparison 1 Anti-TNF dose reduction versus anti-TNF continuation, Outcome 3 Proportion switched to another biologic.

Analysis 1.4. Comparison 1 Anti-TNF dose reduction versus anti-TNF continuation, Outcome 4 Proportion radiographic progression (mSvdH > 0.5).

Analysis 1.5. Comparison 1 Anti-TNF dose reduction versus anti-TNF continuation, Outcome 5 Function (Health Assessment Questionnaire).

Analysis 1.6. Comparison 1 Anti-TNF dose reduction versus anti-TNF continuation, Outcome 6 Number of serious adverse events.

Analysis 1.7. Comparison 1 Anti-TNF dose reduction versus anti-TNF continuation, Outcome 7 Withdrawals due to adverse events.

Analysis 1.8. Comparison 1 Anti-TNF dose reduction versus anti-TNF continuation, Outcome 8 Proportion of participants with a flare.

Analysis 1.9. Comparison 1 Anti-TNF dose reduction versus anti-TNF continuation, Outcome 9 Quality of life.

Comparison 2. Anti-TNF discontinuation versus anti-TNF continuation

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean disease activity score (DAS28)	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 Discontinuation without restarting, or with restarting and LOCF analysis	2	733	Mean Difference (IV, Random, 95% CI)	0.96 [0.67, 1.25]
1.2 Discontinuation with restarting without LOCF analysis	1	692	Mean Difference (IV, Random, 95% CI)	0.29 [0.14, 0.44]
2 Proportion persistent remission (DAS28)	6		Risk Ratio (IV, Random, 95% CI)	Subtotals only
3 Proportion radiographic progression (mSvdH > 0.5)	3	549	Risk Ratio (IV, Random, 95% CI)	1.69 [1.10, 2.59]
4 Function (Health Assessment Questionnaire)	4	1498	Mean Difference (IV, Random, 95% CI)	0.18 [0.05, 0.31]
5 Number of serious adverse events	8	2095	Risk Ratio (IV, Random, 95% CI)	1.29 [0.82, 2.03]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6 Withdrawals due to adverse events	4	1116	Risk Ratio (IV, Random, 95% CI)	1.46 [0.75, 2.84]
7 Proportion flare	5		Risk Ratio (IV, Random, 95% CI)	Totals not selected
7.1 DAS28 ≥ 3.2 and Δ DAS ≥ 0.6 (24 to 52 weeks' follow-up)	3		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
7.2 DAS28 ≥ 3.2 OR Δ DAS ≥ 0.6 (follow-up 52 weeks)	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
7.3 DAS28 ≥ 2.6 OR Δ DAS > 1.2 (follow-up 28 weeks)	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
7.4 Proportion failure (follow-up 48 weeks)	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
8 Quality of life	2	733	Mean Difference (IV, Random, 95% CI)	-0.10 [-0.13, -0.07]

Analysis 2.1. Comparison 2 Anti-TNF discontinuation versus anti-TNF continuation, Outcome 1 Mean disease activity score (DAS28).

Analysis 2.2. Comparison 2 Anti-TNF discontinuation versus anti-TNF continuation, Outcome 2 Proportion persistent remission (DAS28).

Analysis 2.3. Comparison 2 Anti-TNF discontinuation versus anti-TNF continuation, Outcome 3 Proportion radiographic progression (mSvdH > 0.5).

Analysis 2.4. Comparison 2 Anti-TNF discontinuation versus anti-TNF continuation, Outcome 4 Function (Health Assessment Questionnaire).

Analysis 2.5. Comparison 2 Anti-TNF discontinuation versus anti-TNF continuation, Outcome 5 Number of serious adverse events.

Analysis 2.6. Comparison 2 Anti-TNF discontinuation versus anti-TNF continuation, Outcome 6 Withdrawals due to adverse events.

Analysis 2.7. Comparison 2 Anti-TNF discontinuation versus anti-TNF continuation, Outcome 7 Proportion flare.

Analysis 2.8. Comparison 2 Anti-TNF discontinuation versus anti-TNF continuation, Outcome 8 Quality of life.

Comparison 3. Anti-TNF disease activity-guided dose tapering versus anti-TNF continuation

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean disease activity score (DAS28)	3	357	Mean Difference (IV, Random, 95% CI)	0.25 [-0.17, 0.67]
2 Proportion persistent remission (DAS28)	1	180	Risk Ratio (IV, Random, 95% CI)	0.89 [0.75, 1.06]
3 Proportion switched to another biologic	2	317	Risk Ratio (IV, Random, 95% CI)	0.62 [0.25, 1.54]
4 Proportion radiographic progression (mSvdH > 0.5 or > 1.0)	2	312	Risk Ratio (IV, Random, 95% CI)	1.45 [0.77, 2.73]
5 Function (Health Assessment Questionnaire)	1	123	Mean Difference (IV, Random, 95% CI)	0.20 [-0.02, 0.42]
6 Number of serious adverse events	2	317	Risk Ratio (IV, Random, 95% CI)	1.24 [0.42, 3.70]
7 Proportion flare	3		Risk Ratio (IV, Random, 95% CI)	Totals not selected
7.1 DAS28-ESR >2.6 with Δ DAS28-ESR > 0.6 after 18 months	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.2 Δ DAS28-CRP > 1.2 OR Δ DAS28-CRP > 0.6 and current DAS28-CRP $\geq$ 3.2 for > 3 months at 9 months' follow-up	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
7.3 Δ DAS28-CRP > 1.2 OR Δ DAS28-CRP > 0.6 and current DAS28-CRP $\geq$ 3.2 for > 3 months at 18 months' follow-up	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
7.4 Δ DAS28-CRP > 1.2 OR Δ DAS28-CRP > 0.6 and current DAS28-CRP $\geq$ 3.2 for < 3 months at 9 months' follow-up	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
7.5 Δ DAS28-CRP > 1.2 OR Δ DAS28-CRP > 0.6 and current DAS28-CRP $\geq$ 3.2 for < 3 months at 18 months' follow-up	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
7.6 DAS28 > 2.6, SDAI > 5 or ACR/EULAR criteria not fulfilled (follow-up 24 weeks)	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
7.7 DAS28 > 2.6, SDAI > 5 or ACR/EULAR criteria not fulfilled (follow-up 48 weeks)	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
7.8 DAS28 > 2.6, SDAI > 5 or ACR/EULAR criteria not fulfilled (follow-up 72 weeks)	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
7.9 DAS28 > 2.6, SDAI > 5 or ACR/EULAR criteria not fulfilled (follow-up 96 weeks)	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
8 Change in other medication	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
8.1 Use of intramuscular or intra-articular glucocorticoid injections at 18 months	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
8.2 Use of oral glucocorticoids at 18 months	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
8.3 DMARDs reduction or discontinuation after 18 months	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
8.4 DMARD initiation or dose escalation after 18 months	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
8.5 Use of a DMARD at 18 months	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 3.1. Comparison 3 Anti-TNF disease activity-guided dose tapering versus anti-TNF continuation, Outcome 1 Mean disease activity score (DAS28).

Analysis 3.2. Comparison 3 Anti-TNF disease activity-guided dose tapering versus anti-TNF continuation, Outcome 2 Proportion persistent remission (DAS28).

Analysis 3.3. Comparison 3 Anti-TNF disease activity-guided dose tapering versus anti-TNF continuation, Outcome 3 Proportion switched to another biologic.

Analysis 3.4. Comparison 3 Anti-TNF disease activity-guided dose tapering versus anti-TNF continuation, Outcome 4 Proportion radiographic progression (mSvdH > 0.5 or > 1.0).

Analysis 3.5. Comparison 3 Anti-TNF disease activity-guided dose tapering versus anti-TNF continuation, Outcome 5 Function (Health Assessment Questionnaire).

Analysis 3.6. Comparison 3 Anti-TNF disease activity-guided dose tapering versus anti-TNF continuation, Outcome 6 Number of serious adverse events.

Analysis 3.7. Comparison 3 Anti-TNF disease activity-guided dose tapering versus anti-TNF continuation, Outcome 7 Proportion flare.

Analysis 3.8. Comparison 3 Anti-TNF disease activity-guided dose tapering versus anti-TNF continuation, Outcome 8 Change in other medication.

APPENDICES

Appendix 1. The Cochrane Library search strategy

#1 MeSH descriptor: [Arthritis, Rheumatoid] explode all trees

#2 caplan* near/2 syndrome

#3 felty* near/2 syndrome

#4 "rheumatoid nodule*"

#5 "rheumatoid vasculitis"

#6 sjogren* near/2 syndrome

#7 "still* disease"

#8 arthritis near/2 rheumat*

#9 (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8)

#10 MeSH descriptor: [Tumor Necrosis Factor-alpha] this term only and with qualifier(s) [Antagonists & Inhibitors – AI]

#11 MeSH descriptor: [Adalimumab] this term only

#12 MeSH descriptor: [Certolizumab Pegol] this term only

#13 MeSH descriptor: [Etanercept] this term only

#14 MeSH descriptor: [Infliximab] this term only

#15 "anti-tumor necrosis factor"

#16 "anti-tumour necrosis factor"

#17 anti-tnf

#18 "tumor necrosis factor" near/3 inhibit*

#19 "tumour necrosis factor" near/3 inhibit*

#20 tnf near/3 inhibit*

#21 tnfi

#22 tnf near/3 block*

#23 bDMARD*

#24 "biologic* DMARD*"

#25 adalimumab

#26 humira

#27 etanercept

#28 enbrel

#29 benepali

#30 infliximab

#31 remicade

#32 remsima

#33 inflectra

#34 golimumab

#35 simponi

#36 certolizumab near/2 pegol

#37 cimzia

#38 (#10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37)

#39 MeSH descriptor: [Dose-Response Relationship, Drug] this term only

#40 MeSH descriptor: [Drug Administration Schedule] this term only

#41 MeSH descriptor: [Remission Induction] this term only

#42 MeSH descriptor: [Withholding Treatment] this term only

#43 down near/3 titrat*

#44 dose near/3 reduc*

#45 dose near/3 de-escalat*

#46 discontinu*

#47 dose near/3 taper*

#48 spac*

#49 cessat*

#50 stop*

#51 interval near/3 widen*

#52 biologic near/2 free

#53 withdraw*

#54 dose near/3 titrat*

#55 (#39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54)

#56 (#9 and #38 and #55)

Appendix 2. MEDLINE search strategy

1 exp arthritis, rheumatoid/

2 (arthritis adj2 rheumat\$).tw.

3 (felty\$ adj2 syndrome).tw.

4 (caplan\$ adj2 syndrome).tw.

5 rheumatoid nodule\$.tw.

6 rheumatoid vasculitis.tw.

7 (sjogren\$ adj2 syndrome).tw.

8 still\$ disease.tw.

9 or/1-8

10 Adalimumab/

- 11 Certolizumab Pegol/
- 12 Etanercept/
- 13 Infliximab/
- 14 Infliximab.tw.
- 15 remicade.tw.
- 16 remsima.tw.
- 17 inflectra.tw.
- 18 adalimumab.tw.
- 19 humira.tw.
- 20 (Certolizumab adj2 pegol).tw.
- 21 cimzia.tw.
- 22 Etanercept.tw.
- 23 enbrel.tw.
- 24 benepali.tw.
- 25 Golimumab.tw.
- 26 simponi.tw.
- 27 Tumor Necrosis Factor-alpha/ai [Antagonists & Inhibitors]
- 28 anti-tnf.tw.
- 29 anti-tumor necrosis factor.tw.
- 30 anti-tumour necrosis factor.tw.
- 31 (Tumor Necrosis Factor adj3 inhibit\$).tw.
- 32 (tumour necrosis factor adj3 inhibit\$).tw.
- 33 (tnf adj3 inhibit\$).tw.
- 34 Tnfi.tw.
- 35 (tnf adj3 block\$).tw.
- 36 bDMARD\$.tw.
- 37 biologic\$ DMARD\$.tw.
- 38 or/10-37
- 39 Dose-Response Relationship, Drug/
- 40 (down adj3 titrat\$).tw.
- 41 (dose adj3 titrat\$).tw.
- 42 (dose adj3 reduc\$).tw.
- 43 (dose adj3 de-escalat\$).tw.
- 44 withdraw\$.tw.
- 45 discontinu\$.tw.

46 (dose adj3 taper\$.tw.
47 (biologic adj2 free).tw.
48 spac\$.tw.
49 cessat\$.tw.
50 stop\$.tw.
51 (interval adj3 widen\$.tw.
52 Drug Administration Schedule/
53 remission induction/
54 Withholding Treatment/
55 or/39-54
56 randomized controlled trial.pt.
57 controlled clinical trial.pt.
58 randomized.ab.
59 randomised.ab
60 placebo.ab.
61 clinical trials as topic.sh.
62 randomly.ab.
63 trial.ti.
64 or/56-63
65 exp animals/ not humans.sh.
66 64 not 65
67 9 and 38 and 55
68 66 and 67

Appendix 3. Embase search strategy

1 exp arthritis, rheumatoid/
2 (arthritis adj2 rheumat\$.tw.
3 (felty\$ adj2 syndrome).tw.
4 (caplan\$ adj2 syndrome).tw.
5 rheumatoid nodule\$.tw.
6 rheumatoid vasculitis.tw.
7 (sjogren\$ adj2 syndrome).tw.
8 still\$ disease.tw.
9 or/1-8
10 infliximab.tw.
11 infliximab/

- 12 remicade.tw.
- 13 remsima.tw.
- 14 inflectra.tw.
- 15 humira.tw.
- 16 adalimumab/
- 17 adalimumab.tw.
- 18 cimzia.tw.
- 19 certolizumab pegol/
- 20 (certolizumab adj2 pegol).tw.
- 21 enbrel.tw.
- 22 etanercept/
- 23 etanercept.tw.
- 24 benepali.tw.
- 25 simponi.tw.
- 26 golimumab/
- 27 golimumab.tw.
- 28 tumor necrosis factor antibody/
- 29 anti-tnf.tw.
- 30 anti-tumor necrosis factor.tw.
- 31 anti-tumour necrosis factor.tw.
- 32 (Tumor Necrosis Factor adj3 inhibit\$).tw.
- 33 (Tumour Necrosis Factor adj3 inhibit\$).tw.
- 34 (tnf adj3 inhibit\$).tw.
- 35 Tnfi.tw.
- 36 (tnf adj3 block\$).tw.
- 37 bDMARD\$.tw.
- 38 biologic\$ DMARD\$.tw.
- 39 or/10-38
- 40 (down adj3 titrat\$).tw.
- 41 (biologic adj2 free).tw.
- 42 drug dose reduction/
- 43 (dose adj3 reduc\$).tw.
- 44 (dose adj3 de-escalat\$).tw.
- 45 discontinu\$.tw.
- 46 (dose adj3 taper\$).tw.

- 47 spac\$.tw.
- 48 cessat\$.tw.
- 49 stop\$.tw.
- 50 (interval adj3 widen\$).tw.
- 51 withdraw\$.tw.
- 52 (dose adj3 titrat\$).tw.
- 53 remission/
- 54 treatment withdrawal/
- 55 dose response/
- 56 or/40-55
- 57 9 and 39 and 56
- 58 random\$.tw.
- 59 factorial\$.tw.
- 60 crossover\$.tw.
- 61 cross over.tw.
- 62 cross-over.tw.
- 63 placebo\$.tw.
- 64 (doubl\$ adj blind\$).tw.
- 65 (singl\$ adj blind\$).tw.
- 66 assign\$.tw.
- 67 allocat\$.tw.
- 68 volunteer\$.tw.
- 69 crossover procedure/
- 70 double blind procedure/
- 71 randomised controlled trial/
- 72 single blind procedure/
- 73 or/58-72
- 74 57 and 73

Appendix 4. Web of Science search strategy

#1 rheumat* NEAR/2 arthritis or caplan* NEAR/2 syndrome or felty* NEAR/2 syndrome or "rheumatoid nodule*" or "rheumatoid vasculitis" or sjogren* NEAR/2 syndrome or "still* disease"

#2 "anti-tumor necrosis factor" or "anti-tumour necrosis factor" or "tumor necrosis factor" NEAR/3 inhibit* or "tumour necrosis factor" NEAR/3 inhibit* or anti-tnf or tn timer/3 inhibit* or tn timer/3 block* or tn timer/3 adalimumab or humira or etanercept or enbrel or benepali or infliximab or remicade or remsima or inflectra or golimumab or simponi or certolizumab NEAR/2 pegol or cimzia or bDMARD* or "biologic* DMARD*"

#3 down NEAR/3 titrat* or dose NEAR/3 reduc* or dose NEAR/3 de-escalat* or discontinu* or dose NEAR/3 taper* or spac* or cessat* or stop* or interval NEAR/3 widen* or dose NEAR/3 titrat* or withdraw* or biologic NEAR/2 free

#4 trial* or random* or control*

#5 #1 AND #2 AND #3 AND #4

Appendix 5. Search strategies trial registries

Registry: US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (clinicaltrials.gov/)

Date of search: 11 April 2018

Search terms and results:

Date	Terms	Hits
11-4-2018	Rheumatoid arthritis AND biologics	470
11-4-2018	Rheumatoid arthritis AND anti TNF	291
11-4-2018	Rheumatoid arthritis AND etanercept	168
11-4-2018	Rheumatoid arthritis AND adalimumab	201
11-4-2018	Rheumatoid arthritis AND infliximab	119
11-4-2018	Rheumatoid arthritis AND golimumab	38
11-4-2018	Rheumatoid arthritis AND certolizumab	71
11-4-2018	Rheumatoid arthritis AND discontinuing	14
11-4-2018	Rheumatoid arthritis AND reducing	250
11-4-2018	Rheumatoid arthritis AND withdrawal	96
11-4-2018	Rheumatoid arthritis AND "dose reduction"	25

Registry: EU Clinical Trials Register (www.clinicaltrialsregister.eu/)

Date of search: 11 April 2018

Search terms and results:

Date	Terms	Hits
11-4-2018	Rheumatoid arthritis AND biologics	66
11-4-2018	Rheumatoid arthritis AND anti TNF	144
11-4-2018	Rheumatoid arthritis AND etanercept	141
11-4-2018	Rheumatoid arthritis AND adalimumab	159
11-4-2018	Rheumatoid arthritis AND infliximab	119

(Continued)

11-4-2018	Rheumatoid arthritis AND golimumab	53
11-4-2018	Rheumatoid arthritis AND certolizumab	56
11-4-2018	Rheumatoid arthritis AND discontinuing	4
11-4-2018	Rheumatoid arthritis AND reducing	25
11-4-2018	Rheumatoid arthritis AND withdrawal	62
11-4-2018	Rheumatoid arthritis AND "dose reduction"	12

Registry: Dutch trial register (www.trialregister.nl)

Date of search: 11-4-2018

Search terms and results:

Date	Terms	Hits
11-4-2018	Rheumatoid arthritis	59
11-4-2018	TNF-blockers	1
11-4-2018	Anti-TNF	11
11-4-2018	TNF	19

Registry: World Health Organization International Clinical Trials Registry Platform (www.who.int/ictcp/en/)

Date of search: 11 April 2018

Search terms and results:

Date	Terms	Hits
11-4-2018	Anti-TNF OR biologic OR adalimumab OR etanercept OR certolizumab OR infliximab OR golimumab AND Rheumatoid arthritis AND dose OR taper OR withdrawal OR discontinuation OR reduce OR titration (recruitment status: ALL)	131

Appendix 6. Risk of bias

Article nr:

Reviewer: BvdB/LV

Date:

Domain	Support for judgement	Judgement low risk of bias, high risk of bias, or unclear risk of bias
<i>Selection bias</i>		
Random sequence generation		
Allocation concealment		
<i>Performance bias</i>		
Blinding of participants and personnel		
<i>Detection bias</i>		
Blinding of outcome assessment (subjective outcomes)		
Blinding of outcome assessment (objective outcomes)		
<i>Attrition bias</i>		
Incomplete outcome data		
<i>Reporting bias</i>		
Selective reporting		
<i>Other bias</i>		
Other sources of bias		

FEEDBACK

Comments - Lo and Tejani, 30 March 2015

Summary

Comment: Written by:

Elaine Lo, MSc. (Clin Pharm), BCPS, PharmD Student Aaron M Tejani, BSc.Pharm, PharmD

We read with interest the review on down-titration and discontinuation strategies of tumor necrosis factor (TNF)-blocking agents for rheumatoid arthritis (RA) in patients with low disease activity and there are a few points we wish to address.

The authors concluded that dose reduction of etanercept after at least 3 to 12 months of low disease activity, seems as effective as continuing the standard dose with respect to disease activity and functional outcomes; while discontinuation of adalimumab and etanercept is inferior to continuation of treatment. The conclusion is driven mainly by the results of the PRESERVE trial², which weighs 59.7% and 30% in the meta-analyses of the dose reduction and discontinuation endpoint respectively. We feel that the conclusion should be rephrased as “in patients who were put on anti-TNF agents (with methotrexate) and improved from moderate to low disease activity for at least 3 to 12 months” to reflect the patient population studied in the PRESERVE trial. This would prevent unintentional extrapolation of the conclusion to patients who start out with severe disease activity or whose disease activity remains unchanged on anti-TNF agents.

The PRESERVE trial is rated as having a low risk of bias for all parameters except “incomplete outcome data” and that differs from our evaluation. PRESERVE is the largest study (n=604) included in the review and the only trial identified for many endpoints. Thus an accurate evaluation of its risk of bias is important in the synthesis of data. Though not reported in PRESERVE, injection site reaction is a significant adverse event with etanercept. In the Cochrane review by Lethaby et al³, more patients receiving etanercept plus DMARD developed injection site reactions than those taking DMARD alone (at six months: 25.6% versus [vs] 3.8%, RR 6.9; 95% CI 2.2 to 21.3). For patients who were given etanercept for 9 months in the open-label phase, the sudden lack of injection site reaction might be a trigger for unblinding in the placebo group despite the double blind design and identical drug package. By the same token, assessors/ study investigators could have been unblinded by the lack of injection site reaction in the placebo group. Potentially compromised blinding for a subjective outcome like Disease activity score-28 (DAS28) meets the criteria for judgment of high risk of performance bias.⁴ Inadequate blinding combined with blocked randomization might increase the risk of selection bias. With a block size of 3, when assignments are revealed because of the characteristic injection site reaction, it might be possible to predict future assignments, thus undermining allocation concealment. The chance of seeing a pattern and hence being able to predict assignment is arguably small in a trial that involves 80 centres recruiting 834 patients. Yet we have no information regarding the distribution of recruitment among centres and how many centres were recruiting at the same time. Selection bias should be unclear rather than low.⁴

We agree with the authors’ assessment that the attrition risk is high in PRESERVE. There were significantly more treatment discontinuation due to unsatisfactory responses in the placebo group compared to the 25mg etanercept and 50mg etanercept group (43 (21.5%) vs 27 (13.4%) vs 4 (2%)). Patients were assumed to be non-responders if they discontinued early because of poor efficacy. This might exaggerate the number of non-responders, especially in the placebo group. There is no objective criteria for discontinuation due to inefficacy described in the trial – patient may not have reached the point of being considered a non-responder when they left the study. Though the benefit of etanercept continuation withstands the test of sensitivity analysis for the outcome of DAS28<3.2, other endpoints with a smaller effect size or lower incidence e.g. normal HAQ-DI and ACR70 may have become insignificant should a different analysis be used. Having mentioned that the risk of unblinding is high, the threshold of discontinuation for a “perceived” lack of drug effect might be lower in PRESERVE than an adequately blinded study. As for patients who discontinued for reasons other than unsatisfactory response, missing data were imputed with last observation carried forward (LOCF) method. There is no information about the number of patients that were affected by LOCF. A patient may be categorized as having low disease activity when he was lost to follow up and imputed as a responder but indeed would be rated as having high disease activity if assessment was done at week 88. It appears that the review authors took the data straight from Table 3 of the PRESERVE trial which do not account for the uncertainty around imputation. We suggest communicating with the authors of PRESERVE about the extent of LOCF/ non-responder imputation and performing sensitivity analyses for outcomes presented in the review (e.g. DAS28<2.6, HAQ-DI etc) like those performed for DAS28<3.2 in the supplementary appendix of PRESERVE.²

We also feel that the reporting for assessment of adverse events (AE) and co-intervention (e.g. methotrexate and glucocorticoid dose) was inadequate in PRESERVE. Besides cost, another reason to attempt dose reduction or discontinuation is to avoid unnecessary exposure to drug toxicity. PRESERVE is the only trial included for the evaluation of serious adverse events (SAE). However, the trial authors did not describe how SAE were assessed or adjudicated. Indeed, PRESERVE captured significantly less SAE and AE compared to other trials comparing etanercept plus methotrexate vs methotrexate alone (e.g. Emery, 2008⁵: SAE 12%, any AE 91%; Weinblatt, 1999⁶: infection 51-63%; Klareskog, 2004⁷: infection AE 81%, 67%-64% PRESERVE²: SAE 3-8%, any AE 53-61%, infection 1-2%). The dose of methotrexate and glucocorticoid is not reported but is deemed pertinent as there seemed to be no restriction on adjustment of these drugs for lack of efficacy. The review authors should consider explaining the risk explicitly to the readers and incorporating this as part of the quality assessment.

The terms “low disease activity” and “remission” were used loosely in the review. Uninformed readers might find this misleading and confusing. For instance, in the plain language summary, the author stated the impact of stopping or lowering the dose of anti-TNF drugs on “RA remission”. However, this is referred to as “persistent low disease activity” in the main text. Under this umbrella of “persistent low disease activity”, the authors pooled outcomes on DAS28 remission, non-failure and DAS28-CRP<2.7 – not remission alone. We suggest the authors revising the wording in the plain language summary from “RA remission” to “persistent low disease activity” for the sake of consistency.

We noted with regret that the authors of the review changed the major outcome from “proportion of patients with a flare” to “proportion of patients with persistent low disease activity”, claiming that the two are highly comparable. Despite the understanding that only 2 of the included studies reported the former outcome, we still want to acknowledge its merit as an endpoint. As revealed in a study by the OMERACT group⁸, the validated flare criteria (i.e. an increase in DAS28>1.2 or >0.6 if DAS28>3.2) was found to be more discriminating and more valid than a threshold criteria (i.e. DAS28>2.6 or 3.2) (see Table 1) It gives a good balance of specificity/ sensitivity in the transition scale where patient/ physician were asked whether disease activity had changed compared with the last visit on a 7-point Likert scale (criterion validity), and is well associated with DMARD/ corticosteroid and CRP change. As pointed out by the review authors, in addition to mean disease activity, a validated RA flare criterion like the OMERACT DAS28-based flare criteria should be considered. We look forward to seeing studies with standardized outcomes for future meta-analyses.

We hope this provides some constructive feedbacks for the next review. We look forward to hearing from you.

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8. van der Maas A, Lie E, Christensen R, et al. Construct and criterion validity of several proposed DAS28-based rheumatoid arthritis flare criteria: an OMERACT cohort validation study. *Annals of the rheumatic diseases* 2013;72(11):1800-5. 10.1136/annrheumdis-2012-202281

I agree with the conflict of interest statement below:

I certify that I have no affiliations with or involvement in any organization or entity with a financial interest in the subject matter of my feedback.

Reply

Hereby our response:

We read the comment by Lo et al on our review 'Down-titration and discontinuation strategies of tumor necrosis factor–blocking agents for rheumatoid arthritis in patients with low disease activity' with interest. Herewith we thank them for taking the time and effort to do this, and provide a point to point response:

First it should be noted that we plan to update the review within the next year already. This because in the original review the majority of studies had not yet been published as a full text article. Since then, some important trials have been published in full, and also we expect some strategy studies to be published within the next months. In this update, we will incorporate the comments by Lo et al were applicable.

With respect to our conclusion that "dose reduction of etanercept after at least 3 to 12 months of low disease activity, seems as effective as continuing the standard dose with respect to disease activity and functional outcomes; while discontinuation of adalimumab and etanercept is inferior to continuation of treatment." We think that this statement is correct. Although PRESERVE study weights in heavily, both Botsios 2007 and van Vollenhoven 2012 did not include only patients that had only moderate disease activity at study start. We therefore think that our conclusion is still valid. In the update we will hopefully be able to include STRASS and DRESS strategy studies, that also did not limit patient inclusion to patients with moderate disease activity at study start

With regard to risk of bias being high due to possible unblinding and blocked randomisation, we disagree. Injection site reaction can occur, but are firstly for the most part limited to the first 6 months of treatment. Also, patients with severe ISR stop treatment. Secondly, low dose etanercept patients could not have been unblinded by sudden, as ISR do not seem to depend on dose. Also, even when unblinding occurred in some patients, it could only give bias in the conservative direction, ie patients and physicians would expect a flare more so in these patients. Estimates for disease activity would not be lower, but higher in these patients. Finally, for radiographic outcome, any unblinding would not play a role. Of course classifying a certain characteristic of a study as having a risk of bias remains a judgement call, but we do not think that it is fair to expect a large risk of bias in the estimates of this study. In the update of the review, we will address these issues more in depth.

Adverse event reporting is indeed overall suboptimal, and we have mentioned this in our conclusion. The same holds true for absence of any cost effectiveness analyses. In the upcoming update, we expect to have more data on this.

"We suggest the authors revising the wording in the plain language summary from "RA remission" to "persistent low disease activity" for the sake of consistency. ". Thanks for the suggestion, we will do this in the next update.

Finally, we agree wholeheartedly with the suggestion to add % patients with flare as outcome. We are the authors by the way of the OMERACT flare criteria paper that is referred to, so we are quite familiar with the upside of using this outcome. Unfortunately, this outcome was not used in the trials we have identified. Furthermore, in strategy studies, the outcome of prolonged flare is probably better reflecting (non) inferiority of a certain tapering strategy, see for ample discussion about this in our recent BMJ paper. www.bmj.com/content/350/bmj.h1389-0.long

Thank again for taking the time to review our systematic review.

Best regards,

Contributors

Dr A.A. (Alfons) den Broeder, on behalf of all co-authors.

WHAT'S NEW

Date	Event	Description
3 June 2019	Amended	Correction to article metadata; no impact on article content.

HISTORY

Protocol first published: Issue 4, 2013

Review first published: Issue 9, 2014

Date	Event	Description
22 May 2019	New citation required and conclusions have changed	One previously included trial was excluded in this update. We included eight additional trials, for a total of 14 studies
29 March 2018	New search has been performed	Conclusions have changed. We have now more evidence on other tumour necrosis factor blocking agents, and disease activity tapering is comparable to continuation of treatment with respect to the proportion of participants with persistent remission and may be comparable regarding disease activity

Date	Event	Description
20 May 2015	Feedback has been incorporated	Incorporated feedback from Lo and Tejani

CONTRIBUTIONS OF AUTHORS

Title and protocol: AAdB, NvH.

Review of abstracts and full-text articles: BJFvdB, NvH, AAdB, LMV.

Data extraction: BJFvdB, NvH, LMV.

Results and analyses: NvH, BJFvdB, WJ, AAdB, AvdM, LMV.

Interpretation of data: NvH, BJFvdB, WJ, AAdB, AvdM, JEV, FHJvdH, MH, LMV.

Draft of the review: NvH, BJFvdB, AAdB, LMV.

Editing of the draft: WJ, AvdM, JEV, FHJvdH, MH.

DECLARATIONS OF INTEREST

Disclosures

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Office space and computer access

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- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

- We removed the sentence: "The intervention should include the option for a patient to restart the anti-TNF agent in case of loss of response." from [Types of interventions](#). We did this because the largest study included in this review did not include the option to restart the anti-TNF agent in case of loss of response. It was not always clear for the other included studies whether participants could restart the anti-TNF agent. We believe the possibility of restarting an anti-TNF agent in case of loss of response is important.
- Different review authors for selecting studies: BJFvdB replaced AAdB in selecting studies, abstracting data, and assessing risk of bias. AAdB was the referee. This change was made because AAdB had time limitations.

- Switch in primary outcome: We made "Proportion of patients with persistent low disease activity" a major outcome and "Proportion of patients with a flare" a minor outcome. We switched these outcomes because the two are highly comparable. Most included studies used the first outcome.
- Additional types of studies: Both superiority and non-inferiority trials were included. One of the studies included in this review was reported to be a non-inferiority study. Also, some of the identified ongoing trials were reported to be non-inferiority studies. A non-inferiority design is the best study design for a down-titration strategy.
- Additional types of participants: standard (or lower) anti-TNF dose. We added the "or lower dose" because some studies might also include participants who used a lower-than-standard dose before entering the study.
- Addition to other sources of bias: We added imbalance in prognostic variables as another source of bias, as we believe this is an important addition for the 'Risk of bias' assessment in our review.
- The outcome "proportion persistent loss of response, refractory to re-installment of the tapered anti-TNF" was changed to "proportion of participants that switched to another biologic due to persistent loss of response, refractory to re-installment of the tapered anti-TNF in the intervention group". We made this change since the definition was not specific enough and insufficiently distinct from the other outcome measures.
- For the outcome "proportion participants with persistent low disease activity" we have chosen to report the proportion of participants in persistent remission to have more data available for this outcome. Since remission is more stringent than low disease activity, we might be more sensitive to differences between continuation and down-titration of anti-TNF.

INDEX TERMS

Medical Subject Headings (MeSH)

Antibodies, Monoclonal, Humanized; Antirheumatic Agents [*therapeutic use]; Arthritis, Rheumatoid [*drug therapy]; Randomized Controlled Trials as Topic; Receptors, Tumor Necrosis Factor [*therapeutic use]; Recurrence; Remission Induction; Tumor Necrosis Factor-alpha [*antagonists & inhibitors]

MeSH check words

Female; Humans; Male; Middle Aged