Canadian Rheumatology Association living guidelines for the pharmacological management of rheumatoid arthritis with disease-modifying anti-rheumatic drugs

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Key indexing terms (MeSH): rheumatoid arthritis, clinical practice guideline, antirheumatic agents, GRADE, patient participation

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Funding: Funding for this guideline was provided by the Canadian Rheumatology Association

Conflicts of interest:

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J Pardo: Funding from Canadian Rheumatology Association to Cochrane Musculoskeletal to provide methodological support for guideline development.

C Barnabe: Honoraria for advisory boards (Gilead, Sanofi, Celltrion) and speaker fees (Sanofi) in past 3 years.

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D. Richards: Volunteer Vice President of Canadian Arthritis Patient Alliance which receives the majority of its funding from independent grants from pharmaceutical companies. DR's employer, Five02 Labs Inc, has received payment in the last 3 years from Novo Nordisk Canada (speaking on living with arthritis and arthritis advocacy) and Lilly Canada (sharing patient story, participating in an advisory board).

P Tugwell: None

N Bansback: None

P Akhavan: Honoraria for advisory boards (Janssen, Eli Lilly, Pfizer, Sandoz, Celltrion, AbbVie, Roche).

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V Bykerk: Consultant: Amgen, BMS, Gilead, Genzyme, Regeneron, UCB; Research funding: Amgen, BMS, Genzyme, Pfizer, Sanofi Aventis, UCB

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Running title: CRA RA Guideline

Word count: 3221

ABSTRACT

Objective: To provide the initial installment of a living guideline that will provide up-to-date guidance on the pharmacological management of patients with rheumatoid arthritis (RA) in Canada.

Methods: The Canadian Rheumatology Association (CRA) formed a multidisciplinary panel composed of rheumatologists, researchers, methodologists, and patients. In this first installment of our living guideline, the panel developed a recommendation for tapering of biologic and targeted synthetic (b/ts) DMARD therapy in patients in sustained remission using the GRADE approach, including a health equity framework developed for the Canadian RA population. The recommendation was adapted from a living guideline of the Australia & New Zealand Musculoskeletal Clinical Trials Network.

Results: In people with RA who are in sustained low disease activity or remission for at least 6 months, we suggest offering stepwise reduction in the dose of b/tsDMARD without discontinuation, in the context of a shared decision, provided patients are able to rapidly access rheumatology care and re-establish their medications if needed. In patients where rapid access to care or re-establishing access to medications is challenging, we conditionally recommend against tapering. A patient decision aid was developed to complement the recommendation.

Conclusion: This living guideline will provide contemporary RA management recommendations for Canadian practice. New recommendations will be added over time and updated, with the latest recommendation, evidence summaries and evidence to decision summaries available through the CRA website (www.rheum.ca).

INTRODUCTION

Rheumatoid Arthritis (RA) is is the most prevalent inflammatory arthritis, affecting an estimated 1.2% of Canadians aged 16 years and older (1). People with RA experience pain, fatigue, functional limitation, work loss and reduced quality of life. The economic burden of RA in Canada was estimated at $5.7 billion annually in 2011, with a rising burden over time due to an aging population (2). The Canadian Rheumatology Association (CRA) developed initial treatment recommendations for RA in 2011/12. Since then, the treatment landscape has changed considerably. Several new DMARDs have been introduced, including targeted synthetic DMARDs with novel mechanisms of action and biosimilars. New evidence continues to emerge to inform decisions between these treatments.

In the setting of continually emerging evidence and new treatments, maintaining up-to-date guidelines is challenging. In a typical guideline development cycle, the entire guideline is updated periodically, typically every 2 or 3 years or longer. In contrast, in a living guideline model, individual recommendations are developed or updated when necessary, ensuring recommendations stay up to date (3). Underpinning living guidelines are living systematic reviews (4). While living systematic reviews and guidelines may require more upfront effort to establish, they also provide efficiencies, as systematic review and guideline teams are continually active and engaged (3). The start-up efforts with each guideline cycle are removed, and the overall workload is diffused over time. Collaboration on systematic reviews across international groups can provide further efficiencies by avoiding duplication of effort.

Objective and need

The objective of these recommendations is to provide guidance for the pharmacological management of RA with DMARDs. The need for this guideline was approved by the Guidelines Committee of the CRA.

Target audience

The target audience are rheumatologists or other primary prescribers of RA medications and their patients with RA, in community and academic practice settings. Recommendations may also be of interest to other provincial and federal RA stakeholders and decision makers.

Target population

These recommendations apply to adult patients (age >18 years old) with RA. This includes patients whose RA began in childhood or adolescence as juvenile idiopathic arthritis (JIA) and has persisted into adulthood.

Perspective

This guideline takes the perspective of treatment decisions made between the rheumatologist and the person living with RA.

MATERIALS AND METHODS

This guideline was developed using the GRADE approach, which provides a systematic process for appraising the certainty of evidence and grading the direction and strength of recommendations (5). Ethics approval was not required.

Organization and panel composition

The CRA assembled a guideline panel that included rheumatologists, researchers, methodologists, and two people living with RA (see Appendix A). Methodological support was provided by the Cochrane Musculoskeletal Centre for evidence synthesis. All panel meetings were held virtually by video calls.

Guideline funding and management of conflicts of interest

The guideline development was supported by in-kind funding from the CRA, a non-profit association that represents Canadian rheumatologists. The CRA also provides ongoing funding to the Cochrane Musculoskeletal Centre. Declarations of potential conflicts of interest (COI) were collected from all panelists using the International Committee of Medical Journal Editors (ICMJE) form. The chair (GSH) and co-chair (JPP), and all members of the voting panel were required to be free of any direct financial COI within the past 36 months, which meant no direct payments including research funding support from any manufacturers of RA therapeutics. Expert panel members with COI were allowed to participate in the discussion but did not vote on the direction or strength of recommendation. All disclosure forms were reviewed and potential COI adjudicated by an independent member of CRA that was not otherwise involved in the present guideline, and discussed with the chair and co-chair in the setting of ambiguity.

The COIs are maintained over time and available online (https://rheum.ca/resources/publications/).

Formulating clinical questions

The initial clinical question for this guideline related to tapering of therapy was chosen by the panel for its importance to decision making and the availability of a recent (and living) Australian systematic review and guideline (6).

Development of Recommendation

The recommendation was developed using the GRADE adolopment approach, which provides a framework for efficient adoption or adaptation of existing guidelines or *de novo* development of recommendations (7). With GRADE adolopment, existing GRADE evidence profiles are used where possible. Evidence to Decision (EtD) profiles, which outline the evidence and rationale for the recommendation, are either generated or modified as necessary to contextualize the recommendation to a different healthcare context.

Prior to the panel meeting, a core team reviewed the published GRADE evidence profile (GSH and JPP) and Evidence to Decision (EtD) profile (GSH, NB, ChB, and JEP), which were developed and are maintained in a living fashion by the Australia & New Zealand Musculoskeletal (ANZMUSC) Clinical Trials Network (6). No changes were made to the evidence profile, but the EtD profile was modified to contextualize to the Canadian context. Health equity was explicitly discussed and considered for each stop in the EtD framework, following a recently published

process that we developed for CRA guidelines (8), informed through stakeholder interviews (9). Within this framework, equity considerations relevant to RA guidelines for six populations at risk for inequities were generated and mapped to each step of the Evidence to Decision framework. These populations included: rural and remote residents, Indigenous Peoples, elderly persons with frailty, minority populations of first-generation immigrants and refugees, persons with low socioeconomic status or who are vulnerably housed, and sex and gender populations.

The evidence profile and modified EtD framework were reviewed by panelists prior to the meeting and then discussed during the online panel meeting, leading to a consensus judgement for each step of the EtD framework/process. The direction (i.e. to recommend or not) and strength of the final recommendation was discussed with all panelists and determined through a formal vote of the qualified voting panelists. A simple majority (>50%) was required to determine the direction of the recommendation, and development of a strong recommendation required 80% agreement (8).

How to read this guideline

In the GRADE approach, recommendations are categorized as strong or conditional (5). A strong recommendation means that all or almost all people with rheumatoid arthritis would choose that intervention. A conditional recommendation means that the majority of people with rheumatoid arthritis in this situation would want the suggested course of action, but many would not (Table 1) (10).

How to use this guideline

This recommendation is intended to help rheumatologists and patients make decisions regarding RA treatment and is not meant to replace clinical judgement. This recommendation is subject to change over time in a living fashion as new evidence emerges and should always consult the CRA website (https://rheum.ca/resources/publications/) for the latest version.

Public commenting

Public commenting will be available through the CRA website. The public comments will be reviewed on an ongoing basis and may be considered in future updates.

Living guidelines

These guidelines will be maintained over time. New recommendations will be added, and existing recommendations may be modified in the setting of new evidence. Readers should consult the online version available at https://rheum.ca/resources/publications/ for the latest version. This article will not be modified over time, but additional journal articles may be published to supplement the online living version and aid in knowledge translation.

RESULTS

Should biologic or targeted synthetic DMARDs be tapered in patients who are in sustained remission or low disease activity?

Recommendation:

In people with RA who have been in sustained low disease activity or remission for at least 6 months, we suggest offering stepwise reduction in the dose of b/tsDMARD without discontinuation, in the context of a shared decision, provided patients are able to rapidly access rheumatology care and re-establish their medications in case of a flare. (conditional recommendation; moderate certainty of evidence).

In patients where rapid access to care or re-establishing access to medications is challenging, we conditionally recommend against tapering. (conditional recommendation; moderate certainty of evidence)

Rationale and key remarks:

- The panel judged that for reduction in therapy, given the moderate certainty evidence of the little negative impact on disease control and that most patients who flare can regain disease control promptly once medications are re-established, a trial of treatment reduction (without complete discontinuation) would be appropriate for many patients to reduce medication burden and possible side effects. Given the increase in flares seen over relatively short follow-up in the trials of discontinuation of treatment, the panel made a conditional recommendation against complete discontinuation of advanced therapies.
- Rapid access to care and ability to re-establish medications was highlighted as a particularly important consideration when deciding whether to taper. The panel felt

that in situations where access to care is difficult, tapering would typically not be recommended. This, however, is also a conditional recommendation, meaning tapering may still be appropriate for some patients in the context of a shared decision.

- The majority of the evidence relates to anti-TNF therapy, although results for other mechanisms of action that have been studied appear similar, including rituximab (11), abatacept (12), tocilizumab (13) and baricitinib (trial studied the reduction of 4mg/day dose to the approved dose in Canada of 2 mg/day) (14).
- This recommendation applies to both biologic originator and biosimilar DMARDs.
- While shared decision-making is implicit in a conditional recommendation, the panel felt it was important to highlight in the recommendation itself, given the wide variability in patient preferences around treatment tapering.

Implementation and practical information:

- Implementation of the recommendation would be supported with models of care that allow rapid access to care from a rheumatology care team, including in populations at risk for inequity, and reimbursement policies that facilitate immediate re-escalation of doses in case of a flare.
- A flare management plan should be discussed with patients prior to tapering. While tapering, patients should be reassessed typically at 3 months. In the case of flare, a typical approach would be to increase the dose back to the previous effective dose.

- Six months of adequate disease control was felt to be the minimum duration. The panel felt that sustained disease control (ideally remission according to a composite measure with no swollen joints) for 12 months would be ideal prior to tapering.
- A tool to support shared decision-making for this recommendation is being developed and will be available through the Canadian Rheumatology Association website [https://rheum.ca/resources/publications/].
- Dose reduction may include extending the interval between doses or reducing the amount with each dose. A typical initial reduction would be 25% of the original effective dose, for example by increasing the interval for adalimumab from every 2 weeks to every 3 weeks. Further reductions (for example, extending the interval to every 4 weeks) may also be possible. Complete discontinuation of the b/tsDMARD is not routinely recommended, although may be possible in some patients; in these patients, a csDMARD should be continued.
- In people taking csDMARD(s) in combination with b/tsDMARDs, the doses of csDMARD(s) should be kept stable during dose reduction of the b/tsDMARD.
- Prior to reducing biologic or targeted synthetic DMARDs, glucocorticoids should be discontinued, if possible.

Monitoring and evaluation:

It will be important to monitor this recommendation in real-world practice, including the frequency of treatment tapering being offered, discussed, and initiated and the resulting clinical

outcomes. We support monitoring of this through existing Canadian RA registries and studies using administrative data, including in populations at risk for inequities.

Evidence to decision (EtD) profile

The following EtD profile was used in the development of this recommendation and is also available at [https://rheum.ca/resources/publications/]. The online version will be updated over time.

Benefits and harms and certainty of evidence:

The panel reviewed the GRADE Evidence Profiles of the ANZMUSC source guideline (6) that summarized the evidence on benefits and harms and certainty of evidence for reduction of treatment (Table 2) and complete discontinuation of treatment (Table 3) and accepted them without modifications. There was moderate certainty evidence that reducing the dose of bDMARD or tsDMARD therapy was associated with little to no difference in disease control over 12 months, both in terms of the proportion of patients in remission (54 out of 100 with continuing treatment versus 49 out of 100 with reduction) and the proportion of patients with a flare (22 out of 100 with continuing treatment versus 27 out of 100 with reduction). There may be a small negative effect on function and the proportion of patients with a minimal amount of radiographic progression (Table 2). There was little to no difference in adverse events, although event rates were low.

There was moderate certainty evidence that discontinuing bDMARD or tsDMARD therapy (Table 3) was associated with a decrease in the proportion of patients with persistent remission (61 out of 100 with continuing treatment versus 34 out of 100 with discontinuation) and an increase in the proportion of patients with a flare (26 out of 100 with continuing treatment versus 49 out of 100 with discontinuation). Discontinuing therapy may also slightly increase the proportion of people with minimal radiographic progression, may lead to a slight deterioration in function and may slightly worsen quality of life (Table 3). There was little to no difference in adverse events, although event rates were low.

Equity considerations: There was no available evidence to conclude that the treatment effects or certainty of evidence would vary for populations facing inequities in rheumatology care and outcomes.

Preferences and values

Recent reviews on RA patient preferences for down titration (15,16) identified several qualitative and mixed-methods studies (17-21). An additional Canadian study published since these reviews assessed preferences of patients and rheumatologists for tapering both biologic and non-biologic therapy (22). Common themes identified in the qualitative work included a desire amongst some patients to reduce medication burden but a fear of flaring, and concern about the ability to successfully recapture disease control. Having a flare management plan, including the ability to rapidly access care and re-escalate doses in the occurrence of a flare is particularly important. There is wide variability in preferences between patients, which is

influenced by patients' lived experiences, side effects, previous tapering experiences, disease trajectory (e.g. severity of disease and number of previously failed therapies), remission duration, and current life roles. This supports the importance of shared decision-making (SDM).

We did not identify any quantitative patient preference studies of treatment tapering in a recent systematic review (23), or an updated Pubmed search (rheumatoid arthritis patient preference*) to August 2021.

Equity considerations: In other patient preference studies in patients with rheumatoid arthritis (not focused on treatment tapering), preferences are often associated with membership in populations at risk for inequities (23). These preferences will reflect both individual and population beliefs and values, informed by population membership, which should be explored in a shared decision-making strategy for tapering.

Resource use

A Cochrane review in 2019 (24) identified two trials in Europe which studied the cost-effectiveness and costs of guided tapering of anti-TNF agents etanercept and adalimumab with anti-TNF continuation (25,26). Both studies found little to no difference in QALYs, but resulted in considerable cost-savings. Modelling studies have projected similar results in the long-term (27). In Canada, it is assumed that dose reduction of b/tsDMARDs will reduce costs for payers (governments and insurers) and may reduce out-of-pocket costs for patients. Out-of-pocket costs will vary by Province, whether patients have supplementary medical insurance, and

depending on their province of residence, age, income and other concomitant prescription drugs. Approximately 8% of Canadians who received a prescription did not take the drug as prescribed because of cost (28).

Equity considerations: Populations facing inequities in rheumatology care and outcomes will have intersecting limitations in available resources to access bDMARDs, therefore tapering may have specific advantages. Specific populations however may not entertain tapering due to the consequences of this choice (e.g. for example, insurers may limit the ability to re-escalate therapy in case of a flare).

Acceptability and feasibility

The acceptability of reducing bDMARDs or tsDMARDs is expected to vary widely between patients. The feasibility of reducing bDMARDs or tsDMARDs may change based on insurance coverage. This is different between the provinces and represents a barrier to implementation.

Equity considerations: Acceptability of tapering likely differs by population membership. Differences in funding reimbursement may impact ability to re-escalate treatment for particular populations (e.g., federal Non-Insured Health Benefits formulary, Seniors plans, etc.) and when there appears to be nonadherence to the recommended dose of an expensive medication, it theoretically may not be reimbursed when renewed.

DISCUSSION

This guideline represents the first installment of CRA living treatment recommendations for RA. This marks the transition to a living mode of guideline development, where individual recommendations will be updated and maintained over time.

This is also the first implementation of our recently published equity framework (8), which was informed through stakeholder interviews amongst Canadian patients and rheumatology providers (9). In the context of this recommendation, equity considerations led to a conditional subgroup recommendation against treatment tapering in situations where rapid access to care is challenging. Importantly, and in line with our equity framework, this subgroup recommendation was linked to the underlying factor (in this case, barriers to accessing care), rather than the population itself. Equitable implementation of this recommendation can be supported through models of care that allow for access to appropriate care for all patients. The populations identified in our equity framework where access to care is systematically different, includes, but may not be limited to people living in rural/remote locations, Indigenous peoples, refugee and first-generation immigrant populations, and persons of low socioeconomic status and vulnerably housed (8,9).

Shared decision-making features prominently in this recommendation. For some patients, the risk of flaring will outweigh the potential benefits. This will depend both on an individual's risk of flare as well as the impact of a flare on their life. While validated predictive tools for an individual's flare risk are not in widespread use, this is an active area of research. Patient preferences for tapering may change over time, so the decision should be revisited. To support

shared decision-making for this recommendation a decision aid has been developed. In the living guideline, we will continue to develop tools to support shared decision-making for preference-sensitive recommendations.

The development of this recommendation was possible through the publication of Australian living recommendations, along with full Evidence to Decision tables and an EtD framework (6). Future recommendations will be supported by ongoing Cochrane living systematic reviews of DMARD therapy (29), also a collaborative effort. In the living guideline model, we will also continue to make use of other guidelines, through the GRADE-adolopment approach. Ideally, international guideline groups in rheumatology would collaborate on living systematic reviews for common clinical questions, saving considerable duplication of effort. Different groups can then contextualize the recommendation to their setting. Published EtD tables aid this process, by presenting the evidence and judgements behind the recommendation according to the structured GRADE process. In our tapering recommendation, our overall recommendation was the same as the source guideline (conditional recommendation for tapering), with some differences in the wording to reflect the importance of shared decision-making and equity concerns regarding access to care. Currently EULAR guidelines state that tapering can be considered, especially if the treatment is combined with a csDMARD (30). American College of Rheumatology guidelines provide a conditional recommend against tapering, although also recommend gradual reduction versus abrupt discontinuation in patients where tapering is being tried (31).

In summary, we present an initial recommendation on tapering of b/tsDMARDs in patients with rheumatoid arthritis. Readers should consult the online version for the latest version of the recommendation.

ACKNOWLEDGEMENTS

The authors thank Sue Ranta and the CRA for administrative support during the development and dissemination of the guideline, and the Australia & New Zealand Musculoskeletal Clinical Trials Network (ANZMUSC), for their work on developing and maintaining the source recommendation that we used for adaptation.

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Table 1. Interpretation of Strong and Conditional Recommendations

Implications for:	**Strong recommendation**	**Conditional recommendation**
Patients	Most individuals in this situation would want the recommended course of action, and only a small proportion would not.	The majority of individuals in this situation would want the suggested course of action, but many would not. Decision aids may be useful in helping patients to make decisions consistent with their individual risks, values and preferences.
Clinicians	Most individuals should follow the recommended course of action. Formal decision aids are not likely to be needed to help individual patients make decisions consistent with their values and preferences.	Recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful in helping individuals to make decisions consistent with their individual risks, values and preferences.

Policy makers	The recommendation can be adopted as policy in most situations. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.	Policymaking will require substantial debate and involvement of various stakeholders. Performance measures should assess if decision-making is appropriate.
Researchers	The recommendation is supported by credible research or other convincing judgments that make additional research unlikely to alter the recommendation. On occasion, a strong recommendation is based on low or very low certainty of the evidence. In such instances, further research may provide important information that alters the recommendations.	The recommendation is likely to be strengthened (for future updates or adaptation) by additional research. An evaluation of the conditions and criteria (and the related judgments, research evidence, and additional considerations) that determined the conditional (rather than strong) recommendation will help identify possible research gaps.

Table 2. GRADE Evidence Profile - Reduction of biologic or targeted synthetic DMARDs versus continuation for rheumatoid arthritis in patients with low disease activity

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** continuation / Dose reduction	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Proportion persistent remission (DAS28) 24 to 52 weeks	Relative risk: 0.9 (CI 95% 0.81 - 1.0) Based on data from 1783 patients in 7 studies	**543** per 1000 / **489** per 1000 Difference: **54 fewer per 1000** (CI 95% 103 fewer - 0 fewer)	**Moderate** Due to serious indirectness	Dose reduction probably has little or no effect on the proportion with persistent remission
Proportion of participants with a flare 52 weeks	Relative risk: 1.23 (CI 95% 0.92 - 1.65) Based on data from 880 patients in 7 studies	**220** per 1000 / **271** per 1000 Difference: **51 more per 1000** (CI 95% 18 fewer - 143 more)	**Moderate** Serious imprecision due to low event rate	Dose reduction probably has little or no effect on the proportion with a flare
Proportion radiographic progression (mSvdH > 0.5) 52 weeks	Relative risk: 1.31 (CI 95% 0.96 - 1.81) Based on data from 865 patients in 4 studies	**152** per 1000 / **199** per 1000 Difference: **47 more per 1000** (CI 95% 6 fewer - 123 more)	**Low** Due to serious indirectness, Due to serious imprecision	Dose reduction may result in little or no effect on the proportion with disease progression, as measured by minimal radiographic progression.
Proportion switched to another biologic 52 weeks to 3.5 years	Relative risk: 0.49 (CI 95% 0.27 - 0.91) Based on data from 640 patients in 3 studies	**95** per 1000 / **47** per 1000 Difference: **48 fewer per 1000** (CI 95% 69 fewer - 9 fewer)	**Low** Due to serious indirectness and serious imprecision due to low event rate	Dose reduction may slightly reduce the proportion who switched to another biologic
Number of serious adverse events 52 weeks to 3.5 years	Relative risk: 0.97 (CI 95% 0.74 - 1.27) Based on data from 2435 patients in 12 studies	**79** per 1000 / **77** per 1000 Difference: **2 fewer per 1000** (CI 95% 21 fewer - 21 more)	**Moderate** Serious imprecision due to low event rates	Dose reduction probably has little or no effect on the number of serious adverse events

Withdrawals due to adverse events 52 weeks to 3.5 years	Relative risk: 1.13 (CI 95% 0.65 - 1.98) Based on data from 1917 patients in 7 studies	**24** per 1000 **27** per 1000 Difference: **3 more per 1000** (CI 95% 8 fewer - 24 more)	**Low** Very serious imprecision due to few events	Dose reduction may have little or no effect on the number of withdrawals due to adverse events
Mean disease activity score (DAS28) 26 to 52 weeks	Measured by: DAS28 Scale: 0.9 - 8 Lower better Based on data from 1888 patients in 10 studies	**2.3** Mean **2.4** Mean Difference: **MD 0.13 higher** (CI 95% 0 higher - 0.26 higher)	**High**	Dose reduction has little or no effect on mean disease activity score
Function (Health Assessment Questionnaire) 26 to 52 weeks	Measured by: Health Assessment Questionnaire Scale: 0 - 3 Lower better Based on data from 1666 patients in 8 studies	**0.52** Mean **0.57** Mean Difference: **MD 0.05 higher** (CI 95% 0.01 higher - 0.09 higher)	**High**	Dose reduction results in a slight deterioration of function
Quality of life 24 to 52 weeks	Measured by: EQ5D 2 trials, SF-12 MCS 1 trial Scale: - Based on data from 632 patients in 3 studies	**41.6** Mean **40.9** Mean Difference: **SMD 0.02 lower** (CI 95% 0.18 lower - 0.13 higher)	**Moderate** Due to serious imprecision	Dose reduction probably has little or no effect on quality of life

Table 3. GRADE Evidence Profile - Discontinuation of biologic or targeted synthetic DMARDs versus continuation for rheumatoid arthritis in patients with low disease activity

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** continuation / Discontinuation	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Proportion persistent remission (DAS28 < 2.6) 28 to 52 weeks	Relative risk: 0.56 (CI 95% 0.43 - 0.72) Based on data from 1188 patients in 6 studies	**612** per 1000 / **343** per 1000 Difference: **269 fewer per 1000** (CI 95% 349 fewer - 171 fewer)	**Moderate** Due to serious indirectness	Discontinuation probably reduces the proportion of participants with persistent remission
Proportion of participants with a flare 24 to 52 weeks	Relative risk: 1.9 (CI 95% 1.41 - 2.57) Based on data from 1540 patients in 6 studies	**262** per 1000 / **493** per 1000 Difference: **235 more per 1000** (CI 95% 107 more - 411 more)	**Moderate** Due to serious indirectness	Discontinuation probably results in more people with a flare
Proportion radiographic progression (mSvdH > 0.5)	Relative risk: 1.69 (CI 95% 1.1 - 2.59) Based on data from 549 patients in 3 studies	**105** per 1000 / **177** per 1000 Difference: **72 more per 1000** (CI 95% 11 more - 167 more)	**Low** Due to serious indirectness, Due to serious imprecision	Discontinuation may slightly increase the proportion of participants with disease progression, as measured by minimal radiographic progression
Number of serious adverse events 28 to 52 weeks	Relative risk: 1.22 (CI 95% 0.8 - 1.86) Based on data from 2248 patients in 9 studies	**57** per 1000 / **70** per 1000 Difference: **13 more per 1000** (CI 95% 11 fewer - 49 more)	**Very low** Due to serious indirectness, and very serious imprecision due to low event rates	We are uncertain whether discontinuation results in fewer serious adverse events, due to the small number of events reported.
Withdrawals due to adverse events 28 to 52 weeks	Relative risk: 1.52 (CI 95% 0.8 - 2.92) Based on data from 1269 patients in 5 studies	**25** per 1000 / **38** per 1000 Difference: **13 more per 1000** (CI 95% 5 fewer - 47 more)	**Very low** Due to serious indirectness, and very serious imprecision due to low event rates	Discontinuation probably slightly worsens disease activity
Mean disease activity score (DAS28) 28 to 52 weeks	Measured by: DAS Scale: 0.9 - 8 Lower better Based on data from 865 patients in 3 studies	**2.62** Mean / **3.28** Mean Difference: **MD 0.68 higher** (CI 95% 0.13 higher - 1.23 higher)	**Moderate** Due to serious indirectness	Discontinuation probably slightly worsens disease activity

Function (Health Assessment Questionnaire)	Measured by: Health Assessment Questionnaire Scale: 0 - 3 Lower better Based on data from 1498 patients in 4 studies	**0.52** Mean **0.7** Mean Difference: **MD 0.18 higher** (CI 95% 0.05 higher - 0.31 higher)	**Low** Due to serious inconsistency, and serious indirectness	Discontinuation may lead to a slight deterioration in function
Quality of life	Measured by: EQ5D Scale: 0 - 1 High better Based on data from 733 patients in 2 studies	**0.6** Mean **0.5** Mean Difference: **MD 0.10 lower** (CI 95% 0.13 lower - 0.07 lower)	**Low** Due to serious indirectness, and serious imprecision	Discontinuation may worsen quality of life slightly