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ORIGINAL ARTICLE

Withdrawal of biologic agents in rheumatoid arthritis: a systematic review and meta-analysis

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Abstract The aim of this study is to assess the efficacy of withdrawing biologics from patients with rheumatoid arthritis in sustained remission or low disease activity. This is a systematic review of clinical trials that randomized withdrawal or continuation of biologics. We searched MEDLINE, Embase, and other databases. Three authors independently selected and extracted the data from the studies. The GRADE approach was employed to assess the quality of the evidence. We calculated meta-analyses of random effects model and estimated the heterogeneity by I^2. The number needed to treat (NNT) was calculated for significant outcomes. We included six trials ($N = 1927$ patients), most were industry-sponsored. Compared to withdrawing, continuing biologics increased the probability of low disease activity (relative risk [RR] = 0.66, 95 % CI 0.51–0.84, $I^2 = 91$ %, NNT = 4, low quality), remission (0.57, 0.44–0.74, $I^2 = 82$ %, NNT = 3, low quality), and radiographic progression (RR = 0.91, 95 % CI 0.85–0.98, $I^2 = 13$ %, NNT = 12, moderate quality). No significant difference was detected in the incidence of serious adverse events, serious infection, malignancy, and scores of improvement of tender and swollen joints between these strategies (low quality). A worse profile of outcomes was experienced by those patients when compared to the ones that continued biologics, but almost half of patients maintained low disease activity after withdrawal. As the quality of evidence was low, the conclusions may change as new results become available. The potential harms and benefits of this decision must be discussed with patients.

Keywords Antirheumatic agents · Remission · Rheumatoid arthritis · Withdrawal · Withholding treatment

Introduction

Treatment of rheumatoid arthritis has greatly progressed with the development of new therapeutic classes and the implementation of alternative strategies for patient treatment and follow-up, including intensive disease control and intervention during the initial phase of symptoms [1]. Among the currently available therapeutic options, biologic drugs have gained prominence. Current approach has resulted in better control of rheumatoid arthritis, including the possibility of sustained remission [2].

Several factors may lead a doctor or a patient to consider interrupting treatment with biologics, especially after a prolonged period of sustained disease remission. These factors may include the high cost of the drugs, their potential adverse effects, the inconvenience of treatment from the patient's perspective, and the possibility of continuing remission after the withdrawal of biologics [3, 4].

Although the withdrawal of biologics is a matter of great importance, it remains a controversial topic, and there is little data to guide decision-making. There is no consistent

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evidence regarding the best course of action following a complete therapeutic response. Some studies suggest that the withdrawal of biologics may be considered for patients in sustained remission, especially if the biological therapy is combined with conventional synthetic drugs [2, 5].

Previous reviews of the discontinuation of biological therapy have been based on observational, quasi-experimental, or extended assessments of clinical trials [6–9]. A Cochrane review assessed the tapering and discontinuation of antitumor necrosis factor (anti-TNF) agents but included non-randomized studies [10]. To date, no summary of randomized trials comparing withdrawal with continuation of biologics in comparable patients has been published.

Our aim was to assess the available evidence on the efficacy and the safety of discontinuing the administration of biologic agents to patients with rheumatoid arthritis compared to continuing the treatment.

Methods

Protocol and registration

The methods for the present study were previously registered in the International Prospective Register of Systematic Reviews (PROSPERO) under registration number CRD42014009883.

Eligibility criteria

We considered randomized clinical trials compared withdrawal with continuation of biologic agents in patients with rheumatoid arthritis as eligible. The outcomes of interest were disease activity and other relevant patient outcomes.

To define rheumatoid arthritis, we used the American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis or the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) rheumatoid arthritis classification criteria [11, 12].

Patients with early or late rheumatoid arthritis were included. Due to differences in physiopathology, patients with juvenile idiopathic arthritis were not included.

We considered biological disease-modifying antirheumatic drugs (bDMARDs) as the major class of drugs that interfere with the entire rheumatoid arthritis process [13]. For the present review, we considered drugs from the following classes to be eligible: anti-TNF agents (adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab), anti-B cell agents (rituximab), T lymphocyte costimulation inhibitors (abatacept), interleukin-6 receptor blockers (tocilizumab), and biosimilars (infliximab).

Information sources and search strategy

We searched the following databases from inception to February 2016: MEDLINE, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), and World Health Organization International Clinical Trials Registry Platform (WHO ICTRP). We also searched the proceedings of the EULAR congress and ACR annual meeting for the years 2001–2015. The references of relevant studies were inspected for eligibility.

The search strategy for MEDLINE (via PubMed) was as follows: (rheumatoid OR "arthritis, rheumatoid"[mesh]) AND (adalimumab OR humira OR "certolizumab pegol" OR cimzia OR etanercept OR enbrel OR golimumab OR simponi OR infliximab OR remicade OR inflectra OR rensima OR rituximab OR mabthera OR rituxan OR abatacept OR orencia OR tocilizumab OR actemra OR "dmard"[tiab] OR "dmards"[tiab] OR "disease modifying antirheumatic drugs"[tiab] OR "antirheumatic agents"[mesh] OR "biological products"[mesh] OR "tnf inhibitors"[tiab] OR "tnf inhibitor"[tiab]) AND ("withholding treatment"[mesh] OR "remission induction"[mesh] OR "remission"[tiab] OR discontinuati*[tiab] or withdraw*[tiab] OR stopping[tiab]) AND ("randomized controlled trial"[pt] OR (("randomized"[tiab] OR "randomised"[tiab]) AND ("controlled"[tiab] AND "trial"[tiab]))). The search strategies used in all databases are described in Supplementary Table 1.

Study selection and data collection process

Three authors (TFG, IRZ, and MTS) independently selected the retrieved studies according to the eligibility criteria. Disagreements were resolved by consensus. The same authors independently abstracted data from the studies using a predefined form. The following data were collected: year, country, design, sample size, mean age, length of follow-up, criteria for discontinuation, withdrawal and maintenance strategy, and outcomes. The primary outcomes were low disease activity and disease remission.

Risk of bias and quality of evidence

We used the Cochrane Collaboration risk of bias tool to address six domains that may impact the methodological quality of individual studies (random sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other potential sources of bias) [14].

The outcomes across studies were ranked as critical, important, or of limited importance according to their relationships to clinical decision-making and patient preferences based on previous discussions of rheumatoid arthritis [15–17]. The quality of evidence of critical and important outcomes was assessed using the Grading of

Recommendations Assessment, Development and Evaluation (GRADE) approach [18]. The evidence quality was rated as high, moderate, low, or very low.

Data analysis

We conducted the meta-analysis using the DerSimonian & Laird model considering random effects. We summarized dichotomous data as the relative risk (RR) and continuous data as the mean difference (MD) and corresponding 95 % confidence intervals (95 % CIs). When possible, we aggregated all biologic drugs in the meta-analysis. Statistical heterogeneity of the results between the studies was assessed using the chi-squared ($p > 0.10$) and Tau-squared tests; the magnitude of the effects was estimated using the I^2 statistic. For significant outcomes, we calculated the number needed to treat (NNT) and the 95 % CI. Data were analyzed using STATA software (version 13.1).

Results

Study selection

The literature search resulted in 1283 records, 1120 of which were assessed for eligibility after removing duplicates (Fig. 1). From the 40 records that were fully assessed, 17 were excluded. The list of excluded records for each reason is available in Supplementary Table 2. Four potentially eligible studies could not be included due to the unavailability of results: three are ongoing RCTs [19–21] and one study was terminated prior to patient enrollment [22]. Six RCTs were included in this review [23–28] (23 individual reports, list of references available in Supplementary Table 3).

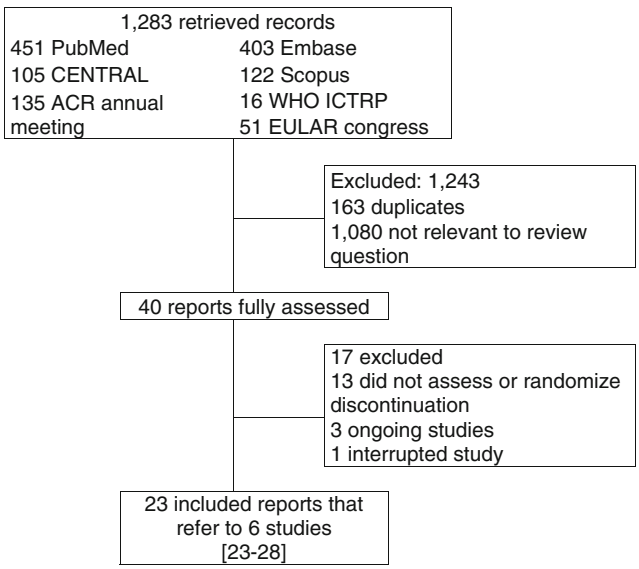

Fig. 1 Selection and inclusion of studies

Characteristics of the included studies

The RCTs were multicenter trials conducted from 2006 to 2014 that recruited patients from all continents (Table 1). In total, 1927 patients with low disease activity or in remission were randomly allocated to discontinue or continue treatment with biologic agents. Two RCTs included only patients with early rheumatoid arthritis who were never treated with methotrexate or biologics prior to the study [23, 25]; the other studies did not indicate the type of rheumatoid arthritis and included patients previously treated with methotrexate alone [24] or with biologics and conventional synthetic DMARD (csDMARD), mostly methotrexate [26–28]. Five RCTs used low disease activity as criteria to randomize the discontinuation [23–26, 28], while one considered remission [27].

Four RCTs included an open-label phase in which all patients were treated with biologics (subcutaneous etanercept 50 mg weekly or adalimumab 40 mg every other week) and methotrexate 7.5–25 mg [23–26]. This phase ranged from 8 to 52 weeks. Three trials also required that the patients had previously been treated with the biologic agent and csDMARD from at least 14 to 6 months [26–28]. Methotrexate was administered orally in the PRESERVE and PRIZE trials [24, 25], orally or subcutaneously in the ADMIRE study [27], and orally, subcutaneously, or intramuscularly in the DOSERA study [26]. The OPTIMA trial did not indicate the route of methotrexate administration [23] as well as the POET study, in which patients used any concomitant csDMARD [28].

In the OPTIMA, PRESERVE, PRIZE, and DOSERA trials, the patients in the withdrawal group received methotrexate together with subcutaneous injections of placebo [23–26]. The PRIZE trial also included a placebo group, in which the patients received placebo injections and placebo capsules [25]. This group was not included in our analyses. ADMIRE and POET studies did not administer placebo injections to the withdrawal group, as their design was open label [27, 28]. Patients who continued biologics were treated with subcutaneous injections of adalimumab 40 mg every other week [23, 27] or etanercept 25 or 50 mg weekly [24–26] together with methotrexate 7.5–25 mg weekly. In POET study, a pragmatic RCT, patients continued the treatment with etanercept (46 %), adalimumab (45 %), infliximab (5 %), golimumab (3 %), or certolizumab (1 %), and concomitant csDMARD, in doses not specified.

Abbott/AbbVie, which markets adalimumab, funded two trials that investigated the withdrawal of adalimumab [23, 27]. Pfizer, the manufacturer of etanercept, funded three RCTs that studied the withdrawal of etanercept [24–26]. POET study was funded by a governmental research agency of the Netherlands.

Table 1 Main characteristics of the included randomized controlled trials

Study	Year	Design (follow-up, weeks)	Clinical condition (mean age, years[a])	Pre-randomization treatment, weekly (length, weeks)	Criteria for discontinuation	Withdrawal strategy, weekly (sample)	Maintenance strategy, weekly (sample)
OPTIMA [23]	2006–2010	RCT, double-blind[c] (52)	Early rheumatoid arthritis, biologic- and methotrexate-naïve (49.1)	Adalimumab 40 mg[b] + methotrexate 7.5–20 mg (26)	Sustained low disease activity (DAS28 < 3.2 at weeks 22 and 26)	Placebo injection[b] + methotrexate 7.5–20 mg (102)	Adalimumab 40 mg[b] + methotrexate 7.5–20 mg (105)
PRESERVE [24]	2008–2009	RCT, double-blind[d] (52)	Moderate rheumatoid arthritis, prior use of methotrexate, biologic-naïve (47.6)	Etanercept 50 mg + methotrexate 10–25 mg (36)	Sustained low disease activity (mean DAS28 ≤ 3.2 from week 12 to 36 and DAS28 ≤ 3.2 at week 36)	Placebo injection + methotrexate 10–25 mg (200)	Etanercept 25 mg (202) or etanercept 50 mg (202) + methotrexate 10–25 mg
PRIZE [25]	2009–2012	RCT, double-blind[e, f] (39)	Early moderate-severe rheumatoid arthritis, biologic- and methotrexate-naïve (49.4)	Etanercept 50 mg + methotrexate 10–25 mg (52)	Low disease activity (DAS28 ≤ 3.2 at week 39 and DAS28 < 2.6 at week 52)	Placebo injection + methotrexate 10–25 mg (65) or placebo injection + placebo capsule[g] (65)	Etanercept 25 mg + methotrexate 10–25 mg (63)
DOSERA [26]	2009–2012	RCT, double-blind[h] (48)	Prior use of biologic and methotrexate (56.1)	Etanercept 50 mg + methotrexate 7.5–25 mg, (8, prior use for at least 56)	Low disease activity (DAS28 ≤ 3.2 for at least 44 weeks)	Placebo injection + methotrexate 7.5–25 mg (23)	Etanercept 25 mg (27) or etanercept 50 mg (23) + methotrexate 7.5–25 mg
ADMIRE [27]	2009–2012	RCT, open label[i] (52)	Prior use of biologic and methotrexate (56.8)	Adalimumab 40 mg[b] + methotrexate 10–25 mg (median 116)	Sustained remission (DAS28 < 2.6 for 3 months)	Methotrexate 10–25 mg (16)	Adalimumab 40 mg[b] + methotrexate 10–25 mg (17)
POET [28]	2012–2014	RCT, open label[k]	Remission or low disease activity rheumatoid arthritis (59.8)	Adalimumab or etanercept or infliximab or golimumab or certolizumab (52) + csDMARD (26)	Remission or sustained low disease activity (DAS28 < 3.2 for 6 months or clinical judgment[l])	csDMARD (531)	Adalimumab or etanercept or infliximab or golimumab or certolizumab[m] + csDMARD (286)

Notes:

RCT randomized controlled trial

csDMARD conventional synthetic disease-modifying antirheumatic drugs

[a] Calculated as the weighted arithmetic mean of the age of total sample

[b] The injection was administered every other week

[c] 161 centers in Europe, North America, South America, Africa, Australia and New Zealand

[d] 80 centers in Europe, Latin America, Asia and Australia

[e] 58 centers in Europe and Asia

[f] The study was performed for more than 65 weeks on all patients without any treatment. This information was not considered in the present review

[g] The placebo group (without methotrexate treatment) was not considered in the present review;

[h] 8 centers in Europe

[i] 16 centers in Sweden

[j] 40 centers in Japan and Korea

[k] 47 centers in the Netherlands

[l] Rheumatologists' clinical impression of remission or stable low disease activity in combination with a baseline DAS28 < 3.2 and at least one C-reactive protein (CRP) level <10 mg/L in the 6 months prior to inclusion

[m] Doses not stated.DAS28, disease activity score of 28 joints

Risk of bias within studies

Two RCTs were graded as having a low risk of bias in the six domains assessed [23, 24] (Fig. 2). The PRIZE trial was judged as high risk of attrition bias: 32 % of the randomly allocated patients did not complete the study. We considered that the higher baseline disease status according to the van der Heijde modification of the Sharp method in the group randomly allocated to receive etanercept 25 mg in the DOSERA trial could result in residual confounding; therefore, we rated this trial as having a high risk of other bias. ADMIRE and POET studies were open-label RCTs, which we rated as having a high risk of performance and detection bias, based on the subjective assessments involved on remission evaluations. ADMIRE exhibited an unclear risk of selection bias due to the poor description of the randomization strategy. We also could not rate the risk of reporting bias of POET study. The full risk of bias assessment is detailed in Supplementary Table 4.

Outcomes and quality of evidence

Maintaining biologics increased the frequency of low disease activity by 34 % ($N = 1828$, low-quality evidence) and disease remission by 43 % ($N = 1623$, low quality evidence) compared to withdrawing biologics (Fig. 3). It would be necessary to continue treating four patients to observe one additional case of low disease activity (95 % CI 3–6) and three patients to observe one additional case of remission (95 % CI 2–5) compared to withdrawing the bDMARD therapy (Table 2).

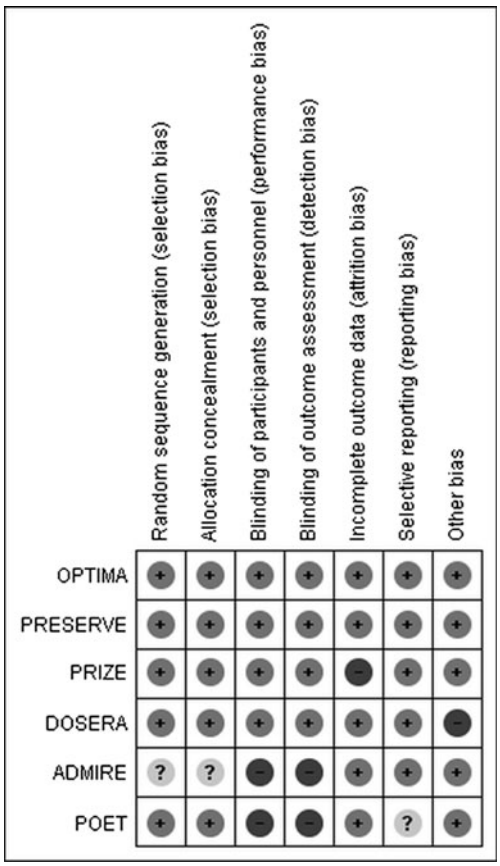

Fig. 2 Risk of bias of the included studies

There was no statistically difference between continuing and discontinuing biologics for serious adverse event, serious infection, malignancy, and ACR scores of improvement of tender and swollen joints (low quality evidence). Outcomes judged as of limited importance presented no statically significance. The individual effect of discontinuing each regimen on important and critical dichotomous outcomes, along with the quality of this evidence is depicted in Supplementary Table 5.

To continue the therapy resulted in lower risk of radiographic progression (NNT = 12, 95 % CI 7–56, moderate quality evidence) when compared to stopping the treatment (Table 3). Patient assessments of pain and disability were poorer in those who interrupted etanercept (moderate quality evidence), but no difference in this outcome was observed between patients who continued and discontinued adalimumab (low quality evidence). The physician global assessment, which indicates disease activity, was not significantly different between withdrawal and continuation of adalimumab but was lower in the groups that continued etanercept 25 or 50 mg. The patient general health assessment revealed more severe disease activity in those that discontinued etanercept, but no significant difference was observed for the withdrawal of adalimumab. Patients that discontinued adalimumab and etanercept 25 mg had more swollen join counts when compared to those who continued the therapy. Discontinuing adalimumab increased the number of tender joint count.

Regarding prognostic variables, POET study found that having a higher baseline DAS 28 score (hazard ratio [HR] = 1.39, 95 % CI 1.21–1.60) and more than 10 years of rheumatoid arthritis (HR = 1.29, 95 % CI 1.03–1.61) were predictors of time to flare.

Discussion

Terminating biologics treatment was associated with poorer patient outcomes when compared to continuing treatment, but half of patients maintained low disease activity (absolute risk = 52 %, 95 % CI 49–55 %) and one third remained in remission (absolute risk = 35 %, 95 % CI 32–38 %) for 9 to 12 months after withdrawing bDMRADs. This result is consistent with a meta-analysis that examined withdrawing all types of DMARDs: patients that tapered or stopped DMARDs had more flares than those who continued, but one third of the patients were free of flares in this strategy after 6–12 months [29].

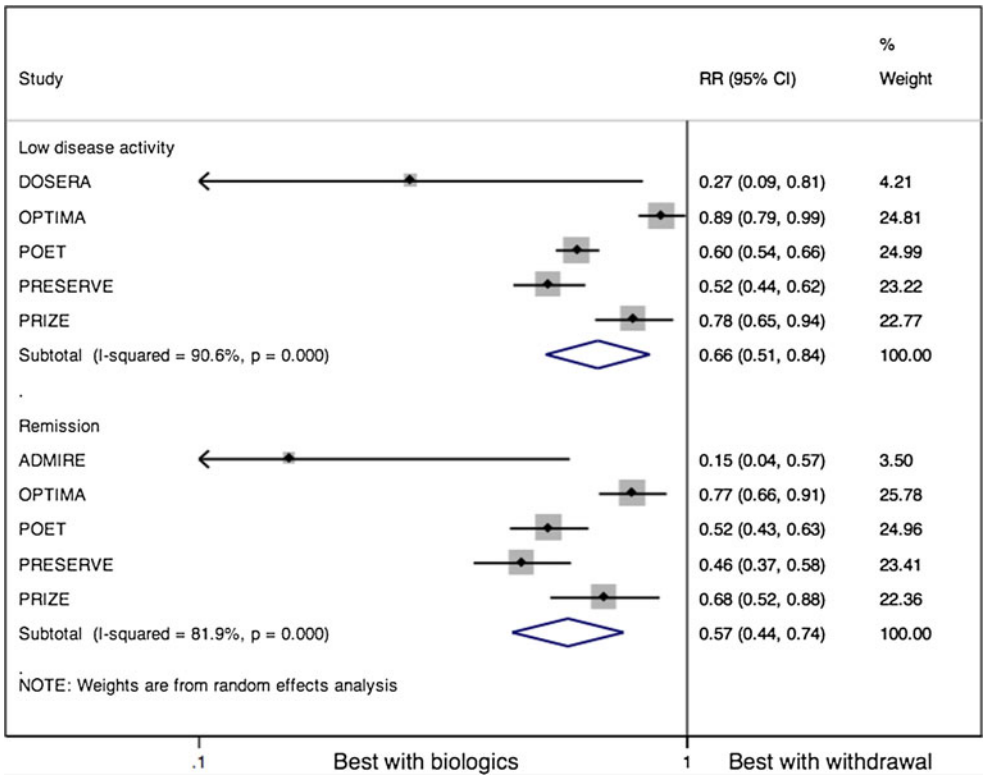

Fig. 3 Effects of withdrawing any biologics on rheumatoid arthritis patients with low disease activity or in remission compared to continuing the therapy

No increased risk of adverse events was observed for continuing or discontinuing biologics. When assessing each biologic agent individually, the results had lower significance than in the meta-analysis of all agents polled. Overall, continuing etanercept resulted in better outcomes, and most outcomes were not significantly different between continuing and discontinuing adalimumab. This pattern may be due to the smaller number of individuals assessed in the RCTs of adalimumab.

The main limitation of present systematic review is the low number of included studies, which is a side effect of our objective to only access studies that randomized stopping the biological therapy. In studies of different designs, the decision to stop the treatment was based on clinical parameters instead of random allocation. Since these criteria can represent a selection bias, the external validity of the results would be compromised. By including solely studies that randomized the withdrawal of bDMARD therapy, present results are more easily attributable to the treatment itself, not the clinical condition of the patients.

Some studies assessing tapering or discontinuation of biologics based on non-randomization criteria are available [30–38]. Present methodological approach led to a restricted number of patients and comparisons, which contributed to the lower quality of the resulting evidence. Our decision to only include trials that randomized the withdrawal was based on the best attempt to avoid confounding bias by only assessing settings that allowed similar prognosis in both groups [39].

Most of the outcomes examined in this meta-analysis were heterogeneous, revealing that there may have been clinical or methodological differences between the studies. We deliberately analyzed some outcomes of all biologics together, which may explain the inconsistency observed. However, even in outcomes analyzed using the same drug and dose regimen, a significant degree of heterogeneity was observed. The clinical criteria to consider patients suitable to randomize the discontinuation slightly differed among the RCTs and may represent a source of heterogeneity.

The companies that market the drugs that were withdrawn funded most of the included RCTs, which may represent a potential reporting bias. Financial conflicts of interest often bias the results in different fields of research [40]. Due to the small number of RCTs available, it was not possible to objectively assess the risk of publication bias [14], but one trial was terminated before enrollment [22].

One possible confounder of the present results is previous treatment with biologics or methotrexate. Patients previously treated with anti-TNF and methotrexate have a poorer prognosis than treatment-naïve individuals [41]. All RCTs included patients who had previously been treated with the assessed biologic agent and csDMARD before randomization for either long- or short term. Additionally, the duration of follow-up was too short to determine the long-term efficacy and safety of biologic withdrawal.

Concerns of clinicians and patients regarding the discontinuation of bDMARD therapy include the risk of diminished clinical

Table 2 Effects of withdrawing any biologics compared to continuing the treatment and quality of the evidence of critical and important dichotomous outcomes

Outcome (reference to studies)	RR	95 % CI	N; I^2 (%)	Importance	Quality of evidence
Low disease activity [23–26, 28][a]	0.66	0.51–0.84	1828; 91	Critical	Low[b, c,]
Remission [23–26, 28][d]	0.57	0.44–0.74	1623; 82	Critical	Low[b, c]
Serious adverse event [23, 26–28]	1.11	0.57–2.16	1258; 28	Critical	Low[b, e]
Serious infection [23, 24, 28]	1.20	0.57–2.52	1628; 0	Critical	Low[b, e]
ACR70 [23–25]	0.65	0.41–1.02	937; 93	Critical	Low[b, c, f]
ACR50 [23–25]	0.72	0.47–1.09	937; 89	Important	Low[b, c, f]
Radiographic progression [23, 24, 26]	0.91	0.85–0.98	800; 13	Important	Moderate[b, f]
Malignancy [23, 24]	0.80	0.26–2.41	1628; 0	Important	Low[b, e]
Other adverse event [23, 24, 26–28]	0.93	0.78–1.10	1734; 63	Limited	Not assessed
Herpes zoster [23, 24, 26, 27]	0.84	0.25–2.82	917; 0	Limited	Not assessed
Any non-serious treatment-emergent adverse event [23, 24]	0.88	0.76–1.02	811; 0	Limited	Not assessed
Treatment-emergent serious adverse event [23, 24]	1.56	0.86–2.83	811; 0	Limited	Not assessed
ACR 20 [23, 24]	0.82	0.63–1.06	937; 92	Limited	Not assessed
ACR/EULAR remission [24, 25]	0.46	0.21–1.01	729; 89	Limited	Not assessed

Notes:

RR relative risk

95 % CI 95 % confidence interval

ACR American College of Rheumatology

ACR20 ACR score of improvement by 20 % of tender and swollen joints

ACR50 ACR score of improvement by 50 % of tender and swollen joints

ACR70 ACR score of improvement by 70 % of tender and swollen joints

[a] Disease activity score of 28 joints (DAS28) ≤3.2

[b] The available evidence is almost limited to adalimumab and etanercept and does not support a general recommendation to any biologic agent (indirectness)

[c] Serious inconsistency, probably related with potential subgroup effects due to dosage or biologic agent adopted

[d] DAS28 < 2.6

[e] Serious imprecision due to a limited number of events

[f] Suspected publication bias due to potential financial conflicts of interest

results, infusion reactions after reintroducing the biologics if needed (for example, in cases of flares) or immunogenicity amplification (by the production of antidrug antibodies) [42]. Data from observational studies indicate that a treatment restarted after interruption remains effective, resulting in reduced disease activity after several months [43, 44]. Consistent with this finding, 85 % of the patients that restarted anti-TNF in POET study regained low disease activity within 6 months [28].

As half of patients that discontinued biologics remained in low disease activity, it is a priority to investigate the differences between patients that succeeded stopping bDMARD therapy and those that had a flare. The use of imaging to predict flare would be probably useful to identify patients that would benefit from discontinuing treatment. An extension of POET study (POET-US) found that patients with ultrasound signs of arthritis in one or more joints had a greater risk of flare after 9 months of discontinuation (HR 1.77 95 % CI 1.16–2.70) and shorter relapse-free period compared to patients without such signs [45]. Another study found that ultrasonography allowed identifying patients to successfully taper and discontinue biologicals after remission in a short period of observation [46]. Future research should focus on evaluating the best prognostic factors indicating withdrawal of biologic agents, including all of the relevant subgroups and biologic agents, and determining long-term safety of withdrawing bDMARDs, as supported by the EULAR research agenda [1].

In conclusion, discontinuing biologics appears to represent a viable approach for patients with sustained remission or low disease activity, but this strategy is associated with an increased risk of recurrence of rheumatoid arthritis. The low quality of the current evidence must be considered when recommending the continuation or withdrawal of biologics in such patients. Further research is necessary to improve the quality of evidence and to identify subgroups that would benefit from the discontinuation of bDMARDs as well as factors that would guide this treatment decision. In clinical practice, discussing the risks and benefits with each patient in

Table 3 Effects of withdrawing biologics compared to continuing the treatment in continuous outcomes

Outcome (reference to studies)	Withdrawal of biologics compared to the indicated treatment								
	Adalimumab 40 mg			Etanercept 50 mg			Etanercept 25 mg		
	MD	95 % CI	$N; I^2$ (%)	MD	95 % CI	$N; I^2$ (%)	MD	95 % CI	$N; I^2$ (%)
Disability (HAQ-DI, 0–3 scale) [23, 24]	0.03	−0.08, 0.14	207	0.30	0.19, 0.41	402	0.13	0.04, 0.42	530; 66
Pain (VAS, 0–100 mm) [23, 24]	2.10	−1.18, 5.38	207	15.40	11.16, 19.64	402	12.60	8.17, 17.03	402
C-reactive protein (mg/L) [23, 24, 26]	1.80	−3.01, 6.91	207	2.55	−0.61, 5.70	416; 13	2.25	−0,24, 4.75	544; 80
Tender joint count [23, 24, 26]	1.50	0.70, 2.30	207	1.45	−0.42, 3.31	416; 92	1.45	−0.41, 3.31	416; 93
Swollen joint count [23, 24, 26]	0.80	0.21, 1.39	207	0.52	−2.68, 3.73	416; 67	1.44	0.86, 2.03	416; 0
Physician global assessment [23, 24]	0.11	−0.17, 0.38	207	0.80	0.59, 1.00	402	0.68	0.48, 0.88	402
General health visual analogue scale score (0–100 mm) [23, 24]	1.50	−1.90, 4.90	207	13.10	9.45, 17.75	402	11.10	6.89, 15.31	402

Notes:
MD mean difference
95 % CI 95 % confidence interval
HAQ-DI health assessment questionnaire disability index
VAS visual analogue scale
ACR20 American College of Rheumatology score of improvement by 20 % of tender and swollen joints

sustained remission appears to remain the more reasonable option to settle continuing or discontinuing treatment with biologics.

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Compliance with ethical standards

Conflict of interest LMHM is a consultant, board member, and/or speaker for Roche, Pfizer, AbbVie, UCB, Hospira, Janssen, and Lilly. None of the other authors receive or have received benefits from commercial sources for the work reported in this manuscript or have any other financial interests that could create potential conflicts of interest with respect to this work.

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