Little Evidence for Usefulness of Biomarkers for Predicting Successful Dose Reduction or Discontinuation of a Biologic Agent in Rheumatoid Arthritis

A Systematic Review

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Objective. To systematically review studies addressing prediction of successful dose reduction or discontinuation of a biologic agent in rheumatoid arthritis (RA).

Methods. PubMed, Embase, and Cochrane Library databases were searched for studies that examined the predictive value of biomarkers for successful dose reduction or discontinuation of a biologic agent in RA. Two reviewers independently selected studies, and extracted data and assessed the risk of bias. A biomarker was classified as a "potential predictor" if the univariate association was either strong (odds ratio or hazard ratio >2.0 or <0.5) or statistically significant. For biomarkers that were studied multiple times, qualitative best-evidence synthesis was performed separately for the prediction of successful dose reduction and discontinuation. Biomarkers that were defined in ≥75% of the studies as potential predictors were regarded as "predictor" for the purposes of our study.

Results. Of 3,029 nonduplicate articles initially searched, 16 articles regarding 15 cohorts were included in the present study. Overall, 17 biomarkers were studied multiple times for the prediction of successful dose reduction, and 33 for the prediction of successful discontinuation of a biologic agent. Three predictors were identified: higher adalimumab trough level for successful dose reduction and lower Sharp/van der Heijde erosion score and shorter symptom duration at the start of a biologic agent for successful discontinuation.

Conclusion. The predictive value of a wide variety of biomarkers for successful dose reduction or discontinuation of biologic treatment in RA has been investigated. We identified only 3 biomarkers as predictors, in just 2 studies. The strength of the evidence is limited by the low quality of the included studies and the likelihood of reporting bias and multiple testing.

Treatment of rheumatoid arthritis (RA) is based on the "hit hard, hit early" strategy. Starting treatment early and achieving low disease activity as soon as possible by using a combination of disease-modifying antirheumatic drugs (DMARDs) (including glucocorticoids) and rapid escalation to biologics, if necessary, are pivotal in this strategy (1).

However, a disadvantage of such a strategy is that it leads to overtreatment with biologic agents in a considerable number of patients (2). Overtreatment is associated with an increased risk of adverse effects such as dose-dependent serious infections, as well as higher medication costs (3). In order to reduce overtreatment, the start of intensive treatment should be followed by attempts to find the lowest individual effective dose. This can be done in patients with low disease activity by discontinuing the biologic agent all at once, or tapering the dosage. In general, discontinuation all at once of

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a biologic agent has proven to be inferior to continuing biologic treatment with respect to disease activity and radiologic outcomes and function (4). Alternatively, tapering of a biologic agent guided by disease activity (dose reduction until either disease activity increases or the biologic agent can be stopped) appears to be feasible, safe, and effective in RA patients with low disease activity or whose disease is in remission (4).

The ability to accurately predict the success of dose reduction or discontinuation of a biologic agent is likely to constitute a major improvement over the current trial-and-error, disease activity–guided tapering. When it can be predicted that dose reduction will be unsuccessful, dose reduction should not even be attempted. Such predictions would prevent disease flares, minimize physician efforts, and ease uncertainty in patients. Additionally, when it can be predicted that discontinuation will be successful, the dose tapering phase can be skipped and the biologic can be stopped directly, saving time and medication cost.

A biomarker is defined as a characteristic objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention (5). Patient characteristics, biochemical tests, and imaging measurements can all serve as biomarkers. If there is a biomarker that can accurately predict the success of dose reduction or discontinuation prior to the tapering of a biologic, it could be used for optimizing treatment in daily clinical care.

As previous narrative reviews have demonstrated, it remains challenging to identify those patients whose treatment with biologic agents can be tapered without risk of a flare (6–9). In the past few years, several studies have investigated various biomarkers for predicting successful tapering of different biologic agents. To our knowledge, these results have not yet been systematically summarized. Therefore, we conducted analysis of all prospective studies with a predefined tapering protocol, in order to provide an overview of the investigated biomarkers for predicting successful dose reduction or discontinuation of biologic treatment in RA.

MATERIALS AND METHODS

Search strategy. In November 2015, a search was conducted using PubMed, Embase, and Cochrane Library databases for studies that examined the predictive value of biomarkers for the success of dose reduction or discontinuation of biologic treatment in patients with RA. The search strategy (see Supplementary Table 1, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.39946/abstract) consisted of the Haynes broad filter (recommended for finding predictive research) (10), keywords regarding the patient group, as well as the outcome of interest

(successful dose reduction or discontinuation). The patient group consisted of those who were treated with any registered biologic agent for RA (i.e., abatacept, adalimumab, certolizumab, etanercept, golimumab, infliximab, rituximab, or tocilizumab) at a standard dosing regimen for >24 weeks, who had low disease activity, and in whom the dosage of a biologic agent was subsequently reduced or discontinued. Anakinra was excluded because it is now rarely used due to lack of efficacy. The search was not limited by language, nor by year or type of publication. Included articles and excluded reviews were used for cross checking of references.

Study selection. This review was conducted and reported according to the procedures outlined in the PRISMA Statement (11). Two reviewers (EB, FB) independently selected articles, primarily by title and abstract and subsequently by review of the full text (when necessary). Any disagreement was resolved by consensus meetings with another reviewer (LT). During full-text analyses, studies were excluded if 1) biomarkers were not determined or data on them were not collected prior to tapering of biologic agents, 2) follow-up periods were <3 months or >24 months, 3) <20 participants were included in the cohort or a retrospective design was utilized, or 4) they were only reviews or abstracts from a conference. Additionally, studies that analyzed the data in a way that could not provide answers to our primary question (e.g., pooling the outcomes of conventional DMARD and biologic agent tapering or the outcomes of the continuing arm and tapering arm) were also excluded.

Data extraction. Data on study designs, patient characteristics, tapering strategies, biomarkers, outcomes (clinical response criteria), and analysis (association measure between biomarker and outcome) were independently extracted from each article by 2 reviewers (FB, LT) using a data extraction form. The form was pilot tested on 3 randomly selected articles (which were not included in the review) and was refined accordingly. Any doubts were resolved by consultation with a third reviewer (CvdE or AdB).

Quality assessment. Two reviewers (FB, LT) independently assessed the methodologic quality of the included studies using the Quality In Prognosis Studies (QUIPS) tool (12). The tool was operationalized a priori and pilot tested on 3 randomly selected articles that were not included in the review. One of the 6 domains of the tool, study confounding, was excluded because all of the studies included in our review investigated multiple biomarkers in an exploratory manner, making it impossible to summarize all potential confounding factors.

Each of the remaining domains was judged as having low, moderate, or high risk of bias. Disagreements were resolved by discussion and, when necessary, a third reviewer (CvdE) made final decisions. Since the use of a summed score for overall study quality is not recommended, we decided a priori to consider a study of high quality if the 2 domains that we consider to be most important (study participation and statistical analysis) were either both assessed as having a low risk of bias, or one as low risk and the other as moderate (13). Studies not meeting these criteria were considered of low quality.

Statistical analysis and data synthesis. The heterogeneity of the biomarkers, outcome measures, and statistics precluded a quantitative meta-analysis. Therefore, results regarding the predictive value of biomarkers for the success of dose reduction and discontinuation of biologic treatment were qualitatively synthesized in 3 steps.

In step 1, we assessed whether each investigated biomarker was a potential predictor. A biomarker was defined as a potential predictor if the univariate association between the biomarker and the success of dose reduction or discontinuation was either strong (odds ratio [OR] or hazard ratio [HR] >2.0 or <0.5) or statistically significant ($P < 0.05$) (14). If no univariate OR or HR was provided, results of other univariate association measures, multivariate results, or textual conclusions on the statistical significance of findings were used.

In step 2, biomarkers were divided into 5 different categories (patient, treatment, disease activity, laboratory, and imaging measurements) and an overview of biomarkers that were studied multiple times (i.e., in >1 separate study) and those that were studied only once (15) was completed.

In step 3, qualitative best-evidence synthesis of biomarkers (studied multiple times) was performed separately for predicting the success of dose reduction and discontinuation of biologic agents. A biomarker was regarded as a predictor if it was defined as a potential predictor in ≥75% of the studies in which the biomarker was investigated. Subsequently, we defined 4 levels of evidence as used in previous systematic reviews (16,17): 1) strong evidence (consistent findings [≥75% of findings in same direction] in at least 2 high-quality studies), 2) moderate evidence (consistent findings in 1 high-quality study and at least 2 low-quality studies), 3) limited evidence (findings in 1 high-quality study or consistent findings in at least 2 low-quality studies), and 4) conflicting evidence (inconsistent findings irrespective of study quality [<75% of findings in same direction]). Of note, the level of conflicting evidence was checked first before assigning a strong, moderate, or limited evidence level to a biomarker.

RESULTS

Study selection. Through the database search in November 2015, we retrieved 3,029 nonduplicate articles. The cross-checking of references yielded no relevant articles. In total, 21 articles met our selection criteria. However, 5 articles were publications of the BeSt study (Behandel Strategieën voor Reumatoïde Artritis) (18–22) and 2 of the HONOR study (Humira Discontinuation Without Functional and Radiographic Damage Progression Following Sustained Remission) (23,24). Of the BeSt study publications, we only analyzed the article that explicitly answered our primary question (22), as the other articles contained no additional information. Of the two HONOR study publications, we selected the article reporting the study with the longest follow-up time (24), since the outcome measures between these publications were similar. Eventually 16 articles regarding 15 cohorts were included in this review. A flow diagram of the study selection is depicted in Figure 1.

Study characteristics. The characteristics of the included studies are listed in Supplementary Table 2 (available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.39946/abstract). In 7 studies, the dosage of the biologic agent was reduced (25–31) and in 9 studies the biologic agent was discontinued
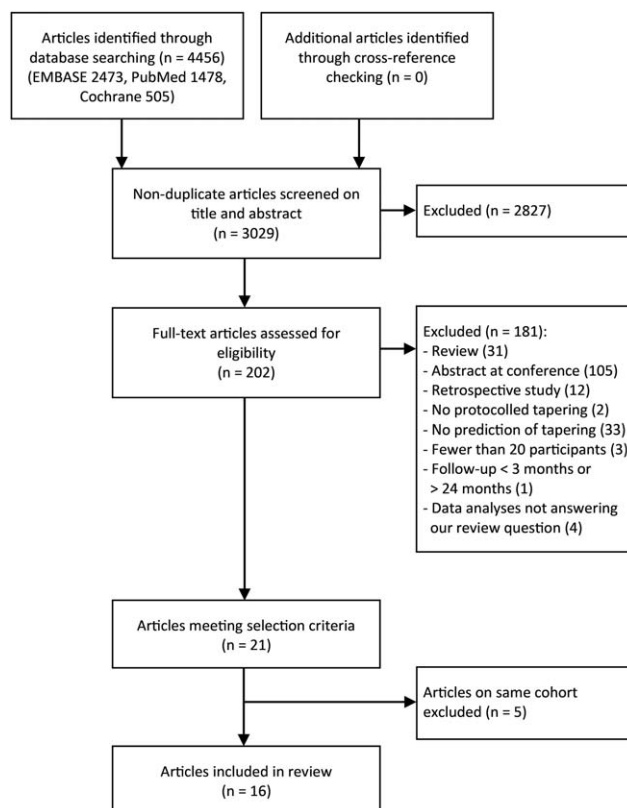

Figure 1. Flow diagram of study selection.

all at once (22,24;32–38). There were 4 randomized controlled trials (22,27,28,30) and 12 observational cohort studies (24–26,29,31–38). Overall, 1,093 participants were included in these studies. They were all in remission or had low disease activity prior to dose reduction or discontinuation of the biologic agent, according to different disease activity criteria. In 11 of the 16 studies (22,24–27,30,34–38), a minimum duration of 6 months of low disease activity was part of the inclusion criteria. Studies varied with respect to sample size (range 21–187), type of biologic agent (abatacept, adalimumab, certolizumab, etanercept, golimumab, infliximab, or tocilizumab), follow-up period (range 24 weeks–24 months), and outcome measure (meeting criteria for low disease activity, remission, or flare).

The included studies examined a wide variety of biomarkers. Fifty-two biomarkers were studied for their predictive value for the success of dose reduction (17 of which were studied multiple times), and 64 biomarkers for the success of discontinuation of a biologic agent (33 of which were studied multiple times).

The predictive value of biomarkers for the prediction of the success of dose reduction and discontinuation of a biologic agent were analyzed separately. The

Table 1. Best-evidence synthesis for prediction of successful dose reduction of a biologic agent*

Biomarker studied	No. of studies	Potential predictor (refs.)†		Quality (refs.)‡		Predictor§	Level of evidence¶
		Yes	No	High	Low		
Age	5	0	5 (25–27,29,31)	1 (25)	4 (26,27,29,31)	No	Moderate
Sex	5	0	5 (25–27,29,31)	1 (25)	4 (26,27,29,31)	No	Moderate
Disease duration	4	1 (31)	3 (25,27,29)	1 (25)	3 (27,29,31)	No	Moderate
Smoking	4	1 (25)	3 (26,27,31)	1 (25)	3 (26,27,31)	No	Limited
No. of previous csDMARDs	3	1 (31)	2 (26,27)	0	3 (26,27,31)	No	Conflicting
No. of previous biologics	2	0	2 (27,31)	0	2 (27,31)	No	Limited
Time from symptom onset to biologic agent	2	0	2 (26,31)	0	2 (26,31)	No	Limited
Duration of current biologic treatment before tapering	3	1 (29)	2 (25,27)	1 (25)	2 (27,29)	No	Conflicting
Concomitant DMARD	4	0	4 (25–27,31)	1 (25)	3 (26,27,31)	No	Moderate
Methotrexate	3	0	3 (25,27,29)	1 (25)	2 (27,29)	No	Moderate
Prednisone	3	0	3 (27,29,31)	0	3 (27,29,31)	No	Limited
DAS28-ESR at tapering	4	2 (29,31)	2 (25,27)	1 (25)	3 (27,29,31)	No	Conflicting
Rheumatoid factor	6	2 (26,30)	4 (25,27,29,31)	1 (25)	5 (26,27,29–31)	No	Conflicting
ACPA	5	0	5 (25,27–29,31)	1 (25)	4 (27–29,31)	No	Moderate
ESR	2	0	2 (27,29)	0	2 (27,29)	No	Limited
CRP	2	1 (29)	1 (27)	0	2 (27,29)	No	Conflicting
Adalimumab trough level	2	2 (28,29)	0	0	2 (28,29)	Yes	Limited

* csDMARDs = conventional synthetic disease-modifying antirheumatic drugs; DAS28-ESR = Disease Activity Score in 28 joints using the erythrocyte sedimentation rate; ACPA = anti–citrullinated peptide antibodies; CRP = C-reactive protein.
† Number of studies with a strong and/or significant association between biomarker and successful dose reduction.
‡ Number of studies with a high/low quality according to the Quality in Prognosis Studies tool.
§ Biomarker defined as potential predictor in ≥75% of the studies in which the biomarker was investigated.
¶ Composite outcome of predictive value and study quality.

DRESS study (Dose Reduction Strategy of Subcutaneous TNF Inhibitors) examined the predictive value of biomarkers for both the success of dose reduction and the success of discontinuation of biologic treatment; data on these biomarkers were therefore included in both analyses (27). For the Spacing of TNF-Blocker Injections in Rheumatoid Arthritis Study (STRASS) (30), only those biomarkers that were investigated in the multivariate analysis and that included the strategy of spacing TNF blockers could be analyzed in our review, since the univariate analysis with maintenance and spacing arms combined was not suitable. The results for the biomarkers that were studied multiple times for prediction of the success of dose reduction and the success of discontinuation are depicted in Supplementary Table 3. In summary, 3 predictors were identified: higher adalimumab trough level for the success of dose reduction, and lower Sharp/van der Heijde erosion score and shorter symptom duration at the start of biologic treatment for the success of discontinuation.

The results for biomarkers that were studied once for the prediction of the success of dose reduction and the success of treatment discontinuation are depicted in Supplementary Table 4 (http://onlinelibrary.wiley.com/doi/10.1002/art.39946/abstract). Ten of 35 biomarkers were classified as potential predictors for the success of dose reduction, and 8 of 31 for discontinuation.

Quality assessment and best-evidence synthesis. A total of 80 domains (5 domains in 16 studies) were judged by two reviewers (FB and LT) who agreed on 65 of 80 domains, representing good interrater agreement ($\kappa = 0.71$) (39). Disagreements were caused by different interpretation of missing data and different judgment of the overall risk of bias of the domain study attrition. According to our predefined criteria, 5 studies were classified as high-quality study and 11 studies as low-quality study (see Supplementary Table 5, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.39946/abstract). Limitations of the studies mostly concerned insufficient data presentation and selective reporting of results. Qualitative best-evidence synthesis for the prediction of the success of dose reduction and the success of discontinuation of a biologic agent is depicted in Tables 1 and 2, respectively.

DISCUSSION

To our knowledge, this is the first systematic review summarizing the predictive value of biomarkers for the success of dose reduction or discontinuation of a biologic agent in RA. Of all the studied biomarkers, we identified 3 as predictors. Of note, each of these 3 biomarkers was only investigated in 2 studies, meaning that more frequent investigation of specific biomarkers yielded

Table 2. Best-evidence synthesis for the prediction of successful discontinuation of a biologic agent*

Biomarker studied	No. of studies	Potential predictor (refs.)†		Quality (refs.)‡		Predictor§	Level of evidence¶
		Yes	No	High	Low		
Age	7	1 (37)	6 (22,24,27,32,33,38)	3 (22,24,37)	4 (27,32,33,38)	No	Strong
Sex	7	0	7 (22,27,32–34,37,38)	3 (22,34,37)	4 (27,32,33,38)	No	Strong
Disease duration	9	4 (22,24,35,37)	5 (27,32–34,38)	4 (22,24,34,37)	5 (27,32,33,35,38)	No	Conflicting
Remission duration	3	1 (38)	2 (33,35)	0	3 (33,35,38)	No	Conflicting
Smoking	2	1 (22)	1 (27)	1 (22)	1 (27)	No	Conflicting
BMI	2	0	2 (22,27)	1 (22)	1 (27)	No	Limited
No. of previous csDMARDs	2	0	2 (27,38)	0	2 (27,38)	No	Limited
No. of previous biologic agents	2	0	2 (27,38)	0	2 (27,38)	No	Limited
Time from symptom onset to biologic agent	2	2 (22,35)	0	1 (22)	1 (35)	Yes	Limited
Duration of current biologic treatment before tapering	4	3 (22,24,38)	1 (27)	2 (22,24)	2 (27,38)	No	Conflicting
Concomitant DMARD	2	0	2 (27,38)	0	2 (27,38)	No	Limited
Methotrexate	4	0	4 (24,27,33,37)	2 (24,37)	2 (27,33)	No	Strong
Prednisone	4	1 (34)	3 (27,33,37)	2 (34,37)	2 (27,33)	No	Moderate
HAQ	8	3 (34–36)	5 (22,24,33,37,38)	4 (22,24,34,37)	4 (32,33,35,38)	No	Conflicting
DAS28-ESR at discontinuation	5	3 (24,34,37)	2 (27,33)	3 (24,34,37)	2 (27,33)	No	Conflicting
DAS28-CRP at discontinuation	3	1 (37)	2 (27,33)	1 (37)	2 (27,33)	No	Conflicting
DAS28-ESR at start of biologic agent	2	0	2 (37,38)	1 (37)	1 (38)	No	Limited
TJC	3	0	3 (22,27,37)	2 (22,37)	1 (27)	No	Strong
SJC	3	0	3 (22,27,37)	2 (22,37)	1 (27)	No	Strong
Disease activity VAS	2	0	2 (22,37)	2 (22,37)	0	No	Strong
SDAI	2	0	2 (24,33)	1 (24)	1 (33)	No	Limited
CDAI	2	0	2 (24,33)	1 (24)	1 (33)	No	Limited
Rheumatoid factor	7	1 (34)	6 (22,24,27,33,37,38)	4 (22,24,34,37)	3 (27,33,38)	No	Strong
ACPA	4	0	4 (22,27,33,38)	1 (22)	3 (27,33,38)	No	Moderate
ESR	4	1 (24)	3 (22,27,37)	3 (22,24,37)	1 (27)	No	Strong
CRP	5	1 (36)	4 (22,24,27,37)	3 (22,24,37)	2 (27,36)	No	Strong
MMP-3 concentration	2	1 (34)	1 (24)	2 (24,34)	0	No	Conflicting
SHS total score	4	1 (37)	3 (22,24,27)	3 (22,24,37)	1 (27)	No	Strong
SHS erosion score	2	2 (22,37)	0	2 (22,37)	0	Yes	Strong
SHS joint space narrowing score	2	0	2 (22,37)	2 (22,37)	0	No	Strong
Yearly SHS progression at discontinuation	2	1 (22)	1 (37)	2 (22,37)	0	No	Conflicting
Gray-scale ultrasound	2	1 (33)	1 (35)	0	2 (33,35)	No	Conflicting
Power Doppler ultrasound	2	1 (33)	1 (35)	0	2 (33,35)	No	Conflicting

* BMI = body mass index; HAQ = Health Assessment Questionnaire; TJC = tender joint count; SJC = swollen joint count; VAS = visual analog scale; SDAI = Simplified Disease Activity Index; CDAI = Clinical Disease Activity Index; MMP-3 = matrix metalloproteinase 3; SHS = Sharp/van der Heijde score (see Table 1 for other definitions).
† Number of studies with a strong and/or significant association between biomarker and successful dose reduction.
‡ Number of studies with a high/low quality according to the Quality in Prognosis Studies tool.
§ Biomarker defined as potential predictor in ≥75% of the studies in which the biomarker was investigated.
¶ Composite outcome of predictive value and study quality.

no consistent predictors. Moreover, 2 of the biomarkers (Sharp/van der Heijde erosion score and shorter symptom duration at the start of biologic treatment) showed a statistically significant but weak association. Therefore, the clinical relevance of these identified predictors could be questioned. Also, our findings regarding the predictive value of the third biomarker (adalimumab trough level) could be questioned considering extensive multiple testing in one study (28) and disputed results in another (29,40).

In addition, of those biomarkers that were studied only once, we found 10 of 35 biomarkers and 8 of 31 biomarkers that were classified as potential predictors for the success of dose reduction and discontinuation of a biologic agent, respectively. Most of them were serum markers and imaging measurements. This may indicate that the assessment of subclinical inflammation by laboratory or imaging testing provides a useful tool to determine a patient's risk of flare (8). However, results with

these biomarkers need to be replicated in other cohorts, with a predefined tapering protocol, before they can be considered predictors.

A strength of this review is that we executed a broad literature search to identify all biomarkers that have ever been investigated for their ability to predict the success of dose reduction or that of discontinuation of a biologic agent. Furthermore, we have performed a best-evidence synthesis to provide an overview of the results, making the review process transparent and reproducible.

For the identification of potential predictors we chose criteria that can be easily met, taking into account the fact that univariate analyses could lead to an overestimation of the strength of associations. However, even with these non-strict criteria, only 3 biomarkers could be defined as predictors.

The studies we included show substantial heterogeneity in study design and outcome definition. Several studies included >1 biologic—precluding investigation of the potential different effect for biologic agents. Regarding outcome definition, all studies used a disease activity measure but the threshold for failure and the time point of assessment differed. To collect comparable information, the use of a standardized outcome definition is essential (41). An increase in the 28-joint Disease Activity Score (DAS28) of >1.2 (or >0.6 if the initial score is ≥3.2) appeared most discriminating and valid, although the Outcome Measures in Rheumatology RA flare group is developing a patient-reported flare questionnaire that could also be used in the future (42,43).

Another important limitation is the low quality of 11 of the 16 included studies, according to the operationalized QUIPS tool. Most of the studies were defined as low quality based on incomplete reporting. This classification may have been caused by the fact that finding predictive markers for successful tapering was rarely the main research question of the included studies. Also, there is no specific guideline for predictive research. In our opinion, the use of the Standards for Reporting Diagnostic Accuracy reporting guidelines (44) should be encouraged to ensure that sufficient information for editors, peer reviewers, and readers is provided to facilitate understanding of how the research was performed and to judge the credibility of the findings.

Furthermore, data analysis was complicated by the statistical methods used in the studies. For example, in some studies data were assessed in a way that could not answer our primary question (e.g., pooling the outcomes of conventional DMARD and biologic agent tapering or the outcomes of the continuing arm and tapering arm). In addition, appropriate association measures (e.g., OR or HR) were rarely reported.

However, if more studies had been of high quality, we would not have found more potential predictors, since the mean frequency of potential predictors in high-quality studies was slightly lower (31.6%) in comparison to low-quality studies (38.6%). This effect of higher-quality studies being associated with lower effect estimates has been well recognized (45).

Finally, positive findings should be interpreted with caution due to reporting bias and multiple testing. It is very likely that negative results found for potential biomarkers were not mentioned by all studies. This means that there would have been stronger evidence for nonpredictive biomarkers if all data were reported. Also, there is a chance of false-positive results due to multiple tests, because some studies simultaneously investigated more than 20 biomarkers without correction for multiple testing by lowering the required P value.

There are currently several studies investigating predictive markers for successful tapering of biologic agents in RA (e.g., STARA [Stopping Anti–Tumor Necrosis Factor Agents in Rheumatoid Arthritis], RA-BioStop [Ultrasound and Withdrawal of Biological DMARDs in Rheumatoid Arthritis], BioRRA [Biomarkers of Remission in Rheumatoid Arthritis]) (46). We would recommend that the various research groups validate the prognostic value of potential predictors and report the predictive value of all their investigated biomarkers with the appropriate association measures.

In conclusion, we investigated the predictive value of a wide variety of biomarkers for the success of dose reduction or discontinuation of a biologic agent in RA. We identified only 3 biomarkers as predictors, in just 2 studies. The strength of the evidence is limited by the low quality of included studies and the likelihood of reporting bias and multiple testing.

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AUTHOR CONTRIBUTIONS

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