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ORIGINAL ARTICLE

DMARD-free remission as novel treatment target in rheumatoid arthritis: A systematic literature review of achievability and sustainability

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ABSTRACT

Objectives Although current treatment guidelines for rheumatoid arthritis (RA) suggest tapering disease-modifying anti-rheumatic drugs (DMARDs), it is unclear whether DMARD-free remission (DFR) is an achievable and sustainable outcome. Therefore, we systematically reviewed the literature to determine the prevalence and sustainability of DFR and evaluated potential predictors for DFR.

Methods A systematic literature search was performed in March 2019 in multiple databases. All clinical trials and observational studies reporting on discontinuation of DMARDs in RA patients in remission were included. Our quality assessment included a general assessment and assessment of the description of DFR. Prevalence of DFR and its sustainability and flares during tapering and after DMARD stop were summarised. Also, potential predictors for achieving DFR were reviewed.

Results From 631 articles, 51 were included, comprising 14 clinical trials and 5 observational studies. DFR definition differed, especially for the duration of DMARD-free state. Considering only high- and moderate-quality studies, DFR was achieved in 5.0%–24.3% and sustained DFR (duration>12 months) in 11.6%–19.4% (both relative to the number of patients eligible for tapering). Flares occurred frequently during DMARD tapering (41.8%–75.0%) and in the first year after achieving DFR (10.4%–11.8%), while late flares, >1 year after DMARD-stop, were infrequent (0.3%–3.5%). Many patient characteristics lacked association with DFR. Absence of autoantibodies and shared epitope alleles increased the chance of achieving DFR.

Conclusions DFR is achievable in RA and is sustainable in ~10%–20% of patients. DFR can become an important outcome measure for clinical trials and requires consistency in the definition. Considering the high rate of flares in the first year after DMARD stop, a DMARD-free follow-up of >12 months is advisable to evaluate sustainability.

Key messages

What is already known about this subject?

- Although current treatment guidelines for rheumatoid arthritis suggest tapering DMARDs when patients are in sustained remission, it is unclear whether DMARD-free remission is an achievable and sustainable outcome.

What does this study add?

- DMARD-free remission is achievable in rheumatoid arthritis and is sustainable in ~10%–20% of patients.

How might this impact on clinical practice or future developments?

- DMARD-free remission can become an important outcome measure for clinical trials, though this requires consistency in the definition.
- We propose to incorporate a DMARD-free follow-up period for at least 1 year, to ensure that DMARD-free remission is sustainable.

INTRODUCTION

In rheumatoid arthritis (RA), early treatment, with disease-modifying antirheumatic drugs (DMARDs), aiming at sustained remission, is nowadays the key element of each management approach.[1 2] As a result, RA has become a controllable disease in which sustained clinical remission is achievable for an increasing number of patients, and tapering and discontinuation of DMARDs have become of emerging interest.[3] Current international guidelines recommend tapering of DMARDs in RA patients with sustained remission.[1 2] Nevertheless, these guidelines are less clear whether DMARDs can be stopped, and the systematic literature review supportive of the most recent EULAR guidelines was not focused on DMARD cessation.[4]

Despite the recommendations in the guidelines, tapering of DMARDs has not been adopted structurally in many clinical practices, presumably because the risk of a disease flare[5] and because the ability to achieve and sustain DMARD-free remission (DFR) is often considered unlikely.[6] On the other hand, there is increasing interest in

achieving DFR, because this is currently the best proxy for cure.[7 8] Clinical trials occasionally report on DFR, but usually not as the primary outcome. Absence of knowledge of DFR prevalence, its sustainability and the characteristics of patients achieving DFR currently hamper the use of DFR as primary outcome.[9]

We aimed to expand the comprehension of the ability to achieve and sustain DFR in RA. Therefore, we conducted a systematic literature search. In addition to the DFR prevalence and sustainability, potential predictors for achieving DFR were explored.

METHODS

Search strategy and selection criteria

This systematic literature review was conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines and the Cochrane review handbook.[10 11] The protocol was registered in the International Prospective Register of Systematic Reviews (CRD42019132558).[12]

The search strategy was developed and performed in collaboration with an experienced librarian (JS). Key terms used for the search were 'Rheumatoid arthritis', 'Antirheumatic drugs', 'Discontinuation' and 'Remission'. These search items were translated into multiple matching synonyms in order to broaden our results. All search elements were combined with the Boolean operators AND/OR. PubMed, Embase, Web of Science, COCHRANE Library, Emcare and Academic Search Premier were systematically searched (supplementary table S1).

All observational cohorts and clinical trials reporting on discontinuation of DMARDs in RA patients, in remission, were included. Study selection was independently carried out by two reviewers (MV and EvM). Cases of disagreement were discussed until consensus was reached. First, all obtained titles were screened, and subsequently abstracts were reviewed after which full-text articles were screened for the predefined inclusion and exclusion criteria (supplementary table S2). If multiple articles were based on the same study, the article which described the prevalence and sustainability of DFR most clearly was selected. Subsequently, the article describing the longest follow-up was used for data extraction.

Data extraction

A standardised data collection form was used to extract the following information: study design, patient characteristics, interventions, glucocorticoids (GCs) usage, organisation of follow-up, outcome measures and loss to follow-up (supplementary table S3). Furthermore, data regarding eligibility criteria for tapering, tapering methods, numbers of patients tapering, description and timing of achieving DFR, sustainment of DFR over time and the occurrence of flares were extensively explored. Also, information regarding predictors of DFR was collected. Data extraction was done independently by two reviewers (MV and EvM), and disagreements were discussed until consensus was reached.

If the methods were incomplete or unclear, the methods of the original study could be used if a reference was available. Clinical trials and observational studies were handled separately, because of fundamental differences in the study design, which could influence achievement and sustainment of DFR, that is, protocolised versus non-protocolised tapering, frequency of monitoring and duration of follow-up.

Quality assessment

Our study quality assessment consisted of two parts, namely a general assessment and an assessment of the description of DFR. For the general quality assessment, we used 13 predefined quality criteria, which were based on Cochrane guidelines (supplementary table S4).[11] The general study quality was considered 'good' if >75% (≥10 items) of these criteria were scored positive. For the DFR quality assessment, we used the following criteria: (1)'DFR definition', referring to whether a definition (eg, remission criterion) of DFR was included, and (2)'DFR duration', referring to whether information on the time between DMARD stop and being appointed as DFR (i.e. the duration of DMARD-free status) was reported. Specific emphasis was put on the duration of DMARD-free state since this attains insight into the sustainability of DFR. When both DFR quality criteria were scored positive, DFR quality was regarded as 'good'.

Studies were regarded as 'high quality' if the general quality, as well as the DFR quality, was good. When the general study quality was good but only one DFR-criterion was fulfilled, studies were regarded as 'moderate quality'. Studies lacking both DFR criteria, or without a good general quality assessment, were scored as 'low quality'.

Data analysis

Extracted data were used to calculate DFR prevalence, defined as the proportion of patients achieving DFR, compared with those eligible for tapering medication. For each prevalence, the CI was calculated. Patients were considered eligible for tapering when they had achieved remission and subsequently were allowed to start tapering their medication. GCs were also considered as DMARDs. We specifically chose not to use the total study population as the denominator, because in some studies specific groups of patients were not allowed to taper their medication due to study protocol.

Sustained DFR (SDFR) was defined as the percentage of patients with a DFR duration of >12 months since DMARD stop, relative to the number of patients eligible for tapering. Reported flares were categorised and summarised according to the time period in which they occurred: (i) during tapering, (ii) in the first year after achieving DFR ('early flares') and (iii) after more than 1 year of DFR ('late flares'). Results on DFR were summarised in a narrative overview, also in relation to study quality. Due to expected heterogeneity in study design and study populations, pooled effect estimates were not calculated.

Additionally, the data were reviewed on potential predictors for achieving DFR. We used the same methods for

data extraction and assessment as described for DFR prevalence. Predictors of DFR were summarised. Results on variables evaluated in more than one high-quality or moderate-quality article were graphically presented, based on statistical significance obtained with regression analysis. If univariate and multivariate analyses were both conducted, results of the multivariate analysis were used. For each predictor, the number of studies and the total number of patients within these studies were presented and the direction of the effect was indicated.

RESULTS

Study selection

Our search resulted in 631 articles, of which 51 articles were considered eligible for inclusion (figure 1). These 51 articles comprised data from 19 studies, 14 clinical trials and 5 observational cohorts.

Quality assessment

Both the quality of the study in general and the description of DFR were evaluated, resulting in a final quality rating. Eleven out of 14 clinical trials and two out of five observational cohorts showed a good general quality (table 1). Notably, the tapering methods were better described for clinical trials than for observational cohorts. Of the 13 studies with a good general quality, seven fulfilled both quality criteria for DFR and were regarded as high quality. These seven high-quality studies comprised five clinical trials and two observational cohorts. Of the remaining six studies, two studies were of moderate quality since only one DFR criterion was fulfilled. The four other studies did not fulfil any DFR quality criteria and were regarded low quality (table 1).

Because of fundamental differences in study design, DFR prevalence and flare rates from clinical trials and observational cohorts were presented separately. Also, only high-quality or moderate-quality studies were presented in the result section. Nonetheless, all prevalence, including those of low-quality studies, can be found in table 2.

Clinical trials

Study characteristics

Study populations varied in RA classification (1987 vs 2010 criteria), disease stage/duration (early vs established) and disease activity (supplementary table S5). Overall, trials were performed in two 'settings': early, DMARD-naïve RA and established RA. Studies including early RA had a treat-to-target approach, and when remission was achieved, DMARDs were tapered. This was all conducted in a relative short period of time (n=7).[13–19] The established RA studies (disease duration 3.1–11.3 years, n=6) either included patients with active disease who first changed DMARD treatment and subsequently became eligible for tapering (n=2)[20 21] or selected patients who were in longstanding remission and were directly considered eligible for tapering (n=4).[22–25] All established RA studies were of low quality, except 1 which was of moderate quality.[18] One study, including patients in sustained remission, did not report disease duration.[19]

DMARD tapering

Tapering of DMARDs was initiated when patients fulfilled the study-specific eligibility criteria for tapering, in which some were stricter than others (supplementary table S5). Methods of tapering varied from immediate DMARD stop to one-by-one gradual tapering of DMARDs over the course of a year. In general, tapering of biologic DMARDs took place before tapering of conventional synthetic DMARDs. Flare rates during tapering ranged from 41.8% to 75.0% (table 2, figure 2).

Definitions of DMARD-free remission

Overall, the remission criterion used to define DFR was mainly DAS44 or DAS28 remission. The DFR rates were either given as a point prevalence, thus at the moment of DMARD stop, or combined with a minimal DFR period of several months (table 2, figure 2). Nevertheless, most studies did not put much emphasis on a minimal duration of the drug-free state as a requirement to achieve DFR. Importantly, three studies that clearly defined DFR (two high-quality, one moderate-quality) allowed i.a. or oral GCs during DFR, without reporting the actual use.[13 17 18]

Prevalence of DMARD-free remission

In the five high-quality clinical trials, the reported prevalence of DFR (DFR <12 months) ranged from 5.0% to 24.3% (relative to the number of patients eligible for tapering). The two moderate-quality studies reported a DFR prevalence of 5.9% and 21.9% (table 2, figure 2), respectively. When studies that allowed GCs while being in DFR were excluded, DFR occurred in 5.0%–23.0%. SDFR (DFR >12 months) was only reported in two clinical trials and showed a prevalence of 11.6% and 19.4% (relative to patients eligible for tapering).

Evaluation of DFR prevalence, in high-quality and moderate-quality studies, in relation to the trial 'settings' was hampered by the fact that only one study was performed in established RA where DMARDs were tapered after prolonged remission,[18] revealing a DFR prevalence of 5.9% compared with the prevalence of 5.0%–24.3% in studies that tapered DMARDs in early RA.[13–17 32]

Early flares (≤12 months after DMARD-stop) were reported in one high-quality study and occurred in 10.4% of patients eligible for tapering. Late flares (>12 months after DMARD-stop) were reported by another study and occurred in 3.5% of patients (table 2).

Observational cohorts

Study characteristics

Patients included in the observational cohorts were diagnosed between 1986 and 2011 (n=5). Patients in the observational cohorts were, compared with clinical trials, included in an earlier time period, but had a longer follow-up. Diagnosis was based on the 1987 criteria[27 29 31] or

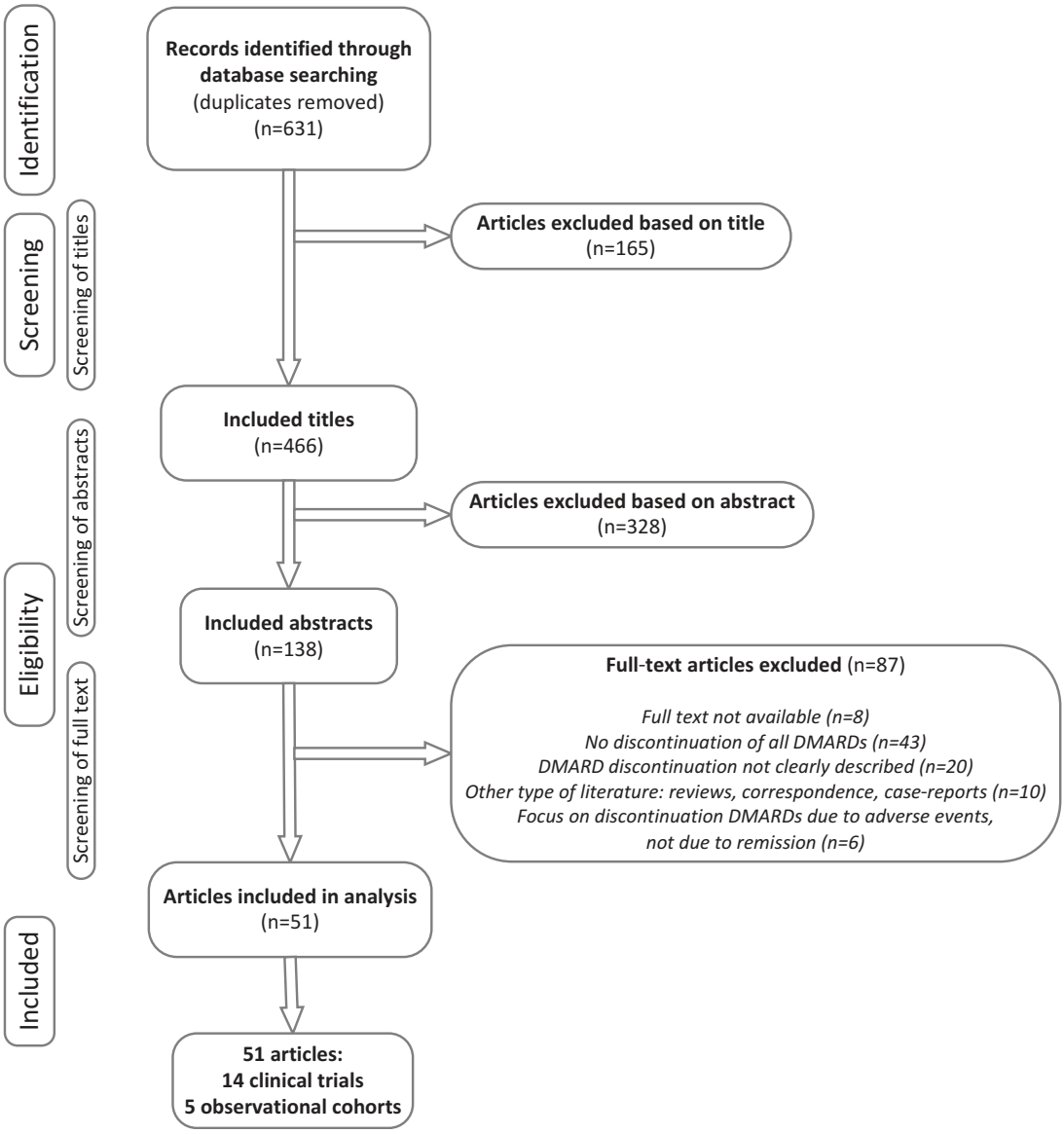

Figure 1 Flow diagram of study selection. DMARDs, disease-modifying antirheumatic drugs.

expert opinion.[28 30] Treatment was less protocolised compared with the clinical trials, and a treat-to-target approach was only used in three studies,[27–29] of which two had a high quality (table 2).

DMARD tapering

Eligibility for tapering was only clearly reported in one study.[28]

Definitions of DMARD-free remission

Remission within DFR was defined as the absence of clinical synovitis (table 2), except for one study that used a DAS28 cut-off (DAS28<2.6).[28] All five observational cohorts reported on SDFR (DFR >12 months), whereas one also reported on DFR after 6 months. In two studies, of which one was a high-quality study, i.a. and oral GC were allowed while being in DFR; the actual use was not reported.

Prevalence of DMARD-free remission

DFR prevalence (<12 months) was 23.6% of patients eligible for tapering and was reported in one high-quality study.[28] The prevalence of SDFR ranged from 11.8% to 17.8% (relative to patients eligible for tapering) (table 2, Figure 2).[27 28] If we exclude the studies that allowed GCs during DFR, one high-quality study remained with an SDFR prevalence of 17.8%.[27] We did not compare DFR prevalence between studies that did and did not apply a treat-to-target approach, because all studies without a treat-to-target approach were of low quality.

Early flares (≤12 months after DMARD stop) were reported in one high-quality study and occurred in

Table 1 Assessment of general study quality and DFR quality, resulting in final categorization as high, moderate or low-quality study

		Clinical trials														Observational studies				
		BeSt	**IMPROVED**	**AVERT**	**tREACH**	**U-ACT-early**	**ACT-RAY**	**El Miedany** *et al*	**PRIZE**	**RETRO**	**Ten Wolde** *et al*	**SUPRISE**	**Brocq** *et al*	**Kita** *et al*	**DREAM trial**	**Leiden EAC**	**DREAM cohort**	**Tiippanna-Kinnunen** *et al*	**ESPOIR**	**ERAS**
DMARD-free remission	DFR definition *(description of DFR criteria)*	+	+	+	+	+	+	-	-	-	-	-	-	-	-	+	+	-	+	+
	DFR duration *(description of DFR period)*	+	+	+	+	+	-	+	-	-	-	-	+	+	-	+	+	-	+	+
DFR-quality		✓	✓	✓	✓	✓	±	±					±	±		✓	✓		+	+
Study population	Selection of patients *(description inclusion/ exclusion criteria)*	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
	Criteria for RA diagnosis	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+
	Baseline characteristics *(description of characteristics)*	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Randomisation *for different study treatments*		+	+	+	+	+	+	+	+	+	+	+	-	-	-			n.a.		
Blinding *of study treatment*		±	±	+	±	+	+	-	+	-	+	-	-	-	-			n.a.		
Intervention	Treatment strategies *(description of strategies)*	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+
	Cut-off point tapering *(description of cut-off point)*	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	-	-	-
	Tapering method *(description of methods)*	+	+	+	+	+	+	+	+	+	+	-	+	-	-	-	-	-	-	-
Follow-up	Organisation follow-up *(frequency of monitoring)*	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	-	-
	Lost to follow up *(description of LTFU)*	+	+	+	+	+	+	?	?	?	-	+	+	+	-	-	+	+	+	+
Data analysis and presentation	Outcome reporting	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	?	+
	Analysis techniques *(description of techniques)*	+	+	+	+	+	+	+	+	+	+	+	-	-	+	+	+	+	?	?
	Missing data *(handling of missing data)*	+	+	?	?	+	?	-	±	?	?	?	?	-	?	+	?	?	?	?

Continued

Table 1 Continued

	Clinical trials												Observational studies								
	BeSt	IMPROVED	AVERT	tREACH	U-ACT-early	ACT-RAY	El Miedany *et al*	PRIZE	RETRO	Ten Wolde *et al*	SUPRISE	Brocq *et al*	Kita *et al*	DREAM trial	Leiden EAC	DREAM cohort	Tiippanna-Kinnunen *et al*	ESPOIR	ERAS
General study quality	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓				✓	✓			
Combined quality	HQ	HQ	HQ	HQ	HQ	MQ	MQ	LQ	LQ	LQ	LQ	LQ	LQ	LQ	HQ	HQ	LQ	LQ	LQ

Studies were assessed for quality of DMARD-free remission: that is, whether definition (yes '+' or no "–") and duration of drug-free state were reported (yes '+' or no "–"). DFR quality was considered good ("✓") when both items were scored as '+', and moderate ('±') when only one of two was scored as good. Subsequently, studies were assessed on general study quality. Criteria for general study quality could be scored: '+' indicating sufficient, "-" indicating not sufficient, '±' indicating moderate, '?' indicating unclear reporting and quality could not be assessed. Study quality was considered good ("✓") when minimally 75% (10 items) were scored as '+'. DFR, DMARD-free remission; DMARD, disease-modifying anti-rheumatic drug; LTFU, lost to follow-up; n.a., not applicable; RA, rheumatoid arthritis. The combined study-quality was considered high ('HQ') when both DFR quality and study quality were good. It was considered moderate ('MQ') when DFR quality was moderate, and study quality was good. Low ('LQ') indicates studies with either insufficient DFR quality or study quality.

11.8% of patients eligible for tapering. Late flares were reported by the other high-quality study and were seen in 0.3% of patients eligible for tapering (table 2).

Predictors of DFR

All factors that were analysed for their potential association with achieving DFR were evaluated (supplementary table S6). Due to heterogeneity in evaluated effect estimates, effect sizes could not be compared and meta-analyses not performed. For predictors that were studied in more than one high-quality or moderate-quality study, the association with achieving DFR is summarised in figure 3 (see also supplementary table S7). The figure includes information on the number of studies with/without an association with DFR, the total number of patients in these studies and the directionality of the effect (if present). The absence of autoantibodies and HLA-shared epitope alleles were predictive for achieving DFR. Many patient characteristics (eg, age, body mass index, swollen joint count (SJC), estimated sedimentation rate (ESR), erosions at baseline) were not associated with the chance of achieving DFR. For some, characteristic findings were inconsistent. Results on symptom duration, for example, showed ambiguous results (supplementary table S6/7).

DISCUSSION

This systematic literature review was conducted in accordance with PRISMA guidelines and provides insight into the occurrence and sustainability of DFR in RA. The prevalence of DFR (DFR≤12 months) was 5.0%–24.3%,[14–17 32] while SDFR (DFR>12 months) was achievable in 11.6%–19.4% of patients eligible for tapering.

Remission criteria used to define DFR varied widely, and the temporal aspect (sustainability) varied as well or was not reported. Moreover, in some studies, concomitant use of GC was allowed while patients were in DFR. This might falsely inflate DFR prevalence, but to what extent this occurred is unclear as actual use was not reported. Exclusion of aforementioned studies did not affect our results. To increase homogeneity, quality criteria were used, and final conclusions were only based on high-uality and moderate-quality studies, which resulted in a narrative overview of DFR prevalence (figure 2).

We observed different DFR prevalence depending on the duration of the DFR period. To allow a fair comparison of DFR prevalence, we categorised the duration of DFR in groups. SDFR was defined as a DMARD-free period >12 months. Higher prevalence was observed when DFR had a less stringent criterion for sustainability (figure 2). In line with this, flares occurred most often during tapering and in the first months after DMARD stop. This time effect underlines the relevance of defining sustainability of DFR in future studies.

DFR and SDFR might be fundamentally different. Short-term DFR might indicate that disease activity was suppressed, but not necessarily resolved, and could revive

Table 2 Prevalence of DMARD-free remission and flares

Study	Inclusion period	N	Study pop charact†	Treatment/Intervention	FU	Tapering: Tapering criteria	Tapering: N	Tapering: Flares during tapering (definition flare)	DMARD-free remission: % DFR achieved* (≤12 m) / Definition of DFR	DMARD-free remission: Time in DFR (months)	Early flares (≤12 m)	% Sustained DFR** (>12 m)	Late flares (>12 m)
Clinical trials													
BeSt[13]	2000–2008	508	Early RA 1987 ACR crit HDA at BL	1: Monotherapy (126) 2: Step-up combi (121) 3: Initial combi (133) 4: Combi with IFX (128) *After 2y tapering possible.*	60 m (5y)	Tapering: DAS44<2.4 DMARD stop: DAS44<1.6 min 6 m	-	-	**22.6%‡** (115/508) DAS44<1.6	5	**10.40%** 53/508 DAS44≥1.6	**11.6%‡** (59/508) at 5y FU DAS44<1.6 min 12 m	-
IMPROVED[14]	2007–2010	479	Early RA 2010 ACR crit HDA at BL	0- 4 m MTx + Pred. >4-8 m DAS28<1.6: taper DAS28>1.6: 1: Triple csDMARDs 2: ADA+MTx	60 m (5y)	DAS44<1.6	-	-	**23.0%** (110/479) DAS44<1.6 or Boolean	12	-	**19.4%** (93/479) at 5y FU DAS44<1.6 or Boolean 12 m	**3.5%** (17/479) at 5y FU
AVERT[15]	2010–2014	351	Early RA Diagnosis by expert opinion HDA at BL ACPA+	0–52 w 1: ABA+MTx (119) 2: ABA (116) 3: MTx (166) >52 w Withdrawal	18 m	DAS28-CRP<3.2	223	-	**18.4%** (41/223) DAS28<2.6	5	-	-	-
tREACH[16]	2007–2011	281	Early RA 2010 ACR crit HDA at BL	1: Triple therapy (183) 2: MTx (98) *Tapering at any time in FU.*	24 m	DAS44<1.6 min 2 visit	141	**41.8%** 59/141 (DAS44≥2.4)	**5.0%** (7/141) DAS44<1.6	6	-	-	-
U-Act-Early[17]	2010–2012	317	Early RA 1987/ 2010 ACR crit HDA at BL	1: TCZ+MTx (106) 2: MTx (103) 3: TCZ (108) *Tapering at any time in FU*	24 m	DAS28<2.6 SJC<4 min 24 w	-	-	**24.3%‡** (77/317) DAS28<2.6 & SJC≤4	3	-	-	-
ACT-RAY[18]	2009–2013	556	Established RA 1987 ACR crit HDA at BL	0–52 w TOCI +MTx *or* TOCI (279/277) >52 w T2 T+ tapering (472)	12-36 m	DAS28<2.6 min 12 w	472	**42.4%** 200/472 (Expert opinion)	**5.9%‡** (28/472) DAS28<2.6	Single timepoint	-	-	-
El Miedany *et al*[19]	-	157	RA duration n.r. 2010 ACR crit Remission at BL	Arm 1–3: Taper DMARDs Arm 4: Stop all DMARDs Arm 5: Control	12 m	DAS28<2.6 min 6 m	32	**75.0%** § 24/32 (DAS>3.2)	**21.9%** (7/32) DAS28<2.6	12	-	-	-
PRIZE[20]	2009–2012	306	Early RA 1987 ACR crit HDA at BL	0–52 w ETA+MTx 52–91 w ETA+MTx *or* MTx *or* placebo 91–117 w Withdrawal	29 m	DAS28<3.2	132	-	**46.9%** (62/132) DAS28<2.6	22-24 w	-	-	-

Continued

Table 2 Continued

Study	Inclusion period	N	Study pop charact†	Treatment/Intervention	FU	Tapering			DMARD-free remission				
						Tapering criteria	N	Flares during tapering (definition flare)	% DFR achieved* (≤12 m) / Definition of DFR	Time in DFR (months)	Early flares (≤12 m)	% Sustained DFR** (>12 m)	Late flares (>12 m)
RETRO[21]	2010–2013	101	Established RA 2010 ACR crit. Remission at BL	1: Continue (38) 2: Tapering (36) 3: Stop DMARD (27)(6 m 50%)	12 m	DAS28<2.6 min 6 m	27	**51.9%** (14/27) (DAS28>2.6)	**48.1%** (13/27) DAS28<2.6	6	-	-	-
Ten Wolde *et al*[22]	-	285	Established RA 1987 ACR crit Remission at BL	1: Continue (142) 2: Switch placebo (143)	12 m	ARA remission (5/6 crit)	143	**37.1%** § (53/143) (Synovitis)	**58%** (83/143) ARA remission (5/6)	12	-	-	-
Brocq *et al*[23]	1995–2005	21	Established RA 2010 ACR crit Remission at BL	TNFi treatment at inclusion Intervention: abrupt stop TNFi	12 m	DAS28<2.6 min 6 m	7	**57.1%** § (4/7) (DAS28>3.2)	**28.6%**‡ (2/7) DAS28<2.6	12	-	-	-
SURPRISE[24]	2009–2012	233	Establ. RA 1987 ACR crit HDA at BL	0–52 w TCZ+MTx or TCZ >52 w Stop TCZ	24 m	DAS28<2.6	53	**66%** § (35/53) (n.r.)	**26.4%**‡ (14/53) DAS28<2.6	12	-	-	-
Kita *et al*[25]	2008–2009	13	Early RA 2010 ACR crit HDA at BL ACPA+	0–52 w Treat-to-target >52 w Stop all DMARDs	24 m	SDAI & BME-33% on MRI	5	**20%** § (1/5) (n.r.)	**60%**‡ (3/5) SDAI remission	12	-	-	-
DREAM trial[26]	2008–2010	187	Established RA 1987 ACR crit LDA at BL	Tapering after 4y TCZ monotherapy	12 m	DAS28<3.2	187	**72.5%** § (136/187) (DAS28>3.2)	**9.1%**‡ (17/187) DAS28<2.6	12 Definition of DFR	-	-	-
Observational studies													
Leiden EAC[27]	1993–2011	889	Early RA 1987 ACR crit. HDA at BL	1993–1995 NSAIDs 1996–1998 Mild DMARDs 1999–2004 Initial MTx >2005 DAS steered	1-18y	-	-	-	-	12	-	**17.8%** (158/889) after 1-18y FU No synovitis min 12 m	**0.3%** (3/889)
DREAM cohort[28]	2006–2009	229	Early RA expert opinion (79% 1987) HDA at BL	Treat-to-target, steered at DAS28<2.6: Initial MTx monotherapy, if DAS28>2.6+ SSZ if DAS28>3.2 TNF inhibitor	5y	DAS28<2.6 min 6 m	-	-	**23.6%**‡ (54/229) DAS28<2.6	6	**11.8%** (27/229) DAS28>2.6	**11.8%**‡ (27/229) after 5y FU DAS28<2.6 min 6 m	-
Tiippanna-Kinnunen *et al*[29]	1986–1989	70	Early RA 1958/1987 crit. HDA at BL	Sawtooth strategy	15y	Clinical remission¶ or minor disease activity	-	-	**28.6%**‡ (20/70) ARA remission‡‡	-	**12.9%** (9/70)	**15.7%**‡ (11/70) after 15y FU ARA remission	-
ESPOIR[30] ††	2000–2005	533	Early RA Clinical diagnosis HDA at BL	Treated with cDMARDs	5y	-	-	-	-	12	-	**5.4%** (29/533) No synovitis min 12 m	-

Continued

Table 2 Continued

Study	Inclusion period	N	Study pop charact†	Treatment/Intervention	FU	Tapering			DMARD-free remission				
						Tapering criteria	N	Flares during tapering (definition flare)	% DFR achieved* (≤12 m)	Time in DFR (months)	Early flares (≤12 m)	% Sustained DFR** (>12 m)	Late flares (>12 m)
									Definition of DFR				
ERAS[31] ††	1986–1996	895	Early RA 1987 ACR crit. HDA at BL	Rheumatologist preference, predominantly MTx, SSZ, HCQ	10y	-	-	-	-	12	-	**9.4%** (84/895) No synovitis min 12 m	-

High-quality studies are indicated in dark green, moderate-quality studies are indicated in light green, and low-quality studies are indicated in white.
*Percentage of patients who achieved DFR divided by patients eligible for tapering.
**Percentage of patients who sustained DFR for more than 12 months divided by patients eligible for tapering.
‡Potential use of intra-articular or systemic corticosteroids, or use of GCS was not clearly described due to which use was doubtful.
§DMARDs were discontinued abruptly without gradual tapering method.
¶Clinical remission defined as no tender joints, no swollen joints, no joint pain by history, ESR<30(female/<20(male) for minimal 12 months. Or prolonged symptom-free phase of disease with minor disease activity.
†Longstanding RA was defined as a disease duration of more than 2 years. All shorter disease- and symptom durations were classified as early RA. In the supplementary table (S1) specific duration of disease and symptom duration can be found.
††Only minimal information could be extracted from the articles in which this study was mentioned. Therefore information is missing, which is not due to insufficient quality of the article.
‡‡ARA remission: morning stiffness absent (or not exceeding 15 min), no fatigue, no joint pain by history, no joint tenderness, no joint or tendon sheath swelling, no elevation of ESR (in 5/6, fatigue is not included in the criteria).
ACR, American College of Rheumatology; ABA, Abatacept; BL, baseline; bDMARDs, biological DMARDs; crit, criteria; csDMARDs, conventional DMARDs; DAS, Disease Activity SCORE; DFR, DMARD-free remission; Establ., established; ETA, etanercept; FU, follow-up; HCQ, hydroxychloroquine; HDA, high disease activity; IFX, infliximab; LDA, low disease activity; rem, remission; MTx, methotrexate; n.r., not reported; RA, rheumatoid arthritis; SSZ, sulfasalazine; SJC, swollen joint count; TCZ, tocilizumab; TNF, tumor necrosis factor; TNFi, TNF-α inhibitor.

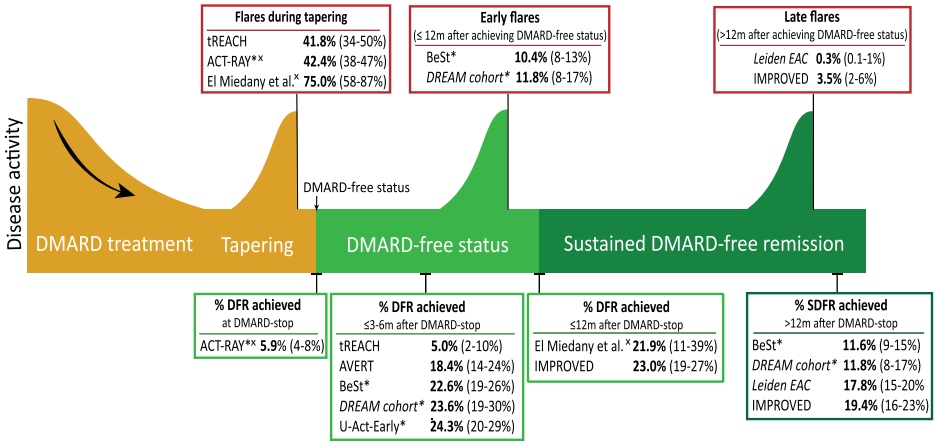

Figure 2 Summary of flare rate and DFR prevalence, all as percentage of the number of patients that were eligible for DMARD tapering, depicted on a timeline. DFR prevalence was grouped by the duration of DFR. Data are presented as DFR percentage (CI). Data were based on high-quality or moderate-quality studies. Prevalence and CIs were calculated using the number of DFR patients divided by the number of patients eligible for tapering. Results from observational studies are indicated in italic. *indicates that studies that allowed the use of i.a. or systemic corticosteroids in patients that were considered to be in DFR(absolute number of patients that used corticosteroids after DMARD stop was not reported) or use in DMARD-free status was not clearly reported. [X] indicates moderate-quality studies. DMARD, disease-modifying antirheumatic drugs; DFR, DMARD-free remission; SDFR, sustained DMARD-free remission.

after the disappearance of suppressive treatment. Moreover, early flares (≤12 months after DFR) occur more often than late flares (>12 months after DFR), which might indicate that autoimmunity was not completely silenced. In our opinion, patients in SDFR (DFR>12 months) better resemble silencing of autoimmunity and may have achieved a proxy for cure. Therefore, SDFR can become an important outcome for clinical trials. Because late flares (often occurring years after DMARD-stop) might be pathophysiologically different from early flares, it is an interesting subject for future studies to explore the triggers or pathophysiologic mechanisms involved in late reactivation of the autoimmune process.

Notably, despite differences in study design, the DFR prevalence observed in observational cohorts and clinical trials was comparable. This supports the robustness of the observed frequencies. We were unable to investigate how long remission should be sustained before tapering can be initiated, because too few high-quality studies were performed in patients with established RA and longstanding remission. Additionally, due to an insufficient amount of studies, nothing can be said about the change of achieving DFR after treatment with certain conventional or biologic DMARDs.

We could not evaluate whether the method of tapering influenced the frequency of SDFR. It has been suggested that gradual tapering results in less flares compared with abrupt cessation.[2] Also, the stringency of the remission criterion for initiation of tapering might be of influence, whereby less stringent criteria might increase the risk of flares. Evaluation of the methods of DMARD tapering was beyond the scope of this review, and a relevant subject for further studies as insight into the most effective tapering method may positively influence the chance to achieve SDFR. Another issue for further studies is the assessment of the likelihood to achieve remission for patients that flare after having been in DFR. From studies on patients that flared during tapering, it is known that the majority of patients achieve remission by restarting the same DMARD.[33] Whether this is similar for patients that flare after DMARD stop is not yet systematically studied.

Studying the prevalence of DFR and predictors for DFR does not answer the question whether the absence of clinical signs and symptoms without treatment exhibited the natural course of RA in these patients,[34] or was induced by DMARD treatment. This could not be answered within our SLR, nor could we compare studies for treatment intensity (eg, reflected by treat-to-target) due to the lack of high-quality studies without a treat-to-target approach. One high-quality study compared a treat-to-target approach that aimed for a DAS<1.6 with an approach that aimed for a DAS<2.4 and reported that patients achieved DFR more often when aimed for a DAS<1.6 (18% vs 8%, respectively), suggesting that intensive treatment is helpful in inducing DFR.[35] However, the clinical trials rarely used DFR as a primary outcome, and, therefore, the question to what extent the frequency of DFR can be achieved by treatment remains a subject for future studies.

Although we tried to find predictors for DFR, it remains uncertain which patients are able to stop their DMARDs successfully. Meta-analyses could not be performed due to the heterogeneity of studies and effect estimates. Therefore, we summarised and graphically presented data on predictors using predefined criteria, but this methodology is far less optimal than meta-analysis. Several patient characteristics (eg, age, SJC, ESR and erosiveness) were not associated with a higher chance of achieving DFR. Results on symptom duration were conflicting, as the relation between DFR and symptom

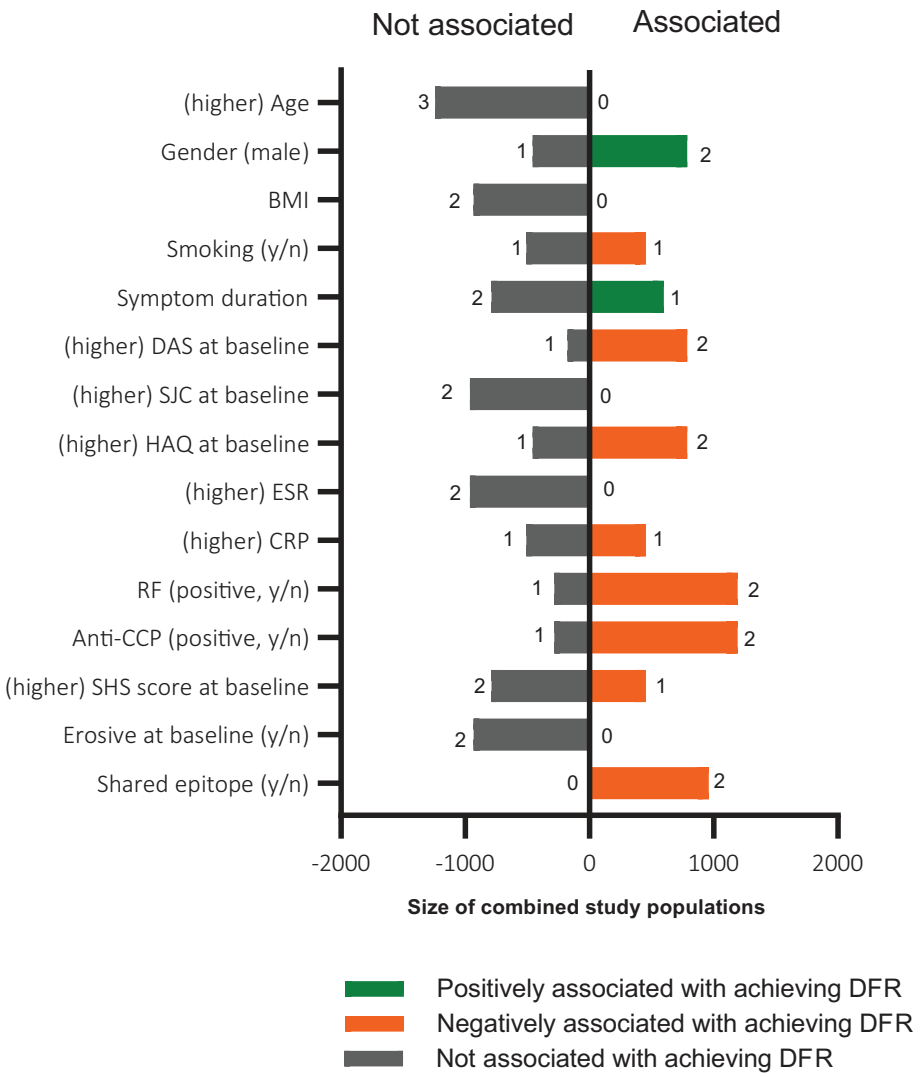

Figure 3 Overview of studied predictors of achieving DMARD-free remission. Data are presented from variables that were reported in >1 study, based on statistical significance obtained in regression analysis. If both univariable and multivariable regression was applied, the result of the multivariable regression was used. Presented are the absence (left panel) and presence of an association with achieving DFR over time (right panel), the number of studies is indicated per predictor, the total number of patients in these studies is plotted on the x-axis. The directionality of the effect is indicated in colours, green indicates an increased risk of achieving DFR, red indicates a decreased risk of achieving DFR. For symptom duration, no differentiation was made for analyses using this as continuous or categorical variable. BMI, body mass index; CRP, C reactive protein; DAS, Disease Activity Score; ESR, estimated sedimentation rate; HAQ, Health Assessment Questionnaire; RF, rheumatoid factor; SJC, swollen joint count.

duration was non-significant, but showed a strong tendency towards significance in part of the studies. Furthermore, it is known that the association with DFR is not linear but refined to a short period of time[30] (ie, the window of opportunity), and associations may remain undetected if symptom duration is analysed as a continuous variable. Absence of autoantibodies was the best predictor for DFR. Although effect sizes were not involved in our analyses, the absence of autoantibodies alone is not sufficient to accurately guide taper decisions in daily practice. Therefore, effective pursuit of SDFR in clinical practice requires more insight into subsets of patients that are likely to achieve SDFR.

Acknowledging the importance of the autoantibody status as predictor, the SDFR prevalence will be different for autoantibody-positive and autoantibody-negative patients. We could not stratify the results on SDFR prevalence for autoantibody status as the prevalence reported in the included cohorts and trials was not always stratified for autoantibodies. However, the studies that included information on autoantibody status in their patient characteristics reported that 52%–100% of patients were autoantibody positive (supplementary table S5).

Since conducting a thorough systematic literature review is time demanding, a time gap exists between

the actual literature search (March 2019) and publication of the results. As a result, relevant articles in this time interval are not included. A non-systematic screening of articles published in this period revealed the BioRRA study,[36] published in December 2019. This study focuses on predictors of flare after DMARD cessation and reported a 52% flare rate (DAS28-CRP≥2.4) after abrupt DMARD cessation. Predictors of flares were, among other things, absence of Boolean remission at baseline, RF positivity and IL-27. Biomarkers predictive of DFR, as identified in other recent studies, were calprotectin levels and several serum protein levels among which SAA.[37 38] Calprotectin and SAA are both acute phase reactants. However, none of these markers were yet validated in independent studies.

From the patients' perspective, achieving SDFR is beneficial; it was recently reported to be associated with normalisation of functional disability and resolution of symptoms, for example, fatigue.[27] Unfortunately, clinical trials infrequently evaluated SDFR. If future trials would be designed with DFR/SDFR as primary outcome, consensus of the definition of remission and the duration of DMARD-free state is required to promote comparability of findings between studies. This may require OMERACT Initiatives.

In conclusion, DFR is achievable in RA and is sustainable in ~10%–20% of patients. DFR can become an important outcome measure for clinical trials and requires consistency in the definition. Considering the relative short follow-up after DMARD stop in current clinical trials and the high rate of flares in the first year after DMARD stop, we propose to incorporate a DMARD-free follow-up of at least 1 year, to ensure that DFR is sustainable.

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