Supplementary materials

Supplementary table S1 – Search strategy

Supplementary table S2 – In- and exclusion criteria study selection

Supplementary table S3 – Data extraction form

Supplementary table S4 – Risk assessment tool

Supplementary table S5 – Summary of studies reporting on discontinuation of DMARDs in RA

Supplementary table S6 – All predictors of DFR retrieved from the literature

Supplementary table S7 – The selection of predictors of DFR used for figure 3

Supplementary table S8 – PRISMA-checklist

Supplementary table S9 – Details search strategy

Supplementary table S1 – Search strategy

Literature search was conducted on 28-3-2019, resulting in the following references:

- PubMed: 408 [RefID/Label 1-408]
- Embase: 394, of which 67 unique [RefID/Label 409-500]
- Web of Science: 255, of which 91 unique [RefID/Label 501-595]
- COCHRANE Library: 166, of which 39 unique [RefID/Label 596-636]
- Emcare: 141, of which 29 unique [RefID/Label 637-668]
- Academic Search Premier: 27, of which 4 unique [RefID/Label 669-672]

In total 638 references were found, of which 7 duplicates.

Total number of articles: 631

Details of the search in the multiple databases are presented in supplementary table S8.

Supplementary table S2 – In- and exclusion criteria study selection

Inclusion criteria (1) Study designs which will be included are all observational studies, including cross-sectional, case-control, prospective and retrospective cohort studies, and intervention studies, controlled and uncontrolled. (2) Patients with rheumatoid arthritis will be included, in which patients should meet the ACR/EULAR 1987 and/or 2010 criteria for RA or RA should been diagnosed by a Rheumatologist (expert opinion). (3) The study should clearly report on DMARD-free remission, i.e. complete discontinuation of all DMARDs, including glucocorticoids is required. The study should report clearly on tapering and complete discontinuation of all DMARDs until eventually a complete DMARD-free state will be achieved. (5) Only studies in English, and Dutch, with available full text will be included. (6) Only studies with full paper articles available will be included. (7) All years of publication will be included.
Exclusion criteria (1) Case-report studies and reviews will be excluded. Reviews were screened for (extra) eligible studies. (2) Studies focussing on disease other than rheumatoid arthritis (also unspecified arthritis) will be excluded. However, studies focussing on other disease next to RA can be included from which the RA data will only be extracted (3) Studies in which the use of not all DMARDs are tapered and completely discontinued. Studies which do not clearly describe if all DMARDs are completely stopped, i.e. no transparency of the DMARD-free state, will also be excluded. (4) Studies should focussing on other reasons for tapering and discontinuation of DMARD then remission, e.g. adverse events, retention etc. will be excluded.

Legend: In- and exclusion criteria used for study selection. ACR: American College of Rheumatology, EULAR: European League Against Rheumatism, RA: Rheumatoid arthritis, DMARD: Disease-modifying antirheumatic drug.

Supplementary table S3 – Data extraction form

(Name of study)	
Articles included	
1. ….	
2. ….	
etc.	
DATA- EXTRACTION form	
Acronym study	
Study design: clinical trial/observational	
Country	
Years of inclusion	
Inclusion criteria	
Exclusion criteria	
RA criteria used	
Study population (n)	
Baseline characteristics (patient characteristics)	
Primary outcome	
Secondary outcomes	
Intervention (arms) (if applicable)	
Medication prescribed during study	
Glucocorticosteroids use (y/n, dosage)	
Follow-up (FU)	
Monitoring during FU	
Lost tot FU	
Remission/DFR specific data extraction	
Remission criteria	
Tapering (start/cut-off point)	
Tapering methods	
DFR definition specified (y/n)	
DFR criteria used	
DFR duration reported	
Sustained DFR reported (y/n)	
Flare definition	
Quantitative data-extraction	
Remission (n)	
Tapering (n)	
DFR (n)	
SDFR (n)	
Flares (n)	
Additional	
Predictors reported	
Estimate of predictor (p-value)	

Legend: Data extraction form used for systematic data-extraction Data extraction forms were fulfilled independently by two reviewers (MV and EvM), disagreements were discussed until consensus was reached. DFR: DMARD-free remission, FU: Follow-up.

Supplementary table S4 – Risk assessment tool

QUALITY ASSESSMENT	
DMARD-free remission	(+) (-) (?)
1. DFR definition *(description of DFR criteria/definition)*	
2. DFR duration *(description of period between DMARD-stop and being appoint as DFR)*	
General study quality	(+) (-) (?)
Study population	
1. Selection of patients *(description of in-/exclusion criteria)*	
2. Criteria used for RA diagnosis	
3. Baseline characteristics study population *(description of characteristics)*	
Randomization	
4. Randomization for different study treatments	
Blinding (combined score)	
5.1. Blinding outcome assessors	
5.2. Blinding patients	
Interventions	
6. Treatment strategies *(description of strategies)*	
7. Cut-off point tapering *(description of cut-off point)*	
8. Tapering methods *(description of methods)*	
Follow-Up	
9. Organisation of follow-up *(frequency of monitoring)*	
10. Lost-to-follow-up	
Analysis & Data presentation	
11. Outcome reporting	
12. Analysis techniques *(description of techniques)*	
13. Missing data *(handling of missing data described)*	

Legend: DMARD: Disease-modifying antirheumatic drug, DFR: DMARD-free remission, RA: Rheumatoid arthritis.

Supplementary table S5 - Summary of studies reporting on discontinuation of DMARDs in rheumatoid arthritis

Clinical trials											
Study	**Inclusion period**	**Study pop** (n)	**Baseline characteristics**	**Intervention**	**Follow Up (years)**	**Monitoring during FU**	**LTFU**	**Remission criteria**	**Tapering (initiation)**	**Tapering Method (duration of tapering)**	**GCs use**
ACT-RAY	2009 - 2013	556	♀ 80.3%, age 53.3y RA 1987 criteria, Disease duration 8.3y DAS28 6.35 at BL (Unresponsive to MTx)	0-52w: TCZ (277) or TCZ+MTx (279) 52-104w: DAS28<2.6 = Tapering (472) DAS28 2.6 – 3.2 = Continue DAS28 >3.2 = + csDMARDs	2	Every 12w	138	DAS28<2.6	DAS28<2.6 at 2 visits	1st bDMARDs 2nd csDMARDs (12-36w)	GCs tapered to 5mg/d after 24w. Tapering in drug-free state not reported.
AVERT	2010 - 2014	351	♀ 77.8%, age 47y(median) No spec. RA criteria Symp duration 0.56y All patients ACPA+ (95% RF+) DAS28-CRP 5.4 at BL	0-52w: ABA+MTx or ABA or MTx 52-72w: Tapering if DAS28<3.2	1.5	Every 3m	12	DAS28-CRP<2.6	DAS28<3.2 After 52 w ABA+MTx or ABA or MTx	bDMARD abrupt, MTx + GCs gradual (1 month)	GCS tapered after 12m in 1 month time.
BeSt	2000 - 2002	508	♀ 68%, age 54y 1987 RA criteria Symp duration 23-26w (median) RF+ 65% DAS44 4.3-4.5 at BL	Arm1 = Monotherapy Arm2 = Step-up therapy Arm3 = csDMARDs combi-therapy Arm4 = MTx+TOCI	5	Every 3m	82 (at 5y)	DAS44<1.6	Tapering: DAS44<2.4 Stop: DAS44<1.6 min 6m	One by one & gradual tapering (time for taper n.r.)	i.a. allowed
IMPROVED	2007 - 2010	479	♀ 68%, age 52y 2010 RA criteria Symp duration 18w (median) ACPA 55%, RF+ 56% DAS44 3.2±0.91**	0-4m: MTx (+GCs bridging) >4m: - DAS44<1.6 = Tapering - DAS44>1.6: Arm1 = MTx + bDMARDs Arm2 = MTx + csDMARDs	5	Every 4m	112	DAS44<1.6 or Boolean remission (ACR 2011)	DAS44<1.6	Gradual (MTx in 10w, tapering times other DMARDs n.r.)	GCs tapered.
PRIZE	2009 - 2012	306	♀ 64.8%, age 49y Symp duration 6.8m 1987 RA criteria ACPA+ 65.8% DAS28 5.8 at BL	0-52w: 50 mg ETA+MTx 52-91w: 25 mg ETA+MTx or MTx or PBO 91-117w: Tapering if DAS28<3.2	±2 (27m)	Every 3m	97	DAS28<2.6	DAS28<3.2	52-91w: 50% bDMARD >91w: Abrupt stop bDMARDS, than taper csDMARDs in 2-4w	GCs tapered, complete withdrawal at 39w

										(total tapering time 41-43w)	
RETRO	2010 - 2013	101	♀ 62%, age 57y (median) 2010 RA criteria Disease duration 5y ACPA+ 60% DAS28 1.91 at BL	Arm 1 = Continuation DMARDs Arm 2 = Tapering DMARDs Arm 3 = Discontinuation DMARDs	1	Every 3m	n.r.	DAS28<2.6	DAS28< 2.6 for min 6m (3 visits)	Gradual: 6m 50% dose reduction than stop. (6m tapering)	GCs tapered
tREACH	2007 - 2011	281	♀ 68%, age 53.2y 2010 RA criteria (95%) Symp duration 166d ACPA 80% DAS44 3.36 at BL (mean)	Arm 1 = Triple therapy (MTx+SSZ+HCQ) (183) Arm 2 = MTx monotherapy (166)	2	Every 3m	76	DAS44<1.6 at 2 visits	DAS44<1.6 at 2 visits	Gradual: Dose reduction 50% → 25% → stop (6m tapering)	Bridging at start study, afterwards GCs tapered.
U-Act-Early	2010 - 2012	317	♀ 67%, age 54y 1987/2010 RA criteria Disease duration 25d (median) ACPA 70% DAS28 5.2 at BL	Arm 1 = TOCI+MTx (106) Arm 2= TOCI (103) Arm 3 = MTx (108)	2	No fixed visits, ± every 4w	80	DAS28<2.6 & SJC ≤4	DAS28<2.6 & SJC ≤4 for 24w (= sustained remission)	MTx gradual 5mg/w until 10 mg →stop (1m no tapering) bDMARDs to 50% 3m →stop (total tapering time ±4-6m)	Incidental GCS i.a. allowed, and p.o. once a year max 2w
Brocq et al	1999 - 2005	21	♀ 61.9%, age 61y 1987 RA criteria ACPA 53% Disease duration 11.3y Rem duration 19.2m	Discontinuation of TNFi	1	Every 1m	1	DAS28<2.6 min 6m	DAS<2.6 min 6m (inclusion criterion)	Abrupt DMARD stop	3 patients used GCs, max 5mg/d
El Miedany et al.	Not reported (<2016)	157	♀ 61.4%, age n.r. 2010 RA criteria Disease duration n.r. (>18m) ACPA+ 62% DAS28 2.08 at BL Use of stable cs+bDMARDs	Arm 1 = bDMARDs 50% (32) Arm 2 = cs+bDMARDs 50% (32) Arm 3 = bDMARDs stop (32) Arm 4 = cs+bDMARDs stop (32) Arm 5 = continuation (32)	1	Every 1m	3	DAS28<2.6 min 6m	Protocol (arm 4)	Abrupt DMARD stop (arm 3+4)	GCs were not allowed in study.
SURPRISE	2009 - 2012	233	♀ 89%, age 55.9y 1987 RA criteria Disease duration 3.5y RF+ 72.5% DAS28 5.0	Arm 1 = TOCI + MTx (ADD-ON) Arm 2 = TOCI (SWITCH)	2	Every 3m	4	DAS28<2.6	DAS28<2.6	Abrupt DMARD stop	GCs allowed, 15.1% used GCs (mean 3.4mg/d)

Kita et al.	2008 - 2009	13	♀ 69.2%, age 59.2y Disease duration 13.7w 2010 RA criteria SDAI 20.2 at BL ACPA+/RF+ 100%	0-12m: Treat-to-target > 12m: Tapering if SDAI remission	1	Every 3m	1	SDAI	SDAI for 12m + 33% reduction BME on MRI	Assumable abrupt DMARD stop	GCs allowed at BL, unclear whether GCs were tapered.
Ten Wolde et al.	n.r. <1997	285	♀ 58%, age 61.1y Disease duration 10.6y 1987 RA criteria ARA remission (5/6 criteria) at BL RF+ 70%	Arm 1 = Continue treatment Arm 2 = Switch to placebo (abrupt)	1	4, 8, 12, 26 52w	9	ARA remission[A] (5 out of 6)	Protocol	Abrupt switch to placebo	GCs not allowed.
DREAM trial	2008 - 2010	187	♀ 87.7%, age 57y (median) 1987 RA criteria RA duration 7.8y (median) DAS28 1.5 (median)	Discontinuation TCZ	1	Every 1m	161	DAS28<2.6	DAS28<3.2	Abrupt DMARD stop	GCs allowed, at start of tapering (dose 0-7.0 mg/d)
Observational studies											
Study	**Inclusion period**	**Study pop** (n)	**Baseline characteristics**	**Treatment strategy**	**Follow Up** (years)	**Monitoring during FU**	**LTFU**	**Remission criteria**	**Tapering (initiation)**	**Tapering Method**	**GCS use**
DREAM cohort	2006 - 2009	229	♀ 63.3%, age 57.5y RA expert opinion (79% 1987 RA) Symp duration (median) 13w ACPA 58.6 DAS28 4.9	Treat-to-target, steered at DAS28<2.6: initial MTx monotherapy, if DAS28>2.6 + SSZ if DAS28>3.2 TNF-inhibitor	5	Every 3m	58	DAS28<2.6	DAS28<2.6 for 6m	Gradual (duration of tapering n.r.)	<10mg/d, i.a. permitted
Tiippanna-Kinnunen et al	1986 - 1989	70	♀ 79.3%, age 44y 1987 RA criteria Disease duration 8m RF 65%	Saw-tooth strategy: gold, SSZ of HCQ	15	Year 1-3: every 3-4 months, then visits at: 5y, 7y, 10y and 15y	17***	ARA remission (5/6 criteria)	'Clinical remission[B] min 12m' or 'symptom-free & prolonged minor disease activity'	n.r.	<10mg in active disease, in remission i.a. allowed
Leiden EAC	1993 - 2011	889	♀ 66.7%, age 56.5y 1987 RA criteria Symp duration 4.4m (median) ACPA 52.4% SJC 6-12 (median)	'93-'95 NSAIDs '96-'98 Mild DMARDs (HCQ, SSZ) '99-'02 Initial treatment: MTx/SSZ > 2002 Treat-to-target: initial MTx	1-19	BL, 4 months, annually	n.r.	Remission criteria not specified. DFR: No clinical synovitis	n.r.	Not protocolized	Not allowed by definition of DFR

ESPOIR	2002 - 2005	533	♀ 75.8%, age 48.8y RA expert opinion Symp duration (median) 21.3w SJC 7 (median)	Treated with csDMARDs	5	Every 6 months first 2 years, afterwards annually	n.r.	n.r.	n.r.	n.r.	Unknown
ERAS	1986 - 1996	895	♀ 69% age 52y ACR criteria Symp duration 8.3m RF 63% SJC 14 (median)	Rheumatologist preference, predominantly MTx, SSZ, HCQ	10	Every 4m, at some point annually	384*** (30%)	n.r.	n.r.	n.r.	Unknown
LTFU: Loss to follow-up											

Legend: Data is presented as mean, unless otherwise indicated.

** Both the UA and RA population together (n=610), *** Due to retrospective design, LTFU not taken into account as part of the study population.

[A] ARA remission: morning stiffness absent (or not exceeding 15 minutes), 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). [B] 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.

ACR: American College of Rheumatology, ADA: Adalimumab, 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, GCs: glucocorticosteroids, HCQ: Hydroxychloroquine, HDA: High disease activity, IFX: Infliximab, n.r.: not reported, LDA: Low disease activity, rem: remission, MTx: Methotrexate, m: months, RA: rheumatoid arthritis, symp: symptom, SSZ: Sulfasalazine, n.r.: not reported, TCZ: Tocilizumab, TNFi: TNF-α inhibitor, w: weeks, y: years.

Supplementary table S6 – All predictors of DFR retrieved from the literature

CLINICAL BIOMARKERS		
✗	**Age**	✓
v.d. Woude et al. (2012) (BeSt, n=508)[L] *OR 1.01(0.98-1.03)*	no associations between age and DFR have been reported within the included articles	
v.d. Woude et al. (2009) (LEAC, n=454)[C] *HR 1.02(0.99-1.03)*		
Kuijper et al. (2016)(tREACH, n=281)[L] *OR 0.995(CI not specified)*		
v.d. Woude et al. (2012) (LEAC, n=424) [L] *OR 1.02(0.998-1.04)*		
v.d. Woude et al. (2009) (ERAS, n=895) [C] *HR 1.00(0.98-1.01)*		
de Rooy et al. (2011) (LEAC, n=676) [L] *OR 0.99(0.97-1.00) (not achieving DFR)*		
v.d. Kooij et al. (2009) (BeSt, n=508)[B] *nDFR 54y, DFR 56y*		
Ajeganova et al. (2016)(LEAC, n=886) *nDFR 57.4y, DFR 56.3y* [B]		
Emery et al. (2018)(PRIZE, n=65)[L] *(no estimates specified)*		
✗	**Gender**	✓
v.d. Woude et al. (2009)(LEAC, n=454)[C] *Female: HR 1.28(0.74-2.19)*	Kuijper et al. (2016)(tREACH, n=281)[L] *Female: OR 0.352* [M] (CI not specified)*	↑
v.d. Woude et al. (2009) (ERAS, n=895)[C] *Female: HR 0.78(0.50-1.2)*	v.d. Woude et al. (2012) (BeSt, n=508) [L] *Male: OR 2.39(1.26-4.53)* [M]*	↑
de Rooy et al. (2011)(LEAC) [L] *Female, OR 0.85 90.50-1.45) (not achieving DFR)*	v.d. Kooij et al. (2008)(BeSt) [L] *Male:DFR 52% vs nDFR 29%*[M]* *(OR not specified)*	↑
v.d. Woude et al. (2012) (LEAC, n=424)[L] *Female, OR 1.19(0.62-2.28)*		
Nishimoto et al. (2014)(DREAM, n=187)[C] *Male HR 0.61(0.37-1.00)*		
Ajeganova et al.(2016)(LEAC, n=886)[B] *Female: nDFR63%, DFR 68%*		
Emery et al. (2018)(PRIZE, n=65)[L] *Male (no estimates specified)*		
✗	**BMI**	✓
v.d. Woude et al. (2012) (LEAC, n=424)[L] *OR 0.95(0.83-1.08)*	de Rooy et al. (2011)(LEAC) [L] *OR 1.11(1.01-1.23)*,[U] (not achieving DFR)*	↓
v.d. Woude et al. (2012) (BeSt, n=508)[L] *O R0.96(0.88-1.04)*		
v.d. Woude et al. (2009)(ERAS, n=895)[C] *HR 0.98(0.93-1.04)*		
✗	**Smoking**	✓
v.d. Woude et al. (2012) (BeSt, n=508)[L] *OR 0.69(0.36-1.33)*	v.d. Woude et al. (2009) (LEAC, n=454)[C] *HR 0.56(0.34-0.94)* [U]*	↓
v.d. Woude et al. (2009) (ERAS, n=895)[C] *HR 0.54(0.29-1.02)*	v.d. Woude et al (2012) (LEAC, n=424) [L] *OR 0.48(0.25-0.93)*[U]*	↓
Ajeganova et al. (2016)(LEAC, n=886) *Smoking ever: nDFR 54%, DFR 56%* [B]		
✗	**Family history of RA**	✓
v.d. Woude et al. (2009)(LEAC, n=454)[C] *HR 0.55(0.30-1.04)*	de Rooy et al. (2011) (LEAC, n=676) [L] *OR 2.27(1.18-4.36)* [U] (not achieving DFR)*	↓

✗		✓	
v.d. Woude et al. (2009)(ERAS, n=895)[C] *HR 0.87(0.53-1.44)*			
Miscellaneous			
v.d. Woude et al. (2009) (LEAC, n=454) [C] *Absence comorbidities HR 0.98(0.59-1.61)*		Kuijper et al. (2016)(tREACH, n=281) [L] *Paid work: OR 0.438*[M] (CI not specified)*	↓
Kuijper et al. (2016)(tREACH, n=281) [L] *Dutch ethnicity OR 3.316[U] (CI not specified)*			
(shorter) Symptom duration			
v.d. Woude et al. (2012)(BeSt, n=508) (cont) [C] *O R0.99(0.98-1.00) (cont. in weeks)*		v.d. Linden et al. (2010) (LEAC, n=598) [C] ≥12w symptoms vs <12w *HR 1.90*[M] (1.18 - 3.05)(not achieving DFR)*	↑
Kuijper et al. (2016)(tREACH, n=281) [L] *OR 1.00 (CI not specified) (measure symp duration not specified)*		v.d. Woude et al. (2009) (ERAS, n=895) [C] *HR 0.94*[M](0.89-0.99) (continuous in months)*	↑
Akdemir et al. (2018)(BeSt/IMPROVED, n=133/175)[L] *OR 0.98 (0.97-1.00) (continuous in weeks)*		v.d. Woude et al. (2009) (LEAC, n=454) [C] *HR 0.94(0.88-0.99)*[U] (continuous in months)*	↑
Emery et al. (2018)(PRIZE, n=65)[L] *(no estimates specified)*		v.d. Kooij et al. (2009)(BeSt, n=508) [L] *DFR:18w(11-33), nDFR:24w(14-56)*[M] (continuous)* *(OR not specified)*	↑
Nishimoto et al.(2014)(DREAM, n=187)[C] *Disease duration (<7.8y vs >7.8y (median)) HR 0.81(0.60-1.00)*		de Rooy et al. (2011)(LEAC, n=676) [L] *OR 1.02(1.01-1.03)*[L, U] (continuous in weeks)(not achieving DFR)*	↑
		v.d. Woude et al. (2012) (LEAC, n=424) [L] *OR0.98(0.96-0.99)*[U] (cont. in weeks)*	↑
		Ajeganova et al. (2016)(LEAC, n=886) [B] *nDFR:4.7(2.4-8.6), DFR:2.9(1.8-6.5)** (continuous in months)*	↑
Disease activity score at baseline			
Akdemir et al. (2018)(BeSt/IMPROVED, n=133/175)[L] *OR 0.94(0.58-1.53)* *Only IMPROVED data selected for figure*		v.d. Woude et al. (2012)(BeSt. N=508) [L] *OR 0.63(0.43-0.94)*[M]*	↓
Emery et al. (2018)(PRIZE, n=65)[L] *(no estimates specified)*		Kuijper et al. (2016)(tREACH, n=281) [L] *OR 0.587*[M] (CI not specified)*	↓
		v.d. Woude et al. (2009) (ERAS, n=895) [C] *HR 0.65**(0.55-0.76)[U]*	↓
		v.d. Kooij et al. (2008)(BeSt, n=508) [B] *nDFR 4.5 vs. DFR 4.1**	↓
		Nishimoto et al. (2014)(DREAM, n=187) [C] *HR 0.59 (0.44-0.81)[U]*	↓
Swollen Joint Count at baseline			
v.d. Woude et al. (2009) (LEAC, n=454)[C] – 44-SJC *HR 1.00(0.96-1.04)*		v.d. Woude et al. (2009)(ERAS, n=895) – 44-SJC *HR 0.97*(0.95-0.99)[C,M]*	↓
v.d. Woude et al. (2012)(BeSt, n=508)[L] *OR 1.01(0.97-1.06)*			
v.d. Woude et al. (2012)(LEAC, n=424)[L] *OR 0.99(0.94-1.04)*			
de Rooy et al. (2011)(LEAC, n=676)[L] *OR 0.99(0.96-1.02)(not achieving DFR)*			
Ajeganova et al. (2016)(LEAC, n=886)[B] – 66-SJC *nDFR 8(4-15), DFR 8(4-13)*			
Emery et al. (2018)(PRIZE, n=65)[L] *(no estimates specified)*			
Tender Joint Count at baseline			
Ajeganova et al. (2016)(LEAC, n=886)[B] – 68-TJC *nDFR 7(5-11), DFR 8(5-11)*		v.d. Woude et al. (2009) (ERAS, n=895) - RAI [C] *HR 0.92**(0.88-0.97)[M]*	↓
Morning stiffness			
v. Nies et al. (2015)(LEAC, n=807)[C] *HR 0.85(0.65-1.11)*		v.d. Kooij et al. (2008)(BeSt, n=508)[B] *VAS morning stiffness: nDFR 60(24) vs DFR 54(24)**	↓
v. Nies et al. (2015)(ESPOIR, n=353)[C] *HR 0.80(0.50-1.29)*			

✗		✓	
de Rooy et al (2011)(LEAC, n=676)[L] *OR 1.00(0.99-1.01) (not achieving DFR)*			
Ajeganova et al. (2016)(LEAC, n=886)[B] *Morning stiffness VAS: nDFR 64(36-81), DFR 57(36-76)*			
✗	**Miscellaneous**	✓	
v.d. Woude et al. (2009)(LEAC, n=454)[C] *Acute onset HR1.55(0.94-2.56)* *Onset in small joints HR1.48(0.91-2.40)* *Onset symmetrical symptoms HR1.24(0.72-2.14)*		v.d. Woude et al. (2009) (ERAS, n=895) - Acute onset symp [C] *HR 2.03*(1.15-3.59)* [M]	↑
v.d. Woude et al. (2009) (ERAS, n=895) [C] *Start small joints HR1.27(0.80-2.04)* *Start symm sympt 1.18(0.67-2.07)*		Burgers et al. (2018)(LEAC) [C] *LJI HR1.4(1.0-2.0)** [M]	↑
de Rooy et al. (2011) (LEAC, n=676)[L] *Chronic vs acute OR1.55(0.93-2.59)* *Small vs Large joints OR 0.66(0.34-1.28)* *Upper vs lower extremitites OR 0.76(0.35-1.62)* *Upper and lower vs lower extremities OR 1.01(0.47-2.26)* *Symm vs asymm symptoms OR 0.89(0.51-1.55)*			
✗	**HAQ**	✓	
v.d. Woude et al. (2009)(LEAC, n=454)[C] - m-HAQ *HR 1.06(0.74-1.52)*		v.d. Woude et al. (2012) (BeSt, n=508) [L] *OR 0.63(0.40-0.98)* [U]*	↓
v.d. Woude et al. (2012)(LEAC, n=424)[B] *OR 1.26(0.78-2.03)*		Kuijper et al. (2016)(tREACH, n=281) [L] *OR 0.515* [U]*	
Ajeganova et al. (2016)(LEAC, n=886)[B] *nDFR 1.0(0.63-1.50), DFR 1.0(0.62-1.50)*		v.d. Woude et al. (2009)(ERAS, n=895) - m-HAQ [C] *HR 0.66*(0.44-0.99)* [M]	↓
Emery et al. (2018)(PRIZE, n=65)[L] *(no estimates specified)*		v.d. Kooij et al. (2008)(BeSt, n=508) [B] *nDFR 1.4 vs. DFR 1.2**	↓
		Nishimoto et al. (2014)(DREAM, n=187) [C] *HR 0.73(0.53-0.99)* [U]	↓
✗	**Visual Analogue Scale**	✓	
Ajeganova et al. (2016) - VAS pain [B] *nDFR 52(34-70), DFR 48(29-65)*		v.d. Kooij et al. (2008)(BeSt, n=508) *VAS pain: nDFR 55 vs DFR 45*** [B] *VAS disease activity: nDFR 61(23) vs DFR 55(19)** [B]	↓
Emery et al. (2018)(PRIZE, n=65) -VAS pain [B] *(no estimates specified)*		Ajeganova et al. (2016)(LEAC, n=886) [B] *VAS patient: nDFR55(34-76), DFR:51(33-67)** *VAS fatigue: nDFR:50(17-70), DFR:40(12-60)**	↓
✗	**Miscellaneous**	✓	
Kuijper et al. (2016)(tREACH, n=281) – SF36 [L] *OR 1.056(CI not specified)*			
Emery et al. (2018)(PRIZE) - SF36/mTSS/SGA score [L] *(no estimates specified)*			
Nishimoto et al. (2014)(DREAM, n=187) *Steinbrocker stage [C] HR 0.77(0.57-1.04)* *Steinbrocker class [C] HR 0.82(0.20-3.33)*			
LABORATORY BIOMARKERS			
✗	**Reuma factor**	✓	
Kuijper et al. (2016)(tREACH, n=281) [L] *OR 1.399 (CI not specified)*		v.d. Linden et al. (2009)(LEAC, n=687) [C] *HR 4.7 (2.8-8.0)* [U] (for not achieving DFR)*	↓
		v.d. Woude et al. (2012)(BeSt, n=508) [L] *OR 0.39(0.21-0.70)* [U]*	↓
		v.d. Woude et al. (2009) (ERAS, n=895) [C] *HR0.28**(0.16-0.49)* [M]	↓
		v.d. Woude et al. (2009) (LEAC, n=454) [C] *HR 0.17(0.10-0.31)* [U]**	↓
		de Rooy et al. (2011) (LEAC, n=676) [L] *OR6.66(3.69-12.02)** [U] (not achieving DFR)*	↓
		v.d. Linden et al. (2011)(LEAC) [C] *RF level >3x ref: HR 5.7(2.9-11.4)*** [C, M]	↓

	RF50 HR 3.1(1.2-7.6)[M]	
	v.d. Woude et al. (2012)(LEAC, n=424) [L] *OR 0.22(0.11-0.44)** [U]	↓
	Ajeganova et al. (2016)(LEAC, n=886) [B] *nDFR:65% RF+, DFR:31% RF+*** *(low or high ACPA positive not isgn different nDFR/DFR)*	↓
	v.d. Kooij et al. (2008)(BeSt, n=508) [B] *IgM RF neg: nDFR 33% vs DFR 48%**	↓
	Nishimoto et al. (2014)(DREAM, n=187) [C] *HR 0.53(0.33-0.85)* [U]	↓
	Emery et al. (2018)(PRIZE, n=65)[L,U*] *(no estimates specified)*	↓
✗	**Anti-CCP**	✓
Kuijper et al. (2016)(tREACH, n=281) [L] *OR 0.636 (CI not specified)*	v.d. Woude et al. (2012)(BeSt, n=508) [L] *OR 0.20(0.10-0.39)**,[M]*	↓
	v.d. Linden et al. (2009)(LEAC), n=687) [C] *anti-CCP-2 HR 11.6(5.8-23.4)* [U] *anti-CCP3 HR 6.0(3.4-10.4)* [U] *(for not achieving DFR)*	↓
	v.d. Woude et al. (2009) (LEAC, n=454) [C] *HR0.09(0.04-0.20)** [M]*	↓
	v.d. Linden et al. (2011)(LEAC, n=598) [C] *HR 11.3 (5.6-22.7)** [M]* *(not achieving DFR)*	↓
	de Rooy et al. (2011)(LEAC, n=676) [L] *OR11.46(5.85-22.46)** [U] (not achieving DFR)*	↓
	v.d. Kooij et al. (2008)(BeSt, n=508) [L] *Anti-CCP neg: DFR 57% vs nDFR 36%* [M]* *(OR not specified)*	↓
	Ajeganova et al. (2016)(LEAC, n=886)) [B] *nDFR 62% ACPA+, DFR 18% ACPA+***	↓
	Emery et al. (2018)(PRIZE, n=65)[L,U*] *(no estimates specified)*	↓
	v.d. Broek et al.(2012)(BeSt, n=484) [L] *RR 0.4(0.3-0.7)*,[M]*	↓
✗	**Anti-MCV**	✓
	v.d. Linden et al. (2009) [C] *HR 4.9 (3.0-8.2)* [U] (not achieving DFR)*	↓
	de Rooy et al. (2011, n=676) [L] *OR 6.13(3.48-10.79)** [U] (not achieving DFR)*	↓
✗	**CRP**	✓
v.d. Woude et al. (2012) (BeSt, n=508) [I] *OR 1.00(0.99-1.01)*	v.d. Woude et al. (2009)(LEAC, n=454) [C] *HR 0.99(0.98-1.0)* [M]*	↓
v.d. Woude et al. (2012)(LEAC, n=424)[L] *OR 1.00(0.99-1.01)*		
de Rooy et al. (2011)(LEAC, n=676)[L] *OR 1.01 (0.997-1.1013) (not achieving DFR)*		
Ajeganova et al. (2016)(LEAC, n=886)[B] *nDFR 15(6-38), DFR 16(16-33)*		
Emery et al. (2018)(PRIZE, n=65)[L] *(no estimates specified)*		
✗	**ESR**	✓
v.d. Woude et al. (2009) (LEAC, n=454)[C] *HR 0.99(0.98-1.00)*		
v.d. Woude et al. (2012)(BeSt, n=508) *OR 0.99(-0.98-1.00)*		
v.d. Woude et al. (2009) (ERAS, n=895)[C] *HR 0.99(0.99-1.00)*		
de Rooy et al. (2011)(LEAC, n=676)[L]		

OR 1.01(0.995-1.015)		
v.d. Woude et al. (2012)(LEAC, n=424) [L] *OR 1.00(0.99-1.01)*		
Ajeganova et al. (2016)(LEAC, n=886)[B] *nDFR 32(18-53), DFR 29(16-48)*		
Emery et al. (2018)(PRIZE, n=65)[L] *(no estimates specified)*		
✗	**IL-2**	✓
	v. Steenbergen et al. (2015)(LEAC) - serum IL2Rx levels [C] *Lower IL2 levels: HR0.83(0.70-0.98)* [U]*	↓
✗	**IL-6**	✓
	Nishimoto et al. (2014) (DREAM, n=187) [C] *IL-6 (<35pg/ml vs >35pg/ml) HR 0.41 (0.27-0.63) *[M]*	↓
✗	**MMP-3**	✓
	Nishimoto et al. (2014)(DREAM, n=187) [C] *MMP-3 (normal vs abnormal) HR0.29(0.19-0.43) *[M]*	↓
✗	**Shared Epitope**	✓
v. Heemst et al. (2015)(LEAC, n=441) *HLA DRB1*13 higher chance DFR*, but after stratification for ACPA status was this effect no longer present.*	v.d. Woude et al. (2009) (LEAC, n=454) - HLA [C] *HR 0.46 (0.29-.75)*[,U]*	↓
v. Steenbergen et al. (2015)(LEAC, n=645) *rs1896368 (DKK-1)/rs1896367/rs1528873 /rs26232(C5orf30)/rs11908352(MMP-9)/rs451066/rs1485305 (OPG)*	v.d. Woude et al. (2012)(BeSt, n=508) [L] *OR 0.46(0.25-0.85)*[U]*	↓
	v.d. Woude et al. (2009)(ERAS, n=895) - HLA [C] *HR 0.44(0.26-0.73)*[M]*	↓
	de Rooy et al. (2011) (LEAC, n=676)- HLA [L] *OR2.25(1.35-3.74)**[,U] (not achieving DFR)*	↓
	v.d. Woude et al. (2012)(LEAC, n=424) [L] *OR0.35(0.19-0.66)*[U]*	↓
✗	**Other**	✓
de Rooy et al. (2011)(LEAC, n=676)[L] *CD40 non-G carrier OR 0.78(0.17-3.54)*	v.d. Linden et al. (2009) *Combinations of auto-antibodies* *anti-CCP2 & RF HR 15.6 (6.7-36.4)* [C, U] *anti-CCP2 & anti-MCV HR 14.0(6.4-31.0)* [C, U] *anti-MCV&RF HR11.5(5.4-24.5)* [C, U] *1/2/3 auto-antibodies:* *HR 3.7(1.1-12.3)* [C,U], *HR 15.5(5.9-14.2)* [C,U] *HR17.1(6.8-43.3)* [C, U] *(HRs for not achieving DFR)*	↓
v. Steenbergen et al. (2015) (ESPOIR, n=622) - IL2RA[C]		
Teitsma et al. (2017)(U-Act-Early, n=60) *No networks in CD14+ cells could identified between DFR and nDFR.*	Teitsma et al. (2017)(U-Act-Early, n=60) *Pathways related to transcription/translation related to DFR in patients treated with MTx/TOCI and pathways related to migration of white blood cells and G-protein coupled receptors in TOZI arm and pathways involved in response to bacterial/biotic relates stimulus.*	↑
	v. Steenbergen et al. (2015) (LEAC, n=645) - IL2RA [C] *HR 2.27(1.06-4.84)*[M]*	↑
IMAGING BIOMARKERS		
✗	**Sharp v.d. Heijden score**	✓
Kuijper et al. (2016)(tREACH, n=281) [L] *OR 0.993(CI not specified)*	v.d. Woude et al. 2009)(LEAC, n=454) [C] *HR 0.95*(0.90-0.99)** [U]	↓
v.d. Woude et al. (2012)(BeSt, n=508)[L] *OR0.98(0.94-1.02)*		
v.d. Kooij et al. (2008)(BeSt, n=508)[B] *Total SHS: nDFR 4.0(1.5-9.0), nDFR 3.3(1.0-6.9)*		

v.d. Woude et al. (2012)(Leiden EAC, n=424)[L] *OR0.97(0.93-1.01)*		
Akdemir et al. (2018)(BeSt/IMPROVED, n=133/175)[L] *OR 0.94(0.83-1.07)*		
Emery et al. (2018)(PRIZE, n=65)[L] *(no estimates specified)*		
✗	**Larsen score**	✓
v.d. Woude et al. (2009)(ERAS, n=895)[C] HR 0.94(0.88-1.00)		
✗	**Erosive at baseline**	✓
v.d. Woude et al. (2012)(LEAC, n=424)[L] *OR0.52(0.99-1.01)*		
v.d. Woude et al. (2012)(BeSt, n=508)[L] *OR0.70(0.37-1.31)*		
v.d. Kooij et al. (2008)(BeSt, n=508)[B] *Erosive (%): nDFR 72%, DFR 69%*		
✗	**MRI**	✓
Burgers et al. (2018)(LEAC, n=238)[C] *BME HR 0.96(0.99-1.02)[M]* *Synovitis 1.04(0.95-1.15)[M]* *Tenosynovitis 1.03(0.95-1.11)[M]*		

Legend: All factors which were statistically tested for a potential association with achieving DFR were included in these overview, categorised by type of biomarker. Effect estimates were reported. If no regression analysis was conducted, numerical values compared between DFR and nDFR were reported.

** P<0.001, * p<0.05, DFR: DMARD-free remission, nDFR: no DMARD-free remission.

[B] Differences in baseline characteristics between DFR and non-DFR tested with t-test etc. [L] Logistic regression analysis [c] Cox regression analysis [U] Univariate, [M] Multivariate

Anti-MCV: anti-mutated citrullinated vimentin, CRP: C-reactive protein, DFR: DMARD-free remission, ESR: estimated sedimentation ratio, IL: interleukin, nDFR: no DMARD-free remission, SJC: swollen joint count, symp: symptom, HR: Hazard ratio, HLA: Human leukocyte antigen, OR: Odds ratio.

Supplementary table S7 – The selection of predictors of DFR used for figure 3

✗	**Age**	✓	
v.d. Woude et al. (2012) (BeSt, n=508)[L] *OR 1.01(0.98-1.03)* **v.d. Woude et al. (2009)** (LEAC, n=454)[C] *HR 1.02(0.99-1.03)* **Kuijper et al. (2016)** (tREACH, n=281)[L] *OR 0.995(CI not specified)*		no associations between age and DFR have been reported within the included articles	
✗	**Gender**	✓	
v.d. Woude et al. (2009) (LEAC, n=454)[C] *Female: HR 1.28(0.74-2.19)*		**Kuijper et al. (2016)** (tREACH, n=281)[L] *Female: OR 0.352*[*,M] (CI not specified)* **v.d. Woude et al. (2012)** (BeSt, n=508)[L] *Male: OR 2.3 9*[*M] (1.26-4.53)*	↑ ↑
✗	**BMI**	✓	
v.d. Woude et al. (2012) (LEAC, n=424)[L] *OR 0.95(0.83-1.08)* **v.d. Woude et al. (2012)** (BeSt, n=508)[L] *OR 0.96(0.88-1.04)*		no associations between BMI and DFR have been reported within the included articles	
✗	**Smoking**	✓	
v.d. Woude et al. (2012) (BeSt, n=508)[L] *OR 0.69(0.36-1.33)*		**v.d. Woude et al. (2009)** (LEAC, n=454)[C] *HR 0.56*[*U] (0.34-0.94)*	↓
✗	**(shorter) Symptom duration**	✓	
v.d. Woude et al. (2012) (BeSt, n=508) (cont)[C] *O R0.99(0.98-1.00) (cont. in weeks)* **Kuijper et al. (2016)** (tREACH, n=281)[L] *OR 1.00 (CI not specified) (measure symp duration not specified)*		**v.d. Linden et al. (2010)** (LEAC, n=598)[C] ≥12w symptoms vs <12w *HR 1.90*[*M] (1.18 - 3.05)(not achieving DFR)*	↑
✗	**Disease activity score at baseline**	✓	
Akdemir et al. (2018) (IMPROVED, n=175)[L] *OR 0.94(0.58-1.53)* *Only IMPROVED data selected for figure*		**v.d. Woude et al. (2012)** (BeSt. N=508)[L] *OR 0.63*[*M] (0.43-0.94)* **Kuijper et al. (2016)** (tREACH, n=281)[L] *OR 0.587*[*M] (CI not specified)*	↓ ↓
✗	**Swollen Joint Count at baseline**	✓	
v.d. Woude et al. (2009) (LEAC, n=454)[C] – 44-SJC *HR 1.00(0.96-1.04)* **v.d. Woude et al. (2012)** (BeSt, n=508)[L] *OR 1.01(0.97-1.06)*		no associations between SJC and DFR have been reported within the included articles	
✗	**HAQ**	✓	
v.d. Woude et al. (2009) (LEAC, n=454)[C] - m-HAQ *HR 1.06(0.74-1.52)*		**v.d. Woude et al. (2012)** (BeSt, n=508)[L] *OR 0.63(0.40-0.98)*[*, U]* **Kuijper et al. (2016)** (tREACH, n=281)[L] *OR 0.515*[*U]*	↓ ↓
✗	**Reuma factor**	✓	
Kuijper et al. (2016) (tREACH, n=281)[L] *OR 1.399 (CI not specified)*		**v.d. Linden et al. (2009)** (LEAC, n=687)[C] *HR 4.7 (2.8-8.0) *[U] (for not achieving DFR)* **v.d. Woude et al. (2012)** (BeSt, n=508)[L] *OR 0.39(0.21-0.70)*[*U]*	↓ ↓
✗	**Anti-CCP**	✓	
Kuijper et al. (2016) (tREACH, n=281)[L] *OR 0.636 (CI not specified)*		**v.d. Woude et al. (2012)** (BeSt, n=508)[L] *OR 0.20(0.10-0.39)*[**M]* **v.d. Linden et al. (2009)**(LEAC), n=687)[C] *anti-CCP-2 HR 11.6(5.8-23.4)*[U] *anti-CCP3 HR 6.0(3.4-10.4)*[U] *(for not achieving DFR)*	↓ ↓

✗	**CRP**	✓	
v.d. Woude et al. (2012) (BeSt, n=508) [L] *OR 1.00(0.99-1.01)*		**v.d. Woude et al. (2009)**(LEAC, n=454) [C] *HR 0.99* [M] (0.98-1.0)*	↓
✗	**ESR**	✓	
v.d. Woude et al. (2009) (LEAC, n=454)[C] *HR 0.99(0.98-1.00)* **v.d. Woude et al. (2012)** (BeSt, n=508) [L] *OR 0.99 (-0.98-1.00)*		no associations between ESR and DFR have been reported within the included articles	
✗	**Sharp v.d. Heijden score**	✓	
Kuijper et al. (2016) (tREACH, n=281) [L] *OR 0.993(CI not specified)* **v.d. Woude et al. (2012)** (BeSt, n=508)[L] *OR0.98(0.94-1.02)*		**v.d. Woude et al. (2009)** (LEAC, n=454) [C] *HR 0.95* [U] (0.90-0.99)*	↓
✗	**Erosive at baseline**	✓	
v.d. Woude et al. (2012) (LEAC, n=424)[L] *OR0.52(0.99-1.01)* **v.d. Woude et al. (2012)** (BeSt, n=508)[L] *OR0.70(0.37-1.31)*		no associations between erosive at baseline and DFR have been reported within the included articles	
✗	**Shared Epitope**	✓	
		v.d. Woude et al. (2009) (LEAC, n=454) - HLA [C] *HR 0.46 (0.29-.75)*[U]* **v.d. Woude et al. (2012)** (BeSt, n=508) [L] *OR 0.46(0.25-0.85)*[U]*	↓ ↓

Legend: Based on supplementary table S6 predictors were selected for a narrative overview (figure 3). Only high and moderate-quality studies were selected which reported on factors associated with DFR, tested by means of regression techniques. When more factors were repeatedly reported by the same study, the study including the largest study population and subsequent longest follow-up were included.

** P<0.001, * p<0.05, [B] Differences in baseline characteristics between DFR and non-DFR tested with t-test etc. [L] Logistic regression analysis [c] Cox regression analysis [U] Univariate, [M] Multivariate.

Anti-MCV: anti-mutated citrullinated vimentin, CRP: C-reactive protein, DFR: DMARD-free remission, ESR: estimated sedimentation ratio, nDFR: no DMARD-free remission, SJC: swollen joint count, symp: symptom, HR: Hazard ratio, HLA: Human leukocyte antigen, OR: Odds ratio.

Supplementary table S9 – PRISMA checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5 Suppl S2
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5 Suppl S1
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Suppl S1 + S9
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5 Figure 1 Suppl S2
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5/6 Suppl S3)

Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5/6 Suppl S3)
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6 Table 1. Suppl S4
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7 Suppl S4
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6 Suppl S4
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7 Suppl S3
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8 Figure 1.
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8-11 Suppl S5
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	8 Table 1.
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	8-11 Figure 2. Table 2. Suppl S5
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Not applicable
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Table 1.

Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Figure 3.
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	12-16
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	12-16

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Supplementary table S9 – Details search strategy

PubMed

http://www.ncbi.nlm.nih.gov/pubmed?otool=leiden

(("disease modifying anti rheumatic"[tw] OR "disease modifying anti rheumatoid"[tw] OR "disease modifying antirheumatic"[tw] OR "disease modifying antirheumatoid"[tw] OR "DMARD"[tw] OR "DMARDs"[tw] OR "bDMARD"[tw] OR "bDMARDs"[tw] OR "cDMARD"[tw] OR "cDMARDs"[tw] OR "csDMARD"[tw] OR "csDMARDs"[tw] OR "Antirheumatic Agents"[Mesh:noexp] OR "Antirheumatic Agents"[Pharmacological Action] OR "1-((4,5-bis(4-methoxyphenyl)-2-thiazoyl)carbonyl)-4-methylpiperazine"[tw] OR "1-((4-methylsulfonyl)phenyl)-3-trifluoromethyl-5-(4-fluorophenyl)pyrazole"[tw] OR "1-(4-chlorobenzoyl)-3-(2-(1H-imidazol-1-yl)-2-oxoethyl)-5-methoxy-2-methyl-1H-indole"[tw] OR "2-(4-(quinolin-2-yl-methoxy)phenyl)-2-cyclopentylacetic acid"[tw] OR "2-(4-acetoxyphenyl)-2-chloro-N-methylethylamine"[tw] OR "2-aminomethyl-4-t-butyl-6-iodophenol"[tw] OR "2-diethylaminoethanol"[tw] OR "3-methyl-2-(3-pyridyl)-1-indoleoctanoic acid"[tw] OR "4,5-Dihydro-1-(3-(trifluoromethyl)phenyl)-1H-pyrazol-3-amine"[tw] OR "4-(5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzenesulfonamide"[tw] OR "4-(acetylamino)benzeneacetic acid"[tw] OR "4-bromo-2,7-dimethoxy-3H-phenothiazin-3-one"[tw] OR "6-(4-fluorophenyl)-2,3-dihydro-5-(4-pyridinyl)imidazo(2,1-b)thiazole"[tw] OR "6-acetylaminocaproic acid"[tw] OR "6-ethoxy-3-(4-methanesulfonylphenyl)-4-phenylpyran-2-one"[tw] OR "7-methoxy-alpha-methyl-2-naphthaleneacetic acid"[tw] OR "A 771726"[tw] OR "Abatacept"[tw] OR "aceclofenac"[tw] OR "acemetacin"[tw] OR "acetaminophen, aspirin, caffeine drug combination"[tw] OR "acetaminophen, butalbital, caffeine drug combination"[tw] OR "acetaminophen, hydrocodone drug combination"[tw] OR "acetosyringone"[tw] OR "acetovanillone"[tw] OR "acetylsalicylic acid lysinate"[tw] OR "Adalimumab"[tw] OR "Adapalene"[tw] OR "Adapalene, Benzoyl Peroxide Drug Combination"[tw] OR "alclofenac"[tw] OR "Allopurinol"[tw] OR "alminoprofen"[tw] OR "alpha-pentyl-3-(2-quinolinylmethoxy)benzenemethanol"[tw] OR "amiprilose"[tw] OR "Ampyrone"[tw] OR "amylase, phosphates, proteases drug combinations"[tw] OR "andrographolide"[tw] OR "anisodamine"[tw] OR "anisodine"[tw] OR "antiflammin P2"[tw] OR "Antipyrine"[tw] OR "Apazone"[tw] OR "apremilast"[tw] OR "Arteparon"[tw] OR "Arthrotec"[tw] OR "Aspirin"[tw] OR "aspirin, aluminum hydroxide, magnesium hydroxide drug combination"[tw] OR "aspirin, butalbital and caffeine drug combination"[tw] OR "aspirin, meprobamate drug combination"[tw] OR "atrinositol"[tw] OR "Auranofin"[tw] OR "Aurothioglucose"[tw] OR "aurotioprol"[tw] OR "Azathioprine"[tw] OR "azulene"[tw] OR "baicalin"[tw] OR "balsalazide"[tw] OR "bendazac"[tw] OR "bendazac lysine"[tw] OR "benorilate"[tw] OR "benoxaprofen"[tw] OR "Benzbromarone"[tw] OR "benziodarone"[tw] OR "benzobarbital"[tw] OR "berbamine"[tw] OR "betulinic acid"[tw] OR "bevonium"[tw] OR "BI 607812 BS"[tw] OR "biphenylylacetic acid"[tw] OR "boldine"[tw] OR "borage oil"[tw] OR "boswellic acid"[tw] OR "bromfenac"[tw] OR "bucillamine"[tw] OR "Bufexamac"[tw] OR "bumadizone"[tw] OR "butibufen"[tw] OR "carbaspirin calcium"[tw] OR "carprofen"[tw] OR "caryophyllene"[tw] OR "castanospermine"[tw] OR "CDP 571"[tw] OR "Celecoxib"[tw] OR "cepharanthine"[tw] OR "Certolizumab Pegol"[tw] OR "Chloroquine"[tw] OR "chloroquine diphosphate"[tw] OR "choline magnesium trisalicylate"[tw] OR "chrysarobin"[tw] OR "Clonixin"[tw] OR "Colchicine"[tw] OR "CP 96345"[tw] OR "Curcumin"[tw] OR "CX 659S"[tw] OR

"Cyclophosphamide"[tw] OR "Cyclosporine"[tw] OR "DAB(486)-interleukin 2"[tw] OR "dauricine"[tw] OR "dexketoprofen trometamol"[tw] OR "Diclofenac"[tw] OR "diclofenac hydroxyethylpyrrolidine"[tw] OR "difenpiramide"[tw] OR "Diflunisal"[tw] OR "dimephosphon"[tw] OR "Dipyrone"[tw] OR "diucifon"[tw] OR "droxicam"[tw] OR "DuP 697"[tw] OR "E6011"[tw] OR "ebselen"[tw] OR "ecallantide"[tw] OR "eltenac"[tw] OR "enfenamic acid"[tw] OR "enkephalin-Leu, Ala(2)-Arg(6)-"[tw] OR "Epirizole"[tw] OR "Etanercept"[tw] OR "ethenzamide"[tw] OR "Ethonium"[tw] OR "Etodolac"[tw] OR "etofenamate"[tw] OR "Etoricoxib"[tw] OR "evening primrose oil"[tw] OR "Febuxostat"[tw] OR "fenamic acid"[tw] OR "fenbufen"[tw] OR "fenclofenac"[tw] OR "fenflumizole"[tw] OR "Fenoprofen"[tw] OR "fentiazac"[tw] OR "fepradinol"[tw] OR "Feprazone"[tw] OR "ferulic acid"[tw] OR "flobufen"[tw] OR "floctafenine"[tw] OR "flosulide"[tw] OR "flunixin"[tw] OR "flunixin meglumine"[tw] OR "flunoxaprofen"[tw] OR "fluproquazone"[tw] OR "Flurbiprofen"[tw] OR "flurbiprofen axetil"[tw] OR "FR 167653"[tw] OR "FR 173657"[tw] OR "Glatiramer Acetate"[tw] OR "glucametacin"[tw] OR "Gold Sodium Thiomalate"[tw] OR "Gold Sodium Thiosulfate"[tw] OR "guacetisal"[tw] OR "Halofenate"[tw] OR "helenalin"[tw] OR "heliodermin"[tw] OR "hemodes"[tw] OR "higenamine"[tw] OR "Hydroxychloroquine"[tw] OR "Ibuprofen"[tw] OR "ibuproxam"[tw] OR "icatibant"[tw] OR "IH 764-3"[tw] OR "imidazole-2-hydroxybenzoate"[tw] OR "indacrinone"[tw] OR "indobufen"[tw] OR "Indomethacin"[tw] OR "Indoprofen"[tw] OR "Infliximab"[tw] OR "Interleukin 1 Receptor Antagonist Protein"[tw] OR "Interleukin-4"[tw] OR "iodoantipyrine"[tw] OR "isoxicam"[tw] OR "kebuzone"[tw] OR "Ketoprofen"[tw] OR "ketoprofen lysine"[tw] OR "Ketorolac"[tw] OR "Ketorolac Tromethamine"[tw] OR "L 745337"[tw] OR "L 778736"[tw] OR "lesinurad"[tw] OR "Levamisole"[tw] OR "licofelone"[tw] OR "lipoxin A4"[tw] OR "lipoxin B4"[tw] OR "lisofylline"[tw] OR "lobenzarit"[tw] OR "lonazolac"[tw] OR "lornoxicam"[tw] OR "loxoprofen"[tw] OR "LQFM-091"[tw] OR "lumiracoxib"[tw] OR "Magnesium Salicylate"[tw] OR "magnolol"[tw] OR "manoalide"[tw] OR "Masoprocol"[tw] OR "mavrilimumab"[tw] OR "Meclofenamic Acid"[tw] OR "Mefenamic Acid"[tw] OR "Meloxicam"[tw] OR "Mesalamine"[tw] OR "Methotrexate"[tw] OR "methyl salicylate"[tw] OR "mizoribine"[tw] OR "MK 473"[tw] OR "mofebutazone"[tw] OR "mofezolac"[tw] OR "N-(2-cyclohexyloxy-4-nitrophenyl)methanesulfonamide"[tw] OR "N-(9H-(2,7-dimethylfluoren-9-ylmethoxy)carbonyl)leucine"[tw] OR "N-succinimidyl-1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indole-3-acetate"[tw] OR "Nabumetone"[tw] OR "nafamostat"[tw] OR "Naproxen"[tw] OR "Nebacetin"[tw] OR "nepafenac"[tw] OR "nifenazone"[tw] OR "Niflumic Acid"[tw] OR "nimesulide"[tw] OR "nitroaspirin"[tw] OR "Olopatadine Hydrochloride"[tw] OR "olsalazine"[tw] OR "olvanil"[tw] OR "oren gedoku to"[tw] OR "orgotein"[tw] OR "oxaceprol"[tw] OR "Oxaprozin"[tw] OR "Oxyphenbutazone"[tw] OR "palmidrol"[tw] OR "parecoxib"[tw] OR "parthenolide"[tw] OR "Penicillamine"[tw] OR "peoniflorin"[tw] OR "phenidone"[tw] OR "Phenylbutazone"[tw] OR "pimecrolimus"[tw] OR "pirfenidone"[tw] OR "Piroxicam"[tw] OR "piroxicam-beta-cyclodextrin"[tw] OR "pirprofen"[tw] OR "Probenecid"[tw] OR "proglumetacin"[tw] OR "propacetamol"[tw] OR "propionylcarnitine"[tw] OR "propyphenazone"[tw] OR "proquazone"[tw] OR "Prospidium"[tw] OR "pyranoprofen"[tw] OR "pyrazolone"[tw] OR "pyrogenal"[tw] OR "rasburicase"[tw] OR "Resveratrol"[tw] OR "rifamycin SV"[tw] OR "Rituximab"[tw] OR "RNS60"[tw] OR "rofecoxib"[tw] OR "rosmarinic acid"[tw] OR "Rumalon"[tw] OR "saiko-keishi-to"[tw] OR "saikosaponin"[tw] OR "salicin"[tw] OR "salicylamide"[tw] OR "Salicylates"[tw] OR "salicylsalicylic acid"[tw] OR "SB 203580"[tw] OR "SC 299"[tw] OR "SC 41930"[tw] OR "SC 560"[tw] OR "semapimod"[tw] OR "seratrodast"[tw] OR

"serratiopeptidase"[tw] OR "shikonin"[tw] OR "sinapaldehyde"[tw] OR "sinomenine"[tw] OR "Sodium Salicylate"[tw] OR "ST 679"[tw] OR "Sul-121"[tw] OR "Sulfasalazine"[tw] OR "Sulfinpyrazone"[tw] OR "Sulindac"[tw] OR "sulindac sulfide"[tw] OR "sulindac sulfone"[tw] OR "Suprofen"[tw] OR "suxibuzone"[tw] OR "T0001"[tw] OR "tanshinone"[tw] OR "taxifolin"[tw] OR "tenidap"[tw] OR "tenoxicam"[tw] OR "tepoxalin"[tw] OR "tiaprofenic acid"[tw] OR "tiaramide"[tw] OR "Ticrynafen"[tw] OR "tinoridine"[tw] OR "tisopurine"[tw] OR "tolfenamic acid"[tw] OR "Tolmetin"[tw] OR "tramadol, dexketoprofen drug combination"[tw] OR "tranilast"[tw] OR "traxanox"[tw] OR "tribenoside"[tw] OR "upadacitinib"[tw] OR "ursolic acid"[tw] OR "valdecoxib"[tw] OR "verinurad"[tw] OR "zileuton"[tw] OR "zomepirac"[tw] OR "Zoxazolamine"[tw]) AND ("drug free remission"[tw] OR "drug free remissions"[tw] OR "drug free clinical remission"[tw] OR "drug free disease remission"[tw] OR "DMARD-free remission"[tw] OR (("drug free"[tw] OR "DMARD free"[tw]) AND ("remission"[tw] OR remiss*[tw] OR "Remission Induction"[mesh])) OR "stable remission"[tw] OR "stable remissions"[tw] OR "stable disease remission"[tw] OR "sustained remission"[tw] OR "sustained remissions"[tw] OR "sustained disease remission"[tw] OR "sustained disease remissions"[tw] OR "stable clinical remission"[tw] OR "sustained clinical remission"[tw] OR "sustained clinical remissions"[tw] OR "sustained complete remission"[tw] OR "sustained complete remissions"[tw] OR "stable complete remission"[tw] OR "stable complete remissions"[tw] OR (("stable"[ti] OR "sustained"[ti]) AND ("remission"[ti] OR remiss*[ti] OR "Remission Induction"[mesh])) OR (("drug tapering"[tw] OR "drug taper"[tw] OR "treatment tapering"[tw] OR "medication taper"[tw] OR "medication tapering"[tw] OR "tapering"[tw] OR "taper"[tw] OR "drug discontinuation"[tw] OR "treatment discontinuation"[tw] OR "discontinuation"[tw] OR "cessation"[tw]) AND ("remission"[tw] OR remiss*[tw] OR "Remission Induction"[mesh]))) AND ("Arthritis, Rheumatoid"[Mesh:noexp] OR "rheumatoid arthritis"[tw] OR (rheumatoid*[tw] AND arthriti*[tw]))) NOT (("Case Reports"[ptyp] OR "case report"[ti] OR "Editorial"[ptyp] OR "Comment"[ptyp]) NOT ("Review"[ptyp] OR "Clinical Study"[ptyp])) AND (english[la] OR dutch[la])