

ONLINE SUPPLEMENTARY DATA

SUPPLEMENTARY DATA 1: Search strategies

Embase (including Medline) 4496

('rheumatoid arthritis'/de OR ((rheuma* NEXT/1 arthrit*) OR (RA AND (rheuma* OR arthrit*))) :ab,ti) AND ('disease modifying antirheumatic drug'/exp OR (DMARD* OR (disease NEAR/3 modif*) OR methotrexat* OR metotrex* OR mexate OR amethopterin* OR ametofterin* OR emthexat* OR emtrexat* OR ledertrexat* OR MTX OR novatrex OR rheumatex OR leflunomide OR Arava OR arabloc OR salazosulfapyridin* OR salicylazosulfapyridin* OR sulfasalazin* OR Azulfidin* OR Sulfazin* OR Salazopyrin* OR sulphasalazin* OR sulphazin* OR chloroquin* OR aralen* OR arthrochin* OR nivaquin* OR hydroxychloroquin* OR hydroxychlorochin* OR HCQ OR plaquenil* OR ercoquin* OR chlorochin* OR quinolin* OR quensyl* OR penicillamin* OR dimethylcystein* OR cuprimin* OR depen* OR gold* OR monogold* OR aurothiomalat* OR myochrysin* OR tauredon* OR organogold* OR azathioprin* OR azothioprin* OR imuran* OR immuran* OR cyclosporin* OR Neoral* OR Gengraf* OR Sandimmun* OR CyA OR etanercept* OR Enbrel* OR ((TNF* OR factor*) NEAR/3 (block* OR antagon* OR anti* OR inhibit* OR 'fusion protein')) OR TNFis* OR adalimumab* OR Humira* OR Trudexa* OR certolizumab* OR Cimzia* OR CDP870 OR 'CDP 870' OR golimumab* OR Simponi OR infliximab* OR ((Mab OR monoclonal) NEAR/3 cA2) OR Remicade OR Avakine OR Revellex OR abatacept* OR Oencia* OR 'BMS 188667' OR BMS188667 OR CTLA4 OR 'CTLA 4' OR belatacept* OR BMS224818 OR 'BMS 224818' OR Nulojix* OR (('interleukin 1' OR interleukin1 OR 'il 1' OR II1 OR 'interleukin 6' OR interleukin6 OR 'il 6' OR II6) NEAR/3 (block* OR antagon* OR anti* OR inhibit*)) OR Anril* OR Kineret* OR Anakinra* OR rituximab* OR Mabthera OR Rituxan OR Reditux* OR CD20 OR 'CD 20' OR tocilizumab* OR Actemra* OR Roactemra* OR Atlizumab* OR biological* OR Tetracyclin* OR Minocyclin* OR Azithromycin* OR Doxycyclin* OR cyclophosphamid* OR Cytoxan* OR Endoxan* OR tacrolimus* OR Prograf) :ab,ti,de) AND ('drug dose reduction'/de OR 'drug dose titration'/de OR 'treatment withdrawal'/de OR ((dos* OR treatm* OR therap* OR medic*) NEAR/5 (reduc* OR adjust* OR withdraw* OR withhold* OR withheld* OR stop* OR taper* OR titrat* OR discontin* OR cessat* OR lower* OR retract* OR ceas* OR diminish* OR deescal* OR 'de escalation' OR 'de escalations' OR 'de escalating' OR 'de escalate' OR 'de escalated')) :ab,ti)

OVID-SP (Medline)

("Arthritis, Rheumatoid"/ OR ((rheuma* ADJ arthrit*) OR (RA AND (rheuma* OR arthrit*))) :ab,ti.) AND ((DMARD* OR (disease ADJ3 modif*) OR methotrexat* OR metotrex* OR mexate OR amethopterin* OR ametofterin* OR emthexat* OR emtrexat* OR ledertrexat* OR MTX OR novatrex OR rheumatex OR leflunomide OR Arava OR arabloc OR salazosulfapyridin* OR salicylazosulfapyridin* OR sulfasalazin* OR Azulfidin* OR Sulfazin* OR Salazopyrin* OR sulphasalazin* OR sulphazin* OR chloroquin* OR aralen* OR arthrochin* OR nivaquin* OR hydroxychloroquin* OR hydroxychlorochin* OR HCQ OR plaquenil* OR ercoquin* OR chlorochin* OR quinolin* OR quensyl* OR penicillamin* OR dimethylcystein* OR cuprimin* OR depen* OR gold* OR aurothiomalat* OR myochrysin* OR tauredon* OR organogold* OR azathioprin* OR azothioprin* OR imuran* OR immuran* OR cyclosporin* OR Neoral* OR Gengraf* OR Sandimmun* OR CyA OR etanercept* OR Enbrel* OR "TNFR-Fc fusion protein" OR ((TNF* OR factor*) ADJ3 (block* OR antagon* OR anti* OR inhibit*)) OR TNFis* OR adalimumab* OR Humira* OR Trudexa* OR certolizumab* OR Cimzia* OR CDP870 OR "CDP 870" OR golimumab* OR Simponi OR infliximab* OR ((Mab OR monoclonal) ADJ3 cA2) OR Remicade OR Avakine OR Revellex OR abatacept* OR Oencia* OR "BMS 188667" OR BMS188667 OR CTLA4 OR "CTLA 4" OR belatacept* OR BMS224818 OR "BMS 224818" OR Nulojix* OR (('interleukin 1' OR interleukin1 OR "il 1" OR II1 OR "interleukin 6" OR interleukin6 OR "il 6" OR II6) ADJ3 (block* OR antagon* OR anti* OR inhibit*)) OR Anril* OR Kineret* OR Anakinra* OR rituximab* OR Mabthera OR Rituxan OR Reditux* OR CD20 OR "CD 20" OR tocilizumab* OR Actemra* OR Roactemra* OR Atlizumab* OR biological* OR Tetracyclin* OR Minocyclin* OR Azithromycin* OR Doxycyclin* OR cyclophosphamid* OR Cytoxan* OR Endoxan* OR tacrolimus* OR Prograf).mp.) AND ("Dose response relationship, Drug"/ OR "Withholding Treatment"/ OR ((dos* OR treatm* OR therap* OR medic*) ADJ5 (reduc* OR adjust* OR withdraw* OR withhold* OR withheld* OR stop* OR taper* OR titrat* OR discontin* OR cessat* OR lower* OR retract* OR ceas* OR diminish* OR (de ADJ escalat*))) :ab,ti.)

Cochrane Central

((rheuma* NEXT/1 arthrit*) OR (RA AND (rheuma* OR arthrit*))) :ab,ti) AND ((DMARD* OR (disease NEAR/3 modif*) OR methotrexat* OR metotrex* OR mexate OR amethopterin* OR ametofterin* OR emthexat* OR emtrexat* OR ledertrexat* OR MTX OR novatrex OR rheumatex OR leflunomide OR Arava OR arabloc OR salazosulfapyridin* OR salicylazosulfapyridin* OR sulfasalazin* OR Azulfidin* OR Sulfazin* OR Salazopyrin* OR sulphasalazin* OR sulphazin* OR chloroquin* OR aralen* OR arthrochin* OR nivaquin* OR hydroxychloroquin* OR hydroxychlorochin* OR HCQ OR plaquenil* OR ercoquin* OR chlorochin* OR quinolin* OR quensyl* OR penicillamin* OR dimethylcystein* OR cuprimin* OR depen* OR gold* OR monogold* OR aurothiomalat* OR myochrysin* OR tauredon* OR organogold* OR azathioprin* OR azothioprin* OR imuran* OR immuran* OR cyclosporin* OR Neoral* OR Gengraf* OR Sandimmun* OR CyA OR etanercept* OR Enbrel* OR ((TNF* OR factor*) NEAR/3 (block* OR antagon* OR anti* OR inhibit* OR 'fusion protein')) OR TNFis* OR adalimumab* OR Humira* OR Trudexa* OR certolizumab* OR Cimzia* OR CDP870 OR "CDP 870" OR golimumab* OR Simponi OR infliximab* OR ((Mab OR monoclonal) NEAR/3 cA2) OR Remicade OR Avakine OR Revellex OR abatacept* OR Oencia* OR "BMS 188667" OR BMS188667 OR CTLA4 OR "CTLA 4" OR belatacept* OR BMS224818 OR "BMS 224818" OR Nulojix* OR (('interleukin 1' OR interleukin1 OR "il 1" OR II1 OR "interleukin 6" OR

Online supplement to: Flare Rate in Patients with Rheumatoid Arthritis in Low Disease Activity or Remission Tapering or Stopping Synthetic or Biologic DMARD: A Systematic Review. *The Journal of Rheumatology*. doi:10.3899/jrheum.141520

interleukin6 OR "il 6" OR Il6) NEAR/3 (block* OR antagonist* OR anti* OR inhibit*) OR Anril* OR Kineret* OR Anakinra* OR rituximab* OR Mabthera OR Rituxan OR Reditux* OR CD20 OR "CD 20" OR tocilizumab* OR Actemra* OR Roactemra* OR Atlizumab* OR biological* OR Tetracyclin* OR Minocyclin* OR Azithromycin* OR Doxycyclin* OR cyclophosphamid* OR Cytoxan* OR Endoxan* OR tacrolimus* OR Prograf):ab,ti,kw) AND (((dos* OR treat* OR therap* OR medic*) NEAR/5 (reduc* OR adjust* OR withdraw* OR withhold* OR withheld* OR stop* OR taper* OR titrat* OR discontin* OR cessat* OR lower* OR retract* OR ceas* OR diminish* OR deescal* OR "de escalation" OR "de escalations" OR "de escalating" OR "de escalate" OR "de escalated"))):ab,ti)

PubMed

((((rheuma*[tiab] AND arthrit*[tiab]) OR (RA[tiab] AND (rheuma*[tiab] OR arthrit*[tiab]))) AND ((DMARD*[tiab] OR (disease[tiab] AND modif*[tiab]) OR methotrexat*[tiab] OR metotrex*[tiab] OR mexate OR amethopterin*[tiab] OR amethopterin*[tiab] OR emthexat*[tiab] OR emtrexat*[tiab] OR ledertrexat*[tiab] OR MTX[tiab] OR novatrex[tiab] OR rheumatrex[tiab] OR leflunomide[tiab] OR Arava[tiab] OR arabloc[tiab] OR salazosulfapyridin*[tiab] OR salicylazosulfapyridin*[tiab] OR sulfasalazin*[tiab] OR Azulfidin*[tiab] OR Sulfazin*[tiab] OR Salazopyrin*[tiab] OR sulphasalazin*[tiab] OR sulphazin*[tiab] OR chloroquin*[tiab] OR aralen*[tiab] OR arthrochin*[tiab] OR nivaquin*[tiab] OR hydroxychloroquin*[tiab] OR hydroxychlorochin*[tiab] OR HCQ OR plaquenil*[tiab] OR ercoquin*[tiab] OR chlorochin*[tiab] OR quinolin*[tiab] OR quensyl*[tiab] OR penicillamin*[tiab] OR dimethylcystein*[tiab] OR cuprimin*[tiab] OR depen*[tiab] OR gold[tiab] OR aurothiomalat*[tiab] OR myochrysin*[tiab] OR tauredon*[tiab] OR organogold*[tiab] OR azathioprin*[tiab] OR azothioprin*[tiab] OR imuran*[tiab] OR immuran*[tiab] OR cyclosporin*[tiab] OR Neoral*[tiab] OR Gengraf*[tiab] OR Sandimmun*[tiab] OR CyA OR etanercept*[tiab] OR Enbrel*[tiab] OR TNFR-Fc fusion protein[tiab] OR ((TNF*[tiab] OR factor*[tiab]) AND (block*[tiab] OR antagonist*[tiab] OR anti*[tiab] OR inhibit*[tiab])) OR TNFis*[tiab] OR adalimumab*[tiab] OR Humira*[tiab] OR Trudexa*[tiab] OR certolizumab*[tiab] OR Cimzia*[tiab] OR CDP870 OR CDP 870 OR golimumab*[tiab] OR Simponi[tiab] OR infliximab*[tiab] OR ((Mab[tiab] OR monoclonal[tiab]) AND cA2[tiab]) OR Remicade[tiab] OR Avakine[tiab] OR Revellex[tiab] OR abatacept*[tiab] OR Orencia*[tiab] OR BMS 188667[tiab] OR BMS188667[tiab] OR CTLA4[tiab] OR CTLA 4[tiab] OR belatacept*[tiab] OR BMS224818[tiab] OR BMS 224818[tiab] OR Nulojix*[tiab] OR ((interleukin 1[tiab] OR interleukin1[tiab] OR il 1[tiab] OR Il1[tiab] OR interleukin 6[tiab] OR interleukin6[tiab] OR il 6[tiab] OR Il6[tiab]) AND (block*[tiab] OR antagonist*[tiab] OR anti*[tiab] OR inhibit*[tiab])) OR Anril*[tiab] OR Kineret*[tiab] OR Anakinra*[tiab] OR rituximab*[tiab] OR Mabthera[tiab] OR Rituxan[tiab] OR Reditux*[tiab] OR CD20[tiab] OR CD 20[tiab] OR tocilizumab*[tiab] OR Actemra*[tiab] OR Roactemra*[tiab] OR Atlizumab*[tiab] OR biological*[tiab] OR Tetracyclin*[tiab] OR Minocyclin*[tiab] OR Azithromycin*[tiab] OR Doxycyclin*[tiab] OR cyclophosphamid*[tiab] OR Cytoxan*[tiab] OR Endoxan*[tiab] OR tacrolimus*[tiab] OR Prograf)) AND (((dos*[tiab] OR treatm*[tiab] OR therap*[tiab] OR medic*[tiab]) AND (reduc*[tiab] OR adjust*[tiab] OR withdraw*[tiab] OR withhold*[tiab] OR withheld*[tiab] OR stop*[tiab] OR taper*[tiab] OR titrat*[tiab] OR discontin*[tiab] OR cessat*[tiab] OR lower*[tiab] OR retract*[tiab] OR ceas*[tiab] OR diminish*[tiab] OR (de escalat*[tiab]))) AND (publisher[sb] OR 2012/11/20:3000[mhda])

SUPPLEMENTARY DATA 2: Modification to Downs and Black's list¹ used for Quality assessment

Available from the authors on request.

SUPPLEMENTARY DATA 3: Quality Assessment

sDMARD

	(2) Luis 1999	(3) Fleischmann 2005	(4) Heimans 2013	(5) ten Wolde 1996
Flare rate	8%	42%	35%	37%
Study design	RCT	single-arm	single-arm	RCT
DMARD	conventional	conventional	conventional/ TNF-blocker	conventional
1	yes	Partially	yes	yes
2	no	Yes	yes	yes
3	partially	Yes	yes	partially
4	yes	Yes	yes	yes
5	partly	Partially	yes	yes
6	yes	Yes	yes	yes
7	xxxxxxxxxxxx	xxxxxxxxxxxx	xxxxxxxxxxxx	xxxxxxxxxxxx
8	yes	Yes	NA	yes
9	yes	Unclear	no	yes
10	xxxxxxxxxxxx	xxxxxxxxxxxx	xxxxxxxxxxxx	xxxxxxxxxxxx
11	yes	Yes	yes	yes
12	unclear	unclear	unclear	unclear
13	yes	Yes	yes	yes
14	no	NA	no	yes
15	yes	Unclear	yes	yes
16	xxxxxxxxxxxx	xxxxxxxxxxxx	xxxxxxxxxxxx	xxxxxxxxxxxx
17a	yes	NA	yes	yes
17b	yes	Yes	yes	yes
17c	NA	NA	yes	NA
18	yes	Yes	yes	yes
19	unclear	Unclear	unclear	unclear
20	yes	Yes	yes	yes
21	yes	NA	yes	yes
22	yes	NA	yes	yes
23	yes	NA	yes	yes
24	partly	NA	yes	Yes
25	xxxxxxxxxxxx	xxxxxxxxxxxx	xxxxxxxxxxxx	Xxxxxxxxxxxxx
26	yes	Yes	yes	Yes
27	no	yes	no	Yes

TNF inhibitors 1/2

	(6) Maneiro 2013	(7) Harigai 2012	(8) van der Maas 2012	(9) Brocq 2009	(10) Tanaka 2010	(11) van den Broek 2011	(12) Smolen 2013
Flare rate	19.1%	54%	54%	63%	40%	20%	57.4% ; 20.9%
Study design	cohort	cohort	single-arm	single-arm	single-arm	single-arm	RCT
DMARD	TNF-blocker	TNF-blocker	TNF-blocker	TNF-blocker	TNF-blocker	TNF-blocker	TNF-blocker
	moderate	moderate	moderate	moderate	good	good	good
1	unclear	Yes	Yes	Yes	Yes	Partially	partly
2	yes	Yes	Yes	Yes	Yes	Yes	yes
3	yes	Yes	Yes	Yes	Partially	Yes	yes
4	yes	Yes	Yes	Yes	Yes	Yes	yes
5	unclear	Partially	Yes	Yes	Yes	Yes	yes
6	yes	Yes	Yes	Yes	Yes	Yes	yes
7	xxxxxxxxxxxx	xxxxxxxxxxxx	xxxxxxxxxxxx	xxxxxxxxxxxx	xxxxxxxxxxxx	xxxxxxxxxxxx	xxxxxxxxxxxx
8	yes	No	Yes	Yes	Yes	Yes	yes
9	yes	Unclear*	Unclear*	Unclear*	Partially	Unclear*	no
10	xxxxxxxxxxxx	xxxxxxxxxxxx	xxxxxxxxxxxx	xxxxxxxxxxxx	xxxxxxxxxxxx	xxxxxxxxxxxx	xxxxxxxxxxxx
11	unclear	Yes	Yes	Partially	Unclear	Yes	unclear
12	unclear	unclear	unclear	unclear	Unclear	unclear	unclear
13	unclear	Yes	Yes	Yes	Yes	Yes	yes
14	no	NA	NA	NA	NA	NA	yes
15	no	Unclear	Unclear	Unclear	Partially	Unclear	yes
16	xxxxxxxxxxxx	xxxxxxxxxxxx	xxxxxxxxxxxx	xxxxxxxxxxxx	xxxxxxxxxxxx	xxxxxxxxxxxx	xxxxxxxxxxxx
17a	NA	NA	NA	NA	NA	NA	yes
17b	yes	Yes	Yes	Yes	Yes	Yes	yes
17c	NA	NA	NA	Yes	Yes	Yes	yes
18	yes	Yes	Yes	Yes	Yes	Yes	yes
19	unclear	Unclear	Unclear	Unclear	Unclear	Unclear	yes
20	yes	Yes	Yes	Yes	Yes	Yes	yes
21	NA	Yes	NA	NA	NA	NA	yes
22	NA	Yes	NA	NA	NA	NA	yes
23	NA	No	NA	NA	NA	NA	yes
24	NA	NA	NA	NA	NA	NA	yes
25	xxxxxxxxxxxx	xxxxxxxxxxxx	xxxxxxxxxxxx	xxxxxxxxxxxx	xxxxxxxxxxxx	xxxxxxxxxxxx	xxxxxxxxxxxx
26	yes	Unclear*	Unclear*	Unclear*	Unclear	Unclear*	unclear
27	no	no	no	no	yes	yes	yes

TNF inhibitors 2/2

	(13) Smolen 2014	(14) Kavanaugh 2014	(15) Raffener 2014
Flare rate	19%	26.60%	11%
Study design	RCT	observational	RCT
DMARD	TNF-blocker	TNF-blocker	TNF-blocker
	good	good	good
1	Yes	Yes	Yes
2	Yes	Yes	Yes
3	Yes	Yes	Yes
4	Yes	Yes	Yes
5	Yes	Yes	Yes
6	Yes	Yes	Yes
7	xxxxxxxxxxxx	xxxxxxxxxxxx	xxxxxxxxxxxx
8	Yes	No	Yes
9	no	No	No
10	xxxxxxxxxxxx	xxxxxxxxxxxx	xxxxxxxxxxxx
11	yes	yes	Yes
12	unclear	yes	unclear
13	Yes	yes	Yes
14	Yes	Not Applicable	Yes
15	Yes	No	unclear
16	xxxxxxxxxxxx	xxxxxxxxxxxx	xxxxxxxxxxxx
17a	Yes	Yes	Yes
17b	Yes	Yes	Yes
17c	Yes	Not Applicable	Yes
18	Yes	Yes	Yes
19	Unclear	No	unclear
20	Yes	Yes	Yes
21	Yes	Not Applicable	Yes
22	Yes	Not Applicable	Yes
23	Yes	Not Applicable	Yes
24	Yes	Not Applicable	unclear
25	xxxxxxxxxxxx	xxxxxxxxxxxx	xxxxxxxxxxxx
26	Yes	No	unclear
27	Yes	yes	Yes

(16) Tanaka 2015	(17) Iwamoto 2014	(18) Emery 2014	(19) Marks 2015
40%	38%	21%; 46%; 64%	63%
cohort	cohort	RCT	cohort
TNF-blocker	TNF-blocker	TNF-blocker	TNF-blocker
no pooling	no pooling	no pooling	no pooling
Yes	Yes	Yes	Yes
Yes	Yes	Yes	Yes
Yes	Yes	Yes	Partially
Yes	Yes	Yes	Yes
Yes	Partially	Yes	Yes
Yes	Yes	Yes	Yes
xxxxxxxxxxxx	xxxxxxxxxxxx	xxxxxxxxxxxx	xxxxxxxxxxxx
Yes	yes	Yes	yes
unclear	no	unclear	no
xxxxxxxxxxxx	xxxxxxxxxxxx	xxxxxxxxxxxx	xxxxxxxxxxxx
Yes	unclear	Yes	yes
Yes	unclear	Yes	no
Yes	yes	Yes	yes
No	no	Yes	no
No	Partially	Yes	unclear
xxxxxxxxxxxx	xxxxxxxxxxxx	xxxxxxxxxxxx	xxxxxxxxxxxx
Yes	NA	Yes	unclear
Yes	Yes	Yes	yes
Yes	NA	no	NA
Yes	Yes	Yes	unclear
unclear	unclear	unclear	unclear
Yes	Yes	Yes	Yes
Yes	NA	Yes	Yes
Yes	NA	Yes	Yes
No	NA	Yes	NA
NA	NA	Yes	NA
xxxxxxxxxxxx	xxxxxxxxxxxx	xxxxxxxxxxxx	xxxxxxxxxxxx
Yes	unclear	Yes	no
no	No	Yes	no

Tocilizumab

	(20) Aguilar 2013	(21) Nishimoto 2014	(22) van Herwaarden 2014
Flare rate	55%	86.6%	41%
Study design	cohort	single-arm	cohort
DMARD	tocilizumab	tocilizumab	tocilizumab
1	yes	yes	yes
2	yes	yes	yes
3	partially	yes	yes
4	yes	yes	yes
5	partly	yes	yes
6	yes	yes	yes
7	xxxxxxxxxxxx	xxxxxxxxxxxx	xxxxxxxxxxxx
8	yes	yes	yes
9	no	yes	unclear
10	xxxxxxxxxxxx	xxxxxxxxxxxx	xxxxxxxxxxxx
11	yes	yes	yes
12	unclear	unclear	unclear
13	unclear	unclear	yes
14	no	no	NA
15	no	no	no
16	xxxxxxxxxxxx	xxxxxxxxxxxx	xxxxxxxxxxxx
17a	NA	NA	yes
17b	yes	yes	yes
17c	NA	NA	NA
18	yes	yes	yes
19	yes	unclear	yes
20	yes	yes	yes
21	NA	NA	NA
22	NA	NA	NA
23	NA	NA	NA
24	NA	NA	NA
25	xxxxxxxxxxxx	xxxxxxxxxxxx	xxxxxxxxxxxx
26	unclear	yes	unclear
27	no	yes	no

Abatacept

	(23) Emery 2015	(24) Westhovens 2014	(25) Takeuchi 2014
Flare rate	75%; 72%; 83%	34%	41%
Study design	single-arm	RCT	cohort
DMARD	abatacept	abatacept	abatacept
Yes	yes	yes	yes
Yes	yes	yes	yes
Yes	yes	yes	yes
Yes	yes	yes	yes
Partially	yes	yes	yes
Yes	yes	yes	yes
xxxxxxxxxxxx	xxxxxxxxxxxx	xxxxxxxxxxxx	xxxxxxxxxxxx
Partially	yes	yes	yes
no	no	no	no
xxxxxxxxxxxx	xxxxxxxxxxxx	xxxxxxxxxxxx	xxxxxxxxxxxx
yes	yes	yes	yes
unclear	yes	no	no
yes	yes	yes	yes
no	yes	no	no
unclear	yes	unclear	unclear
xxxxxxxxxxxx	xxxxxxxxxxxx	xxxxxxxxxxxx	xxxxxxxxxxxx
Yes	Yes	yes	yes
Yes	Yes	yes	yes
no	NA	yes	yes
Yes	Yes	yes	yes
unclear	Yes	yes	yes
Yes	yes	yes	yes
Yes	yes	yes	yes
Yes	yes	yes	yes
no	yes	no	no
NA	yes	NA	NA
xxxxxxxxxxxx	xxxxxxxxxxxx	xxxxxxxxxxxx	xxxxxxxxxxxx
unclear	yes	yes	yes
no	no	no	no

SUPPLEMENTARY DATA 4

Reported flare rates among studies de-escalating TNF-blockers. Pooled estimates were calculated for studies discontinuing and tapering TNF-blockers.

Study (arm), year	Medication	Charac- teristics	Follow-up	n	Flare rate (95% CI)
<i>Stop</i>					
Smolen (stop), 2013 (12)	etn	s, a	1 year	200	0.57 (0.50-0.64)
Tanaka, 2010 (10)	ifx	s, a	1 year	114	0.45 (0.36-0.54)
van den Broek, 2011 (11)	ifx	s, a, e	1 year	104	0.20 (0.13-0.29)
Maneiro, 2013 (6)	ada, ctz, etn, ifx	s, p	1 year	52	0.19 (0.11-0.32)
Brocq, 2009 (9)	ifx, etn, ada	s, a	1 year	21	0.75 (0.53-0.89)
Harigai, 2012 (7)	ada	s, a	1 year	22	0.55 (0.34-0.74)
Smolen, 2014 (13)	ada	s, a, e	1 year	102	0.19 (0.12-0.27)
Kavanaugh, 2014 (14)	TNFi	s, p	1 year	717	0.27 (0.24-0.30)
Tanaka, 2015 (16)	ada	s, a	24 weeks	52	0.40 (0.28-0.54)
Iwamoto, 2014 (17)	TNFi	s, p	6 months	32	0.38 (0.23-0.55)
Emery (etn stop), 2014 (18)	etn	s, a, e	39 weeks	65	0.46 (0.35-0.58)
Emery (etn + MTX stop), 2014 (18)	etn	s, a, e	39 weeks	65	0.62 (0.49-0.73)
Pooled estimate				1546	0.38 (0.29-0.48)
<i>Tapering</i>					
Smolen (half dose), 2013 (12)	etn	r ¹ , a	1 year	202	0.19 (0.14-0.25)
van der Maas, 2012 (8)	ifx	r ² , p	1 year	51	0.55 (0.41-0.68)
Heimans, 2013 (4)	ada	r ³ , a	4 months	26	0.35 (0.19-0.55)
Raffeiner, 2014 (15)	etn	r ⁴ , p	1 year	159	0.11 (0.07-0.17)
Emery (etn half dose), 2014 (18)	etn	r ¹ , a, e	39 weeks	63	0.21 (0.12-0.32)
Marks, 2015 (19)	TNFi	r ⁵ , p	9 months	69	0.62 (0.50-0.73)
Pooled estimate				570	0.31 (0.16-0.51)

a = co-medication with sDMARDs in all patients

e = early RA

pegol

p = co-medication with sDMARDs in selected patients

r¹ = dose reduction: etn 50 mg/week, dose reduced to etn 25 mg/week

r² = dose reduction: ifx 3 mg/kg, tapered down 0.75 mg/kg every 8-12 weeks

r³ = dose reduction: ada 40 mg/2 weeks, tapered down to MTX monotherapy
disease modifying anti-rheumatic drugs

r⁴ = dose reduction: etn 2x 25mg/week, dose reduced to etn 25mg/week
inhibitor

r⁵ = dose reduction with 1/3 (by increasing interval *1.5)

s = stop

ada = adalimumab

ctz = certolizumab

etn = etanercept

ifx = infliximab

MTX = methotrexate

sDMARDs = synthetic

TNFi = tumor necrosis factor

SUPPLEMENTARY DATA 5

Risk factors for flare addressed in primary studies

Several studies looked at risk factors for flare. Six studies evaluated the effect of using concomitant sDMARD on flare risk after stopping the TNF blocker, but found no significant association^{8, 9, 14, 17, 19, 22}. Of 3 studies^{9, 14, 17}, 1 found a lower risk of disease flare for a longer duration of remission⁹. Of 12 studies evaluating the effect of disease duration^{5, 8-11, 14, 16, 17, 19, 21, 22}, 4 found a significant association between a longer disease duration and an increased risk of flare^{10, 11, 16, 23} and 8 found no association^{5, 8, 9, 14, 17, 21, 22, 25}. Eleven studies assessed the effect of disease activity score on flare rate^{8-11, 14, 16, 17, 21-23, 25}, 5 of which found a significant association for a higher disease activity score at moment of de-escalation^{14, 16, 21, 23, 25}. Other factors that could influence flare rates that were not addressed in the primary studies are taper or stop criterion (e.g., remission or LDA), followup time, and monitoring frequency of disease activity.

SUPPLEMENTARY REFERENCES

1. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health* 1998;52:377-84.
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