The impact of autoantibodies on the efficacy of biological disease-modifying antirheumatic drugs in rheumatoid arthritis: meta-analysis of randomized controlled trials

Supplementary material

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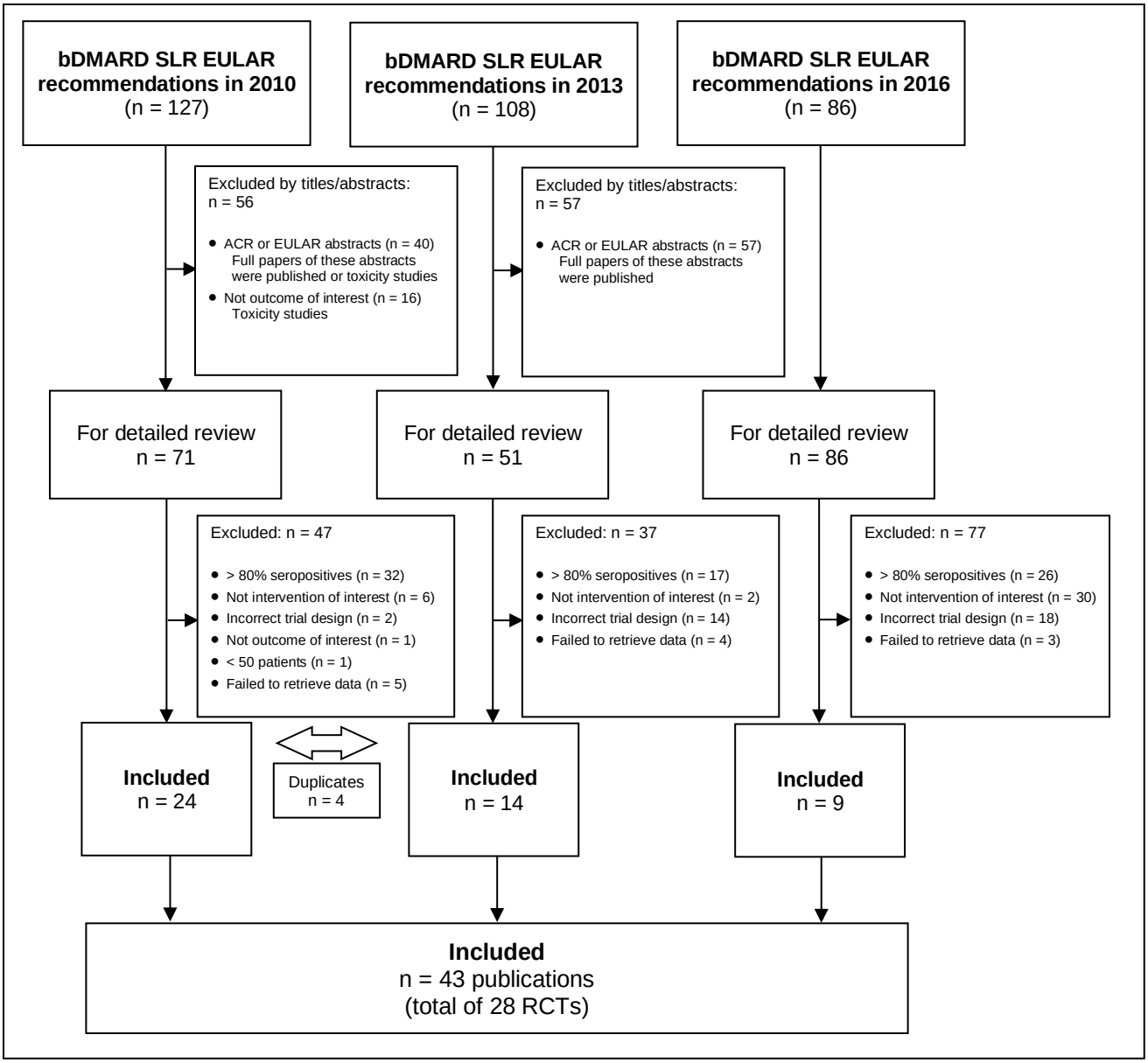
1.0 Flow chart of the trial selection



Online Supplementary Figure S1. Flow chart of the trial selection

The search was performed using previous systematic literature reviews addressing the efficacy of biological disease-modifying anti-rheumatic drugs (bDMARDs) conducted to inform the task force responsible for the EULAR recommendations for the management of RA published in 2010 (Nam JL, et al. Ann Rheum Dis. 2010;69:976-86), updated in 2013 (Nam JL, et al. Ann Rheum Dis. 2014;73:516-28) and 2016 (Nam JL, et al. Ann Rheum Dis. 2017;76:1113-1136).

RCT, randomized controlled trial.

2.0 Tables of Randomized Controlled Trials of Biological DMARDs included in the systematic literature review

2.1 RCTs of bDMARDs+csDMARDs vs csDMARD

Online Supplementary Table S1.1: MTX-naïve or csDMARD-naïve: Autoantibody status of RCTs

Author	Trial name	Interventions	No. of patients	ACPA-status known (n, %)	ACPA-positive (n, %)	Cut-off of ACPA-test	RF-status known (n)	RF-positive (n, %)	Cut-off of RF-test
Emery 2008 [1]	COMET	MTX	263	172 (65.4%)	117 (68.0%)	20 units	NR	NR	NR
		ETN (50mg/week sc) + MTX	265	205 (77.4%)	136 (66.3%)	20 units	NR	NR	NR
Nam 2014 [2]	EMPIRE	MTX	55	52 (94.5%)	42 (80.8%)	10 U/ml	54 (98.2%)	30 (55.6%)	20 IU/ml
		ETN (50mg/week sc) + MTX	55	54 (98.2%)	39 (72.2%)	10 U/ml	55 (100%)	31 (56.4%)	20 IU/ml
Detert 2013 [3]	HIT-HARD	MTX	85	84 (98.8%)	44 (52.4%)	20 units	84 (98.8%)	58 (69.0%)	20 units
		ADA (40mg/2weeks sc) + MTX	87	84 (96.6%)	46 (54.8%)	20 units	84 (96.6%)	57 (67.9%)	20 units
Nam 2014 [4]	IDEA	IV MP (250mg) + MTX	57	52 (91.2%)	39 (75.0%)	10 U/ml	56 (98.2%)	34 (60.7%)	39 IU/ml
		IFX (3mg/kg) + MTX	55	50 (90.9%)	32 (64.0%)	10 U/ml	55 (100%)	27 (49.1%)	39 IU/ml
Leirisalo-Repo 2013 [5]	NEORACo	DMARDs	45	45 (100%)	34 (75.6%)	10 U/ml	45 (100%)	33 (73.3%)	NR[2]
		IFX (3mg/kg) + DMARDs[1]	46	46 (100%)	35 (76.1%)	10 U/ml	46 (100%)	36 (78.3%)	NR[2]
Vollenhoven 2009 [6, 7]	Swefot	DMARDs[1]	130	126 (96.6%)	71 (56.3%)	NR	129 (99.2%)	84 (65.1%)	NR
		IFX (3mg/kg) + MTX	128	116 (90.6%)	80 (69.0%)	NR	127 (99.2%)	88 (69.3%)	NR

MTX, methotrexate; DMARDs, disease-modifying antirheumatic drugs; ETN, etanercept; ADA, adalimumab; IFX, infliximab; sc, subcutaneous; IV, intravenous; MP, methylprednisolone; NR, not recorded

[1]The triple combination of methotrexate (MTX), sulfasalazine (SSZ) and hydroxychloroquine (HCQ)

[2]The RF samples were analyzed locally in the laboratory of the 13 hospitals participating in the study, i.e. the methods varied between the 13 hospitals

Online Supplementary Table S1.2: MTX-naïve or csDMARD-naïve: Baseline characteristics of RCTs

Trial name	Interventions	Autoantibody-subgroups	No. of patients	Mean age (years)	Female (n, %)	Baseline DAS28-ESR (mean, SD)	Baseline DAS28-CRP (mean, SD)	Baseline HAQ-DI (mean, SD)	Baseline SvdH (mean, SD)
COMET [1]	MTX	ACPA-negative	55	55.8 (12.9)	38 (69.1%)	6.4 (0.8)	5.9 (0.8)	1.6 (0.6)	4.5 (5.8)
		ACPA-positive	117	51.6 (12.9)	85 (72.6%)	6.5 (1.0)	6.0 (1.0)	1.7 (0.6)	13.1 (24.2)
	ETN (50mg/week sc) + MTX	ACPA-negative	69	53.1 (15.6)	47 (68.1%)	6.5 (0.9)	6.0 (1.0)	1.7 (0.7)	5.2 (7.2)
		ACPA-positive	136	49.1 (13.9)	105 (77.2%)	6.4 (1.0)	5.9 (1.1)	1.7 (0.7)	7.1 (12.4)
EMPIRE [2]	MTX	ACPA-negative	10	41.4 (13.1)	9 (90%)	28.3 (30.8)	12.4 (21.3)	1.14 (0.34)	7.3 (4.2)
		ACPA-positive	42	50.1 (12.3)	28 (66.7%)	35.3 (26.5)	16.8 (26.7)	0.98 (0.42)	8.5 (8.9)
	MTX	RF-negative	24	44.2 (12.2)	17 (70.8%)	29.0 (26.8)	14.4 (21.9)	0.96 (0,43)	6.3 (5.3)
		RF-positive	30	52.2 (13.3)	22 (73.3%)	39.0 (28.1)	16.6 (27.8)	1.01 (0.42)	10.0 (9.5)
	MTX	ACPA-negative RF-negative	9	39.9 (12.9)	8 (88.9%)	25.8 (31.5)	12.0 (22.6)	1.16 (0.35)	6.6 (3.9)
		ACPA-negative RF-positive	1	55	1 (100%)	51	16	0.97	12.5
		ACPA-positive RF-negative	14	47.9 (11.1)	8 (57.1%)	32.4 (24.9)	16.8 (22.66)	0.91 (0.39)	6.2 (6.3)
		ACPA-positive RF-positive	28	51.3 (12.9)	20 (71.4%)	36.8 (27.7)	16.8 (28.9)	1.01 (0.43)	9.8 (9.9)
	ETN (50mg/week sc) + MTX	ACPA-negative	15	49.2 (13.2)	13 (86.7%)	19.3 (13.5)	5.0 (8.8)	1.03 (0.36)	6.1 (4.4)
		ACPA-positive	39	47.7 (13.9)	39 (100%)	38.3 (30.8)	18.4 (23.6)	0.98 (0.51)	6.7 (5.2)
	ETN (50mg/week sc) + MTX	RF-negative	24	48.9 (13.2)	18 (75%)	25.8 (22.9)	9.6 (14.8)	1.01 (0.35)	7.2 (5.3)
		RF-positive	31	47.1 (14.0)	31 (100%)	37.4 (30.5)	18.5 (24.6)	1.00 (0.56)	6.3 (4.9)
	ETN (50mg/week sc) + MTX	ACPA-negative RF-negative	11	50.4 (13.2)	2 (18.2%)	17.8 (11.4)	4.1 (6.2)	0.99 (0.31)	5.6 (5.0)
		ACPA-negative RF-positive	4	46.0 (14.8)	4 (100%)	23.5 (19.7)	7.5 (15.0)	1.15 (0.51)	7.3 (3.2)

		ACPA-positive RF-negative	12	48.5 (13.9)	8 (66.7%)	35.1 (30.1)	14.6 (19.2)	0.98 (0.36)	7.7 (5.5)
		ACPA-positive RF-positive	27	47.3 (14.2)	22 (81.5%)	39.6 (31.6)	20.1 (25.5)	0.98 (0.58)	6.1 (5.2)
HIT-HARD [3]	MTX	ACPA-negative	40	57.5 (13.2)	26 (65%)	6.1 (0.8)	NR	1.2 (0.7)	14.7 (20.8)
		ACPA-positive	44	48.6 (13.7)	30 (68.2%)	6.3 (1.0)	NR	1.4 (0.7)	9.9 (9.9)
	MTX	RF-negative	26	56.1 (13.7)	16 (61.5%)	6.2 (0.7)	NR	1.2 (0.7)	10.3 (10.1)
		RF-positive	58	51.4 (14.2)	40 (69%)	6.2 (1.0)	NR	1.3 (0.7)	12.2 (16.3)
	MTX	ACPA-negative RF-negative	25	56.1 (14.0)	15 (60%)	6.2 (0.7)	NR	1.2 (0.7)	10.3 (10.5)
		ACPA-negative RF-positive	15	59.9 (12.0)	11 (73.3%)	5.9 (0.9)	NR	1.2 (0.6)	22.7 (32.3)
		ACPA-positive RF-negative	1	57	1 (100%)	NR	NR	1	11
		ACPA-positive RF-positive	43	48.4 (13.8)	29 (67.4%)	6.3 (1.0)	NR	1.4 (0.7)	9.9 (10.1)
	ADA (40mg/2weeks sc) + MTX	ACPA-negative	38	51.0 (11.9)	27 (71.1%)	6.4 (1.0)	NR	1.4 (0.7)	6.9 (5.4)
		ACPA-positive	46	43.6 (11.6)	32 (69.6%)	6.1 (1.0)	NR	1.4 (0.7)	5.8 (4.8)
	ADA (40mg/2weeks sc) + MTX	RF-negative	27	51.9 (12.3)	20 (74.1%)	6.4 (0.9)	NR	1.4 (0.7)	5.4 (4.2)
		RF-positive	57	44.6 (11.6)	39 (68.4%)	6.1 (1.0)	NR	1.4 (0.7)	6.9 (5.5)
	ADA (40mg/2weeks sc) + MTX	ACPA-negative RF-negative	24	52.7 (12.8)	17 (70.8%)	6.4 (1.0)	NR	1.4 (0.7)	5.2 (4.2)
		ACPA-negative RF-positive	14	48.1 (9.9)	10 (71.4%)	6.4 (1.1)	NR	1.4 (0.8)	9.5 (6.1)
		ACPA-positive RF-negative	3	45.3 (4.7)	3 (100%)	6.9 (0.5)	NR	1.8 (0.7)	9.0
		ACPA-positive RF-positive	43	43.5 (12.0)	29 (67.4%)	6.0 (1.0)	NR	1.3 (0.6)	5.7 (4.9)
IDEA [4]	IV MP (250mg) + MTX	ACPA-negative	13	56.5 (9.6)	11 (84.6%)	54.3 (31.5)	40.0 (65.6)	1.15 (0.53)	7.48 (12.70)
		ACPA-positive	39	52.9 (13.2)	28 (71.8%)	50.8 (41.0)	31.1 (37.8)	1.41 (0.50)	10.15 (19.29)
	IV MP (250mg) + MTX	RF-negative	22	52.5 (11.5)	15 (68.2%)	43.8 (29.3)	31.2 (56.4)	1.17 (0.44)	5.50 (6.49)
		RF-positive	34	52.8 (13.7)	25 (73.5%)	58.9 (42.8)	40.8 (52.3)	1.48 (0.51)	11.92 (21.25)

	IFX (3mg/kg) + MTX	ACPA-negative	18	57.9 (13.3)	15 (83.3%)	31.1 (27.0)	20.9 (38.4)	1.34 (0.47)	8.45 (15.39)
		ACPA-positive	32	51.2 (12.9)	17 (53.1%)	44.6 (24.3)	44.5 (41.0)	1.52 (0.57)	4.62 (4.61)
	IFX (3mg/kg) + MTX	RF-negative	28	54.2 (13.7)	20 (71.4%)	36.6 (25.6)	30.2 (39.1)	1.37 (0.45)	7.51 (12.68)
		RF-positive	27	53.1 (12.6)	16 (59.3%)	43.1 (25.5)	41.1 (42.4)	1.49 (0.60)	4.53 (4.24)
NEORACo [5]	DMARDs[1]	ACPA-negative	11	44 (13)	7 (63.6%)	6.5 (1.3)	6.3 (1.2)	1.3 (0.7)	0.2 (0.4)
		ACPA-positive	34	46 (10)	21 (61.8%)	5.1 (1.2)	5.0 (1.0)	0.7 (0.6)	2.7 (5.2)
	DMARDs[1]	RF-negative	12	46 (12)	6 (50%)	6.2 (1.3)	5.9 (1.3)	1.1 (0.7)	0.8 (1.8)
		RF-positive	33	46 (11)	22 (66.7%)	5.2 (1.3)	5.1 (1.1)	0.8 (0.7)	2.6 (5.3)
	DMARDs[1]	ACPA-negative RF-negative	6	45 (14)	3 (50%)	6.7 (1.4)	6.5 (1.3)	1.3 (0.7)	0.3 (0.5)
		ACPA-negative RF-positive	5	43 (14)	4 (80%)	6.3 (1.2)	6 (1.1)	1.3 (0.7)	0.0 (0.0)
		ACPA-positive RF-negative	6	46 (11)	3 (50%)	5.6 (1.1)	5.2 (1.2)	0.9 (0.5)	1.3 (2.4)
		ACPA-positive RF-positive	28	47 (10)	18 (64.3%)	5 (1.2)	4.9 (1.0)	0.7 (0.7)	3.0 (5.6)
	IFX (3mg/kg) + DMARDs[1]	ACPA-negative	11	47 (11)	9 (81.8%)	6.4 (0.8)	6.1 (0.8)	1.5 (0.7)	0.2 (0.4)
		ACPA-positive	35	47 (9)	24 (68.6%)	5.2 (0.9)	4.9 (0.9)	0.9 (0.5)	3.5 (9.1)
	IFX (3mg/kg) + DMARDs[1]	RF-negative	10	45 (11)	8 (80%)	5.9 (1.1)	5.8 (0.9)	1.3 (0.7)	0.8 (1.5)
		RF-positive	36	47 (10)	25 (69.4%)	5.4 (1)	5.0 (1.0)	1.0 (0.6)	3.3 (9.0)
	IFX (3mg/kg) + DMARDs[1]	ACPA-negative RF-negative	7	44 (13)	6 (85.7%)	6.4 (0.9)	6.0 (0.8)	1.4 (0.7)	0.1 (0.4)
		ACPA-negative RF-positive	4	54 (3)	3 (75%)	6.4 (0.9)	6.3 (0.7)	1.7 (0.7)	0.3 (0.5)
		ACPA-positive RF-negative	3	49 (6)	2 (66.7%)	4.8 (0.9)	5.3 (1.1)	1 (0.7)	2.3 (2.1)
		ACPA-positive RF-positive	32	46 (10)	22 (68.8%)	5.3 (0.9)	4.8 (0.9)	0.9 (0.5)	3.7 (9.5)
Swefot [6, 7]	DMARDs[1]	ACPA-negative	55	54.8 (13.7)	46 (83.6%)	4.9 (1.0)	4.6 (0.9)	1.1 (0.6)	4.6 (6.8)
		ACPA-positive	71	51.8 (14.1)	53 (74.6%)	4.8 (1.1)	4.4 (1.1)	0.9 (0.6)	6.3 (11)

	DMARDs[1]	RF-negative	45	55.0 (15.5)	37 (82.2%)	4.8 (1.0)	4.6 (1.1)	1.1 (0.6)	4.4 (6.6)
		RF-positive	84	52.7 (13.1)	63 (75%)	4.8 (1.1)	4.4 (1.0)	0.9 (0.6)	6.2 (10.7)
	DMARDs[1]	ACPA-negative RF-negative	29	57.2 (15.7)	24 (82.8%)	4.8 (0.9)	4.6 (0.9)	1.1 (0.5)	4.2 (5.3)
		ACPA-negative RF-positive	26	52.1 (10.6)	22 (84.6%)	5.0 (1.1)	4.5 (1.0)	1.1 (0.6)	5.2 (8.5)
		ACPA-positive RF-negative	15	50.3 (15.1)	13 (86.7%)	5.0 (1.3)	4.5 (1.4)	1.2 (0.7)	5.2 (8.9)
		ACPA-positive RF-positive	55	52.3 (14.1)	39 (70.9%)	4.7 (1.1)	4.3 (1.0)	0.9 (0.5)	6.8 (11.7)
	IFX (3mg/kg) + MTX	ACPA-negative	36	53.4 (15.7)	27 (75%)	5.1 (0.9)	4.7 (0.8)	1.0 (0.5)	4.0 (6.0)
		ACPA-positive	80	50.8 (12.4)	61 (76.3%)	4.8 (1.0)	4.5 (1.0)	0.9 (0.6)	5.1 (8.0)
	IFX (3mg/kg) + MTX	RF-negative	39	54.5 (14.4)	30 (76.9%)	5.0 (0.9)	4.6 (0.8)	0.9 (0.5)	5.9 (6.7)
		RF-positive	88	50.5 (12.7)	67 (76.1%)	4.9 (1.0)	4.6 (1.0)	1.0 (0.5)	4.0 (7.5)
	IFX (3mg/kg) + MTX	ACPA-negative RF-negative	21	57.1 (15.2)	15 (71.4%)	5.0 (0.9)	4.6 (0.7)	1.0 (0.6)	5.1 (7.1)
		ACPA-negative RF-positive	14	48.9 (15.7)	12 (85.7%)	5.0 (0.9)	4.7 (1.0)	0.9 (0.5)	2.5 (4.0)
		ACPA-positive RF-negative	16	49.6 (12.0)	14 (87.5%)	5.1 (1.0)	4.7 (1.0)	0.8 (0.6)	6.8 (5.8)
		ACPA-positive RF-positive	64	51.1 (12.6)	47 (73.4%)	4.8 (1.0)	4.5 (0.9)	1.0 (0.6)	4.7 (8.4)

SvdH, total Sharp-van der Heijde score; MTX, methotrexate; DMARDs, disease-modifying antirheumatic drugs; ETN, etanercept; ADA, adalimumab; IFX, infliximab; sc, subcutaneous; IV, intravenous; MP, methylprednisolone; NR, not recorded

[1]The triple combination of methotrexate (MTX), sulfasalazine (SSZ) and hydroxychloroquine (HCQ)

Online Supplementary Table S1.3: MTX-naïve or csDMARD-naïve: Risk of bias of RCTs

Trial name	Biological DMARD	ROB1: Random sequence generation	ROB2: Allocation concealment	ROB3: Blinding of participants and personnel	ROB4: Blinding of outcome assessment	ROB5: Incomplete outcome data	ROB6: Other bias	ROB7: Selective reporting
COMET [1]	ETN	L	L	L	L	L	L	L
EMPIRE [2]	ETN	L	L	L	L	L	L	L
HIT-HARD [3]	ADA	U	U	U	U	L	L	L
IDEA [4]	IFX	L	L	L	L	L	L	L
NEORACo [5]	IFX	L	L	L	U	L	L	L
Swefot [6, 7]	IFX	L	L	H	H	H	L	L

ETN, etanercept; ADA, adalimumab; IFX, infliximab

H = high risk; L = low risk; U = unclear risk

Online Supplementary Table S1.4: MTX-naïve or csDMARD-naïve: Disease activity outcomes of RCTs at 6 months

Trial name	Interventions	Autoantibody-subgroups	No. of patients	ACR20 (n, %)	ACR50 (n, %)	ACR70 (n, %)	DAS28-ESR (mean, SD)	ΔDAS28-ESR (mean, SD)	DAS28-ESR <2.6 (n, %)	DAS28-CRP (mean, SD)	ΔDAS28-CRP (mean, SD)	DAS28-CRP <2.6 (n, %)
COMET [1]	MTX	ACPA-negative	55	30 (54.5%)	19 (34.5%)	7 (12.7%)	3.5 (1.4)	-2.9 (1.6)	18 (32.7%)	3.3 (1.2)	-2.6 (1.5)	23 (41.8%)
		ACPA-positive	117	94 (80.3%)	58 (49.6%)	29 (24.8%)	3.7 (1.5)	-2.9 (1.4)	30 (25.6%)	3.4 (1.4)	-2.6 (1.3)	41 (35%)
	ETN (50mg/week sc) + MTX	ACPA-negative	69	51 (73.9%)	38 (55.1%)	22 (31.9%)	2.9 (1.5)	-3.6 (1.8)	33 (47.8%)	2.8 (1.1)	-3.1 (1.6)	37 (53.6%)
		ACPA-positive	136	132 (97.1%)	101 (74.3%)	66 (48.5%)	3 (1.2)	-3.5 (1.2)	55 (40.4%)	2.8 (1)	-3.2 (1.2)	69 (50.7%)
EMPIRE [2]	MTX	ACPA-negative	10	NR	NR	NR	3.9 (1.4)	-0.5 (1.9)	1 (10%)	3.4 (1.3)	-0.6 (1.9)	2 (20%)
		ACPA-positive	42	NR	NR	NR	3 (1.3)	-1.8 (1.4)	14 (33.3%)	2.5 (1.2)	-1.7 (1.4)	24 (57.1%)
	MTX	RF-negative	24	NR	NR	NR	3.2 (1.2)	-1.3 (1.6)	7 (29.2%)	2.6 (1.2)	-1.4 (1.6)	13 (54.2%)
		RF-positive	30	NR	NR	NR	3.3 (1.5)	-1.7 (1.6)	9 (30%)	2.8 (1.3)	-1.5 (1.5)	14 (46.7%)
	MTX	ACPA-negative RF-negative	9	NR	NR	NR	3.7 (1.4)	-0.6 (2)	1 (11.1%)	3.2 (1.2)	-0.7 (2)	2 (22.2%)
		ACPA-negative RF-positive	1	NR	NR	NR	5.7	0.4	0 (0%)	5	0.4	0 (0%)
		ACPA-positive RF-negative	14	NR	NR	NR	2.7 (1)	-1.8 (1.1)	6 (42.9%)	2.1 (1)	-2 (1.2)	11 (78.6%)
		ACPA-positive RF-positive	28	NR	NR	NR	3.2 (1.4)	-1.8 (1.6)	9 (32.1%)	2.7 (1.3)	-1.6 (1.5)	14 (50%)
	ETN (50mg/week sc) + MTX	ACPA-negative	15	NR	NR	NR	3.3 (1.1)	-1.3 (1.1)	4 (26.7%)	2.8 (1)	-1.1 (1.3)	6 (40%)
		ACPA-positive	39	NR	NR	NR	2.4 (1.2)	-2.2 (1.4)	28 (71.8%)	2 (1.1)	-2.2 (1.4)	32 (82.1%)
	ETN (50mg/week sc) + MTX	RF-negative	24	NR	NR	NR	2.9 (1.3)	-1.8 (1.4)	12 (50%)	2.4 (1.2)	-1.9 (1.6)	14 (58.3%)
		RF-positive	31	NR	NR	NR	2.5 (1.1)	-2.1 (1.3)	20 (64.5%)	2.1 (1.1)	-1.9 (1.3)	23 (74.2%)
	ETN (50mg/week sc) + MTX	ACPA-negative RF-negative	11	NR	NR	NR	3.2 (1.2)	-1.5 (1)	3 (27.3%)	2.6 (0.9)	-1.4 (1.1)	5 (45.5%)
		ACPA-negative RF-positive	4	NR	NR	NR	3.6 (0.9)	-0.8 (1.4)	1 (25%)	3.4 (1.2)	-0.2 (1.5)	1 (25%)
		ACPA-positive RF-negative	12	NR	NR	NR	2.6 (1.5)	-2.1 (1.7)	9 (75%)	2 (1.3)	-2.3 (1.9)	10 (83.3%)
		ACPA-positive RF-positive	27	NR	NR	NR	2.3 (1)	-2.3 (1.2)	19 (70.4%)	2 (1)	-2.1 (1.2)	22 (81.5%)
HIT-HARD [3]	MTX	ACPA-negative	40	23 (57.5%)	15 (37.5%)	9 (22.5%)	3.5 (1.7)	-2.6 (1.7)	13 (32.5%)	NR	NR	NR
		ACPA-positive	44	27 (61.4%)	22 (50%)	11 (25%)	3.4 (1.2)	-2.9 (1)	9 (20.5%)	NR	NR	NR
	MTX	RF-negative	26	13 (50%)	9 (34.6%)	4 (15.4%)	3.6 (1.7)	-2.7 (1.8)	7 (26.9%)	NR	NR	NR
		RF-positive	58	37 (63.8%)	28 (48.3%)	16 (27.6%)	3.4 (1.3)	-2.8 (1.3)	15 (25.9%)	NR	NR	NR

	MTX	ACPA-negative RF-negative	25	13 (52%)	9 (36%)	4 (16%)	3.6 (1.7)	-2.7 (1.8)	7 (28%)	NR	NR	NR
		ACPA-negative RF-positive	15	10 (66.7%)	6 (40%)	5 (33.3%)	3.3 (1.7)	-2.5 (1.7)	6 (40%)	NR	NR	NR
	MTX	ACPA-positive RF-negative	1	0 (0%)	0 (0%)	0 (0%)	3.9	NR	0 (0%)	NR	NR	NR
		ACPA-positive RF-positive	43	27 (62.8%)	22 (51.2%)	11 (25.6%)	3.4 (1.2)	-2.9 (1)	9 (20.9%)	NR	NR	NR
	ADA (40mg/2weeks sc) + MTX	ACPA-negative	38	23 (60.5%)	17 (44.7%)	13 (34.2%)	3.2 (1.3)	-3.1 (1.5)	15 (39.5%)	NR	NR	NR
		ACPA-positive	46	36 (78.3%)	32 (69.6%)	24 (52.2%)	2.8 (1.1)	-3.3 (1)	20 (43.5%)	NR	NR	NR
	ADA (40mg/2weeks sc) + MTX	RF-negative	27	15 (55.6%)	13 (48.1%)	12 (44.4%)	3.1 (1.4)	-3.3 (1.4)	12 (44.4%)	NR	NR	NR
		RF-positive	57	44 (77.2%)	36 (63.2%)	25 (43.9%)	3 (1.2)	-3.2 (1.1)	23 (40.4%)	NR	NR	NR
	ADA (40mg/2weeks sc) + MTX	ACPA-negative RF-negative	24	13 (54.2%)	11 (45.8%)	10 (41.7%)	3.1 (1.5)	-3.2 (1.4)	11 (45.8%)	NR	NR	NR
		ACPA-negative RF-positive	14	10 (71.4%)	6 (42.9%)	3 (21.4%)	3.5 (1.1)	-3 (1.6)	4 (28.6%)	NR	NR	NR
		ACPA-positive RF-negative	3	2 (66.7%)	2 (66.7%)	2 (66.7%)	2.9 (0.7)	-4.2 (0.3)	1 (33.3%)	NR	NR	NR
		ACPA-positive RF-positive	43	34 (79.1%)	30 (69.8%)	22 (51.2%)	2.8 (1.2)	-3.2 (1)	19 (44.2%)	NR	NR	NR
IDEA [4]	IV MP (250mg) + MTX	ACPA-negative	13	10 (76.9%)	7 (53.8%)	4 (30.8%)	3.4 (1.7)	-2.5 (1.2)	5 (38.5%)	2.6 (1.5)	-2.6 (1.3)	8 (61.5%)
		ACPA-positive	39	25 (64.1%)	17 (43.6%)	10 (25.6%)	3.6 (1.3)	-1.8 (1.4)	8 (20.5%)	2.9 (1.3)	-1.9 (1.3)	17 (43.6%)
	IV MP (250mg) + MTX	RF-negative	22	15 (68.2%)	10 (45.5%)	7 (31.8%)	3.2 (1.2)	-2.4 (1.4)	9 (40.9%)	2.4 (1.1)	-2.5 (1.5)	13 (59.1%)
		RF-positive	34	24 (70.6%)	17 (50%)	10 (29.4%)	3.9 (1.4)	-1.9 (1.5)	5 (14.7%)	3.1 (1.5)	-2 (1.4)	14 (41.2%)
	IFX (3mg/kg) + MTX	ACPA-negative	18	13 (72.2%)	10 (55.6%)	7 (38.9%)	3.4 (1.6)	-2.1 (2)	6 (33.3%)	2.6 (1.4)	-2.4 (1.7)	10 (55.6%)
		ACPA-positive	32	20 (62.5%)	15 (46.9%)	9 (28.1%)	3.3 (1.1)	-3 (1.5)	7 (21.9%)	2.7 (1.2)	-3.2 (1.6)	11 (34.4%)
	IFX (3mg/kg) + MTX	RF-negative	28	16 (57.1%)	12 (42.9%)	9 (32.1%)	3.5 (1.6)	-2.3 (2)	9 (32.1%)	2.9 (1.5)	-2.5 (1.8)	13 (46.4%)
		RF-positive	27	18 (66.7%)	14 (51.9%)	8 (29.6%)	3.3 (1.1)	-2.8 (1.5)	5 (18.5%)	2.8 (1.3)	-2.9 (1.7)	9 (33.3%)
NEORA Co [5]	DMARDs[1]	ACPA-negative	11	10 (90.9%)	10 (90.9%)	7 (63.6%)	2.5 (1)	-4.1 (1.5)	8 (72.7%)	2.4 (0.9)	-3.9 (1.5)	7 (63.6%)
		ACPA-positive	34	34 (100%)	33 (97.1%)	31 (91.2%)	1.3 (0.7)	-3.8 (1.2)	33 (97.1%)	1.7 (0.5)	-3.3 (1.1)	32 (94.1%)
	DMARDs[1]	RF-negative	12	12 (100%)	11 (91.7%)	9 (75%)	1.6 (0.8)	-4.6 (1.2)	12 (100%)	1.9 (0.6)	-4 (1.4)	10 (83.3%)
		RF-positive	33	32 (97%)	32 (97%)	29 (87.9%)	1.6 (1)	-3.6 (1.3)	29 (87.9%)	1.9 (0.7)	-3.2 (1.1)	29 (87.9%)
	DMARDs[1]	ACPA-negative RF-negative	6	6 (100%)	6 (100%)	4 (66.7%)	2 (0.5)	-4.8 (1.4)	6 (100%)	2 (0.7)	-4.5 (1.6)	5 (83.3%)
		ACPA-negative RF-positive	5	4 (80%)	4 (80%)	3 (60%)	3 (1.2)	-3.3 (1.3)	2 (40%)	2.9 (1)	-3.1 (1.2)	2 (40%)
		ACPA-positive RF-negative	6	6 (100%)	5 (83.3%)	5 (83.3%)	1.3 (0.9)	-4.4 (1.1)	6 (100%)	1.8 (0.5)	-3.4 (1)	5 (83.3%)
		ACPA-positive RF-positive	28	28 (100%)	28 (100%)	26 (92.9%)	1.4 (0.7)	-3.7 (1.3)	27 (96.4%)	1.7 (0.5)	-3.2 (1.1)	27 (96.4%)
	IFX (3mg/kg) + DMARDs[1]	ACPA-negative	11	11 (100%)	11 (100%)	11 (100%)	1.6 (0.7)	-4.8 (1)	10 (90.9%)	1.6 (0.4)	-4.5 (0.9)	11 (100%)
		ACPA-positive	35	35 (100%)	34 (97.1%)	33 (94.3%)	1.2 (0.7)	-4.1 (1.1)	33 (94.3%)	1.6 (0.5)	-3.3 (0.9)	33 (94.3%)
		RF-negative	10	10 (100%)	10 (100%)	10 (100%)	1.2 (0.5)	-4.7 (1.2)	10 (100%)	1.5 (0.3)	-4.3 (1)	10 (100%)

	IFX (3mg/kg) + DMARDs[1]	RF-positive	36	35 (97.2%)	35 (97.2%)	34 (94.4%)	1.3 (0.8)	-4.1 (1.1)	33 (91.7%)	1.6 (0.5)	-3.4 (1)	34 (94.4%)
	IFX (3mg/kg) + DMARDs[1]	ACPA-negative RF-negative	7	7 (100%)	7 (100%)	7 (100%)	1.4 (0.5)	-5 (1.2)	7 (100%)	1.6 (0.3)	-4.5 (1)	7 (100%)
		ACPA-negative RF-positive	4	4 (100%)	4 (100%)	4 (100%)	1.9 (1)	-4.6 (0.6)	3 (75%)	1.8 (0.7)	-4.6 (0.7)	4 (100%)
		ACPA-positive RF-negative	3	3 (100%)	3 (100%)	3 (100%)	0.7 (0.2)	-4.1 (0.9)	3 (100%)	1.4 (0.2)	-3.9 (1.2)	3 (100%)
		ACPA-positive RF-positive	32	31 (96.9%)	31 (96.9%)	30 (93.8%)	1.2 (0.7)	-4 (1.1)	30 (93.8%)	1.6 (0.5)	-3.2 (0.9)	30 (93.8%)
Swefot [6, 7]	DMARDs[1]	ACPA-negative	55	NR	NR	NR	3.6 (1.3)	-1.3 (0.9)	9 (16.4%)	3.6 (1.1)	-1 (0.8)	7 (12.7%)
		ACPA-positive	71	NR	NR	NR	3.5 (1.4)	-1.3 (1.3)	19 (26.8%)	3.4 (1.3)	-1.1 (1.1)	19 (26.8%)
	DMARDs[1]	RF-negative	45	NR	NR	NR	3.5 (1.3)	-1.3 (0.8)	7 (15.6%)	3.5 (1.2)	-1.1 (0.8)	7 (15.6%)
		RF-positive	84	NR	NR	NR	3.6 (1.4)	-1.3 (1.3)	22 (26.2%)	3.4 (1.2)	-1.1 (1.1)	20 (23.8%)
	DMARDs[1]	ACPA-negative RF-negative	29	NR	NR	NR	3.5 (1.1)	-1.2 (0.8)	3 (10.3%)	3.5 (1)	-1 (0.7)	3 (10.3%)
		ACPA-negative RF-positive	26	NR	NR	NR	3.8 (1.5)	-1.3 (1.1)	6 (23.1%)	3.7 (1.2)	-0.9 (1)	4 (15.4%)
		ACPA-positive RF-negative	15	NR	NR	NR	3.6 (1.7)	-1.4 (1)	4 (26.7%)	3.4 (1.5)	-1.2 (0.9)	4 (26.7%)
		ACPA-positive RF-positive	55	NR	NR	NR	3.5 (1.4)	-1.3 (1.4)	15 (27.3%)	3.3 (1.2)	-1.1 (1.2)	15 (27.3%)
	IFX (3mg/kg) + MTX	ACPA-negative	36	NR	NR	NR	3.5 (1.3)	-1.6 (1.3)	10 (27.8%)	3.4 (1.1)	-1.4 (1.2)	11 (30.6%)
		ACPA-positive	80	NR	NR	NR	3.3 (1.5)	-1.5 (1.2)	27 (33.8%)	3.2 (1.2)	-1.4 (1)	26 (32.5%)
	IFX (3mg/kg) + MTX	RF-negative	39	NR	NR	NR	3.4 (1.4)	-1.6 (1.1)	13 (33.3%)	3.2 (1.2)	-1.4 (1)	13 (33.3%)
		RF-positive	88	NR	NR	NR	3.4 (1.5)	-1.5 (1.2)	28 (31.8%)	3.3 (1.2)	-1.3 (1.1)	28 (31.8%)
	IFX (3mg/kg) + MTX	ACPA-negative RF-negative	21	NR	NR	NR	3.4 (1.4)	-1.7 (1.3)	8 (38.1%)	3.3 (1.2)	-1.3 (1.1)	7 (33.3%)
		ACPA-negative RF-positive	14	NR	NR	NR	3.7 (1.1)	-1.3 (1.2)	2 (14.3%)	3.5 (1.1)	-1.2 (1.3)	4 (28.6%)
		ACPA-positive RF-negative	16	NR	NR	NR	3.6 (1.5)	-1.6 (0.9)	4 (25%)	3.1 (1.4)	-1.5 (0.8)	5 (31.3%)
		ACPA-positive RF-positive	64	NR	NR	NR	3.3 (1.5)	-1.5 (1.2)	23 (35.9%)	3.2 (1.2)	-1.3 (1)	21 (32.8%)

MTX, methotrexate; DMARDs, disease-modifying antirheumatic drugs; ADA, adalimumab; IFX, infliximab; sc, subcutaneous; IV, intravenous; MP, methylprednisolone; NR, not recorded

[1]The triple combination of methotrexate (MTX), sulfasalazine (SSZ) and hydroxychloroquine (HCQ)

**DAS28-ESR and DAS28-CRP were assessed 6, 12 and 24 months after randomization (9, 15 and 27 months from baseline and MTX start)*

Online Supplementary Table S1.5: MTX-naïve or csDMARD-naïve: Physical function and Radiographic progression of RCTs at 6 months

Author	Interventions	Autoantibody-subgroups	No. of patients	HAQ-DI (mean, SD)	ΔHAQ-DI (mean, SD)	HAQ-DI response ≥0.22 (n, %)	SvdH (mean, SD)	ΔSvdH (mean, SD)	ΔSvdH ≤0 (n, %)	ΔSvdH ≤0.5 (n, %)
Emery 2008 [1]	MTX	ACPA-negative	55	0.9 (0.7)	-0.7 (0.6)	39 (70.9%)	NR	NR	NR	NR
		ACPA-positive	117	0.9 (0.7)	-0.8 (0.6)	92 (78.6%)	NR	NR	NR	NR
	ETN (50mg/week sc) + MTX	ACPA-negative	69	0.8 (0.7)	-0.9 (0.8)	54 (78.3%)	NR	NR	NR	NR
		ACPA-positive	136	0.6 (0.6)	-1.1 (0.6)	121 (89%)	NR	NR	NR	NR
EMPIRE [2]	MTX	ACPA-negative	10	1 (0.5)	-0.1 (0.6)	4 (40%)	NR	NR	NR	NR
		ACPA-positive	42	0.7 (0.5)	-0.3 (0.5)	24 (57.1%)	NR	NR	NR	NR
	MTX	RF-negative	24	0.7 (0.5)	-0.3 (0.6)	12 (50%)	NR	NR	NR	NR
		RF-positive	30	0.8 (0.5)	-0.2 (0.4)	15 (50%)	NR	NR	NR	NR
	MTX	ACPA-negative RF-negative	9	1 (0.5)	-0.1 (0.6)	4 (44.4%)	NR	NR	NR	NR
		ACPA-negative RF-positive	1	1.1	0.1	0 (0%)	NR	NR	NR	NR
		ACPA-positive RF-negative	14	0.5 (0.4)	-0.4 (0,48)	9 (64.3%)	NR	NR	NR	NR
		ACPA-positive RF-positive	28	0.8 (0.6)	-0.2 (0.5)	15 (53.6%)	NR	NR	NR	NR
	ETN (50mg/week sc) + MTX	ACPA-negative	15	0.9 (0.5)	-0.1 (0.4)	7 (46.7%)	NR	NR	NR	NR
		ACPA-positive	39	0.4 (0.6)	-0.5 (0.5)	29 (74.4%)	NR	NR	NR	NR
	ETN (50mg/week sc) + MTX	RF-negative	24	0.7 (0.6)	-0.3 (0.5)	15 (62.5%)	NR	NR	NR	NR
		RF-positive	31	0.5 (0.6)	-0.5 (0.4)	22 (71%)	NR	NR	NR	NR
	ETN (50mg/week sc) + MTX	ACPA-negative RF-negative	11	0.9 (0.5)	-0.1 (0.4)	5 (45.5%)	NR	NR	NR	NR
		ACPA-negative RF-positive	4	0.8 (0.5)	-0.3 (0.4)	2 (50%)	NR	NR	NR	NR
		ACPA-positive RF-negative	12	0.4 (0.5)	-0.6 (0.4)	9 (75%)	NR	NR	NR	NR
		ACPA-positive RF-positive	27	0.4 (0.6)	-0.5 (0.4)	20 (74.1%)	NR	NR	NR	NR
HIT-HARD [3]	MTX	ACPA-negative	40	0.7 (0.6)	-0.4 (0.6)	22 (55%)	NR	NR	NR	NR
		ACPA-positive	44	0.7 (0.6)	-0.7 (0.6)	27 (61.4%)	NR	NR	NR	NR
	MTX	RF-negative	26	0.8 (0.6)	-0.4 (0.7)	13 (50%)	NR	NR	NR	NR
		RF-positive	58	0.7 (0.6)	-0.7 (0.6)	36 (62.1%)	NR	NR	NR	NR
	MTX	ACPA-negative RF-negative	25	0.8 (0.6)	-0.4 (0.7)	12 (48%)	NR	NR	NR	NR
		ACPA-negative RF-positive	15	0.6 (0.5)	-0.6 (0.6)	10 (66.7%)	NR	NR	NR	NR
	MTX	ACPA-positive RF-negative	1	0.1	-0.9	0 (0%)	NR	NR	NR	NR
		ACPA-positive RF-positive	43	0.7 (0.6)	-0.7 (0.6)	26 (60.5%)	NR	NR	NR	NR
		ACPA-negative	38	0.7 (0.7)	-0.7 (0.7)	24 (63.2%)	NR	NR	NR	NR

	ADA (40mg/2weeks sc) + MTX	ACPA-positive	46	0.3 (0.3)	-1.1 (0.6)	39 (84.8%)	NR	NR	NR	NR
	ADA (40mg/2weeks sc) + MTX	RF-negative	27	0.6 (0.6)	-0.8 (0.8)	17 (63%)	NR	NR	NR	NR
		RF-positive	57	0.4 (0.5)	-0.9 (0.6)	46 (80.7%)	NR	NR	NR	NR
	ADA (40mg/2weeks sc) + MTX	ACPA-negative RF-negative	24	0.6 (0.6)	-0.8 (0.7)	15 (62.5%)	NR	NR	NR	NR
		ACPA-negative RF-positive	14	0.9 (0.7)	-0.5 (0.5)	9 (64.3%)	NR	NR	NR	NR
		ACPA-positive RF-negative	3	0.2 (0.2)	-1.6 (1.1)	2 (66.7%)	NR	NR	NR	NR
		ACPA-positive RF-positive	43	0.3 (0.4)	-1.1 (0.6)	37 (86%)	NR	NR	NR	NR
IDEA [4]	IV MP (250mg) + MTX	ACPA-negative	13	0.7 (0.5)	-0.5 (0.4)	8 (61.5%)	10.9 (20.2)	3.4 (7.9)	6 (46.2%)	8 (61.5%)
		ACPA-positive	39	0.8 (0.6)	-0.6 (0.4)	33 (84.6%)	11.7 (19.9)	1.5 (2.7)	17 (43.6%)	20 (51.3%)
	IV MP (250mg) + MTX	RF-negative	22	0.7 (0.5)	-0.5 (0.5)	14 (63.6%)	7 (7.2)	1.5 (2.2)	8 (36.4%)	11 (50%)
		RF-positive	34	0.8 (0.6)	-0.7 (0.4)	31 (91.2%)	14.1 (23.7)	2.2 (5.4)	18 (52.9%)	20 (58.8%)
	IFX (3mg/kg) + MTX	ACPA-negative	18	0.7 (0.6)	-0.6 (0.6)	14 (77.8%)	9.4 (15.3)	0.9 (2.1)	10 (55.6%)	12 (66.7%)
		ACPA-positive	32	0.7 (0.5)	-0.9 (0.6)	26 (81.3%)	5.4 (5.1)	0.8 (1.4)	18 (56.3%)	19 (59.4%)
	IFX (3mg/kg) + MTX	RF-negative	28	0.8 (0.5)	-0.6 (0.5)	21 (75%)	8.5 (12.8)	1 (1.9)	14 (50%)	17 (60.7%)
		RF-positive	27	0.6 (0.5)	-0.9 (0.6)	22 (81.5%)	5.2 (4.5)	0.7 (1.3)	15 (55.6%)	15 (55.6%)
NEORACo [5]	DMARDs[1]	ACPA-negative	11	0.2 (0.3)	-1.1 (0.7)	11 (100%)	NR	NR	NR	NR
		ACPA-positive	34	0.1 (0.2)	-0.6 (0.6)	23 (67.6%)	NR	NR	NR	NR
	DMARDs[1]	RF-negative	12	0.1 (0.2)	-1 (0.7)	12 (100%)	NR	NR	NR	NR
		RF-positive	33	0.1 (0.2)	-0.7 (0.6)	22 (66.7%)	NR	NR	NR	NR
	DMARDs[1]	ACPA-negative RF-negative	6	0 (0.1)	-1.3 (0.7)	6 (100%)	NR	NR	NR	NR
		ACPA-negative RF-positive	5	0.4 (0.3)	-0.9 (0.6)	5 (100%)	NR	NR	NR	NR
		ACPA-positive RF-negative	6	0.2 (0.3)	-0.7 (0.5)	6 (100%)	NR	NR	NR	NR
		ACPA-positive RF-positive	28	0 (0.1)	-0.6 (0.6)	17 (60.7%)	NR	NR	NR	NR
	IFX (3mg/kg) + DMARDs[1]	ACPA-negative	11	0 (0.1)	-1.4 (0.7)	11 (100%)	NR	NR	NR	NR
		ACPA-positive	35	0.1 (0.2)	-0.9 (0.5)	32 (91.4%)	NR	NR	NR	NR
	IFX (3mg/kg) + DMARDs[1]	RF-negative	10	0 (0.1)	-1.2 (0.7)	10 (100%)	NR	NR	NR	NR
		RF-positive	36	0.1 (0.2)	-1 (0.5)	33 (91.7%)	NR	NR	NR	NR
	IFX (3mg/kg) + DMARDs[1]	ACPA-negative RF-negative	7	0 (0.1)	-1.3 (0.7)	7 (100%)	NR	NR	NR	NR
		ACPA-negative RF-positive	4	0 (0)	-1.7 (0.7)	4 (100%)	NR	NR	NR	NR
		ACPA-positive RF-negative	3	0 (0)	-1 (0.7)	3 (100%)	NR	NR	NR	NR
		ACPA-positive RF-positive	32	0.1 (0.2)	-0.9 (0.5)	29 (90.6%)	NR	NR	NR	NR
Swefot [6, 7]	DMARDs[1]	ACPA-negative	55	0.9 (0.6)	-0.3 (0.4)	37 (67.3%)	NR	NR	NR	NR
		ACPA-positive	71	0.7 (0.6)	-0.3 (0.4)	43 (60.6%)	NR	NR	NR	NR

	DMARDs[1]	RF-negative	45	0.8 (0.6)	-0.4 (0.4)	28 (62.2%)	NR	NR	NR	NR
		RF-positive	84	0.7 (0.6)	-0.2 (0.4)	52 (61.9%)	NR	NR	NR	NR
	DMARDs[1]	ACPA-negative RF-negative	29	0.8 (0.5)	-0.3 (0.4)	21 (72.4%)	NR	NR	NR	NR
		ACPA-negative RF-positive	26	0.9 (0.7)	-0.3 (0.4)	16 (61.5%)	NR	NR	NR	NR
		ACPA-positive RF-negative	15	0.7 (0.8)	-0.5 (0.4)	7 (46.7%)	NR	NR	NR	NR
		ACPA-positive RF-positive	55	0.7 (0.6)	-0.2 (0.4)	35 (63.6%)	NR	NR	NR	NR
	IFX (3mg/kg) + MTX	ACPA-negative	36	0.7 (0.5)	-0.3 (0.4)	28 (77.8%)	NR	NR	NR	NR
		ACPA-positive	80	0.6 (0.6)	-0.3 (0.5)	50 (62.5%)	NR	NR	NR	NR
	IFX (3mg/kg) + MTX	RF-negative	39	0.6 (0.6)	-0.3 (0.4)	25 (64.1%)	NR	NR	NR	NR
		RF-positive	88	0.7 (0.5)	-0.3 (0.5)	58 (65.9%)	NR	NR	NR	NR
	IFX (3mg/kg) + MTX	ACPA-negative RF-negative	21	0.7 (0.6)	-0.3 (0.3)	15 (71.4%)	NR	NR	NR	NR
		ACPA-negative RF-positive	14	0.7 (0.4)	-0.2 (0.5)	12 (85.7%)	NR	NR	NR	NR
		ACPA-positive RF-negative	16	0.6 (0.5)	-0.1 (0.4)	9 (56.3%)	NR	NR	NR	NR
		ACPA-positive RF-positive	64	0.6 (0.6)	-0.3 (0.5)	41 (64.1%)	NR	NR	NR	NR

SvdH, van der Heijde modified total Sharp score; MTX, methotrexate; DMARDs, disease-modifying antirheumatic drugs; ADA, adalimumab; IFX, infliximab; sc, subcutaneous; IV, intravenous; MP, methylprednisolone; NR, not recorded

[1]The triple combination of methotrexate (MTX), sulfasalazine (SSZ) and hydroxychloroquine (HCQ)

**HAQ-DI was assessed 6, 12 and 24 months after randomization (9, 15 and 27 months from baseline and MTX start)*

Online Supplementary Table S1.6: MTX-naïve or csDMARD-naïve: Pooled outcomes of Radiographic progression at 6 months

Outcomes	Number of trials	Relative risk ratios/Differences of differences (95% CI)	I^2
ACPA(+) / ACPA(-) in bDMARD+csDMARD vs ACPA(+) / ACPA(-) in csDMARD			
		Relative Risk Ratios (95%CI)	
Delta SvdH ≤0	n = 1	1.07 (0.46, 2.50)	0%
Delta SvdH ≤0.5	n = 1	1.07 (0.54, 2.10)	0%
		Difference of differences (95% CI)	
SvdH	n = 1	-4.77 (-19.36, 9.82)	0%
Delta SvdH	n = 1	1.74 (-2.79, 6.27)	0%
RF(+) / RF(-) in bDMARD+csDMARD vs RF(+) / RF(-) in csDMARD			
		Relative Risk Ratios (95%CI)	
Delta SvdH ≤0	n = 1	0.77 (0.35, 1.71)	0%
Delta SvdH ≤0.5	n = 1	0.78 (0.40, 1.53)	0%
		Difference of differences (95% CI)	
SvdH	n = 1	**-10.37 (-20.24, -0.50)**	0%
Delta SvdH	n = 1	-0.96 (-3.17, 1.25)	0%

SvdH, van der Heijde modified total Sharp score

Bold: estimates that are statistically significant, i.e.p<0.05

Online Supplementary Table S2.1: MTX-IR RA or csDMARD-IR: Autoantibody status of RCTs

Author	Trial name	Interventions	No. of patients	ACPA-status known (n, %)	ACPA-positive (n, %)	Cut-off of ACPA-test	RF-status known (n)	RF-positive (n, %)	Cut-off of RF-test
Kremer 2006 [8-10]	AIM	MTX	219	NR	NR	NR	198 (90.4%)	171 (86.4%)	20 IU/ml
		ABT (10mg/kg according to weight range) + MTX	433	NR	NR	NR	397 (91.7%)	349 (87.9%)	20 IU/ml
Choy 2012 [11]		MTX	121	NR	NR	NR	114 (94.2%)	93 (81.6%)	14 IU/ml
		CZP (400mg/4weeks sc) + MTX	126	NR	NR	NR	119 (94.4%)	89 (74.8%)	14 IU/ml
Kay 2008 [12]		MTX	35	NR	NR	NR	34 (97.1%)	27 (79.4%)	NR
		GLM (50mg/4weeks sc) + MTX	35	NR	NR	NR	32 (91.4%)	28 (87.5%)	NR
Kim 2007 [13]		MTX	63	NR	NR	NR	63 (100%)	52 (82.5%)	10 IU/ml
		ADA (40mg/2weeks sc) + MTX	65	NR	NR	NR	65 (100%)	50 (76.9%)	10 IU/ml
Smolen 2008 [14]	OPTION	MTX	204	NR	NR	NR	204 (100%)	144 (70.6%)	15 U/ml
		TCZ (8mg/kg/4weeks) + MTX	205	NR	NR	NR	205 (100%)	171 (83.4%)	15 U/ml
Keystone 2008 [15, 16]	RAPID1	MTX	199	NR	NR	NR	198 (99.5%)	164 (82.8%)	14 IU/ml
		CZP (200mg/2weeks sc) + MTX	393	NR	NR	NR	392 (99.7%)	312 (79.6%)	14 IU/ml
Smolen 2009 [17, 18]	RAPID2	MTX	127	NR	NR	NR	124 (97.6%)	97 (78.2%)	14 IU/ml
		CZP (200mg/2weeks sc) + MTX	246	NR	NR	NR	240 (97.6%)	186 (77.5%)	14 IU/ml
	SERENE	MTX	172	168 (97.7%)	137 (81.5%)	NR	172 (100%)	129 (75.0%)	15 units

Emery 2010 [19]		RTX (2× 1000mg) + MTX	170	167 (98.2%)	138 (82.6%)	NR	170 (100%)	125 (73.5%)	15 units
Behrens 2021 [20]	AMARA	LEF	47	47 (100%)	28 (59.6%)	10 U/ml	47 (100%)	25 (53.2%)	15 IU/ml
		RTX (2× 1000mg) + LEF	93	92 (98.9%)	51 (55.4%)	10 U/ml	92 (98.9%)	54 (58.7%)	15 IU/ml
Smolen 2015 [21]	CERTAIN	DMARD	98	97 (99.0%)	56 (57.7%)	10 kIU/l	96 (98.0%)	66 (68.8%)	14 IU/ml
		CZP (200mg/2weeks sc) + DMARD	96	94 (97.9%)	62 (66.0%)	10 kIU/l	94 (97.9%)	71 (75.5%)	14 IU/ml
Combe 2006 [22, 23]		SSZ	50	NR	NR	NR	48 (96.0%)	33 (68.8%)	20 units
		ETN (2× 25mg/week sc) + SSZ	101	NR	NR	NR	96 (95.0%)	68 (70.8%)	20 units
Furst 2003 [24]	STAR	DMARD	318	NR	NR	NR	318 (100%)	237 (74.5%)	15 IU/ml
		ADA (40mg/2weeks sc) + DMARD	318	NR	NR	NR	318 (100%)	243 (76.4%)	15 IU/ml
Klareskog 2004 [25-28]	TEMPO	MTX	228	NR	NR	NR	219 (96.1%)	164 (74.9%)	20 IU/ml
		ETN (2× 25mg/week sc) + MTX	231	NR	NR	NR	227 (98.3%)	177 (78%)	20 IU/ml
Genovese 2008 [29]	TOWARD	DMARD	413	NR	NR	NR	413 (100%)	311 (75.3%)	15 units
		TCZ (8mg/kg/4weeks) + DMARD	803	NR	NR	NR	803 (100%)	624 (77.7%)	15 units

MTX, methotrexate; LEF, leflunomide; DMARD, disease-modifying antirheumatic drug; SSZ, sulfasalazine; ABT, abatacept; CZP, certolizumab pegol; GLM, golimumab; ADA, adalimumab; TCZ, tocilizumab; RTX, rituximab; ETN, etanercept; sc, subcutaneous; NR, not recorded

Online Supplementary Table S2.2: MTX-IR RA or csDMARD-IR: Baseline characteristics of RCTs

Trial name	Interventions	Autoantibody-subgroups	No. of patients	Mean age (years)	Female (n, %)	Baseline DAS28-ESR (mean, SD)	Baseline DAS28-CRP (mean, SD)	Baseline HAQ-DI (mean, SD)	Baseline SvdH (mean, SD)
AIM [8-10]	MTX	RF-negative	27	50.1 (13.0)	21 (77.8%)	6.8 (0.9)	6.3 (0.9)	1.5 (0.6)	30.5 (30.5)
		RF-positive	171	50.3 (12.5)	21 (12.3%)	6.8 (0.9)	6.3 (0.9)	1.7 (0.6)	43.2 (35.6)
	ABT (10mg/kg according to weight range) + MTX	RF-negative	48	46.3 (16.0)	35 (72.9%)	6.7 (0.7)	6.3 (0.7)	1.4 (0.6)	36.0 (34.9)
		RF-positive	349	51.2 (13.0)	274 (78.5%)	6.8 (0.9)	6.3 (0.9)	1.7 (0.7)	45.4 (37.7)
Choy 2012 [11]	MTX	RF-negative	21	54.1 (12.2)	19 (90.5%)	6.1 (1.2)	5.8 (1.0)	1.4 (0.8)	NR
		RF-positive	93	55.3 (11.3)	59 (63.4%)	6.4 (0.9)	6.0 (0.7)	1.5 (0.6)	NR
	CZP (400mg/4weeks sc) + MTX	RF-negative	30	51.5 (15.2)	25 (83.3%)	6.2 (0.7)	5.7 (0.7)	1.4 (0.6)	NR
		RF-positive	89	52.7 (11.3)	62 (69.7%)	6.3 (1.0)	5.9 (0.9)	1.4 (0.6)	NR
Kay 2008 [12]	MTX	RF-negative	7	46.6 (10.9)	3 (42.9%)	6.3 (1.0)	5.9 (0.7)	1.6 (0.6)	NR
		RF-positive	27	56.3 (12.6)	22 (81.5%)	6.4 (0.8)	5.8 (0.8)	1.3 (0.7)	NR
	GLM (50mg/4weeks sc) + MTX	RF-negative	4	57.3 (4.0)	4 (100%)	6.4 (1.1)	5.9 (1.1)	2.1 (0.4)	NR
		RF-positive	28	56.9 (10.5)	24 (85.7%)	6.6 (1.1)	6.1 (1.0)	1.7 (0.4)	NR
Kim 2007 [13]	MTX	RF-negative	11	42.9 (8.4)	9 (81.8%)	NR	NR	NR	NR
		RF-positive	52	51.3 (10.4)	45 (86.5%)	NR	NR	NR	NR
	ADA (40mg/2weeks sc) + MTX	RF-negative	15	42.4 (9.2)	13 (86.7%)	NR	NR	NR	NR
		RF-positive	50	50.3 (9.8)	49(98.0%)	NR	NR	NR	NR
OPTION [14]	MTX	RF-negative	60	50.0 (11.5)	51 (85.0%)	6.8 (0.8)	NR	1.5 (0.6)	NR
		RF-positive	144	50.9 (12.3)	108 (75.0%)	6.8 (0.9)	NR	1.6 (0.7)	NR

	TCZ (8mg/kg/4weeks) + MTX	RF-negative	34	49.6 (12.0)	28 (82.4%)	6.7 (0.9)	NR	1.7 (0.6)	NR
		RF-positive	171	51.1 (11.7)	147 (86.0%)	6.8 (0.9)	NR	1.5 (0.6)	NR
RAPID1 [15, 16]	MTX	RF-negative	34	51.3 (13.8)	27 (79.4%)	6.9 (0.94)	6.1 (1.0)	1.5 (0.6)	19.6 (34.0)
		RF-positive	164	52.6 (10.7)	140 (85.4%)	7.0 (0.84)	6.3 (0.9)	1.7 (0.6)	43.1 (45.6)
	CZP (200mg/2weeks sc) + MTX	RF-negative	80	49.2 (12.3)	67 (83.8%)	6.7 (0.87)	6.0 (0.8)	1.4 (0.6)	20.5 (43.6)
		RF-positive	312	52.0 (11.3)	256 (82.1%)	7.0 (0.77)	6.3 (0.8)	1.7 (0.6)	43.2 (49.8)
RAPID2 [17, 18]	MTX	RF-negative	27	47.0 (12.1)	23 (85.2%)	6.7 (0.9)	5.9 (0.9)	1.6 (0.7)	19.3 (32.3)
		RF-positive	97	52.7 (11.6)	81 (83.5%)	6.9 (0.8)	6.2 (0.9)	1.6 (0.6)	53.2 (61.9)
	CZP (200mg/2weeks sc) + MTX	RF-negative	54	52.6 (13.4)	44 (81.5%)	6.8 (0.9)	6.1 (0.9)	1.7 (0.5)	21.7 (40.1)
		RF-positive	186	52.1 (10.4)	157 (84.4%)	6.9 (0.8)	6.2 (0.8)	1.6 (0.6)	44.8 (51.6)
SERENE [19]	MTX	ACPA-negative	31	52.6 (8.9)	27 (87.1%)	NR	NR	1.5 (0.6)	52.6 (8.9)
		ACPA-positive	137	51.9 (13.2)	117 (85.4%)	NR	NR	1.7 (0.6)	51.9 (13.2)
	MTX	RF-negative	43	53.8 (10.5)	40 (93.0%)	NR	NR	1.6 (0.6)	53.8 (10.5)
		RF-positive	129	51.6 (12.9)	107 (82.9%)	NR	NR	1.7 (0.6)	51.6 (12.9)
	MTX	ACPA-negative RF-negative	25	53.2 (9.7)	23 (92.0%)	NR	NR	1.5 (0.6)	53.2 (9.7)
		ACPA-negative RF-positive	6	49.2 (4.3)	4 (66.7%)	NR	NR	1.3 (0.6)	49.2 (4.3)
		ACPA-positive RF-negative	17	54.5 (12.2)	16 (94.1%)	NR	NR	1.7 (0.7)	54.5 (12.2)
		ACPA-positive RF-positive	120	51.6 (13.4)	101 (84.2%)	NR	NR	1.7 (0.6)	51.6 (13.4)
	RTX (2× 1000mg) + MTX	ACPA-negative	29	49.4 (13.1)	27 (93.1%)	NR	NR	1.4 (0.6)	49.4 (13.1)
		ACPA-positive	138	51.6 (12.7)	108 (78.3%)	NR	NR	1.6 (0.6)	51.6 (12.7)
	RTX (2× 1000mg) + MTX	RF-negative	45	49.1 (12.1)	40 (88.9%)	NR	NR	1.4 (0.5)	49.1 (12.1)
		RF-positive	125	52.1 (12.8)	98 (78.4%)	NR	NR	1.7 (0.6)	52.1 (12.8)

	RTX (2× 1000mg) + MTX	ACPA-negative RF-negative	24	48.0 (13.2)	22 (91.7%)	NR	NR	1.3 (0.5)	48.0 (13.2)
		ACPA-negative RF-positive	5	55.8 (11.6)	5 (100%)	NR	NR	2.0 (0.4)	55.8 (11.6)
		ACPA-positive RF-negative	19	50.2 (11.1)	16 (84.2%)	NR	NR	1.3 (0.5)	50.2 (11.1)
		ACPA-positive RF-positive	119	51.9 (12.9)	92 (77.3%)	NR	NR	1.7 (0.7)	51.9 (12.9)
AMARA [20]	LEF	ACPA-negative	19	56.8 (7.0)	17(89.5%)	5.3 (0.6)	5.4 (0.7)	1.2 (0.5)	NR
		ACPA-positive	28	55.6 (11.6)	21 (75.0%)	5.7 (1.3)	5.7 (1.2)	1.5 (0.7)	NR
	LEF	RF-negative	22	57.0 (10.0)	20 (90.9%)	5.2 (0.8)	5.2 (0.9)	1.2 (0.6)	NR
		RF-positive	25	55.3 (10.0)	18 (72.0%)	5.8 (1.2)	5.8 (1.1)	1.5 (0.7)	NR
	LEF	ACPA-negative RF-negative	18	56.9 (7.2)	16 (88.9%)	5.3 (0.6)	5.4 (0.7)	1.2 (0.5)	NR
		ACPA-negative RF-positive	1	55	1 (100%)	4.4	4.8	1.8	NR
		ACPA-positive RF-negative	4	57.3 (20.3)	4 (100%)	4.6 (1.3)	4.4 (1.0)	1.4 (0.9)	NR
		ACPA-positive RF-positive	24	55.3 (10.2)	17 (70.8%)	5.9 (1.2)	5.9 (1.1)	1.5 (0.7)	NR
	RTX (2× 1000mg) + LEF	ACPA-negative	41	58.0 (12.3)	33 (80.5%)	5.3 (0.9)	5.3 (1.0)	1.2 (0.6)	NR
		ACPA-positive	51	55.8 (11.3)	32 (62.7%)	5.7 (1.0)	5.5 (1.1)	1.2 (0.7)	NR
	RTX (2× 1000mg) + LEF	RF-negative	38	59.2 (10.2)	32 (84.2%)	5.6 (0.9)	5.6 (0.9)	1.3 (0.6)	NR
		RF-positive	54	55.0 (12.5)	33 (61.1%)	5.5 (1.1)	5.3 (1.1)	1.1 (0.7)	NR
	RTX (2× 1000mg) + LEF	ACPA-negative RF-negative	32	59.3 (10.6)	26 (81.3%)	5.5 (0.9)	5.5 (0.9)	1.3 (0.5)	NR
		ACPA-negative RF-positive	9	53.2 (17.1)	7 (77.8%)	4.9 (1.0)	4.6 (0.9)	0.9 (0.8)	NR
		ACPA-positive RF-negative	6	58.5 (8.7)	6 (100%)	6.2 (0.7)	5.7 (0.6)	1.6 (0.6)	NR
		ACPA-positive RF-positive	45	55.4 (11.6)	26 (57.8%)	5.7 (1.1)	5.5 (1.1)	1.2 (0.7)	NR
CERTAIN [21]	DMARD	ACPA-negative	41	53.6 (13.9)	32 (78.0%)	4.53 (0.39)	3.85 (0.44)	0.98 (0.60)	NR
		ACPA-positive	56	54.0 (11.3)	42 (75.0%)	4.44 (0.30)	3.86 (0.35)	1.08 (0.61)	NR

		RF-negative	30	52.7 (13.5)	23 (76.7%)	4.51 (0.33)	3.83 (0.37)	1.02 (0.54)	NR
		RF-positive	66	54.4 (12.0)	50 (75.8%)	4.45 (0.34)	3.87 (0.39)	1.05 (0.62)	NR
		ACPA-negative RF-negative	27	52.7 (14.1)	21 (77.8%)	4.54 (0.34)	3.85 (0.38)	1.04 (0.55)	NR
		ACPA-negative RF-positive	12	54.6 (14.9)	9 (75.0%)	4.50 (0.49)	3.89 (0.54)	0.91 (0.67)	NR
		ACPA-positive RF-negative	3	52.7 (8.5)	2 (66.7%)	4.33 (0.16)	3.69 (0.17)	0.92 (0.56)	NR
		ACPA-positive RF-positive	53	54.1 (11.4)	40 (75.5%)	4.44 (0.31)	3.87 (0.35)	1.10 (0.62)	NR
	CZP (200mg/2weeks sc) + DMARD	ACPA-negative	32	53.8 (14.1)	27 (84.4%)	4.50 (0.50)	3.80 (0.46)	1.05 (0.65)	NR
		ACPA-positive	62	53.1 (10.8)	52 (83.9%)	4.47 (0.34)	3.78 (0.35)	1.15 (0.60)	NR
		RF-negative	23	55.0 (13.7)	19 (82.6%)	4.53 (0.35)	3.76 (0.37)	1.00 (0.72)	NR
		RF-positive	71	53.0 (11.5)	61 (85.9%)	4.48 (0.46)	3.82 (0.43)	1.16 (0.58)	NR
		ACPA-negative RF-negative	19	55.5 (14.2)	16 (84.2%)	4.59 (0.35)	3.85 (0.35)	1.10 (0.72)	NR
		ACPA-negative RF-positive	12	51.1 (14.7)	11 (91.7%)	4.33 (0.68)	3.74 (0.62)	1.05 (0.51)	NR
		ACPA-positive RF-negative	4	52.3 (12.7)	3 (75.0%)	4.22 (0.13)	3.37 (0.13)	0.53 (0.52)	NR
		ACPA-positive RF-positive	58	53.2 (10.8)	49 (84.5%)	4.49 (0.35)	3.81 (0.34)	1.20 (0.58)	NR
Combe 2006 [22, 23]	SSZ	RF-negative	15	51.4 (12.2)	12 (80.0%)	7.3 (1.2)	7.0 (0.9)	1.7 (0.4)	NR
		RF-positive	33	53.3 (13.1)	28 (84.8%)	7.4 (1.2)	6.9 (1.1)	1.6 (0.6)	NR
	ETN (2× 25mg/week sc) + SSZ	RF-negative	28	52 (10.3)	20 (71.4%)	7.2 (1.3)	7.0 (0.9)	1.3 (0.6)	NR
		RF-positive	68	50.7 (13.1)	56 (82.4%)	7.5 (1.3)	7.0 (1.2)	1.7 (0.5)	NR
STAR [24]	DMARD	RF-negative	81	54.9	61	NR	NR	NR	NR
		RF-positive	237	56.1	191	NR	NR	NR	NR
	ADA (40mg/2weeks sc) + DMARD	RF-negative	75	53.6	60	NR	NR	NR	NR
		RF-positive	243	55.5	193	NR	NR	NR	NR

TEMPO [25-28]	MTX	RF-negative	55	51.4 (13.2)	48 (87.3%)	6.2 (0.9)	6 (0.8)	1.7 (0.7)	26.2 (46.7)
		RF-positive	164	53.6 (12.5)	124 (75.6%)	6.9 (1.0)	6.4 (0.9)	1.7 (0.7)	42.8 (52.1)
	ETN (2× 25mg/week sc) + MTX	RF-negative	50	52 (13.5)	44 (88.0%)	6.5 (1.0)	6.1 (0.8)	1.6 (0.6)	32.2 (52.4)
		RF-positive	177	52.5 (12.1)	123 (69.5%)	6.9 (1.0)	6.5 (0.9)	1.8 (0.6)	37.9 (47)
TOWARD [29]	DMARD	RF-negative	102	52.4 (13.7)	87 (85.3%)	6.4 (1.0)	NR	1.5 (0.6)	NR
		RF-positive	311	53.9 (12.9)	259 (83.3%)	6.7 (1.0)	NR	1.6 (0.6)	NR
	TCZ (8mg/kg/4weeks) + DMARD	RF-negative	179	50.9 (13.5)	147 (82.1%)	6.6 (1.0)	NR	1.4 (0.6)	NR
		RF-positive	624	53.6 (12.2)	507 (81.3%)	6.7 (1.0)	NR	1.5 (0.6)	NR

SvdH, van der Heijde modified total Sharp score; MTX, methotrexate; LEF, leflunomide; DMARD, disease-modifying antirheumatic drug; SSZ, sulfasalazine; ABT, abatacept; CZP, certolizumab pegol; GLM, golimumab; ADA, adalimumab; TCZ, tocilizumab; RTX, rituximab; ETN, etanercept; sc, subcutaneous; NR, not recorded

Online Supplementary Table S2.3: MTX-IR RA or csDMARD-IR: Risk of bias of RCTs

Trial name	Biological DMARD	ROB1: Random sequence generation	ROB2: Allocation concealment	ROB3: Blinding of participants and personnel	ROB4: Blinding of outcome assessment	ROB5: Incomplete outcome data	ROB6: Other bias	ROB7: Selective reporting
AIM [8-10]	ABT	L	L	L	L	L	L	L
Choy 2012 [11]	CZP	L	L	L	L	L	L	L
Kay 2008 [12]	GLM	L	L	L	L	L	L	L
Kim 2007 [13]	ADA	L	L	L	L	L	L	L
OPTION [14]	TCZ	L	L	L	L	L	L	L
RAPID1 [15,16]	CZP	L	L	L	L	L	L	L
RAPID2 [17, 18]	CZP	L	L	L	L	L	L	L
SERENE [19]	RTX	U	U	L	U	L	L	L
AMARA [20]	RTX	L	L	L	L	L	L	L
CERTAIN [21]	CZP	L	L	L	L	U	L	L
Combe 2006 [22, 23]	ETN	L	L	L	L	L	L	L
STAR [24]	ADA	L	L	L	L	L	L	L
TEMPO [25-28]	ETN	L	L	L	L	L	L	L
TOWARD [29]	TCZ	L	L	L	L	L	L	L

ABT, abatacept; CZP, certolizumab pegol; GLM, golimumab; ADA, adalimumab; TCZ, tocilizumab; RTX, rituximab; ETN, etanercept

L = low risk; U = unclear risk

Online Supplementary Table S2.4: MTX-IR RA or csDMARD-IR: Disease activity outcomes of RCTs at 6 months

Trial name	Interventions	Autoantibody-subgroups	No. of patients	ACR20 (n, %)	ACR50 (n, %)	ACR70 (n, %)	DAS28-ESR (mean, SD)	ΔDAS28-ESR (mean, SD)	DAS28-ESR <2.6 (n, %)	DAS28-CRP (mean, SD)	ΔDAS28-CRP (mean, SD)	DAS28-CRP <2.6 (n, %)
AIM [8-10]	MTX	RF-negative	27	9 (33.3%)	2 (7.4%)	2 (7.4%)	5.3 (1.4)	-1.5 (1.2)	0 (0%)	4.9 (1.4)	-1.6 (1.2)	0 (0%)
		RF-positive	171	70 (40.9%)	34 (19.9%)	12 (7%)	5.3 (1.3)	-1.5 (1.4)	1 (0.6%)	4.8 (1.3)	-1.5 (1.4)	6 (3.5%)
	ABT (10mg/kg according to weight range) + MTX	RF-negative	48	29 (60.4%)	17 (35.4%)	7 (14.6%)	4.2 (1.3)	-2.4 (1.3)	5 (10.4%)	4 (1.2)	-2.2 (1.2)	6 (12.5%)
		RF-positive	349	240 (68.8%)	138 (39.5%)	71 (20.3%)	4.3 (1.3)	-2.5 (1.4)	29 (8.3%)	3.9 (1.3)	-2.5 (1.3)	53 (15.2%)
Choy 2012 [11]	MTX	RF-negative	21	3 (14.3%)	1 (4.8%)	0 (0%)	5.5 (1.3)	-0.5 (0.7)	0 (0%)	5.2 (1.1)	-0.6 (0.7)	0 (0%)
		RF-positive	93	23 (24.7%)	6 (6.5%)	2 (2.2%)	5.5 (1.4)	-0.8 (1.3)	1 (1.1%)	5.1 (1.4)	-0.8 (1.3)	2 (2.2%)
	CZP (400mg/4weeks sc) + MTX	RF-negative	30	13 (43.3%)	6 (20%)	0 (0%)	4.5 (1)	-1.7 (1.3)	1 (3.3%)	4.2 (1)	-1.5 (1.1)	1 (3.3%)
		RF-positive	89	41 (46.1%)	15 (16.9%)	0 (0%)	4.4 (1.3)	-1.7 (1.3)	3 (3.4%)	4.1 (1.2)	-1.8 (1.3)	6 (6.7%)
Kay 2008[1] [12]	MTX	RF-negative	7	4 (57.1%)	1 (14.3%)	0 (0%)	4.9 (1.0)	-1.6 (0.5)	0 (0%	4.5 (0.7)	-1.4 (0.6	0 (0%)
		RF-positive	27	8 (29.6%)	1 (3.7%)	0 (0%)	5.5 (1.2)	-0.8 (1.1)	0 (0%	5.0 (1.2)	-0.7 (1.0)	0 (0%)
	GLM (50mg/4weeks sc) + MTX	RF-negative	4	3 (75%)	1 (25%)	0 (0%)	4.6 (1.0)	-1.9 (0.7)	0 (0%	4.1 (1.2)	-1.8 (0.9)	0 (0%)
		RF-positive	28	16 (57.1%)	11 (39.3%)	3 (10.7%)	4.5 (1.3)	-2.2 (1.5)	2 (7.1%)	4.1 (1.3)	-2.1 (1.4)	4 (14.3%)
Kim 2007 [13]	MTX	RF-negative	11	9 (81.8%)	4 (36.4%)	0 (0%)	NR	NR	NR	NR	NR	NR
		RF-positive	52	23 (44.2%)	7 (13.5%)	5 (9.6%)	NR	NR	NR	NR	NR	NR

	ADA (40mg/2weeks sc) + MTX	RF-negative	15	11 (73.3%)	8 (53.3%)	3 (20%)	NR	NR	NR	NR	NR	NR
		RF-positive	50	33 (66%)	22 (44%)	11 (22%)	NR	NR	NR	NR	NR	NR
OPTION [14]	MTX	RF-negative	60	15 (25%)	6 (10%)	2 (3.3%)	NR	NR	NR	NR	NR	NR
		RF-positive	144	39 (27.1%)	16 (11.1%)	2 (1.4%)	NR	NR	NR	NR	NR	NR
	TCZ (8mg/kg/4weeks) + MTX	RF-negative	34	11 (32.4%)	8 (23.5%)	5 (14.7%)	NR	NR	NR	NR	NR	NR
		RF-positive	171	109 (63.7%)	82 (48%)	40 (23.4%)	NR	NR	NR	NR	NR	NR
RAPID1 [15, 16]	MTX	RF-negative	34	5 (14.7%)	2 (5.9%)	NR	6 (1.4)	-0.9 (1.2)	0 (0%)	5.6 (1.3)	-0.5 (1)	0 (0%)
		RF-positive	164	22 (13.4%)	13 (7.9%)	NR	6.4 (1.5)	-0.6 (1.3)	3 (1.8%)	5.7 (1.5)	-0.6 (1.3)	7 (4.3%)
	CZP (200mg/2weeks sc) + MTX	RF-negative	80	42 (52.5%)	28 (35%)	NR	4.6 (1.6)	-2.2 (1.6)	10 (12.5%)	4.1 (1.4)	-1.8 (1.5)	10 (12.5%)
		RF-positive	312	190 (60.9%)	116 (37.2%)	NR	4.5 (1.6)	-2.5 (1.5)	35 (11.2%)	4 (1.5)	-2.3 (1.4)	57 (18.3%)
RAPID2 [17, 18]	MTX	RF-negative	27	2 (7.4%)	1 (3.7%)	1 (3.7%)	6.2 (1.3)	-0.5 (1.3)	1 (3.7%)	5.7 (1.2)	-0.3 (1.2)	0 (0%)
		RF-positive	97	9 (9.3%)	3 (3.1%)	0 (0%)	6.3 (1.2)	-0.5 (1)	0 (0%)	5.9 (1.2)	-0.4 (1)	0 (0%)
	CZP (200mg/2weeks sc) + MTX	RF-negative	54	30 (55.6%)	17 (31.5%)	11 (20.4%)	4.6 (1.5)	-2.2 (1.3)	9 (16.7%)	4.2 (1.4)	-1.9 (1.4)	7 (13%)
		RF-positive	186	109 (58.6%)	62 (33.3%)	27 (14.5%)	4.6 (1.4)	-2.3 (1.4)	14 (7.5%)	4.1 (1.3)	-2.1 (1.3)	28 (15.1%)
SERENE [19]	MTX	ACPA-negative	31	7 (22.6%)	5 (16.1%)	3 (9.7%)	NR	NR	NR	NR	NR	NR
		ACPA-positive	137	35 (25.5%)	10 (7.3%)	5 (3.6%)	NR	NR	NR	NR	NR	NR
	MTX	RF-negative	43	12 (27.9%)	5 (11.6%)	3 (7%)	NR	NR	NR	NR	NR	NR
		RF-positive	129	32 (24.8%)	11 (8.5%)	6 (4.7%)	NR	NR	NR	NR	NR	NR

	MTX	ACPA-negative RF-negative	25	5 (20%)	3 (12%)	2 (8%)	NR	NR	NR	NR	NR	NR
		ACPA-negative RF-positive	6	2 (33.3%)	2 (33.3%)	1 (16.7%)	NR	NR	NR	NR	NR	NR
		ACPA-positive RF-negative	17	6 (35.3%)	1 (5.9%)	0 (0%)	NR	NR	NR	NR	NR	NR
		ACPA-positive RF-positive	120	29 (24.2%)	9 (7.5%)	5 (4.2%)	NR	NR	NR	NR	NR	NR
	RTX (2× 1000mg) + MTX	ACPA-negative	29	17 (58.6%)	9 (31%)	3 (10.3%)	NR	NR	NR	NR	NR	NR
		ACPA-positive	138	68 (49.3%)	34 (24.6%)	13 (9.4%)	NR	NR	NR	NR	NR	NR
	RTX (2× 1000mg) + MTX	RF-negative	45	26 (57.8%)	11 (24.4%)	4 (8.9%)	NR	NR	NR	NR	NR	NR
		RF-positive	125	60 (48%)	32 (25.6%)	12 (9.6%)	NR	NR	NR	NR	NR	NR
	RTX (2× 1000mg) + MTX	ACPA-negative RF-negative	24	15 (62.5%)	8 (33.3%)	3 (12.5%)	NR	NR	NR	NR	NR	NR
		ACPA-negative RF-positive	5	2 (40%)	1 (20%)	0 (0%)	NR	NR	NR	NR	NR	NR
		ACPA-positive RF-negative	19	10 (52.6%)	3 (15.8%)	1 (5.3%)	NR	NR	NR	NR	NR	NR
		ACPA-positive RF-positive	119	58 (48.7%)	31 (26.1%)	12 (10.1%)	NR	NR	NR	NR	NR	NR
AMARA [20]	LEF	ACPA-negative	19	6 (31.6%)	3 (15.8%)	1 (5.3%)	4.5 (1.2)	-0.81 (1.25)	1 (5.3%)	4.3 (1.4)	-1 (1.2)	3 (15.8%)
		ACPA-positive	28	7 (25%)	4 (14.3%)	2 (7.1%)	4.8 (1.5)	-0.91 (1.64)	2 (7.1%)	4.8 (1.6)	-0.8 (1.8)	3 (10.7%)
	LEF	RF-negative	22	6 (27.3%)	3 (13.6%)	1 (4.5%)	4.5 (1.1)	-0.65 (1.33)	1 (4.5%)	4.4 (1.3)	-0.8 (1.3)	3 (13.6%)
		RF-positive	25	7 (28%)	4 (16%)	2 (8%)	4.8 (1.6)	-1.06 (1.61)	2 (8%)	4.8 (1.7)	-1 (1.9)	3 (12%)
	LEF	ACPA-negative RF-negative	18	6 (33.3%)	3 (16.7%)	1 (5.6%)	4.5 (1.2)	-0.84 (1.28)	1 (5.6%)	4.3 (1.4)	-1 (1.3)	3 (16.7%)
		ACPA-negative RF-positive	1	0 (0%)	0 (0%)	0 (0%)	4.2	-0.24	0 (0%)	4.2	-0.6	0 (0%)

		ACPA-positive RF-negative	4	0 (0%)	0 (0%)	0 (0%)	4.8 (0.2)	0.21 (1.37)	0 (0%)	4.8 (0.5)	0.4 (0.8)	0 (0%)
		ACPA-positive RF-positive	24	7 (29.2%)	4 (16.7%)	2 (8.3%)	4.8 (1.6)	-1.1 (1.63)	2 (8.3%)	4.8 (1.7)	-1 (1.9)	3 (12.5%)
	RTX (2× 500 or 1000mg) + LEF	ACPA-negative	41	14 (34.1%)	7 (17.1%)	2 (4.9%)	4.2 (1.6)	-1.15 (1.18)	8 (19.5%)	4.3 (1.7)	-1 (1.4)	9 (22%)
		ACPA-positive	51	29 (56.9%)	15 (29.4%)	12 (23.5%)	3.9 (1.6)	-1.87 (1.41)	18 (35.3%)	3.6 (1.7)	-1.9 (1.5)	16 (31.4%)
	RTX (2× 500 or 1000mg) + LEF	RF-negative	38	14 (36.8%)	6 (15.8%)	2 (5.3%)	4.3 (1.5)	-1.27 (1.2)	7 (18.4%)	4.3 (1.7)	-1.4 (1.2)	8 (21.1%)
		RF-positive	54	29 (53.7%)	16 (29.6%)	12 (22.2%)	3.8 (1.6)	-1.75 (1.43)	19 (35.2%)	3.6 (1.7)	-1.7 (1.6)	17 (31.5%)
	RTX (2× 500 or 1000mg) + LEF	ACPA-negative RF-negative	32	11 (34.4%)	4 (12.5%)	1 (3.1%)	4.4 (1.5)	-1.05 (1.11)	5 (15.6%)	4.5 (1.7)	-1 (1.3)	6 (18.8%)
		ACPA-negative RF-positive	9	3 (33.3%)	3 (33.3%)	1 (11.1%)	3.4 (1.5)	-1.53 (1.42)	3 (33.3%)	3.5 (1.6)	-1.1 (1.6)	3 (33.3%)
		ACPA-positive RF-negative	6	3 (50%)	2 (33.3%)	1 (16.7%)	3.7 (1.4)	-2.44 (1.03)	2 (33.3%)	3.4 (1.4)	-2.3 (0.9)	2 (33.3%)
		ACPA-positive RF-positive	45	26 (57.8%)	13 (28.9%)	11 (24.4%)	3.9 (1.6)	-1.79 (1.45)	16 (35.6%)	3.6 (1.8)	-1.8 (1.6)	14 (31.1%)
CERTAIN [21]	DMARD	ACPA-negative	41	8 (19.5%)	6 (14.6%)	2 (4.9%)	4.3 (1.2)	-0.2 (1.3)	1 (2.4%)	4 (1.2)	0.2 (1.3)	7 (17.1%)
		ACPA-positive	56	7 (12.5%)	1 (1.8%)	1 (1.8%)	4.5 (1.2)	0 (1.2)	4 (7.1%)	4 (1.1)	0.2 (1.1)	4 (7.1%)
		RF-negative	30	7 (23.3%)	5 (16.7%)	2 (6.7%)	4.3 (1.2)	-0.2 (1.3)	1 (3.3%)	3.9 (1.3)	0.1 (1.3)	6 (20%)
		RF-positive	66	7 (10.6%)	1 (1.5%)	1 (1.5%)	4.5 (1.2)	0 (1.2)	4 (6.1%)	4.1 (1.1)	0.2 (1.1)	5 (7.6%)
		ACPA-negative RF-negative	27	6 (22.2%)	5 (18.5%)	2 (7.4%)	4.3 (1.3)	-0.2 (1.4)	1 (3.7%)	4 (1.4)	0.1 (1.3)	1 (3.7%)
		ACPA-negative RF-positive	12	1 (8.3%)	0 (0%)	0 (0%)	4.5 (1)	0 (1)	0 (0%)	4.2 (1.1)	0.4 (1.2)	0 (0%)
		ACPA-positive RF-negative	3	1 (33.3%)	0 (0%)	0 (0%)	4 (0.3)	-0.3 (0.3)	0 (0%)	3.3 (0.5)	-0.4 (0.6)	0 (0%)

		ACPA-positive RF-positive	53	6 (11.3%)	1 (1.9%)	1 (1.9%)	4.5 (1.2)	0.1 (1.2)	4 (7.5%)	4.1 (1.2)	0.2 (1.1)	4 (7.5%)
	CZP (200mg/2weeks sc) + DMARD	ACPA-negative	32	13 (40.6%)	8 (25%)	4 (12.5%)	3.4 (1.3)	-1.1 (1.3)	9 (28.1%)	3.1 (1.3)	-0.7 (1.2)	10 (31.3%)
		ACPA-positive	62	22 (35.5%)	12 (19.4%)	5 (8.1%)	3.3 (1)	-1.2 (0.9)	14 (22.6%)	3 (0.9)	-0.7 (0.9)	17 (27.4%)
		RF-negative	23	10 (43.5%)	6 (26.1%)	3 (13%)	3.3 (1.6)	-1.2 (1.4)	8 (34.8%)	3.1 (1.3)	-0.6 (1.3)	6 (26.1%)
		RF-positive	71	24 (33.8%)	13 (18.3%)	6 (8.5%)	3.4 (1)	-1.1 (0.9)	14 (19.7%)	3.1 (0.9)	-0.7 (0.9)	20 (28.2%)
		ACPA-negative RF-negative	19	7 (36.8%)	4 (21.1%)	2 (10.5%)	3.5 (1.6)	-1.1 (1.5)	5 (26.3%)	3.3 (1.4)	-0.5 (1.4)	5 (26.3%)
		ACPA-negative RF-positive	12	5 (41.7%)	3 (25%)	2 (16.7%)	3.3 (0.9)	-1 (1)	3 (25%)	2.9 (1)	-0.8 (1.1)	3 (25%)
		ACPA-positive RF-negative	4	3 (75%)	2 (50%)	1 (25%)	2.3 (0.8)	-1.9 (0.7)	3 (75%)	2.3 (0.7)	-1.1 (0.5)	3 (75%)
		ACPA-positive RF-positive	58	19 (32.8%)	10 (17.2%)	4 (6.9%)	3.4 (1)	-1.1 (0.9)	11 (19%)	3.1 (0.9)	-0.7 (0.9)	11 (19%)
Combe 2006 [22, 23]	SSZ	RF-negative	15	1 (6.7%)	0 (0%)	0 (0%)	7.1 (1.6)	-0.2 (1.2)	0 (0%)	6.9 (1.4)	-0.1 (1.3)	0 (0%)
		RF-positive	33	12 (36.4%)	7 (21.2%)	1 (3%)	6 (1.9)	-1.4 (1.9)	2 (6.1%)	5.7 (1.8)	-1.3 (1.9)	1 (3%)
	ETN (2× 25mg/week sc) + SSZ	RF-negative	28	19 (67.9%)	13 (46.4%)	5 (17.9%)	4.3 (2.4)	-3 (2)	9 (32.1%)	4.4 (2.1)	-2.6 (1.9)	4 (14.3%)
		RF-positive	68	51 (75%)	37 (54.4%)	18 (26.5%)	4.4 (1.8)	-3.1 (1.6)	9 (13.2%)	4.2 (1.6)	-2.9 (1.4)	8 (11.8%)
STAR [24]	DMARD	RF-negative	81	29 (35.8%)	10 (12.3%)	2 (2.5%)	NR	NR	NR	NR	NR	NR
		RF-positive	237	82 (34.6%)	26 (11%)	9 (3.8%)	NR	NR	NR	NR	NR	NR
	ADA (40mg/2weeks sc) + DMARD	RF-negative	75	34 (45.3%)	17 (22.7%)	8 (10.7%)	NR	NR	NR	NR	NR	NR
		RF-positive	243	134 (55.1%)	75 (30.9%)	39 (16%)	NR	NR	NR	NR	NR	NR

TEMPO [25-28]	MTX	RF-negative	55	34 (61.8%)	13 (23.6%)	7 (12.7%)	4.1 (1.5)	-2.1 (1.5)	10 (18.2%)	3.9 (1.2)	-2 (1.3)	8 (14.5%)
		RF-positive	164	128 (78%)	74 (45.1%)	26 (15.9%)	4.4 (1.5)	-2.5 (1.4)	19 (11.6%)	4 (1.4)	-2.4 (1.3)	28 (17.1%)
	ETN (2× 25mg/week sc) + MTX	RF-negative	50	39 (78%)	28 (56%)	15 (30%)	3.6 (1.5)	-2.9 (1.2)	7 (14%)	3.6 (1.4)	-2.5 (1.2)	15 (30%)
		RF-positive	177	147 (83.1%)	106 (59.9%)	65 (36.7%)	3.5 (1.5)	-3.4 (1.4)	55 (31.1%)	3.3 (1.4)	-3.1 (1.3)	64 (36.2%)
TOWARD [29]	DMARD	RF-negative	102	24 (23.5%)	9 (8.8%)	7 (6.9%)	NR	NR	NR	NR	NR	NR
		RF-positive	311	77 (24.8%)	28 (9%)	5 (1.6%)	NR	NR	NR	NR	NR	NR
	TCZ (8mg/kg/4weeks) + DMARD	RF-negative	179	96 (53.6%)	57 (31.8%)	31 (17.3%)	NR	NR	NR	NR	NR	NR
		RF-positive	624	391 (62.7%)	244 (39.1%)	134 (21.5%)	NR	NR	NR	NR	NR	NR

MTX, methotrexate; LEF, leflunomide; DMARD, disease-modifying antirheumatic drug; SSZ, sulfasalazine; ABT, abatacept; CZP, certolizumab pegol; GLM, golimumab; ADA, adalimumab; TCZ, tocilizumab; RTX, rituximab; ETN, etanercept; sc, subcutaneous; NR, not recorded

[1]The primary endpoint was at 16 weeks.

Online Supplementary Table S2.5: MTX-IR RA or csDMARD-IR: Physical function and Radiographic progression of RCTs at 6 months

Trial name	Interventions	Autoantibody-subgroups	No. of patients	HAQ-DI (mean, SD)	ΔHAQ-DI (mean, SD)	HAQ-DI response ≥0.22 (n, %)	SvdH (mean, SD)	ΔSvdH (mean, SD)	ΔSvdH ≤0 (n, %)	ΔSvdH ≤0.5 (n, %)
AIM [8-10]	MTX	RF-negative	27	1.3 (0.6)	-0.3 (0.5)	12 (44.4%)	NR	NR	NR	NR
		RF-positive	171	1.2 (0.7)	-0.5 (0.7)	90 (52.6%)	NR	NR	NR	NR
	ABT (10mg/kg according to weight range) + MTX	RF-negative	48	0.8 (0.6)	-0.6 (0.6)	34 (70.8%)	NR	NR	NR	NR
		RF-positive	349	1.1 (0.7)	-0.6 (0.6)	241 (69.1%)	NR	NR	NR	NR
Choy 2012 [11]	MTX	RF-negative	21	1.3 (0.7)	0 (0.4)	3 (14.3%)	NR	NR	NR	NR
		RF-positive	93	1.4 (1.1)	-0.1 (0.5)	23 (24.7%)	NR	NR	NR	NR
	CZP (400mg/4weeks sc) + MTX	RF-negative	30	1.2 (0.7)	-0.2 (0.5)	14 (46.7%)	NR	NR	NR	NR
		RF-positive	89	1.1 (0.7)	-0.4 (0.5)	43 (48.3%)	NR	NR	NR	NR
Kay 2008[1] [12]	MTX	RF-negative	7	1.5 (0.7)	-0.3 (0.3)	6 (85.7%)	NR	NR	NR	NR
		RF-positive	27	1.2 (0.7)	-0.1 (0.5)	20 (74.1%))	NR	NR	NR	NR
	GLM (50mg/4weeks sc) + MTX	RF-negative	4	1.3 (0.9)	-0.7 (0.8)	4 (100%)	NR	NR	NR	NR
		RF-positive	28	1.0 (0.5)	-0.6 (0.5)	22 (78.6%)	NR	NR	NR	NR
Kim 2007 [13]	MTX	RF-negative	11	NR	NR	NR	NR	NR	NR	NR
		RF-positive	52	NR	NR	NR	NR	NR	NR	NR
	ADA (40mg/2weeks sc) + MTX	RF-negative	15	NR	NR	NR	NR	NR	NR	NR
		RF-positive	50	NR	NR	NR	NR	NR	NR	NR
OPTION [14]	MTX	RF-negative	60	NR	NR	NR	NR	NR	NR	NR
		RF-positive	144	NR	NR	NR	NR	NR	NR	NR
	TCZ (8mg/kg/4weeks) + MTX	RF-negative	34	NR	NR	NR	NR	NR	NR	NR
		RF-positive	171	NR	NR	NR	NR	NR	NR	NR
RAPID1 [15, 16]	MTX	RF-negative	34	1.5 (0.7)	-0.1 (0.5)	11 (32.4%)	21.3 (36.7)	0.1 (1)	23 (67.6%)	24 (70.6%)
		RF-positive	164	1.6 (0.7)	-0.2 (0.5)	69 (42.1%)	45.2 (46.7)	1.6 (4.1)	73 (44.5%)	77 (47%)
	CZP (200mg/2weeks sc) + MTX	RF-negative	80	1 (0.7)	-0.4 (0.5)	50 (62.5%)	21.1 (44)	0.7 (3.5)	56 (70%)	62 (77.5%)
		RF-positive	312	1.1 (0.7)	-0.6 (0.6)	227 (72.8%)	42.8 (47.3)	0 (3.1)	187 (59.9%)	211 (67.6%)
RAPID2 [17, 18]	MTX	RF-negative	27	1.5 (0.6)	-0.1 (0.5)	10 (37%)	20.2 (32.4)	0.3 (1.2)	19 (70.4%)	19 (70.4%)
		RF-positive	97	1.4 (0.6)	-0.2 (0.5)	37 (38.1%)	57.3 (64.8)	1.6 (4.6)	44 (45.4%)	44 (45.4%)
	CZP (200mg/2weeks sc) + MTX	RF-negative	54	1.2 (0.7)	-0.4 (0.4)	39 (72.2%)	28.6 (53.4)	0 (0.9)	40 (74.1%)	44 (81.5%)
		RF-positive	186	1.1 (0.6)	-0.6 (0.5)	138 (74.2%)	45.3 (52.1)	0.3 (3.1)	108 (58.1%)	120 (64.5%)

SERENE [19]	MTX	ACPA-negative	31	NR	NR	NR	NR	NR	NR	NR
		ACPA-positive	137	NR	NR	NR	NR	NR	NR	NR
	MTX	RF-negative	43	NR	NR	NR	NR	NR	NR	NR
		RF-positive	129	NR	NR	NR	NR	NR	NR	NR
	MTX	ACPA-negative RF-negative	25	NR	NR	NR	NR	NR	NR	NR
		ACPA-negative RF-positive	6	NR	NR	NR	NR	NR	NR	NR
		ACPA-positive RF-negative	17	NR	NR	NR	NR	NR	NR	NR
		ACPA-positive RF-positive	120	NR	NR	NR	NR	NR	NR	NR
	RTX (2× 1000mg) + MTX	ACPA-negative	29	NR	NR	NR	NR	NR	NR	NR
		ACPA-positive	138	NR	NR	NR	NR	NR	NR	NR
	RTX (2× 1000mg) + MTX	RF-negative	45	NR	NR	NR	NR	NR	NR	NR
		RF-positive	125	NR	NR	NR	NR	NR	NR	NR
	RTX (2× 1000mg) + MTX	ACPA-negative RF-negative	24	NR	NR	NR	NR	NR	NR	NR
		ACPA-negative RF-positive	5	NR	NR	NR	NR	NR	NR	NR
		ACPA-positive RF-negative	19	NR	NR	NR	NR	NR	NR	NR
		ACPA-positive RF-positive	119	NR	NR	NR	NR	NR	NR	NR
AMARA [20]	LEF	ACPA-negative	19	1.1 (0.6)	-0.1 (0.6)	3 (15.8%)	NR	NR	NR	NR
		ACPA-positive	28	1.4 (0.7)	-0.2 (0.7)	6 (21.4%)	NR	NR	NR	NR
	LEF	RF-negative	22	1.2 (0.7)	-0.1 (0.6)	4 (18.2%)	NR	NR	NR	NR
		RF-positive	25	1.4 (0.6)	-0.2 (0.7)	5 (20%)	NR	NR	NR	NR
	LEF	ACPA-negative RF-negative	18	1.1 (0.6)	-0.1 (0.6)	3 (16.7%)	NR	NR	NR	NR
		ACPA-negative RF-positive	1	NR	NR	0 (0%)	NR	NR	NR	NR
		ACPA-positive RF-negative	4	1.5 (1)	0.1 (0.1)	1 (25%)	NR	NR	NR	NR
		ACPA-positive RF-positive	24	1.4 (0.6)	-0.2 (0.7)	5 (20.8%)	NR	NR	NR	NR
	RTX (2× 1000mg) + LEF	ACPA-negative	41	1.1 (0.6)	-0.1 (0.4)	5 (12.2%)	NR	NR	NR	NR
		ACPA-positive	51	0.9 (0.7)	-0.2 (0.5)	7 (13.7%)	NR	NR	NR	NR
	RTX (2× 1000mg) + LEF	RF-negative	38	1.3 (0.5)	0 (0.4)	6 (15.8%)	NR	NR	NR	NR
		RF-positive	54	0.9 (0.7)	-0.2 (0.5)	6 (11.1%)	NR	NR	NR	NR
	RTX (2× 1000mg) + LEF	ACPA-negative RF-negative	32	1.3 (0.6)	0 (0.4)	5 (15.6%)	NR	NR	NR	NR
		ACPA-negative RF-positive	9	0.7 (0.5)	-0.4 (0.5)	0 (0%)	NR	NR	NR	NR
		ACPA-positive RF-negative	6	1.4 (0.6)	-0.1 (0.7)	1 (16.7%)	NR	NR	NR	NR
		ACPA-positive RF-positive	45	0.9 (0.7)	-0.2 (0.5)	6 (13.3%)	NR	NR	NR	NR
	DMARD	ACPA-negative	41	0.8 (0.7)	-0.1 (0.5)	15 (36.6%)	NR	NR	NR	NR

CERTAIN [21]		ACPA-positive	56	1.1 (0.7)	0 (0.5)	16 (28.6%)	NR	NR	NR	NR
		RF-negative	30	0.9 (0.7)	-0.2 (0.5)	12 (40%)	NR	NR	NR	NR
		RF-positive	66	1.1 (0.7)	0 (0.5)	18 (27.3%)	NR	NR	NR	NR
		ACPA-negative RF-negative	27	0.9 (0.7)	-0.2 (0.5)	11 (40.7%)	NR	NR	NR	NR
		ACPA-negative RF-positive	12	0.9 (0.6)	0 (0.5)	3 (25%)	NR	NR	NR	NR
		ACPA-positive RF-negative	3	0.8 (0.4)	-0.1 (0.2)	1 (33.3%)	NR	NR	NR	NR
		ACPA-positive RF-positive	53	1.1 (0.7)	0 (0.5)	15 (28.3%)	NR	NR	NR	NR
	CZP (200mg/2weeks sc) + DMARD	ACPA-negative	32	0.9 (0.7)	-0.2 (0.6)	14 (43.8%)	NR	NR	NR	NR
		ACPA-positive	62	0.9 (0.6)	-0.3 (0.4)	32 (51.6%)	NR	NR	NR	NR
		RF-negative	23	0.8 (0.8)	-0.2 (0.6)	9 (39.1%)	NR	NR	NR	NR
		RF-positive	71	0.9 (0.6)	-0.3 (0.4)	37 (52.1%)	NR	NR	NR	NR
		ACPA-negative RF-negative	19	0.9 (0.8)	-0.1 (0.6)	7 (36.8%)	NR	NR	NR	NR
		ACPA-negative RF-positive	12	0.8 (0.6)	-0.3 (0.5)	7 (58.3%)	NR	NR	NR	NR
		ACPA-positive RF-negative	4	0.3 (0.4)	-0.2 (0.2)	2 (50%)	NR	NR	NR	NR
		ACPA-positive RF-positive	58	0.9 (0.6)	-0.3 (0.4)	30 (51.7%)	NR	NR	NR	NR
Combe 2006 [22, 23]	SSZ	RF-negative	15	1.6 (0.7)	-0.1 (0.5)	8 (53.3%)	NR	NR	NR	NR
		RF-positive	33	1.4 (0.8)	-0.2 (0.6)	13 (39.4%)	NR	NR	NR	NR
	ETN (2× 25mg/week sc) + SSZ	RF-negative	28	0.9 (0.8)	-0.4 (0.4)	20 (71.4%)	NR	NR	NR	NR
		RF-positive	68	1 (0.7)	-0.7 (0.6)	54 (79.4%)	NR	NR	NR	NR
STAR [24]	DMARD	RF-negative	81	NR	NR	NR	NR	NR	NR	NR
		RF-positive	237	NR	NR	NR	NR	NR	NR	NR
	ADA (40mg/2weeks sc) + DMARD	RF-negative	75	NR	NR	NR	NR	NR	NR	NR
		RF-positive	243	NR	NR	NR	NR	NR	NR	NR
TEMPO [25-28]	MTX	RF-negative	55	1.1 (0.8)	-0.6 (0.6)	40 (72.7%)	NR	NR	NR	NR
		RF-positive	164	1 (0.8)	-0.7 (0.6)	135 (82.3%)	NR	NR	NR	NR
	ETN (2× 25mg/week sc) + MTX	RF-negative	50	0.8 (0.7)	-0.8 (0.6)	40 (80%)	NR	NR	NR	NR
		RF-positive	177	0.9 (0.7)	-0.9 (0.7)	158 (89.3%)	NR	NR	NR	NR
TOWARD [29]	DMARD	RF-negative	102	NR	NR	NR	NR	NR	NR	NR
		RF-positive	311	NR	NR	NR	NR	NR	NR	NR
		RF-negative	179	NR	NR	NR	NR	NR	NR	NR

	TCZ (8mg/kg/4weeks) + DMARD	RF-positive	624	NR	NR	NR	NR	NR	NR	NR

SvdH, van der Heijde modified total Sharp score; MTX, methotrexate; LEF, leflunomide; DMARD, disease-modifying antirheumatic drug; SSZ, sulfasalazine; ABT, abatacept; CZP, certolizumab pegol; GLM, golimumab; ADA, adalimumab; TCZ, tocilizumab; RTX, rituximab; ETN, etanercept; sc, subcutaneous; NR, not recorded

[1]The primary endpoint was at 16 weeks.

Online Supplementary Table S2.6: MTX-IR RA or csDMARD-IR: Pooled outcomes of Radiographic progression at 6 months

Outcomes	Number of trials	Relative risk ratios/Differences of differences (95% CI)	I^2
		Relative Risk Ratios (95%CI)	
Delta SvdH ≤0	n = 2	1.26 (0.98, 1.62)	0%
Delta SvdH ≤0.5	n = 2	**1.27 (1.01, 1.61)**	0%
		Difference of differences (95% CI)	
SvdH	n = 2	-9.49 (-26.94, 7.97)	29%
Delta SvdH	n = 2	**-1.56 (-2.74, -0.39)**	0%

SvdH, van der Heijde modified total Sharp score

Bold: estimates that are statistically significant, i.e.p<0.05

Online Supplementary Table S3.1: TNFi-IR: Autoantibody status of RCTs

Author	Trial name	Interventions	No. of patients	ACPA-status known (n, %)	ACPA-positive (n, %)	Cut-off of ACPA-test	RF-status known (n)	RF-positive (n, %)	Cut-off of RF-test
Genovese 2005 [30-32]	ATTAIN	DMARD	133	NR	NR	NR	127 (95.5%)	97 (76.4%)	20 IU/ml
		ABT (10mg/kg according to weight range) + DMARD	258	NR	NR	NR	241 (93.4%)	189 (78.4%)	20 IU/ml
Smolen 2009 [33]	GO-AFTER	DMARD	150	NR	NR	NR	146 (97.3%)	108 (74.0%)	NR
		GLM (50mg/4weeks sc) + DMARD	147	NR	NR	NR	143 (97.3%)	104 (72.7%)	NR
Emery 2008 [34, 35]	RADIATE	MTX	160	NR	NR	NR	160 (100%)	120 (75.0%)	15 units
		TCZ (8mg/kg/4weeks) + MTX	175	NR	NR	NR	175 (100%)	139 (79.4%)	15 units

DMARD, disease-modifying antirheumatic drug; MTX, methotrexate; ABT, abatacept; GLM, golimumab; TCZ, tocilizumab; sc, subcutaneous; NR, not recorded

Online Supplementary Table S3.2: TNFi-IR: Baseline characteristics of RCTs

Trial name	Interventions	Autoantibody-subgroups	No. of patients	Mean age (years)	Female (n, %)	Baseline DAS28-ESR (mean, SD)	Baseline DAS28-CRP (mean, SD)	Baseline HAQ-DI (mean, SD)	Baseline SvdH (mean, SD)
ATTAIN [30-32]	DMARD	RF-negative	30	49.5 (13.4)	24 (80.0%)	6.7 (1.0)	6.4 (0.7)	1.7 (0.7)	NR
		RF-positive	97	53.6 (10.9)	79 (81.4%)	7.0 (0.9)	6.6 (0.8)	1.9 (0.6)	NR
	ABT (10mg/kg according to weight range) + DMARD	RF-negative	52	50.6 (11.8)	49 (94.2%)	6.7 (0.9)	6.3 (0.8)	1.8 (0.6)	NR
		RF-positive	189	54.1 (12.4)	141 (74.6%)	6.9 (1.0)	6.6 (0.9)	1.9 (0.6)	NR
GO-AFTER [33]	DMARD	RF-negative	38	54.1 (15.6)	32 (84.2%)	6.1 (1.3)	5.6 (1.0)	1.6 (0.6)	NR
		RF-positive	108	55.1 (12.1)	93 (86.1%)	6.3 (1.1)	5.7 (1.1)	1.6 (0.6)	NR
	GLM (50mg/4weeks sc) + DMARD	RF-negative	39	51.8 (13.1)	28 (71.8%)	6.3 (1.2)	5.9 (1.0)	1.6 (0.6)	NR
		RF-positive	104	53.9 (10.9)	79 (76.0%)	6.4 (1.3)	6.0 (1.2)	1.6 (0.7)	NR
RADIATE [34, 35]	MTX	RF-negative	40	52.1 (15.2)	31 (77.5%)	6.5 (0.9)	NR	1.6 (0.6)	NR
		RF-positive	120	54.1 (12.6)	95 (79.2%)	6.9 (1.1)	NR	1.7 (0.6)	NR
	TCZ (8mg/kg/4weeks) + MTX	RF-negative	36	51.1 (13.9)	31 (86.1%)	6.6 (0.9)	NR	1.9 (0.5)	NR
		RF-positive	139	54.6 (12.4)	115 (82.7%)	6.8 (0.9)	NR	1.7 (0.6)	NR

SvdH, van der Heijde modified total Sharp score; DMARD, disease-modifying antirheumatic drug; MTX, methotrexate; ABT, abatacept; GLM, golimumab; TCZ, tocilizumab; sc, subcutaneous; NR, not recorded

Online Supplementary Table S3.3: TNFi-IR: Risk of bias of RCTs

Study	Biological DMARD	ROB1: Random sequence generation	ROB2: Allocation concealment	ROB3: Blinding of participants and personnel	ROB4: Blinding of outcome assessment	ROB5: Incomplete outcome data	ROB6: Other bias	ROB7: Selective reporting
ATTAIN [30-32]	ABT	L	L	L	L	L	L	L
GO-AFTER [33]	GLM	L	L	L	U	L	L	L
RADIATE [34, 35]	TCZ	L	L	L	L	L	L	L

ABT, abatacept; GLM, golimumab; TCZ, tocilizumab

L = low risk; U = unclear risk

Online Supplementary Table S3.4: TNFi-IR: Disease activity outcomes of RCTs at 6 months

Trial name	Interventions	Autoantibody-subgroups	No. of patients	ACR20 (n, %)	ACR50 (n, %)	ACR70 (n, %)	DAS28-ESR (mean, SD)	ΔDAS28-ESR (mean, SD)	DAS28-ESR <2.6 (n, %)	DAS28-CRP (mean, SD)	ΔDAS28-CRP (mean, SD)	DAS28-CRP <2.6 (n, %)
ATTAIN [30-32]	DMARD	RF-negative	30	9 (30%)	2 (6.7%)	0 (0%)	6 (1.1)	-0.8 (1.1)	0 (0%)	5.5 (1)	-0.9 (1.1)	0 (0%)
		RF-positive	97	16 (16.5%)	3 (3.1%)	2 (2.1%)	5.9 (1.3)	-0.8 (1.4)	1 (1%)	5.5 (1.3)	-0.9 (1.2)	1 (1%)
	ABT (10mg/kg according to weight range) + DMARD	RF-negative	52	19 (36.5%)	5 (9.6%)	2 (3.8%)	5.2 (1.3)	-1.4 (1.4)	1 (1.9%)	4.8 (1.2)	-1.5 (1.1)	2 (3.8%)
		RF-positive	189	103 (54.5%)	45 (23.8%)	23 (12.2%)	4.7 (1.5)	-2.2 (1.5)	18 (9.5%)	4.4 (1.4)	-2.2 (1.4)	21 (11.1%)
GO-AFTER [33]	DMARD	RF-negative	38	6 (15.8%)	2 (5.3%)	1 (2.6%)	5.4 (1.4)	-0.5 (1.2)	2 (5.3%)	5 (1.2)	-0.5 (1.2)	1 (2.6%)
		RF-positive	108	18 (16.7%)	4 (3.7%)	2 (1.9%)	5.2 (1.4)	-1 (1.5)	1 (0.9%)	4.7 (1.3)	-1 (1.3)	2 (1.9%)
	GLM (50mg/4weeks sc) + DMARD	RF-negative	39	7 (17.9%)	1 (2.6%)	1 (2.6%)	5.5 (1.6)	-0.9 (1.3)	2 (5.1%)	5.1 (1.4)	-0.8 (1.1)	1 (2.6%)
		RF-positive	104	36 (34.6%)	20 (19.2%)	11 (10.6%)	4.7 (1.6)	-1.7 (1.3)	10 (9.6%)	4.4 (1.5)	-1.6 (1.2)	12 (11.5%)
RADIATE [34, 35]	MTX	RF-negative	40	5 (12.5%)	1 (2.5%)	0 (0%)	NR	NR	NR	NR	NR	NR
		RF-positive	120	11 (9.2%)	5 (4.2%)	2 (1.7%)	NR	NR	NR	NR	NR	NR
	TCZ (8mg/kg/4weeks) + MTX	RF-negative	36	13 (36.1%)	4 (11.1%)	0 (0%)	NR	NR	NR	NR	NR	NR
		RF-positive	139	75 (54%)	47 (33.8%)	22 (15.8%)	NR	NR	NR	NR	NR	NR

DMARD, disease-modifying antirheumatic drug; MTX, methotrexate; ABT, abatacept; GLM, golimumab; TCZ, tocilizumab; sc, subcutaneous; NR, not recorded

Online Supplementary Table S3.5: TNFi-IR: Physical function and Radiographic progression of RCTs at 6 months

Trial name	Interventions	Autoantibody-subgroups	No. of patients	HAQ-DI (mean, SD)	ΔHAQ-DI (mean, SD)	HAQ-DI response ≥0.22 (n, %)	SvdH (mean, SD)	ΔSvdH (mean, SD)	ΔSvdH ≤0 (n, %)	ΔSvdH ≤0.5 (n, %)
ATTAIN [30-32]	DMARD	RF-negative	30	1.5 (0.7)	-0.1 (0.4)	6 (20%)	NR	NR	NR	NR
		RF-positive	97	1.7 (0.6)	-0.2 (0.4)	36 (37.1%)	NR	NR	NR	NR
	ABT (10mg/kg according to weight range) + DMARD	RF-negative	52	1.4 (0.7)	-0.4 (0.5)	25 (48.1%)	NR	NR	NR	NR
		RF-positive	189	1.3 (0.7)	-0.6 (0.6)	115 (60.8%)	NR	NR	NR	NR
GO-AFTER [33]	DMARD	RF-negative	38	1.4 (0.8)	0.1 (0.4)	32 (84.2%)	NR	NR	NR	NR
		RF-positive	108	1.3 (0.8)	0.3 (0.6)	83 (76.9%)	NR	NR	NR	NR
	GLM (50mg/4weeks sc) + DMARD	RF-negative	39	1.5 (0.7)	0.1 (0.4)	38 (97.4%)	NR	NR	NR	NR
		RF-positive	104	1.2 (0.8)	0.3 (0.5)	83 (79.8%)	NR	NR	NR	NR
RADIATE [34, 35]	MTX	RF-negative	40	NR	NR	NR	NR	NR	NR	NR
		RF-positive	120	NR	NR	NR	NR	NR	NR	NR
	TCZ (8mg/kg/4weeks) + MTX	RF-negative	36	NR	NR	NR	NR	NR	NR	NR
		RF-positive	139	NR	NR	NR	NR	NR	NR	NR

SvdH, van der Heijde modified total Sharp score; DMARD, disease-modifying antirheumatic drug; MTX, methotrexate; ABT, abatacept; GLM, golimumab; TCZ, tocilizumab; sc, subcutaneous; NR, not recorded

2.2 RCTs of Biological DMARD monotherapy

Online Supplementary Table S4.1: Biological DMARD monotherapy: Autoantibody status of RCTs

Author	Trial name	Interventions	No. of patients	ACPA-status known (n, %)	ACPA-positive (n, %)	Cut-off of ACPA-test	RF-status known (n)	RF-positive (n, %)	Cut-off of RF-test
Kaneko 2016 [36]	SURPRISE	TCZ (8mg/kg/4weeks)	115	NR	NR	NR	102 (88.7%)	82 (80.4%)	15 IU/ml
		TCZ (8mg/kg/4weeks) + MTX	111	NR	NR	NR	105 (94.6%)	78 (74.3%)	15 IU/ml
Jones 2010 [37]	AMBITION	MTX	284	NR	NR	NR	284 (100%)	212 (74.6%)	15 units
		TCZ (8mg/kg/4weeks)	288	NR	NR	NR	288 (100%)	214 (74.3%)	15 units
Takeuchi 2013 [38]		MTX	176	NR	NR	NR	176 (100%)	138 (78.4%)	15 units
		ETN (2× 25mg/week sc)	182	NR	NR	NR	182 (100%)	147 (80.8%)	15 units

MTX, methotrexate; TCZ, tocilizumab; ETN, etanercept; sc, subcutaneous; NR, not recorded

Online Supplementary Table S4.2: Biological DMARD monotherapy: Baseline characteristics of RCTs

Trial name	Interventions	Autoantibody-subgroups	No. of patients	Mean age (years)	Female (n, %)	Baseline DAS28-ESR (mean, SD)	Baseline DAS28-CRP (mean, SD)	Baseline HAQ-DI (mean, SD)	Baseline SvdH (mean, SD)
SURPRISE [36]	TCZ (8mg/kg/4weeks)	RF-negative	20	56.4 (12.8)	17 (85.0%)	5.2 (1.4)	4.5 (1.3)	1.0 (0.7)	22.8 (24.3)
		RF-positive	82	56.9 (12.2)	72 (87.8%)	5.3 (1.2)	4.5 (1.2)	1.0 (0.7)	29.6 (33.1)
	TCZ (8mg/kg/4weeks) + MTX	RF-negative	27	54.0 (14.4)	26 (96.3%)	4.5 (1.0)	3.9 (0.9)	0.9 (0.5)	30.8 (53.0)
		RF-positive	78	56.7 (10.4)	66 (84.6%)	5.2 (1.1)	4.4 (1.0)	1.0 (0.7)	36.8 (58.8)
AMBITION [37]	MTX	RF-negative	72	52.2 (12.8)	56 (77.8%)	6.7 (0.8)	NR	1.4 (0.6)	NR
		RF-positive	212	49.3 (12.9)	168 (79.2%)	6.8 (0.9)	NR	1.6 (0.6)	NR
	TCZ (8mg/kg/4weeks)	RF-negative	74	51.3 (12.0)	56 (75.7%)	6.7 (0.9)	NR	1.5 (0.6)	NR
		RF-positive	214	50.5 (13.4)	182 (85.0%)	6.8 (1.0)	NR	1.6 (0.7)	NR
Takeuchi 2013 [38]	MTX	RF-negative	38	50.1 (12.6)	31 (81.6%)	5.8 (1.2)	5.3 (1.1)	0.9 (0.6)	39.2 (44.8)
		RF-positive	138	50.5 (11.8)	109 (79.0%)	5.9 (1.1)	5.2 (1.1)	1 (0.7)	44.4 (46.9)
	ETN (2× 25mg/week sc)	RF-negative	35	53.2 (10.6)	25 (71.4%)	5.4 (1.0)	4.9 (1.1)	0.7 (0.6)	26.6 (23.2)
		RF-positive	147	51.5 (11.2)	120 (81.6%)	5.9 (1.0)	5.3 (1.0)	1.1 (0.7)	45.4 (44)

SvdH, van der Heijde modified total Sharp score; MTX, methotrexate; TCZ, tocilizumab; ETN, etanercept; sc, subcutaneous; NR, not recorded

Online Supplementary Table S4.3: Biological DMARD monotherapy: Risk of bias of RCTs

Trial name	Biological DMARD	ROB1: Random sequence generation	ROB2: Allocation concealment	ROB3: Blinding of participants and personnel	ROB4: Blinding of outcome assessment	ROB5: Incomplete outcome data	ROB6: Other bias	ROB7: Selective reporting
SURPRISE [36]	TCZ	L	L	H	H	H	L	L
AMBITION [37]	TCZ	U	U	L	L	L	L	L
Takeuchi 2013 [38]	ETN	L	L	L	L	L	L	L

TCZ, tocilizumab; ETN, etanercept

L = low risk; U = unclear risk

Online Supplementary Table S4.4: Biological DMARD monotherapy: Disease activity outcomes of RCTs at 6 months

Trial name	Interventions	Autoantibody-subgroups	No. of patients	ACR20 (n, %)	ACR50 (n, %)	ACR70 (n, %)	DAS28-ESR (mean, SD)	ΔDAS28-ESR (mean, SD)	DAS28-ESR <2.6 (n, %)	DAS28-CRP (mean, SD)	ΔDAS28-CRP (mean, SD)	DAS28-CRP <2.6 (n, %)
SURPRISE [36]	TCZ (8mg/kg/4weeks)	RF-negative	20	16 (80%)	13 (65%)	10 (50%)	2.4 (1)	-2.6 (1.2)	11 (55%)	2 (0.9)	-2.1 (1.2)	15 (75%)
		RF-positive	82	56 (68.3%)	44 (53.7%)	27 (32.9%)	2.6 (1.4)	-2.6 (1.4)	50 (61%)	2.4 (1.2)	-2.2 (1.4)	54 (65.9%)
	TCZ (8mg/kg/4weeks) + MTX	RF-negative	27	16 (59.3%)	11 (40.7%)	5 (18.5%)	2.1 (1)	-2.7 (1.2)	18 (66.7%)	2.1 (1)	-2.1 (1.1)	21 (77.8%)
		RF-positive	78	64 (82.1%)	46 (59%)	29 (37.2%)	2.1 (1.2)	-3 (1.3)	56 (71.8%)	2 (1)	-2.3 (1.1)	58 (74.4%)
AMBITION [37]	MTX	RF-negative	72	29 (40.3%)	21 (29.2%)	7 (9.7%)	NR	NR	NR	NR	NR	NR
		RF-positive	212	120 (56.6%)	74 (34.9%)	36 (17%)	NR	NR	NR	NR	NR	NR
	TCZ (8mg/kg/4weeks)	RF-negative	74	46 (62.2%)	27 (36.5%)	17 (23%)	NR	NR	NR	NR	NR	NR
		RF-positive	214	155 (72.4%)	100 (46.7%)	63 (29.4%)	NR	NR	NR	NR	NR	NR
Takeuchi 2013 [38]	MTX	RF-negative	38	18 (47.4%)	11 (28.9%)	4 (10.5%)	3.7 (1.2)	-2 (1.4)	5 (13.2%)	3.2 (1.2)	-1.9 (1.3)	9 (23.7%)
		RF-positive	138	77 (55.8%)	43 (31.2%)	17 (12.3%)	4 (1.4)	-1.8 (1.2)	20 (14.5%)	3.5 (1.3)	-1.8 (1.2)	30 (21.7%)
	ETN (2× 25mg/week sc)	RF-negative	35	22 (62.9%)	15 (42.9%)	10 (28.6%)	3 (1)	-2.4 (1.3)	11 (31.4%)	2.7 (1)	-2.1 (1.2)	13 (37.1%)
		RF-positive	147	110 (74.8%)	76 (51.7%)	36 (24.5%)	3.5 (1.3)	-2.5 (1.2)	32 (21.8%)	2.9 (1.2)	-2.4 (1.2)	63 (42.9%)

MTX, methotrexate; TCZ, tocilizumab; ETN, etanercept; sc, subcutaneous; NR, not recorded

Online Supplementary Table S4.5: Biological DMARD monotherapy: Physical function and Radiographic progression of RCTs at 6 months

Trial name	Interventions	Autoantibody-subgroups	No. of patients	HAQ-DI (mean, SD)	ΔHAQ-DI (mean, SD)	HAQ-DI response ≥0.22 (n, %)	SvdH (mean, SD)	ΔSvdH (mean, SD)	ΔSvdH ≤0 (n, %)	ΔSvdH ≤0.5 (n, %)
SURPRISE [36]	TCZ (8mg/kg/4weeks)	RF-negative	20	0.6 (0.8)	-0.4 (0.9)	9 (45%)	NR	NR	NR	NR
		RF-positive	82	0.6 (0.6)	-0.4 (0.6)	46 (56.1%)	NR	NR	NR	NR
	TCZ (8mg/kg/4weeks) + MTX	RF-negative	27	0.7 (0.6)	-0.2 (0.5)	17 (63%)	NR	NR	NR	NR
		RF-positive	78	0.5 (0.6)	-0.4 (0.5)	44 (56.4%)	NR	NR	NR	NR
AMBITION [37]	MTX	RF-negative	72	NR	NR	NR	NR	NR	NR	NR
		RF-positive	212	NR	NR	NR	NR	NR	NR	NR
	TCZ (8mg/kg/4weeks)	RF-negative	74	NR	NR	NR	NR	NR	NR	NR
		RF-positive	214	NR	NR	NR	NR	NR	NR	NR
Takeuchi 2013 [38]	MTX	RF-negative	38	0.4 (0.5)	-0.4 (0.6)	17 (44.7%)	NR	NR	NR	NR
		RF-positive	138	0.6 (0.6)	-0.4 (0.6)	73 (52.9%)	NR	NR	NR	NR
	ETN (2× 25mg/week sc)	RF-negative	35	0.2 (0.4)	-0.5 (0.4)	22 (62.9%)	NR	NR	NR	NR
		RF-positive	147	0.5 (0.6)	-0.6 (0.6)	105 (71.4%)	NR	NR	NR	NR

SvdH, van der Heijde modified total Sharp score; MTX, methotrexate; TCZ, tocilizumab; ETN, etanercept; sc, subcutaneous; NR, not recorded

2.3 Head-to-head RCTs of bDMARDs

Online Supplementary Table S5.1: Head-to-head RCTs of bDMARDs: Autoantibody status of RCTs

Author	Trial name	Interventions	No. of patients	ACPA-status known (n, %)	ACPA-positive (n, %)	Cut-off of ACPA-test	RF-status known (n)	RF-positive (n, %)	Cut-off of RF-test
Gabay 2013 [39]	ADACTA	ADA (40mg/2weeks sc)	162	162 (100%)	115 (71.0%)	NR	162 (100%)	119 (73.5%)	15 units
		TCZ (8mg/kg/4weeks)	163	163 (100%)	125 (76.7%)	NR	163 (100%)	121 (74.2%)	15 units
Weinblatt 2013 [40-43]	AMPLE	ABT (125mg/week sc)	318	251 (78.9%)	185 (73.7%)	25 AU/ml	251 (78.9%)	204 (81.3%)	6 U/ml
		ADA (40mg/2weeks sc)	328	257 (78.4%)	203 (79.0%)	25 AU/ml	258 (78.7%)	223 (86.4%)	6 U/ml

ADA, adalimumab; TCZ, tocilizumab; ABT, abatacept; sc, subcutaneous; NR, not recorded

Online Supplementary Table S5.2: Head-to-head RCTs of bDMARDs: Baseline characteristics of RCTs

Trial name	Interventions	Autoantibody-subgroups	No. of patients	Mean age (years)	Female (n, %)	Baseline DAS28-ESR (mean, SD)	Baseline DAS28-CRP (mean, SD)	Baseline HAQ-DI (mean, SD)	Baseline SvdH (mean, SD)
ADACTA [39]	ADA (40mg/2weeks sc)	ACPA-negative	47	56.2 (11.2)	39 (83.0%)	6.8 (1.0)	NR	1.7 (0.7)	NR
		ACPA-positive	115	52.1 (12.8)	94 (81.7%)	6.8 (0.9)	NR	1.7 (0.6)	NR
	ADA (40mg/2weeks sc)	RF-negative	43	56.8 (10.6)	36 (83.7%)	6.8 (0.9)	NR	1.7 (0.6)	NR
		RF-positive	119	52.1 (12.9)	97 (81.5%)	6.8 (1.0)	NR	1.7 (0.6)	NR
	ADA (40mg/2weeks sc)	ACPA-negative RF-negative	36	57.0 (11.1)	30 (83.3%)	6.8 (0.9)	NR	1.6 (0.6)	NR
		ACPA-negative RF-positive	11	53.7 (11.7)	9 (81.8%)	6.5 (1.1)	NR	2.0 (0.7)	NR
		ACPA-positive RF-negative	7	55.7 (8.0)	6 (85.7%)	6.5 (0.8)	NR	1.8 (0.5)	NR
		ACPA-positive RF-positive	108	51.9 (13.0)	88 (81.5%)	6.8 (0.9)	NR	1.7 (0.6)	NR
	TCZ (8mg/kg/4weeks)	ACPA-negative	38	54.3 (11.4)	32 (84.2%)	6.6 (0.8)	NR	1.5 (0.5)	NR
		ACPA-positive	125	54.5 (13.4)	97 (77.6%)	6.7 (1.0)	NR	1.6 (0.7)	NR
	TCZ (8mg/kg/4weeks)	RF-negative	42	52.4 (11.4)	36 (85.7%)	6.6 (0.8)	NR	1.5 (0.6)	NR
		RF-positive	121	55.1 (13.4)	93 (76.9%)	6.8 (1.0)	NR	1.7 (0.7)	NR
	TCZ (8mg/kg/4weeks)	ACPA-negative RF-negative	28	54.3 (11.0)	26 (92.9%)	6.6 (0.7)	NR	1.5 (0.5)	NR
		ACPA-negative RF-positive	10	54.3 (12.9)	6 (60.0%)	6.8 (1.2)	NR	1.5 (0.6)	NR
		ACPA-positive RF-negative	14	48.6 (11.6)	10 (71.4%)	6.6 (1.0)	NR	1.3 (0.6)	NR
		ACPA-positive RF-positive	111	55.2 (13.5)	87 (78.4%)	6.8 (1.0)	NR	1.7 (0.7)	NR
AMPLE [40-43]	ABT (125mg/week sc)	ACPA-negative	66	53.0 (11.9)	56 (84.8%)	NR	5.4 (1.2)	1.4 (0.6)	11.6 (18.0)
		ACPA-positive	185	49.8 (12.2)	152 (82.2%)	NR	5.5 (1.1)	1.5 (0.7)	21.7 (37.3)

	ABT (125mg/week sc)	RF-negative	47	54.1 (10.9)	38 (80.9%)	NR	5.5 (1.2)	1.5 (0.6)	10.6 (15.7)
		RF-positive	204	49.9 (12.4)	170 (83.3%)	NR	5.5 (1.1)	1.5 (0.7)	21.0 (36.3)
	ABT (125mg/week sc)	ACPA-negative RF-negative	38	54.1 (10.6)	29 (76.3%)	NR	5.5 (1.2)	1.4 (0.6)	11.4 (17.1)
		ACPA-negative RF-positive	28	51.4 (13.5)	27 (96.4%)	NR	5.2 (1.2)	1.3 (0.6)	11.9 (19.6)
		ACPA-positive RF-negative	9	54.0 (12.6)	9 (100%)	NR	5.4 (1.5)	1.6 (0.7)	7.3 (6.7)
		ACPA-positive RF-positive	176	49.6 (12.2)	143 (81.3%)	NR	5.6 (1.1)	1.5 (0.7)	22.5 (38.1)
	ADA (40mg/2weeks sc)	ACPA-negative	54	55.4 (12.5)	46 (85.2%)	NR	5.3 (1.1)	1.3 (0.6)	11.8 (18.6)
		ACPA-positive	203	50.0 (12.7)	164 (80.8%)	NR	5.6 (1.1)	1.5 (0.7)	20.6 (31.0)
	ADA (40mg/2weeks sc)	RF-negative	35	55.8 (11.6)	28 (80.0%)	NR	5.4 (1.0)	1.4 (0.6)	11.2 (14.9)
		RF-positive	223	50.4 (12.9)	182 (81.6%)	NR	5.5 (1.1)	1.5 (0.7)	19.8 (30.5)
	ADA (40mg/2weeks sc)	ACPA-negative RF-negative	26	56.3 (12.0)	20 (76.9%)	NR	5.5 (1.0)	1.5 (0.5)	9.1 (13.4)
		ACPA-negative RF-positive	28	54.6 (13.6)	26 (92.9%)	NR	5.3 (1.2)	1.3 (0.6)	11.8 (18.3)
		ACPA-positive RF-negative	9	54.3 (10.9)	8 (88.9%)	NR	5.1 (1.1)	1.2 (0.8)	17.3 (18.0)
		ACPA-positive RF-positive	194	49.8 (12.8)	156 (80.4%)	NR	5.6 (1.1)	1.5 (0.7)	20.7 (31.6)

SvdH, van der Heijde modified total Sharp score; ADA, adalimumab; TCZ, tocilizumab; ABT, abatacept; sc, subcutaneous; NR, not recorded

Online Supplementary Table S5.3: Head-to-head RCTs of bDMARDs: Risk of bias of RCTs

Trial name	Biological DMARD	ROB1: Random sequence generation	ROB2: Allocation concealment	ROB3: Blinding of participants and personnel	ROB4: Blinding of outcome assessment	ROB5: Incomplete outcome data	ROB6: Other bias	ROB7: Selective reporting
ADACTA [39]	ADA/TCZ	L	L	L	L	L	L	L
AMPLE [40-43]	ABT/ADA	U	U	H	L	L	L	L

ADA, adalimumab; TCZ, tocilizumab; ABT, abatacept

H = high risk; L = low risk; U = unclear risk

Online Supplementary Table S5.4: Head-to-head RCTs of bDMARDs: Disease activity outcomes of RCTs at 6 months

Trial name	Interventions	Autoantibody-subgroups	No. of patients	ACR20 (n, %)	ACR50 (n, %)	ACR70 (n, %)	DAS28-ESR (mean, SD)	ΔDAS28-ESR (mean, SD)	DAS28-ESR <2.6 (n, %)	DAS28-CRP (mean, SD)	ΔDAS28-CRP (mean, SD)	DAS28-CRP <2.6 (n, %)
ADACTA [39]	ADA (40mg/2weeks sc)	ACPA-negative	47	27 (57.4%)	14 (29.8%)	6 (12.8%)	NR	NR	NR	NR	NR	NR
		ACPA-positive	115	55 (47.8%)	31 (27%)	23 (20%)	NR	NR	NR	NR	NR	NR
	ADA (40mg/2weeks sc)	RF-negative	43	25 (58.1%)	14 (32.6%)	5 (11.6%)	NR	NR	NR	NR	NR	NR
		RF-positive	119	57 (47.9%)	31 (26.1%)	24 (20.2%)	NR	NR	NR	NR	NR	NR
	ADA (40mg/2weeks sc)	ACPA-negative RF-negative	36	22 (61.1%)	12 (33.3%)	4 (11.1%)	NR	NR	NR	NR	NR	NR
		ACPA-negative RF-positive	11	5 (45.5%)	2 (18.2%)	2 (18.2%)	NR	NR	NR	NR	NR	NR
		ACPA-positive RF-negative	7	3 (42.9%)	2 (28.6%)	1 (14.3%)	NR	NR	NR	NR	NR	NR
		ACPA-positive RF-positive	108	52 (48.1%)	29 (26.9%)	22 (20.4%)	NR	NR	NR	NR	NR	NR
	TCZ (8mg/kg/4weeks)	ACPA-negative	38	22 (57.9%)	12 (31.6%)	8 (21.1%)	NR	NR	NR	NR	NR	NR
		ACPA-positive	125	84 (67.2%)	65 (52%)	45 (36%)	NR	NR	NR	NR	NR	NR
	TCZ (8mg/kg/4weeks)	RF-negative	42	23 (54.8%)	13 (31%)	8 (19%)	NR	NR	NR	NR	NR	NR
		RF-positive	121	83 (68.6%)	64 (52.9%)	45 (37.2%)	NR	NR	NR	NR	NR	NR
	TCZ (8mg/kg/4weeks)	ACPA-negative RF-negative	28	15 (53.6%)	8 (28.6%)	5 (17.9%)	NR	NR	NR	NR	NR	NR
		ACPA-negative RF-positive	10	7 (70%)	4 (40%)	3 (30%)	NR	NR	NR	NR	NR	NR

		ACPA-positive RF-negative	14	8 (57.1%)	5 (35.7%)	3 (21.4%)	NR	NR	NR	NR	NR	NR
		ACPA-positive RF-positive	111	76 (68.5%)	60 (54.1%)	42 (37.8%)	NR	NR	NR	NR	NR	NR
AMPLE [40-43]	ABT (125mg/week sc)	ACPA-negative	66	43 (65.2%)	20 (30.3%)	9 (13.6%)	NR	NR	NR	3.4 (1.2)	-2 (1.4)	16 (24.2%)
		ACPA-positive	185	131 (70.8%)	89 (48.1%)	49 (26.5%)	NR	NR	NR	3.2 (1.3)	-2.3 (1.3)	63 (34.1%)
	ABT (125mg/week sc)	RF-negative	47	27 (57.4%)	12 (25.5%)	6 (12.8%)	NR	NR	NR	3.8 (1.4)	-1.7 (1.6)	8 (17%)
		RF-positive	204	147 (72.1%)	97 (47.5%)	52 (25.5%)	NR	NR	NR	3.2 (1.2)	-2.3 (1.3)	71 (34.8%)
	ABT (125mg/week sc)	ACPA-negative RF-negative	38	22 (57.9%)	10 (26.3%)	4 (10.5%)	NR	NR	NR	3.7 (1.2)	-1.8 (1.5)	6 (15.8%)
		ACPA-negative RF-positive	28	21 (75%)	10 (35.7%)	5 (17.9%)	NR	NR	NR	3 (1.1)	-2.2 (1.2)	10 (35.7%)
		ACPA-positive RF-negative	9	5 (55.6%)	2 (22.2%)	2 (22.2%)	NR	NR	NR	3.9 (2.1)	-1.4 (1.8)	2 (22.2%)
		ACPA-positive RF-positive	176	126 (71.6%)	87 (49.4%)	47 (26.7%)	NR	NR	NR	3.2 (1.2)	-2.3 (1.3)	61 (34.7%)
	ADA (40mg/2weeks sc)	ACPA-negative	54	28 (51.9%)	16 (29.6%)	8 (14.8%)	NR	NR	NR	3.6 (1.3)	-1.7 (1.2)	14 (25.9%)
		ACPA-positive	203	151 (74.4%)	88 (43.3%)	54 (26.6%)	NR	NR	NR	3.2 (1.4)	-2.4 (1.4)	78 (38.4%)
	ADA (40mg/2weeks sc)	RF-negative	35	19 (54.3%)	9 (25.7%)	6 (17.1%)	NR	NR	NR	3.6 (1.5)	-1.8 (1.2)	12 (34.3%)
		RF-positive	223	161 (72.2%)	96 (43%)	57 (25.6%)	NR	NR	NR	3.2 (1.4)	-2.3 (1.4)	81 (36.3%)
	ADA (40mg/2weeks sc)	ACPA-negative RF-negative	26	13 (50%)	5 (19.2%)	3 (11.5%)	NR	NR	NR	3.8 (1.4)	-1.7 (1.2)	7 (26.9%)
		ACPA-negative RF-positive	28	15 (53.6%)	11 (39.3%)	5 (17.9%)	NR	NR	NR	3.5 (1.3)	-1.7 (1.2)	7 (25%)
		ACPA-positive RF-negative	9	6 (66.7%)	4 (44.4%)	3 (33.3%)	NR	NR	NR	3 (1.7)	-2 (1.2)	5 (55.6%)

		ACPA-positive RF-positive	194	145 (74.7%)	84 (43.3%)	51 (26.3%)	NR	NR	NR	3.2 (1.4)	-2.4 (1.4)	73 (37.6%)

ADA, adalimumab; TCZ, tocilizumab; ABT, abatacept; sc, subcutaneous; NR, not recorded

Online Supplementary Table S5.5: Head-to-head RCTs of bDMARDs: Physical function and Radiographic progression of RCTs at 6 months

Trial name	Interventions	Autoantibody-subgroups	No. of patients	HAQ-DI (mean, SD)	ΔHAQ-DI (mean, SD)	HAQ-DI response ≥0.22 (n, %)	SvdH (mean, SD)	ΔSvdH (mean, SD)	ΔSvdH ≤0 (n, %)	ΔSvdH ≤0.5 (n, %)
ADACTA [39]	ADA (40mg/2weeks sc)	ACPA-negative	47	NR	NR	NR	NR	NR	NR	NR
		ACPA-positive	115	NR	NR	NR	NR	NR	NR	NR
	ADA (40mg/2weeks sc)	RF-negative	43	NR	NR	NR	NR	NR	NR	NR
		RF-positive	119	NR	NR	NR	NR	NR	NR	NR
	ADA (40mg/2weeks sc)	ACPA-negative RF-negative	36	NR	NR	NR	NR	NR	NR	NR
		ACPA-negative RF-positive	11	NR	NR	NR	NR	NR	NR	NR
		ACPA-positive RF-negative	7	NR	NR	NR	NR	NR	NR	NR
		ACPA-positive RF-positive	108	NR	NR	NR	NR	NR	NR	NR
	TCZ (8mg/kg/4weeks)	ACPA-negative	38	NR	NR	NR	NR	NR	NR	NR
		ACPA-positive	125	NR	NR	NR	NR	NR	NR	NR
	TCZ (8mg/kg/4weeks)	RF-negative	42	NR	NR	NR	NR	NR	NR	NR
		RF-positive	121	NR	NR	NR	NR	NR	NR	NR
	TCZ (8mg/kg/4weeks)	ACPA-negative RF-negative	28	NR	NR	NR	NR	NR	NR	NR
		ACPA-negative RF-positive	10	NR	NR	NR	NR	NR	NR	NR
		ACPA-positive RF-negative	14	NR	NR	NR	NR	NR	NR	NR
		ACPA-positive RF-positive	111	NR	NR	NR	NR	NR	NR	NR
AMPLE [40-43]	ABT (125mg/week sc)	ACPA-negative	66	0.9 (0.7)	-0.5 (0.6)	39 (59.1%)	NR	NR	NR	NR
		ACPA-positive	185	0.8 (0.7)	-0.7 (0.7)	133 (71.9%)	NR	NR	NR	NR
	ABT (125mg/week sc)	RF-negative	47	1.1 (0.7)	-0.4 (0.6)	27 (57.4%)	NR	NR	NR	NR
		RF-positive	204	0.8 (0.7)	-0.7 (0.7)	145 (71.1%)	NR	NR	NR	NR
	ABT (125mg/week sc)	ACPA-negative RF-negative	38	1 (0.7)	-0.4 (0.5)	23 (60.5%)	NR	NR	NR	NR
		ACPA-negative RF-positive	28	0.7 (0.6)	-0.6 (0.6)	16 (57.1%)	NR	NR	NR	NR
		ACPA-positive RF-negative	9	1.2 (0.9)	-0.5 (1)	4 (44.4%)	NR	NR	NR	NR
		ACPA-positive RF-positive	176	0.8 (0.7)	-0.7 (0.7)	129 (73.3%)	NR	NR	NR	NR
	ADA (40mg/2weeks sc)	ACPA-negative	54	1 (0.6)	-0.7 (0.4)	27 (50%)	NR	NR	NR	NR
		ACPA-positive	203	0.9 (0.7)	-0.7 (0.6)	142 (70%)	NR	NR	NR	NR
	ADA (40mg/2weeks sc)	RF-negative	35	1 (0.7)	-0.3 (0.4)	19 (54.3%)	NR	NR	NR	NR
		RF-positive	223	0.9 (0.7)	-0.6 (0.6)	151 (67.7%)	NR	NR	NR	NR

	ADA (40mg/2weeks sc)	ACPA-negative RF-negative	26	1.1 (0.6)	-0.4 (0.4)	14 (53.8%)	NR	NR	NR	NR
		ACPA-negative RF-positive	28	1 (0.6)	-0.3 (0.4)	13 (46.4%)	NR	NR	NR	NR
		ACPA-positive RF-negative	9	0.9 (0.8)	-0.3 (0.5)	5 (55.6%)	NR	NR	NR	NR
		ACPA-positive RF-positive	194	0.8 (0.7)	-0.7 (0.6)	137 (70.6%)	NR	NR	NR	NR

SvdH, van der Heijde modified total Sharp score; ADA, adalimumab; TCZ, tocilizumab; ABT, abatacept; sc, subcutaneous; NR, not recorded

3.0 Tables of efficacy outcome measures at 12 and 24 months

3.1 RCTs of bDMARDs+csDMARDs vs csDMARDs

Online Supplementary Table S6.1: MTX-naïve or csDMARD-naïve: Disease activity outcomes of RCTs at 12 months

Trial name	Interventions	Autoantibody-subgroups	No. of patients	ACR20 (n, %)	ACR50 (n, %)	ACR70 (n, %)	DAS28-ESR (mean, SD)	ΔDAS28-ESR (mean, SD)	DAS28-ESR <2.6 (n, %)	DAS28-CRP (mean, SD)	ΔDAS28-CRP (mean, SD)	DAS28-CRP <2.6 (n, %)
COMET [1]	MTX	ACPA-negative	55	33 (60%)	23 (41.8%)	12 (21.8%)	3.2 (1.6)	-3.2 (1.6)	24 (43.6%)	3.1 (1.2)	-2.8 (1.5)	24 (43.6%)
		ACPA-positive	117	93 (79.5%)	74 (63.2%)	45 (38.5%)	3.6 (1.5)	-3 (1.6)	33 (28.2%)	3.2 (1.3)	-2.7 (1.5)	46 (39.3%)
	ETN (50mg/week sc) + MTX	ACPA-negative	69	49 (71%)	41 (59.4%)	31 (44.9%)	2.7 (1.4)	-3.8 (1.6)	40 (58%)	2.7 (1.1)	-3.3 (1.4)	42 (60.9%)
		ACPA-positive	136	132 (97.1%)	109 (80.1%)	76 (55.9%)	2.8 (1.2)	-3.7 (1.4)	70 (51.5%)	2.6 (1)	-3.3 (1.2)	77 (56.6%)
NEORACo [5]	DMARDs[1]	ACPA-negative	11	10 (90.9%)	9 (81.8%)	6 (54.5%)	2.7 (1.5)	-3.8 (1.7)	8 (72.7%)	2.6 (1.3)	-3.7 (1.6)	8 (72.7%)
		ACPA-positive	34	34 (100%)	31 (91.2%)	30 (88.2%)	1.4 (0.7)	-3.7 (1.4)	33 (97.1%)	1.7 (0.5)	-3.3 (1.2)	33 (97.1%)
	DMARDs[1]	RF-negative	12	12 (100%)	11 (91.7%)	9 (75%)	1.9 (1)	-4.3 (1.1)	11 (91.7%)	2 (0.7)	-3.9 (1.2)	11 (91.7%)
		RF-positive	33	32 (97%)	29 (87.9%)	27 (81.8%)	1.7 (1.1)	-3.6 (1.5)	30 (90.9%)	1.9 (0.9)	-3.2 (1.3)	30 (90.9%)
	DMARDs[1]	ACPA-negative RF-negative	6	6 (100%)	6 (100%)	4 (66.7%)	2.4 (1)	-4.3 (1.1)	5 (83.3%)	2.2 (0.8)	-4.2 (1.1)	5 (83.3%)
		ACPA-negative RF-positive	5	4 (80%)	3 (60%)	2 (40%)	3.1 (2)	-3.2 (2.3)	3 (60%)	2.9 (1.7)	-3.1 (2)	3 (60%)
		ACPA-positive RF-negative	6	6 (100%)	5 (83.3%)	5 (83.3%)	1.3 (0.7)	-4.3 (1.1)	6 (100%)	1.7 (0.6)	-3.6 (1.3)	6 (100%)
		ACPA-positive RF-positive	28	28 (100%)	26 (92.9%)	25 (89.3%)	1.4 (0.7)	-3.6 (1.4)	27 (96.4%)	1.7 (0.5)	-3.2 (1.2)	27 (96.4%)
	IFX (3mg/kg) + DMARDs[1]	ACPA-negative	11	11 (100%)	11 (100%)	10 (90.9%)	1.7 (0.5)	-4.8 (1)	11 (100%)	1.7 (0.3)	-4.5 (0.9)	11 (100%)

		ACPA-positive	35	35 (100%)	33 (94.3%)	31 (88.6%)	1.5 (0.9)	-3.8 (1.2)	32 (91.4%)	1.6 (0.6)	-3.2 (1.1)	32 (91.4%)
	IFX (3mg/kg) + DMARDs[1]	RF-negative	10	10 (100%)	10 (100%)	9 (90%)	1.4 (0.6)	-4.6 (1.2)	10 (100%)	1.6 (0.3)	-4.2 (1)	10 (100%)
		RF-positive	36	36 (100%)	34 (94.4%)	32 (88.9%)	1.6 (0.9)	-3.8 (1.2)	33 (91.7%)	1.7 (0.6)	-3.3 (1.1)	33 (91.7%)
	IFX (3mg/kg) + DMARDs[1]	ACPA-negative RF-negative	7	7 (100%)	7 (100%)	6 (85.7%)	1.6 (0.5)	-4.8 (1.2)	7 (100%)	1.7 (0.3)	-4.4 (1)	7 (100%)
		ACPA-negative RF-positive	4	4 (100%)	4 (100%)	4 (100%)	1.7 (0.6)	-4.7 (0.6)	4 (100%)	1.6 (0.2)	-4.7 (0.6)	4 (100%)
		ACPA-positive RF-negative	3	3 (100%)	3 (100%)	3 (100%)	0.8 (0.3)	-4 (1)	3 (100%)	1.4 (0.2)	-3.9 (1.2)	3 (100%)
		ACPA-positive RF-positive	32	32 (100%)	30 (93.8%)	28 (87.5%)	1.5 (0.9)	-3.7 (1.3)	29 (90.6%)	1.7 (0.7)	-3.2 (1.1)	29 (90.6%)
Swefot [6, 7]	DMARDs[1]	ACPA-negative	55	NR	NR	NR	3.5 (1.3)	-1.4 (1.4)	13 (23.6%)	3.4 (1.1)	-1.2 (1.3)	12 (21.8%)
		ACPA-positive	71	NR	NR	NR	3.2 (1.2)	-1.5 (1.1)	20 (28.2%)	3.1 (1)	-1.2 (1)	21 (29.6%)
	DMARDs[1]	RF-negative	45	NR	NR	NR	3.1 (1.1)	-1.8 (1.3)	14 (31.1%)	3.1 (0.9)	-1.5 (1.2)	13 (28.9%)
		RF-positive	84	NR	NR	NR	3.4 (1.3)	-1.3 (1.2)	22 (26.2%)	3.3 (1.2)	-1.1 (1.1)	22 (26.2%)
	DMARDs[1]	ACPA-negative RF-negative	29	NR	NR	NR	3 (1.1)	-1.7 (1.5)	10 (34.5%)	3.1 (0.9)	-1.5 (1.3)	8 (27.6%)
		ACPA-negative RF-positive	26	NR	NR	NR	4 (1.2)	-1 (1.2)	3 (11.5%)	3.8 (1.3)	-0.8 (1.1)	4 (15.4%)
		ACPA-positive RF-negative	15	NR	NR	NR	3.2 (1.1)	-1.8 (1)	3 (20%)	3.1 (1)	-1.6 (1)	5 (33.3%)
		ACPA-positive RF-positive	55	NR	NR	NR	3.2 (1.3)	-1.4 (1.1)	17 (30.9%)	3.1 (1)	-1.2 (1)	16 (29.1%)
	IFX (3mg/kg) + MTX	ACPA-negative	36	NR	NR	NR	3.3 (1.4)	-1.7 (1.3)	10 (27.8%)	3.2 (1.3)	-1.5 (1.2)	14 (38.9%)
		ACPA-positive	80	NR	NR	NR	3.2 (1.5)	-1.6 (1.2)	26 (32.5%)	3.1 (1.3)	-1.5 (1.1)	39 (48.8%)

	IFX (3mg/kg) + MTX	RF-negative	39	NR	NR	NR	3.2 (1.4)	-1.8 (1.3)	15 (38.5%)	3 (1.2)	-1.6 (1.1)	17 (43.6%)
		RF-positive	88	NR	NR	NR	3.3 (1.5)	-1.6 (1.2)	26 (29.5%)	3.1 (1.3)	-1.4 (1.1)	40 (45.5%)
	IFX (3mg/kg) + MTX	ACPA-negative RF-negative	21	NR	NR	NR	3.2 (1.5)	-1.8 (1.4)	7 (33.3%)	3.1 (1.4)	-1.5 (1.3)	8 (38.1%)
		ACPA-negative RF-positive	14	NR	NR	NR	3.5 (1.2)	-1.5 (1.1)	3 (21.4%)	3 (1.3)	-1.5 (1.2)	6 (42.9%)
		ACPA-positive RF-negative	16	NR	NR	NR	3.2 (1.3)	-1.9 (1.2)	6 (37.5%)	3 (1.1)	-1.7 (1.1)	7 (43.8%)
		ACPA-positive RF-positive	64	NR	NR	NR	3.2 (1.6)	-1.5 (1.3)	20 (31.3%)	3.1 (1.4)	-1.4 (1.1)	32 (50%)

MTX, methotrexate; DMARDs, disease-modifying antirheumatic drugs; ETN, etanercept; IFX, infliximab; NR; sc, subcutaneous; not recorded

[1]The triple combination of methotrexate (MTX), sulfasalazine (SSZ) and hydroxychloroquine (HCQ)

**DAS28-ESR and DAS28-CRP were assessed 6, 12 and 24 months after randomization (9, 15 and 27 months from baseline and MTX start)*

Online Supplementary Table S6.2: MTX-naïve or csDMARD-naïve: Physical function and Radiographic progression of RCTs at 12 months

Trial name	Interventions	Autoantibody-subgroups	No. of patients	HAQ-DI (mean, SD)	ΔHAQ-DI (mean, SD)	HAQ-DI response ≥0.22 (n, %)	SvdH (mean, SD)	ΔSvdH (mean, SD)	ΔSvdH ≤0 (n, %)	ΔSvdH ≤0.5 (n, %)
COMET [1]	MTX	ACPA-negative	55	0.8 (0.7)	-0.8 (0.6)	43 (78.2%)	5.3 (7.7)	0.6 (4)	34 (61.8%)	36 (65.5%)
		ACPA-positive	117	0.8 (0.7)	-0.9 (0.7)	93 (79.5%)	16.1 (26.8)	3 (6.3)	32 (27.4%)	44 (37.6%)
	ETN (50mg/week sc) + MTX	ACPA-negative	69	0.7 (0.7)	-1 (0.8)	54 (78.3%)	5.1 (7)	-0.1 (1.2)	47 (68.1%)	56 (81.2%)
		ACPA-positive	136	0.5 (0.6)	-1.1 (0.6)	123 (90.4%)	7.6 (12.9)	0.5 (2.9)	82 (60.3%)	95 (69.9%)
NEORACo [5]	DMARDs[1]	ACPA-negative	11	0.3 (0.5)	-1 (0.7)	11 (100%)	NR	NR	NR	NR
		ACPA-positive	34	0 (0.1)	-0.6 (0.6)	23 (67.6%)	NR	NR	NR	NR
	DMARDs[1]	RF-negative	12	0.1 (0.3)	-1 (0.7)	12 (100%)	NR	NR	NR	NR
		RF-positive	33	0.1 (0.3)	-0.6 (0.6)	22 (66.7%)	NR	NR	NR	NR
	DMARDs[1]	ACPA-negative RF-negative	6	0.1 (0.2)	-1.2 (0.8)	6 (100%)	NR	NR	NR	NR
		ACPA-negative RF-positive	5	0.6 (0.6)	-0.7 (0.7)	5 (100%)	NR	NR	NR	NR
		ACPA-positive RF-negative	6	0.2 (0.3)	-0.7 (0.5)	6 (100%)	NR	NR	NR	NR
		ACPA-positive RF-positive	28	0 (0.1)	-0.6 (0.6)	17 (60.7%)	NR	NR	NR	NR
	IFX (3mg/kg) + DMARDs[1]	ACPA-negative	11	0 (0)	-1.5 (0.7)	11 (100%)	NR	NR	NR	NR
		ACPA-positive	35	0.1 (0.3)	-0.9 (0.5)	32 (91.4%)	NR	NR	NR	NR
	IFX (3mg/kg) + DMARDs[1]	RF-negative	10	0 (0)	-1.3 (0.7)	10 (100%)	NR	NR	NR	NR
		RF-positive	36	0.1 (0.3)	-0.9 (0.5)	33 (91.7%)	NR	NR	NR	NR
	IFX (3mg/kg) + DMARDs[1]	ACPA-negative RF-negative	7	0 (0)	-1.4 (0.7)	7 (100%)	NR	NR	NR	NR
		ACPA-negative RF-positive	4	0 (0.1)	-1.6 (0.6)	4 (100%)	NR	NR	NR	NR
		ACPA-positive RF-negative	3	0 (0)	-1 (0.7)	3 (100%)	NR	NR	NR	NR
		ACPA-positive RF-positive	32	0.1 (0.3)	-0.8 (0.5)	29 (90.6%)	NR	NR	NR	NR
Swefot [6, 7]	DMARDs[1]	ACPA-negative	55	0.8 (0.6)	-0.3 (0.5)	43 (78.2%)	NR	NR	NR	NR
		ACPA-positive	71	0.6 (0.6)	-0.4 (0.4)	38 (53.5%)	NR	NR	NR	NR
	DMARDs[1]	RF-negative	45	0.7 (0.6)	-0.4 (0.5)	34 (75.6%)	NR	NR	NR	NR
		RF-positive	84	0.6 (0.6)	-0.3 (0.4)	48 (57.1%)	NR	NR	NR	NR
	DMARDs[1]	ACPA-negative RF-negative	29	0.8 (0.6)	-0.3 (0.5)	24 (82.8%)	NR	NR	NR	NR
		ACPA-negative RF-positive	26	0.9 (0.7)	-0.3 (0.4)	19 (73.1%)	NR	NR	NR	NR
		ACPA-positive RF-negative	15	0.6 (0.6)	-0.6 (0.4)	10 (66.7%)	NR	NR	NR	NR
		ACPA-positive RF-positive	55	0.5 (0.5)	-0.3 (0.4)	28 (50.9%)	NR	NR	NR	NR
	IFX (3mg/kg) + MTX	ACPA-negative	36	0.7 (0.6)	-0.3 (0.4)	27 (75%)	NR	NR	NR	NR

		ACPA-positive	80	0.6 (0.5)	-0.3 (0.5)	57 (71.3%)	NR	NR	NR	NR
	IFX (3mg/kg) + MTX	RF-negative	39	0.6 (0.6)	-0.3 (0.4)	27 (69.2%)	NR	NR	NR	NR
		RF-positive	88	0.7 (0.5)	-0.3 (0.5)	64 (72.7%)	NR	NR	NR	NR
	IFX (3mg/kg) + MTX	ACPA-negative RF-negative	21	0.7 (0.7)	-0.3 (0.5)	15 (71.4%)	NR	NR	NR	NR
		ACPA-negative RF-positive	14	0.8 (0.5)	-0.2 (0.4)	11 (78.6%)	NR	NR	NR	NR
		ACPA-positive RF-negative	16	0.6 (0.5)	-0.2 (0.3)	11 (68.8%)	NR	NR	NR	NR
		ACPA-positive RF-positive	64	0.6 (0.6)	-0.3 (0.5)	46 (71.9%)	NR	NR	NR	NR

SvdH, van der Heijde modified total Sharp score; MTX, methotrexate; DMARDs, disease-modifying antirheumatic drugs; ETN, etanercept; IFX, infliximab; NR; sc, subcutaneous; not recorded

[1]The triple combination of methotrexate (MTX), sulfasalazine (SSZ) and hydroxychloroquine (HCQ)

**HAQ-DI was assessed 6, 12 and 24 months after randomization (9, 15 and 27 months from baseline and MTX start)*

Online Supplementary Table S6.3: MTX-naïve or csDMARD-naïve: Disease activity outcomes of RCTs at 24 months

Trial name	Interventions	Autoantibody-subgroups	No. of patients	ACR20 (n, %)	ACR50 (n, %)	ACR70 (n, %)	DAS28-ESR (mean, SD)	ΔDAS28-ESR (mean, SD)	DAS28-ESR <2.6 (n, %)	DAS28-CRP (mean, SD)	ΔDAS28-CRP (mean, SD)	DAS28-CRP <2.6 (n, %)
COMET [1]	MTX	ACPA-negative	55	NR	NR	NR	3.3 (1.8)	-3.2 (1.8)	26 (47.3%)	3.1 (1.5)	-2.8 (1.6)	23 (41.8%)
		ACPA-positive	117	NR	NR	NR	3 (1.5)	-3.5 (1.7)	52 (44.4%)	2.8 (1.3)	-3.2 (1.5)	61 (52.1%)
	ETN (50mg/week sc) + MTX	ACPA-negative	69	NR	NR	NR	2.5 (1.2)	-4 (1.5)	41 (59.4%)	2.5 (0.9)	-3.4 (1.3)	38 (55.1%)
		ACPA-positive	136	NR	NR	NR	3 (1.5)	-3.4 (1.5)	71 (52.2%)	2.7 (1.4)	-3.2 (1.4)	80 (58.8%)
NEORACo [5]	DMARDs[1]	ACPA-negative	11	11 (100%)	9 (81.8%)	7 (63.6%)	2.3 (1)	-4.2 (1.5)	7 (63.6%)	2.3 (1)	-4 (1.1)	8 (72.7%)
		ACPA-positive	34	33 (97.1%)	33 (97.1%)	26 (76.5%)	1.3 (0.6)	-3.9 (1.3)	33 (97.1%)	1.7 (0.5)	-3.3 (1.1)	32 (94.1%)
	DMARDs[1]	RF-negative	12	12 (100%)	12 (100%)	9 (75%)	1.5 (1)	-4.7 (1.3)	10 (83.3%)	1.8 (0.7)	-4.2 (1)	11 (91.7%)
		RF-positive	33	32 (97%)	30 (90.9%)	24 (72.7%)	1.6 (0.8)	-3.7 (1.3)	30 (90.9%)	1.8 (0.7)	-3.3 (1.1)	29 (87.9%)
	DMARDs[1]	ACPA-negative RF-negative	6	6 (100%)	6 (100%)	5 (83.3%)	2 (0.9)	-4.7 (1.3)	4 (66.7%)	2 (0.9)	-4.5 (1.4)	5 (83.3%)
		ACPA-negative RF-positive	5	5 (100%)	3 (60%)	2 (40%)	2.7 (1)	-3.6 (1.7)	3 (60%)	2.7 (0.9)	-3.3 (1.5)	3 (60%)
		ACPA-positive RF-negative	6	6 (100%)	6 (100%)	4 (66.7%)	0.9 (0.7)	-4.7 (1.4)	6 (100%)	1.6 (0.4)	-3.7 (1.3)	6 (100%)
		ACPA-positive RF-positive	28	27 (96.4%)	27 (96.4%)	22 (78.6%)	1.4 (0.6)	-3.7 (1.3)	27 (96.4%)	1.7 (0.5)	-3.2 (1)	26 (92.9%)
	IFX (3mg/kg) + DMARDs[1]	ACPA-negative	11	10 (90.9%)	10 (90.9%)	9 (81.8%)	2.1 (1.4)	-4.3 (1.4)	9 (81.8%)	2.1 (1.1)	-4 (1.1)	9 (81.8%)
		ACPA-positive	35	35 (100%)	35 (100%)	31 (88.6%)	1.4 (0.8)	-3.8 (1.2)	32 (91.4%)	1.6 (0.6)	-3.3 (1.1)	32 (91.4%)

	IFX (3mg/kg) + DMARDs[1]	RF-negative	10	10 (100%)	10 (100%)	9 (90%)	1.5 (0.7)	-4.4 (1.2)	9 (90%)	1.7 (0.5)	-4.2 (1)	9 (90%)
		RF-positive	36	35 (97.2%)	35 (97.2%)	31 (86.1%)	1.6 (1.1)	-3.8 (1.2)	32 (88.9%)	1.7 (0.8)	-3.3 (1.1)	32 (88.9%)
	IFX (3mg/kg) + DMARDs[1]	ACPA-negative RF-negative	7	7 (100%)	7 (100%)	6 (85.7%)	1.8 (0.7)	-4.6 (1.3)	6 (85.7%)	1.9 (0.6)	-4.2 (1.1)	6 (85.7%)
		ACPA-negative RF-positive	4	3 (75%)	3 (75%)	3 (75%)	2.6 (2.3)	-3.8 (1.6)	3 (75%)	2.5 (1.8)	-3.8 (1.3)	3 (75%)
		ACPA-positive RF-negative	3	3 (100%)	3 (100%)	3 (100%)	0.9 (0.3)	-3.9 (1.1)	3 (100%)	1.3 (0.1)	-4.1 (1)	3 (100%)
		ACPA-positive RF-positive	32	32 (100%)	32 (100%)	28 (87.5%)	1.4 (0.8)	-3.8 (1.2)	29 (90.6%)	1.6 (0.6)	-3.2 (1.1)	29 (90.6%)
Swefot [6, 7]	DMARDs[1]	ACPA-negative	55	NR	NR	NR	3 (1.3)	-1.9 (1.4)	24 (43.6%)	2.9 (1.1)	-1.7 (1.3)	22 (40%)
		ACPA-positive	71	NR	NR	NR	2.9 (1.2)	-2 (1.4)	27 (38%)	2.7 (1.1)	-1.8 (1.3)	32 (45.1%)
	DMARDs[1]	RF-negative	45	NR	NR	NR	2.9 (1.2)	-1.9 (1.6)	17 (37.8%)	3 (1)	-1.7 (1.5)	16 (35.6%)
		RF-positive	84	NR	NR	NR	2.9 (1.3)	-2 (1.3)	36 (42.9%)	2.7 (1.1)	-1.7 (1.1)	40 (47.6%)
	DMARDs[1]	ACPA-negative RF-negative	29	NR	NR	NR	2.7 (1.2)	-2 (1.6)	15 (51.7%)	2.9 (1)	-1.8 (1.5)	12 (41.4%)
		ACPA-negative RF-positive	26	NR	NR	NR	3.3 (1.4)	-1.8 (1.2)	9 (34.6%)	2.9 (1.2)	-1.6 (1)	10 (38.5%)
		ACPA-positive RF-negative	15	NR	NR	NR	3.4 (1)	-1.7 (1.6)	1 (6.7%)	3.2 (0.9)	-1.4 (1.6)	3 (20%)
		ACPA-positive RF-positive	55	NR	NR	NR	2.7 (1.2)	-2.1 (1.3)	26 (47.3%)	2.6 (1.1)	-1.8 (1.2)	28 (50.9%)
	IFX (3mg/kg) + MTX	ACPA-negative	36	NR	NR	NR	3.3 (1.3)	-1.8 (1.2)	12 (33.3%)	3 (1.2)	-1.7 (1.1)	15 (41.7%)
		ACPA-positive	80	NR	NR	NR	3.2 (1.5)	-1.6 (1.4)	29 (36.3%)	3 (1.3)	-1.6 (1.2)	33 (41.3%)
	IFX (3mg/kg) + MTX	RF-negative	39	NR	NR	NR	3.2 (1.5)	-1.8 (1.3)	18 (46.2%)	2.9 (1.4)	-1.7 (1.1)	19 (48.7%)

		RF-positive	88	NR	NR	NR	3.2 (1.4)	-1.6 (1.3)	29 (33%)	3 (1.2)	-1.6 (1.1)	35 (39.8%)
	IFX (3mg/kg) + MTX	ACPA-negative RF-negative	21	NR	NR	NR	3 (1.4)	-2 (1)	10 (47.6%)	2.8 (1.2)	-1.8 (1.1)	10 (47.6%)
		ACPA-negative RF-positive	14	NR	NR	NR	3.7 (1.2)	-1.3 (1.4)	2 (14.3%)	3.3 (1.2)	-1.3 (1.2)	5 (35.7%)
		ACPA-positive RF-negative	16	NR	NR	NR	3.5 (1.7)	-1.5 (1.7)	6 (37.5%)	3.2 (1.6)	-1.5 (1.3)	7 (43.8%)
		ACPA-positive RF-positive	64	NR	NR	NR	3.1 (1.4)	-1.6 (1.3)	23 (35.9%)	2.9 (1.2)	-1.6 (1.2)	26 (40.6%)

MTX, methotrexate; DMARDs, disease-modifying antirheumatic drugs; ETN, etanercept; IFX, infliximab; NR; sc, subcutaneous; not recorded

[1]The triple combination of methotrexate (MTX), sulfasalazine (SSZ) and hydroxychloroquine (HCQ)

**DAS28-ESR and DAS28-CRP were assessed 6, 12 and 24 months after randomization (9, 15 and 27 months from baseline and MTX start)*

Online Supplementary Table S6.4: MTX-naïve or csDMARD-naïve: Physical function and Radiographic progression of RCTs at 24 months

Trial name	Interventions	Autoantibody-subgroups	No. of patients	HAQ-DI (mean, SD)	ΔHAQ-DI (mean, SD)	HAQ-DI response ≥0.22 (n, %)	SvdH (mean, SD)	ΔSvdH (mean, SD)	ΔSvdH ≤0 (n, %)	ΔSvdH ≤0.5 (n, %)
COMET [1]	MTX	ACPA-negative	55	0.7 (0.7)	-0.8 (0.7)	40 (72.7%)	5.4 (8.5)	0.9 (5)	31 (56.4%)	38 (69.1%)
		ACPA-positive	117	0.7 (0.7)	-1 (0.7)	94 (80.3%)	17.7 (29.5)	4.6 (11.2)	34 (29.1%)	38 (32.5%)
	ETN (50mg/week sc) + MTX	ACPA-negative	69	0.7 (0.7)	-1 (0.7)	55 (79.7%)	5.1 (7)	0 (1.3)	50 (72.5%)	56 (81.2%)
		ACPA-positive	136	0.6 (0.7)	-1.1 (0.7)	121 (89%)	7.6 (13)	0.5 (3.4)	80 (58.8%)	92 (67.6%)
NEORACo [5]	DMARDs[1]	ACPA-negative	11	0.2 (0.2)	-1.2 (0.7)	11 (100%)	2 (3)	1.8 (3.1)	6 (54.5%)	NR
		ACPA-positive	34	0.1 (0.3)	-0.6 (0.5)	23 (67.6%)	4.1 (6.3)	1.3 (2.3)	18 (52.9%)	NR
	DMARDs[1]	RF-negative	12	0.1 (0.2)	-1 (0.7)	12 (100%)	1.5 (2.1)	0.7 (2.1)	8 (66.7%)	NR
		RF-positive	33	0.1 (0.3)	-0.6 (0.5)	22 (66.7%)	4.3 (6.4)	1.7 (2.6)	16 (48.5%)	NR
	DMARDs[1]	ACPA-negative RF-negative	6	0 (0.1)	-1.3 (0.7)	6 (100%)	0.8 (1)	0.5 (1.2)	4 (66.7%)	NR
		ACPA-negative RF-positive	5	0.3 (0.3)	-1 (0.7)	5 (100%)	3.4 (4.1)	3.4 (4.1)	2 (40%)	NR
		ACPA-positive RF-negative	6	0.1 (0.3)	-0.7 (0.6)	6 (100%)	2.2 (2.8)	0.8 (2.8)	4 (66.7%)	NR
		ACPA-positive RF-positive	28	0.1 (0.3)	-0.5 (0.5)	17 (60.7%)	4.5 (6.8)	1.4 (2.2)	14 (50%)	NR
	IFX (3mg/kg) + DMARDs[1]	ACPA-negative	11	0.1 (0.3)	-1.4 (0.7)	11 (100%)	0.2 (0.4)	0 (0.5)	10 (90.9%)	NR
		ACPA-positive	35	0.1 (0.3)	-0.8 (0.5)	32 (91.4%)	3.3 (6.7)	-0.3 (2.9)	27 (77.1%)	NR
	IFX (3mg/kg) + DMARDs[1]	RF-negative	10	0 (0.1)	-1.2 (0.7)	10 (100%)	0.6 (1.3)	-0.2 (0.4)	10 (100%)	NR
		RF-positive	36	0.1 (0.3)	-0.9 (0.5)	33 (91.7%)	3.1 (6.6)	-0.2 (2.9)	27 (75%)	NR
	IFX (3mg/kg) + DMARDs[1]	ACPA-negative RF-negative	7	0 (0.1)	-1.3 (0.7)	7 (100%)	0 (0)	-0.1 (0.3)	7 (100%)	NR
		ACPA-negative RF-positive	4	0.2 (0.4)	-1.4 (0.6)	4 (100%)	0.5 (0.6)	0.3 (0.5)	3 (75%)	NR
		ACPA-positive RF-negative	3	0 (0)	-1 (0.7)	3 (100%)	2 (1.7)	-0.3 (0.6)	3 (100%)	NR
		ACPA-positive RF-positive	32	0.1 (0.3)	-0.8 (0.4)	29 (90.6%)	3.4 (7)	-0.3 (3.1)	24 (75%)	NR
Swefot [6, 7]	DMARDs[1]	ACPA-negative	55	0.7 (0.6)	-0.4 (0.5)	36 (65.5%)	NR	NR	NR	NR
		ACPA-positive	71	0.5 (0.5)	-0.4 (0.5)	39 (54.9%)	NR	NR	NR	NR
	DMARDs[1]	RF-negative	45	0.7 (0.6)	-0.4 (0.5)	28 (62.2%)	NR	NR	NR	NR
		RF-positive	84	0.5 (0.5)	-0.4 (0.5)	46 (54.8%)	NR	NR	NR	NR
	DMARDs[1]	ACPA-negative RF-negative	29	0.7 (0.6)	-0.4 (0.5)	19 (65.5%)	NR	NR	NR	NR
		ACPA-negative RF-positive	26	0.8 (0.6)	-0.3 (0.5)	17 (65.4%)	NR	NR	NR	NR
		ACPA-positive RF-negative	15	0.8 (0.7)	-0.4 (0.6)	9 (60%)	NR	NR	NR	NR
		ACPA-positive RF-positive	55	0.5 (0.4)	-0.4 (0.5)	29 (52.7%)	NR	NR	NR	NR
	IFX (3mg/kg) + MTX	ACPA-negative	36	0.7 (0.6)	-0.3 (0.4)	23 (63.9%)	NR	NR	NR	NR

		ACPA-positive	80	0.6 (0.5)	-0.3 (0.6)	47 (58.8%)	NR	NR	NR	NR
	IFX (3mg/kg) + MTX	RF-negative	39	0.6 (0.6)	-0.3 (0.4)	23 (59%)	NR	NR	NR	NR
		RF-positive	88	0.6 (0.5)	-0.4 (0.6)	52 (59.1%)	NR	NR	NR	NR
	IFX (3mg/kg) + MTX	ACPA-negative RF-negative	21	0.6 (0.7)	-0.4 (0.3)	12 (57.1%)	NR	NR	NR	NR
		ACPA-negative RF-positive	14	0.8 (0.5)	-0.8 (0.4)	10 (71.4%)	NR	NR	NR	NR
		ACPA-positive RF-negative	16	0.6 (0.5)	-0.1 (0.4)	10 (62.5%)	NR	NR	NR	NR
		ACPA-positive RF-positive	64	0.5 (0.5)	-0.4 (0.6)	37 (57.8%)	NR	NR	NR	NR

SvdH, van der Heijde modified total Sharp score; MTX, methotrexate; DMARDs, disease-modifying antirheumatic drugs; ETN, etanercept; IFX, infliximab; NR; sc, subcutaneous; not recorded

[1]The triple combination of methotrexate (MTX), sulfasalazine (SSZ) and hydroxychloroquine (HCQ)

**HAQ-DI was assessed 6, 12 and 24 months after randomization (9, 15 and 27 months from baseline and MTX start)*

Online Supplementary Table S7.1: MTX-IR or csDMARD-IR: Disease activity outcomes of RCTs at 12 months

Trial name	Interventions	Autoantibody-subgroups	No. of patients	ACR20 (n, %)	ACR50 (n, %)	ACR70 (n, %)	DAS28-ESR (mean, SD)	ΔDAS28-ESR (mean, SD)	DAS28-ESR <2.6 (n, %)	DAS28-CRP (mean, SD)	ΔDAS28-CRP (mean, SD)	DAS28-CRP <2.6 (n, %)
AIM [8-10]	MTX	RF-negative	27	8 (29.6%)	4 (14.8%)	2 (7.4%)	5.4 (1.6)	-1.2 (1.2)	5 (18.5%)	5 (1.6)	-1.5 (1.3)	0 (0%)
		RF-positive	171	74 (43.3%)	36 (21.1%)	12 (7%)	5 (1.1)	-1.8 (1.2)	4 (2.3%)	4.5 (1.2)	-1.8 (1.2)	4 (2.3%)
	ABT (10mg/kg according to weight range) + MTX	RF-negative	48	32 (66.7%)	23 (47.9%)	16 (33.3%)	3.7 (1.2)	-2.9 (1.3)	11 (22.9%)	3.6 (1.2)	-2.7 (1.3)	11 (22.9%)
		RF-positive	349	263 (75.4%)	171 (49%)	100 (28.7%)	3.9 (1.3)	-3 (1.4)	79 (22.6%)	3.5 (1.2)	-2.8 (1.3)	79 (22.6%)
Kay 2008 [12]	MTX	RF-negative	7	0 (0%)	0 (0%)	0 (0%)	NR	NR	NR	NR	NR	NR
		RF-positive	27	0 (0%)	0 (0%)	0 (0%)	NR	NR	NR	NR	NR	NR
	GLM (50mg/4weeks sc) + MTX	RF-negative	4	4 (100%)	1 (25%)	1 (25%)	NR	NR	NR	NR	NR	NR
		RF-positive	28	15 (53.6%)	11 (39.3%)	5 (17.9%)	NR	NR	NR	NR	NR	NR
RAPID1 [15, 16]	MTX	RF-negative	34	5 (14.7%)	3 (8.8%)	NR	5.9 (1.5)	-1 (1.5)	1 (2.9%)	5.5 (1.3)	-0.6 (1.3)	0 (0%)
		RF-positive	164	21 (12.8%)	12 (7.3%)	NR	6.3 (1.4)	-0.7 (1.3)	2 (1.2%)	5.7 (1.5)	-0.6 (1.3)	6 (3.7%)
	CZP (200mg/2weeks sc) + MTX	RF-negative	80	36 (45%)	26 (32.5%)	NR	4.5 (1.5)	-2.2 (1.6)	7 (8.8%)	4 (1.5)	-1.9 (1.7)	17 (21.3%)
		RF-positive	312	172 (55.1%)	123 (39.4%)	NR	4.3 (1.7)	-2.7 (1.6)	55 (17.6%)	3.8 (1.6)	-2.5 (1.5)	83 (26.6%)
SERENE [19]	MTX	ACPA-negative	31	14 (45.2%)	7 (22.6%)	2 (6.5%)	NR	NR	NR	NR	NR	NR
		ACPA-positive	137	77 (56.2%)	30 (21.9%)	15 (10.9%)	NR	NR	NR	NR	NR	NR
	MTX	RF-negative	43	16 (37.2%)	8 (18.6%)	4 (9.3%)	NR	NR	NR	NR	NR	NR

		RF-positive	129	79 (61.2%)	30 (23.3%)	14 (10.9%)	NR	NR	NR	NR	NR	NR
	MTX	ACPA-negative RF-negative	25	8 (32%)	5 (20%)	2 (8%)	NR	NR	NR	NR	NR	NR
		ACPA-negative RF-positive	6	6 (100%)	2 (33.3%)	0 (0%)	NR	NR	NR	NR	NR	NR
		ACPA-positive RF-negative	17	7 (41.2%)	3 (17.6%)	2 (11.8%)	NR	NR	NR	NR	NR	NR
		ACPA-positive RF-positive	120	70 (58.3%)	27 (22.5%)	13 (10.8%)	NR	NR	NR	NR	NR	NR
	RTX (2× 1000mg) + MTX	ACPA-negative	29	16 (55.2%)	6 (20.7%)	1 (3.4%)	NR	NR	NR	NR	NR	NR
		ACPA-positive	138	79 (57.2%)	49 (35.5%)	21 (15.2%)	NR	NR	NR	NR	NR	NR
	RTX (2× 1000mg) + MTX	RF-negative	45	27 (60%)	13 (28.9%)	2 (4.4%)	NR	NR	NR	NR	NR	NR
		RF-positive	125	70 (56%)	44 (35.2%)	21 (16.8%)	NR	NR	NR	NR	NR	NR
	RTX (2× 1000mg) + MTX	ACPA-negative RF-negative	24	13 (54.2%)	5 (20.8%)	0 (0%)	NR	NR	NR	NR	NR	NR
		ACPA-negative RF-positive	5	3 (60%)	1 (20%)	1 (20%)	NR	NR	NR	NR	NR	NR
		ACPA-positive RF-negative	19	12 (63.2%)	6 (31.6%)	1 (5.3%)	NR	NR	NR	NR	NR	NR
		ACPA-positive RF-positive	119	67 (56.3%)	43 (36.1%)	20 (16.8%)	NR	NR	NR	NR	NR	NR
Combe 2006 [22, 23]	SSZ	RF-negative	15	4 (26.7%)	0 (0%)	0 (0%)	6.8 (2)	-0.5 (1.6)	0 (0%)	6.6 (1.7)	-0.4 (1.6)	0 (0%)
		RF-positive	33	10 (30.3%)	3 (9.1%)	0 (0%)	6.7 (1.9)	-0.7 (1.7)	1 (3%)	6.3 (1.9)	-0.6 (1.7)	1 (3%)
	ETN (2× 25mg/week sc) + SSZ	RF-negative	28	21 (75%)	14 (50%)	6 (21.4%)	3.8 (2.2)	-3.4 (1.9)	10 (35.7%)	4 (1.9)	-3 (1.7)	6 (21.4%)
		RF-positive	68	53 (77.9%)	38 (55.9%)	20 (29.4%)	4.2 (1.8)	-3.3 (1.6)	11 (16.2%)	3.9 (1.6)	-3.1 (1.5)	14 (20.6%)

TEMPO [25-28]	MTX	RF-negative	55	39 (70.9%)	17 (30.9%)	7 (12.7%)	4 (1.6)	-2.2 (1.5)	13 (23.6%)	3.9 (1.3)	-2.1 (1.3)	7 (12.7%)
		RF-positive	164	124 (75.6%)	76 (46.3%)	32 (19.5%)	4.4 (1.6)	-2.6 (1.5)	23 (14%)	3.9 (1.5)	-2.5 (1.5)	41 (25%)
	ETN (2× 25mg/week sc) + MTX	RF-negative	50	41 (82%)	33 (66%)	18 (36%)	3.4 (1.4)	-3.1 (1.3)	12 (24%)	3.3 (1.4)	-2.8 (1.4)	19 (38%)
		RF-positive	177	152 (85.9%)	124 (70.1%)	78 (44.1%)	3.3 (1.5)	-3.6 (1.5)	69 (39%)	3.1 (1.4)	-3.4 (1.4)	81 (45.8%)

MTX, methotrexate; SSZ, sulfasalazine; ABT, abatacept; CZP, certolizumab pegol; RTX, rituximab; ETN, etanercept; sc, subcutaneous; NR, not recorded

Online Supplementary Table S7.2: MTX-IR or csDMARD-IR: Physical function and Radiographic progression of RCTs at 12 months

Trial name	Interventions	Autoantibody-subgroups	No. of patients	HAQ-DI (mean, SD)	ΔHAQ-DI (mean, SD)	HAQ-DI response ≥0.22 (n, %)	SvdH (mean, SD)	ΔSvdH (mean, SD)	ΔSvdH ≤0 (n, %)	ΔSvdH ≤0.5 (n, %)
AIM [8-10]	MTX	RF-negative	27	1.2 (0.6)	-0.4 (0.5)	11 (40.7%)	32.8 (30.6)	0.3 (1.3)	17 (63%)	19 (70.4%)
		RF-positive	171	1.2 (0.7)	-0.5 (0.6)	80 (46.8%)	48.4 (36.6)	2.7 (5.5)	55 (32.2%)	66 (38.6%)
	ABT (10mg/kg according to weight range) + MTX	RF-negative	48	0.8 (0.7)	-0.7 (0.8)	31 (64.6%)	36.4 (35.8)	0.9 (2.6)	23 (47.9%)	30 (62.5%)
		RF-positive	349	1 (0.7)	-0.7 (0.6)	239 (68.5%)	47.5 (38)	1.2 (3.4)	154 (44.1%)	184 (52.7%)
RAPID1 [15, 16]	MTX	RF-negative	34	1.4 (0.7)	-0.1 (0.6)	13 (38.2%)	21.6 (36.3)	0.4 (1.9)	22 (64.7%)	24 (70.6%)
		RF-positive	164	1.6 (0.7)	-0.2 (0.5)	70 (42.7%)	47 (47.7)	3.3 (8.5)	71 (43.3%)	74 (45.1%)
	CZP (200mg/2weeks sc) + MTX	RF-negative	80	1 (0.7)	-0.4 (0.6)	48 (60%)	22.3 (44)	1.1 (6.6)	57 (71.3%)	63 (78.8%)
		RF-positive	312	1.1 (0.7)	-0.6 (0.6)	228 (73.1%)	43 (48.2)	0.3 (5.4)	193 (61.9%)	214 (68.6%)
Combe 2006 [22, 23]	SSZ	RF-negative	15	1.6 (0.7)	-0.1 (0.5)	9 (60%)	NR	NR	NR	NR
		RF-positive	33	1.5 (0.7)	-0.1 (0.6)	11 (33.3%)	NR	NR	NR	NR
	ETN (2× 25mg/week sc) + SSZ	RF-negative	28	0.9 (0.8)	-0.4 (0.4)	22 (78.6%)	NR	NR	NR	NR
		RF-positive	68	1 (0.8)	-0.7 (0.7)	55 (80.9%)	NR	NR	NR	NR
TEMPO [25-28]	MTX	RF-negative	55	1.2 (0.8)	-0.5 (0.6)	38 (69.1%)	26 (45.6)	2.8 (12.6)	27 (49.1%)	30 (54.5%)
		RF-positive	164	1 (0.8)	-0.7 (0.6)	133 (81.1%)	43.1 (51.8)	0.3 (2.6)	76 (46.3%)	88 (53.7%)
	ETN (2× 25mg/week sc) + MTX	RF-negative	50	0.8 (0.7)	-0.8 (0.6)	41 (82%)	32 (52.1)	-0.2 (1)	31 (62%)	36 (72%)
		RF-positive	177	0.8 (0.7)	-1 (0.7)	156 (88.1%)	36.7 (46.1)	-1.2 (2.9)	125 (70.6%)	141 (79.7%)

SvdH, van der Heijde modified total Sharp score; MTX, methotrexate; SSZ, sulfasalazine; ABT, abatacept; CZP, certolizumab pegol; ETN, etanercept; sc, subcutaneous; NR, not recorded

Online Supplementary Table S7.3: MTX-IR or csDMARD-IR: Disease activity outcomes of RCTs at 24 months

Trial name	Interventions	Autoantibody-subgroups	No. of patients	ACR20 (n, %)	ACR50 (n, %)	ACR70 (n, %)	DAS28-ESR (mean, SD)	ΔDAS28-ESR (mean, SD)	DAS28-ESR <2.6 (n, %)	DAS28-CRP (mean, SD)	ΔDAS28-CRP (mean, SD)	DAS28-CRP <2.6 (n, %)
AIM [8-10]	MTX	RF-negative	27	9 (33.3%)	7 (25.9%)	5 (18.5%)	3.9 (1.8)	-3.1 (1.5)	4 (14.8%)	3.4 (1.7)	-3.1 (1.4)	5 (18.5%)
		RF-positive	171	104 (60.8%)	81 (47.4%)	41 (24%)	3.6 (1.2)	-3.2 (1.3)	26 (15.2%)	3.3 (1.1)	-3 (1.3)	37 (21.6%)
	ABT (10mg/kg according to weight range) + MTX	RF-negative	48	30 (62.5%)	25 (52.1%)	15 (31.3%)	3.3 (1.2)	-3.5 (1.2)	13 (27.1%)	3.3 (1.2)	-3 (1.2)	11 (22.9%)
		RF-positive	349	245 (70.2%)	171 (49%)	107 (30.7%)	3.6 (1.2)	-3.2 (1.3)	56 (16%)	3.3 (1.1)	-3.1 (1.2)	78 (22.3%)
Combe 2006 [22, 23]	SSZ	RF-negative	15	3 (20%)	0 (0%)	0 (0%)	7 (1.6)	-0.2 (1.4)	0 (0%)	6.8 (1.6)	-0.2 (1.4)	0 (0%)
		RF-positive	33	13 (39.4%)	5 (15.2%)	1 (3%)	6.6 (2)	-0.8 (1.9)	2 (6.1%)	6.2 (2)	-0.7 (1.9)	2 (6.1%)
	ETN (2× 25mg/week sc) + SSZ	RF-negative	28	22 (78.6%)	15 (53.6%)	7 (25%)	3.8 (2.1)	-3.4 (1.9)	7 (25%)	3.9 (1.8)	-3.1 (1.7)	5 (17.9%)
		RF-positive	68	52 (76.5%)	41 (60.3%)	19 (27.9%)	4.1 (1.9)	-3.4 (1.8)	17 (25%)	3.8 (1.7)	-3.2 (1.6)	19 (27.9%)
TEMPO [25-28]	MTX	RF-negative	55	NR	NR	NR	4 (1.8)	-2.2 (1.7)	13 (23.6%)	3.9 (1.4)	-2.1 (1.5)	10 (18.2%)
		RF-positive	164	NR	NR	NR	4.4 (1.8)	-2.5 (1.7)	28 (17.1%)	3.9 (1.6)	-2.4 (1.5)	43 (26.2%)
	ETN (2× 25mg/week sc) + MTX	RF-negative	50	NR	NR	NR	3.1 (1.4)	-3.4 (1.3)	18 (36%)	3.1 (1.4)	-3 (1.3)	23 (46%)
		RF-positive	177	NR	NR	NR	3.1 (1.5)	-3.7 (1.4)	74 (41.8%)	3 (1.3)	-3.5 (1.3)	83 (46.9%)

MTX, methotrexate; SSZ, sulfasalazine; ABT, abatacept; ETN, etanercept; sc, subcutaneous; NR, not recorded

Online Supplementary Table S7.4: MTX-IR or csDMARD-IR: Physical function and Radiographic progression of RCTs at 24 months

Trial name	Interventions	Autoantibody-subgroups	No. of patients	HAQ-DI (mean, SD)	ΔHAQ-DI (mean, SD)	HAQ-DI response ≥0.22 (n, %)	SvdH (mean, SD)	ΔSvdH (mean, SD)	ΔSvdH ≤0 (n, %)	ΔSvdH ≤0.5 (n, %)
AIM [8-10]	MTX	RF-negative	27	1 (0.8)	-0.7 (0.9)	8 (29.6%)	21.7 (28.6)	0.5 (1.7)	6 (22.2%)	7 (25.9%)
		RF-positive	171	1 (0.7)	-0.7 (0.7)	120 (70.2%)	34 (30.5)	2.1 (5.1)	54 (31.6%)	61 (35.7%)
	ABT (10mg/kg according to weight range) + MTX	RF-negative	48	0.7 (0.6)	-0.8 (0.7)	31 (64.6%)	21 (29.5)	1 (2.4)	13 (27.1%)	18 (37.5%)
		RF-positive	349	1 (0.6)	-0.7 (0.7)	216 (61.9%)	30.3 (28.7)	1 (2.5)	125 (35.8%)	152 (43.6%)
Combe 2006 [22, 23]	SSZ	RF-negative	15	1.7 (0.6)	-0.1 (0.5)	7 (46.7%)	NR	NR	NR	NR
		RF-positive	33	1.5 (0.8)	-0.1 (0.6)	12 (36.4%)	NR	NR	NR	NR
	ETN (2× 25mg/week sc) + SSZ	RF-negative	28	0.9 (0.7)	-0.5 (0.4)	22 (78.6%)	NR	NR	NR	NR
		RF-positive	68	1 (0.8)	-0.7 (0.7)	53 (77.9%)	NR	NR	NR	NR
TEMPO [25-28]	MTX	RF-negative	55	1.1 (0.8)	-0.6 (0.7)	37 (67.3%)	54.5 (71.9)	0.5 (3.1)	19 (34.5%)	19 (34.5%)
		RF-positive	164	1 (0.8)	-0.7 (0.7)	126 (76.8%)	35.5 (46.4)	1.4 (4.8)	53 (32.3%)	56 (34.1%)
	ETN (2× 25mg/week sc) + MTX	RF-negative	50	0.7 (0.7)	-0.9 (0.7)	41 (82%)	35.6 (54)	-0.3 (1.4)	24 (48%)	31 (62%)
		RF-positive	177	0.7 (0.7)	-1.1 (0.7)	158 (89.3%)	39.6 (47.6)	-1 (3.8)	98 (55.4%)	111 (62.7%)

SvdH, van der Heijde modified total Sharp score; MTX, methotrexate; SSZ, sulfasalazine; ABT, abatacept; ETN, etanercept; sc, subcutaneous; NR, not recorded

Online Supplementary Table S8.1: TNFi-IR: Disease activity outcomes of RCTs at 12 months

Trial name	Interventions	Autoantibody-subgroups	No. of patients	ACR20 (n, %)	ACR50 (n, %)	ACR70 (n, %)	DAS28-ESR (mean, SD)	ΔDAS28-ESR (mean, SD)	DAS28-ESR <2.6 (n, %)	DAS28-CRP (mean, SD)	ΔDAS28-CRP (mean, SD)	DAS28-CRP <2.6 (n, %)
ATTAIN [30-32]	DMARD	RF-negative	30	11 (36.7%)	6 (20%)	0 (0%)	5.1 (1.3)	-1.5 (1.5)	1 (3.3%)	4.7 (1.4)	-1.6 (1.4)	2 (6.7%)
		RF-positive	97	50 (51.5%)	30 (30.9%)	14 (14.4%)	4.7 (1.4)	-2.2 (1.5)	2 (2.1%)	4.1 (1.4)	-2.4 (1.4)	14 (14.4%)
	ABT (10mg/kg according to weight range) + DMARD	RF-negative	52	15 (28.8%)	3 (5.8%)	2 (3.8%)	5 (0.9)	-1.6 (0.9)	0 (0%)	4.5 (1)	-1.7 (1.1)	2 (3.8%)
		RF-positive	189	106 (56.1%)	56 (29.6%)	32 (16.9%)	4.4 (1.5)	-2.5 (1.5)	15 (7.9%)	4 (1.4)	-2.5 (1.4)	17 (9%)
GO-AFTER [33]	DMARD	RF-negative	38	12 (31.6%)	6 (15.8%)	5 (13.2%)	4.7 (1.6)	-1.4 (1.3)	3 (7.9%)	4.3 (1.5)	-1.2 (1.3)	3 (7.9%)
		RF-positive	108	47 (43.5%)	26 (24.1%)	6 (5.6%)	4.5 (1.4)	-1.8 (1.5)	6 (5.6%)	4.1 (1.3)	-1.7 (1.4)	9 (8.3%)
	GLM (50mg/4weeks sc) + DMARD	RF-negative	39	15 (38.5%)	5 (12.8%)	2 (5.1%)	4.8 (1.7)	-1.6 (1.4)	4 (10.3%)	4.6 (1.4)	-1.3 (1)	3 (7.7%)
		RF-positive	104	46 (44.2%)	25 (24%)	10 (9.6%)	4.3 (1.6)	-2 (1.4)	12 (11.5%)	4 (1.4)	-2 (1.3)	12 (11.5%)

DMARD, disease-modifying antirheumatic drug; ABT, abatacept; GLM, golimumab; sc, subcutaneous

Online Supplementary Table S8.2: TNFi-IR: Physical function and Radiographic progression of RCTs at 12 months

Trial name	Interventions	Autoantibody-subgroups	No. of patients	HAQ-DI (mean, SD)	ΔHAQ-DI (mean, SD)	HAQ-DI response ≥0.22 (n, %)	SvdH (mean, SD)	ΔSvdH (mean, SD)	ΔSvdH ≤0 (n, %)	ΔSvdH ≤0.5 (n, %)
ATTAIN [30-32]	DMARD	RF-negative	30	1.3 (0.7)	-0.2 (0.4)	9 (30%)	NR	NR	NR	NR
		RF-positive	97	1.4 (0.7)	-0.5 (0.5)	50 (51.5%)	NR	NR	NR	NR
	ABT (10mg/kg according to weight range) + DMARD	RF-negative	52	1.3 (0.7)	-0.4 (0.6)	23 (44.2%)	NR	NR	NR	NR
		RF-positive	189	1.3 (0.7)	-0.6 (0.6)	113 (59.8%)	NR	NR	NR	NR
GO-AFTER [33]	DMARD	RF-negative	38	1.4 (0.9)	0.1 (0.5)	24 (63.2%)	NR	NR	NR	NR
		RF-positive	108	1.2 (0.8)	0.4 (0.7)	69 (63.9%)	NR	NR	NR	NR
	GLM (50mg/4weeks sc) + DMARD	RF-negative	39	1.5 (0.6)	0.2 (0.3)	33 (84.6%)	NR	NR	NR	NR
		RF-positive	104	1.1 (0.8)	0.4 (0.6)	68 (65.4%)	NR	NR	NR	NR

SvdH, van der Heijde modified total Sharp score; DMARD, disease-modifying antirheumatic drug; ABT, abatacept; GLM, golimumab; sc, subcutaneous; NR, not recorded

Online Supplementary Table S8.3: TNFi-IR: Disease activity outcomes of RCTs at 24 months

Trial name	Interventions	Autoantibody-subgroups	No. of patients	ACR20 (n, %)	ACR50 (n, %)	ACR70 (n, %)	DAS28-ESR (mean, SD)	ΔDAS28-ESR (mean, SD)	DAS28-ESR <2.6 (n, %)	DAS28-CRP (mean, SD)	ΔDAS28-CRP (mean, SD)	DAS28-CRP <2.6 (n, %)
ATTAIN [30-32]	DMARD	RF-negative	30	9 (30%)	4 (13.3%)	2 (6.7%)	4.9 (1.4)	-1.9 (1.1)	1 (3.3%)	4.7 (1.1)	-1.9 (1)	1 (3.3%)
		RF-positive	97	39 (40.2%)	25 (25.8%)	11 (11.3%)	4.6 (1.2)	-2.4 (1.3)	1 (1%)	4.1 (1.3)	-2.4 (1.4)	6 (6.2%)
	ABT (10mg/kg according to weight range) + DMARD	RF-negative	52	16 (30.8%)	10 (19.2%)	3 (5.8%)	4.3 (1.1)	-2.4 (1.2)	1 (1.9%)	3.9 (1.1)	-2.3 (1.2)	3 (5.8%)
		RF-positive	189	93 (49.2%)	55 (29.1%)	29 (15.3%)	4 (1.5)	-2.7 (1.5)	21 (11.1%)	3.7 (1.3)	-2.8 (1.4)	19 (10.1%)

DMARD, disease-modifying antirheumatic drug; ABT, abatacept

Online Supplementary Table S8.4: TNFi-IR: Physical function and Radiographic progression of RCTs at 24 months

Trial name	Interventions	Autoantibody-subgroups	No. of patients	HAQ-DI (mean, SD)	ΔHAQ-DI (mean, SD)	HAQ-DI response ≥0.22 (n, %)	SvdH (mean, SD)	ΔSvdH (mean, SD)	ΔSvdH ≤0 (n, %)	ΔSvdH ≤0.5 (n, %)
ATTAIN [30-32]	DMARD	RF-negative	30	1.2 (0.7)	-0.3 (0.5)	7 (23.3%)	NR	NR	NR	NR
		RF-positive	97	1.3 (0.7)	-0.6 (0.6)	42 (43.3%)	NR	NR	NR	NR
	ABT (10mg/kg according to weight range) + DMARD	RF-negative	52	1.2 (0.8)	-0.5 (0.6)	18 (34.6%)	NR	NR	NR	NR
		RF-positive	189	1.1 (0.7)	-0.6 (0.6)	87 (46%)	NR	NR	NR	NR

SvdH, van der Heijde modified total Sharp score; DMARD, disease-modifying antirheumatic drug; MTX, methotrexate; ABT, abatacept; NR, not recorded

3.2 RCTs of bDMARD monotherapy

Online Supplementary Table S9.1: RCTs of bDMARD monotherapy: Disease activity outcomes of RCTs at 12 months

Trial name	Interventions	Autoantibody-subgroups	No. of patients	ACR20 (n, %)	ACR50 (n, %)	ACR70 (n, %)	DAS28-ESR (mean, SD)	ΔDAS28-ESR (mean, SD)	DAS28-ESR <2.6 (n, %)	DAS28-CRP (mean, SD)	ΔDAS28-CRP (mean, SD)	DAS28-CRP <2.6 (n, %)
SURPRISE [36]	TCZ (8mg/kg/4weeks)	RF-negative	20	15 (75%)	15 (75%)	11 (55%)	2.1 (1)	-3 (1.2)	16 (80%)	1.7 (0.9)	-2.5 (1.2)	17 (85%)
		RF-positive	82	64 (78%)	51 (62.2%)	36 (43.9%)	2.3 (1.5)	-3 (1.7)	57 (69.5%)	2.2 (1.3)	-2.5 (1.5)	62 (75.6%)
	TCZ (8mg/kg/4weeks) + MTX	RF-negative	27	16 (59.3%)	13 (48.1%)	8 (29.6%)	2.2 (1.3)	-2.7 (1.1)	19 (70.4%)	2.2 (1.1)	-2.1 (1)	20 (74.1%)
		RF-positive	78	63 (80.8%)	53 (67.9%)	41 (52.6%)	2 (1.3)	-3.1 (1.4)	58 (74.4%)	1.9 (1)	-2.4 (1.2)	62 (79.5%)
Takeuchi 2013 [38]	MTX	RF-negative	38	21 (55.3%)	16 (42.1%)	8 (21.1%)	3.3 (1.1)	-2.4 (1.2)	7 (18.4%)	2.7 (1.1)	-2.5 (1.1)	14 (36.8%)
		RF-positive	138	75 (54.3%)	46 (33.3%)	20 (14.5%)	3.5 (1.2)	-2.2 (1.3)	27 (19.6%)	3 (1.1)	-2.1 (1.2)	40 (29%)
	ETN (2× 25mg/week sc)	RF-negative	35	22 (62.9%)	19 (54.3%)	15 (42.9%)	2.8 (1.2)	-2.7 (1.4)	15 (42.9%)	2.2 (1.1)	-2.7 (1.4)	23 (65.7%)
		RF-positive	147	105 (71.4%)	81 (55.1%)	46 (31.3%)	3.3 (1.4)	-2.7 (1.3)	42 (28.6%)	2.7 (1.3)	-2.6 (1.2)	62 (42.2%)

MTX, methotrexate; TCZ, tocilizumab; ETN, etanercept; sc, subcutaneous

Online Supplementary Table S9.2: RCTs of bDMARD monotherapy: Physical function and Radiographic progression of RCTs at 12 months

Trial name	Interventions	Autoantibody-subgroups	No. of patients	HAQ-DI (mean, SD)	ΔHAQ-DI (mean, SD)	HAQ-DI response ≥0.22 (n, %)	SvdH (mean, SD)	ΔSvdH (mean, SD)	ΔSvdH ≤0 (n, %)	ΔSvdH ≤0.5 (n, %)
SURPRISE [36]	TCZ (8mg/kg/4weeks)	RF-negative	20	0.5 (0.7)	-0.6 (0.9)	12 (60%)	24 (25.2)	1.3 (3.2)	11 (55%)	12 (60%)
		RF-positive	82	0.6 (0.8)	-0.5 (0.6)	50 (61%)	31 (34)	1.4 (3.9)	48 (58.5%)	54 (65.9%)
	TCZ (8mg/kg/4weeks) + MTX	RF-negative	27	0.5 (0.6)	-0.4 (0.5)	19 (70.4%)	31.7 (53.2)	0.8 (1.2)	11 (40.7%)	16 (59.3%)
		RF-positive	78	0.5 (0.6)	-0.4 (0.6)	47 (60.3%)	37.3 (58.9)	0.5 (1.6)	44 (56.4%)	54 (69.2%)
Takeuchi 2013 [38]	MTX	RF-negative	38	0.3 (0.6)	-0.5 (0.7)	19 (50%)	46.7 (53.1)	3.8 (7.6)	11 (28.9%)	12 (31.6%)
		RF-positive	138	0.5 (0.5)	-0.5 (0.6)	63 (45.7%)	54.8 (50.7)	7.9 (11.6)	24 (17.4%)	29 (21%)
	ETN (2× 25mg/week sc)	RF-negative	35	0.3 (0.5)	-0.5 (0.5)	19 (54.3%)	28.4 (24.4)	0.3 (3.1)	18 (51.4%)	21 (60%)
		RF-positive	147	0.4 (0.6)	-0.7 (0.6)	99 (67.3%)	50.5 (48.3)	3.7 (9.7)	50 (34%)	59 (40.1%)

SvdH, van der Heijde modified total Sharp score; MTX, methotrexate; TCZ, tocilizumab; ETN, etanercept; sc, subcutaneous

3.3 Head-to-head RCTs of bDMARDs

Online Supplementary Table S10.1: Head-to-head RCTs of bDMARDs: Disease activity outcomes of RCTs at 12 months

Trial name	Interventions	Autoantibody-subgroups	No. of patients	ACR20 (n, %)	ACR50 (n, %)	ACR70 (n, %)	DAS28-ESR (mean, SD)	ΔDAS28-ESR (mean, SD)	DAS28-ESR <2.6 (n, %)	DAS28-CRP (mean, SD)	ΔDAS28-CRP (mean, SD)	DAS28-CRP <2.6 (n, %)
AMPLE [40-43]	ABT (125mg/week sc)	ACPA-negative	66	38 (57.6%)	24 (36.4%)	9 (13.6%)	NR	NR	NR	3.2 (1.3)	-2.2 (1.4)	20 (30.3%)
		ACPA-positive	185	128 (69.2%)	95 (51.4%)	69 (37.3%)	NR	NR	NR	2.9 (1.2)	-2.6 (1.4)	77 (41.6%)
	ABT (125mg/week sc)	RF-negative	47	24 (51.1%)	15 (31.9%)	6 (12.8%)	NR	NR	NR	3.3 (1.1)	-2.2 (1.4)	11 (23.4%)
		RF-positive	204	142 (69.6%)	104 (51%)	72 (35.3%)	NR	NR	NR	3 (1.2)	-2.6 (1.4)	86 (42.2%)
	ABT (125mg/week sc)	ACPA-negative RF-negative	38	20 (52.6%)	11 (28.9%)	4 (10.5%)	NR	NR	NR	3.4 (1.1)	-2.1 (1.4)	9 (23.7%)
		ACPA-negative RF-positive	28	18 (64.3%)	13 (46.4%)	5 (17.9%)	NR	NR	NR	3 (1.5)	-2.2 (1.4)	11 (39.3%)
		ACPA-positive RF-negative	9	4 (44.4%)	4 (44.4%)	2 (22.2%)	NR	NR	NR	2.5 (0.9)	-2.4 (1.9)	2 (22.2%)
		ACPA-positive RF-positive	176	124 (70.5%)	91 (51.7%)	67 (38.1%)	NR	NR	NR	2.9 (1.2)	-2.6 (1.4)	75 (42.6%)
	ADA (40mg/2weeks sc)	ACPA-negative	54	29 (53.7%)	19 (35.2%)	4 (7.4%)	NR	NR	NR	3.2 (1.1)	-2.1 (1.2)	13 (24.1%)
		ACPA-positive	203	138 (68%)	101 (49.8%)	64 (31.5%)	NR	NR	NR	3 (1.3)	-2.6 (1.3)	74 (36.5%)
	ADA (40mg/2weeks sc)	RF-negative	35	20 (57.1%)	11 (31.4%)	2 (5.7%)	NR	NR	NR	3.3 (1.2)	-2 (1.2)	7 (20%)
		RF-positive	223	148 (66.4%)	110 (49.3%)	67 (30%)	NR	NR	NR	2.9 (1.2)	-2.6 (1.3)	81 (36.3%)
	ADA (40mg/2weeks sc)	ACPA-negative RF-negative	26	13 (50%)	8 (30.8%)	1 (3.8%)	NR	NR	NR	3.5 (1.1)	-1.9 (1.4)	4 (15.4%)

		ACPA-negative RF-positive	28	16 (57.1%)	11 (39.3%)	3 (10.7%)	NR	NR	NR	3.1 (1.1)	-2 (1.3)	9 (32.1%)
		ACPA-positive RF-negative	9	7 (77.8%)	3 (33.3%)	1 (11.1%)	NR	NR	NR	3 (1.4)	-2.1 (0.7)	3 (33.3%)
		ACPA-positive RF-positive	194	131 (67.5%)	98 (50.5%)	63 (32.5%)	NR	NR	NR	3 (1.3)	-2.6 (1.3)	71 (36.6%)

ADA, adalimumab; ABT, abatacept; sc, subcutaneous; NR, not recorded

Online Supplementary Table S10.2: Head-to-head RCTs of bDMARDs: Physical function and Radiographic progression of RCTs at 12 months

Trial name	Interventions	Autoantibody-subgroups	No. of patients	HAQ-DI (mean, SD)	ΔHAQ-DI (mean, SD)	HAQ-DI response ≥0.22 (n, %)	SvdH (mean, SD)	ΔSvdH (mean, SD)	ΔSvdH ≤0 (n, %)	ΔSvdH ≤0.5 (n, %)
AMPLE [40-43]	ABT (125mg/week sc)	ACPA-negative	66	0.9 (0.7)	-0.5 (0.7)	41 (62.1%)	10.9 (17.5)	0.1 (0.9)	45 (68.2%)	49 (74.2%)
		ACPA-positive	185	0.7 (0.7)	-0.8 (0.7)	129 (69.7%)	22.4 (37)	0.8 (2.9)	100 (54.1%)	117 (63.2%)
	ABT (125mg/week sc)	RF-negative	47	0.9 (0.7)	-0.5 (0.6)	27 (57.4%)	10.2 (15.6)	0.3 (0.8)	31 (66%)	35 (74.5%)
		RF-positive	204	0.7 (0.7)	-0.8 (0.7)	143 (70.1%)	21.6 (36)	0.7 (2.8)	114 (55.9%)	131 (64.2%)
	ABT (125mg/week sc)	ACPA-negative RF-negative	38	1 (0.7)	-0.5 (0.5)	23 (60.5%)	10.9 (17)	0.3 (0.9)	24 (63.2%)	27 (71.1%)
		ACPA-negative RF-positive	28	0.7 (0.6)	-0.6 (0.8)	18 (64.3%)	10.9 (18.5)	-0.2 (1)	21 (75%)	22 (78.6%)
		ACPA-positive RF-negative	9	0.9 (0.8)	-0.9 (0.9)	4 (44.4%)	7.3 (6.9)	0 (0.6)	7 (77.8%)	8 (88.9%)
		ACPA-positive RF-positive	176	0.7 (0.7)	-0.8 (0.7)	125 (71%)	23.2 (37.7)	0.9 (2.9)	93 (52.8%)	109 (61.9%)
	ADA (40mg/2weeks sc)	ACPA-negative	54	0.9 (0.7)	-0.4 (0.5)	27 (50%)	12.5 (19.3)	0.3 (2.3)	35 (64.8%)	40 (74.1%)
		ACPA-positive	203	0.8 (0.7)	-0.7 (0.7)	137 (67.5%)	22.5 (37)	0.9 (8)	135 (66.5%)	148 (72.9%)
	ADA (40mg/2weeks sc)	RF-negative	35	1 (0.7)	-0.4 (0.5)	18 (51.4%)	11.4 (16.3)	0 (2)	26 (74.3%)	29 (82.9%)
		RF-positive	223	0.7 (0.7)	-0.7 (0.7)	147 (65.9%)	21.8 (36.1)	0.9 (7.7)	145 (65%)	160 (71.7%)
	ADA (40mg/2weeks sc)	ACPA-negative RF-negative	26	1.1 (0.7)	-0.4 (0.6)	13 (50%)	9 (14.3)	-0.2 (1.2)	18 (69.2%)	21 (80.8%)
		ACPA-negative RF-positive	28	0.9 (0.6)	-0.4 (0.5)	14 (50%)	12.4 (18.9)	0.3 (2.3)	17 (60.7%)	19 (67.9%)
		ACPA-positive RF-negative	9	0.9 (0.8)	-0.3 (0.5)	5 (55.6%)	17.9 (20.3)	0.6 (3.4)	8 (88.9%)	8 (88.9%)
		ACPA-positive RF-positive	194	0.7 (0.7)	-0.8 (0.7)	132 (68%)	22.8 (37.6)	1 (8.2)	127 (65.5%)	140 (72.2%)

SvdH, van der Heijde modified total Sharp score; ADA, adalimumab; ABT, abatacept; sc, subcutaneous

Online Supplementary Table S10.3: Head-to-head RCTs of bDMARDs: Disease activity outcomes of RCTs at 24 months

Trial name	Interventions	Autoantibody-subgroups	No. of patients	ACR20 (n, %)	ACR50 (n, %)	ACR70 (n, %)	DAS28-ESR (mean, SD)	ΔDAS28-ESR (mean, SD)	DAS28-ESR <2.6 (n, %)	DAS28-CRP (mean, SD)	ΔDAS28-CRP (mean, SD)	DAS28-CRP <2.6 (n, %)
AMPLE [40-43]	ABT (125mg/week sc)	ACPA-negative	66	31 (47%)	23 (34.8%)	13 (19.7%)	NR	NR	NR	3.2 (1.5)	-2.1 (1.6)	23 (34.8%)
		ACPA-positive	185	128 (69.2%)	97 (52.4%)	70 (37.8%)	NR	NR	NR	3.2 (1.4)	-2.1 (1.3)	86 (46.5%)
	ABT (125mg/week sc)	RF-negative	47	18 (38.3%)	14 (29.8%)	7 (14.9%)	NR	NR	NR	3.3 (1.6)	-2.1 (1.7)	14 (29.8%)
		RF-positive	204	141 (69.1%)	106 (52%)	76 (37.3%)	NR	NR	NR	2.7 (1.2)	-2.8 (1.5)	95 (46.6%)
	ABT (125mg/week sc)	ACPA-negative RF-negative	38	15 (39.5%)	11 (28.9%)	5 (13.2%)	NR	NR	NR	3.4 (1.6)	-2.1 (1.7)	10 (26.3%)
		ACPA-negative RF-positive	28	16 (57.1%)	12 (42.9%)	8 (28.6%)	NR	NR	NR	2.9 (1.3)	-2.2 (1.6)	13 (46.4%)
		ACPA-positive RF-negative	9	3 (33.3%)	3 (33.3%)	2 (22.2%)	NR	NR	NR	2.7 (1.1)	-2.2 (1.8)	4 (44.4%)
		ACPA-positive RF-positive	176	125 (71%)	94 (53.4%)	68 (38.6%)	NR	NR	NR	2.7 (1.2)	-2.9 (1.4)	82 (46.6%)
	ADA (40mg/2weeks sc)	ACPA-negative	54	24 (44.4%)	17 (31.5%)	13 (24.1%)	NR	NR	NR	2.7 (1.1)	-2.9 (1.4)	15 (27.8%)
		ACPA-positive	203	134 (66%)	108 (53.2%)	67 (33%)	NR	NR	NR	2.7 (1.3)	-2.8 (1.3)	92 (45.3%)
	ADA (40mg/2weeks sc)	RF-negative	35	18 (51.4%)	13 (37.1%)	9 (25.7%)	NR	NR	NR	3.1 (1.4)	-2.2 (1.4)	11 (31.4%)
		RF-positive	223	141 (63.2%)	113 (50.7%)	72 (32.3%)	NR	NR	NR	2.8 (1.3)	-2.7 (1.3)	97 (43.5%)
	ADA (40mg/2weeks sc)	ACPA-negative RF-negative	26	10 (38.5%)	7 (26.9%)	5 (19.2%)	NR	NR	NR	3.4 (1.4)	-2 (1.4)	6 (23.1%)

		ACPA-negative RF-positive	28	14 (50%)	10 (35.7%)	8 (28.6%)	NR	NR	NR	3.2 (1.4)	-2 (1.4)	9 (32.1%)
		ACPA-positive RF-negative	9	8 (88.9%)	6 (66.7%)	4 (44.4%)	NR	NR	NR	2.3 (1.2)	-2.7 (1.3)	5 (55.6%)
		ACPA-positive RF-positive	194	126 (64.9%)	102 (52.6%)	63 (32.5%)	NR	NR	NR	2.7 (1.3)	-2.8 (1.3)	87 (44.8%)

ADA, adalimumab; ABT, abatacept; sc, subcutaneous; NR, not recorded

Online Supplementary Table S10.4: Head-to-head RCTs of bDMARDs: Physical function and Radiographic progression of RCTs at 24 months

Trial name	Interventions	Autoantibody-subgroups	No. of patients	HAQ-DI (mean, SD)	ΔHAQ-DI (mean, SD)	HAQ-DI response ≥0.22 (n, %)	SvdH (mean, SD)	ΔSvdH (mean, SD)	ΔSvdH ≤0 (n, %)	ΔSvdH ≤0.5 (n, %)
AMPLE [40-43]	ABT (125mg/week sc)	ACPA-negative	66	0.8 (0.6)	-0.5 (0.6)	34 (51.5%)	10.5 (17.9)	0.2 (1.1)	42 (63.6%)	47 (71.2%)
		ACPA-positive	185	0.7 (0.7)	-0.8 (0.7)	121 (65.4%)	22.8 (35.7)	1.3 (4.8)	87 (47%)	106 (57.3%)
	ABT (125mg/week sc)	RF-negative	47	1 (0.6)	-0.4 (0.6)	20 (42.6%)	10.1 (16.1)	0.4 (1.2)	27 (57.4%)	31 (66%)
		RF-positive	204	0.7 (0.7)	-0.8 (0.7)	135 (66.2%)	21.6 (34.6)	1.1 (4.5)	102 (50%)	122 (59.8%)
	ABT (125mg/week sc)	ACPA-negative RF-negative	38	1 (0.6)	-0.4 (0.5)	17 (44.7%)	10.1 (17.4)	0.4 (1.3)	23 (60.5%)	25 (65.8%)
		ACPA-negative RF-positive	28	0.6 (0.6)	-0.7 (0.7)	17 (60.7%)	11 (18.7)	0 (0.9)	19 (67.9%)	22 (78.6%)
		ACPA-positive RF-negative	9	0.9 (0.9)	-0.6 (1)	3 (33.3%)	9.7 (6.6)	0 (0.5)	4 (44.4%)	6 (66.7%)
		ACPA-positive RF-positive	176	0.7 (0.7)	-0.8 (0.7)	118 (67%)	23.3 (36.3)	1.3 (4.9)	83 (47.2%)	100 (56.8%)
	ADA (40mg/2weeks sc)	ACPA-negative	54	0.9 (0.7)	-0.4 (0.6)	21 (38.9%)	13.2 (20.9)	0.6 (2.7)	26 (48.1%)	28 (51.9%)
		ACPA-positive	203	0.7 (0.6)	-0.8 (0.7)	121 (59.6%)	22.8 (37.3)	1.4 (10.5)	114 (56.2%)	128 (63.1%)
	ADA (40mg/2weeks sc)	RF-negative	35	1 (0.7)	-0.4 (0.7)	13 (37.1%)	12.7 (18.2)	0.9 (3)	19 (54.3%)	20 (57.1%)
		RF-positive	223	0.7 (0.6)	-0.8 (0.7)	130 (58.3%)	22.2 (36.6)	1.3 (10.2)	122 (54.7%)	137 (61.4%)
	ADA (40mg/2weeks sc)	ACPA-negative RF-negative	26	1.1 (0.7)	-0.3 (0.7)	7 (26.9%)	10.1 (16.6)	0.8 (1.7)	12 (46.2%)	13 (50%)
		ACPA-negative RF-positive	28	0.9 (0.6)	-0.4 (0.6)	14 (50%)	13.2 (20.4)	0.7 (2.7)	14 (50%)	15 (53.6%)
		ACPA-positive RF-negative	9	0.8 (0.5)	-0.4 (0.7)	6 (66.7%)	18.3 (21)	1 (4.7)	7 (77.8%)	7 (77.8%)
		ACPA-positive RF-positive	194	0.7 (0.6)	-0.8 (0.7)	115 (59.3%)	23 (38)	1.5 (10.8)	107 (55.2%)	121 (62.4%)

SvdH, van der Heijde modified total Sharp score; ADA, adalimumab; ABT, abatacept; sc, subcutaneous

4.0 References

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