Supplementary table 2. Summary of studies on therapeutic strategies for RA patients with true refractory disease

1st Author, publication year	Study design	Patients (total n)	Failed treatment (inclusiecriterium en aantal in baselinetabel)	Disease activity at baseline (mean (SD))	Disease duration of RA (mean)	Intervention group Description	n	Comparator Description	n	Outcome Description^1	Time point^2	Number and percentage of responders in interventio n group	Number and percentage of responders in control group	OR (95%CI)	Risk ratio (95% CI)	Mean outcome in intervention group (SD)	Mean outcome in control group (SD)	Mean difference (standard error, 95% CI)	p-value	Other	Risk of bias^3	Risk of bias of individual studies included in SLR^4
STUDIES IN PATIENTS FAILING ≥2B/TSDMARDS																						
Alternative TNFi vs rituximab																						
Blom, 2011	Non-RCT	154	Failure of ≥2 TNFis	DAS28 5.21	9.9Y	Alternative TNFi (Infliximab (n=21, 3mg/kg, loading dose W0, W2, W6, thereafter q8w); Etanercept (n=22, 50mg 1/W or 25mg 2/W, subcutaneous); Adalimumab (n=21, 40mg q2w, subcutaneous))	64	Rituximab (2 times 1000mg with 2W interval, retreatment at 6M)	90	DAS28	6M					4.54 (1.40)	3.91 (1.25)		p=0.021		High	
										DAS28	12M					NR	4.2 (1.4)		p=0.140			
										HAQ	12M								p=0.0537	Better in RTX group		
Finckh, 2010 (Subanalysis)	Subanalysis RCT	69	Failure of ≥2 TNFi	NR	NR	Alternative TNFi (Adalimumab 40mg subcutaneously every 2 weeks (51%), etanercept subcutaneously 50mg/week (26%), infliximab intravenously starting with 3mg/kg (23%))	12	Rituximab (2 times 1000mg at days 1 and 15, intravenous)	57	DAS28	Change from BL until 6M					-0.75 (95%CI -1.18- -0.32)	-1.31 (95%CI -1.53- -1.10)		ns		High	
Alternative TNFi vs mavrilimumab																						
Weinblatt, 2018 (Subanalysis	Subanalysis RCT	6	Inadequate response to 2 TNFi (excluding golimumab)	NR	NR	Mavrilimumab (100mg q2w, subcutaneous)	4	Golimumab (50mg q4w and placebo every 2 other weeks)	2	ACR20 response	24W	2 (66.7%)	0 (0%)								High	
Tocilizumab vs placebo																						
Emery, 2008 (Subanalysis)	Subanalysis RCT	176	Failure of 2 TNFis	NR	NR	Tocilizumab (8mg/kg, q4w, intravenous)	52	Placebo	64	ACR20 response	24W	26 (50.0%)	7 (10.9%)								High	
										ACR50 response	24W	16 (30.8%)	1 (1.6%)									
										ACR70 response	24W	8 (15.4%)	0 (0.0%)									
						Tocilizumab (4mg/kg, q4w, intravenous)	60	Placebo	64	ACR20 response	24W	17 (28.3%)	7 (10.9%)									
										ACR50 response	24W	8 (13.3%)	1 (1.6%)									
										ACR70 response	24W	2 (3.3%)	0 (0.0%)									
		62	Failure of 3 TNFis	NR	NR	Tocilizumab (8mg.kg, q4w, intravenous)	26	Placebo	18	ACR20 response	24W	14 (53.8%)	1 (5.6%)									
										ACR50 response	24W	5 (19.2%)	0 (0.0%)									
										ACR70 response	24W	2 (7.7%)	0 (0.0%)									
						Tocilizumab (4mg/kg, q4w, intravenous)	18	Placebo	18	ACR20 response	24W	4 (22.2%)	1 (5.6%)									
										ACR50 response	24W	4 (22.2%)	0 (0.0%)									
										ACR70 response	24W	0 (0.0%)	0 (0.0%)									
Tofacitinib vs placebo																						
Burmester, 2013 (Subanalysis)	Subanalysis RCT	141	Inadequate response to 2 TNFi	NR	NR	Tofacitinib (5mg 2/D, oral)	37	Placebo	37	ACR20 response	3M	14 (37.8%)	4 (10.8%)								High	
						Tofacitinib (10mg 2/D, oral)	30	Placebo	37	ACR20 response	3M	16 (53.3%)	4 (10.8%)									
		41	Inadequate response to ≥3 TNFi	NR	NR	Tofacitinib (5mg 2/D, oral)	11	Placebo	9	ACR20 response	3M	4 (36.4%)	2 (22.2%)									
						Tofacitinib (10mg 2/D, oral)	12	Placebo	9	ACR20 response	3M	5 (41.7%)	2 (22.2%)									
Baricitinib vs placebo																						
Genovese, 2018a (Subanalysis of	Subanalysis RCT	211	Failure of ≥2 TNFi	NR	NR	Baricitinib (2mg/D, oral)	43	Placebo	69	ACR20 response	12W	19 (38%)	6 (13%)								High	
										CDAI ≤10	12W	1 (2%)	9 (18%)									
						Baricitinib (4mg/D, oral)	54	Placebo	69	ACR20 response	12W	24 (53%)	6 (13%)									
										CDAI ≤10	12W	1 (2%)	9 (20%)									
Genovese, 2016 (see also below, failure		143	Failure of ≥3 bDMARDs	NR	NR	Baricitinib (2mg/D, oral)	50	Placebo	47	ACR20 response	12W	31 (43%)	17 (25%)									
										CDAI ≤10	12W	3 (4%)	16 (22%)									
						Baricitinib (4mg/D, oral)	45	Placebo	47	ACR20 response	12W	38 (54%)	17 (25%)									
										CDAI ≤10	12W	3 (4%)	14 (20%)									
Upadacitinib vs placebo																						
Kremer, 2016 (Subanalysis (see also below, failure	Subanalysis RCT	276	Failure of ≥2 TNFi	NR	NR	Upadacitinib (3mg 2/D, oral)	16	Placebo	13	ACR20 response	12W	53%	34%								High	
						Upadacitinib (6mg 2/D, oral)	16	Placebo	13	ACR20 response	12W	58%	34%									
						Upadacitinib (12mg 2/D, oral)	15	Placebo	13	ACR20 response	12W	67%	34%									
						Upadacitinib (18mg 2/D, oral)	17	Placebo	13	ACR20 response	12W	71%	34%									
Weinblatt, 2019^ (Subanalysis Genovese, 2018b)	Subanalysis RCT	137	Failure of 2 bDMARDs			Upadacitinib 15mg/D	40	Placebo	46	ACR20 response	12W	70.0%	32.6%						p<0.001		High	
										ACR50 response	12W	32.5%	14.2%						ns			
										ACR70 response	12W	5.0%	8.7%						ns			
										DAS28-CRP ≤3.2	12W	45.0%	13.0%						p<0.01			
										CDAI ≤10	12W	27.5%	17.4%						ns			
										CDAI ≤2.8	12W	5.0%	4.3%						ns			
						Upadacitinib 30mg/D	51	Placebo	46	ACR20 response	12W	58.8%	32.6%						p<0.01			
										ACR50 response	12W	35.3%	14.2%						p<0.05			
										ACR70 response	12W	21.6	8.7%						ns			
										DAS28-CRP ≤3.2	12W	37.3%	13.0%						p<0.01			
										CDAI ≤10	12W	31.4%	17.4%						ns			
										CDAI ≤2.8	12W	5.9%	4.3%						ns			
		125	Failure of ≥3 bDMARD			Upadacitinib 15mg/D	38	Placebo	40	ACR20 response	12W	65.8%	22.5%						p<0.001			
										ACR50 response	12W	39.5%	7.5%						p<0.01			
										ACR70 response	12W	13.2%	2.5%						ns			
										DAS28-CRP ≤3.2	12W	42.1%	10.0%						p<0.01			
										CDAI ≤10	12W	34.2%	7.5%						p<0.01			
										CDAI ≤2.8	12W	7.9%	2.5%						ns			
						Upadacitinib 30mg/D	47	Placebo	40	ACR20 response	12W	51.1%	22.5%						p<0.01			
										ACR50 response	12W	29.8%	7.5%						p<0.01			
										ACR70 response	12W	17.0%	2.5%						p<0.05			

											DAS28-CRP ≤3.2	12W	40.4%	10.0%				p<0.01				
											CDAI ≤10	12W	27.7%	7.5%				p<0.05				
											CDAI ≤2.8	12W	8.5%	2.5%				ns				
Filgotinib vs placebo																						
Genovese, 2019	RCT	211	Failure of 2 bDMARDs			Filgotinib (100mg/D)	33	Placebo	36	ACR20 response	12W	57.6%	33.3%				ns			Moderate	
						Filgotinib (200mg/D)	37	Placebo	36	ACR20 response	12W	70.3%	33.3%				p<0.01				
			Failure of ≥3 bDMARD			Filgotinib (100mg/D)	34	Placebo	34	ACR20 response	12W	58.8%	17.6%				p<0.001				
						Filgotinib (200mg/D)	37	Placebo	34	ACR20 response	12W	70.3%	17.6%				p<0.001				
STUDIES IN PATIENTS FAILING ≥1B/TSDMARDS (NOT SPECIFICALLY ≥2B/TSDMARDS)																						
B/TSDMARD VS PLACEBO/CSDMARD																						
b/sDMARD vs placebo/csDMARD																						
Singh, 2017	SLR: RCTs 12	3364	Failure of TNFi	NR	>2Y	bDMARD	373 (3 studies)	Placebo	175	ACR50 response					4.10 (1.97-8.55)			Biologic (with or without MTX) or tofacitinib (with MTX) use was associated with clinically meaningful and statistically significant benefits (ACR50, HAQ, remission) compared to placebo or an active comparator (MTX/other traditional DMARDs) among people with RA previously unsuccessfully treated with biologics.	Low	Low-moderate		
						bDMARD + MTX	955 (3 studies)	MTX/other csDMARDs	524	ACR50 response					4.07 (2.76-5.99)							
						Tofacitinib + MTX	(1 study)	MTX		ACR50 response					3.24 (1.78-5.89)							
Alternative TNFi vs placebo																						
Kim, 2014	SLR: RCTs 6	1524	Failure of TNFi	HAQ 1.6-1.9	9.6-21.6Y (range)	Golimumab + DMARD	153	Placebo + DMARD	NR	ACR20 response	6M	32.1%	15.5%	2.577 (1.518-4.496)				Switching to non-TNF biologics was more effective than cycling TNFa inhibitor in TNF-IR patients; Probability (OR>1): 0.001; OR>1 favours golimumab	Moderate	Low-Moderate		
										ACR50 response	6M	15.7%	4.2%	4.254 (1.947-10.550,-)				Probability (OR>1): 0.028; OR>1 favours golimumab				
										ACR70 response	6M	5.1%	1.3%	4.211 (1.605-13.460)				Probability (OR>1): 0.014; OR>1 favours golimumab				
										HAQ	Change from BL until 6M						-0.140 (-, -0.255- -	Probability (OR>1): 0.000; OR>1 favours golimumab				
						Abatacept + DMARD	256	Placebo + DMARD	NR	ACR20 response	6M	43.7%	15.5%	4.226 (2.606-7.023)				Probability (OR>1): 0.021; OR>1 favours abatacept				
										ACR50 response	6M	23.1%	4.2%	6.866 (2.900-20.870)				Probability (OR>1): 0.192; OR>1 favours abatacept				
										ACR70 response	6M	9.9%	1.3%	8.574 (2.312-56.850)				Probability (OR>1): 0.176; OR>1 favours abatacept				
										HAQ	Change from BL until 6M						-0.400 (-, -0.499- -	Probability (OR>1): 0.744; OR>1 favours abatacept				
						Rituximab + DMARD	298	Placebo + DMARD	NR	ACR20 response	6M	47.0%	15.5%	4.822 (3.176-7.492)				Probability (OR>1): 0.039; OR>1 favours rituximab				
										ACR50 response	6M	24.0%	4.2%	7.231 (3.1812-15.490)				Probability (OR>1): 0.169; OR>1 favours rituximab				
										ACR70 response	6M	17.3%	1.3%	16.220 (4.575-121.800)				Probability (OR>1): 0.473; OR>1 favours rituximab				
										HAQ	Change from BL until 6M						-0.300 (-, -0.397- -	Probability (OR>1): 0.05; OR>1 favours rituximab				
						Tocilizumab + DMARD	170	Placebo + DMARD	NR	ACR20 response	6M	62.4%	15.5%	9.060 (5.064-17.000)				Probability (OR>1): 0.939; OR>1 favours tocilizumab				
										ACR50 response	6M	32.2%	4.2%	10.83 (4.731-29.690)				Probability (OR>1): 0.611; OR>1 favours tocilizumab				
										ACR70 response	6M	14.4%	1.3%	12.900 (3.474-86.120)				Probability (OR>1): 0.337; OR>1 favours tocilizumab				
										HAQ	Change from BL until 6M						-0.340 (-, -0.453- -	Probability (OR>1): 0.204; OR>1 favours tocilizumab				
						Golimumab + DMARD	153	Abatacept	256	ACR20 response	6M	32.1%	43.7%	1.639 (0.786-3.408)				Probability (OR>1): 0.907; OR>1 favours abatacept				
										ACR50 response	6M	15.7%	23.1%	1.623 (0.454-6.247)				Probability (OR>1): 0.772; OR>1 favours abatacept				
										ACR70 response	6M	5.1%	9.9%	2.048 (0.361-16.470)				Probability (OR>1): 0.784; OR>1 favours abatacept				
										HAQ	Change from BL until 6M						-0.260 (-, -0.411- -	Probability (OR>1): 1.000; OR>1 favours abatacept				
						Golimumab + DMARD	153	Rituximab	298	ACR20 response	6M	32.1%	47.0%	1.871 (0.937-3.725)				Probability (OR>1): 0.962; OR>1 favours rituximab				
										ACR50 response	6M	15.7%	24.0%	1.702 (0.558-5.087)				Probability (OR>1): 0.830; OR>1 favours rituximab				
										ACR70 response	6M	5.1%	17.3%	3.876 (0.685-35.370)				Probability (OR>1): 0.935; OR>1 favours rituximab				
										HAQ	Change from BL until 6M						-0.160 (-, -0.310- -	Probability (OR>1): 0.982; OR>1 favours rituximab				
						Golimumab + DMARD	153	Tocilizumab	170	ACR20 response	6M	32.1%	62.4%	3.520 (1.567-7.946)				Probability (OR>1): 0.999; OR>1 favours tocilizumab				
										ACR50 response	6M	15.7%	32.2%	2.552 (0.752-9.100)				Probability (OR>1): 0.933; OR>1 favours tocilizumab				
										ACR70 response	6M	5.1%	14.4%	3.107 (0.532-25.490)				Probability (OR>1): 0.892; OR>1 favours tocilizumab				
										HAQ	Change from BL until 6M						-0.200 (-, -0.360- -	Probability (OR>1): 0.993; OR>1 favours tocilizumab				
Malottki, 2011	SLR: RCTs 5; Non-RCTs 30	NR	Failure of 1 TNFi	NR	NR	Rituximab	(1 RCT)	Placebo	NR	ACR20 response	6M				2.85 (2.08-3.91)			Suggest that rituximab and abatacept are more effective than supportive care; Alternative TNFi some benefit, although uncertainties regarding magnitude of treatment effects and	Moderate	NR		
										ACR70 response	6M				12.14 (2.96-49.86)							

										DAS28	Change from BL until 6M					-1.50 (95%CI -1.74- -1.26)	cost-effectiveness.				
										HAQ	Change from BL until 6M					-0.30 (95%CI -0.40- -0.20)					
						Abatacept	(1 RCT)	Placebo	NR	ACR20 response	6M				2.56 (1.77-3.69)						
										ACR70 response	6M				6.70 (1.62-27.80)						
										DAS28	Change from BL until 6M					-1.27 (95CI -1.62- - 0.93)					
										HAQ	Change from BL until 6M					-0.34					
						Alternative TNFi	**(28 uncontrolled studies)**	**NA**	**NA**	**Effectiveness**							Improvement				
Abatacept vs placebo																					
Alivernini, 2009	SLR: RCTs 4; non-RCTs 5	9030	Failure of ≥1 TNFi	NR	NR	Adalimumab after failure of infliximab or etanercept	-	-	-	ACR70 response		13%					Efficacy, irrespective of mode of action, in reaching ACR70 response is 5-15% for alternative TNFi, rituximab, abatacept and tocilizumab (except in two studies).	High	NR		
						Adalimumab after failure of infliximab	-	-	-	ACR70 response		33%									
						Rituximab after failure of TNFi	-	Placebo	-	ACR70 response		12%									
						Abatacept after failure of TNFi	**-**	**Placebo**	**-**	**ACR70 response**		**10.2%**	**1.5%**								
						Tocilizumab after failure of TNFi	-	Placebo	-	ACR70 response		12.4%									
Kim, 2014	SLR: RCTs 6	1524	Failure of TNFi	HAQ 1.6-1.9	9.6-21.6Y (range)	Golimumab + DMARD	153	Placebo + DMARD	NR	ACR20 response	6M	32.1%	15.5%	4.577 (1.518-4.496)			Switching to non-TNF biologics was more effective than cycling TNFa inhibitor in TNF-IR patients; Probability (OR>1): 0.001; OR>1 favours golimumab	Moderate	Low-Moderate		
										ACR50 response	6M	15.7%	4.2%	4.254 (1.947-10.550,-)			Probability (OR>1): 0.028; OR>1 favours golimumab				
										ACR70 response	6M	5.1%	1.3%	4.211 (1.605-13.460)			Probability (OR>1): 0.014; OR>1 favours golimumab				
										HAQ	Change from BL until 6M					-0.140 (-, -0.255- -	Probability (OR>1): 0.000; OR>1 favours golimumab				
						Abatacept + DMARD	**256**	**Placebo + DMARD**	**NR**	**ACR20 response**	**6M**	**43.7%**	**15.5%**	**4.226 (2.606-7.023)**			**Probability (OR>1): 0.021; OR>1 favours abatacept**				
										ACR50 response	**6M**	**23.1%**	**4.2%**	**6.866 (2.900-20.870)**			**Probability (OR>1): 0.192; OR>1 favours abatacept**				
										ACR70 response	**6M**	**9.9%**	**1.3%**	**8.574 (2.312-56.850)**			**Probability (OR>1): 0.176; OR>1 favours abatacept**				
										HAQ	**Change from BL until 6M**					**-0.400 (-, -0.499- -**	**Probability (OR>1): 0.744; OR>1 favours abatacept**				
						Rituximab + DMARD	298	Placebo + DMARD	NR	ACR20 response	6M	47.0%	15.5%	4.822 (3.176-7.492)			Probability (OR>1): 0.039; OR>1 favours rituximab				
										ACR50 response	6M	24.0%	4.2%	7.231 (3.1812-15.490)			Probability (OR>1): 0.169; OR>1 favours rituximab				
										ACR70 response	6M	17.3%	1.3%	16.220 (4.575-121.800)			Probability (OR>1): 0.473; OR>1 favours rituximab				
										HAQ	Change from BL until 6M					-0.300 (-, -0.397- -	Probability (OR>1): 0.05; OR>1 favours rituximab				
						Tocilizumab + DMARD	170	Placebo + DMARD	NR	ACR20 response	6M	62.4%	15.5%	9.060 (5.064-17.000)			Probability (OR>1): 0.939; OR>1 favours tocilizumab				
										ACR50 response	6M	32.2%	4.2%	10.83 (4.731-29.690)			Probability (OR>1): 0.611; OR>1 favours tocilizumab				
										ACR70 response	6M	14.4%	1.3%	12.900 (3.474-86.120)			Probability (OR>1): 0.337; OR>1 favours tocilizumab				
										HAQ	Change from BL until 6M					-0.340 (-, -0.453- -	Probability (OR>1): 0.204; OR>1 favours tocilizumab				
						Golimumab + DMARD	153	Abatacept	256	ACR20 response	6M	32.1%	43.7%	1.639 (0.786-3.408)			Probability (OR>1): 0.907; OR>1 favours abatacept				
										ACR50 response	6M	15.7%	23.1%	1.623 (0.454-6.247)			Probability (OR>1): 0.772; OR>1 favours abatacept				
										ACR70 response	6M	5.1%	9.9%	2.048 (0.361-16.470)			Probability (OR>1): 0.784; OR>1 favours abatacept				
										HAQ	Change from BL until 6M					-0.260 (-, -0.411- -	Probability (OR>1): 1.000; OR>1 favours abatacept				
						Golimumab + DMARD	153	Rituximab	298	ACR20 response	6M	32.1%	47.0%	1.871 (0.937-3.725)			Probability (OR>1): 0.962; OR>1 favours rituximab				
										ACR50 response	6M	15.7%	24.0%	1.702 (0.558-5.087)			Probability (OR>1): 0.830; OR>1 favours rituximab				
										ACR70 response	6M	5.1%	17.3%	3.876 (0.685-35.370)			Probability (OR>1): 0.935; OR>1 favours rituximab				
										HAQ	Change from BL until 6M					-0.160 (-, -0.310- -	Probability (OR>1): 0.982; OR>1 favours rituximab				
						Golimumab + DMARD	153	Tocilizumab	170	ACR20 response	6M	32.1%	62.4%	3.520 (1.567-7.946)			Probability (OR>1): 0.999; OR>1 favours tocilizumab				
										ACR50 response	6M	15.7%	32.2%	2.552 (0.752-9.100)			Probability (OR>1): 0.933; OR>1 favours tocilizumab				
										ACR70 response	6M	5.1%	14.4%	3.107 (0.532-25.490)			Probability (OR>1): 0.892; OR>1 favours tocilizumab				
										HAQ	Change from BL until 6M					-0.200 (-, -0.360- -	Probability (OR>1): 0.993; OR>1 favours tocilizumab				

Lee, 2016	SLR: RCTs 4	1796	Inadequate response to TNFi	NR	NR	Tocilizumab 4mg		Tofacitinib 10mg		ACR20 response	24W-6M		1.05 (0.47-2.39)				OR>1 favours tocilizumab 4mg; Tocilizumab highest performance regarding early good response based on ACR 20 response, followed by rituximab, abatacept and tofacitinib.	Moderate	Low
						Abatacept		Tocilizumab 4mg		ACR20 response	24W-6M		1.06 (0.46-2.28)				OR>1 favours abatacept		
						Abatacept		Tofacitinib 10mg		ACR20 response	24W-6M		1.10 (0.54-2.31)				OR>1 favours abatacept		
						Rituximab		Abatacept		ACR20 response	24W-6M		1.14 (0.59-2.15)				OR>1 favours rituximab		
						Tofacitinib 10mg		Tofacitinib 5mg		ACR20 response	24W-6M		1.14 (0.71-1.86)				OR>1 favours tofacitinib 10mg		
						Rituximab		Tocilizumab 4mg		ACR20 response	24W-6M		1.20 (0.56-2.50)				OR>1 favours rituximab		
						Tocilizumab 4mg		Tofacitinib 5mg		ACR20 response	24W-6M		1.20 (0.54-2.75)				OR>1 favours tocilizumab 4mg		
						Rituximab		Tofacitinib 10mg		ACR20 response	24W-6M		1.26 (0.64-2.46)				OR>1 favours rituximab		
						Abatacept		Tofacitinib 5mg		ACR20 response	24W-6M		1.26 (0.61-2.63)				OR>1 favours abatacept		
						Rituximab		Tofacitinib 5mg		ACR20 response	24W-6M		1.44 (0.73-2.82)				OR>1 favours rituximab		
						Tocilizumab 8mg		Rituximab		ACR20 response	24W-6M		1.92 (0.93-4.04)				OR>1 favours tocilizumab 8mg		
						Tocilizumab 8mg		Abatacept		ACR20 response	24W-6M		2.17 (1.01-4.89)				OR>1 favours tocilizumab 8mg		
						Tocilizumab 8mg		Tocilizumab 4mg		ACR20 response	24W-6M		2.29 (1.47-3.61)				OR>1 favours tocilizumab 8mg		
						Tocilizumab 8mg		Tofacitinib 10mg		ACR20 response	24W-6M		2.40 (1.09-5.41)				OR>1 favours tocilizumab 8mg		
						Tocilizumab 8mg		Tofacitinib 5mg		ACR20 response	24W-6M		2.74 (1.26-6.27)				OR>1 favours tocilizumab 8mg		
						Tofacitinib 5mg		Placebo		ACR20 response	24W-6M		3.30 (1.95-5.66)				OR>1 favours tofacitinib 5mg		
						Tofacitinib 10mg		Placebo		ACR20 response	24W-6M		3.76 (2.24-6.50)				OR>1 favours tofacitinib 10mg		
						Tocilizumab 4mg		Placebo		ACR20 response	24W-6M		3.94 (2.19-7.48)				OR>1 favours tocilizumab 4mg		
						Abatacept		**Placebo**		**ACR20 response**	**24W-6M**		**4.15 (2.58-7.00)**				OR>1 favours abatacept		
						Rituximab		Placebo		ACR20 response	24W-6M		4.73 (3.14-7.27)				OR>1 favours rituximab		
						Tocilizumab 8mg		Placebo		ACR20 response	24W-6M		9.04 (5.15-17.08)				OR>1 favours tocilizumab 8mg		
Malottki, 2011	SLR: RCTs 5; Non-RCTs 30	NR	Failure of 1 TNFi	NR	NR	Rituximab	(1 RCT)	Placebo	NR	ACR20 response	6M			2.85 (2.08-3.91)			Suggest that rituximab and abatacept are more effective than supportive care; Alternative TNFi some benefit, although uncertainties regarding magnitude of treatment effects and cost-effectiveness.	Moderate	NR
										ACR70 response	6M			12.14 (2.96-49.86)					
										DAS28	Change from BL until 6M				-1.50 (95%CI -1.74- -1.26)				
										HAQ	Change from BL until 6M				-0.30 (95%CI -0.40- -0.20)				
						Abatacept	**(1 RCT)**	**Placebo**	**NR**	**ACR20 response**	**6M**			**2.56 (1.77-3.69)**					
										ACR70 response	**6M**			**6.70 (1.62-27.80)**					
										DAS28	**Change from BL until 6M**				**-1.27 (95CI -1.62- -0.93)**				
										HAQ	**Change from BL until 6M**				**-0.34**				
						Alternative TNFi	(28 uncontrolled studies)	NA	NA	Effectiveness							Improvement		
Rtixumab vs placebo																			
Alivernini, 2009	SLR: RCTs 4; non-RCTs 5	9030	Failure of ≥1 TNFi	NR	NR	Adalimumab after failure of infliximab or etanercept	-	-	-	ACR70 response		13%					Efficacy, irrespective of mode of action, in reaching ACR70 response is 5-15% for alternative TNFi, rituximab, abatacept and tocilizumab (except in two studies).	High	NR
						Adalimumab after failure of infliximab	-	-	-	ACR70 response		33%							
						Rituximab after failure of TNFi	-	Placebo	-	**ACR70 response**		**12%**							
						Abatacept after failure of TNFi	-	Placebo	-	ACR70 response		10.2%	1.5%						
						Tocilizumab after failure of TNFi	-	Placebo	-	ACR70 response		12.4%							
Greenwald, 2011	RCT	51	Failure of TNFi	DAS28-ESR 6.7; HAQ 1.4	10.4Y	**Rituximab (2 times 500mg at days 1 and 15, intravenous)**	**33**	**Placebo**	**18**	**ACR20 response**	**24W**	**30%**	**17%**					Moderate	
										ACR50 response	**24W**	**12%**	**6%**						
										ACR70 response	**24W**	**0%**	**0%**						
										DAS-ESR ≤3.2	**24W**	**25%**	**11%**						
										HAQ-DI improvement of ≥0.25	**24W**	**28 (46.4%)**	**4 (22.2%)**						
Kim, 2014	SLR: RCTs 6	1524	Failure of TNFi	HAQ 1.6-1.9	9.6-21.6Y (range)	Golimumab + DMARD	153	Placebo + DMARD	NR	ACR20 response	6M	32.1%	15.5%	2.577 (1.518-4.496)			Switching to non-TNF biologics was more effective than cycling TNFa inhibitor in TNF-IR patients; Probability (OR>1): 0.001; OR>1 favours golimumab	Moderate	Low-Moderate
										ACR50 response	6M	15.7%	4.2%	4.254 (1.947-10.550,-)			Probability (OR>1): 0.028; OR>1 favours golimumab		
										ACR70 response	6M	5.1%	1.3%	4.211 (1.605-13.460)			Probability (OR>1): 0.014; OR>1 favours golimumab		
										HAQ	Change from BL until 6M				-0.140 (-, -0.255- -		Probability (OR>1): 0.000; OR>1 favours golimumab		
						Abatacept + DMARD	256	Placebo + DMARD	NR	ACR20 response	6M	43.7%	15.5%	4.226 (2.606-7.023)			Probability (OR>1): 0.021; OR>1 favours abatacept		
										ACR50 response	6M	23.1%	4.2%	6.866 (2.900-20.870)			Probability (OR>1): 0.192; OR>1 favours abatacept		
										ACR70 response	6M	9.9%	1.3%	8.574 (2.312-56.850)			Probability (OR>1): 0.176; OR>1 favours abatacept		
										HAQ	Change from BL until 6M				-0.400 (-, -0.499- -		Probability (OR>1): 0.744; OR>1 favours abatacept		
						Rituximab + DMARD	**298**	**Placebo + DMARD**	**NR**	**ACR20 response**	**6M**	**47.0%**	**15.5%**	**4.822 (3.176-7.492)**			**Probability (OR>1): 0.039; OR>1 favours rituximab**		
										ACR50 response	**6M**	**24.0%**	**4.2%**	**7.231 (3.1812-15.490)**			**Probability (OR>1): 0.169; OR>1 favours rituximab**		
										ACR70 response	**6M**	**17.3%**	**1.3%**	**16.220 (4.575-121.800)**			**Probability (OR>1): 0.473; OR>1 favours rituximab**		

										HAQ	Change from BL until 6M						-0.300 (-, -0.397- -		Probability (OR>1): 0.05; OR>1 favours rituximab				
						Tocilizumab + DMARD	170	Placebo + DMARD	NR	ACR20 response	6M	62.4%	15.5%	9.060 (5.064-17.000)					Probability (OR>1): 0.939; OR>1 favours tocilizumab				
										ACR50 response	6M	32.2%	4.2%	10.83 (4.731-29.690)					Probability (OR>1): 0.611; OR>1 favours tocilizumab				
										ACR70 response	6M	14.4%	1.3%	12.900 (3.474-86.120)					Probability (OR>1): 0.337; OR>1 favours tocilizumab				
										HAQ	Change from BL until 6M						-0.340 (-, -0.453- -		Probability (OR>1): 0.204; OR>1 favours tocilizumab				
						Golimumab + DMARD	153	Abatacept	256	ACR20 response	6M	32.1%	43.7%	1.639 (0.786-3.408)					Probability (OR>1): 0.907; OR>1 favours abatacept				
										ACR50 response	6M	15.7%	23.1%	1.623 (0.454-6.247)					Probability (OR>1): 0.772; OR>1 favours abatacept				
										ACR70 response	6M	5.1%	9.9%	2.048 (0.361-16.470)					Probability (OR>1): 0.784; OR>1 favours abatacept				
										HAQ	Change from BL until 6M						-0.260 (-, -0.411- -		Probability (OR>1): 1.000; OR>1 favours abatacept				
						Golimumab + DMARD	153	Rituximab	298	ACR20 response	6M	32.1%	47.0%	1.871 (0.937-3.725)					Probability (OR>1): 0.962; OR>1 favour rituximab				
										ACR50 response	6M	15.7%	24.0%	1.702 (0.558-5.087)					Probability (OR>1): 0.830; OR>1 favours rituximab				
										ACR70 response	6M	5.1%	17.3%	3.876 (0.685-35.370)					Probability (OR>1): 0.935; OR>1 favours rituximab				
										HAQ	Change from BL until 6M						-0.160 (-, -0.310- -		Probability (OR>1): 0.982; OR>1 favours rituximab				
						Golimumab + DMARD	153	Tocilizumab	170	ACR20 response	6M	32.1%	62.4%	3.520 (1.567-7.946)					Probability (OR>1): 0.999; OR>1 favours tocilizumab				
										ACR50 response	6M	15.7%	32.2%	2.552 (0.752-9.100)					Probability (OR>1): 0.933; OR>1 favours tocilizumab				
										ACR70 response	6M	5.1%	14.4%	3.107 (0.532-25.490)					Probability (OR>1): 0.892; OR>1 favours tocilizumab				
										HAQ	Change from BL until 6M						-0.200 (-, -0.360- -		Probability (OR>1): 0.993; OR>1 favours tocilizumab				
Lee, 2016	SLR: RCTs 4	1796	Inadequate response to TNFi	NR	NR	Tocilizumab 4mg		Tofacitinib 10mg		ACR20 response	24W-6M			1.05 (0.47-2.39)					OR>1 favours tocilizumab 4mg; Tocilizumab highest performance regarding early good response based on ACR 20 response, followed by rituximab, abatacept and tofacitinib.	Moderate	Low		
						Abatacept		Tocilizumab 4mg		ACR20 response	24W-6M			1.06 (0.46-2.28)					OR>1 favours abatacept				
						Abatacept		Tofacitinib 10mg		ACR20 response	24W-6M			1.10 (0.54-2.31)					OR>1 favours abatacept				
						Rituximab		Abatacept		ACR20 response	24W-6M			1.14 (0.59-2.15)					OR>1 favours rituximab				
						Tofacitinib 10mg		Tofacitinib 5mg		ACR20 response	24W-6M			1.14 (0.71-1.86)					OR>1 favours tofacitinib 10mg				
						Rituximab		Tocilizumab 4mg		ACR20 response	24W-6M			1.20 (0.56-2.50)					OR>1 favours rituximab				
						Tocilizumab 4mg		Tofacitinib 5mg		ACR20 response	24W-6M			1.20 0.54-2.75)					OR>1 favours tocilizumab 4mg				
						Rituximab		Tofacitinib 10mg		ACR20 response	24W-6M			1.26 (0.64-2.46)					OR>1 favours rituximab				
						Abatacept		Tofacitinib 5mg		ACR20 response	24W-6M			1.26 (0.61-2.63)					OR>1 favours abatacept				
						Rituximab		Tofacitinib 5mg		ACR20 response	24W-6M			1.44 (0.73-2.82)					OR>1 favours rituximab				
						Tocilizumab 8mg		Rituximab		ACR20 response	24W-6M			1.92 (0.93-4.04)					OR>1 favours tocilizumab 8mg				
						Tocilizumab 8mg		Abatacept		ACR20 response	24W-6M			2.17 (1.01-4.89)					OR>1 favours tocilizumab 8mg				
						Tocilizumab 8mg		Tocilizumab 4mg		ACR20 response	24W-6M			2.29 (1.47-3.61)					OR>1 favours tocilizumab 8mg				
						Tocilizumab 8mg		Tofacitinib 10mg		ACR20 response	24W-6M			2.40 (1.09-5.41)					OR>1 favours tocilizumab 8mg				
						Tocilizumab 8mg		Tofacitinib 5mg		ACR20 response	24W-6M			2.74 (1.26-6.27)					OR>1 favours tocilizumab 8mg				
						Tofacitinib 5mg		Placebo		ACR20 response	24W-6M			3.30 (1.95-5.66)					OR>1 favours tofacitinib 5mg				
						Tofacitinib 10mg		Placebo		ACR20 response	24W-6M			3.76 (2.24-6.50)					OR>1 favours tofacitinib 10mg				
						Tocilizumab 4mg		Placebo		ACR20 response	24W-6M			3.94 (2.19-7.48)					OR>1 favours tocilizumab 4mg				
						Abatacept		Placebo		ACR20 response	24W-6M			4.15 (2.58-7.00)					OR>1 favours abatacept				
						Rituximab		**Placebo**		**ACR20 response**	**24W-6M**			**4.73 (3.14-7.27)**					OR>1 favours rituximab				
						Tocilizumab 8mg		Placebo		ACR20 response	24W-6M			9.04 (5.15-17.08)					OR>1 favours tocilizumab 8mg				
Malottki, 2011	SLR: RCTs 5; Non-RCTs 30	NR	Failure of 1 TNFi	NR	NR	**Rituximab**	(1 RCT)	**Placebo**	NR	ACR20 response	6M				**2.85 (2.08-3.91)**				Suggest that rituximab and abatacept are more effective than supportive care; Alternative TNFi some benefit, although uncertainties regarding magnitude of treatment effects and cost-effectiveness.	Moderate	NR		
										ACR70 response	**6M**				**12.14 (2.96-49.86)**								
										DAS28	**Change from BL until 6M**						**-1.50 (95%CI -1.74- -1.26)**						
										HAQ	**Change from BL until 6M**						**-0.30 (95%CI -0.40- -0.20)**						
						Abatacept	(1 RCT)	Placebo	NR	ACR20 response	6M				2.56 (1.77-3.69)								
										ACR70 response	6M				6.70 (1.62-27.80)								
										DAS28	Change from BL until 6M						-1.27 (95CI -1.62- - 0.93)						
										HAQ	Change from BL until 6M						-0.34						
						Alternative TNFi	(28 uncontrolled studies)	NA	NA	Effectiveness									Improvement				
Vital, 2015	RCT	25	Insufficient response to rituximab	DAS28-CRP 5.8	7.0-9.5Y	Additional dose of rituximab at W4 (1000mg,	12	Placebo	13	ACR20 response	28W	66.6%	61.5%					p=0.79		Low			

			(persistent B cells)		(range of medians)	intravenous)				ACR50 response ACR70 response EULAR good response EULAR good/moderate response	28W 28W 28W 28W	25.0% 8.3% 33.3% 91.6%	30.7% 30.7% 46.1% 76.9%			p=0.748 p=0.161 p=0.513 p=0.315			
Tocilizumab vs placebo																				
Alivernini, 2009	SLR: RCTs 4; non-RCTs 5	9030	Failure of ≥1 TNFi	NR	NR	Adalimumab after failure of infliximab or etanercept Adalimumab after failure of infliximab Rituximab after failure of TNFi Abatacept after failure of TNFi **Tocilizumab after failure of TNFi**	- - - - -	- - Placebo Placebo **Placebo**	- - - - -	ACR70 response ACR70 response ACR70 response ACR70 response **ACR70 response**		13% 33% 12% 10.2% **12.4%**	1.5%					Efficacy, irrespective of mode of action, in reaching ACR70 response is 5-15% for alternative TNFi, rituximab, abatacept and tocilizumab (except in two studies).	High	NR
Kim, 2014	SLR: RCTs 6	1524	Failure of TNFi	HAQ 1.6-1.9	9.6-21.6Y (range)	Golimumab + DMARD	153	Placebo + DMARD	NR	ACR20 response	6M	32.1%	15.5%	2.577 (1.518-4.496)				Switching to non-TNF biologics was more effective than cycling TNFa inhibitor in TNF-IR patients; Probability (OR>1): 0.001; OR>1 favours golimumab	Moderate	Low-Moderate
										ACR50 response	6M	15.7%	4.2%	4.254 (1.947-10.550,-)				Probability (OR>1): 0.028; OR>1 favours golimumab		
										ACR70 response	6M	5.1%	1.3%	4.211 (1.605-13.460)				Probability (OR>1): 0.014; OR>1 favours golimumab		
										HAQ	Change from BL until 6M					-0.140 (-, -0.255- -		Probability (OR>1): 0.000; OR>1 favours golimumab		
						Abatacept + DMARD	256	Placebo + DMARD	NR	ACR20 response	6M	43.7%	15.5%	4.226 (2.606-7.023)				Probability (OR>1): 0.021; OR>1 favours abatacept		
										ACR50 response	6M	23.1%	4.2%	6.866 (2.900-20.870)				Probability (OR>1): 0.192; OR>1 favours abatacept		
										ACR70 response	6M	9.9%	1.3%	8.574 (2.312-56.850)				Probability (OR>1): 0.176; OR>1 favours abatacept		
										HAQ	Change from BL until 6M					-0.400 (-, -0.499- -		Probability (OR>1): 0.744; OR>1 favours abatacept		
						Rituximab + DMARD	298	Placebo + DMARD	NR	ACR20 response	6M	47.0%	15.5%	4.822 (3.176-7.492)				Probability (OR>1): 0.039; OR>1 favours rituximab		
										ACR50 response	6M	24.0%	4.2%	7.231 (3.1812-15.490)				Probability (OR>1): 0.169; OR>1 favours rituximab		
										ACR70 response	6M	17.3%	1.3%	16.220 (4.575-121.800)				Probability (OR>1): 0.473; OR>1 favours rituximab		
										HAQ	Change from BL until 6M					-0.300 (-, -0.397- -		Probability (OR>1): 0.05; OR>1 favours rituximab		
						Tocilizumab + DMARD	**170**	**Placebo + DMARD**	**NR**	**ACR20 response**	**6M**	**62.4%**	**15.5%**	**9.060 (5.064-17.000)**				**Probability (OR>1): 0.939; OR>1 favours tocilizumab**		
										ACR50 response	**6M**	**32.2%**	**4.2%**	**10.83 (4.731-29.690)**				**Probability (OR>1): 0.611; OR>1 favours tocilizumab**		
										ACR70 response	**6M**	**14.4%**	**1.3%**	**12.900 (3.474-86.120)**				**Probability (OR>1): 0.337; OR>1 favours tocilizumab**		
										HAQ	**Change from BL until 6M**					**-0.340 (-, -0.453- -**		**Probability (OR>1): 0.204; OR>1 favours tocilizumab**		
						Golimumab + DMARD	153	Abatacept	256	ACR20 response	6M	32.1%	43.7%	1.639 (0.786-3.408)				Probability (OR>1): 0.907; OR>1 favours abatacept		
										ACR50 response	6M	15.7%	23.1%	1.623 (0.454-6.247)				Probability (OR>1): 0.772; OR>1 favours abatacept		
										ACR70 response	6M	5.1%	9.9%	2.048 (0.361-16.470)				Probability (OR>1): 0.784; OR>1 favours abatacept		
										HAQ	Change from BL until 6M					-0.260 (-, -0.411- -		Probability (OR>1): 1.000; OR>1 favours abatacept		
						Golimumab + DMARD	153	Rituximab	298	ACR20 response	6M	32.1%	47.0%	1.871 (0.937-3.725)				Probability (OR>1): 0.962; OR>1 favours rituximab		
										ACR50 response	6M	15.7%	24.0%	1.702 (0.558-5.087)				Probability (OR>1): 0.830; OR>1 favours rituximab		
										ACR70 response	6M	5.1%	17.3%	3.876 (0.685-35.370)				Probability (OR>1): 0.935; OR>1 favours rituximab		
										HAQ	Change from BL until 6M					-0.160 (-, -0.310- -		Probability (OR>1): 0.982; OR>1 favours rituximab		
						Golimumab + DMARD	153	Tocilizumab	170	ACR20 response	6M	32.1%	62.4%	3.520 (1.567-7.946)				Probability (OR>1): 0.999; OR>1 favours tocilizumab		
										ACR50 response	6M	15.7%	32.2%	2.552 (0.752-9.100)				Probability (OR>1): 0.933; OR>1 favours tocilizumab		
										ACR70 response	6M	5.1%	14.4%	3.107 (0.532-25.490)				Probability (OR>1): 0.892; OR>1 favours tocilizumab		
										HAQ	Change from BL until 6M					-0.200 (-, -0.360- -		Probability (OR>1): 0.993; OR>1 favours tocilizumab		
Lee, 2016	SLR: RCTs 4	1796	Inadequate response to TNFi	NR	NR	Tocilizumab 4mg		Tofacitinib 10mg		ACR20 response	24W-6M			1.05 (0.47-2.39)				OR>1 favours tocilizumab 4mg; Tocilizumab highest performance regarding early good response based on ACR 20 response, followed by rituximab, abatacept and tofacitinib.	Moderate	Low
						Abatacept		Tocilizumab 4mg		ACR20 response	24W-6M			1.06 (0.46-2.28)				OR>1 favours abatacept		
						Abatacept		Tofacitinib 10mg		ACR20 response	24W-6M			1.10 (0.54-2.31)				OR>1 favours abatacept		
						Rituximab		Abatacept		ACR20 response	24W-6M			1.14 (0.59-2.15)				OR>1 favours rituximab		
						Tofacitinib 10mg		Tofacitinib 5mg		ACR20 response	24W-6M			1.14 (0.71-1.86)				OR>1 favours tofacitinib 10mg		
						Rituximab		Tocilizumab 4mg		ACR20 response	24W-6M			1.20 (0.56-2.50)				OR>1 favours rituximab		
						Tocilizumab 4mg		Tofacitinib 5mg		ACR20 response	24W-6M			1.20 (0.54-2.75)				OR>1 favours tocilizumab 4mg		
						Rituximab		Tofacitinib 10mg		ACR20 response	24W-6M			1.26 (0.64-2.46)				OR>1 favours rituximab		
						Abatacept		Tofacitinib 5mg		ACR20 response	24W-6M			1.26 (0.61-2.63)				OR>1 favours abatacept		
						Rituximab		Tofacitinib 5mg		ACR20 response	24W-6M			1.44 (0.73-2.82)				OR>1 favours rituximab		
						Tocilizumab 8mg		Rituximab		ACR20 response	24W-6M			1.92 (0.93-4.04)				OR>1 favours tocilizumab 8mg		
						Tocilizumab 8mg		Abatacept		ACR20 response	24W-6M			2.17 (1.01-4.89)				OR>1 favours tocilizumab 8mg		
						Tocilizumab 8mg		Tocilizumab 4mg		ACR20 response	24W-6M			2.29 (1.47-3.61)				OR>1 favours tocilizumab 8mg		
						Tocilizumab 8mg		Tofacitinib 10mg		ACR20 response	24W-6M			2.40 (1.09-5.41)				OR>1 favours tocilizumab 8mg		

					Tocilizumab 8mg		Tofacitinib 5mg		ACR20 response	24W-6M		2.74 (1.26-6.27)						OR>1 favours tocilizumab 8mg		
					Tofacitinib 5mg		Placebo		ACR20 response	24W-6M		3.30 (1.95-5.66)						OR>1 favours tofacitinib 5mg		
					Tofacitinib 10mg		Placebo		ACR20 response	24W-6M		3.76 (2.24-6.50)						OR>1 favours tofacitinib 10mg		
					Tocilizumab 4mg		**Placebo**		**ACR20 response**	**24W-6M**		**3.94 (2.19-7.48)**						OR>1 favours tocilizumab 4mg		
					Abatacept		Placebo		ACR20 response	24W-6M		4.15 (2.58-7.00)						OR>1 favours abatacept		
					Rituximab		Placebo		ACR20 response	24W-6M		4.73 (3.14-7.27)						OR>1 favours rituximab		
					Tocilizumab 8mg		**Placebo**		**ACR20 response**	**24W-6M**		**9.04 (5.15-17.08)**						OR>1 favours tocilizumab 8mg		
Sarilumab vs placebo																						
Fleischmann, 2017	RCT	546	Failure of TNFi (inefficacy or intolerance)	DAS28-CRP 6.2; HAQ-DI 1.8	12.1Y	Sarilumab (150mg, q2w, subcutaneous)	181	Placebo	181	ACR20 response	24W	101 (55.8%)	61 (33.7%)				p<0.0001		Moderate	
										ACR50 response	24W	67 (37.0%)	33 (18.2%)				p<0.0001			
										ACR70 response	24W	36 (19.9%)	13 (7.2%)				p<0.001			
										DAS28-CRP	Change from BL until 24W				-2.4 (0.11)	-1.4 (0.12)		Adjusted for previous anti-TNF agents, region, visit, treatment-by-visit interaction, and baseline score as covariates		
										HAQ-DI	Change from BL until 12W				-0.46, LSM	-0.26, LSM	p=0.0007	Adjusted for previous anti-TNF agents, region, visit, treatment-by-visit interaction, and baseline score as covariates		
						Sarilumab (200mg, q2w, subcutaneous)	184	Placebo	181	ACR20 response	24W	112 (60.9%)	61 (33.7%)				p<0.0001			
										ACR50 response	24W	75 (40.8%)	33 (18.2%)				p<0.0001			
										ACR70 response	24W	30 (16.3%)	13 (7.2%)				p<0.01			
										DAS28-CRP	Change from BL until 24W				-2.8 (0.11)	-1.4 (0.12)		Adjusted for previous anti-TNF agents, region, visit, treatment-by-visit interaction, and baseline score as covariates		
										HAQ-DI	Change from BL until 12W				-0.47, LSM	-0.26, LSM	p=0.0004	Adjusted for previous anti-TNF agents, region, visit, treatment-by-visit interaction, and baseline score as covariates		
Genovese, 2017^ (Additional analysis on	RCT	546	Failure of TNFi (inadequate response or intolerance)	HAQ-DI <0.5: 2.7%	NR	Sarilumab (150mg, q2w, subcutaneous)	181	Placebo	181	CDAI ≤10	24W	58 (32.0%)	33 (18.2%)				p<0.05		High	
										SDAI ≤11	24W	59 (32.6%)	30 (16.6%)				p<0.05			
						Sarilumab (200mg, q2w, subcutaneous)	184	Placebo	181	CDAI ≤10	24W	65 (35.3%)	33 (18.2%)				p<0.05			
Secukinumab vs placebo																						
Huang, 2019	SLR (3 RCTs)	1292	Failure of ≥1 TNFi	NR	NR	Secukinumab 75 or 150mg (Subcutaneous at BL, W1, W2, W3, W4 and then q4W; or Intraveneous 10mg/kg at BL, W2, W4 and then _mg q4W)	859	Placebo	433	ACR20	24W			1.64 (1.33-2.01)				RR>1 favours secukinumab	Moderate	Low-moderate
										ACR50	24W			1.77 (1.17-2.66)						
										ACR70	24W			2.03 (1.14-3.60)						
						Secukinumab 150mg (Subcutaneous at BL, W1, W2, W3, W4 and then q4W; or Intraveneous 10mg/kg at BL, W2, W4 and then _mg q4W)	431	Placebo	433	ACR20	24W			1.66 (1.33-2.08)				RR>1 favours secukinumab		
										ACR50	24W			1.88 (1.29-2.72)						
										ACR70	24W			2.15 (1.15-4.02)						
						Secukinumab 75mg (Subcutaneous at BL, W1, W2, W3, W4 and then q4W; or Intraveneous 10mg/kg at BL, W2, W4 and then _mg q4W)	428	Placebo	433	ACR20	24W			1.62 (1.29-2.03)				RR>1 favours secukinumab		
										ACR50	24W			1.68 (0.99-2.85)						
										ACR70	24W			1.81 (0.78-4.21)						
Olokizumab vs placebo																						
Genovese, 2014c	RCT	221	Failure of TNFi	DAS28-CRP 5.77; CDAI 38.90 (14.3-71.2), median (range); HAQ-DI 1.63 (0.0-3.0), median (range)	9.99Y	Olokizumab (all doses, subcutaneous)	132	Placebo	22	ACR20 response	12W						p=0.0636	Favours olokizumab	Low	
										ACR50 response	12W						p=0.0574	Favours olokizumab		
						Olokizumab (60mg q4w, subcutaneous)	22	Placebo (q4w)	22	ACR20 response	12W	12 (75.0%)	1 (5.0%)							
										ACR50 response	12W	6 (37.5%)	0 (0%)							
										DAS28-ESR	Change from BL until 12W				-2.04 (0.26) (LS mean (SE))	-0.16 (0.25) (LS mean (SE))				
										CDAI	Change from BL until 12W				-18.51 (-69.2-48.0) (median (range))	-3.03 (-44.1-23.8) (median (range))				
										HAQ-DI	Change from BL until 12W				-0.50 (-1.6- -0.1) (median (range))	0.06 (-1.0-2.1) (median (range))				
						Olokizumab (60mg q2w, subcutaneous)	20	Placebo (q2w)	22	ACR20 response	12W	6 (35.3%)	7 (33.3%)							
										ACR50 response	12W	3 (17.6%)	1 (4.8%)							
										DAS28-ESR	Change from BL until 12W				-1.53 (0.27) (LS mean (SE))	-0.65 (0.25) (LS mean (SE))				
										CDAI	Change from BL until 12W				-8.00 (-36.5-19.0) (median (range))	-8.95 (-41.5-13.8) (median (range))				
										HAQ-DI	Change from BL until 12W				-0.25 (-1.0-0.9) (median (range))	0.00 (-1.0-0.6) (median (range))				
						Olokizumab (120mg q4w, subcutaneous)	23			ACR20 response	12W	11 (61.1%)								
										ACR50 response	12W	3 (16.7%)								

										DAS28-ESR	Change from BL until 12W			-1.57 (0.26) (LS mean (SE))	-1.79 (0.18) (LS mean (SE))			
										CDAI	Change from BL until 12W			-19.09 (-35.2-8.8) (median (range))	-17.30 (-49.2-15.1) (median (range))			
										HAQ-DI	Change from BL until 12W			-0.25 (-1.5-0.4) (median (range))	-0.26 (-1.5-0.3) (median (range))			
						Olokizumab (120mg q2w, subcutaneous)	22			ACR20 response	12W	10 (50.0%)						
										ACR50 response	12W	5 (25.0%)						
										DAS28-ESR	Change from BL until 12W			-2.05 (0.25) (LS mean (SE))				
										CDAI	Change from BL until 12W			-14.65 (-57.9-14.3) (median (range))				
										HAQ-DI	Change from BL until 12W			-0.25 (-0.9-1.4) (median (range))				
						Olokizumab (240mg q4w, subcutaneous)	22			ACR20 response	12W	7 (33.3%)						
										ACR50 response	12W	3 (1.43%)						
										DAS28-ESR	Change from BL until 12W			-1.59 (0.25) (LS mean (SE))				
										CDAI	Change from BL until 12W			-12.99 (-42.9-4.0) (median (range))				
										HAQ-DI	Change from BL until 12W			0.00 (-1.0-0.5) (median (range))				
						Olokizumab (240mg q2w, subcutaneous)	22			ACR20 response	12W	11 (52.4%)						
										ACR50 response	12W	5 (23.8%)						
										DAS28-ESR	Change from BL until 12W			-1.80 (0.25) (LS mean (SE))				
										CDAI	Change from BL until 12W			-16.30 (-58.2-8.9) (median (range))				
										HAQ-DI	Change from BL until 12W			-0.38 (-1.6-0.1) (median (range))				
Takeuchi, 2016	RCT	119	Failure of TNFi	DAS28-CRP 5.3 (3.4-8.0), median (range); CDAI 30.3 (12.6-70.4), median (range); SDAI 51.3 (19.5-149.8), median (range); HAQ-DI 1.13 (0.0-3.0), median (range)	7.0Y, median	Olokizumab (60mg q4w and placebo every 2 other weeks, subcutaneous)	32	Placebo	29	ACR20 response	12W	58.7%	21.9%			p=0.0090		High
										ACR50 response	12W	35.7%	8.6%			p=0.0310		
										ACR70 response	12W	9.6%	3.8%			ns		
										DAS28-ESR	Change from BL until 12W			-267 (95%CI -310- -224), LSM	-056 (95%CI -102- -010, -), LSM	p<0.0001		
										CDAI	Change from BL until 12W			-152 (95%CI -191- -114), LSM	-75 (95%CI -116- -34), LSM	p=0.0039		
										SDAI	Change from BL until 12W			-394 (95%CI -459- -330), LSM	-75 (95%CI -141- -04), LSM	p<0.0001		
										HAQ	Change from BL until 12W			-04 (95%CI -05- -02), LSM	0.0 (95%CI -02-0.2), LSM	p=0.0005		
						Olokizumab (60mg q2w or 120mg q4w and placebo every 2 other weeks, subcutaneous)	32	Placebo	29	ACR20 response	12W	62.5%	21.9%			p=0.0041		
										ACR50 response	12W	42.1%	8.6%			p=0.0125		
										ACR70 response	12W	22.5%	3.8%			ns		
										DAS28-ESR	Change from BL until 12W			-289 (95%CI -332- -246), LSM	-056 (95%CI -102- -010, -), LSM	p<0.0001		
										CDAI	Change from BL until 12W			-197 (-235- -159), LSM	-75 (95%CI -116- -34), LSM			
										SDAI	Change from BL until 12W			-446 (95%CI -510- -383), LSM	-75 (95%CI -141- -04), LSM			
										HAQ	Change from BL until 12W			-04 (95%CI -05- -02), LSM	0.0 (95%CI -02-0.2), LSM			
						Olokizumab (120mg q2w or 240mg q4w and placebo every 2 other weeks, subcutaneous)	26	Placebo	29	ACR20 response	12W	73.8%	21.9%			p=0.0009		
										ACR50 response	12W	39.1%	8.6%			p=0.0203		
										ACR70 response	12W	17.1%	3.8%			p=0.0886		
										DAS28-ESR	Change from BL until 12W			-318 (95%CI -366- -269), LSM	-056 (95%CI -102- -010, -), LSM	p<0.0001		
										CDAI	Change from BL until 12W			-208 (95%CI -251- -164), LSM	-75 (95%CI -116- -34), LSM	p<0.0001		
										SDAI	Change from BL until 12W			-461 (95%CI -533- -388), LSM	-75 (95%CI -141- -04), LSM	p<0.0001		
										HAQ	Change from BL until 12W			-04 (95%CI -05- -02), LSM	0.0 (95%CI -02-0.2), LSM	p=0.0023		
Tofacitinib vs placebo																			
Charles-Schoeman,	Non-RCT	705	Failure of ≥1 bDMARD	DAS28 6.4; SDAI 39.3; CDAI 37.4; HAQ-DI 1.4	8.79Y	Tofacitinib (5mg, 2/D, oral)	258	Placebo	191	ACR20 response	3M	112 (43.4%)	47 (24.6%)			p<0.0001		Moderate

2016										ACR50 response	3M	63 (24.4%)	20 (10.5%)					p<0.0001				
										ACR70 response	3M	25 (9.7%)	6 (3.1%)					p<0.05				
										DAS28	Change from BL until 3M					-1.62	-0.78	p<0.0001				
										CDAI ≤10	3M	29.5%	14.4%					p<0.001				
										SDAI ≤11	3M	29.8%	13.8%					p<0.0001				
										HAQ-DI	Change from BL until 3M					-0.31	-0.09	p<0.0001				
					Tofacitinib (10mg, 2/D, oral)	251	Placebo	191	ACR20 response	3M	130 (51.8%)	47 (24.6%)					p<0.0001				
										ACR50 response	3M	70 (27.9%)	20 (10.5%)					p<0.0001				
										ACR70 response	3M	31 (12.4%)	6 (3.1%)					p<0.001				
										DAS28	Change from BL until 3M					-1.98	-0.78	p<0.0001				
										CDAI ≤10	3M	35.9%	14.4%					p<0.0001				
										SDAI ≤11	3M	38.3%	13.8%					p<0.0001				
										HAQ-DI	Change from BL until 3M					-0.42	-0.09	p<0.0001				
Charles-Schoeman, 2017^	RCT	838	Failure of ≥1 bDMARD	NR	NR	Tofacitinib (5mg, 2/D, oral)	NR	Placebo	NR	ACR20 response	3M	43.5%	24.6%					p<0.0001			Moderate	
										DAS28-ESR ≤3.2	3M	12.7%	4.9%					p<0.05				
						Tofacitinib (10mg, 2/D, oral)	NR	Placebo	NR	ACR20 response	3M	50.6%	24.6%					p<0.0001				
										DAS28-ESR ≤3.2	3M	15.8%	4.9%					p<0.001				
Fleischmann, 2012	RCT	140	Failure of ≥1 bDMARD (inefficacy or toxicity)	NR	NR	Tofacitinib (5mg 2/D, oral)	46	Placebo	34	ACR20 response	3M	42.9%	17.7%					p=0.06			Moderate	
						Tofacitinib (10mg 2/D, oral)	60	Placebo	34	ACR20 response	3M	62.5%	17.7%					p<0.001				
Lee, 2016	SLR: RCTs 4	1796	Inadequate response to TNFi	NR	NR	Toclizumab 4mg		Tofacitinib 10mg		ACR20 response	24W-6M			1.05 (0.47-2.39)						OR>1 favours toclizumab 4mg; Tocilizumab highest performance regarding early good response based on ACR 20 response, followed by rituximab, abatacept and tofacitinib.	Moderate	Low
						Abatacept		Tocilizumab 4mg		ACR20 response	24W-6M			1.06 (0.46-2.28)						OR>1 favours abatacept		
						Abatacept		Tofacitinib 10mg		ACR20 response	24W-6M			1.10 (0.54-2.31)						OR>1 favours abatacept		
						Rituximab		Abatacept		ACR20 response	24W-6M			1.14 (0.59-2.15)						OR>1 favours rituximab		
						Tofacitinib 10mg		Tofacitinib 5mg		ACR20 response	24W-6M			1.14 (0.71-1.86)						OR>1 favours tofacitinib 10mg		
						Rituximab		Tocilizumab 4mg		ACR20 response	24W-6M			1.20 (0.56-2.50)						OR>1 favours rituximab		
						Toclizumab 4mg		Tofacitinib 5mg		ACR20 response	24W-6M			1.20 (0.54-2.75)						OR>1 favours tocilizumab 4mg		
						Rituximab		Tofacitinib 10mg		ACR20 response	24W-6M			1.26 (0.64-2.46)						OR>1 favours rituximab		
						Abatacept		Tofacitinib 5mg		ACR20 response	24W-6M			1.26 (0.61-2.63)						OR>1 favours abatacept		
						Rituximab		Tofacitinib 5mg		ACR20 response	24W-6M			1.44 (0.73-2.82)						OR>1 favours rituximab		
						Toclizumab 8mg		Rituximab		ACR20 response	24W-6M			1.92 (0.93-4.04)						OR>1 favours tocilizumab 8mg		
						Toclizumab 8mg		Abatacept		ACR20 response	24W-6M			2.17 (1.01-4.89)						OR>1 favours tocilizumab 8mg		
						Toclizumab 8mg		Tocilizumab 4mg		ACR20 response	24W-6M			2.29 (1.47-3.61)						OR>1 favours tocilizumab 8mg		
						Toclizumab 8mg		Tofacitinib 10mg		ACR20 response	24W-6M			2.40 (1.09-5.41)						OR>1 favours tocilizumab 8mg		
						Toclizumab 8mg		Tofacitinib 5mg		ACR20 response	24W-6M			2.74 (1.26-6.27)						OR>1 favours tocilizumab 8mg		
						Tofacitinib 5mg		**Placebo**		**ACR20 response**	**24W-6M**			**3.30 (1.95-5.66)**						OR>1 favours tofacitinib 5mg		
						Tofacitinib 10mg		**Placebo**		**ACR20 response**	**24W-6M**			**3.76 (2.24-6.50)**						OR>1 favours tofacitinib 10mg		
						Toclizumab 4mg		Placebo		ACR20 response	24W-6M			3.94 (2.19-7.48)						OR>1 favours tocilizumab 4mg		
						Abatacept		Placebo		ACR20 response	24W-6M			4.15 (2.58-7.00)						OR>1 favours abatacept		
						Rituximab		Placebo		ACR20 response	24W-6M			4.73 (3.14-7.27)						OR>1 favours rituximab		
						Toclizumab 8mg		Placebo		ACR20 response	24W-6M			9.04 (5.15-17.08)						OR>1 favours tocilizumab 8mg		
Strand, 2015	RCT	399	Failure of ≥1 TNFi	HAQ 1.58	11.3-13.0Y	Tofacitinib (5mg 2/D, oral)	133	Placebo	132	HAQ	Change from BL until 3M					-0.43 (0.04), LSM	-0.18 (0.04), LSM	p<0.0001			Low	
(Additional analysis on						Tofacitinib (10mg 2/D, oral)	134	Placebo	132	HAQ	Change from BL until 3M					-0.46 (0.04), LSM	-0.18 (0.04), LSM	p<0.0001				
Vieira, 2016	SLR: RCTs 5	2136	Inadequate response to TNFi	NR	9.6-13.0Y (range)	Tofacitinib		Placebo		ACR70 response	12W			3.80 (2.05-6.80)						OR>1 favours tofacitinib; Efficacy of tofacitinib comparable with bDMARDs	Moderate	Low
										ACR70 response	24W			5.77 (3.26-9.84)						OR>1 favours tofacitinib; Network meta-analysis		
								Abatacept		ACR70 response	12W			ns						OR>1 favours tofacitinib		
										ACR70 response	24W			ns						OR>1 favours tofacitinib		
								Golimumab		ACR70 response	14W			ns						OR>1 favours tofacitinib		
										ACR70 response	24W			1.50 (0.70-3.25)						OR>1 favours tofacitinib		
								Tocilizumab		ACR70 response	12W			ns						OR>1 favours tofacitinib		
										ACR70 response	24W			ns						OR>1 favours tofacitinib		
								Rituximab		ACR70 response	12W			ns						OR>1 favours tofacitinib		
										ACR70 response	24W			0.53 (0.27-1.02)						OR>1 favours tofacitinib		
Upadacitinib vs placebo																						
Genovese, 2018b	RCT	499	Failure of bDMARDs (inadequate response)	DAS28-CRP 5.8; CDAI 40.9; SDAI 42.5; HAQ-DI 1.6	13.2Y	Upadacitinib (15mg/D, oral)	164	Placebo	169	ACR20 response	12W	106 (65%)	48 (28%)					p<0.0001			Low	
										ACR50 response	12W	56 (34%)	20 (12%)					p<0.0001				
										ACR70 response	12W	19 (12%)	11 (7%)					p=0.1104				
										DAS28-CRP	Change from BL until 12W							p<0.0001				
										CDAI ≤10	12W	32%	14%					p=0.0002				
										SDAI ≤11	12W	34%	14%					p<0.0001				
										HAQ-DI	Change from BL until 12W					-0.41 (95%CI -0.50- -0.33)	-0.16 (95%CI -0.25- -0.08)	p<0.0001				
						Upadacitinib (30mg/D, oral)	165	Placebo	169	ACR20 response	12W	93 (56%)	48 (28%)					p<0.0001				
										ACR50 response	12W	59 (36%)	20 (12%)					p<0.0001				
										ACR70 response	12W	38 (23%)	11 (7%)					p<0.0001				
										DAS28-CRP	Change from BL until 12W							p<0.0001				
										CDAI ≤10	12W	34%	14%					p<0.0001				
										SDAI ≤11	12W	35%	14%					p<0.0001				
										HAQ-DI	Change from BL until 12W					-0.44 (95%CI -0.52- -0.35)	-0.16 (95%CI -0.25- -0.08)	p<0.0001				
Kremer, 2016	RCT	276	Inadequate response to TNFi	DAS28-CRP 5.8; CDAI 41; HAQ-DI 1.6	11.9Y	Upadacitinib (3mg 2/D, oral)	55	Placebo	56	ACR20 response	12W	53%	34%					p<0.05			Low	
										ACR50 response	12W	24%	16%					ns				
										ACR70 response	12W	13%	4%					ns				
										DAS28-CRP	Change from BL until 12W					-1.9	-1.1	p<0.01				
										HAQ-DI	Change from BL until 12W					-0.3% (95%CI -0.4- -0.1)	-0.2% (95%CI -0.4- -0.1)	ns				

					Upadacitinib (6mg 2/D, oral)	55	Placebo	56	ACR20 response	12W	58%	34%						p<0.01		
									ACR50 response	12W	36%	16%						p<0.05		
									ACR70 response	12W	26%	4%						p<0.01		
									DAS28-CRP	Change from BL until 12W						-2.2	-1.1	p<0.001		
									HAQ-DI	Change from BL until 12W						-0.5% (95%CI -0.6- -0.3)	-0.2% (95%CI -0.4- -0.1)	p<0.01		
					Upadacitinib (12mg 2/D, oral)	55	Placebo	56	ACR20 response	12W	67%	34%						p<0.001		
									ACR50 response	12W	38%	16%						p<0.01		
									ACR70 response	12W	22%	4%						p<0.01		
									DAS28-CRP	Change from BL until 12W						-2.5	-1.1	p<0.001		
									HAQ-DI	Change from BL until 12W						-0.5% (95%CI -0.6- -0.3)	-0.2% (95%CI -0.4- -0.1)	p<0.05		
					Upadacitinib (18mg 2/D, oral)	55	Placebo	56	ACR20 response	12W	71%	34%						p<0.001		
									ACR50 response	12W	42%	16%						p<0.01		
									ACR70 response	12W	22%	4%						p<0.01		
									DAS28-CRP	Change from BL until 12W						-2.3	-1.1	p<0.001		
									HAQ-DI	Change from BL until 12W						-0.5% (95%CI -0.7- -0.4)	-0.2% (95%CI -0.4- -0.1)	p<0.01		
Other b/tsDMARDs vs placebo																					
Aletaha, 2017	RCT	878	Failure of ≥1 bDMARD (refractory or intolerant)	DAS-CRP: 5.88 (1.00)	12.45Y (8.89)	Sirukumab (100mg q2w, subcutaneous)	292	Placebo	294	ACR20 response	24W	126 (43%)	76 (26%)						p<0.0001		Low
										ACR50 response	24W	64 (22%)	26 (9%)						p<0.0001		
										ACR70 response	24W	29 (10%)	12 (4%)						p=0.0257		
										DAS28-CRP	Change from BL until 24W						-2.12 (1.41)	-0.71 (0.41)	-1.40 (-, -1.62 - -1.18)	p<0.0001	
										SDAI	Change from BL until 24W						-18.8 (16.9)	-9.2 (17.2)	-9.5 (-, -12.32- -6.73)	p<0.0001	
										CDAI	Change from BL until 24W						-16.8 (16.6)	-9.2 (16.5)	-7.6 (-, -10.32- -4.89)	p<0.0001	
										HAQ-DI ≤0.5	24W	56 (19%)	37 (13%)						0.07 (-, 0.01-0.13)	p=0.0289	
					Sirukumab (50mg q4w, subcutaneous)	292	Placebo	294	ACR20 response	24W	126 (43%)	76 (26%)						p<0.0001		
									ACR50 response	24W	61 (21%)	26 (9%)						p<0.0001		
									DAS28-CRP	Change from BL until 24W						-2.01 (1.47)	-0.71 (0.41)	-1.26 (-, -1.48-1.04)	p<0.0001	
									SDAI	Change from BL until 24W						-17.1 (17.9)	-9.2 (17.2)	-7.9 (-, -10.68- -5.09)	p<0.0001	
									CDAI	Change from BL until 24W						-15.3 (17.5)	-9.2 (16.5)	-6.1 (-, -8.84- -3.41)	p<0.0001	
									HAQ-DI ≤0.5	24W	37 (13%)	37 (13%)						0.03 (-, -0.03-0.08)	p=0.385	
Cohen, 2019^	RCT	98	Failure of ≥1 TNFi	NR	NR	Fenebrutinib (200mg, 2/D)	48	Placebo	50	ACR50 response	12W	12 (25%)	6 (12%)						p=0.0650		Moderate
										DAS28-CRP	Change from BL until 12W						-1.96	-1.20		p=0.0002	
Genovese, 2011a	RCT	219	Failure of bDMARDs	DAS28 6.22; HAQ-DI 1.69	12.0Y	Fostamatinib disodium (100mg 2/D, oral)	146	Placebo	73	ACR20 response	3M	38%	37%						p=0.84		Moderate
										ACR50 response	3M	22%	12%						p=0.09		
										ACR70 response	3M	9%	5%						p=0.37		
										DAS28-CRP	Change from BL until 3M						-1.62 (1.4)	-1.27 (1.7)		p=0.15	
										HAQ-DI	Change from BL until 3M						-0.34 (0.59)	-0.25 (0.56)			
Genovese, 2011b	RCT	256	Failure of TNFi	DAS28-CRP 6.2; HAQ-DI 1.9	12.8Y	Atacicept (25mg 2/W for 4W, then q1w for 21W, subcutaneous)	66	Placebo	62	ACR20 response	26W	30%	29%	1.06 (0.65-1.74)					ns		Low
										ACR50 response	26W	14%	7%						ns		
										ACR70 response	26W	6%	0%						ns		
										EULAR good/moderate response	26W	32%	42%								
						Atacicept (75mg 2/W for 4W, then q1w for 21W, subcutaneous)	62	Placebo	62	ACR20 response	26W	27%	29%	0.98 (0.58-1.64)					ns		
										ACR50 response	26W	11%	7%						ns		
										ACR70 response	26W	5%	0%						ns		
										EULAR good/moderate response	26W	36%	42%								
						Atacicept (150mg 2/W for 4W, then q1w for 21W, subcutaneous)	64	Placebo	62	ACR20 response	26W	39%	29%	1.44 (0.92-2.24)					ns		
										ACR50 response	26W	11%	7%						ns		
										ACR70 response	26W	0%	0%						ns		
										EULAR good/moderate response	26W	53%	42%								
Genovese, 2013	RCT	100	Failure of TNFi	DAS28-CRP 6.0; HAQ-DI 1.7	10.4Y	Tabalumab (30mg at W0, W3 and W6, intravenous)	35	Placebo	35	ACR20 response	16W	9 (25.7%)	6 (17.1%)						p=0.198		Moderate
										ACR50 response	16W	4 (11.4%)	1 (2.9%)						p=0.101		
										ACR70 response	16W	1 (2.9%)	0 (0%)						p=0.411		
										EULAR good/moderate response	16W	13 (37.1%)	15 (44.1%)						p=0.398		
										DAS28-CRP	Change from BL until 16W						-1.29 (0.93)	-0.61 (1.04)		p=0.016	
						Tabalumab (80mg at W0, W3 and W6, intravenous)	35	Placebo	35	ACR20 response	16W	8 (28.6%)	6 (17.1%)						p=0.198		
										ACR50 response	16W	4 (14.3%)	1 (2.9%)						p=0.101		
										ACR70 response	16W	1 (3.6%)	0 (0%)						p=0.411		
										EULAR good/moderate response	16W	17 (65.4%)	15 (44.1%)						p=0.398		
										DAS28-CRP	Change from BL until 16W						-1.29 (0.93)	-0.61 (1.04)		p=0.016	
Genovese, 2014a	RCT	188	Failure of TNFi	DAS28-CRP 5.8; CDAI 40; HAQ-DI 1.6	11Y	Ixekizumab (80mg at W0, 1, 2 then q2w, subcutaneous)	65	Placebo	64	ACR20 response	12W	40%	23%						p<0.05		Moderate
										ACR50 response	12W	20%	8%						p<0.05		
										ACR70 response	12W	3%	3%						ns		
										EULAR response (not further specified)	12W	60%	37%						p<0.05		

										DAS28-CRP	Change from BL until 12W			-1.3, LSM	-0.6, LSM		ps0.05			
										CDAI	Change from BL until 12W			-15.3, LSM	-6.4, LSM		ps0.05			
										HAQ-DI	Change from BL until 12W			-0.2, LSM	-0.2, LSM		ns			
						Ixekizumab (180mg at W0, 1, 2, then q2w, subcutaneous)	59	Placebo	64	ACR20 response	12W	39%	23%				p<0.05			
										ACR50 response	12W	17%	8%				ns			
										ACR70 response	12W	10%	3%				ns			
										EULAR response (not further specified)	12W	66%	37%				p<0.05			
										DAS28-CRP	Change from BL until 12W			-1.6, LSM	-0.6, LSM		ps0.05			
										CDAI	Change from BL until 12W			-15.6, LSM	-6.4, LSM		ps0.05			
										HAQ-DI	Change from BL until 12W			-0.3, LSM	-0.2, LSM		ns			
Genovese, 2014b	RCT	322	Failure of 1 TNFi	DAS28-CRP 5.86; HAQ-DI 1.6	7.9-10.0Y (median)	Fostamatinib (100mg 2/D, oral)	105	Placebo	109	ACR20 response	24W	38 (36.2%)	23 (21.1%)				p=0.004			Moderate
										ACR50 response	24W	19 (18.1%)	9 (8.3%)				p=0.014			
										ACR70 response	24W	15 (14.3%)	3 (2.8%)				p<0.001			
										DAS-CRP ≤3.2	24W	26 (24.8%)	6 (5.5%)				s			
										HAQ-DI reduction ≥0.22	24W	44 (41.9%)	26 (23.9%)				s			
						Fostamatinib (100mg 2/D for 4W, then 150mg/D, oral)	108	Placebo	109	ACR20 response	24W	30 (27.8%)	23 (21.1%)				s			
										ACR50 response	24W	14 (13.0%)	9 (8.3%)				p=0.168			
										ACR70 response	24W	3 (2.8%)	3 (2.8%)				p=0.180			
										DAS-CRP ≤3.2	24W	12 (11.1%)	6 (5.5%)				-			
										HAQ-DI reduction ≥0.22	24W	34 (31.5%)	26 (23.9%)				-			
Genovese, 2016	RCT	527	Failure of bDMARD(s)	DAS28-ESR 5.5; SDAI 43; HAQ-DI 1.74	14Y	Baricitinib (2mg/D, oral)	174	Placebo	176	ACR20 response	24W						ps0.001	Favours baricitinib		Moderate
										DAS28-CRP	24W						ps0.001	Favours baricitinib		
										SDAI ≤3.3	24W	5%	2%				ns			
										HAQ-DI	24W						ps0.001	Favours baricitinib		
						Baricitinib (4mg/D, oral)	177	Placebo	176	ACR20 response	24W						ps0.001	Favours baricitinib		
										DAS28-CRP	24W						ps0.001	Favours baricitinib		
										SDAI ≤3.3	24W	9%	2%				p=0.14			
										HAQ-DI	24W						ps0.001	Favours baricitinib		
Genovese, 2019	RCT	448	Failure of ≥1 bDMARD	DAS28-CRP 5.9 (0.96); CDAI 41.2; SDAI 43.0; HAQ 1.66	9.8-10.3Y (range of medians)	Filgotinib (200mg/D)	148	Placebo	148	ACR20 response	24W	69.4%	34.5%				ps0.001			Moderate
										ACR50 response	24W	45.6%	18.9%				ps0.01			
										ACR70 response	24W	32.0%	8.1%				ps0.01			
										DAS28-CRP	Change from BL until 24W						ps0.001			
										CDAI	Change from BL until 24W			-30.9 (13.77)	-25.4 (14.4)		ps0.05			
										SDAI	Change from BL until 24W			-32.1 (14.41)	-24.9 (14.84)					
										HAQ	Change from BL until 24W			-0.75 (0.62)	-0.42 (0.60)		p<0.001			
						Filgotinib (100mg/D)	153	Placebo	148	ACR20 response	24W	54.9%	34.5%				ps0.001			
										ACR50 response	24W	35.3%	18.9%				ps0.01			
										ACR70 response	24W	20.3%	8.1%				ps0.01			
										DAS28-CRP	Change from BL until 24W						ps0.001			
										CDAI	Change from BL until 24W			-27.8 (13.54)	-25.4 (14.4)		ps0.05			
										SDAI	Change from BL until 24W			-28.8 (14.41)	-24.9 (14.84)					
										HAQ	Change from BL until 24W			-0.60 (0.66)	-0.42 (0.60)		p=0.003			
Schiff, 2015	RCT	456	Inadequate response to TNFi	DAS28-CRP 5.87; HAQ-DI 1.67	8.2Y	Tabalumab (120mg q4w, loading dose 240mg, subcutaneous)	153	Placebo	155	ACR20 response	24W	17.6%	20%				ns			High
						Tabalumab (90mg q2w, loading dose 180mg, subcutaneous)	148	Placebo	155	ACR20 response	24W	24.3%	20%				ns			
Tak, 2012	RCT	836	Inadequate response to TNFi	DAS28 6.5; HAQ-DI 1.7	12.3Y	Ocrelizumab (200mg at days 1 and 15 and at W24 and 26)	277	Placebo	277	ACR20 response	48W	48.7%	19.5%				p<0.0001			High
										ACR50 response	48W	19.3%	NR				p<0.0001			
										ACR70 response	48W	6.6%	NR				p<0.005			
										DAS28 <2.6	48W	11.9%	1.4%			10.5% (-, 6-15)	p<0.0001			
										HAQ-DI reduction ≥0.25	24W	52.3%	32.9%			19.4% (-, 11-28)	p<0.0001			
						Ocrelizumab (500mg at days 1 and 15 and at W24 and 26)	282	Placebo	277	ACR20 response	48W	50.7%	19.5%				p<0.0001			
										ACR50 response	48W	20.8%	NR				p<0.0001			
										ACR70 response	48W	6.7%	NR				p<0.05			
										DAS28 <2.6	48W	12.1%	1.4%			10.5% (-, 6-15)	p<0.0001			
										HAQ-DI reduction ≥0.25	24W	58.5%	32.9%			25.0% (-, 17-33)	p<0.0001			
van Vollenhoven, 2015	RCT	27	Insufficient response to rituximab	DAS28-CRP 5.6 (1.0)	12.6Y	Atacicept (150mg 1/w, subcutaneous)	18	Placebo	9	ACR20 response	25W						ns			High
										ACR50 response	25W						ns			
										ACR70 response	25W						ns			
COMPARISON OF DIFFERENT B/TSDMARDS																						
Comparison of different b/tsDMARD																						
Lee, 2016	SLR: RCTs 4	1796	Inadequate response to TNFi	NR	NR	Tocilizumab 4mg		Tofacitinib 10mg		ACR20 response	24W-6M		1.05 (0.47-2.39)					OR>1 favours tocilizumab 4mg; Tocilizumab highest performance regarding early good response based on ACR 20 response, followed by rituximab, abatacept and tofacitinib.	Moderate	Low
						Abatacept		Tocilizumab 4mg		ACR20 response	24W-6M		1.06 (0.46-2.28)					OR>1 favours abatacept		
						Abatacept		Tofacitinib 10mg		ACR20 response	24W-6M		1.10 (0.54-2.31)					OR>1 favours abatacept		
						Rituximab		Abatacept		ACR20 response	24W-6M		1.14 (0.59-2.15)					OR>1 favours rituximab		
						Tofacitinib 10mg		Tofacitinib 5mg		ACR20 response	24W-6M		1.14 (0.71-1.86)					OR>1 favours tofacitinib 10mg		
						Rituximab		Tocilizumab 4mg		ACR20 response	24W-6M		1.20 (0.56-2.50)					OR>1 favours rituximab		
						Tocilizumab 4mg		Tofacitinib 5mg		ACR20 response	24W-6M		1.20 (0.54-2.75)					OR>1 favours tocilizumab 4mg		
						Rituximab		Tofacitinib 10mg		ACR20 response	24W-6M		1.26 (0.64-2.46)					OR>1 favours rituximab		
						Abatacept		Tofacitinib 5mg		ACR20 response	24W-6M		1.26 (0.61-2.63)					OR>1 favours abatacept		
						Rituximab		Tofacitinib 5mg		ACR20 response	24W-6M		1.44 (0.73-2.82)					OR>1 favours rituximab		
						Tocilizumab 8mg		Rituximab		ACR20 response	24W-6M		1.92 (0.93-4.04)					OR>1 favours tocilizumab 8mg		
						Tocilizumab 8mg		Abatacept		ACR20 response	24W-6M		2.17 (1.01-4.89)					OR>1 favours tocilizumab 8mg		
						Tocilizumab 8mg		Tocilizumab 4mg		ACR20 response	24W-6M		2.29 (1.47-3.61)					OR>1 favours tocilizumab 8mg		
						Tocilizumab 8mg		Tofacitinib 10mg		ACR20 response	24W-6M		2.40 (1.09-5.41)					OR>1 favours tocilizumab 8mg		
						Tocilizumab 8mg		Tofacitinib 5mg		ACR20 response	24W-6M		2.74 (1.26-6.27)					OR>1 favours tocilizumab 8mg		

						Tofacitinib 5mg		Placebo		ACR20 response	24W-6M		3.30 (1.95-5.66)					OR>1 favours tofacitinib 5mg			
						Tofacitinib 10mg		Placebo		ACR20 response	24W-6M		3.76 (2.24-6.50)					OR>1 favours tofacitinib 10mg			
						Toclizumab 4mg		Placebo		ACR20 response	24W-6M		3.94 (2.19-7.48)					OR>1 favours tocilizumab 4mg			
						Abatacept		Placebo		ACR20 response	24W-6M		4.15 (2.58-7.00)					OR>1 favours abatacept			
						Rituximab		Placebo		ACR20 response	24W-6M		4.73 (3.14-7.27)					OR>1 favours rituximab			
						Toclizumab 8mg		Placebo		ACR20 response	24W-6M		9.04 (5.15-17.08)					OR>1 favours tocilizumab 8mg			
Vieira, 2016	SLR: RCTs 5	2136	Inadequate response to TNFi	NR	9.6-13.0Y (range)	Tofacitinib		Placebo		ACR70 response	12W		3.80 (2.05-6.80)					**OR>1 favours tofacitinib; Efficacy of tofacitinib comparable with bDMARDs**	Moderate	Low	
										ACR70 response	24W		5.77 (3.26-9.84)					OR>1 favours tofacitinib; Network meta-analysis			
								Abatacept		ACR70 response	12W		ns					OR>1 favours tofacitinib			
										ACR70 response	24W		ns					OR>1 favours tofacitinib			
								Golimumab		ACR70 response	14W		ns					OR>1 favours tofacitinib			
										ACR70 response	24W		1.50 (0.70-3.25)					OR>1 favours tofacitinib			
								Tocilizumab		ACR70 response	12W		ns					OR>1 favours tofacitinib			
										ACR70 response	24W		ns					OR>1 favours tofacitinib			
								Rituximab		ACR70 response	12W		ns					OR>1 favours tofacitinib			
										ACR70 response	24W		0.53 (0.27-1.02)					OR>1 favours tofacitinib			
Alternative TNFi vs alternative TNFi																						
Alivernini, 2009	SLR: RCTs 4; non-RCTs 5	9030	Failure of ≥1 TNFi	NR	NR	Adalimumab after failure of infliximab or etanercept	-	-	-	ACR70 response		13%						Efficacy, irrespective of mode of action, in reaching ACR70 response is 5-15% for alternative TNFi, rituximab, abatacept and tocilizumab (except in two studies).	High	NR	
						Adalimumab after failure of inlifximab	-	-	-	ACR70 response		33%										
						Rituximab after failure of TNFi	-	Placebo	-	ACR70 response		12%										
						Abatacept after failure of TNFi	-	Placebo	-	ACR70 response		10.2%	1.5%									
						Toclizumab after failure of TNFi	-	Placebo	-	ACR70 response		12.4%										
Chatzidionysiou, 2013	Non-RCT	328	Failure of 1 TNFi	DAS28 4.95 (Infliximab/adalimumab 4.87 (1.27); Etanercept 4.86 (1.21); Rituximab 5.3 (1.29); p=0.06 infliximab/adalimumab vs	6.9Y	Infliximab or adalimumab	161	Etanercept	98	EULAR good response	6M	12 (13.8%)	16 (33.3%)								High	
										EULAR good/moderate response	6M	38 (43.7%)	32 (66.7%)									
										DAS28	Change from BL until 6M					-0.67 (1.36)	-1.4 (1.51)	p=0.006				
										HAQ	Change from BL until 6M					-0.07 (0.51)	-0.23 (0.41)	ns				
Chatzidionysiou, 2015	Non-RCT	952	Failure of 1 TNFi	DAS28 4.91 (Infliximab 5.0 (±1.3); etanercept 5.1 (±1.4); adalimumab 4.7 (±1.4); p=0.001); HAQ: 1.1	8.6Y	Infliximab (no high disease activity at BL)	31	Etanercept (no high disease activity at BL)	184	DAS28	Change from BL until 6M					-0.6(1.4)	-0.8(1.3)	p=0.09			High	
						Etanercept (no high disease activity at BL)	184	Adalimumab (no high disease activity at BL)	199	DAS28	Change from BL until 6M					-0.8(1.3)	-0.4(1.3)	p=0.09				
						Adalimumab (no high disease activity at BL)	199	Infliximab (no high disease activity at BL)	31	DAS28	Change from BL until 6M					-0.4(1.3)	-0.6(1.4)	p=0.09				
						Infliximab (high disease activity at BL)	28	Etanercept (high disease activity at BL)	188	DAS28	Change from BL until 6M					-1.8(1.3)	-1.9(1.5)	p=0.05				
						Etanercept (high disease activity at BL)	188	Adalimumab (high disease activity at BL)	136	DAS28	Change from BL until 6M					-1.9(1.5)	-1.4(1.6)	p=0.05				
						Adalimumab (high disease activity at BL)	136	Infliximab (high disease activity at BL)	28	DAS28	Change from BL until 6M					-1.4(1.6)	-1.8(1.3)	p=0.05				
						Infliximab → etanercept	242	Infliximab → adalimumab	101	DAS28	Change from BL until 6M					-1.6(1.5)	-1.2(1.6)					
						Etanercept → infliximab	58	Etanercept → adalimumab	329	DAS28	Change from BL until 6M					-1.2(1.6)	-0.7(1.5)					
						Adalimumab → infliximab	16	Adalimumab → etanercept	206	DAS28	Change from BL until 6M					-0.6(0.9)	-1.2(1.6)					
Cohen, 2005	Non-RCT	38	Failure of 1 TNFi (etanercept or infliximab)	DAS28 5.7 (1.7)	13.5Y	Alternative TNFi (etanercept or infliximab)	38			EULAR good response	3M	15 (40%)									High	
										EULAR good/moderate response	3M	22 (58%)										
										DAS28	3M					3.87						
						Infliximab to etanercept (25mg 2/W, subcutaneous)	24	Etanercept to infliximab (3mg/kg at W0, 2 and 8, then q8w, intravenous)	14	EULAR good response	3M	11 (46%)	4 (29%)									
										EULAR good/moderate response	3M	14 (58.5%)	8 (58%)									
										DAS28	Change from BL until 3M					Decrease compared to BL	Decrease compared to BL					
Smolen, 2016	RCT	122	Primary non-response to either certolizumab pegol or adalimumab at 12W	DAS28-ESR 6.0; CDAI 33.4; HAQ-DI 1.4	NR	Certolizumab pegol (400mg at W0, 2 and 4, then 200mg q2w)	57	Adalimumab (40mg q2w) + placebo at W0, 2 and 4	65	ACR20 response	52W	33.3%	38.5%								Low	
										ACR50 response	52W	26.3%	27.7%									
										ACR70 response	52W	12.3%	13.8%									
										DAS-ESR ≤3.2	52W	22.8%	12.3%									
										CDAI ≤10	52W	28.1%	27.7%									
Zhang, 2018	Non-RCT	48	Inadequate response to TNFi	NR	5.24Y	TNFi: Intra-articular injection in knee joints	8	TNFi: Subcutaneous injection (etanercept 2/W)	20	DAS28-ESR	Change from BL until 4W					(95%CI 0.04-0.38)	(95%CI 0.29-0.57)	p=0.081			High	
						TNFi: Intra-articular injection in knee joints	8	TNFi: Combination of intra-articular and subcutaneous injections	20	DAS28-ESR	Change from BL until 4W					(95%CI 0.04-0.38)	(95%CI 0.23-0.47)	p=0.182				
						TNFi: Subcutaneous injection (etanercept 2/W)	20	TNFi: Combination of intra-articular and subcutaneous injections	20	DAS28-ESR	Change from BL until 4W					(95%CI 0.29-0.57)	(95%CI 0.23-0.47)	p=0.656				
Alternative TNFi vs non-TNFi bDMARD																						
Alivernini, 2009	SLR: RCTs 4; non-RCTs 5	9030	Failure of ≥1 TNFi	NR	NR	Adalimumab after failure of infliximab or etanercept	-	-	-	ACR70 response		13%						Efficacy, irrespective of mode of action, in reaching ACR70 response is 5-15% for alternative TNFi, rituximab, abatacept and tocilizumab (except in two studies).	High	NR	
						Adalimumab after failure of inlifximab	-	-	-	ACR70 response		33%										
						Rituximab after failure of TNFi	-	Placebo	-	ACR70 response		12%										
						Abatacept after failure of TNFi	-	Placebo	-	ACR70 response		10.2%	1.5%									
						Toclizumab after failure of TNFi	-	Placebo	-	ACR70 response		12.4%										
Gonzalez-Vacarezza, 2014	SLR: RCTs 24	6357	Failure of TNFi	NR	0.9-13Y (range)	Rituximab		Etanercept		ACR50 response				0.475 (0.253-0.892)				OR>1 favours RTX	Moderate	NR	Appropriate to introduce tocilizumab in the coverage and remove infliximab.	
						Rituximab		Etanercept		ACR70 response				0.231 (0.0590-0.902)				OR>1 favours RTX				
						Toclizumab		Infliximab		ACR70 response				2.42 (1.36-4.34)				OR>1 favours tocilizumab				
						Rituximab		Tocilizumab in third line treatment		ACR20 response				1.79 (1.01-3.18)				OR>1 favours tocilizumab				
Gottenberg, 2016	RCT	300	Insufficient response to TNFi	DAS28-ESR 5.1 (1.1); HAQ 1.3 (0.6)	10.0Y	Non-TNFi biologic (abatacept 33 (23%), rituximab 41 (28%), tocilizumab 70 48%))	146	Alternative TNFi (adalimumab 57 (39%), certolizumab 23 (16%), etanercept 53 (36%), infliximab 8 (5%))	146	EULAR good/moderate response	52W	78 (60%)	57 (43%)	1.99 (1.22-3.25)			17.0% (-, 5.1-28.9)	p=0.006		High	
										DAS28-ESR	Change from BL until 52W						-0.38 (-,-0.69- -0.08)	p=0.01				

										HAQ-DI	52W						-0.02 (-, -0.13-0.09)	p=0.75	Adjusted for baseline difference		
Kim, 2014	SLR: RCTs 6	1524	Failure of TNFi	HAQ 1.6-1.9	9.6-21.6Y (range)	Golimumab + DMARD	153	Placebo + DMARD	NR	ACR20 response	6M	32.1%	15.5%	2.577 (1.518-4.496)					Switching to non-TNF biologics was more effective than cycling TNFa inhibitor in TNF-IR patients; Probability (OR>1): 0.001; OR>1 favours golimumab	Moderate	Low-Moderate
										ACR50 response	6M	15.7%	4.2%	4.254 (1.947-10.550,-)					Probability (OR>1): 0.028; OR>1 favours golimumab		
										ACR70 response	6M	5.1%	1.3%	4.211 (1.605-13.460)					Probability (OR>1): 0.014; OR>1 favours golimumab		
										HAQ	Change from BL until 6M						-0.140 (-, -0.255- -		Probability (OR>1): 0.000; OR>1 favours golimumab		
						Abatacept + DMARD	256	Placebo + DMARD	NR	ACR20 response	6M	43.7%	15.5%	4.226 (2.606-7.023)					Probability (OR>1): 0.021; OR>1 favours abatacept		
										ACR50 response	6M	23.1%	4.2%	6.866 (2.900-20.870)					Probability (OR>1): 0.192; OR>1 favours abatacept		
										ACR70 response	6M	9.9%	1.3%	8.574 (2.312-56.850)					Probability (OR>1): 0.176; OR>1 favours abatacept		
										HAQ	Change from BL until 6M						-0.400 (-, -0.499- -		Probability (OR>1): 0.744; OR>1 favours abatacept		
						Rituximab + DMARD	298	Placebo + DMARD	NR	ACR20 response	6M	47.0%	15.5%	4.822 (3.176-7.492)					Probability (OR>1): 0.039; OR>1 favours rituximab		
										ACR50 response	6M	24.0%	4.2%	7.231 (3.1812-15.490)					Probability (OR>1): 0.169; OR>1 favours rituximab		
										ACR70 response	6M	17.3%	1.3%	16.220 (4.575-121.800)					Probability (OR>1): 0.473; OR>1 favours rituximab		
										HAQ	Change from BL until 6M						-0.300 (-, -0.397- -		Probability (OR>1): 0.05; OR>1 favours rituximab		
						Tocilizumab + DMARD	170	Placebo + DMARD	NR	ACR20 response	6M	62.4%	15.5%	9.060 (5.064-17.000)					Probability (OR>1): 0.939; OR>1 favours tocilizumab		
										ACR50 response	6M	32.2%	4.2%	10.83 (4.731-29.690)					Probability (OR>1): 0.611; OR>1 favours tocilizumab		
										ACR70 response	6M	14.4%	1.3%	12.900 (3.474-86.120)					Probability (OR>1): 0.337; OR>1 favours tocilizumab		
										HAQ	Change from BL until 6M						-0.340 (-, -0.453- -		Probability (OR>1): 0.204; OR>1 favours tocilizumab		
						Golimumab + DMARD	153	Abatacept	256	ACR20 response	6M	32.1%	43.7%	1.639 (0.786-3.408)					Probability (OR>1): 0.907; OR>1 favours abatacept		
										ACR50 response	6M	15.7%	23.1%	1.623 (0.454-6.247)					Probability (OR>1): 0.772; OR>1 favours abatacept		
										ACR70 response	6M	5.1%	9.9%	2.048 (0.361-16.470)					Probability (OR>1): 0.784; OR>1 favours abatacept		
										HAQ	Change from BL until 6M						-0.260 (-, -0.411- -		Probability (OR>1): 1.000; OR>1 favours abatacept		
						Golimumab + DMARD	153	Rituximab	298	ACR20 response	6M	32.1%	47.0%	1.871 (0.937-3.725)					Probability (OR>1): 0.962; OR>1 favours rituximab		
										ACR50 response	6M	15.7%	24.0%	1.702 (0.558-5.087)					Probability (OR>1): 0.830; OR>1 favours rituximab		
										ACR70 response	6M	5.1%	17.3%	3.876 (0.685-35.370)					Probability (OR>1): 0.935; OR>1 favours rituximab		
										HAQ	Change from BL until 6M						-0.160 (-, -0.310- -		Probability (OR>1): 0.982; OR>1 favours rituximab		
						Golimumab + DMARD	153	Tocilizumab	170	ACR20 response	6M	32.1%	62.4%	3.520 (1.567-7.946)					Probability (OR>1): 0.999; OR>1 favours tocilizumab		
										ACR50 response	6M	15.7%	32.2%	2.552 (0.752-9.100)					Probability (OR>1): 0.933; OR>1 favours tocilizumab		
										ACR70 response	6M	5.1%	14.4%	3.107 (0.532-25.490)					Probability (OR>1): 0.892; OR>1 favours tocilizumab		
										HAQ	Change from BL until 6M						-0.200 (-, -0.360- -		Probability (OR>1): 0.993; OR>1 favours tocilizumab		
Nam, 2017	SLR: SLRs 2; RCTs 2	RCTs: 431	Failure of TNFi	NR	NR	Second TNFi or non-TNFi		Other bDMARD		Efficacy									Benefit; Insufficient evidence to prioritise either strategy	Moderate	Low
Wei, 2017	Non-RCT	613	Failure of TNFi	DAS28-ESR 3.8 (1.3)	NR	Alternative TNFi (adalimumab 23%)	332	bDMARD with different mechanism of action (rituximab 14.7%)	281	CDAI	Change from BL until 1Y				-4.81	-7.54	p=0.037, ns after adjustment for CDAI at			High	
(Alternative) TNFi vs abatacept																					
Akiyama, 2016	Non-RCT	63	Failure of tocilizumab	CDAI: 24.2 (1.5)	11.4Y (1.2)	TNFi (19 infliximab, 3 adalimumab, 8 etanercept, 9 golimumab, 3 certolizumab-pegol) for 24W	42	Abatacept for 24W	21	CDAI≤10 (remission or LDA)	24W	64.3%	23.8%					p=0.003		High	
Harrold, 2015c	Non-RCT	1177	Failure of TNFi	CDAI 22.1; mHAQ 0.6 (ABA 0.7, TNFi 0.6, p=0.047)	12.5Y	Abatacept	431	TNFi	746	mACR20 response	12M			0.87 (0.59-1.29, -)					OR>1 favours abatacept; Adjusted for numberof prior anti-TNF medications, baselinedisease activity, rheumatoid arthritisdisease severity and concomitantmedications	High	
										mACR50 response	12M			0.86 (0.58-1.27, -)					OR>1 favours abatacept; Adjusted for numberof prior anti-TNF medications, baselinedisease activity, rheumatoid arthritisdisease severity and concomitantmedications		
										mACR70 response	12M			1.12 (0.56-2.24, -)					OR>1 favours abatacept; Adjusted for numberof prior anti-TNF medications, baselinedisease activity, rheumatoid arthritisdisease severity and concomitantmedications		
										mDAS	Change from BL until 12M				1.03	1.03		p=0.93			
										mCDAI	Change from BL until 12M						-1.64 (-, -3.47-0.19)				

									Improvement of ≥0.25 in mHAQ	12M			0.74 (0.48-1.15, -)					OR>1 favours abatacept; Adjusted for numberof prior anti-TNF medications, baselinedisease activity, rheumatoid arthritisdisease severity and concomitantmedications		
Kim, 2014	SLR: RCTs 6	1524	Failure of TNFi	HAQ 1.6-1.9	9.6-21.6Y (range)	Golimumab + DMARD	153	Placebo + DMARD	NR	ACR20 response	6M	32.1%	15.5%	2.577 (1.518-4.496)				Switching to non-TNF biologics was more effective than cycling TNFa inhibitor in TNF-IR patients; Probability (OR>1): 0.001; OR>1 favours golimumab	Moderate	Low-Moderate
										ACR50 response	6M	15.7%	4.2%	4.254 (1.947-10.550,-)				Probability (OR>1): 0.028; OR>1 favours golimumab		
										ACR70 response	6M	5.1%	1.3%	4.211 (1.605-13.460)				Probability (OR>1): 0.014; OR>1 favours golimumab		
										HAQ	Change from BL until 6M					-0.140 (-, -0.255- -		Probability (OR>1): 0.000; OR>1 favours golimumab		
						Abatacept + DMARD	256	Placebo + DMARD	NR	ACR20 response	6M	43.7%	15.5%	4.226 (2.606-7.023)				Probability (OR>1): 0.021; OR>1 favours abatacept		
										ACR50 response	6M	23.1%	4.2%	6.866 (2.900-20.870)				Probability (OR>1): 0.192; OR>1 favours abatacept		
										ACR70 response	6M	9.9%	1.3%	8.574 (2.312-56.850)				Probability (OR>1): 0.176; OR>1 favours abatacept		
										HAQ	Change from BL until 6M					-0.400 (-, -0.499- -		Probability (OR>1): 0.744; OR>1 favours abatacept		
						Rituximab + DMARD	298	Placebo + DMARD	NR	ACR20 response	6M	47.0%	15.5%	4.822 (3.176-7.492)				Probability (OR>1): 0.039; OR>1 favours rituximab		
										ACR50 response	6M	24.0%	4.2%	7.231 (3.1812-15.490)				Probability (OR>1): 0.169; OR>1 favours rituximab		
										ACR70 response	6M	17.3%	1.3%	16.220 (4.575-121.800)				Probability (OR>1): 0.473; OR>1 favours rituximab		
										HAQ	Change from BL until 6M					-0.300 (-, -0.397- -		Probability (OR>1): 0.05; OR>1 favours rituximab		
						Tocilizumab + DMARD	170	Placebo + DMARD	NR	ACR20 response	6M	62.4%	15.5%	9.060 (5.064-17.000)				Probability (OR>1): 0.939; OR>1 favours tocilizumab		
										ACR50 response	6M	32.2%	4.2%	10.83 (4.731-29.690)				Probability (OR>1): 0.611; OR>1 favours tocilizumab		
										ACR70 response	6M	14.4%	1.3%	12.900 (3.474-86.120)				Probability (OR>1): 0.337; OR>1 favours tocilizumab		
										HAQ	Change from BL until 6M					-0.340 (-, -0.453- -		Probability (OR>1): 0.204; OR>1 favours tocilizumab		
						Golimumab + DMARD	**153**	**Abatacept**	**256**	**ACR20 response**	**6M**	**32.1%**	**43.7%**	**1.639 (0.786-3.408)**				**Probability (OR>1): 0.907; OR>1 favours abatacept**		
										ACR50 response	**6M**	**15.7%**	**23.1%**	**1.623 (0.454-6.247)**				**Probability (OR>1): 0.772; OR>1 favours abatacept**		
										ACR70 response	**6M**	**5.1%**	**9.9%**	**2.048 (0.361-16.470)**				**Probability (OR>1): 0.784; OR>1 favours abatacept**		
										HAQ	**Change from BL until 6M**					**-0.260 (-, -0.411- -**		**Probability (OR>1): 1.000; OR>1 favours abatacept**		
						Golimumab + DMARD	153	Rituximab	298	ACR20 response	6M	32.1%	47.0%	1.871 (0.937-3.725)				Probability (OR>1): 0.962; OR>1 favours rituximab		
										ACR50 response	6M	15.7%	24.0%	1.702 (0.558-5.087)				Probability (OR>1): 0.830; OR>1 favours rituximab		
										ACR70 response	6M	5.1%	17.3%	3.876 (0.685-35.370)				Probability (OR>1): 0.935; OR>1 favours rituximab		
										HAQ	Change from BL until 6M					-0.160 (-, -0.310- -		Probability (OR>1): 0.982; OR>1 favours rituximab		
						Golimumab + DMARD	153	Tocilizumab	170	ACR20 response	6M	32.1%	62.4%	3.520 (1.567-7.946)				Probability (OR>1): 0.999; OR>1 favours tocilizumab		
										ACR50 response	6M	15.7%	32.2%	2.552 (0.752-9.100)				Probability (OR>1): 0.933; OR>1 favours tocilizumab		
										ACR70 response	6M	5.1%	14.4%	3.107 (0.532-25.490)				Probability (OR>1): 0.892; OR>1 favours tocilizumab		
										HAQ	Change from BL until 6M					-0.200 (-, -0.360- -		Probability (OR>1): 0.993; OR>1 favours tocilizumab		
Alternative TNFi vs rituximab																					
Brown, 2018	RCT	122	Failure of ≥1 TNFi	DAS28 6.1 (1.1); CDAI 38.3 (13.31); SDAI 40.2 (14.04)	6.7Y	TNFi (etanercept, adalimumab, certolizumab pegol, golimumab, infliximab)	41	Rituximab (1000mg at days 1 en 15, intravenous)	40	ACR20 response	48W	54.8%	42.9%						High	
										ACR50 response	48W	29.0%	20.7%							
										ACR70 response	48W	16.1%	0%							
										EULAR good response	48W	26.8%	5.0%							
										DAS28	Reduction from BL until 24W				1.47 (0.85-2.08)	1.17 (0.56-1.77)	0.30 (95% confidence interval (CI) −0.45 to 1.05) p=0.436			
										CDAI	48W				19.3 (5.7-28.8), median (IQR)	20.3 (5.3-32.3), median (IQR)				
										SDAI	48W				20.1 (7.9-27.2), median (IQR)	20.1 (5.3-34.0), median (IQR)				
Chatzidionysiou, 2013	Non-RCT	328	Failure of 1 TNFi	DAS28 4.95 (Infliximab/adalimumab 4.87 (1.27); Etanercept 4.86 (1.21); Rituximab 5.3 (1.29); p=0.06 infliximab/adalimumab vs rituximab); HAQ:1.19	6.9Y	Etanercept	98	Rituximab	69	EULAR good response	6M	16 (33.3%)	8 (22.9%)						High	
										EULAR good/moderate response	6M	32 (66.7%)	27 (77.1%)							
										DAS28	Change from BL until 6M				-1.4 (1.51)	-1.7 (1.18)	ns			
										HAQ	Change from BL until 6M				-0.23 (0.41)	-0.16 (0.54)	ns			
						Rituximab	69	Infliximab or adalimumab	161	EULAR good response	6M	8 (22.9%)	12 (13.8%)							

			(Infliximab/adalimumab 1.14(0.65); Etanercept 1.14(0.62); Rituximab 1.43(0.57); p=0.007							EULAR good/moderate response	6M	27 (77.1%)	38 (43.7%)												
										DAS28	Change from BL until 6M						-1.7 (1.18)	-0.67 (1.36)	p<0.0001						
										HAQ	Change from BL until 6M						-0.16 (0.54)	-0.07 (0.51)	ns						
Emery, 2015	Non-RCT	728	Failure of TNFi	DAS28-ESR 5.02 (Rituximab 5.2 (1.2); alternative TNFi 4.8 (1.3); p<0.0001); HAQ-DI 1.4	8.45Y	Rituximab	405	Alternative TNFi	323	DAS28-3-ESR	Change from BL until 6M						-1.5(0.2), LSM (SD)	`-1.1 (0.2), LSM (SD)	p=0.007					High	
										HAQ-DI	Change from BL until 6M						−0.6 (0.2), LSM (SD)	−0.5 (0.2), LSM (SD)	p=0.337						
Gomez-Reino, 2012	Non-RCT	1124	Failure of TNFi	DAS28 5.3 (RTX 5.5; TNFi 5.0; p<0.0001)	NR	Rituximab	591	Alternative TNFi	533	EULAR good response	12M	64%	60%												
										EULAR good/moderate response	12M	82%	76%												
										DAS28	Change from BL until 12M								ns						
										HAQ-DI reduction ≥0.22	12M								p=0.06						
						Rituximab	121	Etanercept	78	DAS28	Change from BL until 12M						-1.81 (1.60)	-1.66 (1.49)	p=0.36						
						Rituximab	121	Adalimumab	104	DAS28	Change from BL until 12M						-1.81 (1.60)	-1.55 (1.49)	p=0.05						
Gonzalez-Vacarezza, 2014	SLR: RCTs 24	6357	Failure of TNFi	NR	0.9-13Y (range)	Rituximab		Etanercept		ACR50 response				0.475 (0.253-0.892)					OR>1 favours RTX	Appropriate to introduce tocilizumab in the coverage and remove infliximab.	Moderate	NR			
						Rituximab		Etanercept		ACR70 response				0.231 (0.0590-0.902)					OR>1 favours RTX						
						Tocilizumab		Infliximab		ACR70 response				2.42 (1.36-4.34)					OR>1 favours tocilizumab						
						Rituximab		Tocilizumab in third line treatment		ACR20 response				1.79 (1.01-3.18)					OR>1 favours tocilizumab						
Harrold, 2015a	Non-RCT	1002	Failure of ≥1 TNFi	CDAI 25.8; mHAQ 0.68	12.6Y	Rituximab	265	TNFi	737 (trimmed popula	mACR20 response	1Y	36.6%	28.7%	1.66 (1.17-2.36, -)					p=0.02	OR>1 favours rituximab; Adjusted for baseline demographics,disease activity, comorbidity and medication use (past and current)	High				
										mACR50 response	1Y	21.1%	17.4%	1.53 (1.01-2.30, -)					p=0.17	OR>1 favours rituximab; Adjusted for baseline demographics,disease activity, comorbidity and medication use (past and current)					
										mACR70 response	1Y	10.2%	8.8%	1.59 (0.92-2.76, -)					p=0.46	OR>1 favours rituximab; Adjusted for baseline demographics,disease activity, comorbidity and medication use (past and current)					
										CDAI low disease activity/remission	1Y	34.3%	33.7%	1.35 (0.95-1.91, -)					p=0.82	OR>1 favours rituximab; Adjusted for baseline demographics,disease activity, comorbidity and medication use (past and current)					
										Improvement of ≥0.25 in mHAQ	1Y	33.2%	24.2%	1.46 (1.01-2.12, -)					p=0.004	OR>1 favours rituximab; Adjusted for baseline demographics,disease activity, comorbidity and medication use (past and current)					
Kekow, 2012	Non-RCT	196	Failure of TNFi	DAS28 5.5	7.85Y	Rituximab (1000mg, 2-4 infusions, intravenous)	90	Alternative TNFi (etanercept 44.3%, adalimumab 40.6%, infliximab 15.1%)	106	EULAR good response	End of observation (median 189D)	27 (30%)	16 (15.1%)						p=0.0216		High				
										EULAR good/moderate response	End of observation (median 189D)	70 (77.8%)	69 (65.1%)						p=0.0216						
										DAS28-CRP	Change from BL until end of observation (median 189D)						-1.64 (-, -1.92-1.36)	-1.19 (-, -1.42-0.96)	p=0.013						
Kim, 2014	SLR: RCTs 6	1524	Failure of TNFi	HAQ 1.6-1.9	9.6-21.6Y (range)	Golimumab + DMARD	153	Placebo + DMARD	NR	ACR20 response	6M	32.1%	15.5%	2.577 (1.518-4.496)						Switching to non-TNF biologics was more effective than cycling TNFa inhibitor in TNF-IR patients; Probability (OR>1): 0.001; OR>1 favours golimumab	Moderate	Low-Moderate			
										ACR50 response	6M	15.7%	4.2%	4.254 (1.947-10.550,-)						Probability (OR>1): 0.028; OR>1 favours golimumab					
										ACR70 response	6M	5.1%	1.3%	4.211 (1.605-13.460)						Probability (OR>1): 0.014; OR>1 favours golimumab					
										HAQ	Change from BL until 6M								-0.140 (-, -0.255- -	Probability (OR>1): 0.000; OR>1 favours golimumab					
						Abatacept + DMARD	256	Placebo + DMARD	NR	ACR20 response	6M	43.7%	15.5%	4.226 (2.606-7.023)						Probability (OR>1): 0.021; OR>1 favours abatacept					
										ACR50 response	6M	23.1%	4.2%	6.866 (2.900-20.870)						Probability (OR>1): 0.192; OR>1 favours abatacept					
										ACR70 response	6M	9.9%	1.3%	8.574 (2.312-56.850)						Probability (OR>1): 0.176; OR>1 favours abatacept					
										HAQ	Change from BL until 6M								-0.400 (-, -0.499- -	Probability (OR>1): 0.744; OR>1 favours abatacept					
						Rituximab + DMARD	298	Placebo + DMARD	NR	ACR20 response	6M	47.0%	15.5%	4.822 (3.176-7.492)						Probability (OR>1): 0.039; OR>1 favours rituximab					
										ACR50 response	6M	24.0%	4.2%	7.231 (3.1812-15.490)						Probability (OR>1): 0.169; OR>1 favours rituximab					
										ACR70 response	6M	17.3%	1.3%	16.220 (4.575-121.800)						Probability (OR>1): 0.473; OR>1 favours rituximab					
										HAQ	Change from BL until 6M								-0.300 (-, -0.397- -	Probability (OR>1): 0.05; OR>1 favours rituximab					
						Tocilizumab + DMARD	170	Placebo + DMARD	NR	ACR20 response	6M	62.4%	15.5%	9.060 (5.064-17.000)						Probability (OR>1): 0.939; OR>1 favours tocilizumab					
										ACR50 response	6M	32.2%	4.2%	10.83 (4.731-29.690)						Probability (OR>1): 0.611; OR>1 favours tocilizumab					
										ACR70 response	6M	14.4%	1.3%	12.900 (3.474-86.120)						Probability (OR>1): 0.337; OR>1 favours tocilizumab					

										HAQ	Change from BL until 6M						-0.340 (-, -0.453- -		Probability (OR>1): 0.204; OR>1 favours tocilizumab					
						Golimumab + DMARD	153	Abatacept	256	ACR20 response	6M	32.1%	43.7%	1.639 (0.786-3.408)					Probability (OR>1): 0.907; OR>1 favours abatacept					
										ACR50 response	6M	15.7%	23.1%	1.623 (0.454-6.247)					Probability (OR>1): 0.772; OR>1 favours abatacept					
										ACR70 response	6M	5.1%	9.9%	2.048 (0.361-16.470)					Probability (OR>1): 0.784; OR>1 favours abatacept					
										HAQ	Change from BL until 6M						-0.260 (-, -0.411- -		Probability (OR>1): 1.000; OR>1 favours abatacept					
						Golimumab + DMARD	**153**	**Rituximab**	**298**	**ACR20 response**	**6M**	**32.1%**	**47.0%**	**1.871 (0.937-3.725)**					**Probability (OR>1): 0.962; OR>1 favours rituximab**					
										ACR50 response	**6M**	**15.7%**	**24.0%**	**1.702 (0.558-5.087)**					**Probability (OR>1): 0.830; OR>1 favours rituximab**					
										ACR70 response	**6M**	**5.1%**	**17.3%**	**3.876 (0.685-35.370)**					**Probability (OR>1): 0.935; OR>1 favours rituximab**					
										HAQ	**Change from BL until 6M**						**-0.160 (-, -0.310- -**		**Probability (OR>1): 0.982; OR>1 favours rituximab**					
						Golimumab + DMARD	153	Tocilizumab	170	ACR20 response	6M	32.1%	62.4%	3.520 (1.567-7.946)					Probability (OR>1): 0.999; OR>1 favours tocilizumab					
										ACR50 response	6M	15.7%	32.2%	2.552 (0.752-9.100)					Probability (OR>1): 0.933; OR>1 favours tocilizumab					
										ACR70 response	6M	5.1%	14.4%	3.107 (0.532-25.490)					Probability (OR>1): 0.892; OR>1 favours tocilizumab					
										HAQ	Change from BL until 6M						-0.200 (-, -0.360- -		Probability (OR>1): 0.993; OR>1 favours tocilizumab					
Soliman, 2012	Non-RCT	1328	Failure of 1 TNFi	DAS28 6.0 (p<0.001)	14.2Y	**Rituximab**	**387**	**Alternative TNFi**	**941**	**EULAR good response**	**6M**	**17.1%**	**13.5%**					p=0.04			High			
										EULAR good/moderate response	6M	54.8%	46.3%	1.31 (1.02-1.69, 0.04)					Adjusted by propensity score including Disease Activity Score in 28 joints, comorbidities, the failed anti-TNF therapy, and interaction between age and reasonfor switching (Response vs non-response)					
										DAS28	Change from BL until 6M				-1.3 (95%CI -1.5- -1.2)	-1.2 (95%CI '-1.3- -1.1)		p=0.12						
										HAQ	Change from BL until 6M				-0.13 (95%CI -0.17- -0.08)	-0.11 (95%CI -0.13- -0.08)		p=0.51						
Torrente-Segarra, 2016	Non-RCT	103	Inappropriate response or intolerance to TNFi	DAS28 5.37 (1.7)	5.8Y	**Rituximab**	**54**	**Alternative TNFi (Etanercept 23 (47%); Adalimumab 16 (32%); Infliximab 10 (20%))**	**49**	**EULAR good response**	**6M**	**21.6%**	**25.7%**					ns			High			
										EULAR good/moderate response	6M	64.8%	60.0%					ns						
										DAS28	6M				4.2 (2.1)	4.76 (1.9)		p=0.298						
										HAQ	6M				0.82 (0.68)	0.59 (0.69)		p=0.960						
Alternative TNFi vs tocilizumab																								
Gonzalez-Vacarezza, 2014	SLR: RCTs 24	6357	Failure of TNFi	NR	0.9-13Y (range)	Rituximab		Etanercept		ACR50 response							0.475 (0.253-0.892)	OR>1 favours RTX	Appropriate to introduce tocilizumab in the coverage and remove infliximab.	Moderate	NR			
						Rituximab		Etanercept		ACR70 response							0.231 (0.0590-0.902)	OR>1 favours RTX						
						Tocilizumab		Infliximab		ACR70 response							**2.42 (1.36-4.34)**	**OR>1 favours tocilizumab**						
						Rituximab		Tocilizumab in third line treatment		ACR20 response							1.79 (1.01-3.18)	OR>1 favours tocilizumab						
Harrold, 2018	Non-RCT	1073	Failure of TNFi	CDAI 27.2-28.1 (range); mHAQ 0.7	11.5-12.9Y (range)	TNFi + MTX ≤10mg	108	Tocilizumab (96% intravenously every 4 weeks; 4% subcutaneously (7 every 2 weeks, 3 every week, 2 missing information))	283 (trimmed population)	mACR20 response	6M			1.16 (0.69-1.97)					OR>1 favours tocilizumab; Adjusted for age, sex, race (white vs. nonwhite), disabled,retired, baseline CDAI, baseline mHAQ, baseline patient pain, baseline prednisone use/dose, baseline BMI, prior biologic use, prior TNFi use, and ACR functional class.	High				
										mACR50 response	6M			1.42 (0.75-2.70)					OR>1 favours tocilizumab; Adjusted for age, sex, race (white vs. nonwhite), disabled,retired, baseline CDAI, baseline mHAQ, baseline patient pain, baseline prednisone use/dose, baseline BMI, prior biologic use, prior TNFi use, and ACR functional class.					
										CDAI	Change from BL until 6M			-0.15 (-2.92-2.62)					OR>1 favours tocilizumab; Adjusted for age, sex, race (white vs. nonwhite), disabled,retired, baseline CDAI, baseline mHAQ, baseline patient pain, baseline prednisone use/dose, baseline BMI, prior biologic use, prior TNFi use, and ACR functional class.					
										mHAQ	Change from BL until 6M			-0.02 (-0.12-0.08)					OR>1 favours tocilizumab; Adjusted for age, sex, race (white vs. nonwhite), disabled,retired, baseline CDAI, baseline mHAQ, baseline patient pain, baseline prednisone use/dose, baseline BMI, prior biologic use, prior TNFi use, and ACR functional class.					

						TNFi + MTX >10 to ≤15mg	186	Tocilizumab (96% intravenously every 4 weeks; 4% subcutaneously (7 every 2 weeks, 3 every week, 2 missing information))	300 (trimmed population)	mACR20 response	6M			0.98 (0.63-1.52)		OR>1 favours tocilizumab; Adjusted for age, sex, race (white vs. nonwhite), disabled,retired, baseline CDAI, baseline mHAQ, baseline patient pain, baseline prednisone use/dose, baseline BMI, prior biologic use, prior TNFi use, and ACR functional class.	
										mACR50 response	6M			1.19 (0.70-2.03)		OR>1 favours tocilizumab; Adjusted for age, sex, race (white vs. nonwhite), disabled,retired, baseline CDAI, baseline mHAQ, baseline patient pain, baseline prednisone use/dose, baseline BMI, prior biologic use, prior TNFi use, and ACR functional class.	
										CDAI	Change from BL until 6M			-0.30 (-2.83-2.22)		OR>1 favours tocilizumab; Adjusted for age, sex, race (white vs. nonwhite), disabled,retired, baseline CDAI, baseline mHAQ, baseline patient pain, baseline prednisone use/dose, baseline BMI, prior biologic use, prior TNFi use, and ACR functional class.	
										mHAQ	Change from BL until 6M			0.01 (-0.07-0.09)		OR>1 favours tocilizumab; Adjusted for age, sex, race (white vs. nonwhite), disabled,retired, baseline CDAI, baseline mHAQ, baseline patient pain, baseline prednisone use/dose, baseline BMI, prior biologic use, prior TNFi use, and ACR functional class.	
						TNFi + MTX >15 to ≤20mg	273	Tocilizumab (96% intravenously every 4 weeks; 4% subcutaneously (7 every 2 weeks, 3 every week, 2 missing information))	292 (trimmed population)	mACR20 response	6M			1.68 (1.10-2.56)		OR>1 favours tocilizumab; Adjusted for age, sex, race (white vs. nonwhite), disabled,retired, baseline CDAI, baseline mHAQ, baseline patient pain, baseline prednisone use/dose, baseline BMI, prior biologic use, prior TNFi use, and ACR functional class.	
										mACR50 response	6M			1.70 (1.00-2.89)		OR>1 favours tocilizumab; Adjusted for age, sex, race (white vs. nonwhite), disabled,retired, baseline CDAI, baseline mHAQ, baseline patient pain, baseline prednisone use/dose, baseline BMI, prior biologic use, prior TNFi use, and ACR functional class.	
										CDAI	Change from BL until 6M			-1.65 (-3.84-0.54)		OR>1 favours tocilizumab; Adjusted for age, sex, race (white vs. nonwhite), disabled,retired, baseline CDAI, baseline mHAQ, baseline patient pain, baseline prednisone use/dose, baseline BMI, prior biologic use, prior TNFi use, and ACR functional class.	
										mHAQ	Change from BL until 6M			-0.02 (-0.10-0.06)		OR>1 favours tocilizumab; Adjusted for age, sex, race (white vs. nonwhite), disabled,retired, baseline CDAI, baseline mHAQ, baseline patient pain, baseline prednisone use/dose, baseline BMI, prior biologic use, prior TNFi use, and ACR functional class.	
						TNFi + MTX >20mg	107	Tocilizumab (96% intravenously every 4 weeks; 4% subcutaneously (7 every 2 weeks, 3 every week, 2 missing information))	285 (trimmed population)	mACR20 response	6M			0.99 (0.59-1.69)		OR>1 favours tocilizumab; Adjusted for age, sex, race (white vs. nonwhite), disabled,retired, baseline CDAI, baseline mHAQ, baseline patient pain, baseline prednisone use/dose, baseline BMI, prior biologic use, prior TNFi use, and ACR functional class.	
										mACR50 response	6M			1.57 (0.78-3.15)		OR>1 favours tocilizumab; Adjusted for age, sex, race (white vs. nonwhite), disabled,retired, baseline CDAI, baseline mHAQ, baseline patient pain, baseline prednisone use/dose, baseline BMI, prior biologic use, prior TNFi use, and ACR functional class.	
										CDAI	Change from BL until 6M			-1.43 (-5.12-2.25)		OR>1 favours tocilizumab; Adjusted for age, sex, race (white vs. nonwhite), disabled,retired, baseline CDAI, baseline mHAQ, baseline patient pain, baseline prednisone use/dose, baseline BMI, prior biologic use, prior TNFi use, and ACR functional class.	
										mHAQ	Change from BL until 6M			0.02 (-0.09-0.12)		OR>1 favours tocilizumab; Adjusted for age, sex, race (white vs. nonwhite), disabled,retired, baseline CDAI, baseline mHAQ, baseline patient pain, baseline prednisone use/dose, baseline BMI, prior biologic use, prior TNFi use, and ACR functional class.	
Hirabara, 2014	Non-RCT	89	Inadequate efficacy of TNFi	DAS28-CRP 4.6 (1.2); CDAI 22.4 (11.0); SDAI 24.8 (11.6)	9.8Y	Etanercept	26	Tocilizumab	38	CDAI ≤10	52W	70.6%	68.2%		ns		High		

Kim, 2014	SLR: RCTs 6	1524	Failure of TNFi	HAQ 1.6-1.9	9.6-21.6Y (range)	Golimumab + DMARD	153	Placebo + DMARD	NR	ACR20 response	6M	32.1%	15.5%	2.577 (1.518-4.496)					Switching to non-TNF biologics was more effective than cycling TNFa inhibitor in TNF-IR patients; Probability (OR>1): 0.001; OR>1 favours golimumab	Moderate	Low-Moderate
										ACR50 response	6M	15.7%	4.2%	4.254 (1.947-10.550,-)					Probability (OR>1): 0.028; OR>1 favours golimumab		
										ACR70 response	6M	5.1%	1.3%	4.211 (1.605-13.460)					Probability (OR>1): 0.014; OR>1 favours golimumab		
										HAQ	Change from BL until 6M						-0.140 (-, -0.255- -		Probability (OR>1): 0.000; OR>1 favours golimumab		
						Abatacept + DMARD	256	Placebo + DMARD	NR	ACR20 response	6M	43.7%	15.5%	4.226 (2.606-7.023)					Probability (OR>1): 0.021; OR>1 favours abatacept		
										ACR50 response	6M	23.1%	4.2%	6.866 (2.900-20.870)					Probability (OR>1): 0.192; OR>1 favours abatacept		
										ACR70 response	6M	9.9%	1.3%	8.574 (2.312-56.850)					Probability (OR>1): 0.176; OR>1 favours abatacept		
										HAQ	Change from BL until 6M						-0.400 (-, -0.499- -		Probability (OR>1): 0.744; OR>1 favours abatacept		
						Rituximab + DMARD	298	Placebo + DMARD	NR	ACR20 response	6M	47.0%	15.5%	4.822 (3.176-7.492)					Probability (OR>1): 0.039; OR>1 favours rituximab		
										ACR50 response	6M	24.0%	4.2%	7.231 (3.1812-15.490)					Probability (OR>1): 0.169; OR>1 favours rituximab		
										ACR70 response	6M	17.3%	1.3%	16.220 (4.575-121.800)					Probability (OR>1): 0.473; OR>1 favours rituximab		
										HAQ	Change from BL until 6M						-0.300 (-, -0.397- -		Probability (OR>1): 0.05; OR>1 favours rituximab		
						Tocilizumab + DMARD	170	Placebo + DMARD	NR	ACR20 response	6M	62.4%	15.5%	9.060 (5.064-17.000)					Probability (OR>1): 0.939; OR>1 favours tocilizumab		
										ACR50 response	6M	32.2%	4.2%	10.83 (4.731-29.690)					Probability (OR>1): 0.611; OR>1 favours tocilizumab		
										ACR70 response	6M	14.4%	1.3%	12.900 (3.474-86.120)					Probability (OR>1): 0.337; OR>1 favours tocilizumab		
										HAQ	Change from BL until 6M						-0.340 (-, -0.453- -		Probability (OR>1): 0.204; OR>1 favours tocilizumab		
						Golimumab + DMARD	153	Abatacept	256	ACR20 response	6M	32.1%	43.7%	1.639 (0.786-3.408)					Probability (OR>1): 0.907; OR>1 favours abatacept		
										ACR50 response	6M	15.7%	23.1%	1.623 (0.454-6.247)					Probability (OR>1): 0.772; OR>1 favours abatacept		
										ACR70 response	6M	5.1%	9.9%	2.048 (0.361-16.470)					Probability (OR>1): 0.784; OR>1 favours abatacept		
										HAQ	Change from BL until 6M						-0.260 (-, -0.411- -		Probability (OR>1): 1.000; OR>1 favours abatacept		
						Golimumab + DMARD	153	Rituximab	298	ACR20 response	6M	32.1%	47.0%	1.871 (0.937-3.725)					Probability (OR>1): 0.962; OR>1 favours rituximab		
										ACR50 response	6M	15.7%	24.0%	1.702 (0.558-5.087)					Probability (OR>1): 0.830; OR>1 favours rituximab		
										ACR70 response	6M	5.1%	17.3%	3.876 (0.685-35.370)					Probability (OR>1): 0.935; OR>1 favours rituximab		
										HAQ	Change from BL until 6M						-0.160 (-, -0.310- -		Probability (OR>1): 0.982; OR>1 favours rituximab		
						Golimumab + DMARD	**153**	**Tocilizumab**	**170**	**ACR20 response**	**6M**	**32.1%**	**62.4%**	**3.520 (1.567-7.946)**					**Probability (OR>1): 0.999; OR>1 favours tocilizumab**		
										ACR50 response	**6M**	**15.7%**	**32.2%**	**2.552 (0.752-9.100)**					**Probability (OR>1): 0.933; OR>1 favours tocilizumab**		
										ACR70 response	**6M**	**5.1%**	**14.4%**	**3.107 (0.532-25.490)**					**Probability (OR>1): 0.892; OR>1 favours tocilizumab**		
										HAQ	**Change from BL until 6M**						**-0.200 (-, -0.360- -**		**Probability (OR>1): 0.993; OR>1 favours tocilizumab**		
Lauper, 2018	Non-RCT	8608	Failure of bDMARD (not further specified)	DAS28 4.2; CDAI 23.75	8.95Y	Tocilizumab monotherapy	771	TNFi combination therapy	4660	CDAI	Change from BL until 1Y				−3.54	−3.68			Coeff 0.17 (95%CI -1.33-1.66, p=0.83), adjusted by age, gender, disease duration, seropositivity, number of previous bDMARDs, GCs at BL, HAQ at BL	High	
						TNFi monotherapy	1404	TNFi combination therapy	4660	CDAI	Change from BL until 1Y				−3.58	−3.68			Coeff -0.23 (95%CI -1.06-0.60, p=0.59), adjusted by age, gender, disease duration, seropositivity, number of previous bDMARDs, GCs at BL, HAQ at BL		
						Tocilizumab monotherapy	771	Tocilizumab combination therapy	1773	CDAI	Change from BL until 1Y				−3.54	−3.34			Coeff -0.21 (95%CI -1.24-0.83, p=0.70), adjusted by age, gender, disease duration, seropositivity, number of previous bDMARDs, GCs at BL, HAQ at BL		
						Tocilizumab monotherapy	771	TNFi monotherapy	1404	CDAI	Change from BL until 1Y				−3.54	−3.58			Coeff -0.47 (95%CI -1.60-0.66, p=0.41), adjusted by age, gender, disease duration, seropositivity, number of previous bDMARDs, GCs at BL, HAQ at BL		
						Tocilizumab combination therapy	1773	TNFi combination therapy	4660	CDAI	Change from BL until 1Y				−3.34	−3.68			Coeff 0.09 (95%CI -0.56-0.74, p=0.79), adjusted by age, gender, disease duration, seropositivity, number of previous bDMARDs, GCs at BL, HAQ at BL		

					Tocilizumab combination therapy	1773	TNFi monotherapy	1404	CDAI	Change from BL until 1Y			−3.34	−3.58			Coeff 0.21 (95%CI -0.74-1.16, p=0.67), adjusted by age, gender, disease duration, seropositivity, number of previous bDMARDs, GCs at BL, HAQ at BL			
Vial, 2017^	Non-RCT	152	Failure of rituximab	DAS28-ESR 4.8 (1.3)	NR	TNFi	47	Tocilizumab	57	EULAR good/moderate response	12M	7 (70%)	21 (75%)			p=0.95		High		
										DAS28-ESR	12M			3.1 (1.7)	2.5 (1.2)	p=0.04				
Walker, 2015	Non-RCT	265	Failure of rituximab	DAS28-ESR 5.7, median; CDAI 25.1, median; HAQ-DI 1.38-1.56, range of medians	12.0Y	TNFi	89	Tocilizumab	86	EULAR good response	6M	31%	65%			p<0.001		High		
										DAS28-ESR	Change from BL until 6M			2.0 (1.3)	2.9 (1.8)	p<0.001				
										CDAI	Change from BL until 6M			9.9 (15.5)	16.2 (13.8)	p<0.01				
										HAQ-DI	Change from BL until 6M			0.28 (0.62)	0.29 (0.53)	p=0.63				
Abatacept vs rituximab																					
Brown, 2018	RCT	122	Failure of ≥1 TNFi	DAS28 6.1 (1.1); CDAI 38.3 (13.31); SDAI 40.2 (14.04)	6.7Y	Abatacept (125mg/W, subcutaneous)	41	Rituximab (1000mg at days 1 en 15, intravenous)	40	ACR20 response	48W	35.5%	42.9%					High		
										ACR50 response	48W	18.8%	20.7%							
										ACR70 response	48W	12.5%	0							
										EULAR good response	48W	4.9%	5.0%							
										DAS28	Reduction from BL until 24W			1.20 (0.62-1.78)	1.17 (0.56-1.77)	0.04 (−0.72-0.79)	p=0.927			
										CDAI	48W			14.1 (5.9-29.2), median (IQR)	20.3 (5.3-32.3), median (IQR)					
										SDAI	48W			13.7 (IQR 6.3-31.2), median (IQR)	20.1 (5.3-34.0), median (IQR)					
Gottenberg, 2019	non-RCT	3162	Failure of ≥1 TNFi	DAS28-ESR 5.35	10.0-12.0Y (range of medians)	Abatacept	620	Rituximab	1548	EULAR good/moderate response	24M	125 (22.7%)	322 (34.6%)	0.55 (0.39-0.78)				High		
Lee, 2016	SLR: RCTs 4	1796	Inadequate response to TNFi	NR	NR	Tocilizumab 4mg		Tofacitinib 10mg		ACR20 response	24W-6M			1.05 (0.47-2.39)				Moderate	Low		
																		OR>1 favours tocilizumab 4mg; Tocilizumab highest performance regarding early good response based on ACR 20 response, followed by rituximab, abatacept and tofacitinib.			
						Abatacept		Tocilizumab 4mg		ACR20 response	24W-6M			1.06 (0.46-2.28)				OR>1 favours abatacept			
						Abatacept		Tofacitinib 10mg		ACR20 response	24W-6M			1.10 (0.54-2.31)				OR>1 favours abatacept			
						Rituximab		**Abatacept**		**ACR20 response**	**24W-6M**			**1.14 (0.59-2.15)**				OR>1 favours rituximab			
						Tofacitinib 10mg		Tofacitinib 5mg		ACR20 response	24W-6M			1.14 (0.71-1.86)				OR>1 favours tofacitinib 10mg			
						Rituximab		Tocilizumab 4mg		ACR20 response	24W-6M			1.20 (0.56-2.50)				OR>1 favours rituximab			
						Tocilizumab 4mg		Tofacitinib 5mg		ACR20 response	24W-6M			1.20 (0.54-2.75)				OR>1 favours tocilizumab 4mg			
						Rituximab		Tofacitinib 10mg		ACR20 response	24W-6M			1.26 (0.64-2.46)				OR>1 favours rituximab			
						Abatacept		Tofacitinib 5mg		ACR20 response	24W-6M			1.26 (0.61-2.63)				OR>1 favours abatacept			
						Rituximab		Tofacitinib 5mg		ACR20 response	24W-6M			1.44 (0.73-2.82)				OR>1 favours rituximab			
						Tocilizumab 8mg		Rituximab		ACR20 response	24W-6M			1.92 (0.93-4.04)				OR>1 favours tocilizumab 8mg			
						Tocilizumab 8mg		Abatacept		ACR20 response	24W-6M			2.17 (1.01-4.89)				OR>1 favours tocilizumab 8mg			
						Tocilizumab 8mg		Tocilizumab 4mg		ACR20 response	24W-6M			2.29 (1.47-3.61)				OR>1 favours tocilizumab 8mg			
						Tocilizumab 8mg		Tofacitinib 10mg		ACR20 response	24W-6M			2.40 (1.09-5.41)				OR>1 favours tocilizumab 8mg			
						Tocilizumab 8mg		Tofacitinib 5mg		ACR20 response	24W-6M			2.74 (1.26-6.27)				OR>1 favours tocilizumab 8mg			
						Tofacitinib 5mg		Placebo		ACR20 response	24W-6M			3.30 (1.95-5.66)				OR>1 favours tofacitinib 5mg			
						Tofacitinib 10mg		Placebo		ACR20 response	24W-6M			3.76 (2.24-6.50)				OR>1 favours tofacitinib 10mg			
						Tocilizumab 4mg		Placebo		ACR20 response	24W-6M			3.94 (2.19-7.48)				OR>1 favours tocilizumab 4mg			
						Abatacept		Placebo		ACR20 response	24W-6M			4.15 (2.58-7.00)				OR>1 favours abatacept			
						Rituximab		Placebo		ACR20 response	24W-6M			4.73 (3.14-7.27)				OR>1 favours rituximab			
						Tocilizumab 8mg		Placebo		ACR20 response	24W-6M			9.04 (5.15-17.08)				OR>1 favours tocilizumab 8mg			
Abatacept vs tocilizumab																					
Das, 2014	Non-RCT	51	Failure of rituximab	DAS28-ESR 5.73	12Y	Abatacept (<60 kg: 500 mg; ≥60 kg≤100kg: 750 mg; >100 kg: 1000 mg on days 1, 15, 29 and then q28d)	16	Tocilizumab (8mg/kg, q4w)	35	DAS28-ESR	6M			4.94 (0.44)	3.28 (0.26)			High		
Elmedany, 2019	Non-RCT	132	Failure of ≥1 TNFi	DAS28 5.61; HAQ 0.96	7.5Y	Tocilizumab 8mg	68	Abatacept (W0, 2, 4, then q4w, intravenous; <60kg 500mg, 60-100kg	64	DAS28-ESR at 24W				2.4 (0.84)	2.8 (0.78)	ns		High		
										HAQ at 24W				0.89 (1.12)	1.01 (1.24)	ns				
Gottenberg, 2016	RCT	300	Insufficient response to TNFi	DAS28-ESR 5.1 (1.1); HAQ 1.3 (0.6)	10.0Y	Toclizumab	70	Abatacept	33	EULAR good/moderate response	24W	56 (80%)	22 (67%)	1.78 (0.59-5.37)		p=0.30		High		
Gottenberg, 2019	Non-RCT	3162	Failure of ≥1 TNFi	DAS28-ESR 5.35	10.0-12.0Y (range of medians)	Abatacept	620	Tocilizumab	964	EULAR good/moderate response	24M	125 (22.7%)	272 (44.2%)	0.37 (0.21-0.63)				OR>1 favours abatacept	High		
Harrold, 2016	Non-RCT	528	Failure of ≥1 TNFi	CDAI 28.0; mHAQ 0.7 (0.5), mean (SD)	10.5Y	Abatacept	264	Tocilizumab	264 (trimmed popula	CDAI	Change from BL until 6M			-11.3 (14.7)	-9.9 (14.1)	-1.27 (-,-3.65-1.11)	p=0.30		High		
										mHAQ	Change from BL until 6M			-0.12 (0.42)	-0.11 (0.49)	-0.01 (-,-0.09-0.06)	p=0.83				
Hirabara, 2014	Non-RCT	89	Inadequate efficacy of TNFi	DAS28-CRP 4.6 (1.2); CDAI 22.4 (11.0); SDAI 24.8 (11.6)	9.8Y	Abatacept	25	Tocilizumab	38	DAS28-CRP	52W			3.22 (1.11)	2.51 (1.12)		p=0.016		High		
										CDAI ≤10	52W	49.8%	68.2%								
Lee, 2016	SLR: RCTs 4	1796	Inadequate response to TNFi	NR	NR	Tocilizumab 4mg		Tofacitinib 10mg		ACR20 response	24W-6M			1.05 (0.47-2.39)				Moderate	Low		
																		OR>1 favours tocilizumab 4mg; Tocilizumab highest performance regarding early good response based on ACR 20 response, followed by rituximab, abatacept and tofacitinib.			
						Abatacept		**Tocilizumab 4mg**		**ACR20 response**	**24W-6M**			**1.06 (0.46-2.28)**				OR>1 favours abatacept			
						Abatacept		Tofacitinib 10mg		ACR20 response	24W-6M			1.10 (0.54-2.31)				OR>1 favours abatacept			
						Rituximab		Abatacept		ACR20 response	24W-6M			1.14 (0.59-2.15)				OR>1 favours rituximab			
						Tofacitinib 10mg		Tofacitinib 5mg		ACR20 response	24W-6M			1.14 (0.71-1.86)				OR>1 favours tofacitinib 10mg			
						Rituximab		Tocilizumab 4mg		ACR20 response	24W-6M			1.20 (0.56-2.50)				OR>1 favours rituximab			
						Tocilizumab 4mg		Tofacitinib 5mg		ACR20 response	24W-6M			1.20 (0.54-2.75)				OR>1 favours tocilizumab 4mg			
						Rituximab		Tofacitinib 10mg		ACR20 response	24W-6M			1.26 (0.64-2.46)				OR>1 favours rituximab			
						Abatacept		Tofacitinib 5mg		ACR20 response	24W-6M			1.26 (0.61-2.63)				OR>1 favours abatacept			
						Rituximab		Tofacitinib 5mg		ACR20 response	24W-6M			1.44 (0.73-2.82)				OR>1 favours rituximab			

					Tocilizumab 8mg		Rituximab		ACR20 response	24W-6M		1.92 (0.93-4.04)					OR>1 favours tocilizumab 8mg		
					Tocilizumab 8mg		**Abatacept**		**ACR20 response**	**24W-6M**		**2.17 (1.01-4.89)**					OR>1 favours tocilizumab 8mg		
					Tocilizumab 8mg		Tocilizumab 4mg		ACR20 response	24W-6M		2.29 (1.47-3.61)					OR>1 favours tocilizumab 8mg		
					Tocilizumab 8mg		Tofacitinib 10mg		ACR20 response	24W-6M		2.40 (1.09-5.41)					OR>1 favours tocilizumab 8mg		
					Tocilizumab 8mg		Tofacitinib 5mg		ACR20 response	24W-6M		2.74 (1.26-6.27)					OR>1 favours tocilizumab 8mg		
					Tofacitinib 5mg		Placebo		ACR20 response	24W-6M		3.30 (1.95-5.66)					OR>1 favours tofacitinib 5mg		
					Tofacitinib 10mg		Placebo		ACR20 response	24W-6M		3.76 (2.24-6.50)					OR>1 favours tofacitinib 10mg		
					Tocilizumab 4mg		Placebo		ACR20 response	24W-6M		3.94 (2.19-7.48)					OR>1 favours tocilizumab 4mg		
					Abatacept		Placebo		ACR20 response	24W-6M		4.15 (2.58-7.00)					OR>1 favours abatacept		
					Rituximab		Placebo		ACR20 response	24W-6M		4.73 (3.14-7.27)					OR>1 favours rituximab		
					Tocilizumab 8mg		Placebo		ACR20 response	24W-6M		9.04 (5.15-17.08)					OR>1 favours tocilizumab 8mg		
Pascart, 2016	Non-RCT	100	Failure of non-TNFi	DAS28-ESR 5.2 (4.3-5.9), median (IQR)	12Y	Tocilizumab (8mg/kg 1/M, intravenous	36	Abatacept (500, 750 or 1000mg according to body weight, 1/M, intravenous)	49	EULAR good/moderate response	12M	64%	33%				p=0.013		High	
										DAS28-ESR	Change from BL until 12M				36% (0-54), median (IQR)	0% (0-20%), median (IQR)	p=0.002			
Vial, 2017^	Non-RCT	152	Failure of rituximab	DAS28-ESR 4.8 (1.3)	NR	Abatacept	48	Tocilizumab	57	EULAR good/moderate response	12M	16 (73%)	21 (75%)				p=0.95		High	
										DAS28-ESR	12M				3.3 (1.3)	2.5 (1.2)	p=0.04			
Walker, 2015	Non-RCT	265	Failure of rituximab	DAS28-ESR 5.7, median; CDAI 25.1, median; HAQ-DI 1.38-1.56, range of medians	12.0Y	Abatacept	90	Tocilizumab	86	EULAR good response	6M	14%	65%				p<0.001		High	
										DAS28-ESR	Change from BL until 6M				1.1 (1.4)	2.9 (1.8)	p<0.001			
										CDAI	Change from BL until 6M				7.5 (11.5)	16.2 (13.8)	p<0.01			
										HAQ-DI	Change from BL until 6M				0.20 (0.48)	0.29 (0.53)	p=0.63			
Rituximab vs tocilizumab																					
Gonzalez-Vacarezza, 2014	SLR: RCTs 24	6357	Failure of TNFi	NR	0.9-13Y (range)	Rituximab		Etanercept		ACR50 response				0.475 (0.253-0.892)			OR>1 favours RTX	Appropriate to introduce tocilizumab in the coverage and remove infliximab.	Moderate	NR
						Rituximab		Etanercept		ACR70 response				0.231 (0.0590-0.902)			OR>1 favours RTX			
						Tocilizumab		Infliximab		ACR70 response				2.42 (1.36-4.34)			OR>1 favours tocilizumab			
						Rituximab		**Tocilizumab in third line treatment**		**ACR20 response**				**1.79 (1.01-3.18)**			**OR>1 favours tocilizumab**			
Gottenberg, 2016	RCT	300	Insufficient response to TNFi	DAS28-ESR 5.1 (1.1); HAQ 1.3 (0.6)	10.0Y	Tocilizumab	70	Rituximab	41	EULAR good/moderate response	24W	56 (80%)	25 (61%)	2.47 (0.92-6.62)			p=0.07		High	
Gottenberg, 2019	Non-RCT	3162	Failure of ≥1 TNFi	DAS28-ESR 5.35	10.0-12.0Y (range of medians)	Tocilizumab	964	Rituximab	1548	EULAR good/moderate response	24M	272 (44.2%)	322 (34.6%)	1.51 (0.95-2.41)				OR>1 favours tocilizumab	High	
Lee, 2016	SLR: RCTs 4	1796	Inadequate response to TNFi	NR	NR	Tocilizumab 4mg		Tofacitinib 10mg		ACR20 response	24W-6M			1.05 (0.47-2.39)				OR>1 favours tocilizumab 4mg; Tocilizumab highest performance regarding early good response based on ACR 20 response, followed by	Moderate	Low
						Abatacept		Tocilizumab 4mg		ACR20 response	24W-6M			1.06 (0.46-2.28)				OR>1 favours abatacept		
						Abatacept		Tofacitinib 10mg		ACR20 response	24W-6M			1.10 (0.54-2.31)				OR>1 favours abatacept		
						Rituximab		Abatacept		ACR20 response	24W-6M			1.14 (0.59-2.15)				OR>1 favours rituximab		
						Tofacitinib 10mg		Tofacitinib 5mg		ACR20 response	24W-6M			1.14 (0.71-1.86)				OR>1 favours tofacitinib 10mg		
						Rituximab		**Tocilizumab 4mg**		**ACR20 response**	**24W-6M**			**1.20 (0.56-2.50)**				OR>1 favours rituximab		
						Tocilizumab 4mg		Tofacitinib 5mg		ACR20 response	24W-6M			1.20 (0.54-2.75)				OR>1 favours tocilizumab 4mg		
						Rituximab		Tofacitinib 10mg		ACR20 response	24W-6M			1.26 (0.64-2.46)				OR>1 favours rituximab		
						Abatacept		Tofacitinib 5mg		ACR20 response	24W-6M			1.26 (0.61-2.63)				OR>1 favours abatacept		
						Rituximab		Tofacitinib 5mg		ACR20 response	24W-6M			1.44 (0.73-2.82)				OR>1 favours rituximab		
						Tocilizumab 8mg		**Rituximab**		**ACR20 response**	**24W-6M**			**1.92 (0.93-4.04)**				OR>1 favours tocilizumab 8mg		
						Tocilizumab 8mg		Abatacept		ACR20 response	24W-6M			2.17 (1.01-4.89)				OR>1 favours tocilizumab 8mg		
						Tocilizumab 8mg		Tocilizumab 4mg		ACR20 response	24W-6M			2.29 (1.47-3.61)				OR>1 favours tocilizumab 8mg		
						Tocilizumab 8mg		Tofacitinib 10mg		ACR20 response	24W-6M			2.40 (1.09-5.41)				OR>1 favours tocilizumab 8mg		
						Tocilizumab 8mg		Tofacitinib 5mg		ACR20 response	24W-6M			2.74 (1.26-6.27)				OR>1 favours tocilizumab 8mg		
						Tofacitinib 5mg		Placebo		ACR20 response	24W-6M			3.30 (1.95-5.66)				OR>1 favours tofacitinib 5mg		
						Tofacitinib 10mg		Placebo		ACR20 response	24W-6M			3.76 (2.24-6.50)				OR>1 favours tofacitinib 10mg		
						Tocilizumab 4mg		Placebo		ACR20 response	24W-6M			3.94 (2.19-7.48)				OR>1 favours tocilizumab 4mg		
						Abatacept		Placebo		ACR20 response	24W-6M			4.15 (2.58-7.00)				OR>1 favours abatacept		
						Rituximab		Placebo		ACR20 response	24W-6M			4.73 (3.14-7.27)				OR>1 favours rituximab		
						Tocilizumab 8mg		Placebo		ACR20 response	24W-6M			9.04 (5.15-17.08)				OR>1 favours tocilizumab 8mg		
Pascart, 2016	Non-RCT	100	Failure of non-TNFi	DAS28-ESR 5.2 (4.3-5.9), median (IQR)	12Y	Tocilizumab (8mg/kg 1/M, intravenous	36	Rituximab (2 times 1000mg, retreatment according to disease activity)	15	EULAR good/moderate response	12M	64%	40%				ns		High	
										DAS28-ESR	Change from BL until 12M				36% (0-54), median (IQR)	0% (-11-34), median (IQR)	p=0.07			
						Adalimumab after failure of infliximab	-	-	-	ACR70 response		33%								
						Rituximab after failure of TNFi	-	Placebo	-	ACR70 response		12%								
						Abatacept after failure of TNFi	-	Placebo	-	ACR70 response		10.2%	1.5%							
						Toclizumab after failure of TNFi	-	Placebo	-	ACR70 response		12.4%								
Abatacept: combination vs monotherapy																					
Takahashi, 2015	Non-RCT	121	Failure of bDMARD (81% TNFi, 19% tocilizumab)	DAS28-ESR 5.2	13.2Y	Abatacept (W0, 2, 4, then q4w, intravenous) + MTX	56	Monotherapy abatacept (W0, 2, 4, then q4w, intravenous)	42	EULAR good/moderate response	52W	53.7%	35.0%				p=0.072		High	
										DAS28-ESR	Change from BL until 52W				-15.5 (21.5)	-5.0 (18.4)	p=0.065			
						Abatacept (W0, 2, 4, then q4w, intravenous) + Tacrolimus	18	Monotherapy abatacept (W0, 2, 4, then q4w, intravenous)	42	EULAR good/moderate response	52W		66.7%	35.0%			p=0.025			
										DAS28-ESR	Change from BL until 52W				-24.1 (27.1)	-12.0 (24.6)	p=0.075			
Tocilizumab vs tocilizumab (different doses)																					

Lee, 2016	SLR: RCTs 4	1796	Inadequate response to TNFi	NR	NR	Tocilizumab 4mg		Tofacitinib 10mg		ACR20 response	24W-6M			1.05 (0.47-2.39)						OR>1 favours tocilizumab 4mg; Tocilizumab highest performance regarding early good response based on ACR 20 response, followed by rituximab, abatacept and tofacitinib.	Moderate	Low
						Abatacept		Tocilizumab 4mg		ACR20 response	24W-6M			1.06 (0.46-2.28)						OR>1 favours abatacept		
						Abatacept		Tofacitinib 10mg		ACR20 response	24W-6M			1.10 (0.54-2.31)						OR>1 favours abatacept		
						Rituximab		Abatacept		ACR20 response	24W-6M			1.14 (0.59-2.15)						OR>1 favours rituximab		
						Tofacitinib 10mg		Tofacitinib 5mg		ACR20 response	24W-6M			1.14 (0.71-1.86)						OR>1 favours tofacitinib 10mg		
						Rituximab		Tocilizumab 4mg		ACR20 response	24W-6M			1.20 (0.56-2.50)						OR>1 favours rituximab		
						Tocilizumab 4mg		Tofacitinib 5mg		ACR20 response	24W-6M			1.20 (0.54-2.75)						OR>1 favours tocilizumab 4mg		
						Rituximab		Tofacitinib 10mg		ACR20 response	24W-6M			1.26 (0.64-2.46)						OR>1 favours rituximab		
						Abatacept		Tofacitinib 5mg		ACR20 response	24W-6M			1.26 (0.61-2.63)						OR>1 favours abatacept		
						Rituximab		Tofacitinib 5mg		ACR20 response	24W-6M			1.44 (0.73-2.82)						OR>1 favours rituximab		
						Tocilizumab 8mg		Rituximab		ACR20 response	24W-6M			1.92 (0.93-4.04)						OR>1 favours tocilizumab 8mg		
						Tocilizumab 8mg		Abatacept		ACR20 response	24W-6M			2.17 (1.01-4.89)						OR>1 favours tocilizumab 8mg		
						Tocilizumab 8mg		**Tocilizumab 4mg**		**ACR20 response**	**24W-6M**			**2.29 (1.47-3.61)**						OR>1 favours tocilizumab 8mg		
						Tocilizumab 8mg		Tofacitinib 10mg		ACR20 response	24W-6M			2.40 (1.09-5.41)						OR>1 favours tocilizumab 8mg		
						Tocilizumab 8mg		Tofacitinib 5mg		ACR20 response	24W-6M			2.74 (1.26-6.27)						OR>1 favours tocilizumab 8mg		
						Tofacitinib 5mg		Placebo		ACR20 response	24W-6M			3.30 (1.95-5.66)						OR>1 favours tofacitinib 5mg		
						Tofacitinib 10mg		Placebo		ACR20 response	24W-6M			3.76 (2.24-6.50)						OR>1 favours tofacitinib 10mg		
						Tocilizumab 4mg		Placebo		ACR20 response	24W-6M			3.94 (2.19-7.48)						OR>1 favours tocilizumab 4mg		
						Abatacept		Placebo		ACR20 response	24W-6M			4.15 (2.58-7.00)						OR>1 favours abatacept		
						Rituximab		Placebo		ACR20 response	24W-6M			4.73 (3.14-7.27)						OR>1 favours rituximab		
						Tocilizumab 8mg		Placebo		ACR20 response	24W-6M			9.04 (5.15-17.08)						OR>1 favours tocilizumab 8mg		
Ogata, 2018	RCT	41	Inadequate response to tocilizumab intravenously	DAS28 5.7 (1.3); CDAI 33.5 (15.0)	8.4Y	**Tocilizumab** (162mg q1w, subcutaneous)	21	**Tocilizuma**(162mg q2w, subcutaneous)	20	**ACR20 response**	**12W**	**11 (52.4%)**	**4 (20.0%)**								Moderate	
										ACR50 response	**12W**	**8 (38.1%)**	**3 (15.0%)**									
										ACR70 response	12W	3 (14.3%)	3 (15.0%)									
										DAS28-ESR	Change from BL until 12W				-2.1	-0.89	-1.21 (-2.13- -0.30)	p=0.0108				
										CDAI	Change from BL until 12W				-16.0	-8.7	-7.26 (-15.93-1.40)	p=0.0979				
Secukinumab vs secukinumab (different doses)																						
Huang, 2019	SLR (3 RCTs)	1292	Failure of ≥1 TNFi	NR	NR	Secukinumab 150mg (Subcutaneous at BL, W1, W2, W3, W4 and then q4W; or Intraveneous 10mg/kg at BL, W2, W4 and then _mg q4W)	431	Secukinumab 75mg (Subcutaneous at BL, W1, W2, W3, W4 and then q4W; or Intraveneous 10mg/kg at BL, W2, W4 and then _mg q4W)	428	ACR20	24W			1.03 (0.85-1.24)						RR>1 favours secukinumab 150mg	Moderate	Low-moderate
										ACR50	24W			1.06 (0.78-1.44)								
										ACR70	24W			1.32 (0.42-4.18)								
Other bDMARD vs bDMARD																						
Genovese, 2014c	RCT	221	Failure of TNFi	DAS28-CRP 5.77; CDAI 38.90 (14.3-71.2), median (range); HAQ-DI 1.63 (0.0-3.0), median (range)	9.99Y	Olokizumab (all doses, subcutaneous)	132	Tocilizumab (8mg/kg q4w)	43	ACR20 response	12W							ns			Low	
										ACR50 response	12W							ns				
						Olokizumab (60mg q4w, subcutaneous)	22	Tocilizumab (8mg/kg q4w, subcutaneous)	43	ACR20 response	12W	12 (75.0%)	27 (65.9%)									
										ACR50 response	12W	6 (37.5%)	10 (24.4%)									
										DAS28-ESR	Change from BL until 12W				-2.04 (0.26) (LS mean (SE))	-1.79 (0.18) (LS mean (SE))						
										CDAI	Change from BL until 12W				-18.51 (-69.2-48.0) (median (range))	-17.30 (-49.2-15.1) (median (range))						
										HAQ-DI	Change from BL until 12W				-0.50 (-1.6- -0.1) (median (range))	-0.26 (-1.5-0.3) (median (range))						
						Olokizumab (60mg q2w, subcutaneous)	20			ACR20 response	12W	6 (35.3%)											
										ACR50 response	12W	3 (17.6%)											
										DAS28-ESR	Change from BL until 12W				-1.53 (0.27) (LS mean (SE))							
										CDAI	Change from BL until 12W				-8.00 (-36.5-19.0) (median (range))							
										HAQ-DI	Change from BL until 12W				-0.25 (-1.0-0.9) (median (range))							
						Olokizumab (120mg q4w, subcutaneous)	23			ACR20 response	12W	11 (61.1%)											
										ACR50 response	12W	3 (16.7%)											
										DAS28-ESR	Change from BL until 12W				-1.57 (0.26) (LS mean (SE))							
										CDAI	Change from BL until 12W				-19.09 (-35.2-8.8) (median (range))							
										HAQ-DI	Change from BL until 12W				-0.25 (-1.5-0.4) (median (range))							
						Olokizumab (120mg q2w, subcutaneous)	22			ACR20 response	12W	10 (50.0%)											
										ACR50 response	12W	5 (25.0%)											
										DAS28-ESR	Change from BL until 12W				-2.05 (0.25) (LS mean (SE))							
										CDAI	Change from BL until 12W				-14.65 (-57.9-14.3) (median (range))							
										HAQ-DI	Change from BL until 12W				-0.25 (-0.9-1.4) (median (range))							
						Olokizumab (240mg q4w, subcutaneous)	22			ACR20 response	12W	7 (33.3%)											

											ACR50 response	12W	3 (1.43%)								
											DAS28-ESR	Change from BL until 12W					-1.59 (0.25) (LS mean (SE))				
											CDAI	Change from BL until 12W					-12.99 (-42.9-4.0) (median (range))				
											HAQ-DI	Change from BL until 12W					0.00 (-1.0-0.5) (median (range))				
							Olokizumab (240mg q2w, subcutaneous)	22			ACR20 response	12W	11 (52.4%)								
											ACR50 response	12W	5 (23.8%)								
											DAS28-ESR	Change from BL until 12W					-1.80 (0.25) (LS mean (SE))				
											CDAI	Change from BL until 12W					-16.30 (-58.2-8.9) (median (range))				
											HAQ-DI	Change from BL until 12W					-0.38 (-1.6-0.1) (median (range))				
Weinblatt, 2018	RCT	63	Inadequate response to TNFi	DAS28-CRP 6.1	7.2Y	Mavrilimumab (100mg q2w, subcutaneous)	31	Golimumab (50mg q4w and placebo every 2 other weeks)	32		ACR20 response	24W	22 (72.3%)	20 (61.2%)				11.1% (90%CI -7.8-29.9)			High
											ACR50 response	24W						-8.7% (90%CI -28.1-10.7)			
											ACR70 response	24W						-0.7% (90%CI -18.0 - 16.7)			
											DAS28-CRP	24W						-4.0% (90%CI -20.9-12.9)			
											CDAI ≤2.8	24W	6.7%	9.0%							
											SDAI ≤3.3	24W	10.1%	12.1%							
JAKI VS BDMARD																					
JAKI vs (alternative) TNFi																					
Fleischmann, 2019	non-RCT	410	Failure of adalimumab or upadacitinib (switch to other treatment option)	NR	NR	Adalimumab (40mg q2w)	251	Upadacitinib (15mg/D)	159		Change in DAS28-CRP from BL until 6M						-2.40 (-2.58- -2.22)	-2.88 (-3.11- -2.65)			High
											Change in CDAI from BL until 6M						-27.28 (-29.35- -25.21)	-29.47 (-32.23 - -26.71)			
											Change in SDAI from BL until 6M						-28.30 (-30.45- -26.15)	-31.02 (-33.86- -28.19)			
											Change in HAQ-DI from BL until 6M						-0.58 (-0.66- -0.49)	-0.73 (-0.83- -0.63)			
Vieira, 2016	SLR: RCTs 5	2136	Inadequate response to TNFi	NR	9.6-13.0Y (range)	Tofacitinib		Placebo			ACR70 response	12W			3.80 (2.05-6.80)				OR>1 favours tofacitinib; Efficacy of tofacitinib comparable with bDMARDs	Moderate	Low
											ACR70 response	24W			5.77 (3.26-9.84)				OR>1 favours tofacitinib; Network meta-analysis		
								Abatacept			ACR70 response	12W			ns				OR>1 favours tofacitinib		
											ACR70 response	24W			ns				OR>1 favours tofacitinib		
								Golimumab			**ACR70 response**	**14W**			**ns**				OR>1 favours tofacitinib		
											ACR70 response	**24W**			**1.50 (0.70-3.25)**				OR>1 favours tofacitinib		
								Tocilizumab			ACR70 response	12W			ns				OR>1 favours tofacitinib		
											ACR70 response	24W			ns				OR>1 favours tofacitinib		
								Rituximab			ACR70 response	12W			ns				OR>1 favours tofacitinib		
											ACR70 response	24W			0.53 (0.27-1.02)				OR>1 favours tofacitinib		
Tofacitinib vs abatacept																					
Lee, 2016	SLR: RCTs 4	1796	Inadequate response to TNFi	NR	NR	Tocilizumab 4mg		Tofacitinib 10mg			ACR20 response	24W-6M			1.05 (0.47-2.39)				OR>1 favours tocilizumab 4mg; Tocilizumab highest performance regarding early good response based on ACR 20 response, followed by rituximab, abatacept and tofacitinib.	Moderate	Low
						Abatacept		Tocilizumab 4mg			ACR20 response	24W-6M			1.06 (0.46-2.28)				OR>1 favours abatacept		
						Abatacept		**Tofacitinib 10mg**			**ACR20 response**	**24W-6M**			**1.10 (0.54-2.31)**				OR>1 favours abatacept		
						Rituximab		Abatacept			ACR20 response	24W-6M			1.14 (0.59-2.15)				OR>1 favours rituximab		
						Tofacitinib 10mg		Tofacitinib 5mg			ACR20 response	24W-6M			1.14 (0.71-1.86)				OR>1 favours tofacitinib 10mg		
						Rituximab		Tocilizumab 4mg			ACR20 response	24W-6M			1.20 (0.56-2.50)				OR>1 favours rituximab		
						Tocilizumab 4mg		Tofacitinib 5mg			ACR20 response	24W-6M			1.20 (0.54-2.75)				OR>1 favours tocilizumab 4mg		
						Rituximab		Tofacitinib 10mg			ACR20 response	24W-6M			1.26 (0.64-2.46)				OR>1 favours rituximab		
						Abatacept		**Tofacitinib 5mg**			**ACR20 response**	**24W-6M**			**1.26 (0.61-2.63)**				OR>1 favours abatacept		
						Rituximab		Tofacitinib 5mg			ACR20 response	24W-6M			1.44 (0.73-2.82)				OR>1 favours rituximab		
						Tocilizumab 8mg		Rituximab			ACR20 response	24W-6M			1.92 (0.93-4.04)				OR>1 favours tocilizumab 8mg		
						Tocilizumab 8mg		Abatacept			ACR20 response	24W-6M			2.17 (1.01-4.89)				OR>1 favours tocilizumab 8mg		
						Tocilizumab 8mg		Tocilizumab 4mg			ACR20 response	24W-6M			2.29 (1.47-3.61)				OR>1 favours tocilizumab 8mg		
						Tocilizumab 8mg		Tofacitinib 10mg			ACR20 response	24W-6M			2.40 (1.09-5.41)				OR>1 favours tocilizumab 8mg		
						Tocilizumab 8mg		Tofacitinib 5mg			ACR20 response	24W-6M			2.74 (1.26-6.27)				OR>1 favours tocilizumab 8mg		
						Tofacitinib 5mg		Placebo			ACR20 response	24W-6M			3.30 (1.95-5.66)				OR>1 favours tofacitinib 5mg		
						Tofacitinib 10mg		Placebo			ACR20 response	24W-6M			3.76 (2.24-6.50)				OR>1 favours tofacitinib 10mg		
						Tocilizumab 4mg		Placebo			ACR20 response	24W-6M			3.94 (2.19-7.48)				OR>1 favours tocilizumab 4mg		
						Abatacept		Placebo			ACR20 response	24W-6M			4.15 (2.58-7.00)				OR>1 favours abatacept		
						Rituximab		Placebo			ACR20 response	24W-6M			4.73 (3.14-7.27)				OR>1 favours rituximab		
						Tocilizumab 8mg		Placebo			ACR20 response	24W-6M			9.04 (5.15-17.08)				OR>1 favours tocilizumab 8mg		

Vieira, 2016	SLR: RCTs 5	2136	Inadequate response to TNFi	NR	9.6-13.0Y (range)	Tofacitinib	Placebo	ACR70 response	12W	3.80 (2.05-6.80)	OR>1 favours tofacitinib; Efficacy of tofacitinib comparable with bDMARDs	Moderate	Low
								ACR70 response	24W	5.77 (3.26-9.84)	OR>1 favours tofacitinib; Network meta-analysis		
							Abatacept	**ACR70 response**	**12W**	**ns**	OR>1 favours tofacitinib		
								ACR70 response	**24W**	**ns**	OR>1 favours tofacitinib		
							Golimumab	ACR70 response	14W	ns	OR>1 favours tofacitinib		
								ACR70 response	24W	1.50 (0.70-3.25)	OR>1 favours tofacitinib		
							Tocilizumab	ACR70 response	12W	ns	OR>1 favours tofacitinib		
								ACR70 response	24W	ns	OR>1 favours tofacitinib		
							Rituximab	ACR70 response	12W	ns	OR>1 favours tofacitinib		
								ACR70 response	24W	0.53 (0.27-1.02)	OR>1 favours tofacitinib		
Tofacitinib vs rituximab													
Lee, 2016	SLR: RCTs 4	1796	Inadequate response to TNFi	NR	NR	Tocilizumab 4mg	Tofacitinib 10mg	ACR20 response	24W-6M	1.05 (0.47-2.39)	OR>1 favours tocilizumab 4mg; Tocilizumab highest performance regarding early good response based on ACR 20 response, followed by rituximab, abatacept and tofacitinib.	Moderate	Low
						Abatacept	Tocilizumab 4mg	ACR20 response	24W-6M	1.06 (0.46-2.28)	OR>1 favours abatacept		
						Abatacept	Tofacitinib 10mg	ACR20 response	24W-6M	1.10 (0.54-2.31)	OR>1 favours abatacept		
						Rituximab	Abatacept	ACR20 response	24W-6M	1.14 (0.59-2.15)	OR>1 favours rituximab		
						Tofacitinib 10mg	Tofacitinib 5mg	ACR20 response	24W-6M	1.14 (0.71-1.86)	OR>1 favours tofacitinib 10mg		
						Rituximab	Tocilizumab 4mg	ACR20 response	24W-6M	1.20 (0.56-2.50)	OR>1 favours rituximab		
						Tocilizumab 4mg	Tofacitinib 5mg	ACR20 response	24W-6M	1.20 (0.54-2.75)	OR>1 favours tocilizumab 4mg		
						Rituximab	**Tofacitinib 10mg**	**ACR20 response**	**24W-6M**	**1.26 (0.64-2.46)**	OR>1 favours rituximab		
						Abatacept	Tofacitinib 5mg	ACR20 response	24W-6M	1.26 (0.61-2.63)	OR>1 favours abatacept		
						Rituximab	**Tofacitinib 5mg**	**ACR20 response**	**24W-6M**	**1.44 (0.73-2.82)**	OR>1 favours rituximab		
						Tocilizumab 8mg	Rituximab	ACR20 response	24W-6M	1.92 (0.93-4.04)	OR>1 favours tocilizumab 8mg		
						Tocilizumab 8mg	Abatacept	ACR20 response	24W-6M	2.17 (1.01-4.89)	OR>1 favours tocilizumab 8mg		
						Tocilizumab 8mg	Tocilizumab 4mg	ACR20 response	24W-6M	2.29 (1.47-3.61)	OR>1 favours tocilizumab 8mg		
						Tocilizumab 8mg	Tofacitinib 10mg	ACR20 response	24W-6M	2.40 (1.09-5.41)	OR>1 favours tocilizumab 8mg		
						Tocilizumab 8mg	Tofacitinib 5mg	ACR20 response	24W-6M	2.74 (1.26-6.27)	OR>1 favours tocilizumab 8mg		
						Tofacitinib 5mg	Placebo	ACR20 response	24W-6M	3.30 (1.95-5.66)	OR>1 favours tofacitinib 5mg		
						Tofacitinib 10mg	Placebo	ACR20 response	24W-6M	3.76 (2.24-6.50)	OR>1 favours tofacitinib 10mg		
						Tocilizumab 4mg	Placebo	ACR20 response	24W-6M	3.94 (2.19-7.48)	OR>1 favours tocilizumab 4mg		
						Abatacept	Placebo	ACR20 response	24W-6M	4.15 (2.58-7.00)	OR>1 favours abatacept		
						Rituximab	Placebo	ACR20 response	24W-6M	4.73 (3.14-7.27)	OR>1 favours rituximab		
						Tocilizumab 8mg	Placebo	ACR20 response	24W-6M	9.04 (5.15-17.08)	OR>1 favours tocilizumab 8mg		
Vieira, 2016	SLR: RCTs 5	2136	Inadequate response to TNFi	NR	9.6-13.0Y (range)	**Tofacitinib**	Placebo	ACR70 response	12W	3.80 (2.05-6.80)	**OR>1 favours tofacitinib; Efficacy of tofacitinib comparable with bDMARDs**	Moderate	Low
								ACR70 response	24W	5.77 (3.26-9.84)	OR>1 favours tofacitinib; Network meta-analysis		
							Abatacept	ACR70 response	12W	ns	OR>1 favours tofacitinib		
								ACR70 response	24W	ns	OR>1 favours tofacitinib		
							Golimumab	ACR70 response	14W	ns	OR>1 favours tofacitinib		
								ACR70 response	24W	1.50 (0.70-3.25)	OR>1 favours tofacitinib		
							Tocilizumab	ACR70 response	12W	ns	OR>1 favours tofacitinib		
								ACR70 response	24W	ns	OR>1 favours tofacitinib		
							Rituximab	**ACR70 response**	**12W**	**ns**	OR>1 favours tofacitinib		
								ACR70 response	**24W**	**0.53 (0.27-1.02)**	OR>1 favours tofacitinib		
Tofacitinib vs tocilizumab													
Lee, 2016	SLR: RCTs 4	1796	Inadequate response to TNFi	NR	NR	**Tocilizumab 4mg**	**Tofacitinib 10mg**	**ACR20 response**	**24W-6M**	**1.05 (0.47-2.39)**	OR>1 favours tocilizumab 4mg; Tocilizumab highest performance regarding early good response based on ACR 20 response, followed by rituximab, abatacept and tofacitinib.	Moderate	Low
						Abatacept	Tocilizumab 4mg	ACR20 response	24W-6M	1.06 (0.46-2.28)	OR>1 favours abatacept		
						Abatacept	Tofacitinib 10mg	ACR20 response	24W-6M	1.10 (0.54-2.31)	OR>1 favours abatacept		
						Rituximab	Abatacept	ACR20 response	24W-6M	1.14 (0.59-2.15)	OR>1 favours rituximab		
						Tofacitinib 10mg	Tofacitinib 5mg	ACR20 response	24W-6M	1.14 (0.71-1.86)	OR>1 favours tofacitinib 10mg		
						Rituximab	Tocilizumab 4mg	ACR20 response	24W-6M	1.20 (0.56-2.50)	OR>1 favours rituximab		
						Tocilizumab 4mg	**Tofacitinib 5mg**	**ACR20 response**	**24W-6M**	**1.20 (0.54-2.75)**	OR>1 favours tocilizumab 4mg		
						Rituximab	Tofacitinib 10mg	ACR20 response	24W-6M	1.26 (0.64-2.46)	OR>1 favours rituximab		
						Abatacept	Tofacitinib 5mg	ACR20 response	24W-6M	1.26 (0.61-2.63)	OR>1 favours abatacept		
						Rituximab	Tofacitinib 5mg	ACR20 response	24W-6M	1.44 (0.73-2.82)	OR>1 favours rituximab		
						Tocilizumab 8mg	Rituximab	ACR20 response	24W-6M	1.92 (0.93-4.04)	OR>1 favours tocilizumab 8mg		
						Tocilizumab 8mg	Abatacept	ACR20 response	24W-6M	2.17 (1.01-4.89)	OR>1 favours tocilizumab 8mg		
						Tocilizumab 8mg	Tocilizumab 4mg	ACR20 response	24W-6M	2.29 (1.47-3.61)	OR>1 favours tocilizumab 8mg		
						Tocilizumab 8mg	**Tofacitinib 10mg**	**ACR20 response**	**24W-6M**	**2.40 (1.09-5.41)**	OR>1 favours tocilizumab 8mg		
						Tocilizumab 8mg	**Tofacitinib 5mg**	**ACR20 response**	**24W-6M**	**2.74 (1.26-6.27)**	OR>1 favours tocilizumab 8mg		
						Tofacitinib 5mg	Placebo	ACR20 response	24W-6M	3.30 (1.95-5.66)	OR>1 favours tofacitinib 5mg		
						Tofacitinib 10mg	Placebo	ACR20 response	24W-6M	3.76 (2.24-6.50)	OR>1 favours tofacitinib 10mg		
						Tocilizumab 4mg	Placebo	ACR20 response	24W-6M	3.94 (2.19-7.48)	OR>1 favours tocilizumab 4mg		
						Abatacept	Placebo	ACR20 response	24W-6M	4.15 (2.58-7.00)	OR>1 favours abatacept		
						Rituximab	Placebo	ACR20 response	24W-6M	4.73 (3.14-7.27)	OR>1 favours rituximab		
						Tocilizumab 8mg	Placebo	ACR20 response	24W-6M	9.04 (5.15-17.08)	OR>1 favours tocilizumab 8mg		
Vieira, 2016	SLR: RCTs 5	2136	Inadequate response to TNFi	NR	9.6-13.0Y (range)	**Tofacitinib**	Placebo	ACR70 response	12W	3.80 (2.05-6.80)	**OR>1 favours tofacitinib; Efficacy of tofacitinib comparable with bDMARDs**	Moderate	Low
								ACR70 response	24W	5.77 (3.26-9.84)	OR>1 favours tofacitinib; Network meta-analysis		
							Abatacept	ACR70 response	12W	ns	OR>1 favours tofacitinib		
								ACR70 response	24W	ns	OR>1 favours tofacitinib		
							Golimumab	ACR70 response	14W	ns	OR>1 favours tofacitinib		
								ACR70 response	24W	1.50 (0.70-3.25)	OR>1 favours tofacitinib		
							Tocilizumab	**ACR70 response**	**12W**	**ns**	OR>1 favours tofacitinib		

									ACR70 response	24W		ns				OR>1 favours tofacitinib		
							Rituximab		ACR70 response	12W		ns				OR>1 favours tofacitinib		
									ACR70 response	24W		0.53 (0.27-1.02)				OR>1 favours tofacitinib		
Tofacitinib - different doses																			
Lee, 2016	SLR: RCTs 4	1796	Inadequate response to TNFi	NR	NR	Tocilizumab 4mg		Tofacitinib 10mg	ACR20 response	24W-6M		1.05 (0.47-2.39)				OR>1 favours tocilizumab 4mg; Tocilizumab highest performance regarding early good response based on ACR 20 response, followed by rituximab, abatacept and tofacitinib.	Moderate	Low
						Abatacept		Tocilizumab 4mg	ACR20 response	24W-6M		1.06 (0.46-2.28)				OR>1 favours abatacept		
						Abatacept		Tofacitinib 10mg	ACR20 response	24W-6M		1.10 (0.54-2.31)				OR>1 favours abatacept		
						Rituximab		Abatacept	ACR20 response	24W-6M		1.14 (0.59-2.15)				OR>1 favours rituximab		
						Tofacitinib 10mg		**Tofacitinib 5mg**	**ACR20 response**	**24W-6M**		**1.14 (0.71-1.86)**				OR>1 favours tofacitinib 10mg		
						Rituximab		Tocilizumab 4mg	ACR20 response	24W-6M		1.20 (0.56-2.50)				OR>1 favours rituximab		
						Tocilizumab 4mg		Tofacitinib 5mg	ACR20 response	24W-6M		1.20 0.54-2.75)				OR>1 favours tocilizumab 4mg		
						Rituximab		Tofacitinib 10mg	ACR20 response	24W-6M		1.26 (0.64-2.46)				OR>1 favours rituximab		
						Abatacept		Tofacitinib 5mg	ACR20 response	24W-6M		1.26 (0.61-2.63)				OR>1 favours abatacept		
						Rituximab		Tofacitinib 5mg	ACR20 response	24W-6M		1.44 (0.73-2.82)				OR>1 favours rituximab		
						Tocilizumab 8mg		Rituximab	ACR20 response	24W-6M		1.92 (0.93-4.04)				OR>1 favours tocilizumab 8mg		
						Tocilizumab 8mg		Abatacept	ACR20 response	24W-6M		2.17 (1.01-4.89)				OR>1 favours tocilizumab 8mg		
						Tocilizumab 8mg		Tocilizumab 4mg	ACR20 response	24W-6M		2.29 (1.47-3.61)				OR>1 favours tocilizumab 8mg		
						Tocilizumab 8mg		Tofacitinib 10mg	ACR20 response	24W-6M		2.40 (1.09-5.41)				OR>1 favours tocilizumab 8mg		
						Tocilizumab 8mg		Tofacitinib 5mg	ACR20 response	24W-6M		2.74 (1.26-6.27)				OR>1 favours tocilizumab 8mg		
						Tofacitinib 5mg		Placebo	ACR20 response	24W-6M		3.30 (1.95-5.66)				OR>1 favours tofacitinib 5mg		
						Tofacitinib 10mg		Placebo	ACR20 response	24W-6M		3.76 (2.24-6.50)				OR>1 favours tofacitinib 10mg		
						Tocilizumab 4mg		Placebo	ACR20 response	24W-6M		3.94 (2.19-7.48)				OR>1 favours tocilizumab 4mg		
						Abatacept		Placebo	ACR20 response	24W-6M		4.15 (2.58-7.00)				OR>1 favours abatacept		
						Rituximab		Placebo	ACR20 response	24W-6M		4.73 (3.14-7.27)				OR>1 favours rituximab		
						Tocilizumab 8mg		Placebo	ACR20 response	24W-6M		9.04 (5.15-17.08)				OR>1 favours tocilizumab 8mg		
Other																			
Al-Gareeb, 2018	RCT	110	Failure of entanercept	DAS28-ESR 5.22 (intervention 5.51; comparator 4.89, p<0.001)	-	Niclosamide (2 capsules once daily for 8 weeks), in addition to etanercept	48	Placebo (2 capsules once daily for 8 weeks), in addition to etanercept	41	Change in DAS28-ESR from BL until 8W			-10.16% (SEM1.89)	5.11% (SEM 2.28)	p<0.001		Moderate	
EFFICACY OF B/TSDMARDS BY NUMBER OF PREVIOUS FAILED BDMARDS																			
TNFi																			
Smolen, 2014 (Subanalysis)	Subanalysis RCT	461	Failure of ≥1 TNFi	DAS28 median 6.1-6.3; HAQ-DI median 1.5-1.8	8.7-9.8Y, median	Failure of 1 TNFi: Golimumab (50 or 100mg q4w, subcutaneous)	137	Failure of 2 TNFis: Golimumab (50 or 100mg q4w, subcutaneous)	47	ACR20 response	24W	61 (44.5%)	17 (36.2%)					High	
										ACR50 response	24W	30 (21.9%)	11 (23.4%)						
										EULAR good/moderate response	24W	82 (59.9%)	24 (51.1%)						
										HAQ-DI ≥0.25-unit impovement	24W	73 (53.3%)	22 (46.8%)						
						Failure of 1 TNFi: Golimumab (50 or 100mg q4w, subcutaneous)	137	Failure of 3 TNFis: Golimumab (50 or 100mg q4w, subcutaneous)	17	ACR20 response	24W	61 (44.5%)	4 (23.5%)						
										ACR50 response	24W	30 (21.9%)	1 (5.9%)						
										EULAR good/moderate response	24W	82 (59.9%)	10 (58.8%)						
										HAQ-DI ≥0.25-unit impovement	24W	73 (53.3%)	7 (41.2%)						
Abatacept																			
Schiff, 2009 (Subanalysis)	Subanalysis RCT	1046	Failure of TNFi	DAS28-CRP 6.2 (0.7); HAQ-DI 1.7 (0.6)	11.6Y	Failure of 1 TNFi: Abatacept (10mg/kg on days 1, 15 and 29, then q4w)	488	Failure of ≥2 TNFi: Abatacept (10mg/kg on days 1, 15 and 29, then q4w)	540	DAS28	Change from BL until 6M			-2.1 (95%CI -2.2- -2.0)	-2.0 (95%CI -2.1- -1.8)			High	
						Failure of 1 TNFi: Abatacept (10mg/kg on days 1, 15 and 29, then q4w)	488	Failure of 3 TNFi: Abatacept (10mg/kg on days 1, 15 and 29, then q4w)	200	DAS28	Change from BL until 6M			-2.1 (95%CI -2.2- -2.0)	-1.7 (95%CI -1.9- -1.5)	s			
Rituximab																			
Harrold, 2015b	Non-RCT	265	Failure of TNFi	CDAI: Previous 1 TNFi: 17.5; Previous ≥2 TNFi: 24.4 (p=0.001)	13Y	Rituximab: Previous exposure 1 TNFi	114 (trimmed population)	Rituximab: Previous exposure ≥2 TNFi	151 (trimmed population)	CDAI	12M			13.2	18.3			High	
Tocilizumab																			
Emery, 2008 (Subanalysis)	Subanalysis RCT	176	Failure of 2 TNFis	NR	NR	Toclizumab (8mg/kg, q4w, intravenous)	52	Placebo	64	ACR20 response	24W	26 (50.0%)	7 (10.9%)					High	
										ACR50 response	24W	16 (30.8%)	1 (1.6%)						
										ACR70 response	24W	8 (15.4%)	0 (0.0%)						
						Toclizumab (4mg/kg, q4w, intravenous)	60	Placebo	64	ACR20 response	24W	17 (28.3%)	7 (10.9%)						
										ACR50 response	24W	8 (13.3%)	1 (1.6%)						
										ACR70 response	24W	2 (3.3%)	0 (0.0%)						
		62	Failure of 3 TNFis	NR	NR	Toclizumab (8mg.kg, q4w, intravenous)	26	Placebo	18	ACR20 response	24W	14 (53.8%)	1 (5.6%)						
										ACR50 response	24W	5 (19.2%)	0 (0.0%)						
										ACR70 response	24W	2 (7.7%)	0 (0.0%)						
						Toclizumab (4mg/kg, q4w, intravenous)	18	Placebo	18	ACR20 response	24W	4 (22.2%)	1 (5.6%)						
										ACR50 response	24W	4 (22.2%)	0 (0.0%)						
										ACR70 response	24W	0 (0.0%)	0 (0.0%)						
Tofacitinib																			
Burmester, 2013 (Subanalysis)	Subanalysis RCT	399	Inadequate response to 1 TNFi	NR	NR	Tofacitinib (5mg 2/D, oral)	83	Placebo	85	ACR20 response	3M	36 (43.4%)	26 (30.6%)					High	
			Inadequate response to 2 TNFi	NR	NR	Tofacitinib (5mg 2/D, oral)	37	Placebo	37	ACR20 response	3M	14 (37.8%)	4 (10.8%)						
			Inadequate response to ≥3 TNFi	NR	NR	Tofacitinib (5mg 2/D, oral)	11	Placebo	9	ACR20 response	3M	4 (36.4%)	2 (22.2%)						
			Inadequate response to 1 TNFi	NR	NR	Tofacitinib (10mg 2/D, oral)	89	Placebo	85	ACR20 response	3M	43 (48.9%)	26 (30.6%)						
			Inadequate response to 2 TNFi	NR	NR	Tofacitinib (10mg 2/D, oral)	30	Placebo	37	ACR20 response	3M	16 (53.3%)	4 (10.8%)						
			Inadequate response to ≥3 TNFi	NR	NR	Tofacitinib (10mg 2/D, oral)	12	Placebo	9	ACR20 response	3M	5 (41.7%)	2 (22.2%)						

Charles-Schoeman, 2017^ (Subanalysis (see also below, failure ≥1bDMARD)	Subanalysis RCT	838	Failure of 1bDMARD	NR	NR	Tofacitinib (5mg, 2/D, oral)	NR	Placebo	NR	ACR20 response	3M	45.3%	27.2%	p<0.05	High
										DAS28-ESR ≤3.2	3M	11.9%	5.8%	ns	
			Failure of ≥2bDMARDs			Tofacitinib (5mg, 2/D, oral)	NR	Placebo	NR	ACR20 response	3M	40.6%	20.0%	p<0.05	
										DAS28-ESR ≤3.2	3M	14.0%	3.4%	p<0.05	
			Failure of 1bDMARD			Tofacitinib (10mg, 2/D, oral)	NR	Placebo	NR	ACR20 response	3M	50.6%	27.2%	p<0.0001	
										DAS28-ESR ≤3.2	3M	15.7%	5.8%	p<0.05	
			Failure of ≥2bDMARDs			Tofacitinib (10mg, 2/D, oral)	NR	Placebo	NR	ACR20 response	3M	50.6%	20.0%	p<0.0001	
										DAS28-ESR ≤3.2	3M	16.5%	3.4%	p<0.05	
Baricitinib															
Genovese, 2018a (Subanalysis of Genovese, 2016 (see also below, failure	Subanalysis RCT	211	Failure of 1 TNFi	NR	NR	Baricitinib (2mg/D, oral)	102	Placebo	104	ACR20 response	12W	54 (53%)	31 (30%)		High
										CDAI ≤10	12W	25 (25%)	16 (15%)		
						Baricitinib (4mg/D, oral)	104	Placebo	104	ACR20 response	12W	58 (56%)	9 (18%)		
										CDAI ≤10	12W	34 (33%)	16 (15%)		
		211	Failure of ≥2 TNFi	NR	NR	Baricitinib (2mg/D, oral)	43	Placebo	69	ACR20 response	12W	19 (38%)	6 (13%)		
										CDAI ≤10	12W	1 (2%)	9 (18%)		
						Baricitinib (4mg/D, oral)	54	Placebo	69	ACR20 response	12W	24 (53%)	6 (13%)		
										CDAI ≤10	12W	1 (2%)	9 (20%)		
Upadacitinib															
Weinblatt, 2019^ (Subanalysis Genovese, 2018b)	Subanalysis RCT	235	Failure of 1 bDMARD	NR	NR	Upadacitinib 15mg/D	86	Placebo	83	ACR20 response	12W	61.6%	28.9%	p<0.001	High
										ACR50 response	12W	32.6%	0,12	p-0.01	
										ACR70 response	12W	14.0%	7.2%	ns	
										DAS28-CRP ≤3.2	12W	0,43	16.9%	p<0.001	
										CDAI ≤10	12W	32.6%	15.7%	p<0.01	
										CDAI ≤2.8	12W	9.3%	6.0%	ns	
						Upadacitinib 30mg/D	66	Placebo	83	ACR20 response	12W	57.6%	28.9%	p<0.001	
										ACR50 response	12W	39.4%	0,12	p<0.001	
										ACR70 response	12W	27.3%	7.2%	p<0.001	
										DAS28-CRP ≤3.2	12W	0,47	16.9%	p<0.001	
										CDAI ≤10	12W	39.4%	15.7%	p<0.001	
										CDAI ≤2.8	12W	18.2%	6.0%	ns	
		137	Failure of 2 bDMARDs			Upadacitinib 15mg/D	40	Placebo	46	ACR20 response	12W	70.0%	32.6%	p<0.001	
										ACR50 response	12W	32.5%	14.2%	ns	
										ACR70 response	12W	5.0%	8.7%	ns	
										DAS28-CRP ≤3.2	12W	45.0%	13.0%	p<0.01	
										CDAI ≤10	12W	27.5%	17.4%	ns	
										CDAI ≤2.8	12W	5.0%	4.3%	ns	
						Upadacitinib 30mg/D	51	Placebo	46	ACR20 response	12W	58.8%	32.6%	p<0.01	
										ACR50 response	12W	35.3%	14.2%	p<0.05	
										ACR70 response	12W	21.6	8.7%	ns	
										DAS28-CRP ≤3.2	12W	37.3%	13.0%	p<0.01	
										CDAI ≤10	12W	31.4%	17.4%	ns	
										CDAI ≤2.8	12W	5.9%	4.3%	ns	
		125	Failure of ≥3 bDMARD			Upadacitinib 15mg/D	38	Placebo	40	ACR20 response	12W	65.8%	22.5%	p<0.001	
										ACR50 response	12W	39.5%	7.5%	p<0.01	
										ACR70 response	12W	13.2%	2.5%	ns	
										DAS28-CRP ≤3.2	12W	42.1%	10.0%	p<0.01	
										CDAI ≤10	12W	34.2%	7.5%	p<0.01	
										CDAI ≤2.8	12W	7.9%	2.5%	ns	
						Upadacitinib 30mg/D	47	Placebo	40	ACR20 response	12W	51.1%	22.5%	p<0.01	
										ACR50 response	12W	29.8%	7.5%	p<0.01	
										ACR70 response	12W	17.0%	2.5%	p<0.05	
										DAS28-CRP ≤3.2	12W	40.4%	10.0%	p<0.01	
										CDAI ≤10	12W	27.7%	7.5%	p<0.05	
										CDAI ≤2.8	12W	8.5%	2.5%	ns	
Filgotinib															
Genovese, 2019	Subanalysis RCT	448	Failure of 1 bDMARD			Filgotinib (100mg/D)	86	Placebo	77	ACR20 response	12W	57.0%	36.4%	p<0.001	Moderate
						Filgotinib (200mg/D)	73	Placebo	77	ACR20 response	12W	61.6%	36.4%	p<0.01	
			Failure of 2 bDMARDs			Filgotinib (100mg/D)	33	Placebo	36	ACR20 response	12W	57.6%	33.3%	ns	
						Filgotinib (200mg/D)	37	Placebo	36	ACR20 response	12W	70.3%	33.3%	p<0.01	
			Failure of <3 bDMARDs			Filgotinib (100mg/D)	119	Placebo	114	ACR20 response	12W	57.1%	35.1%	p<0.05	
						Filgotinib (200mg/D)	110	Placebo	114	ACR20 response	12W	64.5	35.1%	p<0.001	
			Failure of ≥3 bDMARD			Filgotinib (100mg/D)	34	Placebo	34	ACR20 response	12W	58.8%	17.6%	p<0.001	
						Filgotinib (200mg/D)	37	Placebo	34	ACR20 response	12W	70.3%	17.6%	p<0.001	

ACR; American College of Rheumatology; bDMARD: biological disease modifying antirheumatic drug; BL: baseline; CDAI: clinical disease activity index; CI: confidence interval; CRP: reactive protein C, csDMARD: conventional synthetic disease modifying antirheumatic drug; D: day(s); DAS28: disease activity score assessing 28 joints; DMARD: disease modifying antirheumatic drug; ESR: erythrocyte sedimentation rate; EULAR: European League Against Rheumatism; HAQ(-DI): health assessment questionnaire (-disability index); LSM: least square mean; M: month(s); mACR: modified American College of Rheumatology response (≥…% improvement in tender jointcount and swollen joint count, as well as two or more of the four remaining ACR response components, including physician's global assessment, patient's global assessment, patient's globalpain and mHAQ.); mDAS: modified disease activity score (which is calculated without results of acute phase reactants as well as achievement of remission using the mDAS28 cut-off of <2.6 (eg,baseline mDAS—follow-up mDAS)); mg: milligram; mHAQ: modified Health Assessment Questionnaire; n: number; NR: not reported; (n-)RCT: (non-)randomised controlled trial; ns: not significant; OR: odds ratio; q_w: every_ weeks; RA: rheumatoid arthritis; SD: standard deviation; SDAI: simplified disease activity index; SLR: systematic literature review; TNFi: TNF inhibitor; tsDMARD: targeted synthetic disease modifying antirheumatic drug; W: week(s); Y: year(s); ^: abstract.

1. Composite scores: Change over time, otherwise fixed time point, otherwise LDA, otherwise remission; 2. Latest time point during treatment period that was reported; 3. According to Cochrane Collaboration's tool for individual studies: highest risk of bias as found; According to AMSTAR2 tool for SLRs: Low=zero or one non-critical weakness; Moderate=more than one non-critical weakness; High=one critical flow with or without non-critical weaknessess; Critically high=more than one critical flow with or without non-critical weaknesses; 4. Only applicable for SLRs: Summary of RoB of individual studies, as assessed in SLR