Supplementary table 1. Summary of studies on therapeutic strategies for RA patients with limited drug options

1st Author, publication year	Study design	Patients (total n)	Disease duration of RA (mean)	Contraindication: adverse events, comorbidities or other (percentage of total population)	Intervention group Description	n	Comparator Description	n	Outcome Description	Time point^1	Number and percentage of responders in intervention group	Number and percentage of responders in comparator group	Mean outcome in intervention group (SD)	Mean outcome in control group (SD)	Mean difference (standard error, 95% CI)	p-value	Other	Risk of bias^2	Risk of bias of individual studies included in SLR^3
CARDIOVASCULAR DISEASE																			
Studies comparing patients with vs without comorbidity on treatment effect																			
Studies regarding efficacy																			
Combe, 2019^	Non-RCT	1684	NR	Baricitinib: depression (n=64), osteoporosis (n=113), hepatic disorder (n=222), CV disorder (n=350), pulmonary disorder (n=77), not further explained; Placebo: depression (n=69), osteoporosis (n=134), hepatic disorder (n=202), CV disorder (n=381), pulmonary disorder (n=89), not further explained	Baricitinib (4mg)	350 453 350 453 350 453	Placebo	381 500 381 500 381 500	ACR20 response: with CVD ACR20 response: without CVD ACR50 response: with CVD ACR50 response: without CVD DAS28-hsCRPs3.2: with CVD DAS28-hsCRPs3.2: without CVD	12W	68.3% 66.9% 40.9% 41.3% 44.9% 43.0%	40.7% 38.0% 14.4% 14.4% 15.7% 17.2%						High
Studies regarding safety																			
Deodhar, 2016	RCT	210	7.8Y	DM type 2 13.8% (n=29); Hyperlipidemia 30.0% (n=63)	Etanercept (50mg q1w, DM type 2: 17; Hyperlipidemia: 33)	106	Placebo	104 (DM type 2: 12; Hyperlipidemia: 30)	Fasting glucose (mg/dl): All patients Fasting glucose (mg/dl): DM type 2 Fasting glucose (mg/dl): Hyperlipidemia Hemoglobin A1C%: All patients Hemoglobin A1C%: DM type 2 Hemoglobin A1C%: Hyperlipidemia Total cholesterol (mg/dL): All patients Total cholesterol (mg/dL): DM type 2 Total cholesterol (mg/dL): Hyperlipidemia HDL (mg/dL): All patients HDL (mg/dL): DM type 2 HDL (mg/dL): Hyperlipidemia LDL (mg/dL): All patients LDL (mg/dL): DM type 2 LDL (mg/dL): Hyperlipidemia Triglycerides (mg/dL): All patients Triglycerides (mg/dL): DM type 2 Triglycerides (mg/dL): Hyperlipidemia	12W			97.3 (26.6) 133.1 (47.1) 105.9 (29.3) 5.6 (0.6) 6.7 (0.8) 6.0 (0.8) 184.8 (37.4) 170.0 (33.7) 182.6 (44.5) 61.6 (18.3) 61.9 (19.5) 61.4 (19.1) 96.9 (33.2) 79.3 (31.5) 90.3 (39.3) 131.8 (69.4) 153.8 (71.8) 155.0 (67.8)	95.9 (22.3) 127.3 (42.4) 104.3 (32.1) 5.7 (0.9) 7.0 (2.1) 5.9 (1.3) 190.9 (40.7) 205.6 (36.2) 190.7 (44.2) 60.5 (17.1) 54.7 (13.6) 56.9 (14.0) 103.2 (35.4) 112.1 (32.3) 102.2 (38.2) 139.2 (85.5) 221.9 (170.3) 167.2 (113.4)		ns ns ns ns ns ns ns ns ns ns ns ns ns ns ns ns ns ns		Moderate	
Ikonomidis, 2014	RCT	80	11.8Y	Chronic stable CAD 75% (n=60) vs RA patients without CAD 25% (n=20)	Anakinra (1 injection of 100mg, cross-over to placebo after 48h)	80	Placebo	80	Endothelial and coronary aortic function								Greater improvement in patients with CAD than in those without. No changes in the examined markers were observed after placebo.	High	
Studies comparing different interventions in patients with comorbidity																			
Studies regarding efficacy																			
Combe, 2019^	Non-RCT	1684	NR	Baricitinib: depression (n=64), osteoporosis (n=113), hepatic disorder (n=222), CV disorder (n=350), pulmonary disorder (n=77), not further explained; Placebo: depression (n=69), osteoporosis (n=134), hepatic disorder (n=202), CV disorder (n=381), pulmonary disorder (n=89), not further explained	Baricitinib (4mg)	350 453 350 453 350 453	Placebo	381 500 381 500 381 500	ACR20 response: with CVD ACR20 response: without CVD ACR50 response: with CVD ACR50 response: without CVD DAS28-hsCRPs3.2: with CVD DAS28-hsCRPs3.2: without CVD	12W	68.3% 66.9% 40.9% 41.3% 44.9% 43.0%	40.7% 38.0% 14.4% 14.4% 15.7% 17.2%						High
Hang, 2018	RCT	374	5.4Y	Moderate/high risk of CAD 100%	Baicalin (500mg once daily, oral)	166	Placebo	165	EULAR good/moderate response at 12W	12W	71%	53%				s		Moderate	
Ruscitti, 2019	RCT	39	1Y, median	Type 2 diabetes mellitus	TNFi (adalimumab, certolizumab pegol, etanercept, infliximab, golimumab)	17	Anakinra (100mg/D, subcutaneous)	22	Good EULAR response DAS28 SDAI	6M 6M 6M	62.5%	95.0%	 3.58 (1.45) 14.93 (9.92)	 2.70 (1.16) 7.89 (9.23)		p=0.030 p=0.08 p=0.0048		High	
Studies regarding safety																			
Deodhar, 2017	RCT	210	7.8Y	DM type 2 13.8% (n=29); Hyperlipidemia 30.0% (n=63)	Etanercept (50mg q1w, DM type 2: 17; Hyperlipidemia: 33)	106	Placebo	104 (DM type 2: 12; Hyperlipidemia: 30)	Fasting glucose (mg/dl): All patients Fasting glucose (mg/dl): DM type 2 Fasting glucose (mg/dl): Hyperlipidemia Hemoglobin A1C%: All patients Hemoglobin A1C%: DM type 2 Hemoglobin A1C%: Hyperlipidemia Total cholesterol (mg/dL): All patients Total cholesterol (mg/dL): DM type 2 Total cholesterol (mg/dL): Hyperlipidemia HDL (mg/dL): All patients HDL (mg/dL): DM type 2 HDL (mg/dL): Hyperlipidemia LDL (mg/dL): All patients LDL (mg/dL): DM type 2 LDL (mg/dL): Hyperlipidemia Triglycerides (mg/dL): All patients Triglycerides (mg/dL): DM type 2 Triglycerides (mg/dL): Hyperlipidemia	12W			97.3 (26.6) 133.1 (47.1) 105.9 (29.3) 5.6 (0.6) 6.7 (0.8) 6.0 (0.8) 184.8 (37.4) 170.0 (33.7) 182.6 (44.5) 61.6 (18.3) 61.9 (19.5) 61.4 (19.1) 96.9 (33.2) 79.3 (31.5) 90.3 (39.3) 131.8 (69.4) 153.8 (71.8) 155.0 (67.8)	95.9 (22.3) 127.3 (42.4) 104.3 (32.1) 5.7 (0.9) 7.0 (2.1) 5.9 (1.3) 190.9 (40.7) 205.6 (36.2) 190.7 (44.2) 60.5 (17.1) 54.7 (13.6) 56.9 (14.0) 103.2 (35.4) 112.1 (32.3) 102.2 (38.2) 139.2 (85.5) 221.9 (170.3) 167.2 (113.4)		ns ns ns ns ns ns ns ns ns ns ns ns ns ns ns ns ns ns		Moderate	
Hang, 2018	RCT	374	5.4Y	Moderate/high risk of CAD 100%	Baicalin (500mg once daily, oral)	166	Placebo	165	Levels of triglycerides Total cholesterol LDL-cholesterol	12W			1.12 (0.36) 2.87 (1.23) 1.38 (0.41)	1.87 (0.46) 3.22 (1.07) 1.16 (0.32)		p<0.05 p<0.05 p<0.05		Moderate	
Genovese, 2019^	RCT (TARGET)	546	NR	Diabetes mellitus (baselinefasting glucose >7 mmol/L or baseline HbA1c >6.5%): 78	Sariliumab 200mg q2W + DMARD	17	Placebo	20	HbA1c%	Change from BL until 24W					-0.78	p<0.001		High	
	RCT (MOBILITY)	369	NR	Diabetes mellitus (baselinefasting glucose >7 mmol/L or baseline HbA1c >6.5%): 28	Sariliumab 200mg q2W + DMARD	8	Adalimumab 40mg q2W	14	HbA1c%	Change from BL until 24W					-0.41	p=0.0192			
Ikonomidis, 2014	RCT	80	11.8Y	Chronic stable CAD 75% (n=60) vs RA patients without CAD 25% (n=20)	Anakinra (1 injection of 100mg, cross-over to placebo after 48h)	80	Placebo	80	Endothelial and coronary aortic function								Greater improvement in patients with CAD than in those without. No changes in the examined markers were observed after placebo.	High	
Ruscitti, 2019	RCT	39	1Y, median	Type 2 diabetes mellitus	TNFi (adalimumab, certolizumab pegol, etanercept, infliximab, golimumab)	17	Anakinra (100mg/D, subcutaneous)	22	HbA1c% Fasting plasma glucose	6M 6M			7.64 (0.65) 140.93 (39.45)	6.70 (0.67) 100.81 (11.11)		p<0.001 p<0.001		High	

Sepriano, 2020	SLR (4 studies)	NR	NR	At least one CV risk factor	tsDMARDs (tofacitinib, baricitinib)	NR	TNFi	NR	Occurence of VTEs	NR						Conclusion: "While one observational study performed with 'claims' data showed no significant increased risk of VTE with tofacitinib compared with TNFi, data from RCTs included in this SLR suggest an increased risk of VTE with JAKi. These data are in line with a recent pooled analysis of the baricitinib clinical trials programme, where VTE occurred exclusively among patients on baricitinib 4mg, but not baricitinib 2mg or placebo during the 24-week placebo-controlled period.123 Additional events were observed in patients treated with baricitinib 2 and 4 mg after the first 24 weeks of exposure. An interim analysis of an ongoing open-label study (A3921133) reported an increased risk of blood clots in deep veins and in the lungs with both the 5mg and, especially, with the 10mg twice daily doses of tofacitinib as compared with patients taking TNFi in patients with ≥1CV risk factor.124 125 This interim analysis was published after the literature search (8 March 2019) and after the task force meeting for the EULAR recommendations on the management of RA had already taken place. These data suggest that JAKi increases the risk of VTE, above the underlying effect of RA itself,126 especially in patients with CV risk factors, but the risk is low and with unclear pathogenic mechanisms. Nonetheless, in light of the currently available evidence, the European Medicine Agency (EMA) has issued warnings to use tofacitinib and baricitinib with caution in RA patients with risk factors for VTE. In addition, the Food and Drug Administration did not approve the 4mg dose of baricitinib."	Moderate	
Weinblatt, 2006	RCT	1441	9.7Y	Diabetes mellitus: n=96	Abatacept (<60 kg: 500mg; 60-100kg: 750 mg; >100kg: 1000 mg; at D1, D15, D29 and then q4W)	65	Placebo	31	Serious adverse events, not further classified Infections	21.5% 50.8%	12.9% 58.1%						High	
EXTRA-ARTICULAR MANIFESTATIONS																		
Studies comparing different interventions in patients with comorbidity																		
Studies regarding safety																		
Nakamura, 2012	Non-RCT	86	181.4M	AA amyloidosis secondary to RA 100%	Cyclophosphamide (dose determined by level of 24-h creatinine clearance)	62	Etanercept (25mg 2/W)	24	Serum albumin eGFR Survival	Final observation		3.5 (0.4) 18.6 (9.3)	2.8 (0.5) 24.9 (18.7)	p<0.01 p=0.035	Kaplan-Meier survival curve after treatment, favours etanercept (p=0.025)		High	
HBV																		
Studies comparing patients with vs without comorbidity on treatment effect																		
Studies regarding efficacy																		
Chen, 2017	Non-RCT	63	36M	11.1% (n=7) with chronic HBV infection (HBsAG+, undetectable HBV-DNA), 65.1% (n=41) with resolved HBV infection (anti-HBc+, HBsAG-, undetectable HBV-DNA) and 23.8% (n=15) with non-HBV infection (anti-HBC-, HBsAG-, undetectable HBV-DNA)	Tocilizumab (8mg/kg q4w, intravenous)	63	NA	NA	DAS28-ESR (<3.2) DAS28-ESR (<2.6)	12W	44(70%) 32(51%)			ns (chronic vs resolved vs non-HBV) ns (chronic vs resolved vs non-HBV)			High	
Studies regarding safety																		
Cantini, 2014	SLR (21 studies)	297	NR	HBV infection: overt (HBsAg+) 13.5% (n=40); occult (anti-HBc+, HBsAg-) 85.5% (n=254); others not specified	TNFi	297	NA	NA	HBV reactivation HBV reactivation: occult HBV infection HBV reactivation: overt infection		3.3% (95%CI 0.7-7.5%) 2.6% (95%CI 0.4-6.6) 10.7 (95%CI 1.4-50.2)				Although HBV reactivation rate is relatively low in patients treated with anti-TNF - for rheumatic and dermatological conditions, the antiviral prophylaxis would be recommended in patients with overt chronic HBV infection	Moderate	NR
Chen, 2017	Non-RCT	63	36M	11.1% (n=7) with chronic HBV infection (HBsAG+, undetectable HBV-DNA), 65.1% (n=41) with resolved HBV infection (anti-HBc+, HBsAG-, undetectable HBV-DNA) and 23.8% (n=15) with non-HBV infection (anti-HBC-, HBsAG-, undetectable HBV-DNA)	Tocilizumab (8mg/kg q4w, intravenous)	63	NA		HBV reactivation	12W	3 (4.8%)					3 patients with chronic HBV infection and without antiviral prophylaxis developed HBV reactivation	High	
Padovan, 2016	Non-RCT	72	12Y	HBV: Inactive carriers (HBsAG-, anti-HBe+, HBV DNA levels <2000 IU/ml, normal LFTs) 65.3%	Abatacept	72	NA	NA	Reactivation of HBV Discontinuation due to HBV		0 (0%) 0		2.3 (1.9)			High	
Studies comparing different interventions in patients with comorbidity																		
Studies regarding safety																		
Papalopoulos, 2018	Non-RCT	212	6.2-7.2Y (median)	Past HBV infection (HBsAG-, anti-HBC+, anti-HBs±) 100%	Non-TNFi bDMARDs	101	TNFi	111	HBV reactivation	24M (median)	2	0		p=0.266		High	
HCV																		
Studies comparing patients with vs without comorbidity on treatment effect																		
Studies regarding efficacy																		
Lin, 2015	Non-RCT	101	5.6Y	HCV (presence of HCV RNA) 19.8% (n=20) versus without HCV 80.2% (n=81)	TNFi (adalimumab (40mg q2w) or etanercept (25mg 2/W)	101	NA	NA	DAS28: HCV DAS28: without HCV	Change from BL until 11M			2.77 (1.16) 2.43 (1.2)	ns (HCV vs without HCV)		High	
Studies regarding safety																		
Brunasso, 2011	SLR (37 studies)	153 (RA 91)	NR	Chronic HCV (not further explained) 100%	Etanercept	110	NA	NA	HCV-related liver disease (stable viral load and/or stable levels of transaminases): Improvement; Stable; Suspected of worsening;Confirmed worsening)	13.15M (mean)	29;74;5;1			NA	The safety profile of anti-TNF-a agents in the setting of HCV infection seems to be acceptable, even if differences in the hepatotoxic profile are apparent between different agents. In the absenceof long-term and large, controlled clinical trials a definitive statement on the safety of anti-TNF-a therapiesin the setting of chronic HCV infection cannot be made.	High	NR
Lin, 2015	Non-RCT	101	5.6Y	HCV (presence of HCV RNA) 19.8% (n=20) versus without HCV 80.2% (n=81)	TNFi (adalimumab (40mg q2w) or etanercept (25mg 2/W)	101	NA	NA	Development of liver injury (defined as chronic Child-Pugh class B or C disease): HCV Development of liver injury (defined as chronic Child-Pugh class B or C disease): without HCV Discontinuation from TNFi, not related to HCV: HCV Discontinuation from TNFi, not related to HCV: without HCV	Within 1Y Within 1Y Within 1 Y Within 1 Y	2 (10%) 1 (1.23%) 2 4			p=0.099 (HCV vs without HCV) ns (HCV vs without HCV)		High	
Studies comparing different interventions in patients with comorbidity																		
Studies regarding safety																		
Chen, 2015^	Non-RCT	26	25.8M	Concomitant HCV infection (presence of HCV viral load) 100%	TNFi	20	Rituximab	6	serum ALT level	After biological therapy				ns		High		

									HCV viral load: TNFi vs rituximab	From BL until end of biologic therapy					p=0.003	HCV viral load increased after rituximab therapy	
Iannone, 2014	RCT	29	6.2Y	HCV (presence of anti-HCV antibodies and HCV viremia by PCR) 100%	MTX (starting dose 10mg/W)	9	NA	NA	Discontinuation of therapy, because of hepatitis C related event	Within 54W	0						High
									Hepatitis C virus viral load (log10)	54W			5.3		ns (compared to BL)		
					Etanercept (50mg/W)	13			Discontinuation of therapy, because of hepatitis C related event	Within 54W	0						
									Hepatitis C virus viral load (log10)	54W			5.5		ns (compared to BL)		
					MTX and Etanercept	7			Discontinuation of therapy, because of hepatitis C related event	Within 54W	0						
									Hepatitis C virus viral load (log10)	54W			5.8		ns (compared to BL)		
HEPATIC DISEASE																		
Studies comparing patients with vs without comorbidity on treatment effect																		
Studies regarding efficacy																		
Combe, 2019^	Non-RCT	1684	NR	Baricitinib: depression (n=64), osteoporosis (n=113),	Baricitinib (4mg)	222	Placebo	202	ACR20 response: with hepatic disorder	12W	67.1%	37.1%					High
				hepatic disorder (n=222), CV disorder (n=350),		581		679	ACR20 response: without hepatic disorder		67.6%	39.8%					
				pulmonary disorder (n=77), not further explained;		222		202	ACR50 response: with hepatic disorder		40.5%	11.4%					
				Placebo: depression (n=69), osteoporosis (n=134),		581		679	ACR50 response: without hepatic disorder		41.3%	15.3%					
				hepatic disorder (n=202), CV disorder (n=381),		222		202	DAS28-hsCRPs3.2: with hepatic disorder		42.8%	12.9%					
				pulmonary disorder (n=89), not further explained		581		679	DAS28-hsCRPs3.2: without hepatic disorder		44.2%	17.7%					
Studies comparing different interventions in patients with comorbidity																		
Studies regarding efficacy																		
Combe, 2019^	Non-RCT	1684	NR	Baricitinib: depression (n=64), osteoporosis (n=113),	Baricitinib (4mg)	222	Placebo	202	ACR20 response: with hepatic disorder	12W	67.1%	37.1%					High
				hepatic disorder (n=222), CV disorder (n=350),		581		679	ACR20 response: without hepatic disorder		67.6%	39.8%					
				pulmonary disorder (n=77), not further explained;		222		202	ACR50 response: with hepatic disorder		40.5%	11.4%					
				Placebo: depression (n=69), osteoporosis (n=134),		581		679	ACR50 response: without hepatic disorder		41.3%	15.3%					
				hepatic disorder (n=202), CV disorder (n=381),		222		202	DAS28-hsCRPs3.2: with hepatic disorder		42.8%	12.9%					
				pulmonary disorder (n=89), not further explained		581		679	DAS28-hsCRPs3.2: without hepatic disorder		44.2%	17.7%					
OBESITY/OVERWEIGHT																		
Studies comparing patients with vs without comorbidity on treatment effect																		
Studies regarding efficacy																		
Gremese, 2013	Non-RCT	641	8.5Y	BMI 24.9 kg/m2; BMI <30: 89.7% (n=575); BMI >30: 10.3% (n=66)	TNFi (adalimumab 40.6%; etanercept 35.4%; infliximab 24%)				DAS28 remission: BMI<30	12M	184 (32.0%)						High
									DAS28 remission: BMI>30		10 (15.2%)						
					Infliximab (3mg/kg after induction, iv)				DAS28 remission: BMI<30		22.4%				p=0.01 (BMI<30		
									DAS28 remission: BMI>30		0%				vs BMI>30)		
					Adalimumab (40mg sc q2w)				DAS28 remission: BMI<30		30.1%				p=0.08 (BMI<30		
									DAS28 remission: BMI>30		14.8%				vs BMI>30)		
					Etanercept (50mg sc q1w)				DAS28 remission: BMI<30		36.2%				p=0.44 (BMI<30		
									DAS28 remission: BMI>30		27.6%				vs BMI>30)		
Klaasen, 2011	Non-RCT	89	80.3M	BMI >30 26.9%	Infliximab (3mg/kg, intravenous)	74	NA	NA	DAS28 responders (ΔDAS28 ≥ 1.2): BMI <30	16W	43				p=0.04 (compared to BMI <30)		High
						15			DAS28 responders (ΔDAS28 ≥ 1.2): BMI >30	16W	7						
Yoo, 2017^	Non-RCT	322	NR	BMI: <25, 25-30, ≥30; % NR	Rituximab or biosimilar CT-P10 (1000mg iv at days 1 and 15)	322	NA	NA	ACR20 response: BMI <25	24W			81.8%		ns (compared to other BMI groups)		High
									ACR20 response: BMI 25-30				75.4%				
									ACR20 response: BMI ≥30				80.0%				
									ACR50 response: BMI <25				53.4%		ns (compared to other BMI groups)		
									ACR50 response: BMI 25-30				49.1%				
									ACR50 response: BMI ≥30				55.7%				
									DAS28: BMI <25	Change from BL until 24W					ns (compared to other BMI groups)		
									DAS28: BMI 25-30								
									DAS28: BMI ≥30								
Studies comparing different interventions in patients with comorbidity																		
Studies regarding efficacy																		
Burmester, 2017^	Non-RCT	369	7.3Y	BMI 27.2 (BMI 25-30 31.7% (n=117), BMI >30 22.0% (n=81))	Adalimumab (40mg q2w plus placebo, subcutaneous)	185	Sarilumab (200mg q2w plus placebo, subcutaneous)	184	DAS28-ESR: BMI <25	Change from BL until 24W				<0 (favours sarilumab)	p=0.047		High
									DAS28-ESR: BMI 25-30					<0 (favours sarilumab)			
									DAS28-ESR: BMI >30					0			
OSTEOPOROSIS/OSTEOPENIA																		
Studies comparing patients with vs without comorbidity on treatment effect																		
Studies regarding efficacy																		
Combe, 2019^	Non-RCT	1684	NR	Baricitinib: depression (n=64), osteoporosis (n=113),	Baricitinib (4mg)	113	Placebo	134	ACR20 response: with osteoporosis	12W	65.5%	32.1%					High
				hepatic disorder (n=222), CV disorder (n=350),		690		747	ACR20 response: without osteoporosis		67.8%	40.4%					
				pulmonary disorder (n=77), not further explained;		113		134	ACR50 response: with osteoporosis		40.7%	11.9%					
				Placebo: depression (n=69), osteoporosis (n=134),		690		747	ACR50 response: without osteoporosis		41.2%	14.9%					
				hepatic disorder (n=202), CV disorder (n=381),		113		134	DAS28-hsCRPs3.2: with osteoporosis		46.9%	12.7%					
				pulmonary disorder (n=89), not further explained		690		747	DAS28-hsCRPs3.2: without osteoporosis		43.3%	17.3%					
Studies comparing different interventions in patients with comorbidity																		
Studies regarding efficacy																		
Combe, 2019^	Non-RCT	1684	NR	Baricitinib: depression (n=64), osteoporosis (n=113),	Baricitinib (4mg)	113	Placebo	134	ACR20 response: with osteoporosis	12W	65.5%	32.1%					High
				hepatic disorder (n=222), CV disorder (n=350),		690		747	ACR20 response: without osteoporosis		67.8%	40.4%					
				pulmonary disorder (n=77), not further explained;		113		134	ACR50 response: with osteoporosis		40.7%	11.9%					
				Placebo: depression (n=69), osteoporosis (n=134),		690		747	ACR50 response: without osteoporosis		41.2%	14.9%					
				hepatic disorder (n=202), CV disorder (n=381),		113		134	DAS28-hsCRPs3.2: with osteoporosis		46.9%	12.7%					
				pulmonary disorder (n=89), not further explained		690		747	DAS28-hsCRPs3.2: without osteoporosis		43.3%	17.3%					
Nakamura, 2017	Non-RCT	43	17.5Y	Osteoporosis 100%	Denosumab (60mg/6M, subcutaneous)	22	Denosumab + vitamin D ((762.5mg of precipitated calcium carbonate, 200IU of cholecalciferol, 59.2mg of magnesium	21	DAS28-CRP	Change from BL until 12M			2.7 (0.3)	2.0 (0.3)	p=0.0793		High
Studies regarding safety																		
Nakamura, 2017	Non-RCT	43	17.5Y	Osteoporosis 100%	Denosumab (60mg/6M, subcutaneous)	22	Denosumab + vitamin D ((762.5mg of precipitated calcium carbonate, 200IU of cholecalciferol, 59.2mg of magnesium	21	Lumbar BMD	Change from BL until 12M			0.74 (0.03)	0.72 (0.04)	p=0.6983		High
									Hips (femoral head) BMD				0.49 (0.02)	0.54 (0.03)	p=0.2236		

Shin, 2017	RCT	149	7.7Y	Osteopenia (reduced BMD) 100%	Ibradonate (150mg q4w, oral)	76	Placebo	73	Lumbar BMD	Change from BL until 48W			+3.7% (5.1%)	-1.9% (4.4%)	p=0.0073		Low
PREGNANCY/LACTATION																	
Studies comparing different interventions in patients with comorbidity																	
Studies regarding safety																	
Clowse, 2016	Non-RCT	31	NR	Pregnancy 100%	Tofacitinib (5mg 2/D)	8	Tofacitinib (10mg, 2/D)	9	congenital malformation	NR	1	0					High
									spontaneus abortion		1	1					
									healthy newborn		6	5					
									medical termination		0	1					
									lost to follow-up		0	2					
					Tofacitinib (15mg 2/D)	1	Tofacitinib (20mg/D) + MTX 25mg	1	congenital malformation		0	0					
									spontaneus abortion		1	0					
									healthy newborn		0	1					
									medical termination		0	0					
									lost to follow-up		0	0					
					Tofacitinib (5mg/D) + MTX 2.5mg	1	NA		congenital malformation		0						
									spontaneus abortion		0						
									healthy newborn		1						
									medical termination		0						
									lost to follow-up		0						
					Tofacitinib (5mg 2/D) + MTX 10mg	1	Tofacitinib (5mg 2/D) + MTX 17.5mg	1	congenital malformation		0	0					
									spontaneus abortion		0	0					
Götestam Skorpen, 2016	SLR (69 nRCTs, 250 case series/reports) - EULAR points to consider	NR (patients with RMDs)	NR	Maternal exposure, lactation	All cs/b/tsDMARDs + prednisone	NR	NA	NA	Safe to continue - Maternal exposure							Points to consider for use of antirheumatic drugs in pregnancy*Grade of recommendation†: 1 csDMARDs‡ proven compatible with pregnancy are hydroxychloroquine, chloroquine, sulfasalazine, azathioprine, ciclosporin, tacrolimus and colchicine. They should be continued in pregnancy for maintenance of remission or treatment of a disease flare. (B); 2 csDMARDs‡ methotrexate, mycophenolate mofetil and cyclophosphamide are teratogenic and should be withdrawn before pregnancy. (B); 3 Non-selective COX inhibitors and prednisone should be considered for use in pregnancy if needed to control active disease symptoms. NSAIDs should be restricted to the first and second trimesters. (B); 4 In severe, refractory maternal disease during pregnancy methylprednisolone pulses, intravenous immunoglobulin or even second or third trimester use of cyclophosphamide should be considered. (D); 5 csDMARDs‡, tsDMARDs§ and anti-inflammatory drugs with insufficient documentation concerning use in pregnancy should be avoided until further evidence is available. This applies to leflunomide, mepacrine, tofacitinib and selective COX II inhibitors. (B–D); 6 Among bDMARDs¶ continuation of TNF inhibitors during the first part of pregnancy should be considered. Etanercept and certolizumab may be considered for use throughout pregnancy due to low rate of transplacental passage. (B); 7 bDMARDs¶ rituximab, anakinra, tocilizumab, abatacept, belimumab and ustekinumab have limited documentation on safe use in pregnancy and should be replaced before conception by other medication. They should be used during pregnancy only when no other pregnancy-compatible drug can effectively control maternal disease. (D) Points to consider for use of antirheumatic drugs during lactation*Grade of recommendation†: 1csDMARDs‡ and anti-inflammatory drugs compatible with breast feeding should be considered for continuation during lactation provided the child does not have conditions that contraindicate it. This applies to hydoxychloroquine, chloroquine, sulfasalazine, azathioprine, ciclosporin, tacrolimus, colchicine, prednisone, immunoglobulin, non-selective COX inhibitors and celecoxib. (D) 2csDMARDs‡, tsDMARDs§ and anti-inflammatory drugs with no or limited data on breast feeding should be avoided in lactating women. This applies to methotrexate, mycophenolate mofetil, cyclophosphamide, leflunomide, tofacitinib and cyclooxygenase II inhibitors other than celecoxib. (D); 3Low transfer to breast milk has been shown for infliximab, adalimumab, etanercept and certolizumab. Continuation of TNF inhibitors should be considered compatible with breast feeding. (D); 4bDMARDs¶ with no data on breast feeding such as rituximab, anakinra, belimumab, ustekinumab, tocilizumab and abatacept should be avoided during lactation if other therapy is available to control the disease. Based on pharmacological properties of bDMARDs¶, lactation should not be discouraged when using these agents, if no other options are available.	Moderate
Hoeltzenbein, 2016	Non-RCT	288 (RA 235; JIA 20; Other 7; Unknown 26)	NR	Pregnancy 100%	Tocilizumab	288	NA	NA	Live births	164							High
									Spontaneous abortions	70							
									Elective terminations of pregancy	53							
									Stillbirth	1							
									Malformations	11							
									Rate of preterm birth	31.2%							
									Adverse pregnancy outcomes	0							
Mouyis, 2019	SLR (84 nRCTs)	611 males with preconceptional exposure and outcomes on fertility; 5986 with	NR	Men trying to conceive	Cyclophosphamide, TNFi, abatacept, rituximab, azathioprine, cyclosporine A, hydroxychloroquine, leflunomide, methotrexate or mycophenolate mofetil	NR										Conclusion: Aside from the known adverse impact of cyclophosphamide and sulfasalazine on spermatogenesis, overall there was no firm evidence of harm to fertility or pregnancy outcomes with paternal exposure to anti-TNF therapies, abatacept, rituximab, azathioprine, cyclosporine A, hydroxychloroquine, leflunomide, methotrexate or mycophenolate mofetil. There was no evidence found pertaining to the effects of male exposure to IVIG, tacrolimus, golimumab, anakinra or belimumabon fertility or pregnancy outcomes.	Moderate	High

Sammaritano, 2020	SLR (53 nRCTs) - ACR guideline	NR (patients with RMDs)	NR	Paternal and maternal exposure, lactation	All cs/b/tsDMARDs + prednisone	NR	NA	NA	Safe to continue - Paternal exposure				Strongly recommend continuing: Azathioprine/ 6-mercaptopurine, Colchicine, Hydroxychloroquine, Tumor necrosis factor inhibitors (all) Conditionally recommend continuing: Anakinra, Cyclooxygenase 2 inhibitors, Cyclosporine, Leflunomide, Methotrexate, Mycophenolate mofetil, Mycophenolic acid, Nonsteroidal anti-inflammatory drugs, Rituximab, Sulfasalazine (semen analysis if delayed conception), Tacrolimus Strongly recommend discontinuing: Cyclophosphamide (discontinue 12 weeks prior to attempted conception) Conditionally recommend discontinuing: Thalidomide (discontinue 4 weeks prior to attempted conception) Unable to make a recommendation due to limited data: Abatacept, Apremilast, Baricitinib, Belimumab, Secukinumab, Tocilizumab, Tofacitinib, Ustekinumab	Moderate
									Safe to continue - Maternal exposure - pre-conception				Strongly recommend continuing: Hydroxychloroquine, Sulfasalazine, Colchicine, Azathioprine/6-mercaptopurine, Certolizumab Conditionally recommend continuing: Prednisone (taper to <20mg/day by adding pregnancy-compatible immunosuppressants), Cyclosporine (monitor blood pressure), Tacrolimus (monitor blood pressure), Nonsteroidal antiinflammatory drugs (cyclooxygenase 2 inhibitors not preferred, discontinue if the woman is having difficulty conceiving), Infliximab (continue through conception), Etanercept (continue through conception), Adalimumab (continue through conception), Golimumab (continue through conception), Rituximab (discontinue at conception), Anakinra (discontinue at conception), Belimumab (discontinue at conception), Abatacept (discontinue at conception), Tocilizumab (discontinue at conception), Secukinumab (discontinue at conception), Ustekinumab (discontinue at conception) Strongly recommend discontinuing: Methotrexate (stop 1-3 months prior to conception), Leflunomide (cholestyramine washout if detectable levels), Mycophenolate mofetil and mycophenolic acid (stop >6 weeks prior to conception to assess disease stability), Cyclophosphamide (stop 3 months prior to conception), Thalidomide (stop 1-3 months prior to conception) Conditionally recommend discontinuing: - Unable to make a recommendation due to limited data: Tofacitinib, Apremilast, Baricitinib (unable to determine due to lack of data; small molecular size suggests transfer across the placenta and into breast milk)	
									Safe to continue - Maternal exposure - during pregnancy				Strongly recommend continuing: Hydroxychloroquine, Sulfasalazine, Colchicine, Azathioprine/6-mercaptopurine, Certolizumab Conditionally recommend continuing: Prednisone, Cyclosporine, Tacrolimus, Nonsteroidal antiinflammatory drugs (cyclooxygenase 2 inhibitors not preferred), Infliximab, Etanercept, Adalimumab, Golimumab, Rituximab, Cyclophosphamide (Life-/organ-threatening disease in second and third trimesters) Strongly recommend discontinuing: Methotrexate (stop and give folic acid 5mg/day), Leflunomide (stop and give cholestyramine washout), Mycophenolate mofetil and mycophenolic acid, Thalidomide Conditionally recommend discontinuing: Anakinra (discontinue during pregnancy), Belimumab (discontinue during pregnancy), Abatacept (discontinue during pregnancy), Tocilizumab (discontinue during pregnancy), Secukinumab (discontinue during pregnancy), Ustekinumab (discontinue during pregnancy) Unable to make a recommendation due to limited data: Tofacitinib, Apremilast, Baricitinib (unable to determine due to lack of data; small molecular size suggests transfer across the placenta and into breast milk)	
									Safe to continue - Maternal exposure - breastfeading				Strongly recommend continuing: Hydroxychloroquine, Sulfasalazine, Colchicine, Certolizumab, Infliximab, Etanercept, Adalimumab, Golimumab, Rituximab Conditionally recommend continuing: Azathioprine/6-mercaptopurine (low transfer), Prednisone (after a dose of >20mg, delay breastfeeding for 4 hours), Cyclosporine (low transfer), Tacrolimus (low transfer), Nonsteroidal antiinflammatory drugs (cyclooxygenase 2 inhibitors not preferred, ibuprofen preferred), Anakinra (expect minimal transfer due to large molecular size, but no available data), Belimumab (expect minimal transfer due to large molecular size, but no available data), Abatacept (expect minimal transfer due to large molecular size, but no available data), Tocilizumab (expect minimal transfer due to large molecular size, but no available data), Secukinumab (expect minimal transfer due to large molecular size, but no available data), Ustekinumab (expect minimal transfer due to large molecular size, but no available data) Strongly recommend discontinuing: Leflunomide, Mycophenolate mofetil and mycophenolic acid, Cyclophosphamide, Thalidomide Conditionally recommend discontinuing: Methotrexate (limited data suggest low transfer) Unable to make a recommendation due to limited data: Tofacitinib, Apremilast, Baricitinib (unable to determine due to lack of data; small molecular size suggests transfer across the placenta and into breast	
PSYCHOLOGICAL DISEASE															
Studies comparing patients with vs without comorbidity on treatment effect															
Studies regarding efficacy															
Combe, 2019^	Non-RCT	1684	NR	Baricitinib: depression (n=64), osteoporosis (n=113),	Baricitinib (4mg)	64	Placebo	69	ACR20 response: with depression	12W	59.4%	31.9%			High

				hepatic disorder (n=222), CV disorder (n=350), pulmonary disorder (n=77), not further explained; Placebo: depression (n=69), osteoporosis (n=134), hepatic disorder (n=202), CV disorder (n=381), pulmonary disorder (n=89), not further explained		739 64 739 64 739		812 69 812 69 812	ACR20 response: without depression ACR50 response: with depression ACR50 response: without depression DAS28-hsCRPs3.2: with depression DAS28-hsCRPs3.2: without depression		68.2% 34.4% 41.7% 31.3% 44.9%	39.8% 8.7% 14.9% 13.0% 16.9%				
Studies comparing different interventions in patients with comorbidity																
Studies regarding efficacy																
Combe, 2019^	Non-RCT	1684	NR	Baricitinib: depression (n=64), osteoporosis (n=113), hepatic disorder (n=222), CV disorder (n=350), pulmonary disorder (n=77), not further explained; Placebo: depression (n=69), osteoporosis (n=134), hepatic disorder (n=202), CV disorder (n=381), pulmonary disorder (n=89), not further explained	Baricitinib (4mg)	803	Placebo	881	ACR20 response: Overall ACR20 response: Depression ACR50 response: Overall ACR50 response: Depression DAS28-hsCRPs3.2: Overall DAS28-hsCRPs3.2: Depression	12W	542 (67.5%) 38 (59.4%) 330 (41.4%) 22 (34.4%) 352 (43.8%) 20 (31.3%)	345 (39.2%) 22 (31.9%) 127 (14.4%) 9 (13.0%) 146 (18.2%) 9 (13.0%)				High
Studies regarding safety																
Abramkin, 2017^	Non-RCT	128	NR	Mental disorder (100%)	csDMARDs csDMARDs + andidepressants (sertraline or mianserine) csDMARDs + bDMARDs csDMARDs + bDMARDs + andidepressants (sertraline or mianserine) csDMARDs csDMARDs + andidepressants (sertraline or mianserine) csDMARDs + bDMARDs csDMARDs + bDMARDs + andidepressants (sertraline or mianserine) csDMARDs csDMARDs + andidepressants (sertraline or mianserine) csDMARDs + bDMARDs csDMARDs + bDMARDs + andidepressants (sertraline or mianserine) csDMARDs csDMARDs + andidepressants (sertraline or mianserine) csDMARDs + bDMARDs csDMARDs + bDMARDs + andidepressants (sertraline or mianserine)	32 37 27 9 32 37 27 9 32 37 27 9 32 37 27 9	NA	NA	Frequency of major depressive disorder Frequency of minor depressive disorder Frequency of anxiety disorder Frequency of cognitive disorder	Change from BL until 5Y	+18.2% -47.4% +2.1% -66.7% +2.2% -26.3% +11.7% -16.7% -23.7% -26.3% -18.5% -16.7% +14.0% -18.9% +7.2% -14.3%		0.09 <0.001 ns 0.03 ns <0.001 ns ns 0.021 <0.001 0.047 ns 0.16 0.25 ns ns	Compared to baseline	High
Strand, 2018^	RCT (TARGET)	546	NR	Probable major depressive disorder 59.5%; Probable Probable depressed mood and anhedonia 50.4%	Sarilumab (200mg q2w)	NR	Placebo	NR	Domains on SF-36 mental health: Probable major depressive disorder Domains on SF-36 mental health: Probable depressed mood and anhedonia Domains on SF-36 mental health: Probable major depressive disorder Domains on SF-36 mental health: Probable depressed mood and anhedonia	24W			p<0.05 p<0.05 p<0.05 p<0.05	Intervention higher on all domains except for role-emotional Intervention higher on all domains Intervention higher on all domains except for role-emotional and physical functioning Intervention higher on all domains except for role-emotional and physical functioning	High
	RCT (MOBILITY)	1197	NR	Probable major depressive disorder 60.2%; Probable Probable depressed mood and anhedonia 51.6%												
PULMONARY DISEASE																
Studies comparing patients with vs without comorbidity on treatment effect																
Studies regarding efficacy																
Combe, 2019^	Non-RCT	1684	NR	Baricitinib: depression (n=64), osteoporosis (n=113), hepatic disorder (n=222), CV disorder (n=350), pulmonary disorder (n=77), not further explained; Placebo: depression (n=69), osteoporosis (n=134), hepatic disorder (n=202), CV disorder (n=381), pulmonary disorder (n=89), not further explained	Baricitinib (4mg)	77 726 77 726 77 726	Placebo	89 792 89 792 89 792	ACR20 response: with pulmonary disorder ACR20 response: without pulmonary disorder ACR50 response: with pulmonary disorder ACR50 response: without pulmonary disorder DAS28-hsCRPs3.2: with pulmonary disorder DAS28-hsCRPs3.2: without pulmonary disorder	12W	66.2% 67.6% 40.3% 41.2% 37.7% 44.5%	32.6% 39.9% 12.4% 14.6% 16.9% 16.5%				High
Studies comparing different interventions in patients with comorbidity																
Studies regarding efficacy																
Combe, 2019^	Non-RCT	1684	NR	Baricitinib: depression (n=64), osteoporosis (n=113), hepatic disorder (n=222), CV disorder (n=350), pulmonary disorder (n=77), not further explained; Placebo: depression (n=69), osteoporosis (n=134), hepatic disorder (n=202), CV disorder (n=381), pulmonary disorder (n=89), not further explained	Baricitinib (4mg)	77 726 77 726 77 726	Placebo	89 792 89 792 89 792	ACR20 response: with pulmonary disorder ACR20 response: without pulmonary disorder ACR50 response: with pulmonary disorder ACR50 response: without pulmonary disorder DAS28-hsCRPs3.2: with pulmonary disorder DAS28-hsCRPs3.2: without pulmonary disorder	12W	66.2% 67.6% 40.3% 41.2% 37.7% 44.5%	32.6% 39.9% 12.4% 14.6% 16.9% 16.5%				High
Studies regarding safety																
Suissa, 2019	Non-RCT	5324	NR	COPD 100%	Abatacept	1807	Another bDMARD (matched cohort)	3547	Combination of hospitalized COPD exacerbation, bronchitis and hospitalized pneumonia or influenca Hospitalized COPD exacerbation Bronchitis Hospitalized pneumonia or influenza Pneumonia or influenza as outpatient					HR: 0.87 (0.68-1.12); OR >1 favours abatacept HR: 0.60 (0.32-1.11); OR >1 favours abatacept HR: 0.80 (0.56-1.14); OR >1 favours abatacept HR: 1.39 (0.91-2.13); OR >1 favours abatacept HR: 1.05 (0.86-1.29); OR >1 favours abatacept	High
Weinblatt, 2006	RCT	1441	9.7Y	COPD: n=54	Abatacept (<60 kg: 500mg; 60-100kg: 750 mg; >100kg: 1000 mg; at D1, D15, D29 and then q4W)	37	Placebo	17	Serious respiratory adverse events Adverse events involving the respiratory system Infections		4 (11%) 43.2% 59.5%	0 23.5% 58.8%		p=0.31		High
RENAL DISEASE																
Studies comparing different interventions in patients with comorbidity																
Studies regarding efficacy																
Mori, 2015^	Non-RCT	371	10.9Y	Renal insufficiency (eGFR <30ml/min) 24.8% (n=92) versus without renal insufficiency 75.2% (n=279)	Tocilizumab	64 106	Tocilizumab + MTX	28 173	CDAI: Renal insufficiency CDAI: Without renal insufficiency	Change from BL until 24W			13.1 (95%CI 10.4-15.8) 14.9 (95%CI 12.7-17.1)	13.6 (95%CI 9.5-17.7) 12.1 (95%CI 10.5-13.8)	p=0.25 (between patient groups) p=0.25 (between patient groups)		High

Studies regarding safety														
Mori, 2015^	Non-RCT	371	10.9Y	Renal insufficiency (eGFR <30ml/min) 24.8% (n=92)	Tocilizumab	64	Tocilizumab + MTX	28	Discontinuation: Renal insufficiency	Within 24W	4 (6.3%)	5 (7.8%)		High
				versus without renal insufficiency 75.2% (n=279)		106		173	Discontinuation: Without renal insufficiency		10 (9.4%)	15 (14.2%)		

ACR: American College of Rheumatology; AE: adverse event; ALT: alanine transaminase; anti-HBc: hepatitis B core antigen; AST: aspartate transaminase; bDMARD: biologic disease-modifying antirheumatic drug; BL: baseline; BMD: bone mineral density; BMI: body mass index; CAD: coronary artery disease; csDMARD: conventional synthetic disease-modifying antirheumatic drug; CV(D): cardiovascular disease; D: day; DAS28: disease activity score assessing 28 joints; dL: deciliter; DM: diabetes mellitus; DNA: deoxyribonucleic acid; eGFR: estimated glomerular filtration rate; ESR: erythrocyte sedimentation rate; h: hour; HBV: hepatitis B virus; HCV: hepatitis C virus; HDL: high density lipoprotein; hsCRP: high sensitivity C-reactive protein; ILD: interstitial lung disease; IQR: interquartile range; I.U: international unit; kg: kilogram; JIA: juvenile idiopathic arthritis; LDL: low density lipoprotein; M: month(s); mg: miligram; ml: milliliter; MTX: methotrexate; n: number; NA: not applicable; NR: not reported; (n-)RCT: (non-)randomised controlled trial; ns: not significant; NSAID: non-steroidal anti-inflammatory drug; OR: odds ratio; q_w; once every___ weeks; RA: rheumatoid arthritis; SD: standard deviation; SF-36: short form general health questionnaire using 36 items; SLR: systematic literature review; TNFi: TNF inhibitor; W: week(s); Y: year(s); ^: abstract or letter.

1. Latest time point during treatment period that was reported; 2. 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; 3. Only applicable for SLRs: Summary of RoB of individual studies, as assessed in SLR