Rheumatoid arthritis-associated interstitial lung disease: epidemiology, risk/prognostic factors, and treatment landscape

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Supplementary material

Comorbidities associated with ILD

One study reported frequencies of comorbidities in RA-ILD and matched ILD-free RA patients, including ischaemic heart disease (RA-ILD: 13%, RA: 10.2%), congestive heart failure (RA-ILD: 8.5%, RA: 4.4%), and diabetes (RA-ILD: 9.9%, RA: 7.4%) (1). The second study reported that over an evaluation period of 10 years, the most commonly diagnosed RA-ILD-related comorbidities were hypertension (41–61% across study period), gastroesophageal reflux disease (46.1–54.1%), dyslipidaemia (34.7–52.4%), coronary artery disease (21.3–25.8%), diabetes (21–26.3%), and acute bronchitis/pneumonia (33.5–38.4%) (2).

FEV1, FEV1/FVC, and ILD Exacerbation

Two studies (3, 4) reported mean FEV1 percent predicted values, ranging from 62% (MMF at 6 months) (4) to 83.57% (SD: 20.36%; anti-TNFs at 1 year) (3). FEV1/FVC ratio was reported by one study, with mean values ranging from 82.42 (SD: 10.59; anti-TNFs + MTX) to 87.52 (SD: 8.34; MTX + HCQ) at one year (3). Among three studies reporting (5-7), proportions of participants experiencing exacerbation of ILD ranged from 7.69% (TOC at 4–120 weeks) (5) to 31.82% (RTX + MPS at 6–12 months) (6).

Table S1. TLR Search Strategies: DOC Search
Searched: March 4, 2019

Set #	Searches	Results
1	((**Rheumatoid arthritis** OR arthritis-associated) <in title> AND **Interstitial Lung Disease** <in title>) AND (**Prognostic Factors** OR **Risk** OR **Prevalence** OR **Comorbidity** OR **Morbidity** OR **Survival** OR **Mortality** OR **Incidence Rate** OR **Incidences** OR **Epidemiology**) <in abstract>	107

Note. Bold terms are linked to the DOC Search ontology and therefore for all synonyms, misspellings, and inflections of that term are also searched (linked vocabularies include MEDDRA, ICD10, ICD10CM, ICD9CM, HPO, SNOMED, NCIT, MESH, NDFRT, GHDX, ASCO subjects). Non-bold terms are free text words: DOC Search will include an exact match in the title or abstract.

Table S2. TLR Search Strategies: Embase Search for Conference Abstracts (ACR and EULAR 2016-Present)
Searched: December 26, 2018

Set #	Searches	Results
1	exp rheumatoid arthritis/ or (rheumatoid arthritis or RA).ti,ab.	243096
2	exp interstitial lung disease/ or (interstitial or organizing pneumonia or ILD).ti,ab.	159307
3	1 and 2	5639
4	European League Against Rheumatism.so.	16131
5	EULAR.cf.	23647
6	American College of Rheumatology.so.	22108
7	ACR.cf.	19920
8	or/4-7	48932
9	3 and 8	484
10	(exp animal/ or nonhuman/) not exp human/	5981647
11	9 not 10	463
12	english.lg.	26899955
13	11 and 12	463
14	limit 13 to yr="2016 -Current"	195
15	conference abstract.pt.	3239057
16	3 and 15	1419
17	16 not 10	1357
18	12 and 17	1356
19	limit 18 to yr="2016 -Current"	500

Table S3. SLR Search Strategies: MEDLINE (via PubMed)
Searched: Inception – December 26, 2018

Set #	Searches	Results
1	"Arthritis, Rheumatoid"[Mesh] OR rheumatoid arthritis[tiab] OR RA[tiab]	166651
2	"Lung Diseases, Interstitial"[Mesh] OR interstitial[tiab] OR organizing pheumonia[tiab] OR ILD[tiab]	137361
3	1 AND 2	2703
4	“animals”[mesh] NOT “humans”[mesh]	4530043
5	3 NOT 4	2624
6	English[Language]	24546266
7	5 AND 6	1902

Table S4. SLR Search Strategies: Embase (via OVID)
Searched: Inception – December 26, 2018 (journal articles), 2016 – December 26, 2018 (meeting abstracts)
Embase Segment Used: 1974 to 2018 December 24

Set #	Searches	Results
1	exp rheumatoid arthritis/ or (rheumatoid arthritis or RA).ti,ab.	243096
2	exp interstitial lung disease/ or (interstitial or organizing pneumonia or ILD).ti,ab.	159307
3	1 and 2	5639
4	(exp animal/ or nonhuman/) not exp human/	5981647
5	3 not 4	5480
6	english.lg.	26899955
7	5 and 6	4803
8	case report.ti. or (book or chapter or conference review or editorial or letter note or press or review).pt.	3483628
9	7 not 8	3560
10	(article or article in press or conference paper).pt.	21121032
11	9 and 10	1917
12	European League Against Rheumatism.so.	16131
13	EULAR.cf.	23647
14	American College of Rheumatology.so.	22108
15	ACR.cf.	19920
16	or/12-15	48932
17	9 and 16	461
18	limit 17 to yr="2016 -Current"	193
19	conference abstract.pt.	3239057
20	9 and 19	1334
21	limit 20 to yr="2016 -Current"	488
22	21 not 18	295
23	11 or 18 or 22	2405
24	remove duplicates from 23	2372

Table S5. SLR Search Strategies: Cochrane Central Database of Controlled Trials (via OVID)
Searched: Inception – December 26, 2018

Set #	Searches	Results
1	Arthritis, Rheumatoid/ or (rheumatoid arthritis or RA).ti,ab.	12381
2	Lung Diseases, Interstitial/ or (interstitial or organizing pneumonia or ILD).ti,ab.	2495
3	1 and 2	52
4	limit 3 to embase records	37
5	limit 3 to medline records	13
6	4 or 5	50
7	3 not 6	2

Table S6. SLR Search Strategies: ClinicalTrials.gov (via DOC Search)
Searched: 2016 – December 26, 2018

Set #	Searches	Results
1	(Rheumatoid arthritis AND Interstitial Lung Disease) AND ClinicalTrials.gov	19

Table S7. SLR Search Strategies: Clinicaltrialsregister.eu
Searched: 2016 – December 26, 2018

Set #	Searches	Results
1	Rheumatoid arthritis AND interstitial lung	2

Table S8. Summary of Available Efficacy Outcomes

Author & Year	ACR20	ACR50	ACR 70	DAS28	Sharp Score	Dyspnea	MMRC, Dyspnea	DLCO	FVC	FEV 1	FEV1/ FVC	ILD Exacerbation
Akiyama *et al.* 2016 (5)	N	N	N	Y	N	N	N	N	N	N	N	Y
Chamizo-Carmona *et al.* 2018 (8)	N	N	N	Y	N	N	N	N	N	N	N	N
Chartrand *et al.* 2016 (9)	N	N	N	N	N	N	N	N	Y	N	N	N
Detorakis *et al.* 2016 (3)	N	N	N	Y	N	N	N	Y	Y	Y	Y	N
Fernández-Díaz *et al.* 2016a (10)	N	N	N	Y	N	N	Y	Y	Y	N	N	N
Fernández-Díaz *et al.* 2016b (11)	N	N	N	Y	N	N	Y	Y	Y	N	N	N
Fernández-Díaz *et al.* 2017a (12)	N	N	N	Y	N	N	Y	Y	Y	N	N	N
Fernández-Díaz *et al.* 2017b (13)	N	N	N	Y	N	N	Y	Y	Y	N	N	N
Fernández-Díaz *et al.* 2017c (14)	N	N	N	Y	N	N	Y	Y	Y	N	N	N
Fernández-Díaz *et al.* 2018a (15)†	N	N	N	Y	N	Y	Y	Y	Y	N	N	N
Fernández-Díaz *et al.* 2018b (16)	N	N	N	N	N	N	Y	Y	Y	N	N	N
Fischer 2013 *et al.* (17)	N	N	N	N	N	N	N	N	Y	N	N	N
Koo *et al.* 2015 (18)	N	N	N	N	N	N	N	N	N	N	N	Y
Md Yusof *et al.* 2017 (6)	N	N	N	Y	N	N	N	Y	Y	N	N	Y
Mena-Vazquez *et al.* 2018 (7)	N	N	N	Y	N	N	N	N	N	N	N	Y
Nakashita *et al.* 2016 (19)	N	N	N	Y	N	N	N	N	N	N	N	N
Narvaez *et al.* 2018 (20)	N	N	N	Y	N	N	N	Y	Y	N	N	N
Santhanam and Rahulan 2018 (4)	N	N	N	N	N	N	N	Y	Y	N	N	N
van der Schee *et al.* 1989 (21)	N	N	N	N	N	N	N	Y	N	N	N	N

†=Outcomes were extracted both from this primary publication as well as a linked secondary publication (Fernández-Díaz *et al.* 2017d (22)).
Abbreviations: ACR=American College of Rheumatology, DAS28=Disease Activity Score-28, DLCO=diffusing capacity for carbon monoxide, FEV1=forced expiratory volume, FVC=forced vital capacity, ILD=interstitial lung disease, MMRC=Modified Medical Research Council, N=no; Y=yes.

Table S9. Disease Activity Score 28 (DAS28)

DAS28				
Author & Year	**Intervention(s)**	**Timepoint**	**N**	**DAS28 Mean (SD) or median (IQR)**
Akiyama *et al.* 2016 (5)	Tocilizumab 8 mg/kg q4w ¥ [Interstitial Lung Disease, N/A] [Interstitial Lung Disease, No Exacerbations, Acute, None]	24 wk	71	2.4 (SD ± 1)
		48 wk	71	2.4 (SD ± 1)
		72 wk	71	2.3 (SD ± 1.2)
		96 wk	71	2.2 (SD ± 1.2)
		120 wk	71	2.2 (SD ± 1.1)
	Tocilizumab 8 mg/kg q4w ¥ [Interstitial Lung Disease, N/A] [Interstitial Lung Disease, Exacerbations, Acute]	24 wk	4	4.4 (SD ± 1.8)
Fernández-Díaz *et al.* 2016a (10)	Abatacept 10 mg/kg qmt / 125 mg qw +/- Immunosuppressor ¥	13 wk	30	3.9 (IQR: 2.4 – 4.5)
		26 wk	25	3.3 (IQR: 2.3 – 4.4)
		52 wk	21	3.7 (IQR: 2.4 – 4.6)
Fernández-Díaz *et al.* 2016b (11)	Abatacept 10 mg/kg qmt / 125 mg qw +/- DMARDs ¥	13 wk	55	2.61 (IQR: 2.14 – 4.04)
		26 wk	55	3.1 (IQR: 2.2 – 4.18)
		52 wk	55	3.55 (IQR: 2.3 – 4.4)
		26 wk	32	3.61 (SD ± 0.98)
		52 wk	32	2.89 (SD ± 0.93)
Fernández-Díaz *et al.* 2017a (12)	Tocilizumab 8 mg/kg qmt +/- DMARD ¥	13 wk	12	3.35 (SD ± 1.19)
		26 wk	12	3.23 (SD ± 1.04)
		52 wk	12	2.98 (SD ± 0.95)
Fernández-Díaz *et al.* 2017c (14)	Rituximab 1 g q6mt + Methylprednisolone +/- DMARDs 12mo	13 wk	18	3.21 (SD ± 0.73)
		26 wk	18	3.44 (SD ± 0.87)
		52 wk	18	2.83 (SD ± 0.7)
Fernández-Díaz *et al.* 2018a (15)†	Abatacept ¥ [Bronchiolitis Obliterans or Cryptogenic Organizing Pneumonia]	13 wk	8	2.3 (IQR: 1.9 – 4.4)
		26 wk	9	2.8 (IQR: 1.9 – 3.7)
		52 wk	9	3.1 (IQR: 2.3 – 4.9)
	Abatacept ¥ [Pneumonia, Interstitial, Non-Specific]	13 wk	8	3.1 (IQR: 2.2 – 4.8)
		26 wk	13	3.1 (IQR: 2.6 – 4.6)
		52 wk	10	3.1 (IQR: 2.3 – 3.9)
	Abatacept ¥ [Pneumonia, Interstitial, Usual]	13 wk	17	3 (IQR: 2.2 – 4.8)
		26 wk	14	3.7 (IQR: 2.2 – 4.9)
		52 wk	14	3.8 (IQR: 2.5 – 5.1)
Md Yusof 2017 (6)	Rituximab 1000 mg + Methylprednisolone 100 mg NR cycles (+prn)	52 wk	56	4.07 (SD NR)
DAS28-CRP				

Author & Year	Intervention(s)	Timepoint	N	DAS28-CRP Mean (SD) or median (IQR)
Fernández-Díaz *et al.* 2017b (13)	Rituximab 2 g q6mt + Methylprednisolone 100 mg q6mt +/- DMARD 12mo	13 wk	32	3.70 (SD ± 1.19)
		26 wk	32	3.61 (SD ± 0.98)
		52 wk	32	2.89 (SD ± 0.93)
DAS28-ESR				
Author & Year	**Intervention(s)**	**Timepoint**	**N**	**DAS28-ESR Mean (SD) or median (IQR)**
Detorakis 2016 (3)	(Infliximab 3 mg/kg q8w (3 mg/kg 0, 2, 6wk induction) / Etanercept 50 mg qw / Adalimumab 40 mg qd) + Methotrexate 7.5 mg qw 1yr	52 wk	42	3.27 (SD ± 1.67)
	Methotrexate min 7.5 mg qw +/- Hydroxychloroquine mean 400 mg qd 1yr		44	4.22 (SD ± 1.5)
Fernández-Díaz *et al.* 2018a (15)†	Abatacept 10 mg/kg q4w / 125 mg qw 1yr	13 wk	63	3.57 (SD ± 1.2)
		26 wk	63	3.34 (SD ± 1.25)
		52 wk	63	3.51 (SD ± 1.24)
Mena-Vazquez 2018 (7)	DMARDs 12mo	52 wk	41	2.54 (SD ± 1.12)
Nakashita 2016 (19)	Abatacept 1yr	52 wk	16	2.84 (SD ± 0.83)
Narvaez 2018 (20)	Rituximab mean 4 cycles	Median: 126 wk [Total: 52 wk – 308 wk]	23	2.6 (SD ± 0.7)

Note all timepoints were converted into weeks for ease of comparison.
†=Outcomes were extracted both from this primary publication as well as a linked secondary publication (Fernández-Díaz *et al.* 2017d (22)).
[_]=subgroup
+/-= with or without
¥=length of treatment or dosage not reported
Abbreviations: CRP=C-Reactive Protein, DAS28=Disease Activity Score-28, DMARD=disease-modifying anti-rheumatic drug, ESR=erythrocyte sedimentation rate, IQR=interquartile range, NR=not reported, prn=pro re nata, q4w=every 4 weeks, q8w=every 8 weeks, q6mt=every 6 months, qw=every week, SD=standard deviation, wk=week.

Table S10. Modified Medical Research Council (MMRC) Scale, Dyspnea: Worsening, Stable, Improvement

Author & Year	Intervention(s)	Timepoint	N	Worsening n (%)	Stable n (%)	Improvement n (%)
Fernández-Díaz 2016a (10)	Abatacept 10 mg/kg qmt / 125 mg qw +/- Immunosuppressor ¥	Baseline – 3 mo	34	1 (2.9%)	26 (76.5%)	7 (20.6%)
		Baseline – 6 mo	25	0 (0%)	18 (72%)	7 (28%)
		Baseline – 12 mo	22	1 (4.5%)	14 (63.7%)	7 (31.8%)
Fernández-Díaz 2016b (11)	Abatacept 10 mg/kg qmt / 125 mg qw +/- DMARDs ¥	Baseline – 3 mo	55	1 (1.81%)	45 (81.8%)	9 (16.4%)
		Baseline – 6 mo	55	1 (2.7%)	40 (72.2%)	14 (25%)
		Baseline – 12 mo	55	4 (7.5%)	35 (62.9%)	16 (29.6%)
Fernández-Díaz 2017a (12)	Tocilizumab 8 mg/kg qmt +/- DMARD ¥	Baseline – 3 mo	11	0 (0%)	11 (100%)	0 (0%)
		Baseline – 6 mo	8	1 (13%)	7 (87%)	0 (0%)
		Baseline – 12 mo	11	1 (9%)	8 (73%)	2 (18%)
Fernández-Díaz 2017b (13)	Rituximab 2 g q6mt + Methylprednisolone 100 mg q6mt +/- DMARD 12mo	Baseline – 3 mo	22	0 (0%)	14 (63.64%)	8 (36.36%)
		Baseline – 6 mo	24	0 (0%)	14 (58.33%)	10 (41.67%)
		Baseline – 12 mo	25	1 (4%)	15 (60%)	9 (36%)
Fernández-Díaz 2017c (14)	Rituximab 1 g q6mt + Methylprednisolone +/- DMARDs 12mo	Baseline – 3 mo	15	0 (0%)	10 (67%)	5 (33%)
		Baseline – 6 mo	16	0 (0%)	10 (63%)	6 (37%)
		Baseline – 12 mo	16	0 (0%)	10 (63%)	6 (37%)
Fernández-Díaz 2018a (15)†	Abatacept ¥ [Bronchiolitis Obliterans or Cryptogenic Organizing Pneumonia]	Baseline – 3 mo	16	0 (0%)	13 (81.3%)	3 (18.7%)
		Baseline – 6 mo	15	0 (0%)	11 (73.3%)	4 (26.7%)
		Baseline – 12 mo	8	0 (0%)	6 (75%)	2 (25%)
	Abatacept ¥ [Pneumonia, Interstitial, Non-Specific]	Baseline – 3 mo	16	1 (6.2%)	12 (75%)	3 (18.8%)
		Baseline – 6 mo	15	0 (0%)	12 (76.9%)	3 (23.1%)
		Baseline – 12 mo	10	0 (0%)	7 (70%)	3 (30%)
	Abatacept ¥ [Pneumonia, Interstitial, Usual]	Baseline – 3 mo	27	0 (0%)	18 (65.4%)	9 (34.6%)
		Baseline – 6 mo	24	2 (8.4%)	17 (70.8%)	5 (20.8%)
		Baseline – 12 mo	13	3 (23.1%)	7 (53.8%)	3 (23.1%)
	Abatacept 10 mg/kg q4w / 125 mg qw 1yr	Baseline – 3 mo	63	1 (2%)	44 (70%)	18 (28%)
		Baseline – 6 mo	55	2 (4%)	40 (72%)	13 (24%)
		Baseline – 12 mo	36	4 (11%)	22 (61%)	10 (28%)
Fernández-Díaz 2018b (16)	Abatacept 1yr	Baseline – 12 mo	63	7 (11.4%)	38 (61.1%)	18 (28%)
	Rituximab 1yr		30	1 (4.1%)	19 (62.1%)	8 (26.6%)
	Tocilizumab 1yr		25	1 (5.6%)	20 (78.9%)	4 (15.4%)

†=Outcomes were extracted both from this primary publication as well as a linked secondary publication (Fernández-Díaz *et al.* 2017d (22)).
[_]=subgroup; +/-= with or without; ¥=length of treatment or dosage not reported.
Abbreviations: DMARD=disease-modifying anti-rheumatic drug, MMRC=Modified Medical Research Council, mo=month, NR=not reported, q4w=every 4 weeks, yr = year.

Table S11. Diffusing Capacity for Carbon Monoxide (DLCO): Absolute Change, Percent Change, Single Breath Percent Predicted

DLCO, Change				
Author & Year	**Intervention(s)**	**Timepoint**	**N**	**Mean (SD) or median (IQR)**
Narvaez *et al.* 2018 (20)	Rituximab mean 4 cycles	Median: 29 mo [Total: 12 mo – 71 mo]	23	7.93 (mean, SD NR)
DLCO, % Change				
Author & Year	**Intervention(s)**	**Timepoint**	**N**	**Mean (SD) or median (IQR)**
Md Yusof *et al.* 2017 (6)	Rituximab 1000 mg + Methylprednisolone 100 mg NR cycles (+prn)	Baseline – 12 mo	56	-1.3 (IQR: -8.7 – 6.4)
DLCO, Single Breath % Predicted				
Author & Year	**Intervention(s)**	**Timepoint**	**N**	**Mean (SD) or median (IQR)**
Detorakis *et al.* 2016 (3)	(Infliximab 3 mg/kg q8w (3 mg/kg 0, 2, 6wk induction) / Etanercept 50 mg qw / Adalimumab 40 mg qd) + Methotrexate 7.5 mg qw 1yr	12 mo	42	78.31 (SD ± 20.69)
	Methotrexate min 7.5 mg qw +/- Hydroxychloroquine mean 400 mg qd 1yr		44	79.56 (SD ± 24.97)
van der Schee *et al.* 1989 (21)	Penicillamine 750 mg qd + Prednisone 60-NL mg 6mo < (-) Prednisone median 48mo	≥ 12 mo	5	69 (SD ± 26.46)

All time points were converted to months for ease of comparison.

+/-= with or without

¥=length of treatment or dosage not reported

Abbreviations: DLCO=diffusing capacity for carbon monoxide, IQR=interquartile range, mo=month, NR=not reported, prn=pro re nata, q8w=every 8 weeks, qd=everyday/daily, qw=every week, SD: standard deviation.

Table S12. Diffusing Capacity for Carbon Monoxide (DLCO): Worsening, Stable, Improvement

DLCO, Worsening or Improvement ≥10%						
Author & Year	**Intervention(s)**	**Timepoint**	**N**	**Worsening n (%)**	**Stable n (%)**	**Improvement n (%)**
Fernández-Díaz *et al.* 2016a (10)	Abatacept 10 mg/kg qmt / 125 mg qw +/- Immunosuppressor ¥	Baseline – 3 mo	9	1 (11.2%)	4 (44.4%)	4 (44.4%)
		Baseline – 6 mo	7	3 (42.9%)	3 (42.9%)	1 (14.2%)
		Baseline – 12 mo	8	2 (25%)	5 (62.5%)	1 (12.5%)
Fernández-Díaz *et al.* 2016b (11)	Abatacept 10 mg/kg qmt / 125 mg qw +/- DMARDs ¥	Baseline – 3 mo	55	5 (8.3%)	32 (58.4%)	18 (33.3%)
		Baseline – 6 mo	55	14 (25%)	32 (58.3%)	9 (16.7%)
		Baseline – 12 mo	55	8 (14.3%)	31 (57.1%)	16 (28.6%)
Fernández-Díaz *et al.* 2017a (12)	Tocilizumab 8 mg/kg qmt +/- DMARD ¥	Baseline – 3 mo	2	1 (50%)	1 (50%)	0 (0%)
		Baseline – 6 mo	4	1 (25%)	3 (75%)	0 (0%)
		Baseline – 12 mo	9	0 (0%)	9 (100%)	0 (0%)
Fernández-Díaz *et al.* 2017b (13)	Rituximab 2 g q6mt + Methylprednisolone 100 mg q6mt +/- DMARD 12mo	Baseline – 3 mo	9	1 (11.11%)	8 (88.89%)	0 (0%)
		Baseline – 6 mo	14	2 (14.29%)	10 (71.43%)	2 (14.29%)
		Baseline – 12 mo	20	2 (10%)	15 (75%)	3 (15%)
Fernández-Díaz *et al.* 2017c (14)	Rituximab 1 g q6mt + Methylprednisolone +/- DMARDs 12mo	Baseline – 3 mo	6	1 (17%)	5 (83%)	0 (0%)
		Baseline – 6 mo	3	0 (0%)	1 (33%)	2 (67%)
		Baseline – 12 mo	12	2 (17%)	8 (66%)	2 (17%)
Fernández-Díaz *et al.* 2018a (15)†	Abatacept ¥ [Bronchiolitis Obliterans or Cryptogenic Organizing Pneumonia]	Baseline – 3 mo	2	0 (0%)	1 (50%)	1 (50%)
		Baseline – 6 mo	3	1 (33.3%)	2 (66.7%)	0 (0%)
		Baseline – 12 mo	6	1 (16.7%)	3 (50%)	2 (33.33%)
	Abatacept ¥ [Pneumonia, Interstitial, Non-Specific]	Baseline – 3 mo	4	0 (0%)	4 (100%)	0 (0%)
		Baseline – 6 mo	3	1 (33.3%)	2 (66.7%)	0 (0%)
		Baseline – 12 mo	3	1 (33.3%)	2 (66.7%)	0 (0%)
	Abatacept ¥ [Pneumonia, Interstitial, Usual]	Baseline – 3 mo	7	0 (0%)	5 (71.4%)	2 (28.6%)
		Baseline – 6 mo	5	1 (20%)	3 (60%)	1 (20%)
		Baseline – 12 mo	7	0 (0%)	5 (71.6%)	2 (28.6%)
	Abatacept 10 mg/kg q4w / 125 mg qw 1yr	Baseline – 3 mo	28	0 (0%)	25 (89%)	3 (11%)
		Baseline – 6 mo	22	3 (14%)	16 (72%)	3 (14%)
		Baseline – 12 mo	23	2 (8%)	14 (62%)	7 (30%)
Fernández-Díaz *et al.* 2018b (16)	Abatacept 1yr	Baseline – 12 mo	63	7 (10.4%)	39 (62.6%)	20 (32%)
	Rituximab 1yr	Baseline – 12 mo	30	2 (7.5%)	22 (72%)	8 (25.2%)
	Tocilizumab 1yr	Baseline – 12 mo	25	0 (0%)	23 (93.6%)	2 (9.1%)
DLCO, Any Worsening or Improvement						
Author & Year	**Intervention(s)**	**Timepoint**	**N**	**Worsening n (%)**	**Stable n (%)**	**Improvement n (%)**

Narvaez *et al.* 2018 (20)	Rituximab mean 4 cycles	Median: 29 mo [Total: 12 mo – 71 mo]	23	NR	NR	13 (56%)

All timepoints have been converted to months.
†=Outcomes were extracted both from this primary publication as well as a linked secondary publication (Fernández-Díaz *et al.* 2017d (22)).
[_]=subgroup
+/-= with or without
¥=length of treatment or dosage not reported
Abbreviations: DLCO=diffusing capacity for carbon monoxide, DMARD=disease-modifying anti-rheumatic drug, mo=month, NR=not reported, q4w:every 4 weeks, q6mt=every 6 months, qmt=every month, qw=every week, yr=year.

Table S13. Forced Vital Capacity (FVC): Absolute Change, Percent Change, Percent Predicted

FVC, Change				
Author & Year	**Intervention(s)**	**Timepoint**	**N**	**Mean (SD) or median (IQR)**
Narvaez *et al.* 2018 (20)	Rituximab mean 4 cycles	Median: 29 mo [Total: 12 mo – 71 mo]	23	0.86 (Mean)
FVC, % Change				
Author & Year	**Intervention(s)**	**Timepoint**	**N**	**Mean (SD) or median (IQR)**
Md Yusof *et al.* 2017 (6)	Rituximab 1000 mg + Methylprednisolone 100 mg NR cycles (+prn)	Baseline – 12 mo	56	1.2 (IQR: -6 – 8.6)
FVC, % Predicted				
Author & Year	**Intervention(s)**	**Timepoint**	**N**	**Mean (SD) or median (IQR)**
Chartrand *et al.* 2016 (9)	Rituximab 1000 mg / 375 mg/m^2 ¥ [Medical History, Rheumatoid Arthritis, N / A]	6 mo	15	74.16 (Mean)
Detorakis *et al.* 2016 (3)	(Infliximab 3 mg/kg q8w (3 mg/kg 0, 2, 6wk induction) / Etanercept 50 mg qw / Adalimumab 40 mg qd) + Methotrexate 7.5 mg qw 1yr	12 mo	42	88.48 (SD ± 19.93)
	Methotrexate min 7.5 mg qw +/- Hydroxychloroquine mean 400 mg qd 1yr	12 mo	44	85.18 (SD ± 17.98)
Fischer *et al.* 2013 (17)	Mycophenolate Mofetil NR-3000 mg qd median 897d (++ Prednisone) [Rheumatoid Arthritis]	40 mo	18	74 (Mean)
Santhanam and Rahulan 2018 (4)	Mycophenolate mofetil 2yr [Rheumatoid Arthritis]	6 mo	12	60 (Mean)
		12 mo	12	61 (Mean)
		24 mo	12	62 (Mean)

All timepoints converted to months for ease of comparison.
[_]=subgroup
++=add-on
+/-= with or without
¥=length of treatment or dosage not reported
Abbreviations: d=day, DMARD=disease-modifying anti-rheumatic drug, FVC=forced vital capacity, mo=month, IQR=interquartile range, NR=not reported, prn=pro re nata, q8w=every 8 weeks, qd=everyday/daily, qw=every week, SD=standard deviation, yr=year.

Table S14. Forced Vital Capacity (FVC): Worsening, Stable, Improvement

FVC % Predicted, Worsening or Improvement <10%						
Author & Year	**Intervention(s)**	**Timepoint**	**N**	**Worsening n (%)**	**Stable n (%)**	**Improvement n (%)**
Chartrand *et al.* 2016 (9)	Rituximab 1000 mg / 375 mg/m^2 ¥ [Medical History, Rheumatoid arthritis, N/A] [Rituximab, multiple cycles]	Baseline – 6 mo	9	0 (0%)	NR	3 (33.33%)
FVC % Predicted, Worsening or Improvement >10%						
Author & Year	**Intervention(s)**	**Timepoint**	**N**	**Worsening n (%)**	**Stable n (%)**	**Improvement n (%)**
Chartrand *et al.* 2016 (9)	Rituximab 1000 mg / 375 mg/m^2 ¥ [Medical History, Rheumatoid arthritis, N/A] [Rituximab, multiple cycles]	Baseline – 6 mo	9	2 (22.22%)	NR	4 (44.44%)
FVC, Worsening or Improvement ≥10%						
Author & Year	**Intervention(s)**	**Timepoint**	**N**	**Worsening n (%)**	**Stable n (%)**	**Improvement n (%)**
Fernández-Díaz *et al.* 2016a (10)	Abatacept 10 mg/kg qmt / 125 mg qw +/- Immunosuppressor ¥	Baseline – 3 mo	10	1 (10%)	7 (70%)	2 (20%)
		Baseline – 6 mo	11	2 (18.1%)	5 (45.5%)	4 (36.4%)
		Baseline – 12 mo	12	2 (16.7%)	7 (58.3%)	3 (25%)
Fernández-Díaz *et al.* 2016b (11)	Abatacept 10 mg/kg qmt / 125 mg qw +/- DMARDs ¥	Baseline – 3 mo	55	4 (7.7%)	47 (84.6%)	4 (7.7%)
		Baseline – 6 mo	55	1 (2%)	29 (53.3%)	15 (26.7%)
		Baseline – 12 mo	55	6 (11.1%)	34 (61.2%)	15 (27.7%)
Fernández-Díaz *et al.* 2017a (12)	Tocilizumab 8 mg/kg qmt +/- DMARD ¥	Baseline – 3 mo	2	0 (0%)	2 (100%)	0 (0%)
		Baseline – 6 mo	5	0 (0%)	5 (100%)	0 (0%)
		Baseline – 12 mo	9	1 (12%)	6 (67%)	2 (23%)
Fernández-Díaz *et al.* 2017b (13)	Rituximab 2 g q6mt + Methylprednisolone 100 mg q6mt +/- DMARD 12mo	Baseline – 12 mo	26	3 (11%)	14 (70%)	2 (10%)
		Baseline – 6 mo	12	1 (8.33%)	1 (8.33%)	10 (83.33%)
		Baseline – 12 mo	22	1 (4.55%)	16 (72.73%)	5 (22.73%)
Fernández-Díaz *et al.* 2017c (14)	Rituximab 1 g q6mt + Methylprednisolone +/- DMARDs 12mo	Baseline – 3 mo	10	2 (20%)	7 (70%)	1 (10%)
		Baseline – 6 mo	5	0 (0%)	5 (100%)	0 (0%)
		Baseline – 12 mo	13	0 (0%)	10 (77%)	3 (23%)
Fernández-Díaz *et al.* 2018a (15)†	Abatacept ¥ [Bronchiolitis Obliterans or Cryptogenic Organizing Pneumonia]	Baseline – 3 mo	2	0 (0%)	2 (100%)	0 (0%)
		Baseline – 6 mo	3	0 (0%)	3 (100%)	0 (0%)
		Baseline – 12 mo	7	2 (28.6%)	2 (28.6%)	3 (42.86%)
	Abatacept ¥ [Pneumonia, Interstitial, Non-Specific]	Baseline – 3 mo	4	1 (25%)	3 (75%)	0 (0%)
		Baseline – 6 mo	7	2 (28.6%)	1 (14.3%)	4 (57.1%)
		Baseline – 12 mo	5	0 (0%)	3 (60%)	2 (40%)
	Abatacept ¥	Baseline – 3 mo	12	0 (0%)	10 (83%)	2 (16.7%)

	[Pneumonia, Interstitial, Usual]	Baseline – 6 mo	6	0 (0%)	5 (83.3%)	1 (16.7%)
		Baseline – 12 mo	10	0 (0%)	10 (100%)	0 (0%)
	Abatacept 10 mg/kg q4w / 125 mg qw 1yr	Baseline – 3 mo	33	1 (3%)	30 (91%)	2 (6%)
		Baseline – 6 mo	33	3 (10%)	24 (72%)	6 (18%)
		Baseline – 12 mo	26	NR	19 (72%)	4 (17%)
Fernández-Díaz *et al.* 2018b (16)	Abatacept 1yr	Baseline – 12 mo	63	8 (12.1%)	47 (74.1%)	10 (15.5%)
	Rituximab 1yr		30	2 (5.8%)	24 (81.5%)	4 (14.6%)
	Tocilizumab 1yr		25	4 (14.2%)	20 (80.6%)	2 (6.8%)
FVC, Any Worsening or Improvement						
Author & Year	**Intervention(s)**	**Timepoint**	**N**	**Worsening n (%)**	**Stable n (%)**	**Improvement n (%)**
Narvaez *et al*. 2018 (20)	Rituximab mean 4 cycles	Median: 29 mo [Total: 12 mo – 71 mo]	23	NR	NR	4 (17%)

All timepoints were converted to months for ease of comparison.
†=Outcomes were extracted both from this primary publication as well as a linked secondary publication (Fernández-Díaz *et al.* 2017d (22)).
[_]=subgroup
+/-= with or without
¥=length of treatment or dosage not reported.
Abbreviations: DMARD=disease-modifying anti-rheumatic drug, FVC=forced vital capacity, mo=month, NR=not reported, q4w:every 4 weeks, q6mt=every 6 months, qmt=every month, qw=every week, yr=year.

Table S15. Summary of Available Safety Outcomes

Author & Year	Study Withdrawal	Study Withdrawal due to AE	Serious AE	Severe AE	Abdominal Pain	Diarrhea	Dizziness	Headache	Injection Site Reaction	Leukopenia	Nausea	Pruritus	Rash	Upper Respiratory Tract Infection
Akiyama *et al.* 2016 (5)	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Chamizo-Carmona *et al.* 2018 (8)	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Chartrand *et al.* 2016 (9)	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Detorakis *et al.* 2016 (3)	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Fernández-Díaz *et al.* 2016a (10)	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Fernández-Díaz *et al.* 2016b (11)	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Fernández-Díaz *et al.* 2017a (12)	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Fernández-Díaz *et al.* 2017b (13)	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Fernández-Díaz *et al.* 2017c (14)	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Fernández-Díaz *et al.* 2018a (15)†	Y	Y	N	N	N	N	N	N	Y	N	N	N	N	N
Fernández-Díaz *et al.* 2018b (16)	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Fischer 2013 *et al.* (17)	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Koo *et al.* 2015 (18)	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Md Yusof *et al.* 2017 (6)	N	N	N	Y	N	N	N	N	N	N	N	N	N	N
Mena-Vazquez *et al.* 2018 (7)	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Nakashita *et al.* 2016 (19)	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Narvaez *et al.* 2018 (20)	N	Y	N	Y	N	N	N	N	N	N	N	N	N	N
Santhanam and Rahulan 2018 (4)	N	N	N	N	N	N	N	N	N	N	N	N	N	N
van der Schee *et al.* 1989 (21)	N	N	N	N	N	N	N	N	N	N	N	N	N	N

†=Outcomes were extracted both from this primary publication as well as a linked secondary publication (Fernández-Díaz *et al.* 2017d (22)).
Abbreviations: N=no; Y=yes.

Study Quality Assessment

Study quality assessments were conducted on all 19 studies included in the SLR using the Newcastle-Ottawa Scale (NOS), as all identified studies were non-randomised (**Table S16**). Overall, studies were rated as low or moderate quality, with two studies (10.5%) receiving a final score of 2 (8, 20), seven studies (36.8%) receiving a final score of 3, (3, 10-14, 16) six studies (31.6%) receiving a final score of 4 (4, 7, 9, 17, 18, 21), and four studies (21.1%) receiving a final score of 5 (5, 6, 15, 19). For the NOS Selection criteria, the majority of the studies (12 studies, 63.2%) were allocated only 2 stars (4, 6, 8-13, 16-18). Among these 12 studies, five were not awarded a star for representativeness of the exposed cohort because the studies reported data from a single hospital or did not provide a description (4, 6, 9, 17, 18) and seven did not provide any description on the ascertainment of exposure (8, 10-14, 16). For the Comparability criteria, the majority of the studies (17 studies, 89.5%) were allocated no stars because they did not control for factors such as smoking status, age, sex genetic factors, rheumatoid factor, ACPA, etc. (4, 5, 7-21). Finally, one study (5.3%) (8) was allocated no stars and nine studies (47.4%) (3, 7, 10-14, 16, 20) were allocated one star for the Outcome/Exposure criteria. The study receiving no stars for Outcome/Exposure criteria did not provide any description of ascertainment of exposure between cases and controls and did not provide any statement regarding the non-response rate (8). The nine studies receiving only one star generally provided follow-up periods that were long enough for outcomes to occur (3 months—71 months), but failed to provide any description of outcome assessment and either reported follow-up proportions <90% (10-12, 14, 20) of participants or did not provide a description of follow-up proportions (3, 7, 13, 16).

Table S16. Quality Assessment Summary for NOS

Study	Study Design	Selection	Comparability	Outcome	Final Score
Akiyama *et al.* 2016 (5)	Case-Control	***		**	5
Chamizo-Carmona *et al.* 2018 (8)	Case-Control	**			2
Chartrand *et al.* 2016 (9)	Cohort	**		**	4
Detorakis *et al.* 2016 (3)	Cohort	*	*	*	3
Fernández-Díaz *et al.* 2016a (10)	Cohort	**		*	3
Fernández-Díaz *et al.* 2016b (11)	Cohort	**		*	3
Fernández-Díaz *et al.* 2017a (12)	Cohort	**		*	3
Fernández-Díaz *et al.* 2017b (13)	Cohort	**		*	3
Fernández-Díaz *et al.* 2017c (14)	Cohort	**		*	3
Fernández-Díaz *et al.* 2018a (15)†	Cohort	***		**	5
Fernández-Díaz *et al.* 2018b (16)	Cohort	**		*	3
Fischer 2013 *et al.* (17)	Cohort	**		**	4
Koo *et al.* 2015 (18)	Cohort	**		**	4
Md Yusof *et al.* 2017 (6)	Cohort	**	*	**	5
Mena-Vazquez *et al.* 2018 (7)	Cohort	***		*	4
Nakashita *et al.* 2016 (19)	Cohort	***		**	5
Narvaez *et al.* 2018 (20)	Cohort	*		*	2
Santhanam and Rahulan 2018 (4)	Cohort	**		**	4
van der Schee *et al.* 1989 (21)	Cohort	*		***	4

†=The quality assessment was performed based both on the primary publication as well as a linked secondary publication (Fernández-Díaz *et al.* 2017d (22)).

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