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Supplement 1: Information Retrieval

Data Sources and Searches

Databases searched for relevant primary studies and secondary publications (systematic reviews and HTA reports) were MEDLINE (1946 to February 2017), EMBASE (1974 to February 2017) and the Cochrane Central Register of Controlled Trials (January 2017). The Cochrane Database of Systematic Reviews (Cochrane Reviews), the Database of Abstracts of Reviews of Effects (Other Reviews), and the Health Technology Assessment Database (Technology Assessments) were searched for relevant secondary publications. Search strategies were developed by one information specialist and checked by another.

Search Strategies

Searches in bibliographic databases

1. Embase

Search interface: Ovid

- Embase 1974 to 2017 February 21

The following filters were adopted:

- Systematic review: Wong[1] – High specificity strategy
- RCT: Wong[1] – Strategy minimizing difference between sensitivity and specificity

#	Searches
1	exp Rheumatoid Arthritis/
2	(rheuma* adj6 arthritis).ab,ti.
3	1 or 2
4	(Rituximab* or Abatacept* or Etanercept* or Infliximab* or Adalimumab* or Certolizumab* or Golimumab* or Anakinra* or Tocilizumab*).mp.
5	"recombinant interleukin 1 receptor blocking agent"/
6	or/4-5
7	and/3,6
8	(random* or double-blind*).tw.
9	placebo*.mp.
10	or/8-9
11	(meta analysis or systematic review or MEDLINE).tw.
12	7 and (10 or 11)
13	12 not medline*.cr.
14	13 not (exp animal/ not exp humans/)
15	14 not (Conference Abstract or Conference Review).pt.

#	Searches
16	15 not Editorial.pt.

2. MEDLINE

Search interface: Ovid

- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations February 17, 2017
- Ovid MEDLINE(R) 1946 to February Week 2 2017
- Ovid MEDLINE(R) Daily Update February 17, 2017
- Ovid MEDLINE(R) Epub Ahead of Print February 17, 2017

The following filters were adopted:

- Systematic review: Wong[1] – High specificity strategy
- RCT: Lefebvre [2] – Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity- and precision-maximizing

#	Searches
1	exp Arthritis, Rheumatoid/
2	(rheuma* adj6 arthritis).ab,ti.
3	1 or 2
4	(Rituximab* or Abatacept* or Etanercept* or Infliximab* or Adalimumab* or Certolizumab* or Golimumab* or Anakinra* or Tocilizumab*).mp.
5	"Interleukin 1 Receptor Antagonist Protein"/
6	4 or 5
7	3 and 6
8	randomized controlled trial.pt.
9	controlled clinical trial.pt.
10	randomized.ab.
11	placebo.ab.
12	clinical trial as topic/
13	randomly.ab.
14	trial.ti.
15	or/8-14
16	exp animals/ not humans.sh.
17	15 not 16
18	cochrane database of systematic reviews.jn.

#	Searches
19	(search or MEDLINE or systematic review).tw.
20	meta analysis.pt.
21	or/18-20
22	7 and (17 or 21)
23	22 not (editorial or comment).pt.

3. PubMed

Search interface: NLM

- PubMed – as supplied by publisher
- PubMed – in process
- PubMed – pubmednotmedline

Search	Query
#18	Search (rheuma* [TIAB] AND arthritis [TIAB])
#19	Search (Rituximab OR Abatacept OR Etanercept OR Infliximab OR Adalimumab OR Certolizumab OR Golimumab OR Anakinra OR Tocilizumab)
#20	Search "Interleukin 1 Receptor Antagonist Protein"[Mesh]
#21	Search (clinical trial*[tiab] or random*[tiab] or placebo[tiab] or trial[ti])
#22	Search (search[tiab] or meta analysis[tiab] or MEDLINE[tiab] or systematic review[tiab])
#23	Search (#18 AND (#19 OR #20) AND (#21 OR #22))
#24	Search (#23 NOT medline[sb])

4. The Cochrane Library

Search interface: Wiley

- Cochrane Database of Systematic Reviews: Issue 2 of 12, February 2017
- Database of Abstracts of Reviews of Effect: Issue 2 of 4, April 2015
- Cochrane Central Register of Controlled Trials: Issue 1 of 12, January 2017
- Health Technology Assessment Database: Issue 4 of 4, October 2016

ID	Search
#1	[mh "Arthritis, Rheumatoid"]
#2	(rheuma* near/6 arthritis):ti,ab
#3	#1 or #2

ID	Search
#4	Rituximab* or Abatacept* or Etanercept* or Infliximab* or Adalimumab* or Certolizumab* or Golimumab* or Anakinra* or Tocilizumab*
#5	[mh "Interleukin 1 Receptor Antagonist Protein"]
#6	#4 or #5
#7	#3 and #6 Publication Year from 2012 to 2016, in Cochrane Reviews (Reviews and Protocols) and Trials
#8	rheuma* near/6 arthritis
#9	(#1 or #8) and #6 Publication Year from 2012 to 2016, in Other Reviews and Technology Assessments

Searches in study registries

1. ClinicalTrials.gov

Provider: U.S. National Institutes of Health

- URL: http://www.clinicaltrials.gov
- Type of search: Expert Search

Suchstrategie
Rheumatoid arthritis AND (Abatacept OR BMS 188667 OR Adalimumab OR ABTD2E7 OR D2E2 OR Anakinra OR rHIL-1ra OR Certolizumab OR CDP 870 OR Etanercept OR TNFR:Fc OR WAY_143050 OR SB4 OR Golimumab OR cnto 148 OR rTNV148B OR SCH 900259 OR Infliximab OR SB2 OR cA2 OR CT-P13 OR Rituximab OR RO45-2294 OR CT-P10 OR Tocilizumab OR RO4877533 OR myeloma receptor antibody)

2. EU Clinical Trials Register

Provider: European Medicines Agency

- URL: https://www.clinicaltrialsregister.eu/ctr-search/search
- Type of search: Basic Search

Suchstrategie
(Abatacept OR "BMS 188667" OR "BMS188667" OR Adalimumab OR ABTD2E7 OR D2E2 OR "ABP 501" OR ABP501 OR Anakinra OR "rHIL-1ra" OR "rHIL1ra" OR Certolizumab OR "CDP 870" OR "CDP870" OR Etanercept OR "TNFR:Fc" OR "WAY_143050" OR SB4 OR Golimumab OR "cnto 148" OR "cnto148" OR "rTNV148B" OR "SCH 900259" OR "SCH900259" OR Infliximab OR SB2 OR cA2 OR "CT-P13" OR "CTP13" OR Rituximab OR "RO45-2294" OR "RO452294" OR "CT-P10" OR "CTP10" OR Tocilizumab OR RO4877533 OR "myeloma receptor antibody") AND arthritis

3. International Clinical Trials Registry Platform Search Portal

Provider: World Health Organization

- URL: http://apps.who.int/trialsearch/
- Type of search: Standard Search

Suchstrategie
Abatacept AND arthritis OR "BMS 188667" AND arthritis OR "BMS188667" AND arthritis OR Adalimumab AND arthritis OR ABTD2E7 AND arthritis OR D2E2 AND arthritis OR "ABP 501" AND arthritis OR Anakinra AND arthritis OR "rHIL-1ra" AND arthritis OR "rHIL1ra" AND arthritis OR Certolizumab AND arthritis OR "CDP 870" AND arthritis OR "CDP870" AND arthritis OR Etanercept AND arthritis OR "TNFR:Fc" AND arthritis OR "WAY_143050" AND arthritis OR SB4 AND arthritis OR Golimumab AND arthritis OR "cnto 148" AND arthritis OR "cnto148" AND arthritis OR "rTNV148B" AND arthritis OR "SCH 900259" AND arthritis OR "SCH900259" AND arthritis OR Infliximab AND arthritis OR SB2 AND arthritis OR "CT-P13" AND arthritis OR "CTP13" AND arthritis OR Rituximab AND arthritis OR "RO45-2294" AND arthritis OR "RO452294" AND arthritis OR "CT-P10" AND arthritis OR "CTP10" AND arthritis OR Tocilizumab AND arthritis OR RO4877533 AND arthritis OR "myeloma receptor antibody" AND arthritis

4. Clinical Study Report (CSR) Synopses

Provider: AbbVie

- URL: https://www.abbvie.com/our-science/clinical-trials/clinical-trials-data-and-information-sharing/clinical-study-report-csr-synopses.html

Suchstrategie
List of products alphabetized by generic name: Adalimumab – Humira Studied Indications or Disease: Rheumatoid Arthritis

5. Our Clinical Studies

Provider: UCB

- URL: http://www.ucb.com/our-science/Our-clinical-studies

Suchstrategie
Compounds / Cimzia (certolizumab pegol) Disease area studied / Rheumatoid Arthritis

6. Trials

Provider: Yale University

- URL: http://yoda.yale.edu/browsetrials/generic-name
- Type of search: Advanced Search

Suchstrategie
Trials By Generic Name / Advanced Search / OR Filter by: / Condition Studied / Arthritis, Rheumatoid

7. Clinical Trial Results

Provider: Bristol-Myers Squibb

- URL: http://www.bms.com/clinical_trials/results/Pages/therapeutic_areas.aspx

Suchstrategie
Select a therapeutic area: Immunoscience / Disease Area Studied / Rheumatoid Arthritis Select a therapeutic area: Immunoscience / Disease Area Studied / Undifferentiated Arthritis

Biologics, doses and treatment regimens considered in the systematic review

Supplement Table 1: Doses and treatment regimens considered in the systematic review

Biologic* (manufacturer)	**Dose and treatment regimen**
Abatacept (Bristol-Myers Squibb GmbH & Co. KGaA)	~ 10 mg per kg body weight, on day 1, 15 and 29, then every 28 days; i. v. injection
	125 mg weekly; s. c. injection
Adalimumab (AbbVie Deutschland GmbH & Co. KG‡)	40 mg every 2 weeks; s. c. injection
Anakinra (Swedish Orphan Biovitrum GmbH)	100 mg daily; s. c. injection
Certolizumab pegol (UCB Pharma GmbH)	400 mg in week 0, 2 and 4, then 200 mg every 2 weeks; s. c. injection
	2 x 200 mg in week 0, 2 and 4, then 200 mg every 2 weeks; s. c. injection
Etanercept (Pfizer Deutschland GmbH‡)	50 mg weekly; s. c. injection
	2 x 25 mg weekly; s. c. injection
Golimumab (MSD SHARP & DOHME GmbH)	50 mg every 4 weeks; s. c. injection
Infliximab (MSD SHARP & DOHME GmbH§)	3 mg per kg body weight in week 0, 2, 6, then every 4 weeks; i. v. injection
Tocilizumab (Roche Pharma AG)	8 mg per kg body weight every 4 weeks; i. v. injection

i. v. = intravenous; s. c. = subcutaneous; TNF = tumor necrosis factor

* Rituximab is not considered because it is not approved for the patient population of interest of the underlying research question, but only after failure of at least 1 TNFα inhibitor. † Further companies were contacted for data on individual studies with this biologic (Lilly Deutschland GmbH, Merck Serono GmbH, Pfizer Deutschland GmbH) or data on biosimilars (Amgen Europe B. V.). ‡ Further companies were contacted for data on individual studies with this biologic (AstraZeneca GmbH) or data on biosimilars (Biogen GmbH, Hexal AG). § Further companies were contacted for data on biosimilars (Biogen GmbH, Mundipharma GmbH, Pfizer Deutschland GmbH).

Source documents available for included studies

Supplement Table 2: Source documents available for studies included in the systematic review

Biologic treatment	Study	Journal publication available	Results reported in clinical trial registry	Clinical study report provided by manufacturer	Additional analyses provided by manufacturer
Placebo-controlled studies					
Abatacept	AIM	yes [3-5]	yes [6-8]	yes [9]	yes [10]
	ASSURE	yes [11]	yes [12-14]	yes [15]	n/a*
	ATTEST	yes [16 17]	yes [18-20]	yes [21]	yes [22]
	IM101071	yes [23]	yes [24 25]	yes [26]	yes [27]
	IM101100	yes [28-33]	yes [34-36]	yes [37]	yes [38]
	IM101124	no	yes [39-41]	yes [42]	yes [43]
Adalimumab	ARMADA	yes [44]	no	yes [45]	yes [46]
	August II	yes [47]	yes [48]	yes [49]	yes [50]
	DE019	yes [51-54]	yes [55]	yes [56]	yes [46]
	IM133001	yes [57]	no	no†	no†
	M02-556	yes [58 59]	no	yes [60]	yes [46]
	ORAL STANDARD	yes [61-64]	yes [65 66]	yes [67]	yes [68 69]
	RA-BEAM	yes [70]	yes [71]	yes [72]	yes [73]
	RADAR	no	yes [74]	yes [75]	yes [46] ‡
	STAR	yes [76 77]	no	yes [78]	yes [46 79]
Anakinra	990145	yes [80]	no	yes [81]	yes [82]
	990757	yes [83-85]	no	yes [86]	yes [82 87]
	20000198	no	no	yes [88]	yes [82]
Certolizumab pegol	CERTAIN	yes [89]	yes [90-92]	yes [93]	yes [94]
	RA0025	no	yes [95]	yes [96]	yes [97 98]
	RAPID 1	yes [99-107]	yes [108 109]	yes [110]	yes [97]
	RAPID 2	yes [107 111 112]	yes [113 114]	yes [115]	yes [97]
Etanercept	0881A1-4532	yes [116 117]	yes [118]	yes [119 120]	yes [121 122]
	16.0014	yes [123 124]	no	yes [125]	yes [121 126]
	ENCOURAGE	yes [127]	no	no§	no§
	RACAT	yes [128 129]	yes [130]	no§	no§
	TEMPO	yes [131-144]	no	yes [145-147]	yes [148 149]
Golimumab	C0524T28	yes [150]	yes [151 152]	yes [153 154]	yes [155]
	GO-FORTH	yes [156-159]	no	yes [160]	yes [161]
	GO-FORWARD	yes [162-173]	yes [174-176]	yes [177]	yes [178]
Infliximab	ATTRACT	yes [171 179-185]	yes [186]	yes [187-189]	yes [190]
	P04280	yes [191]	no	yes [192]	no‖
	SWEFOT	yes [193-205]	no	no§	no§

Biologic treatment	Study	Journal publication available	Results reported in clinical trial registry	Clinical study report provided by manufacturer	Additional analyses provided by manufacturer
Tocilizumab	CWP-TCZ301	yes [206]	no	yes [207]	no‖
	LITHE	yes [208-215]	yes [216]	yes [217-220]	yes [221 222]
	MEASURE	yes [223 224]	yes [225]	yes [226]	yes [227]
	OPTION	yes [214 228 229]	yes [230]	yes [231]	yes [232 233]
	PORTRAIT	no	yes [234]	yes [235]	yes [236]¶
	ROSE	yes [237 238]	yes [239]	yes [240]	yes [241]
	TOWARD	yes [214 242 243]	yes [244]	yes [245]	yes [246]
	TRACE	no	yes [247]	yes [248]	yes [249 250]
Direct comparisons					
Abatacept; Adalimumab	AMPLE	yes [251-256]	yes [257 258]	yes [259 260]	yes [261]
Adalimumab; Certolizumab pegol	EXXELERATE	yes [262-264]	yes [265 266]	yes [267]	yes [97]
Adalimumab; Etanercept	RED SEA	yes [268]	no	no§	no§
Etanercept; Tocilizumab	WA25204	no	yes [269]	yes [270]	n/a**

Studies shown in grey were excluded from the network meta-analyses because results were not available for the relevant subpopulation (RADAR, PORTRAIT), because of missing linkage to the treatment network (0881A1-4532, RACAT) or due to insufficient similarity (SWEFOT, RED SEA, WA25204).

* Additional analyses were not required because all outcomes available from individual patient data were already included in the clinical study report; † a German contact for request of documents and additional analyses could not be identified; ‡ the manufacturer provided data for the overall study population; for the subpopulation required for the systematic review data were not requested because of the small number of patients included in this population (< 10 patients in both study arms); § investigator-initiated trial (authors did not provide clinical study report or additional analyses); ‖ the manufacturer replied that they could not provide the analyses because they had no access to study data; ¶ the manufacturer provided data for the overall study population; for the subpopulation required for the systematic review the manufacturer replied that a reliable reanalysis for the subpopulation was not possible because a corresponding subgroup analysis was not planned; ** additional analyses were not required because the study was excluded due to insufficient similarity

n/a = not applicable

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