The Hospital for Sick Children

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THE USE OF BIOLOGIC RESPONSE MODIFIERS IN POLYARTICULAR COURSE JUVENILE IDIOPATHIC ARTHRITIS – A SYSTEMATIC REVIEW UPDATE

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CONFLICTS OF INTEREST

The authors declare that they do not have any conflicts of interest.

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ABSTRACT

Objective

To systematically review the clinical efficacy and safety evidence of biologic drugs used to treat the polyarticular subtype of juvenile idiopathic arthritis (JIA).

Methods

The peer-reviewed and grey literature were searched between 2000 and 2011 for randomized controlled trials, non-randomized comparative studies, and non-comparative observational cohort studies. The drugs evaluated included etanercept, infliximab, adalimumab, abatacept, anakinra, and ritixumab. Eligible studies included twenty or more patients with JIA, the majority of whom had polyarticular course disease. Outcomes of interest were disease improvement defined by the American College of Rheumatology criteria for Pediatrics, disease flares, rates of inactive disease, remissions, discontinuations, and adverse events (severe and non-severe).

Results

Thirty five studies were included (15 new and 20 from the 2008 review), the majority of which evaluated the efficacy and safety of etanercept. Six randomized controlled trials in patients with polyarticular JIA were identified, including one each for etanercept, infliximab, adalimumab, abatacept, and anakinra, and one looking at infliximab as a first-line therapy. There was strong evidence to support the efficacy and safety of biologics over the short-term, but a lack of long-term data for treatments other than etanercept. Several high-quality, large, and ongoing etanercept registries confirmed the efficacy and safety of etanercept over the long-term. Important differences in the study designs, inconsistent reporting of patient outcomes, and variations in the methods used to define and measure patient response prevented indirect comparisons across studies.

Conclusions

Current evidence shows that a short-term improvement in treatment response is achieved when patients with polyarticular JIA with an inadequate response to conventional treatment are treated with biologics. Long-term effectiveness data, however, are sparse with many unanswered questions surrounding switches between biologics, handling patients that achieve disease remission, and long-term safety concerns. The field of JIA outcomes research is in need of clearly defined outcome measures that are relevant to clinical practice, and uniform reporting of outcomes across studies. Study designs other than RCTs may be important in understanding the role of biologics in JIA over the long-term.

1 OBJECTIVE

As new biologics with indications for juvenile idiopathic arthritis (JIA) continue to be introduced, uncertainties regarding the long-term clinical benefits and safety outcomes persist. In recent years extensive findings from observational and long-term follow-up studies have been reported. These studies may lead to a further understanding of the long term clinical benefit and safety of biologic drugs in JIA. The purpose of this report was to update the systematic review carried out in 2010[1] and summarize new clinical data which could be used to evaluate the efficacy and safety of biologic therapies used to treat polyarticular JIA.

2 METHODS

2.1 Inclusion criteria

2.1.1 Study types

All randomized controlled trials (RCT), non-randomized comparative studies, observational cohort designs, and patient registries were eligible for inclusion. Health technology assessments reports, meta-analyses, and systematic reviews were also eligible. Multiple publications of the same study or cohort of patients were included if outcomes were reported for different patient sub-groups or different study phases or follow-up periods. Unlike the previous review, conference abstracts were not eligible for inclusion in the update.

2.1.2 Study populations

The population of interest was patients with polyarticular-course JIA of any age who presented with an inadequate response to optimized non-biologic or biologic disease modifying anti-rheumatic drug (DMARD) regimens. Eligible studies included those with twenty or more patients with JIA of whom all or the majority had polyarticular course disease.

2.1.3 Interventions

All clinical studies of biologic drugs including etanercept, infliximab, anakinra, adalimumab, abatacept, tocilizumab and rituximab were eligible for inclusion. Studies that presented results for a class of drugs, e.g. different anti-tumor necrosis factor alpha (TNF-α) drugs evaluated as one group, rather than individual drugs, were excluded.

2.1.4 Outcomes

Primary outcomes

The primary outcomes evaluated were the American College of Rheumatology (ACR) criteria for disease improvement and disease flares as defined previously.[1]

Secondary outcomes

Secondary outcomes evaluated were rates of inactive disease, disease remission, drug withdrawal and discontinuation (due to intolerance, lack of efficacy, or patient preference). Safety was evaluated from reports of severe and non-severe adverse drug reactions (infectious or non-infectious). Changes in concomitant DMARD and glucocorticoid use, quality of life, days missed from school or daily activities, radiographic evidence of disease progression, development of antibodies and levels of cellular markers of inflammation were not summarized in the updated systematic review.

Studies that did not report at least one of the primary or secondary outcomes of interest described above were excluded.

2.2 Literature searches

The peer reviewed and grey literature was searched from January 2009 to December 2011 as described previously.[1] Reference lists of identified articles were also hand-searched for eligible publications.

2.3 Study Selection

The titles and abstracts of all publications identified through the systematic literature search were reviewed for eligibility by two researchers and the full-texts of all potentially eligible articles were retrieved. Articles in English, French, Portuguese, German, Slovak, Spanish, and Italian were included. Google translate was used to extract data from studies written in German, Spanish and Italian.

2.4 Data extraction

Data describing the study design, population, interventions, and efficacy and safety outcomes were extracted from eligible articles and summarized for each study. When possible, total numbers of patients achieving a desired primary or secondary outcome (described above) were

extracted from per protocol analyses. Short- and long-term ACR 30, 50, and 70 results were reported, while long-term results based on the most recent follow-up were reported for disease flares, disease remissions, drug discontinuations, and safety. For safety outcomes, the total number of events and the total number of patients were extracted for each outcome when possible. For non-analytic literature reviews of published studies, data were extracted from the original study publications. When possible, data reported exclusively in conference abstracts were replaced by data from the published full-text.

2.5 Quality appraisal

All RCTs were subjected to quality appraisal according to the Jadad criteria[2] and all observational cohort studies, including those that were identified during in the previous systematic review, were appraised using a modified version of the critical appraisal skills program (CASP) tool.[3] The modified CASP tool included only the detailed questions as well as one question about the believability of results. All included studies were also assigned a grade ranging from 1a for high quality systematic reviews to 4 for poor quality cohort and case-control studies based on the Oxford Center for Evidence-based Medicine levels of evidence.[4]

3 RESULTS

3.1 Literature search

The update of the systematic review identified 15 new publications, in addition 23 which were included in the previous report.[1] Three of the previously identified publications[5-7] were excluded from the update as they were conference abstracts and data from five previously included conference abstracts were replaced by data reported in the full-text publications.[8-12] In total, 35 studies published between 2000 and 2011 met the modified inclusion criteria.

3.2 Comparative studies

The design characteristics for all comparative studies are summarized in Table 1. One new RCT was identified (ACUTE-JIA) that compared three arms of treatment: infliximab + MTX, MTX alone, and MTX, sulphasalazine and hydroxychloroquine in combination.[13] Patients in the ACUTE-JIA study were DMARD and systemic corticosteroid-naïve, with early onset (less than 6 months) polyarticular-course JIA.[13] RCTs identified in the previous review included one each for etanercept,[14] infliximab,[15] adalimumab,[16] abatacept,[17] and anakinra.[18] Two large, non-

randomized comparative studies were also added (reported previously as conference abstracts). The first compared etanercept + MTX with etanercept alone or MTX alone[8] and the second compared etanercept alone with etanercept + MTX.[9] The baseline characteristics of patients included in each comparative study can be found in Table 2.

3.3 Non-comparative studies

The design characteristics for all non-comparative studies are summarized in Table 3. A total of 17 new non-comparative, observational studies were added during the update, resulting in a total of 27 included non-comparative studies; 17 for etanercept,[11,19-22,25-36] 3 for infliximab,[23,37,38] 4 for etanercept or infliximab,[12,39-41] and one each for adalimumab,[42] abatacept,[24] and rituximab.[43] Five studies reported results from the open-label extension phases of RCTs for etanercept,[20-22] infliximab,[44] and abatacept.[24] Nine studies reported results from patient registries in the Netherlands,[11] France,[36] Germany,[19,30] Britain,[28] Poland,[29] and Switzerland.[40] Two studies reported switches between anti-TNF-α drugs.[12,41] The remaining studies were a mix of prospective and retrospective studies, including one report on the efficacy and safety of rituximab in patients with severe refractory JIA.[43] The baseline characteristics of patients in each comparative study can be found in Table 4.

3.4 Quality appraisal

Results from the Jadad quality appraisal can be found in Appendix 1. Compared to the five original RCTs, the ACUTE-JIA trial was of lower quality according to the Jadad criteria.[2] Results from the CASP quality appraisal can be found in Appendix 2. Both non-randomized comparative studies of etanercept[8,9] were of high quality according to the modified CASP appraisal. Reports from the open-label extension phases of the etanercept RCT[20-22] were of lower quality than other open-label extension studies. British[28] and Swiss[40] registry reports were found to be of the lowest quality, while reports from all other patient registries were consistent with the quality of evidence reported for phase three extensions. The rituximab study[43] was also of high-quality according to the CASP domains evaluated.

Table 1 Comparative study design characteristics

Evidence Grade	Source of funding	Author, Year	Design	Study Drug	Phase 1			Phase 2			Phase 3[b]	
					Comparator(s)	Duration (months)	n	Comparator	Duration (months)	n (active/ control)	Duration (months)	N
2b	Industry	Giannini, 2009[8]	North American registry	Etanercept	Etanercept + MTX; MTX	36	594	N/A	N/A	N/A	N/A	N/A
2b	Industry	Horneff, 2009[9]	Comparative open-label[a]	Etanercept	Etanercept + MTX	23	604	N/A	N/A	N/A	N/A	N/A
1b	Industry	Lovell, 2000[14]	RCT	Etanercept	None	3	69	Placebo	4	51 (25/26)	N/A	N/A
1b	Industry	Ruperto, 2007[15]	RCT	Infliximab 3mg/kg + MTX	Placebo + MTX	3.5	122	Infliximab 6mg/kg + MTX	7.5	122 (62/60)	N/A	N/A
2b	Funding Agency	Tynjala, 2011[13]	RCT	Infliximab + MTX	MTX; COMBO	13.5	60	N/A	N/A	N/A	N/A	N/A
1b	Industry	Ilowite, 2009[18]	RCT	Anakinra ± MTX	None	3	86	Placebo ± MTX	4	50 (25/25)	12	44
1b	Industry	Lovell, 2008[16]	RCT	Adalimumab ± MTX	None	4	171	Placebo ± MTX	8	133 (68/65)	12	128
1b	Industry	Ruperto, 2008[17]	RCT	Abatacept ± MTX	None	4	190	Placebo ± MTX	6	122 (60/62)	N/A	

Randomized controlled trials and non-randomized studies are reported. Abbreviations: N/A = not applicable; MTX = methotrexate; n = sample size; COMBO = combination therapy (methotrexate, sulphasalazine and hydroxychloroquine)

[a] based on data from the German registry[19]

[b] Open label extension (phase 3) results reported in separate publications for etanercept,[20-22] infliximab, [23] and abatacept.[24] See non-comparative study design characteristics for details (Table 3).

Table 2 Comparative study baseline patient characteristics

Author, Year	Design	Study drug(s)	n	Mean age, years	Female sex, n (%)	Type of onset JIA, n (%)			Mean duration of JIA, years	RF positive, n (%)	Previous MTX or DMARD, n (%)	Concomitant MTX, n (%)
						Polyar-ticular	Systemic	Other				
Giannini, 2009[8]	Open-label registry	MTX	197	9.0	145 (74%)	184 (93%)	13 (7%)	0 (0%)	1.7	34 (17%)	192 (98%)	N/A
		ETN	103	10.8	83 (81%)	95 (92%)	8 (8%)	0 (0%)	4.8	14 (14%)	89 (86%)	0 (0%)
		ETN + MTX	294	10.1	214 (73%)	256 (87%)	15 (5%)	23 (8%)	3.4	69 (24%)	294 (100%)	294(100%)
Horneff, 2009[9]	Comparative registry	ETN alone	100	13.1	58 (58%)	27 (27%)	8 (8%)	65 (65%)	5.5	3 (3%)	100 (100%)	0 (0%)
		ETN + MTX	504	12.5	345 (67%)	223 (43%)	57 (11%)	232 (46%)	4.9	65 (13%)	504 (100%)	504(100%)
Lovell, 2000[14]	RCT	ETN (phase 1)	69	10.5	43 (62%)	40 (58%)	22 (32%)	7 (10%)	5.9	15 (22%)	69 (100%)	0 (0%)
		ETN vs. placebo (phase 2)	51	10.6	34 (67%)	31 (61%)	17 (33%)	3 (6%)	5.8	12 (24%)	51 (100%)	0 (0%)
Tynjala, 2011[13]	RCT	IFX + MTX	19	10.5	13 (68%)	18 (95%)	0 (0%)	1 (5%)	1.5	0 (0%)	0 (0%)	19 (100%)
		COMBO	20	8.3	14 (70%)	17 (85%)	0 (0%)	3 (15%)	2.3	1 (5%)	0 (0%)	N/A
		MTX	20	10.1	11 (55%)	15 (75%)	0 (0%)	5 (25%)	1.8	0 (0%)	0 (0%)	N/A
Ruperto, 2007[15]	RCT	IFX + MTX (phase 1)	60	11.3	NR	36 (60%)	11 (18%)	13 (22%)	4.2	13 (22%)	60 (100%)	60 (100%)
		IFX + MTX vs. placebo + MTX (phase 2)	62	11.1	NR	38 (62%)	8 (13%)	15 (25%)	3.6	14 (24%)	62 (100%)	62 (100%)
Ilowite, 2009[18]	RCT	ANA (phase 1)	86	12.0	63 (73%)	62 (72%)	15 (17%)	9 (10%)	4.7	NR	86 (100%)	67 (78%)
		ANA (phase 2)	50	11.0	15 (60%)	33 (66%)	11 (22%)	6 (12%)	4.1	NR	50 (100%)	41 (82%)
		ANA (phase 3)	44	12.0	31 (70%)	29 (66%)	10 (23%)	5 (11%)	4.8	NR	44 (100%)	38 (86%)
Lovell, 2008[16]	RCT	ADA (phase 1)	86	11.1	67 (78%)	86 (100%)	0 (0%)	0 (0%)	3.6	18 (21%)	18 (21%)	0 (0%)
		ADA + MTX (phase 1)	85	11.4	68 (80%)	85 (100%)	0 (0%)	0 (0%)	4.0	19 (23%)	85 (100%)	85 (100%)
		ADA vs. placebo (phase 2)	133	11.2	103 (77%)	133 (100%)	0 (0%)	0 (0%)	3.9	22 (17%)	87 (65%)	85 (64%)
Ruperto, 2008[17]	RCT	ABA (phase 1)	190	12.4	137 (72%)	122 (64%)	37 (20%)	30 (16%)	4.4	41 (22%)	190 (100%)	NR
		ABA vs. placebo (phase 2)	122	12.3	87 (71%)	80 (66%)	23 (19%)	18 (15%)	3.8	31 (25%)	122 (100%)	NR

Abbreviations: RCT = randomized controlled trial; MTX = methotrexate; ETN = etanercept; IFX= infliximab; ANA = anakinra; ADA = adalimumab; ABA = abatacept; COMBO = combination therapy (methotrexate, sulphasalazine and hydroxychloroquine); RF = rheumatoid factor; n= sample size; JIA = juvenile idiopathic arthritis; NR = not reported

Table 3 Non-Comparative study design characteristics

Evidence grade	Source of funding	Author, Year	Design	Study drug(s)	Duration (months)	n
4	Industry	Mori, 2011[25]	Prospective observational	Etanercept	24	22
2b	Industry	Papsdorf, 2011[26]	Prospective observational[a]	Etanercept ± DMARDs	NR	787
4	NR	Sevcic, 2011[27]	Prospective observational	Etanercept ± MTX	12	72
4	Industry	Southwood, 2011[28]	British registry	Etanercept ± MTX	23 (mean)	434
2b	Industry	Zuber, 2011[29]	Polish registry	Etanercept ± MTX	42 (efficacy); 72 (safety)	188
4	Industry; Public Funding Agency	Otten, 2010[30]	Prospective observational[b]	Etanercept ± MTX	15	179
4	Industry; Public Funding Agency	De Inocencio, 2009[31]	Retrospective chart review	Etanercept ± MTX	12	55
4	NR	Halbig, 2009[32]	Prospective observational[a]	Etanercept ± MTX	24	114
4	Industry	Horneff, 2009b[33]	Open label observational[a]	Etanercept 0.8mg/kg ± MTX	3	20
2b	Public Funding Agency	Prince, 2009[11]	Dutch registry	Etanercept ± MTX	75	146
2b	Industry	Lovell, 2008[21]	Open label extension[c]	Etanercept ± MTX	96	58
4	Public Funding Agency	Nielsen, 2008[34]	Prospective observational	Etanercept ± MTX	12	40
2b	Industry	Lovell, 2006[22]	Open label extension[c]	Etanercept ± MTX	48	58
4	NR	Mori, 2005[35]	Prospective observational	Etanercept ± MTX	3	22
2b	Industry	Horneff, 2004[19]	German registry	Etanercept ± MTX	30	322
2b	Industry	Lovell, 2003[20]	Open label extension[c]	Etanercept ± MTX	24	58
2b	NR	Quartier, 2003[36]	French registry	Etanercept ± MTX	15	61
2b	Industry	Ruperto, 2010[23]	Open label extension[d]	Infliximab + MTX	48	78
4	NR	De Marco, 2007[37]	Prospective observational	Infliximab ± MTX	36	78
4	NR	Gerloni, 2005[38]	Prospective observational	Infliximab + MTX	12	24
4	NR	Lamot, 2011[39]	Retrospective chart review	Etanercept + MTX or Infliximab + MTX	24	41
4	Industry	Sauvain, 2010[40]	Swiss registry	Etanercept or Infliximab ± MTX	24	106
4	Funding Agency	Tynjala, 2009[12]	Retrospective chart review	Etanercept or Infliximab	48	209
4	NR	Gerloni, 2008[41]	Prospective observational	Etanercept or Infliximab	72	163

				or switch		
4	NR	Trachana, 2011[42]	Prospective observational	Adalimumab ± MTX	60	26
2b	Industry	Ruperto, 2010[24]	Open label extension[e]	Abatacept ± MTX	21	153
2b	NR	Alexeeva, 2011[43]	Prospective observational	Rituximab + MTX	24	55

Includes observational, registries, and open-label extension studies. Abbreviations: MTX = methotrexate; DMARD = disease modifying anti-rheumatic drug; n = sample size; NR = not reported

[a] based on data from the German registry [19]

[b] based on data from the Dutch registry [11]

[c] open label extension (phase 3) of the etanercept RCT [14]

[d] open label extension (phase 3) of the infliximab RCT [15]

[e] open label extension (phase 3) of the abatacept RCT [17]

Table 4 Non-comparative study baseline patient characteristics

Author, Year	Design	Study drug(s)	n	Mean age, years	Female, n (%)	Type of onset JIA, n (%)			Mean duration of JIA, years	RF positive, n (%)	Previous MTX or DMARD, n (%)	Concomitant MTX, n (%)
						Polyar-ticular	Systemic	Other				
Mori, 2011[25]	Prospective observational	ETN	22	11.4	18 (82%)	19 (86%)	1 (5%)	2 (9%)	4.7	NR	22 (100%)	0 (0%)
Papsdorf, 2011[26]	Prospective observational[a]	ETN ± MTX	787	12.5	515 (65%)	310 (39%)	102 (13%)	377 (48%)	5.1	80 (10%)	787 (100%)	567 (72%)
Sevcic, 2011[27]	Prospective observational	ETN ± MTX	72	12.9	50 (69%)	42 (58%)	6 (8%)	24 (33%)	7.4	4 (6%)	72 (100%)	Yes (NR)
Southwood, 2011[28]	British registry	ETN ± MTX	434	12.0[g]	295 (68%)	NR	68 (16%)	NR	NR	NR	438 (100%)	279 (57%)
Zuber, 2011[29]	Polish registry	ETN ± MTX	188	10.0	123 (65%)	92 (49%)	28 (15%)	68 (36%)	4.3	13 (7%)	188 (100%)	39 (21%)
Otten, 2010[30]	Prospective observational[b]	ETN ± MTX	179	5.8	126 (70%)	84 (47%)	42 (24%)	51 (27%)	NR	NR	179 (100%)	Yes (NR)
De Inocencio, 2009[31]	Retrospective chart review	ETN responders	55	11.0	36 (66%)	14 (25%)	12 (22%)	29 (53%)	4.8	NR	55 (100%)	Yes (NR)
		ETN non-responders	16	11.6	7 (44%)	7 (44%)	7 (44%)	2 (12%)	7.1	NR	16 (100%)	Yes (NR)
Halbig, 2009[32]	Prospective observational[a]	ETN ± MTX	437[f]	12.1	306 (70%)	191 (44%)	76 (17%)	171 (39%)	5.1	53 (12%)	437 (100%)	362 (83%)
Horneff, 2009b[33]	Open label observational[a]	ETN ± MTX	20	12.9	16 (80%)	16 (80%)	0 (0%)	6 (20%)	4.1	4 (20%)	20 (100%)	12 (60%)
Prince, 2009[11]	Dutch registry	ETN ± MTX	146	11.2[g]	101 (69%)	66 (45%)	39 (27%)	41 (28%)	4.1[g]	11 (8%)	146 (100%)	113 (77%)
Lovell, 2008[21]	Open label extension[c]	ETN ± MTX	26	10.8	21 (81%)	19 (73%)	5 (19%)	2 (8%)	6.4	6 (24%)	26 (100%)	13 (34%)
Nielsen, 2008[34]	Prospective observational	ETN ± MTX	40	NR	25 (63%)	21 (53%)	11 (28%)	7 (18%)	4.4	NR	40 (100%)	30 (75%)
Lovell, 2006[22]	Open label extension[c]	ETN ± MTX	32	10.6	26 (81%)	24 (75%)	6 (19%)	2 (6%)	5.9	8 (27%)	32 (100%)	8 (17%)
Mori, 2005[35]	Prospective observational	ETN	22	11.4	18 (82%)	19 (86%)	1 (5%)	2 (9%)	4.7	11 (50%)	22 (100%)	0 (0%)
Horneff, 2004[19]	German registry	ETN ± MTX	322	NR	NR	133 (41%)	66 (21%)	123 (38%)	NR	NR	322 (100%)	235 (80%)
Lovell, 2003[20]	Open label extension[c]	ETN ± MTX	58	10.0	39 (67%)	34 (59%)	19 (33%)	5 (9%)	5.9	13 (22%)	58 (100%)	10 (17%)
Quartier, 2003[36]	French registry	ETN ± MTX	61	12.2	49 (80%)	13 (21%)	22 (36%)	25 (41%)	6.6	NR	61 (100%)	10 (16%)
Ruperto, 2010[23]	Open label extension[d]	IFX + MTX	78	NR	NR	NR	NR	NR	NR	NR	NR	NR

DeMarco, 2007[37]	Prospective observational	IFX ± MTX	78	20.7	66 (85%)	20 (26%)	20 (26%)	37 (48%)	13.6	8 (10%)	78 (100%)	54 (69%)
Gerloni, 2005[38]	Prospective observational	IFX + MTX	24	22.1	24 (100%)	10 (42%)	5 (21%)	9 (37%)	15.3	1 (4%)	24 (100%)	24 (100%)
Lamot, 2011[39]	Retrospective chart review	ETN or IFX or switch	41	11.0	25 (61%)	25 (61%)	0 (0%)	16 (39%)	4.1	6 (15%)	NR	41 (100%)
Sauvain, 2010[40]	Swiss registry	ETN ± MTX or IFX ± MTX	106	NR	68 (64%)	35 (33%)	8 (8%)	61 (59%)	3.6	NR	106 (100%)	64 (60%)
Tynjala, 2009[12]	Retrospective chart review	ETN IFX	105 104	9.6 10.6	79 (75%) 66 (64%)	66 (63%) 43 (41%)	11 (11%) 2 (2%)	27 (26%) 59 (58%)	5.1 4.9	4 (4%) 5 (5%)	NR NR	NR NR
Gerloni, 2008[41]	Prospective observational	ETN IFX Switched	95 68 45	13.7 21.7 NR	67 (71%) 57 (84%) 16 (36%)	22 (23%) 9 (13%) 13 (29%)	15 (16%) 8 (12%) NR	58 (61%) 51 (75%) 32 (71%)	8.4 13.7 NR	NR NR NR	NR NR NR	NR NR NR
Trachana, 2011[42]	Prospective observational	ADA ± MTX	26	12.6	14 (58%)	8 (31%)	4 (15%)	14 (54%)	7.1	1 (4%)	17 (63%)	25 (93%)
Ruperto, 2010[24]	Open label extension[e]	ABA ± MTX	153	12.3	106 (69%)	100 (65%)	32 (21%)	21 (14%)	4.1	33 (22%)	153 (100%)	120 (78%)
Alexeeva, 2011[43]	Prospective observational	RTX + MTX	55	9.3	30 (55%)	7 (13%)	46 (84%)	2 (4%)	4.5	2 (4%)	55 (100%)	55 (100%)

Abbreviations: OLE = open-label extension; MTX = methotrexate; ETN = etanercept; IFX= infliximab; ANA = anakinra; ADA = adalimumab; ABA = abatacept; RTX = rituximab; n= sample size; JIA = juvenile idiopathic arthritis; NR = not reported

[a] based on data from the German registry[19]

[b] based on data from the Dutch registry[11]

[c] open label extension (phase 3) of the etanercept RCT[14]

[d] open label extension (phase 3) of the infliximab RCT[15]

[e] open label extension (phase 3) of the abatacept RCT[17]

[f] denotes whole registry population not study sample

[g] denotes median value

3.5 Efficacy

Efficacy findings unique from those reported previously, are summarized below. Efficacy results including ACR 30, 50, 70 responses, rates of disease flares, inactive disease, and remissions are summarized in Appendix 3. Rates of discontinuations and reasons are summarized in Appendix 4.

3.5.1 Etanercept

Eight high quality etanercept studies with durations of follow-up that ranged from 15 to 96 months were identified. In the most recent update from the open label extension phase of the etanercept trial,[21] 100% of the residual 11 patients who continued therapy for eight years met the criteria for ACR Ped 70. Results from this study are limited by a small study sample size and the fact that the reported response rate represents only those patients who were proven etanercept responders in phase 1 of the RCT. Other high quality studies with long durations of follow-up were based on data from the Dutch[11] and German patient registries.[19] Registry studies reported lower rates of discontinuation than the open-label extension phases and confirm the long-term efficacy of etanercept in real-world clinical settings.

3.5.2 Infliximab

There were no new studies on the efficacy of infliximab were identified during the update. Two reports included patients treated with either etanercept and infliximab.[39,40] In the retrospective study by Lamot et al,[39] 36% of patients were able to achieve disease remission on medication and 29% were able to achieve disease remission off medication.

3.5.3 Abatacept

The only new study of abatacept was a report on the open-label extension phase of the RCT.[24] After 21 months of continuous therapy, 63% of patients achieved an ACR Ped 70 response and 37% achieved inactive disease. The majority of discontinuations during the open label extension phase were attributed to a lack of efficacy, particularly in patients who were non-responders during phase one.

3.5.4 Adalimumab

One new prospective observational study of adalimumab was included during the update.[42] This study followed a small sample of patients over 60 months with very few reported outcomes for the longest duration of follow-up. All of the 4 patients who continued therapy for 60 months met the criteria for ACR Ped 70.

3.5.5 Anakinra

There were no new studies of the efficacy of anakinra were identified during the update.

3.5.6 Rituximab

A single, high quality, observational study of rituximab[43] demonstrated the efficacy of treatment in 55 patients with severe refractory JIA. After 24 months 93% of treated patients met the ACR Ped 70 criteria and 98% achieved disease remission. Discontinuations were mostly due to disease remission (71% of all discontinuations).

3.6 Safety

There was wide variation in how adverse events were reported across newly added studies (e.g. number of events, number of patients experiencing events, events per 100 patient-years). Studies that followed patients for more than three years reported between 0.02 to 0.13 serious adverse events per patient-year. The most common events were serious infections, which occurred at a rate of 0.02 to 0.15 per patient-year. After eight years of continuous etanercept treatment,[21] there appeared to be no increase in the rate of serious adverse events, with most occurring during the first two years of treatment. In the Dutch etanercept registry, the majority of serious adverse events occurred in systemic JIA patients.[11]

A total of three systemic JIA patients enrolled in the Dutch etanercept registry died after discontinuing etanercept for 8 months; one as a result of suspected macrophage activation syndrome, one as a result of toxic sepsis, and one due to tuberculosis which developed after switching to infliximab therapy.[11] Two deaths were also reported in the British etanercept registry in patients who had discontinued treatment.[28] Another death occurred during an observational study of adalimumab.[42] One patient from the German registry developed thyroid cancer nine months after treatment with etanercept and another developed Non-Hodgkins lymphoma.[9,19]

Non-serious adverse events presented early, usually during the first 3 months of treatment. Reports of all adverse events categorized as serious or non-serious (as described by the author) can be found in Appendix 5.

4 CONCLUSIONS

Findings from the update contribute greatly to our understanding of the long-term efficacy and safety of biologic treatments in polyarticular JIA; in particular etanercept. A number of large, ongoing open-label registries collecting data on patients treated with etanercept over the long-term[11,19,28,29,36] report lower rates of discontinuation than the open-label extension phases.[20-22] Findings from these registries confirm the long-term efficacy of etanercept in real-world clinical settings, and suggest that ongoing treatment may be safe over several years of continued treatment. More long-term safety data is however required to rule out concerns that biologics are associated with the development of malignancies and autoimmune disorders. More long-term data will also allow better predictions of long-term outcomes for those who can tolerate and respond to therapy, as well as a further understanding of the long-term consequences for patients that may not be able to continue the treatment for long periods due to loss of efficacy or intolerance. As the field moves forward, registries have the potential to greatly contribute to our understanding of how patients respond to biologic therapies over time – particularly when to discontinue treatment in patients who achieve disease remission on medication, and the best pathways of care for those who show intolerance or a lack of response.

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APPENDICES

APPENDIX 1 Results of JADAD quality appraisal of randomized controlled trials

Author, year	Drug	Randomization (method described appropriate ?)	Double-blind (appropriately described?)	Wthdrawals and dropouts described?
Lovell, 2000	Etanercept	Randomized, method not described	Yes, vials for administration reconstituted by personnel not involved in patient assessment	Yes
Ruperto, 2007	Infliximab 3mg/kg + MTX	Randomized, no details on method	Double-blind, method described	Yes
Ilowite, 2008	Anakinra ± MTX	Randomized, no details on method	Double-blind, method described	Yes
Lovell, 2008	Adalimumab ± MTX	Randomized, method described	Double-blind, method described	Yes
Ruperto, 2008	Abatacept ± MTX	Randomized, method described	Double-blind, method described	Yes
Tynjala, 2011	Infliximab + MTX	Randomized, method described	No	Yes

Abbreviation: MTX = methotrexate

APPENDIX 2 Results of CASP quality appraisal of observational studies

Author, Year	Drug	Acceptable recruitment?	Accurate measurement of exposure?	Outcomes accurately measured to minimize bias?	Confounding factors identified?	Follow-up complete/long enough?	Results believable?
Mori, 2011	ETN	Yes - ETN naïve poly-JIA, failure on MTX	Yes, concomitant therapy not allowed; MTX washout period 2 weeks prior to baseline assessment	All patients completed 3 month study; Not clear how response rates were determined for patients completing 24 months	No	Discontinuations not reported	Yes, but small sample size, short duration, and discontinuations not reported.
Papsdorf, 2011	ETN ± MTX	Yes - refractory JIA, failure on MTX and/or corticosteroid	Yes, concomitant MTX accounted for in analysis of efficacy and safety (sub-group)	Yes, but multiple physicians/centers	Yes	Yes, Kaplan-Meier analysis used to estimate duration required to reach desired outcomes	Yes
Sevcic, 2011	ETN ± MTX	Yes - poly-JIA, failure on MTX (selection based on available data)	No, concomitant MTX exposure not accounted for, three patients switched to ADA (not clear how analyzed?)	Yes, but multiple physicians/centers	No	Yes, but short duration	Yes, but unclear whether ACR Pedi scores reflect cohort from baseline or time of analysis.
Southwood, 2011	ETN ± MTX	Yes - JIA, failure on MTX	No, concomitant MTX exposure not accounted for	No, only discontinuations measured, no explanation of patient deaths	No	No, data presented as mean duration of follow-up	Yes, but many confounding factors not accounted for
Zuber, 2011	ETN ± MTX	Yes - JIA, failure on MTX	No, concomitant MTX exposure not accounted for	Yes, but multiple physicians/centers	Yes	Yes, but short duration	Yes, but dropout rate not accounted for in measures of effectiveness
Otten, 2010	ETN ± MTX	Yes, specific subset of Dutch regisry (JIA, failure on MTX)	Not clear	Yes, but multiple physicians/centers	Not clear	Yes, but short duration	Yes, ITT analysis carried out but not clear which patient groups were included/excluded.
DeInocen-cio, 2009	ETN ± MTX (responders)	Yes, retrospective study carried out at single center (JIA,	Not clear	Yes	Yes	Yes	Yes

		failure on MTX)					
Giannini, 2009	ETN ± MTX (non-responders)	Yes - systemic, oligo and poly-JIA, various criteria based on treatment arm	No, allowed prior long-term exposure to MTX in ETN groups but not MTX groups; exposure to other DMARDs allowed	No, effectiveness measured by multiple physicians global assessment and joint counts	Yes	Yes	Yes, but not comparable due to different durations of previous drug exposure and concomitant treatments
Halbig, 2009	ETN ± MTX	No, selection based on data availability	Not clear	Yes, but multiple physicians/centers	Yes	No, follow-up incomplete	Yes
Horneff, 2009		Yes (JIA, failure on ≥ 1 DMARD	Yes, no other DMARDs allowed	Yes, but multiple physicians/centers	Yes	No, inconsistent reporting of patient disposition	Yes, ITT analysis included discontinuations due to remission. Those who had not completed 12 months of treatment were excluded from the ITT analysis.
Horneff, 2009b	ETN 0.8mg/kg ± MTX	Yes - biologic naïve poly-JIA, failure on MTX	No, concomitant MTX and other DMARD exposure not accounted for	Yes, but multiple physicians/centers	No	Yes, but short duration	Yes
Prince , 2009	ETN ± MTX	Yes – JIA, failure on MTX	No, concomitant drugs and variable dosing allowed. Patients were allowed to discontinue or begin concomitant therapy during study	Yes, but multiple physicians/centers	Yes	Yes	Yes, ITT analysis included remissions in response rates, but not clear if "too early to judge" and "transitions to adult care" were included. Separate analysis for ILAR sub-types.
Lovell, 2008	ETN ± MTX	Yes - poly-JIA, failure on MTX (continued from previous open label phase)	No, concomitant MTX use increased over time, not accounted for	Yes, but multiple physicians/centers	Yes	No, inconsistent reporting of patient disposition	Yes, LOCF analysis similar to per-protocol results.
Nielsen, 2008	ETN ± MTX	Yes - JIA, failure on MTX (required hand/ wrist	No, concomitant MTX and other DMARD exposure allowed	Yes, but only ACR 30 reported, no safety data, multiple	No	No, droupouts not described and short duration	Yes, but small sample size and droupout rate not considered

		radiograph)		physicians/centers			
Lovell, 2006	ETN ± MTX	Yes - poly-JIA, failure on MTX (continued from previous OLE)	No, concomitant MTX use increased over time, not accounted for	Yes, but multiple physicians/centers	Yes	No, missing values not explained, inconsistent reporting of patient disposition	Yes, but dropout rate not accounted for in measures of effectiveness
Mori ,2005	ETN	Yes - poly-JIA, failure on MTX	Yes, concomitant therapy not allowed; MTX washout period 2 weeks prior to baseline assessment, other DMARDs 1 month prior	Yes, but multiple physicians/centers	Not clear	Yes, but short duration	Yes, but small sample size
Horneff, 2004	ETN ± MTX	No, includes some non-JIA patients (n=12)	Yes, concomitant MTX and corticosteroid treatments accounted for in analysis	Yes, but multiple physicians/centers	Yes	Yes	Yes, LOCF analysis carried out
Lovell, 2003	ETN ± MTX	Yes - poly-JIA, failure on MTX (previously enrolled in RCT)	Yes, concomitant MTX not allowed in first year of study. 10 patients started MTX after 1 year.	Yes, but multiple physicians/centers	Yes	No, inconsistent reporting of patient disposition compared to reports in original RCT	Yes, modified ITT accounted for drop-outs due to lack of efficacy, and AEs. Discontinuation due to remission were excluded from ITT.
Quartier, 2003	ETN ± MTX	Yes - poly-JIA, failure on MTX	Yes, no concomitant DMARD treatment allowed; washout period 2 weeks prior to baseline assessment.	Yes, but multiple physicians/centers	Yes	No, missing values and short duration (longer follow-up data available)	Yes, ITT analysis accounted for dropouts
Ruperto, 2009	IFX + MTX	Yes, JIA patients, failure on MTX)	No, MTX and IFX dose adjustments allowed	Yes, but multiple physicians/centers	Yes	Yes, some missing efficacy data unexplained	Yes, but patients included in ITT analysis not described.
De Marco, 2007	IFX ± MTX	Yes, but no age restriction, single center	No, concomitant MTX and other DMARD exposure and wide-range IFX dose adjustments	No, response measure using both adult and pediatric measures (ACR Ped 30 vs. ACR 20)	Yes	Yes	Yes, explicitly state that improvement rates are based on remaining subjects
Gerloni, 2005	IFX + MTX	Yes, but no age restriction, single center	No, concomitant MTX exposure and wide-range IFX dose adjustments	Yes, single observer	Yes	No, pilot study - many patients without observation at 1yr.	Yes, but dropout rate not accounted for in measures of effectiveness
Lamot, 2011	ETN or IFX or switch	Yes, retrospective	Yes	Yes, but multiple physicians/centers	Yes	Yes	Yes

		study carried out at 2 centers					
Sauvain, 2010	ETN ± MTX or IFX ± MTX	No, includes some non-JIA patients and those with uveitis	Not clear	Not clear	Not clear	Not clear	Not clear
Tynjala, 2009	ETN or IFX	Yes, retrospective chart review (JIA, anti-TNF therapy for > 1 year)	Not clear	Yes, but no efficacy outcomes measured	Yes	Yes, Kaplan-Meier analysis used to estimate duration required to reach desired outcomes	Yes
Gerloni, 2008	ETN or IFX or switch	Not clear	No, concomitant MTX and other DMARD exposure and IFX dose adjustments, unbalanced treatment groups	Yes, but no efficacy outcomes measured	No	Not clear	Not clear, many confounding factors
Alexeeva, 2011	RTX + MTX	Yes, single center	Yes	Yes	Yes	Yes	Yes
Trachana, 2011	ADA ± MTX	Yes, single center (JIA, failure on DMARD or anti-TNF drug)	Not clear	Yes, but multiple physicians/centers	No	No, very few observations beyond 1 yr.	Yes, but many confounding factors not accounted for
Ruperto, 2010	ABA ± MTX	Yes, JIA, failure on DMARD or anti-TNF drug	No, proportion of patients on concomitant MTX not reported	Yes, but multiple physicians/centers	Yes	Yes	Yes, patients from RCT phase 1 and 2 analyzed separately

Abbreviations: JIA = juvenile idiopathic arthritis; DMARD = disease modifying anti-rheumatic drug; MTX = methotrexate; ETN = etanercept; IFX = infliximab; ADA = adalimumab; ABA = abatacept; ANA = anakinra; RTX = rituximab; RCT = randomized controlled trial; ITT = intention to treat; LOCF = last observation carried forward

APPENDIX 3 Efficacy data for all included studies

ACR Ped 30, 50, and 70 responses for patients treated with etanercept

Author, Date		Mori, 2011	Sevcic, 2011	Zuber, 2011	Otten, 2010	De Ino-cencio, 2009	Halbig, 2009	Horneff, 2009		Horneff, 2009b	Prince, 2009	Lovell, 2008	Nielsen, 2008		Lovell, 2006	Mori, 2005	Horneff, 2004	Lovell, 2003	Quar-tier, 2003	Lovell, 2000		
													Radio-graph	None						Phase 1	Phase 2	
Drug(s)		ETN	ETN ± MTX	ETN	ETN	ETN	ETN	ETN	ETN + MTX	ETN 0.8mg/kg	ETN	ETN	ETN ± MTX	ETN ± MTX	ETN	ETN	ETN	ETN	ETN ± MTX	ETN	Place bo	ETN
n (baseline)		24	72	186	179[¶]	71	102[j]	100	504	20	107[j]	58*	40	171	58	22	222*[j]	58[¶]	61[¶]	69	26	25
3 mo.	n	22	71	167	145						107		36	147		22	178		54	69		
	ACRPed 30	20 (91%)	88%	81%	100%					95%	90 (84%)		72%	64%		91%	81%		73%	74%		
	ACRPed 50	20 (91%)	80%	66%	86%					75%	79 (74%)					91%	67%		54%	64%		
	ACRPed 70	17 (77%)	40%	28%	66%					75%	62 (58%)					68%	42%		38%	36%		
6 mo.	n			153		55							36	129			166		44			
	ACRPed 30			86%		76%							67%	74%			88%		61%			
	ACRPed 50			78%		70%											72%		52%			
	ACRPed 70			36%		55%											50%		33%			
7 mo.	n																				26	25
	ACRPed 30																				35%	80%
	ACRPed 50																				23%	72%
	ACRPed 70																				19%	40%
12 mo.	n		61	141				67	419			51	31	66			133		31			
	ACRPed 30		76%	91%				70%	81%			80%	77%	71%			89%		39%			
	ACRPed 50		66%	87%				63%	74%			71%					75%		35%			
	ACRPed 70		56%	54%				45%	62%			59%					58%		26%			
15 mo.	n				131						73											
	ACRPed 30				92%						69 (95%)											
	ACRPed 50				90%						68 (93%)											
	ACRPed 70				77%						58 (80%)											
24 mo.	n	18		95			NR					47					76	51				
	ACRPed 30	94%		95%			97%					82%					81%	35 (69%)				
	ACRPed 50	94%		88%			95%					79%					71%	34 (67%)				
	ACRPed 70	89%		62%			92%					68%					51%	29 (57%)				
27 mo.	n										41											
	ACRPed 30										36 (88%)											
	ACRPed 50										33 (80%)											
	ACRPed 70										30 (73%)											
30 mo.	n																45					
	ACRPed 30																80%					
	ACRPed 50																72%					
	ACRPed 70																51%					
36 mo.	n			56								39										
	ACRPed 30			89%								85%										
	ACRPed 50			82%								76%										
	ACRPed 70			52%								69%										

39 mo.	**n**	20	
	ACRPed 30	15 (75%)	
	ACRPed 50	13 (65%)	
	ACRPed 70	10 (50%)	
48 mo.	**n**	38	32
	ACRPed 30	97%	30 (94%)
	ACRPed 50	92%	29 (90%)
	ACRPed 70	68%	25 (79%)
51 mo.	**n**	15	
	ACRPed 30	13 (87%)	
	ACRPed 50	13 (87%)	
	ACRPed 70	10 (67%)	
63 mo.	**n**	6	
	ACRPed 30	3 (50%)	
	ACRPed 50	3 (50%)	
	ACRPed 70	2 (33%)	
96 mo.	**n**	11	
	ACRPed 30	100%	
	ACRPed 50	100%	
	ACRPed 70	100%	

* denotes last observation carried forward (LOCF) analysis

¶ denotes ITT analysis

ʃ data excludes systemic JIA patients

Abbreviations: mo. = months; n = sample size; ACR Ped = American College of Rheumatology Pediatric criteria for disease improvement; ETN = etanercept; MTX = methotrexate

Rates of disease flares, remissions, and inactive disease for patients treated with etanercept

Author, Date	Papsdorf, 2011		Zuber, 2011	Otten, 2010	Horneff, 2009b	Prince, 2009	Horneff, 2004	Quartier, 2003	Lovell, 2000 (Phase 2)	
Drug(s)	ETN + MTX	ETN	ETN ± MTX	ETN ± MTX	ETN 0.8mg/kg	ETN ± MTX	ETN ± MTX	ETN ± MTX	Placebo	ETN
n (baseline)	567	220	186	179	20	107	222	61	26	25
Treatment duration, months	NR	NR	72	15	3	75	30	15	7	7
Remission	298 (85%)	77 (35%)	23 (12%)	NR	NR	53 (50%)	64 (29%)	NR	NR	NR
Inactive disease	128 (23%)	38 (17%)	NR	69 (38%)	5 (25%)	NR	NR	NR	NR	NR
Disease flares	NR	NR	NR	NR	NR	NR	NR	9 (15%)	21 (81%)	7 (28%)

Abbreviations: n = sample size; ETN = etanercept; MTX = methotrexate; NR= not reported

ACR Ped 30, 50, 70 responses and rates of inactive disease for patients treated with infliximab

Author, Date		Tynjala, 2011			Ruperto, 2010	De Marco, 2007	Ruperto, 2007			Gerloni, 2005
Drug(s)		IFX + MTX	COMBO	MTX alone	IFX + MTX	IFX	IFX + MTX	Placebo	IFX + MTX	IFX + MTX
n (baseline)		20	20	20	78	78	60	62	59	24
3.5 mo.	n						58	59		
	ACRPed 30						64%	49%		
	ACRPed 50						29 (50%)	20 (34%)		
	ACRPed 70						13 (22%)	7 (12%)		
8.5 mo.	n								54	
	ACRPed 30								80%	
	ACRPed 50								70%	
	ACRPed 70								28 (52%)	
12 mo.	n				75	51	55			9
	ACRPed 30				64 (85%)	84%	67%			
	ACRPed 50				61 (81%)	NR	68%			78%
	ACRPed 70				45 (60%)	NR	52%			44%
13.5 mo.	n	19	20	20						
	ACRPed 30	100%	85%	60%						
	ACRPed 50	100%	80%	60%						
	ACRPed 70	100%	70%	60%						
24 mo.	n					30				
	ACRPed 30					90%				
	ACRPed 50					NR				
	ACRPed 70					NR				
48 mo.	n				75	14				
	ACRPed 30	27%			33 (44%)	86%				
	ACRPed 50				30 (40%)					
	ACRPed 70				25 (33%)					
Inactive disease		13 (68%)	8 (40%)	5 (25%)	NR	NR	26 (42%)	25 (42%)	NR	NR
Treatment duration, months		48	48	48	-	-	3.5	3.5	-	-

Abbreviations: mo. = months; n = sample size; ACR Ped = American College of Rheumatology Pediatric criteria for disease improvement; IFX = infliximab; MTX = methotrexate; COMBO = combination therapy (methotrexate, sulphasalazine and hydroxychloroquine); NR= not reported

ACR Ped 30, 50, 70 responses and rates of inactive disease for patients treated with adalimumab

Author, Date		Trachana, 2011	Lovell, 2008 (Phase 1)		Lovell, 2008 (Phase 2 + Phase 3)			
Drug(s)		ADA ± MTX	ADA + MTX	ADA	Placebo	ADA	Placebo + MTX	ADA + MTX
n (baseline)		26	85	86	28	30	37	38
4 mo.	n		83	77				
	ACRPed 30		94%	74%				
	ACRPed 50		91%	64%				
	ACRPed 70		71%	46%				
12 mo.	n	26			28	30	37	38
	ACRPed 30	3 (12%)			32%	57%	38%	63%
	ACRPed 50	2 (8%)			32%	53%	38%	63%
	ACRPed 70	18 (69%)			29%	47%	27%	63%
24 mo.	n	18					128	
	ACRPed 30	2 (8%)					87%	
	ACRPed 50	3 (12%)					84%	
	ACRPed 70	10 (39%)					75%	
36 mo.	n	13						
	ACRPed 30	1 (4%)						
	ACRPed 50	6 (24%)						
	ACRPed 70	6 (24%)						
48 mo.	n	9						
	ACRPed 30	2 (8%)						
	ACRPed 50	3 (12%)						
	ACRPed 70	4 (15%)						
60 mo.	n	4						
	ACRPed 30	0 (0%)						
	ACRPed 50	2 (8%)						
	ACRPed 70	1 (4%)						
Disease flares		NR	NR	NR	20 (71%)	13 (43%)	24 (65%)	14 (37%)
Treatment duration, months		-	-	-	24	24	24	24

Abbreviations: mo. = months; n = sample size; ACR Ped = American College of Rheumatology Pediatric criteria for disease improvement; ADA = adalimumab; MTX = methotrexate; NR= not reported

ACR Ped 30, 50, 70 responses and rates of inactive disease and disease flares for patients treated with abatacept

Author, Date		Ruperto, 2010 (Phase 3)			Ruperto, 2008 (Phase 1)	Ruperto, 2008 (Phase 2)	
Drug(s)		ABA continuous	ABA interrupted	Initial non-responders	ABA	ABA	Placebo
n (baseline)		58	59	36	190	60	62
4 mo.	n				190		
	ACRPed 30				65%		
	ACRPed 50				50%		
	ACRPed 70				28%		
10 mo.	n					49	31
	ACRPed 30					82%	69%
	ACRPed 50					77%	52%
	ACRPed 70					53%	31%
21 mo.	n	51	47	22			
	ACRPed 30	46 (90%)	41 (87%)	19 (73%)			
	ACRPed 50	45 (88%)	39 (83%)	14 (64%)			
	ACRPed 70	38 (75%)	35 (75%)	10 (46%)			
Inactive disease		22/51 (43%)	11/47 (23%)	1/22 (4%)	NR	18 (30%)	7 (11%)
Disease flares		NR	NR	NR	NR	12 (20%)	33 (53%)
Treatment duration, months		21	21	21	-	10	10

Abbreviations: mo. = months; n = sample size; ACR Ped = American College of Rheumatology Pediatric criteria for disease improvement; ABA = abatacept; NR= not reported

ACR Ped 30, 50, 70 responses and rates of inactive disease and disease flares for patients treated with rituximab

Author, Date		Alexeeva, 2011
Drug(s)		RTX
n (baseline)		55
3 mo.	n	55
	ACRPed 30	98%
	ACRPed 50	50%
	ACRPed 70	42%
6 mo.	n	55
	ACRPed 30	98%
	ACRPed 50	75%
	ACRPed 70	70%
18 mo.	n	25
	ACRPed 30	90%
	ACRPed 50	75%
	ACRPed 70	75%
24 mo.	n	25
	ACRPed 30	98%
	ACRPed 50	93%
	ACRPed 70	93%
Remission		54 (98%)
Treatment duration, months		24

Abbreviations: mo. = months; n = sample size; ACR Ped = American College of Rheumatology Pediatric criteria for disease improvement; RTX = rituximab

APPENDIX 4 Rates of discontinuation for all included studies

Author, date	Drug(s)	n (baseline)	Follow-up, months	TOTAL	Adverse events	Lack of efficacy	Disease remission	Compliance/ protocol issues	Patient/ parent request	Physician decision	Lost to follow-up	Other
Mori, 2011	ETN	22	28	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Papsdorf, 2011	ETN ± MTX	787	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Sevcic, 2011	ETN ± MTX	72	12	11 (15%)	2 (18%)	5 (46%)	2 (18%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (18%)
Southwood, 2011	ETN ± MTX	483	24*	100 (21%)	21 (4%)	53 (11%)	9 (2%)	14 (23%)	0 (0%)	0 (0%)	0 (0%)	3 (1%)
Zuber, 2011	ETN ± MTX	188	72	51 (27%)	4 (2%)	9 (5%)	23 (12%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	15 (8%)
Otten, 2010	ETN ± MTX	145	15	10 (7%)	3 (2.1%)	6 (4%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
De Inocencio, 2009	ETN ± MTX	71	12	12 (17%)	NR	NR	NR	NR	NR	NR	NR	NR
Giannini, 2009	MTX alone ETN alone ETN + MTX	197 103 294	36	131 (67%) 56 (54%) 162 (55%)	3 (2%) 2 (2%) 1 (0.5%)	36 (18%) 8 (8%) 59 (20%)	24 (12%) 8 (8%) 12 (4%)	8 (4%) 4 (4%) 13 (4%)	9 (5%) 5 (5%) 11 (4%)	4 (2%) 3 (3%) 4 (1%)	17 (9%) 10 (10%) 14 (5%)	30 (15%) 16 (16%) 48 (16%)
Halbig, 2009	ETN ± MTX	114	24	24 (21%)	6 (5%)	10 (9%)	8 (7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Horneff, 2009	ETN alone ETN + MTX	100 504	12	14 (14%) 51 (10%)	3 (3%) 14 (3%)	8 (8%) 22 (4%)	0 (0%) 6 (1%)	0 (0%) 0 (0%)	2 (2%) 6 (1%)	0 (0%) 0 (0%)	1 (1%) 3 (0.5%)	0 (0%) 0 (0%)
Horneff, 2009b	ETN 0.8mg/kg	20	3	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Prince, 2009	ETN ± MTX	146	75	41 (28%)	6 (4%)	27 (19%)	8 (6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Lovell, 2008	ETN ± MTX	58	96	38 (66%)	4 (7%)	7 (12%)	0 (0%)	3 (5%)	8 (14%)	5 (9%)	3 (5%)	8 (14%)
Nielsen, 2008	ETN ± MTX	40	12	NR	NR	NR	NR	NR	NR	NR	NR	NR
Lovell, 2006	ETN ± MTX	58	48	24 (41%)	4 (7%)	6 (10%)	0 (0%)	2 (3%)	4 (7%)	3 (5%)	2 (3%)	3 (5%)
Mori, 2005	ETN	22	3	NR	NR	NR	NR	NR	NR	NR	NR	NR
Horneff, 2004	ETN ± MTX	256[i]	30	36 (14%)	9 (3.5%)	11 (4%)	12 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	4 (1.6%)
Lovell, 2003	ETN ± MTX (phase 3)	58	24	10 (17%)	1 (2%)	7 (12%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)	1 (2%)	0 (0%)
Quartier, 2003	ETN ± MTX	61	15	27 (45%)	12 (20%)	15 (25%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Lovell, 2000	ETN (phase 1) ETN (phase 2)	69 51	3 7	5 (7%) 25 (49%)	1 (1%) NR	2 (3%) NR	0 (0%) NR	0 (0%) NR	1 (1%) NR	0 (0%) NR	0 (0%) NR	1 (1%) NR
Tynjala, 2011	IFX COMBO MTX	60	13.5	13 (22%)	2 (3%)	11 (18%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Ruperto, 2010	IFX + MTX	78	51	42 (54%)	11 (14%)	8 (10%)	2 (3%)	0 (0%)	11 (14%)	8 (10%)	1 (1%)	1 (1%)
De Marco, 2007	IFX	78	36	54 (69%)	26 (33%)	26 (33%)	2 (2.5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Ruperto, 2007	IFX + MTX (phase 1)	60	13	5 (8%)	1 (2%)	2 (3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (3%)
	IFX + MTX (phase 2)	62	9.5	8 (14%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (2%)	0 (0%)	0 (0%)	7 (12%)
	IFX (phase 3)	109	12	31 (28%)	6 (6%)	3 (3%)	0 (0%)	5 (5%)	2 (2%)	13 (12%)	0 (0%)	2 (2%)
Gerloni, 2005	IFX	24	12	5 (21%)	4 (17%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (4%)
Lamot, 2011	ETN + MTX or IFX + MTX	41	6	NR	NR	NR	NR	NR	NR	NR	NR	NR
Sauvain, 2010	ETN or IFX	106	24	NR	NR	NR	NR	NR	NR	NR	NR	NR
Tynjala, 2009	ETN	105	48	46 (43%)	7 (7%)	29 (28%)	10 (10%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	IFX	104	48	61 (59%)	23 (22%)	21 (20%)	17 (16%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Switch	73	53*	43 (59%)	13 (18%)	26 (36%)	4 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Gerloni, 2008	ETN	95	72	NR	18 (19%)	NR	NR	NR	NR	NR	NR	NR
	IFX	68	72	NR	26 (28%)	NR	NR	NR	NR	NR	NR	NR
Trachana, 2011	ADA ± MTX	26	60	9 (35%)	2 (8%)	7 (27%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Lovell, 2008	ADA (phase 1)	171	4	11 (6%)	3 (2%)	6 (3.5%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (1%)	0 (0%)
	ADA + MTX (phase 1)	133	12	5 (4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)	4 (3%)
	ADA ± MTX (phase 3)	128	26	NR	4 (3%)	NR	NR	NR	NR	NR	NR	NR
Ruperto, 2010	ABA	153	21	42 (27%)	3 (2%)	20 (13%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (2%)	16 (10%)
Ruperto, 2008	ABA (phase 1)	190	4	20 (11%)	1 (1%)	17 (9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)	1 (1%)
	ABA (phase 2)	122	10	42 (34%)	0 (0%)	41 (34%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)
Alexeeva, 2011	RTX	55	24	31 (56%)	1 (2%)	8 (15%)	22 (40%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Ilowite, 2009	ANA (phase 1)	86	3	36 (42%)	4 (5%)	27 (31%)	0 (0%)	0 (0%)	3 (4%)	0 (0%)	0 (0%)	2 (2%)
	ANA (phase 2)	50	7	19 (38%)	0 (0%)	14 (28%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	5 (10%)
	ANA (phase 3)	44	12	7 (16%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (7%)	2 (4%)	2 (4%)	0 (0%)

* represents mean duration of follow-up

Abbreviations: n = sample size; MTX = methotrexate; ETN = etanercept; IFX = infliximab; ADA = adalimumab; ABA = abatacept; ANA = anakinra; RTX = rituximab; COMBO = combination therapy (methotrexate, sulphasalazine and hydroxychloroquine); NR = not reported

APPENDIX 5 Adverse events (serious and non-serious) and deaths reported

Author, Date	Drug(s)	n	Treatment duration, months	Total adverse events	Non serious adverse events	Serious adverse events	Deaths
Mori, 2011	ETN	22	28	22	NR	NR	0
Sevcic, 2011	ETN ± MTX	72	12	13	NR	NR	0
Southwood, 2011	ETN ± MTX	483	24*	21	NR	NR	2
Zuber, 2011	ETN	188	72	1162 (2.96ppy)	NR	23 (0.02ppy)	0
Otten, 2010	ETN	145	15	NR	NR	3	NR
Giannini, 2009	MTX alone	197	36	71	48	0.05ppy	0
	ETN alone	103		42	23	0.07ppy	0
	ETN + MTX	294		137	67	0.06ppy	0
Halbig, 2009	ETN	114	24	8	7	1	0
Horneff, 2009	ETN alone	100	12	21 (0.15ppy)	17	4	0
	ETN + MTX	504		169 (0.16ppy)	121	48	0
Horneff, 2009b	ETN 0.8mg/kg	20	3	74	37	37	0
Prince, 2009	ETN	146	75	65	56	9 (0.029ppy)	3
Lovell, 2008	ETN	58	96	NR	NR	39 (0.12ppy)	0
Nielsen, 2008	ETN ± MTX	40	12	NR	NR	NR	NR
Lovell, 2006	ETN	58	48	NR	NR	29 (0.13ppy)	0
Mori, 2005	ETN	22	3	22	NR	NR	0
Horneff, 2004	ETN	256	30	69	57	12	0
Lovell, 2003	ETN (phase 3)	58	24	NR	NR	13	0
Quartier, 2003	ETN ± MTX	61	15	67	55	12	0
Lovell, 2000	ETN (phase 1)	69	3	130	128	2	0
Tynjala, 2011	IFX	60	13.5	100 (4.8ppy)	99	1	0
	COMBO			106 (5.4ppy)	104	2	0
	MTX			111 (6.5ppy)	93	18	0
Ruperto, 2010	IFX + MTX	78	51	71	54	17	0
De Marco, 2007	IFX	78	36		39	19	2
Ruperto, 2007	IFX + MTX (phase 1)	60	13	58 patients	39 patients	19 patients	1
	IFX + MTX (phase 2)	62	9.5	54 patients	49 patients	5 patients	0
Gerloni, 2005	IFX	24	12	12	NR	NR	NR
Lamot, 2011	ETN+MTX or IFX+MTX	41	6	17 (3 ETN)	NR	NR	NR
Sauvain, 2010	ETN or IFX	106	24	24 (9 ETN)	NR	NR	0

Tynjala, 2009	ETN	105	48	NR	NR	NR	NR
	IFX	104	48	NR	NR	NR	NR
	Switch	73	53*	NR	NR	NR	NR
Gerloni, 2008	ETN	95	72	133	NR	NR	0
	IFX	68	72	71	NR	NR	0
Trachana, 2011	ADA ± MTX	26	60	0.13ppy	127/68	0.03ppy	1
Lovell, 2008	ADA ± MTX (phase 1)	171	4	899	892	7	0
	ADA ± MTX (phase 2)	133	12	713	712	1	0
	ADA ± MTX (phase 3)	128	26	1275	1266	9	0
Ruperto, 2010	ABA	153	21	195	77 patients	23 patients	0
Ruperto, 2008	ABA (phase 1)	190	4	133 patients	127 patients	6 patients	0
	ABA (phase 2)	122	10	71 patients	69 patients	3 (2 placebo)	0
Alexeeva, 2011	RTX	55	24	101	NR	12	0
Ilowite, 2009	ANA (phase 1)	86	3	80 patients	NR	3 patients	0
	ANA (phase 2)	50	7	35 patients	NR	0 patients	0
	ANA (phase 3)	44	12	30 patients	NR	3 patients	0

* represents mean duration of follow-up

Abbreviations: MTX = methotrexate; ETN = etanercept; IFX= infliximab; ANA = anakinra;

ADA = adalimumab; ABA = abatacept; RTX = rituximab; n= sample size; ppy=per patient year