The Hospital for Sick Children

Technology Assessment at Sick Kids (TASK)

THE USE OF BIOLOGICS RESPONSE MODIFIERS IN POLYARTICULAR-COURSE JUVENILE IDIOPATHIC ARTHRITIS

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CONFLICTS OF INTEREST

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

TABLE OF CONTENTS

Appendix 1 Characteristics of Juvenile Idiopathic Arthritis subtypes

Table 1.1 Distribution and characteristics of JIA subtypes

Juvenile idiopathic arthritis (JIA) subtypes	Distribution of JIA subtypes - where	Age of onset	Characteristics	Prognosis
Oligoarthritis pauciarticular	40-60%[1]	Early onset: early childhood, highest between 2-4 years Late onset: > 9 years[2]	≤ 4 joints affected during the 1st 6 months of the disease.[3] Early onset: legs, knees, and ankles are more often affected with an asymmetric presentation.[4] Late onset: hips affected more often.[2] Can be subdivided into:[3] - Persistent oligoarthritis (≤ 4 joints affected throughout the course of the disease). - Extended oligoarthritis (> 4 joints affected after the 1st 6 months). Development of uveitis is common, although the association may vary according to ethnic group.[4, 5] - approx. 50% may evolve into a polyarticular-course - antibodies	**Persistent oligoarthritis** Good prognosis. Remission within 4-5 years, however functional limitation depends on treatment for the disease. **Extended oligoarthritis** Functional disabilities may develop in the future.[5]
Rheumatoid-factor negative polyarthritis	20-25%[1]	Highest between 2-4 years and 6-12 years	≥ 5 joints affected during the 1st 6 months of the disease and rheumatoid factor negative.[3] Large joints (knee, wrist, elbow) are symmetrically affected.[6] Low grade fever and lymphadenopathy. [6]	Outcome is variable.[4]

Rheumatoid-factor positive polyarthritis (> 4 joints affected)	5-10%[1]	Late childhood or adolescence	- ≥ 5 joints affected during the 1st 6 months of the disease and rheumatoid factor positive in ≥ 2 tests performed ≥ 3 months apart.[3] - Large joints (knee, wrist, elbow) are symmetrically affected - Low grade fever and lymphadenopathy - Some patients may develop a disease similar to adult rheumatoid arthritis (especially girls).[6]	Poor clinical prognosis.[5] Presence of widespread joint destruction. [5]
Undifferentiated arthritis	undetermined[1]		Arthritis that does not meet characteristics of any or of ≥ 2 of the other arthritis.	
Systemic arthritis	10-20%[1]	Throughout childhood	- Daily spiking fever (up to 39.5°C) for ≥ 2 weeks - Arthritis of ≥ 1 joints - Evanescent nonpruritic rash or lymphadenopathy, serositis, hepatosplenomegaly. - Anemia, high levels of erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) (ravelli). - Symptoms may be self-limiting. - Approximately 50% of the patients develops chronic and progressive polyarticular arthritis.[3, 6]	Complications Growth retardation, osteoporosis, systemic amyloidosis, macrophage activation syndrome[7] (becoming more rare[4]).
Enthesitis-related arthritis	undetermined[1]	Late childhood or adolescence		Variable – axial skeletal joints damage may occur.[4]
Psoriatic arthritis	5%[1]	Highest between 2-4 years and 9-11 years	Arthritis and psoriasis, or arthritis and ≥ 2 of the following: - dactylitis, nail pitting and onycholisis, or psoriasis in a 1st degree relative.	Not established. [4]

Appendix 2 Proposed treatment for Juvenile Idiopathic Arthritis

Table 2.1 Proposed treatment sequence for different JIA subtypes (Source: Hashkes & Laxer[1, 8])

JIA subtype	Treatments proposed
Oligoarthritis	**NSAIDs** The majority of oligoarthritis patients do not respond to NSAIDs. **Intra-articular corticosteroids, especially triamcinolone hexacetonide** Used in patients who do not respond to NSAIDs or patients with flexion contractures or leg length discrepancies. Patients who do not respond to treatment with intra-articular corticosteroids or in patients with extended oligoarthritis, or small joint involvement should be treated as patients with polyarticular JIA
Polyarticular (RF negative)	**NSAIDs** In general NSAIDs are not effective in polyarticular JIA, should be used as treatment for symptoms. **MTX** Should be started early at a dose of 10 mg/m^2/wk , with subsequent increase to parenteral MTX at 15 mg/m^2/wk if the patient is not responding. **Sulfasalazine and leflunomide** Can be used as alternative to MTX. **Anti-TNF-α s** Can be used if the patient did not respond to the previous drugs. It is still not clear if anti-TNF-αs should be administered in combination with MTX. **Intra-articular corticosteroids** Adjunct use for 1 or some swollen or painful joints. **Systemic corticosteroids** Can be used during flares.
Polyarticular (RF positive)	**MTX ± anti-TNF** Due to the poor prognosis of these patients their treatment should follow the aggressive treatment for adult rheumatoid arthritis, i.e., MTX should be started early and combined with an anti-TNF-α in case of incomplete response to MTX .
Systemic arthritis **Macrophage activation syndrome (MAS)**	**NSAIDs and systemic corticosteroids** Used to treat symptoms such as fever and serositis. **Intra-articular corticosteroids, MTX, anti-TNF drugs, IV immunoglobulin**

	Patients with systemic arthritis seem to have a lower response to these drugs compared to other JIA subtypes, however, more recent evidence suggests that anakinra, an IL-1 receptor antagonist, may be more active in systemic JIA. IV immunoglobulin may be used as a corticosteroid-sparing drug for systemic symptoms. **IV corticosteroid pulses** Can be used in the treatment of MAS. **Cyclosporine** Can be used in the treatment of MAS if the patient is not responding promptly to IV corticosteroid pulses.
Enthesitis-related arthritis	**Sulfasalazine** May be used in the treatment of enthesitis-related arthritis. **Anti-TNF drugs** Enthesitis-related arthritis patients seem to respond to the anti-TNF-α drugs.
Uveitis	**MTX** Can be used early in patients who respond to topical corticosteroids. **Anti-TNF** Can be used in patients refractory to MTX. Among the anti-TNF-α drugs, response seems to be better with infliximab compared to etanercept.

Source: Hashkes & Laxer[1, 8]
IV intravenous / JIA juvenile idiopathic arthritis / MTX methotrexate / NSAIDs non-steroidal anti-inflammatory drugs / RF rheumatoid factor / TNF tumour necrosis factor / wk week

Appendix 3 Terms used in the systematic literature review

Table 3.1 Terms used in the systematic literature review

Systematic literature review – terms used
"etanercept"[All Fields] OR "TNFR-Fc fusion protein"[Substance Name] OR "TNFR-Fc fusion protein"[All Fields]
"infliximab"[Substance Name] OR "infliximab"[All Fields]
"adalimumab"[Substance Name] OR "adalimumab"[All Fields]
"abatacept"[Substance Name] OR "abatacept"[All Fields]
"anakinra"[All Fields] OR "interleukin 1 receptor antagonist protein"[MeSH Terms] OR "interleukin 1 receptor antagonist protein"[All Fields]
"tocilizumab"[Substance Name] OR "tocilizumab"[All Fields]
"rituximab"[Substance Name] OR "rituximab"[All Fields]
Enbrel OR Remicade OR Humira OR Kineret OR Rituxan
"arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "idiopathic"[All Fields] AND "arthritis"[All Fields]) OR "juvenile idiopathic arthritis"[All Fields]
"tumour necrosis factor"[All Fields] OR "tumor necrosis factor-alpha"[MeSH Terms] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factor-alpha"[All Fields]) OR "tumor necrosis factor-alpha"[All Fields] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factor"[All Fields]) OR "tumor necrosis factor"[All Fields] OR ("tnf"[All Fields] AND "alpha"[All Fields]) OR "tnf alpha"[All Fields]
"interleukin-1beta"[MeSH Terms] OR "interleukin-1beta"[All Fields] OR "interleukin 1"[All Fields] OR "interleukin-1"[MeSH Terms] OR "interleukin-1"[All Fields]
"interleukin-6"[MeSH Terms] OR "interleukin-6"[All Fields] OR "interleukin 6"[All Fields]

Appendix 4 Randomized controlled trial quality assessment

Table 4.1 Assessment of the quality of published JIA studies, double-blind phase (According to Jadad et al.[9])

Study	Randomization (is method described appropriate ?)	Double-blind (appropriately described?)	Description of withdrawals and dropouts
Etanercept [10]	Randomized, method not described	Yes, vials for administration reconstituted by personnel not involved in patient assessment	Yes
Infliximab[11]	Randomized, no details on method	Double-blind, method described	Yes
Adalimumab[12]	Randomized, method described	Double-blind, method described	Yes
Abatacept[13]	Randomized, method described	Double-blind, method described	Yes
Anakinra[14] **(polyarticular-course)**	Randomized, no details on method	Double-blind, method described	Yes
Tocilizumab[15] **(systemic JIA)**	Randomized, no details on method	Double-blind, no details on method	Yes

Appendix 5 Characteristics of biologics RCTs in pediatric JIA patients (non-systemic)

Table 5.1 Inclusion and exclusion criteria: RCTs of biologic drugs in JIA

		Etanercept[10]	Adalimumab ± MTX[12]	Abatacept ± MTX[13]	Anakinra[14]	Infliximab + MTX[11]
Inclusion and exclusion criteria (disease state and treatment response)	**Open-label phase**	4-17 years Polyarticular-course (any onset type) JRA Active disease (≥ 5 swollen joints & 3 ≥ joints with LOM)	4-17 years Polyarticular-course JRA (any onset type) Active disease (≥ 5 swollen joints & 3 ≥ joints with LOM)	6-17 years ≥ 5 active joints JIA subtypes: Oligoarticular, polyarticular, or systemic without systemic manifestations Active disease* Patients with uveitis were excluded	2-17 years Polyarticular-course JRA (any onset type) Active disease (≥ 5 swollen joints & ≥ 3 joints with LOM) No systemic disease	4-17 years Polyarticular course JRA No open-label phase
	Double-blind phase	Disease improvement according to ACR Ped 30 at end of open-label phase	Disease improvement according to ACR Ped 30 at end of open-label phase	Disease improvement according to ACR Ped 30 at the end of open-label phase	Disease improvement according to ACR Ped 30 at the end of open-label phase. Flare patients were allowed to switch to other arm of the trial	≥ 5 active joints No active systemic symptoms Patients with active uveitis were excluded
	Open-label extension	Patients included in the previous study phases, even if etanercept was discontinued or had not been effective	Patients included in the previous study phases, even if adalimumab had been discontinued or had not been effective	Patients included in the previous study phases, even if abatacept had been discontinued or had not been effective	Patients included in the previous study phases, even if anakinra had been discontinued or had not been effective	Patients who were judged to benefit from treatment continuation by the physicians at week 44

Inclusion and exclusion criteria (prior anti-rheumatic drug use)	**MTX**	Refractory to MTX (≥10mg/m^2/week)	If previous use, inadequate response or intolerant §§	Failure or intolerance with ≥ 1 DMARD (including anti-TNF-α drug)	Stable dose of MTX for 6 weeks before study start	Suboptimal response to MTX ≥ 3 months
	Biologic drugs	Prior use not allowed¶¶	Prior use not allowed¶¶	Prior use allowed (anti-TNF-α)	Prior use seems to be allowed‡	Prior use not allowed

ACR Ped American College of Rheumatologists, pediatric criteria / DMARD disease-modifying anti-rheumatic drug / JIA juvenile idiopathic arthritis / LOM limitation of motion / MTX methotrexate

‡ Authors mention that biologic drugs should not have been used in the 4 weeks preceding enrollment. We assumed that they could have been used before this period.

§§ Patients with or without prior use of MTX were included in the study. Patients with prior MTX use had to have inadequate response or intolerance to the drug.

¶¶ In cases where prior use of biologic drugs was not mentioned as an inclusion criteria we assumed that it was not allowed. This may especially be the case of etanercept since it was the first anti-TNF-α drug studied.

* Active disease: ≥two active joints and two joints with a limited range of motion.

Appendix 6 Quality of Life and school days missed: Abatacept study

Quality of Life

One RCT on abatacept that included 190 patients evaluated the changes in quality of life using the Child Health Questionnaire (CHQ).[16] At the beginning of the study the authors reported that the patients had a lower quality of life level compared to the general population (values not provided) especially with respect to global health, physical functioning, general health, pain/discomfort, and parental emotional impact.[16] At the end of the 4-month lead-in open-label phase, statistically significant improvements were seen in all domains except family cohesion (14/15). [16] The highest increase was seen in the physical domain[16] (table 6.1). At the end of the double-blind phase, patients treated with abatacept either maintained or continued the improvements while patients in the placebo group experienced a general reduction in 13/15 domains (pain: 8.4 points , sleep problems: 1.2 points).[16] These results were presented as an abstract at a conference[16], therefore further details are not available. The clinical significance of these changes was not discussed by the authors. Additionally, the variance in the results was not provided.

Table 6.1 Changes in CHQ domains: Lead-in phase, abatacept treated patients

CHQ domain	Mean change from baseline
Global health	16.27*
Physical functioning	13.00*
Role/social - physical	11.63*
General health	6.29*
Pain/discomfort	17.29*
Parental time impact	11.18*
Parental emotional impact	10.22*
Role/social emotional	11.82*
Self-esteem	3.81*
Mental health	8.82*
Global behaviour	5.09*
Behaviour	4.13*
Change in health	0.81*
Family activity	7.34*
Family cohesion	1.78

* Statistically significant

The study also evaluated the changes in missed days of activities in patients and their parents due to JIA[17]. The results available are shown in table 6.2.

Table 6.2 Changes in missed days of activities/month for parents and patients treated with abatacept (variance not provided) [17]

		Lead-in open-label phase Mean days missed* / Change from baseline		Double-blind phase Mean days missed* / Change from beginning of double-blind phase	
	Baseline	2 months (n=190)	4 months (n=190)	Abatacept (n=60)	Placebo (n=62)
Missed days of school in previous month (child)	4.1 days	2.7 / -1.4¶ days	2.41 / -1.69¶ days	0.89 / -1.52¶ days	2.97 / 0.56 days
Missed days of usual activities in previous month (parent)	3.5 days	2.11 / -1.39¶ days	1.58 / -1.92¶ days	1.38 / -0.2 days	2.69 / 1.11 days
Days of paid child care /month	1.4 days	0.9 / -0.5¶ days	0.22 / -1.18¶ days	0.17 / -0.05 days	0.17 / -0.05 days

* We calculated the mean days of missed activities during the study based on the mean baseline value and the mean change reported in the abstract.
¶ statistically significant difference.

Appendix 7 Detection of anti-biologic drug and autoantibody detection: Biologics RCTs

Anti-biologic drug antibody detection

The presence of anti-drug antibodies may affect the long-term efficacy of these drugs and put patients at a higher risk for adverse reactions.[18]

The infliximab, adalimumab, anakinra, and tocilizumab (systemic JIA) studies reported the detection of antibodies against these drugs. Presence of anti-biologic drug antibodies was not reported in the abatacept study. Results are shown in table 7.1.

Table 7.1 Anti-biologic antibody detection reported (patients were negative at baseline unless otherwise specified)

	Etanercept[10]	Adalimumab[12]	Anakinra[14]	Infliximab[11, 19]	Tocilizumab[15]
Type of antibody	**Anti-etanercept antibody,**	**Anti-adalimumab antibodies**	**Anti-IL-1ra antibodies**	**Anti-infliximab antibodies**	**Anti-tocilizumab IgE antibodies**
Study phase, n (%) RCTs	DB: 2/ 25 (8%)	OL and DB, OLE phases: 27/171 (16%) 5/85 (6%) – MTX group 22/86 (26%) – no MTX group	OL: 48/64(75%) non-neutralizing 4/64 (6%) neutralizing* DB: Non-neutralizing 13/18 (72%) anakinra 3/9 (33%) placebo Neutralizing 1/9 (11%) placebo OL extension: 36/44 (82%) non-neutralizing	DB: 26 / 102 (25%) 20/56 (38% - 3 mg/kg 6/49 (12%) – 6 mg/kg OLE (week 216): 26/71 (36%)**	OL 3 (5.4%)
Observational studies	2 (3.3%) rise in concentration§	-	-	2 (8.3%) [20]	-

DB double blind / IgE immunoglobulin E / IL-1ra interleukin-1 receptor antagonist / OL open-label / OLE open-label extension / RCT randomized controlled trial

*All patients who were positive for neutralizing anti-IL-1-ra antibody in the open-label phase of the anakinra study did not respond to the drug.
** Infusion-related reaction was observed in 15/26 (57.7%) patients in whom anti-infliximab antibody was detected during the open-label extension.
§ Etanercept treatment later discontinued due to lack of efficacy

All four patients with neutralizing anti-IL-1ra antibodies during the open-label phase did not respond to anakinra.

The adalimumab assessment report from the European Medicines Agency (EMEA) reported a lower efficacy in patients positive for anti-adalimumab antibodies compared to those negative for the antibodies through all phases of the trial.[21] For instance 12/19 (63%) vs. 132/157 (87%), respectively achieved ACR Ped 30 in the lead-in open-label phase.[21] The authors of the adalimumab study reported that the presence of the anti-adalimumab antibody was not associated with a higher rate of treatment discontinuation or an increase in the incidence of serious adverse events.

Not only was the incidence of anti-infliximab antibodies higher in the 3 mg/kg group compared to the 6 mg/kg group, but the antibody titers were also higher in the 3 mg/kg. The frequency of infusion-related reactions was three times higher in patients positive for anti-infliximab antibodies compared to those who were negative. Infusion-related reaction was observed in 15/26 (57.7%) patients in whom anti-infliximab antibody was detected during the open-label extension. The presence of anti-infliximab antibodies may result in a neutralization of the drug, limiting its long-term efficacy or resulting in infusion-related allergic reactions.[20]

Autoantibody detection

Table 7.2 shows the results of autoantibodies' detection from the RCTs.

Table 7.2 Autoantibody detection: Biologics RCTs

	Etanercept[10, 22]	Abatacept[13]	Infliximab[11]	Adalimumab[12]
Type of antibody	**Antinuclear antibodies (ANA) or anti-dsDNA antibodies**	**Anti-dsDNA antibody / ANA**	**Antinuclear antibodies (ANA) or anti-dsDNA antibodies**	**Anti-dsDNA antibodies**
Study phase, n (%)	OL / DB 0 (persistent elevations of autoantibodies) 2-year extension (n=51) ANA – none consistently positive* Anti-dsDNA antibody / antibodies to antiphospholipid antigens: none	Anti-dsDNA antibody OL (day 113) 9/146 (6%)* DB (day 169) 1/43 (2%) ABT group 0 – placebo group ANA OL (day 113) 12/113 (11%)* DB (day 169) 2/34 (6%) ABT group* 1/25 (4%)– placebo group*	DB* Placebo + MTX (0-14 weeks): ANA: 0/30 Anti-dsDNA: 0/30 Infliximab 3mg/kg +MTX (0-52 weeks): ANA: 8/54 (15%) Anti-dsDNA: 7/54 (13%) Infliximab 6mg/kg + MTX (14-52 weeks): ANA: 1/46 (2.2%) Anti-dsDNA: 0/46 (0)	End of DB 15/155 (10%) previously negative anti-dsDNA patients [23]
Clinical manifestations associated with positivity	OL / DB / 2-year ext. There were no signs or symptoms of autoimmune diseases	OL / DB No clinical manifestations of lupus or other autoimmune disease or other manifestations associated with autoantibodies.	-	No frank autoimmune syndromes observed [23]

ABT abatacept / ANA antinuclear antibody / Anti-dsDNA anti-double stranded DNA / DB double blind / MTX methotrexate / OL open-label / ext extension
* Among patients who had negative antibody titre at baseline.

Appendix 8 Baseline characteristics of patients included in non-comparative studies of etanercept and infliximab

Table 8.1 Baseline characteristics of the patients included in the open-label, non-comparative etanercept studies

Baseline characteristics	Quartier[24]	Horneff [25]	Mori[26]	Prince[27]	Horneff[28]		Lovell [22]	Cochino[29]
	ETN ± MTX N=61	ETN N=314	ETN N=22	ETN ± MTX N=146	ETN N=100	ETN + MTX N=504	ETN ± MTX N=58 *	ETN ± MTX N=71
Mean/median age, years	12.2 (4-22)	-	11.4 (4-17)	11.2 years	13.1 (4.5)	12.5 (4.4)	10	12.4 (4-16)
Female, n (%)	49 (80%)	-	18 (81.8%)	101 (69%)	58 (58%)	345 (67%)	39 (67%)	44 (62%)
Type of onset of JIA, n (%) Polyarticular Systemic Oligoarticular	 0 13 (21%) 22 (36%) 24 (39%)	 133(41%) 66 (21%) 64 (20%)	 19 (86.4%) 1 (4.5%) 2 (9.1%)	 66 (44%) 39 (27%) 28 (19%)	-	-	 34 (59%) 19 (33%) 5 (9%)	 51 (72%) 15 (21%)
Rheumatoid factor positive, n (%)	-	-	11 (50%)	11 (8%)	-	-	13 (22%)	
Mean duration of JIA, years (range)	6.6 (1-17)	-	4.72	4.1 (median)	5.5 (4.6)	4.9 (3.6)	5.9	
Type of JIA course studied	Active polyarticular	Several	Active polyarticular	Different subtypes	-	-	Active polyarticular	

ETN etanercept / MTX methotrexate / JIA juvenile idiopathic arthritis

Table 8.1 cont.

	Sourhwood[30]	Giannini[31]	Nielsen[32]	Tynjala[33]**	Saurenmann[34]	Gerloni[35]
	ETN ± MTX N=434	ETN ± MTX N=404	ETN ± MTX N=40	ETN ± DMARDs N=105	ETN or infliximab N=45	ETN N=95
Mean/median age, years	Median: 11 years (2-21)	2-18 years	-	9.6 (2.2-15.9)	14.2 (2.6-32)§	13.7 (1.9-50)
Female, n (%)	295 (68%)	73-81%	25 (63%)	79 (75%)	35 (78%)	67 (71%)
Type of onset of JIA, n (%) Pauciarticular Polyarticular Systemic Oligoarticular	68 (15.7%) s	-	21 (53%) poly 11 (28%) s 7 (18%) ext	66 (62.8%) 11 (10.5%) 19 (18.1%) 1 (1%) p		
Rheumatoid factor positive, n (%)	-	-	-	4 (3.8%)		
Mean duration of JIA, years (range)	-	-	4.4 (2.6 – 7.0) median age onset: 2.9 years	5.1 (0.3 – 13.7)	8.7 (1.8-16.7)	2 (0-6)
Type of JIA course studied	-	-	Polyarticular course	-		

ETN etanercept / JIA juvenile idiopathic arthritis / MTX methotrexate
*Baseline characteristics measured at the start of the open-label phase 1.
§ Mean age at diagnosis plus mean follow-up time since diagnosis.

Table 8.2 Characteristics of patients included in non-comparative infliximab studies

	Gerloni[20] N=24	De Marco[36] N=78	Tynjala[33] N=104	Alexeeva[37] N=72
Mean age at baseline, years (range)	22.1 (8.2-32.5)	20.9 (5.4-34.9)	10.6 (4-16)	4.7 – 10.3 across JIA subtypes
Type of onset of JIA, n (%)				
Pauciarticular	6 (25%)	20 (26%)		23 (32%)
Polyarticular	5 (20.8%)	20 (26%)	47 (44.8%) poly	28 (39%)
Systemic	10 (41.7%)	27 (35%)	2 (1.9%)	21 (29%)
Extended oligoarticular			23 (21.9%) e	
Persistent oligoarticular	3 (12.5%)	6 (7.7%)	15 (14.3%) p	
Psoriatic arthritis		5 (6.4%)		
Enthesitis arthritis				
Mean duration of JRA, years	15.3 (5.2-31.5)	13.5 (0.4 – 31.5)	4.9 (0.3 – 12.8)	Mean: 1-6 years across JIA subtypes
Positive for rheumatoid factor, n (%)	1	8 (10.3%)	5 (4.8%)	NR
Subtype evaluated	Active Polyarticular	several	Outcome: drug discontinuation	several
Median duration of treatment	9.1 months (0.5 – 18.8)	14.7 months (1.5 – 72.4)	Up to 60 months	Up to 1.5 years
Concomitant treatments			DMARDs allowed, not specified	
MTX, n (%)	24 (100%)*	62 (78%)		45 (63%)
Corticosteroids, n (%)	19 (79%)			
Mean dose of infliximab, mg/kg	4.7 ± 1.7 mg/kg (2.9-10)	3-10 mg/kg	-	NR

DMARD disease-modifying anti-rheumatic drug / JIA juvenile idiopathic arthritis / MTX methotrexate / NR not reported
*Median dose of MTX: 15 mg/kg (5-25)
** Includes patients who received etanercept

Appendix 9 Change in concomitant use of other DMARDs

Tables 9.1 and 9.2 show the use of corticosteroids and MTX as reported in the etanercept studies. Methotrexate was the primary non-biologic medication used. As well, two patients received leflunomide and one patient received hydroxychloroquine in the long-term extension [38].

Table 9.1 Use of low-dose systemic corticosteroids (etanercept studies)

	Use at baseline	Withdrawal	Dose decrease
Lovell (4-year extension study)[38]	34/58 (59%)	18/34 (53%)	28/34 (82%) (≤ 5 mg/day)
Horneff (2004)[25]	199 (68%)	50/199 (25%)	-
Quartier[24]	30/61 (49%)	24/30 (80%) year 1	30/30 (100%)
Kimura[39] **(systemic-onset JIA)**	64/82 (78%)	33/64 (52%) - last follow-up	-

JIA juvenile idiopathic arthritis

Table 9.2 Use of methotrexate (etanercept studies)

Methotrexate use Etanercept studies	
Lovell (extension study) [38]	10/58 (17%) year 1 8/47(17%) year 2 10/43 (23%) year 3 13/38 (34%) year 4
Horneff (2004) [25]	235 (80%) Discontinued: 25 (11%)
Kimura[39] **(systemic-onset JIA)**	67/82 (82%) Discontinued: 15/67 (22%)

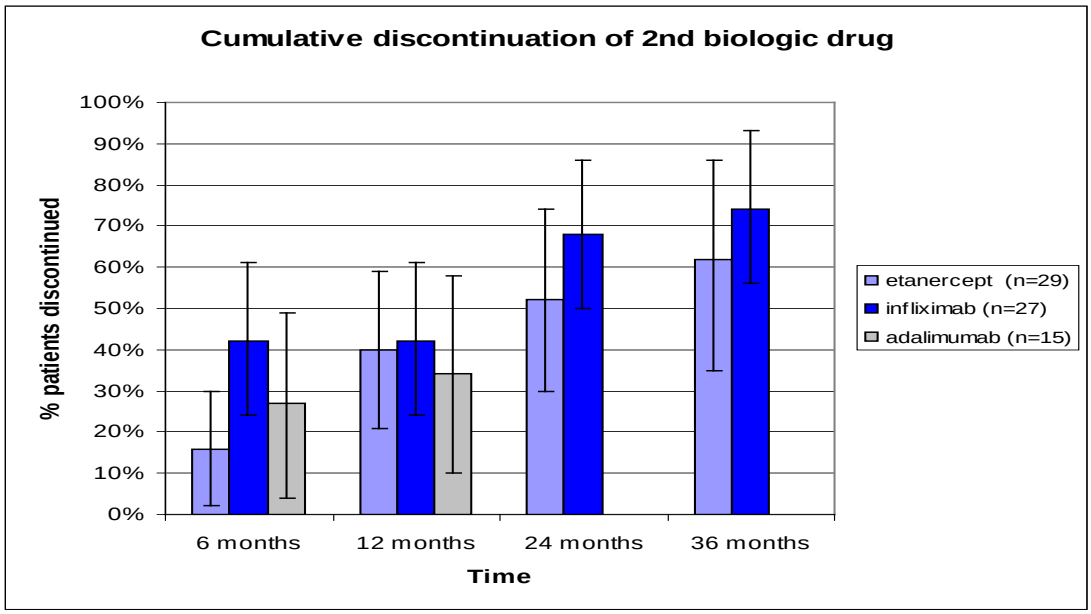
JIA juvenile idiopathic arthritis

Appendix 10 Treatment switch between biologic agents

A retrospective chart review that included 209 JIA patients treated with anti-TNF-α drugs for more than one year evaluated the clinical outcomes of a second anti-TNF-α drug once the first drug either failed or was stopped due to adverse events.[33] All patients were refractory to other DMARDs before starting anti-TNF-α drugs.[33] Etanercept was the first drug in 105 patients, and infliximab in 104 patients.[33] Seventy-three patients switched to a second biologic drug: 29 switched from etanercept to infliximab, 27 from infliximab to etanercept, 15 from either etanercept or infliximab to adalimumab, and two patients switched to anakinra.[33] Among these 73 patients, 43 (59%) discontinued the treatment with the second biologic drug over a mean treatment time of 16.3 months (figure 10.1).[33] In addition, 31 patients successfully re-started the first biologic agent after discontinuation due to a disease flare.[33] Adjusted survival analyses[a] showed that patients with the systemic JIA subtype had a 4.5 fold risk of discontinuations of the second biologic drug compared to patients with non-systemic subtypes (hazard rate (HR): 4.5, 95% CI: 1.8, 11.3, p=0.002).[33] Discontinuation of the first biologic drug due to adverse events or lack of efficacy with etanercept were predictors of discontinuation of the second biologic drug due to adverse events [HR: 6.8, 95% CI: 1.6 , 28.7), and 12.6, 95% CI: 3.1 , 28.5), respectively].[33] The authors concluded that the rates of discontinuation of etanercept and infliximab when used as a second anti-TNF-α agent were similar to when these drugs were used as a first-line agent.[33]

[a] The analyses were adjusted for: baseline biologic drug, age, disease duration, gender, JIA subtype, positive rheumatoid factor, antinuclear antibody, human leukocyte antigen B 27, uveitis, C-reactive protein, erythrocyte sedimendation rate, number of DMARDs, number of active joints, dose of prednisone, first biologic drug, reason for discontinuation of first biologic drug.

Figure 10.1 Rate of discontinuation of the second biologic drug



Error bars represent the 95% confidence interval determined by the authors.
Discontinuations were due to either lack of efficacy, adverse events, or inactive disease (5.5%).

A prospective study evaluating the efficacy of a second anti-TNF-α drug in 40 JIA patients was presented at a conference.[40] The mean age at disease onset was 6.6 ± 5 years, and 18.8 ± 6.9 years at the time the first biologic drug was started.[40] Eighteen patients treated with etanercept switched to either infliximab (n=11), or adalimumab (n=7), and 22 patients switched infliximab to either etanercept (n=19), or adalimumab (n=3) due to either lack of efficacy or intolerance.[40] The mean treatment duration with the first anti-TNF-α was 19.9 ± 16.9 months.[40] After 3-6 months of treatment with the second anti-TNF-α treatment response was good to moderate in 80% of the patients according to the DAS criteria.[40] The authors concluded that discontinuation of an anti-TNF-α due to lack/loss of efficacy or intolerance does not prevent a good response with a second anti-TNF-α.[40]

In the abatacept RCT, 22/57 (39%) patients with prior anti-TNF-α use achieved ACR Ped 30 criteria at the end of the 4-month lead-in open-label phase, whereas patients 101 (76%) without prior anti-TNF-α use achieved ACR Ped 30.[13]

Appendix 11 Adverse events reported in the identified biologics studies

Safety

The adverse events reported in studies evaluating the use of biologics in JIA are summarized below. Studies done exclusively in patients with systemic-onset JIA are also included as specified. Adverse events reported are divided by serious or non-serious adverse events and according to study phase (lead-in open-label, double-blind, and long-term extension).

The association between the study drug and the adverse event was not always clear in the studies as indicated in the tables below. Unrelated events were not included when possible and when this was made clear in the publication. Disease flare and pregnancies were excluded from the tables.

Serious adverse events (RCTs)

Lead-in phase

Table 11.1 summarizes the serious adverse events reported during the lead-in phase of the RCTs. No drug-related serious adverse events reported in the anakinra study (three events occurred that were considered non-related). The infliximab study did not have a lead-in open-label period therefore is not included in this table.

Information regarding concomitant MTX use is provided in table 11.1. In general the studies permitted the use of stable low doses of corticosteroids.

Table 11.1 Serious adverse events reported in the open-label lead-in phase of RCTs

Serious adverse events	Etanercept[10] N=69	Adalimumab[12] N=171	Abatacept[13] N=190	Tocilizumab (systemic-onset)[15] N=56
Length of open-label phase	**3 months**	**4 months**	**4 months**	**1.5 months**
Concomitant use of MTX	0	85 (50%)	140 (74%)	0
Association with the drug	Not clearly stated (unrelated excluded)	Possibly related	Not clearly stated*	Not clearly stated
	% patients with events	N. events / patient	% patients with events	% patients with events
Serious adverse events	2 (2.9%)	7 events (4.1%)	6 (3%)	2 (3.6%)
Depression and personality disorder	1 (1.5%)	-	-	-
Gastroenteritis – flu syndrome	1 (1.5%)	-	-	-
Varicella	-	-	1 (0.5%)	-
Herpes simplex infection	-	0.06 events / patient	-	-
Leucopenia	-	0.06 events / patient	-	-
Neutropenia	-	0.06 events / patient	-	-
Pharyngitis	-	0.06 events / patient	-	-
Pneumonia	-	0.06 events / patient	-	-
Acute leukemia	-	-	1 (0.5%)	-
Ovarian cyst	-	-	1 (0.5%)	-
Urticaria	-	-	-	-
Anaphylactoid reaction	-	-	0	1 (1.8%)
Gastrointestinal hemorrhage	-	-	-	1 (1.8%) presumably caused by high-dose corticosteroids

MTX methotrexate
*Events associated with the underlying disease, 2 patients with flare, and one with arthropathy not included in the table.

Double-blind phase

The serious adverse events reported during the double-blind phase of the RCTs are summarized in Table 11.2. No serious adverse events were reported during the double-blind phase in the etanercept, anakinra and tocilizumab studies.

In the infliximab study each study group had a different duration of follow-up, therefore, crude rates and adjusted for follow-up duration are provided. Although the tables show different rates of adverse events among the three treatment groups (infliximab 3mg/kg, infliximab 6mg/kg, and placebo) the authors concluded that the overall frequency of adverse events was similar among the three groups. The three groups had different lengths of follow-up (infliximab 3mg/kg had 52 weeks, infliximab 6mg/kg had 38 weeks and placebo had14 weeks).

Table 11.2 Serious adverse events reported during the double-blind phase of RCTs

Serious adverse events	Adalimumab[12]		Abatacept[13]		Infliximab[41]			Anakinra (systemic-onset) [42, 43]
Length	**8 months**		**6 months**		**3.5 – 12 months**			**6 months**
Association with the drug	Possibly related		Possibly related*		Not clearly stated			Not clearly stated
Concomitant use of MTX	38 (55%) – adalimumab 37 (57%) - placebo		48 (80%) – abatacept 46 (74%) - placebo		All patients			-
	% patients with event		% patients with event		% patients with event			% patients with event
	Adalimumab N=68	Placebo N=65	Abatacept N=60	Placebo N=62	Infliximab¶ 3 mg/kg N=60 **52 weeks**	Infliximab¶ 6 mg/kg N=57 **38 weeks**	Placebo¶ N=60 **14 weeks**	Not clear if events reported refer to anakinra group (n=12) or both anakinra and placebo groups (n=24) N=12 (N=12 control)
Serious adverse events	0	1 (1.5%)	0	2 (3.2%)	Crude 19 (31.7%) Adjusted¦ 62.4%	Crude 5 (8.8%) Adjusted¦ 24%	Crude 3 (5%) Adjusted¦ 32.9%	5/12 (41.7%) or 5/24 (20.8%)
Infusion-related reactions	-	-	-	-	4 (6.7%)	2 (3.5%)	-	-
Serious infections	-	-	-	-	5 (8.3%)	1 (1.8%)§	2 (3.3%)§	3 (25%)
Gastroduodenitis	0	1 (1.5%)	-	-	-	-	-	-
Varicella	-	-	0	1 (1.6%)	1 (1.7%) – varicella zoster	-	-	-

					+ pneumonia			
Encephalitis	-	-	0	1 (1.6%)	-	-	-	-
Pneumonia	-	-	-	-	4 (6.7%)	-	-	-
Death	-	-	-	-	1 (1.7%)** 6 months after last infusion	-	1 (1.7%)¶¶	-
Crohn's disease	-	-	-	-	-	-	-	1 (8.3%) – ileocolic symptoms started at 3 months leading to the diagnosis of Crohn's disease. Systemic JIA diagnosis was reconsidered

JIA juvenile idiopathic arthritis/; MTX methotrexate
* One patient presented with a hematoma considered unrelated to the study drug, therefore it was not included in the table.
¶ Methotrexate was administered concomitantly with infliximab or placebo in all three groups.
¦ With adjustment of length of follow-up.
§ Type of serious adverse event not specified.
** The patient with systemic-onset JIA had a disease flare 3 months after the last infliximab infusion (discontinued during open-label extension), and was hospitalized and treated. Three months later (6 months after last infliximab infusion) the patient died of cardiac arrest.
¶¶ Ten days after the week 2 placebo infusion, the patient was hospitalized for septic shock, the patient's cardiac function worsened leading to death.

Long-term extension phase

Table 11.3 provides the serious adverse events reported during the long-term extension phase of the RCTs. One case of tuberculosis was diagnosed in the long-term extension of the infliximab study, in a patient with negative pre-treatment tests.[11] Results are not available for the abatacept and infliximab studies.

Table 11.3 Serious adverse events reported during the long-term extension phase of RCTs

Serious adverse events	Anakinra[14] N=44 (29 completed the extension phase) ≥ 5 events / patient	Adalimumab[12] N=128	Etanercept[44]	Tocilizumab[15] N=50 Systemic-onset	Tocilizumab[45] N=128 Systemic onset (abstract)
Length of follow-up (mean/median)	1 year	1 year (230 pt-yrs)	8 years (318 pt-yrs)	1 year	1.5 years (up to 2.8 years)
Association to study drug stated ?	Treatment-emergent	Possibly-related	Not clearly stated	Not clearly stated	Not clearly stated
	# events/pt	# events/pt-yr	# events (%)	# events (%)	# events/pt-yr
Serious adverse events, No. patients (%)	1 (0.02) – treatment-emergent	9 (0.04)	16 ev. /69 patients (57%), 39 SAEs (0.12/pt-yr)	13 (26%) only 5 specified	0.37/pt-year
Nephrosis	1 (0.02)	-	-	-	-
Serious Infections	-	5 (0.02/pt-yr)	9 (15.5%), 0.03/pt-year sepsis, peritonitis, appendicitis, soft tissue infection, postoperative wound infection¦, pyelonephritis	-	0.15/pt-yr
Gastroenteritis	-	-	-	2 (4%)	0.04/pt-yr
Bronchitis	-	-	-	2 (4%)	-
Upper respiratory infections	-	1 (0.004) – bronchopneumonia	-	-	0.03/pt-yr
Pharyngitis	-	1 (0.004)	-	-	-
Varicella	-	2 (0.009)	3 (5%) - aseptic meningitis with cervical subluxation in one case¦	-	-

Tuberculosis	-	0	-	-	-
Rash / allergic reaction	-	-	1 (1.7%)	1 (2%) Anaphylactoid reaction	-
Viral infection	-	1 (0.004)	-	-	-
Demyelinating disease	-	0	0	-	-
Lupus-like syndrome	-	0	0	-	-
Malignancies	-	0	0	-	-
Hematochezia	-	1 (0.004)	-	-	-
Abdominal pain	-	1 (0.004)	1 (1.7%) With epigastric pain	-	-
Epigastric pain	-	-	1 (1.7%)¦	-	-
Arthralgia	-	-	1 (1.7%)	-	-
Dental abscess	-	-	1 (1.7%)¦	-	-
Hydrocephalus	-	1 (0.004)	-	-	-
Death	-	-	-	-	2 (1.6%) due to MAS and cardiac amyloidosis

MAS macrophage activation syndrome / pt-yrs patient-years / SAE serious adverse events

Serious adverse events: Observational studies and registries

Serious adverse events reported in observational studies and registries with etanercept are summarized in table 11.4

Table 11.4 Etanercept serious adverse events reported in etanercept observational studies and registries

Serious adverse events	German registry [25, 46]	Pontikaki et al.[47] and Gerloni et al. [35] ¶¶	Quartier et al.[24]§	Giannini et al.[31]	Prince et al.[27]	Kimura et al.[39] Systemic JIA	Cochino et al. [29] N=71 (abs)
	Etanercept± MTX N=604	Etanercept± MTX N=95	Etanercept± MTX N=61	Etanercept ± MTX N=404	Etanercept ± MTX N=146	Etanercept± MTX N=82	Etanercept + MTX N=71
Length of follow-up	Up to 4 years (1,149 pt-yrs)	12 (1-40)	13 months (0.6-30)	Up to 3 years (12%)	up to 6 years (312 pt-yrs)	Mean: 2.1 year (0.25 , 5.8)	
Association to etanercept?	Not clearly defined	possibly, probably or definitely related	All events probably-related to etanercept	Not clearly defined	Not reported	Likely unrelated	Not clear
Serious adverse events, No. patients (%)	52 (8.6%) 0.045/pt-yr	Event severity not specified	12 (20%) 1 patient was using conc. MTX started just before the event	0.057-0.076/pt-yr	9 patients (6.2%) 0.029/pt-yr	2 (2.4%) **	5 patients (7%)
Malignancies	2 (0.3%) thyroid carcinoma, yolk sac carcinoma	1 (1.1%) thyroid cancer ¦¦	-	-	-	-	-
Lymphoma	1 (0.02%) Hodgkin concomitant MTX	-	-	-	-	-	-

	azathioprine and cyclosporine A						
Psychiatric disorders	1 (0.1%) - hallucinations	-	2 (3.3%)	-	-	-	-
Toxic epidermal necrolysis	1 (0.1%) – concomitant use of contraceptive	-	-	-	-	-	-
Serious Infections	26 (4.3%) §§	2/127 (0.007/pt-year)[35]	-	0.019-0.021/pt-yr medically important infections	4 (2.7%) 0.013/pt-yr uro-sepsis (n=1) and gastrointestinal infection (n=3)	-	2 (2.8%) fulminant acute hepatitis A, 1 death
Rash / allergic reaction	-	-	1 (1.6%) skin rash, vasculitis, systemic symptoms	-	-	-	-
Skin lesions	1 (0.2%)	-	-	-	-	-	-
Infusion-related reaction	1 (0.1%)	-	-	-	-	-	-
Headache	-	-	1 (1.6%) - + marked dysesthesia	-	-	-	-
Crohn's Disease	1 (0.2%)	-	1 (1.6%)	-	1 (0.7%)	-	-
MAS	-	-	1 (1.6%)	-	-	2 (2.4%) during	-

						flare, drug not directly implicated	
Uveitis	4 (0.7%)	-	2 (3.3%)	-	0	-	-
Weight gain	-	-	1 (1.6%) (20 kg)	-	-	-	-
Paresthesia	1 (0.1%)	-	-	-	-	-	-
Lupus-like syndrome	-	-	-	-	-	-	2 (2.8%) demyelinating neuropathy in 1
Retrotubular optic neuritis	-	-	1 (1.6%)	-	-	-	-
Demyelinating disease	1 (0.3%) Febrile seizure with rotavirus enteritis (previous epilepsy) demyelination on MRI, cerebral lesions still present after 6 months. Negative for infection[25]	-	-	-	0	-	-
Epileptic insult	1 (0.2%) seizures	-	-	-	1 (0.7%)	-	-
Pancytopenia / neutropenia	Neutropenia 2 (0.3%)	-	2 (3.3%)	-	-	-	-
Abdominal pain	1 (0.2%)	-	-	-	-	-	-
Pancreatitis	1 (0.2%)	-	-	-	-	-	-

Vomiting	1 (0.2%)	-	-	-	-	-	-
Sarcoisidosis	-	-	-	-	2 (1.4%)	-	1 (1.4%)
Colitis ulcerosa	-	-	-	-	1 (0.7%)	-	-
Papillitis	1 (0.2%)	-	-	-	-	-	-
Stevens-Johnson syndrome	1 (0.2%)	-	-	-	-	-	-
Ovarial cyst bleeding	1 (0.2%)	-	-	-	-	-	-
Colicky cholelithiasis	1 (0.2%)	-	-	-	-	-	-
Elevated serum creatinine	1 (0.2%)	-	-	-	-	-	-
Osteochondritis dissecans	1 (0.2%)	-	-	-	-	-	-
Painful urination	1 (0.2%)	-	-	-	-	-	-

JIA juvenile idiopathic arthritis / MAS macrophage activation syndrome / MRI magnetic resonance imaging / MTX methotrexate / pt-year patient-year
The study by Gerloni et al. did not specify the severity of the adverse events reported.[35]

§ Serious adverse event definition not provided.

** The two patients with systemic JIA who developed MAS had been taking etanercept for 12 and 25 months respectively, and both events occurred during a disease flare, therefore the authors believe that this may not be associated with etanercept.[39] The events resolved after treatment with high-dose corticosteroids, immunosuppressants, and infliximab.[39]

¦¦ Possibly-related to etanercept. Not clearly defined as serious adverse event by the author but meets the criteria for serious adverse events according to other studies

¶¶ - Reported together since Gerloni et al. seems to be an extension of the Pontitaki et al. report

§§ Serious infections reported: upper respiratory tract infections(n=8), soft tissue infections (n=3), pneumonia (n=3), herpes zoster (n=2), gastroenteritis (n=2), further unspecific infections (n=3), and one each: varicella, septic arthritis, sepsis, urinary tract infection.

Table 11.5 summarizes the serious adverse events reported in observational studies with infliximab and anakinra.

Table 11.5 Serious adverse events in observational infliximab studies

Serious Adverse Events	Infliximab Gerloni et al.[35] N=81	Anakinra Lequerre et al.[48] N=20
Association with study drug ?	Possible, probable, definite	Not clearly stated
Severe infections	1 (1.2%)	1 (5%) visceral *Leishmania* infection

Non-serious adverse events (RCTs)

Lead-in phase

Table 11.6 provides the non-serious adverse events reported during the lead-in phase of the biologics' RCTs. The frequency and types of adverse events were not specified in the tocilizumab study in systemic-onset JIA; the most common events were upper respiratory tract infections and gastroenteritis.[15] The authors reported that 10 (17.9%) patients presented mild infusion reactions in the tocilizumab study.[15]

Table 11.6 Non-serious adverse events reported during the lead-in open-label phase of RCTs

Non-serious adverse events	Etanercept[10] N=69	Adalimumab[12] N=171	Abatacept[13] N=190 Events in >5% reported (except injection-site reactions)	Anakinra[14] N=86 Events in ≥ 5 patients reported
Length of open-label phase	3 months	4 months	4 months	3 months
Association with the drug	Association with the drug not clearly stated	Association with the drug not clearly stated	Not clearly stated	Treatment-emergent events
Concomitant use of MTX	0	85 (50%)	140 (74%)	67 (78%)
Measure use in the reports	% patients with events	N. events / patient	% patients with events	% patients with events
Injection-site reactions	27 (39%)	1.8 events / patient	8 (4%)	64 (74%)
Infections		-	68 (36%)	35 (41%)
Upper respiratory tract infections	24 (35%)	0.12 events / patient	14 (7%)	20 (23%)
Opportunistic infections	-	-	-	-
Headache	14 (20%)	-	25 (13%)	19 (22%)
Rhinitis	11 (16%)	-	8 (4%)	-
Abdominal pain	11 (16%)	-	9 (5%) 10 (5%) (upper abdominal pain)	15 (17%)
Vomiting	10 (14%)	0.04 events / patient	-	6 (7%)
Pharyngitis / nasopharyngitis	10 (14%)	0.05 events / patient	11 (6%)	-
Nausea	8 (12%)	-	19 (10%)	7 (8%)

Diarrhea	-	-	17 (9%)	7 (8%)
Gastrointestinal infection / gastroenteritis	8 (12%)	-	1 (0.5%)	-
Rash	7 (10%) Urticaria: 1 (1.5%) 1st dose, lead to drug discontinuation	-	-	9 (11%)
Contusion	-	0.12 events / patient	-	-
Viral infection	-	0.10 events / patient	-	-
Excoriation	-	0.06 events / patient	-	-
Fever	-	-	12 (6%)	14 (16%)
Pain	-	-	-	5 (6%) 6 (7%) - limb
Arthralgia	-	-	-	11 (13%)
Cough	-	-	-	5 (6%)

MTX methotrexate

Double-blind phase

Tables 11.7 and 11.8 summarize the non-serious adverse events reported in the biologics' RCTs.

In the etanercept study, rates of adverse events were not provided but the authors reported that there were no differences in the frequencies of adverse events between the etanercept and placebo groups. Injection site reactions occurred in one patient in each group.[10] The authors also reported that there were no laboratory abnormalities requiring urgent treatment in the etanercept group. Frequency and types of adverse events other than the ones in the table below were not specified in the tocilizumab study in systemic-onset JIA, the most common events were upper respiratory tract infections and gastroenteritis. [15]

Table 11.7 Non-serious adverse events reported during the double-blind phase of the RCTs

Non-serious adverse events	Adalimumab[12]		Abatacept[13]		Infliximab[11]		
Length of double-blind phase	**8 months**		**6 months** Events with frequency >5% reported (except injection-site reactions)		**3.5 – 12 months**		
Association with the drug	Association with the drug not clearly stated		Association with the drug not clearly stated		Not clearly specified		
Concomitant use of MTX	38 (55%) – adalimumab 37 (57%) - placebo		48 (80%) – abatacept 46 (74%) - placebo		All patients		
	# events / patient		% patients with event		% patients with event		
	Adalimumab n=68	**Placebo n=68**	**Abatacept n=60**	**Placebo n=62**	**Infliximab¶ 3 mg/kg n=60 52 weeks**	**Infliximab¶ 6 mg/kg n=57 38 weeks**	**Placebo¶ n=60 14 weeks**
Injection-site reactions	2.1 ev./pt	1.2 ev./pt	1 (2%)	2 (3%)	21 (60%)¦	10 (17.5%)¦	5 (8.3%)¦
Infections	-	-	27 (45%)	27 (44%)	41 (68.3%)	37 (64.9%)	28 (46.7%)
Upper respiratory tract infections	0.2 ev./pt	0.2 ev./pt	4 (7%)	5 (8%)	-	-	-
Opportunistic infections	-	-	-	-	3 (5%)‡	-	-
Headache	-	-	3 (5%)	1 (2%)	-	-	-
Rhinitis	-	-	1 (2%)	4 (7%)	-	-	-
Abdominal pain	-	-	4 (6.7%)*	1 (2%)*	-	-	-
Vomiting	0.06 ev./pt	0.05 ev./pt	-	-	-	-	-
Pharyngitis / nasopharyngitis	0.07 ev./pt	0.2 ev./pt	4 (7%)	3 (5%)	-	-	-

Nausea	-	-	2 (3%)	4 (7%)	-	-	-
Gastrointestinal infection / gastroenteritis	-	-	3 (5%)	1 (2%)	-	-	-
Diarrhea	-	-	1 (2%)	1 (2%)	-	-	-
Rash	-	-	0	0	-	-	-
Contusion	0.2 ev./pt	0.2 ev./pt	-	-	-	-	-
Viral infection	0.2 ev./pt	0.1 ev/pt	-	-	-	-	-
Excoriation	0.24 ev./pt	0.05 ev./pt	-	-	-	-	-
Fever	-	-	4 (7%)	5 (8%)	-	-	-
Uveitis / autoimmune disorders	-	-	0	0	-	-	-
Tuberculosis	-	-	-	-	1/78 (1.3%) – asymptomatic, not clear in which group		

ev event / pt patient / MTX methotrexate
* Includes both abdominal and upper abdominal pain.
¶ Methotrexate was administered concomitantly with infliximab or placebo in all three groups.
¦ Injection site reactions defined as any adverse event that occurred during or within 1 hour following completion of an infusion.
‡ Potential opportunistic infections reported in the 3 mg/kg group (1 of each): moniliasis (vaginal thrush) , moniliasis (oral thrush), herpes zoster. It is not clear if there were any opportunistic infections in the other groups.

Table 11.8 Non-serious adverse events reported during the double-blind phase of the RCTs

Non-serious adverse events	Tocilizumab (systemic-onset)[15]		Anakinra (systemic-onset) [42, 43]	Anakinra[14] (polyarticular-course)	
Length of double-blind phase	**3 months**		**6 months**	**4 months** Events in ≥ 5 patients reported	
Association with the drug	Not clearly stated		Not clearly stated	Treatment-emergent events	
	% patients with event		% patients with event	% patients with event	
	Tocilizumab n=20	Placebo n=23	Anakinra n=12 (control, n=12) not clear if events occurred in anakinra group	Anakinra n=25	Placebo n=25
Injection-site reactions	-	-	2 (16.7%) painful injections	3 (12%)	3 (12%)
Infections	-	-	-	9 (36%)	8 (32%)
Upper respiratory tract infections	2 (10%)	4 (17%)	-	4 (16%)	5 (20%)
Herpes zoster	0	1 (4.3%)	-	-	-
Mononucleosis	1 (5%)*	0	-	-	-
Gastrointestinal infection / gastroenteritis	1 (5%)	1 (4%)	-	-	-
Transient hepatic cytolysis	-	-	1 (8.3%)	-	-
Headache	-	-	-	6 (24%)	1 (4%)
Abdominal pain	-	-	-	3 (12%)	2 (8%)
Nausea	-	-	-	0	0
Diarrhea	-	-	-	3 (12%)	0
Rash	-	-	-	0	3 (12%)
Pain	-	-	-	0 limb: 3 (12%)	2 (8%) limb: 4 (16%)

Arthralgia	-	-	-	1 (4%)	4 (16%)

*Mononucleosis was associated with striking increases in liver enzymes and neutropenia two weeks after the fifth dose of tocilizumab.

Long-term extension phase (RCTs)

Table 11.9 summarizes the non-serious adverse events reported during the long-term extension phase of the biologics' RCTs.

One patient (1/78, 1.3%) was diagnosed with tuberculosis in the long-term extension of the infliximab study. [11] The patient had a negative tuberculosis skin test prior to study start.[11] No non-serious adverse events were reported among 36 patients with a 3-year follow-up in the open-label extension of the infliximab RCT. The information was presented in an abstract, therefore it was not clear if safety data was collected.

Table 11.9 Non-serious adverse events reported during the long-term extension phase of RCTs

Non-serious adverse events	Etanercept[22] n=58	Anakinra[14] n=44 (29 completed the extension phase) ≥ 5 events / patient	Adalimumab[12] n=128 (230 patient-years)	Tocilizumab[15] (systemic-onset) n=56	Tocilizumab[45] (systemic-onset) n=128 (only events that lead to discontinuation)
Length of follow-up	1 year ¶	1 year	1 year – 2 years ?	1 year	-
Association to etanercept	Not clearly stated	Treatment-emergent	Possibly-related	Not clearly stated	-
	# events / patient-year	# events (%)	# events (events/ patient year)	# events (%)	# events/patient-year
Infusion-related reactions	-	2 (5%) – reactions at the application site¦	373 (1.6)	-	2 (1.6%)
Infections	-	16 (36%)	-	-	-
Upper respiratory infections	1.31	5 (11%)	74 (0.32)	19 (34%)	-
Pharyngitis	0.21	-	16 (0.6) nasopharyingitis	33 (59%) nasopharyngitis	-
Skin infections	0.19	-	-	-	-
Flu syndrome	0.17	-	-	-	-
Gastroenteritis	-	-	-	16 (29%)	-
Bronchitis	-	-	-	14/56 (25%)	-
Viral infection	-	-	35 (1.5)	-	-
Tuberculosis	-	-	-	0	-
Rash / allergic reaction	0.11	4 (9%)	-	-	2 (1.6%) anaphylactoid reaction
Otitis	0.13	-	-	-	-
Escoriations	-	-	20 (0.9)	-	-

Conjunctivitis	0	-	-	-	-
Headache	0.84	6 (14%)	-	-	-
Cough	-	3 (7%)	-	-	-
Sore throat	-	4 (9%)	-	-	-
Arthralgia	-	10 (23%)	4 (0.02)	-	-
Pain (limb)	-	5 (11%)	-	-	-
Rhinitis	0.17 / patient-year	-	-	-	-
Nausea	0.11 / patient-year	2 (4.5%)	-	-	-
Diarrhea	-	2 (4.5%)	-	-	-
Vomiting	-	1 (2%)	9 (0.04)	-	-
Abdominal pain	0.36 /patient-year	7 (16%)	-	-	-
Accidental injury	0.11 / patient-year	-	-	-	-
Contusion	-	-	11 (0.05)	-	-
Fever	-	9 (21%)	-	-	-
Pain	-	4 (9%)	-	-	-
Increases in liver enzymes	-	-	-	16 (29%) ALT‡ 12 (21%) AST‡ 10 (18%) LDH	-
Total cholesterol increases	-	-	-	Mild increases mostly within normal range were reported, number of cases not provided	-
Duodenal perforation	-	-	-	-	1 (0.8%)
Gastrointestinal hemorrhage	-	-	-	-	1 (0.8%)

ALT alanine aminotransferase / AST aspartase aminotransferase / LDH lactate dehydrogenase

¶ Only hospitalizations, malignancies, and new signs and symptoms of other connective tissue diseases were reported in the publication.

The most commonly reported adverse events other than infections were headache, abdominal pain, rhinitis, nausea, fever, accidental injury, and rash. Frequencies not provided by the authors.

¦ Types of reactions: inflammation (1, 2%), pain (2, 5%).

‡ Increases in transaminases noted early during tocilizumab administration and tended to decrease during treatment.

Non-serious adverse events: Observational studies and registries

Table 11.10 summarizes the non-serious adverse events reported in etanercept observational studies and registries.

Table 11.10 Non-serious adverse events Etanercept observational studies

Non-serious Adverse Events (number of patients, %)	Horneff et al.[28] n=604 (1,149 pt-yrs)	Gerloni et al.[35] n=127 (258 pt-yr)	Quartier et al. n=32	Kimura et al. [39] n=82	Prince et al. n=146	Southwood et al. [30] n=434 Events leading to discontinuation
Association with study drug	Not clearly specified	Possible, probable, definite (severity not reported)	Not clear if related but drug discontinued	Not clear unless specified	Association to etanercept not reported	Only events leading to discontinuation reported
Adverse events	138 events (0.12/pt-yr)	133 events (0.52/pt-yr)	-	-	56 (38.4%)	-
Infections	58 events (0.05/pt-yr)	34 (0.13/pt-yr)	-	9 (11%)	17 (11.6%)	3 (0.7%) 1 (0.2%) sepsis
Infusion-related reactions	7 (0.006/pt-yr)	12 (0.05/pt-yr)	17 (27.9%) mild	6 (7.3%)	7 (4.8%)	-
Hypercalciuria / kidney stones	-	-	-	3 (3.7%)	-	-
Low white cell count	-	2 (0.08/pt-yr) thrombocytopenia, leukopenia	-	-	-	1 (0.2%)
Urticaria	-	-	-	3 (3.7%) mild urticaria/ other allergic symptoms	-	Eczema flare 1 (0.2%) l

Rash / Skin reactions	8 (0.007/pt-yr)	9 (0.035/pt-yr) skin lesions	10 (16.4%) rash	-	2 (1.4%)	-
Hallucinations	-	-	-	-	-	1 (0.2%)
Neuro-psychological	14 (0.012/pt-yr)	36 (0.14/pt-yr)	-	-	-	-
Concentration disorder	-	-	-	-	3 (2.1%)	-
Optic neuritis	-	-	-	-	-	1 (0.2%)
Reduced vision	-	-	-	-	-	1 (0.2%)
Headache	6 (0.005/pt-yr)	-	7 (11.5%)	6 (7.3%) fatigue, headache myalgia	6 (4.1%)	1 (0.2%)
Crohn's disease	-	5 (3.9%) 0.019/pt-yr	-	-	-	-
Uveitis flare	5 (0.004/pt-yr)	-	-	-	-	1 (0.2%) l
Menorrhagia	-	-	-	-	-	1 (0.2%)
Anxiety	-	-	-	-	-	1 (0.2%)
Low mood	-	-	6 (9.8%) mood changes	-	-	2 (0.5%)
Asthenia/anorexia	-	-	2 (3.3%)	-	5 (3.4%) fatigue	-
Nausea/vomiting	3 (0.003/pt-yr)	-	10 (16.4%) mild gastrointestinal disorders	-	9 (6.2%)	-
Abdominal pain	-	7 (0.027/pt-yr)	-	-	1 (0.7%)	-
Laboratory abnormalities	11 (0.01/pt-yr)	-	-	-	-	-
Bowel pain	8 (0.007/pt-yr)	-	-	-	-	-

Hair loss	1 (0.001/pt-yr)	-	-	-	2 (1.4%)	-
Hypertension	-	3 (0.011)	-	-	-	-
Tachycardia	-	4 (0.015)	-	-	-	-
Macrohematuria	-	1 (0.004)	-	-	-	-
Thoracic pain	-	-	1 (1.6%)	-	-	-
Hematoma	-	-	1 (1.6%)	-	-	-
Chronic cough	-	-	1 (1.6%)	-	2 (1.4%	-
Weight loss	-	-	-	-	1 (0.7%)	-
Osteoporosis	-	-	-	-	1 (0.7%)	-

Pt-yr patient-year

Table 11.11 summarizes the non-serious adverse events reported in the infliximab and anakinra observational studies.

Table 11.11 Non-serious adverse events in the infliximab and anakinra observational studies

Non-serious Adverse Events	Gerloni et al.[20] Infliximab n=24	Gerloni et al.[35] Infliximab n=81	Lequerre et al.[48] Anakinra n=20
Association with study drug ?	Not clearly stated	Possible, probable, definite	
			16 months
	N. patients (%)		N. patients (%)
Adverse events			
Infusion-related reactions	7 (29%)	32 (39.5%)	18 (90%) pain during injections Some patients had local inflammation during the 1st weeks, improved
Infections	-	6 (7.4%)	-
Rhinopharyngitis	-	-	2 (10%)
Varicella	-	-	1 (5%)
Labial herpes	-	-	1 (5%) non-extensive
Cutaneous lesions	-	2 (2.5%)	-
Neuro-psychiatric manifestations	-	17 (21%)	-
Hypertension	-	5 (6.2%)	-
Macrohematuria	-	2 (2.5%)	-

Appendix 12 Case reports on biologic agents

Adverse event	JIA subtype (duration)	Patient characteristics	Biologic used (time on biologic)	Previous / concomitant medications	Authors' conclusions
Diabetes mellitus (DM) type 1[49]	Systemic-onset (3 years), polyarticular course	Female, 7-year old	Etanercept 0.4mg/kg (5 months)	Previous: MTX, steroids	Family history for DM Anti-GAD antibodies were positive before & after etanercept started Predisposition to DM, but may have been triggered by etanercept
Psoriasis[50]	Extended oligoarticular (12 years)	Female, 13 years	Etanercept (2 years)	Concomitant, steroids, MTX (dose gradually reduced/discontinued) Previous: MTX, steroids, chemotherapy, radiotherapy	The patient developed a new rash which evolved, leading to a diagnosis of psoriasis Patient/family had no history of psoriasis Cushingoid features on steroids Believed that the patient may have had psoriatic arthritis from onset However, given the temporal relationship, psoriasis may be associated with etanercept, & may have been induced by the drug.
Autoimmune hepatitis (anti-dsDNA antibody)[51]	Systemic-onset (2 years)	Female, 9 years	Etanercept (10 months) 0.4mg/kg 2x/week increased to 50mg once a week	Concomitant: hydroxychloroquine, NSAID, steroid Previous: MTX, steroid, NSAID	Both etanercept & hydroxychloroquine were discontinued Other therapies were prescribed; after 8 months auto-antibodies were negative Concluded that it is not possible to ascertain if autoimmune hepatitis was triggered by etanercept

DM diabetes mellitus / GAD glutamic acid dearboxylase / MTX methotrexate / NSAID non-steroidal anti-inflammatory drug

Adverse event	JIA subtype (duration)	Patient characteristics	Biologic used (time on biologic)	Previous / concomitant medications	Authors' conclusions
Multifocal septic arthritis and osteomyelitis caused by group A *streptococcus*[52]	Polyarticular (3 years)	Female, 12-years	Etanercept 25mg 2x/week	Concomitant: MTX, naproxen	Complicated course and multiple bone and joint involvement may have been due to immunosuppressive therapy, however JIA may predispose patients to the event
Acute, non-obstructive cholecystitis[53]	Polyarticular	Female, 15-years	Etanercept (0.4mg/kg 2x/week 12 weeks, 0.5mg/kg 2x/week 2 weeks) Infliximab 3mg/kg (20 weeks)	Previous: MTX, sulfasalazine	Event occurred with etanercept and later with infliximab therapy
Fatal (opportunistic) pulmonary infection, tuberculosis not confirmed, cardiac arrest[54]	Systemic (4 years), polyarticular-course	Female, 9 years	Infliximab 20 mg/kg/month	Previous: indomethacin, steroids, MTX, cyclosporine, etanercept	Patients on immunosuppressive agents must be monitored for opportunistic infections possibly of atypical presentation
Mycobacteria tuberculosis peritonitis[55]	JIA (5 years)	Female, 19 years	Etanercept 25mg 2x/week (8 months)	Previous: MTX, steroids	

MTX methotrexate

Adverse event	JIA subtype (duration)	Patient characteristics	Biologic used (time on biologic)	Previous / concomitant medications	Authors' conclusions
Septic abscess[56]	Polyarticular (4 months)	Female, 11 years	Etanercept 25 mg 2x/week (2 months)	Concomitant: MTX, steroid, naproxen	
Infection of urachal cyst during etanercept therapy[57]	Enthesitis-related (6 years)	Male, 17 years	Etanercept 0.4mg/kg 2x/week (18 months)	Concomitant: MTX Previous: NSAIDs, MTX sulfasalazine, steroids	Etanercept was stopped for 2 weeks, then restarted No complications in the subsequent 3 years of treatment
Hodgkin's Lymphoma[58, 59]	Extended oligoarthritis and uveitis (8 years)	Male, 9 years	Infliximab (3.5 years) 5-10mg/kg /dose	Previous: steroids, MTX, cyclosporine, mycophenolate mofetil, etanercept	The association between Hodgkin's lymphoma and the use of anti-TNF-α agents is not clear Confounding factors may include: disease duration and severity, chronic inflammation, and previous immunosuppressive therapy
	Polyarticular (4 years)	Female, 15 years	Etanercept (almost 4 years) 0.4mg/kg 2x/week	Concomitant: MTX (4.3 years)	
	Systemic (8 years)	Female, 10 years	Adalimumab (2.4 years	Previous: NSAID, steroid, MTX, leflunomide, anakinra, cyclophosphamide, etanercept (1 year) Infliximab 3mg/kg, 3 doses	
	Polyarticular (7 years)	Female, 21 years	Etanercept (3.5 years) 25mg 2x/week, then 50mg/week	Concomitant: MTX (6 years intermittently) Previous: NSAID, MTX	

MTX methotrexate / TNF tumour necrosis factor

Adverse event	JIA subtype (duration)	Patient characteristics	Biologic used (time on biologic)	Previous and concomitant medications	Authors' conclusions
Delayed maculopapular, urticarial rash (2 cases)[60]	Systemic-onset (7 and 9 years, respectively)	Female, 10 years Male, 16 years	Infliximab 5 mg/kg Event occurred after 2 doses. Infliximab treatment continued without complications, concomitant steroids stopped after 3rd infusion	Concomitant: steroids, NSAIDs Previous: NSAIDs, steroids, MTX, cyclosporine	"Short-lived cutaneous rash may appear 2-3 weeks after the introduction of infliximab as a delayed hypersensitivity reaction in children"
Hemolytic transfusion reaction[61]	Systemic-onset	Male, 10 months	Infliximab 10 mg/kg (total: 300mg)		Patient received 1 unit of blood transfusion; 3 weeks after transfusion multiple alloantibodies detected including those against red cells Believed that infliximab infusion may have favoured the production of the antibodies
Thymic enlargement (thymic hyperplasia)[62]	Polyarticular (15 years)	Male, 21 years	Etanercept 50mg/week (18 months)	Concomitant: MTX (10 years)	Symptoms resolved after discontinuation of etanercept and MTX MTX and steroids were restarted without complications in 2.5 years of follow-up Unsure if the event was associated with etanercept, however, the symptoms resolved completely after drug discontinuation

MTX methotrexate / NSAID non-steroidal anti-inflammatory drug

Adverse event	JIA subtype (duration)	Patient characteristics	Biologic used (time on biologic before event)	Previous and concomitant medications	Authors' conclusions
Proliferative lupus nephritis and leukocytoclastic vasculitis[63]	Polyarticular (8 years)	Female, 22 years	Etanercept 25mg 2x/week (4 years)	Concomitant: MTX, folic acid, rofecoxib Previous: DMARDs, MTX	Upon etanercept discontinuation there was a rapid resolution of symptoms Drug may have induced the disease.
Systemic lupus erythematosus with irreversible type IV glomerolonephritis and severe obstructive pulmonary disease[64]	Polyarticular (9 years) elevated antinuclear antibodies Anti-dsDNA abnormal periodically Autoimmune markers negative before starting drug	Female, 16 years	Etanercept (signs, symptoms started within 2 months)	Previous: DMARDs, NSAIDs, steroids	Antinuclear, anti-dsDNA and anticardiolipin antibodies and reversible lupus-like syndromes occurred between 2-8 months of starting etanercept The patient developed lupus with multiorgan involvement that improved 1year after discontinuing etanercept, however disease manifestations were irreversible Congruent with drug-induced lupus, with rapid development of anti-dsDNA and other autoantibodies
Drug-induced systemic lupus erythematosus[65] 1/13 (7.7%) patients treated	Polyarticular JIA (10 years)	Male, 12 years	Etanercept 25mg 2x/week (17 months)	Concomitant: steroids	Patient developed drug-induced syndrome similar to systemic lupus erythematosus ANA and anti-dsDNA antibodies negative before etanercept started but rose during treatment Antibody levels decreased with treatment interruption
Cerebral demyelination[66]	Still's disease, polyarthritis	Female, 5 years	Etanercept 0.4mg/kg, 2x/week (1 year)	Previous: naproxen, MTX, steroids	Demyelination could be either part of the disease or an adverse event of anti-TNF-α treatment
Demyelinating disease,	Psoriasis (14	Female, 18	Etanercept 25mg	Previous: MTX, steroids	Anti-TNF-α therapy may exacerbate MS

multiple sclerosis (MS)[67]	years)	years	2x/week (1 year)		There may be a relationship between MS and other TNF-α mediated diseases Symptoms resolved before etanercept discontinuation, however a possible association cannot be ruled out

ANA anti-nuclear antibodies / MS multiple sclerosis / MTX methotrexate / TNF tumour necrosis factor / anti-dsDNA Anti double stranded DNA

Adverse event	JIA subtype (duration)	Patient characteristics	Biologic used (time on biologic before event)	Previous and concomitant medications	Authors' conclusions
Optic neuritis[68]	Extended oligoarticular (10 years) Uveitis (4 years)	Female, 12 years	Etanercept (2.5 months)	Previous: MTX, NSAIDs, steroids, salazopyrin	In patients with JIA and uveitis, deterioration of vision started after etanercept started Optic neuritis resolved in all 4 cases, 3 of which after drug discontinuation Decrease in visual acuity was not related to previous uveitis, but to optic disc swelling and vitreitis (not seen before) Believed that the optic neuritis may have been due to etanercept treatment.
	Oligoarticular (14 years) Uveitis (~14 years)	Female, 17 years	Etanercept (8 months)	Previous: MTX, NSAIDs, steroids, salazopyrin	
	Polyarticular (14 years)	Female, 21 years	Etanercept (18 months)	Previous: MTX, NSAIDs, steroids, gold, sulfasalazine, hydroxychloroquine	
	Spondyloarthropathy (6 years) Uveitis	Male, 18 years	Etanercept (11 months)	Previous: MTX, NSAIDs, steroids, cyclosporine	

NSAID non-steroidal anti-inflammatory drug / MTX methotrexate / TNF tumour necrosis factor

Adverse event	JIA subtype (duration)	Patient characteristics	Biologic used (time on biologic)	Previous / concomitant medications	Authors' conclusions
Macrophage activation syndrome (MAS)[69]	Systemic-onset (3.5 years) , severe polyarticular course	Female, 4.5 years	Etanercept 0.4mg/kg 2x/week (4 doses)	Previous: indomethacin, steroids, MTX, IV immunoglobulin, ibuprofen	MAS symptoms resolved 2-3 days after etanercept was discontinued Giant urticaria adjacent to injection site before MAS developed: "In the absence of an identifiable infection or any other change in medication, etanercept is the most likely triggering factor"
Sarcoid-related uveitis[70]	Polyarticular JIA (5 years)	Male, 9 years	Etanercept (2 months)	Previous: NSAIDs, steroids, MTX	ANA and rheumatoid factor were negative before treatment started Etanercept was discontinued and systemic steroids and MTX were started The rash and uveitis subsided

NSAID non-steroidal anti-inflammatory drug / MTX methotrexate

Appendix 13 Cost analyses

Table 13.1 shows the unit costs used in the cost analyses

Table 13.1. Unit costs used in the cost analyses

Resource	Unit cost ($)	Source
Medication costs		
Abatacept	$440 / 250mg mg vial	Ontario Exceptional Access Program[71]
Adalimumab	$668 / 40mg	RAMQ[72]
Etanercept	$170 / 25mg $336 / 50mg**	RAMQ[72]
Infliximab	$940 / 100mg	RAMQ[72]
Methotrexate	$12.5 / 20mg(2ml) SC injection $0.63 / 2.5mg tablet	Ontario Drug Benefit List[73]
Folic acid	$0.0259 / 5mg tablet	Ontario Drug Benefit List[73]
Acetaminophen	$2.87 / 24 ml (80 mg/ml)	RAMQ[72]
Diphenhydramine	$3.33 / Cost / 50 mg vial	RAMQ[72]
Hydrocortisone	$3.40 / 250mg	RAMQ[72]
Laboratory tests		
Complete blood count with differentials	$13.50	OHIP Schedule of Benefits and Fees, Laboratory Services[74]
Erythrocyte sedimentation rate	$1.60*	OHIP Schedule of Benefits and Fees, Laboratory Services[74]
Blood urea nitrogen	$2.60*	OHIP Schedule of Benefits and Fees, Laboratory Services[74]
C-reactive protein	$3.00*	OHIP Schedule of Benefits and Fees, Laboratory Services[74]
Creatinine	$3.12	OHIP Schedule of Benefits and Fees, Laboratory Services[74]
Liver function tests	$21.30	OHIP Schedule of Benefits and Fees, Laboratory Services[74]
Tuberculin test	$9.00	Vera-Llonch et al.[75]
Chest X-ray	$32.91	CADTH publication[76]
Healthcare personnel		
Physician fees	$29.20 / visit	OHIP Schedule of Benefits and Fees, Physician Services[77]
Nursing fees	[redacted]	HSC, Toronto
Non-healthcare costs		
Productivity costs	$19.13	Statistics Canada 2007 average

	$133.9 (hourly rate * 7 hours)	Canada[78]

HSC Hospital for Sick Children / RAMQ Régie de l'Assurance Maladie du Québec / SC subcutaneous / OHIP Ontario Health Insurance Plan
* Unit costs calculated by multiplying the number of LMS units (Labour, Materials and Supervision) by the cost per unit.
**Price in Ontario: $364.28/50mg[73]

Tables 13.2-13.4 show the calculation of treatment costs with biologics and MTX. Tables 13.5-13.8 show the calculation of costs of pre-medications, annual monitoring costs, concomitant medications, and productivity costs. These costs were used to calculate the treatment costs of biologics and MTX.

Table 13.2 Cost analysis: Biologics administered in hospital

	Drug dosing	# infusions / year	Dose for 40 kg	Cost for presentation	$ / dose	Nursing time (1 nurse: 3 patients)	Pharm-acy costs	Pre-medicat-ion (table 13.5)	Lab tests pre-infusion (table 13.6)	Physician costs	$ / infusion	$ / year
Infliximab	3-7.5 mg/kg * wks 0, 2, 6, & every 8 wks thereafter	8	120mg/dose (3mg/kg) 200mg/dose (5mg/kg) 300mg/dose (7.5mg/kg)	$940/100mg	$ 1,880 (3-5mg/kg) $2,820 (7.5mg/kg)	[redacted] 2.5-hour infusion but about 5 hours stay in total¶	[redacted]	$4.22	$42	$29	$2,034 (3-5mg/kg) $2,974 (7.5mg/kg)	$16,274 (3 or 5 mg/kg) $23,794 (7.5 mg/kg)
Abatacept	10 mg/kg days 1, 15, 29, and every month	14	400 mg/dose	$440 / 250mg	$ 880	[redacted] 1 hour infusion 2 hour stay		-	$42	$29	$982	$ 13,748
Tocilizumab	Not in the market											

In-hospital administration: we assumed 1-hour of nursing time per infusion. At home administration: assumed 1 hour of nursing time once to give instructions on the administration

* 3-10 mg/kg (average 5-7.5 mg) from studies [redacted]

¶ Five hours includes: collection of sample for laboratory work and wait for results (1 hour), drug preparation (30 min -1 hour), laboratory results receipt and IV set up (30 min), infliximab infusion (2.5 hours), observation period post-infusion (1 hour). Vital signs are taken every 30 minutes during infliximab infusion.

Table 13.3 Cost analysis: Biologics administered at home

	Drug dosing	# infusions / year	Dose for 40 kg	Cost of presentation	Cost / dose	$ / year	Pharmacy costs (annual)	Cost for hospital visit	Total cost / year
Etanercept 0.4 mg/kg 2x/week	0.4 mg/kg (max 25mg)	104	16 mg/dose	$170/ 25 mg	$170	$ 17,680	$84/year $7 dispensing fee for a 30-day supply ¶	**$217 / year** $31 (1-hour training) $186 (30 min/month follow-up call with nurse)§	**$17,981**
Etanercept 0.8 mg/kg 2x/week	0.8 mg/kg (max 50mg)	52	32 mg /dose	$170 / 25 mg	$340	$17,680			**$17,981**
Adalimumab	24 mg/m^2 (max. 40mg) every 2 weeks	26	31.2 mg/dose	$668/40 mg	$668	$ 17,368			**$ 17,669**
Anakinra	2mg/kg (max. 100mg) Every day	365	80 mg / dose	$51.5 / 100mg	$51.5	$ 18,798			**$ 19,099**

Assumes no pharmacy preparation costs or physician visits for infusion since drug is administered at home.
¶ Dispensing fee based on patients covered under government-funded drug programs (information provided by Ms. Mariann Nevec, Pharmacy, Hospital for Sick Children).
§ One-hour of nursing time once to give instructions about the administration of the drugs at home was assumed. In addition it was assumed that a nurse could either contact or be contacted by the patient's family in order to provide clarifications on the drug administration (information from Ms. Karen Queffelec, nursing, Hospital for Sick Children. We assumed that this would take 30-minutes per month.

Table 13.4 Cost analysis: Methotrexate

	Drug dosing	# administrations /year	Dose for 40 kg (1.3 m^2)	Cost of presentation	Cost / dose	$ / year
Methotrexate	15 mg/m^2/week*	52	19.5mg / week	$12.5 / 2ml (20mg)	$12.5	$650
Folic acid	1mg/day [2, 79]	365	1 mg/day	$0.0259/5mg	$0.0259	$9

* The mean methotrexate dose reported in the abatacept study was 13 mg/m^2/week.[13] The infliximab study reported methotrexate doses ranging from 10-15mg/m^2/week.[41]

Table 13.5 Cost of pre-medications

	Dosing	Dose for 40 kg	Cost /presentation	$ / dose
Acetaminophen	15 mg/kg PO	600 mg	$2.87 / 24 ml (80 mg/ml)	$ 0.89
Diphenhydramine	1 mg/kg IV	40 mg	$3.33 / 50 mg vial	$ 3.33
Hydrocortisone (if necessary)	5 mg/kg IV	200 mg	$3.40 / 250mg	$ 3.40
Total				$4.22 - $7.62

PO oral administration / IV intravenous

Table 13.6 Annual monitoring costs

Treatment	Tuberculin test (before treatment)[80]	Chest-X-ray (before treatment)[80]	Blood work* every 3 months[80]	Physician visits (every 3 months)[80]	Total
Biologics	$9[75]	$33[76]	$168 (42* x4)	$117 (29.2§ x4)	$327
Non-biologics	0	0	$168 (42 *x4)	$117 (29.2§ x4)	$285

*Laboratory tests: complete blood count ($8.3) with differentials ($5.20), ESR ($1.6), BUN ($2.6), creatinine ($3.12), liver function tests (Alanine aminotransferase $7.8, aspartate aminotransferase $5.2), CRP ($3.1), albumin ($5.20). Based on data from the Ontario Ministry of Health[74].
§ Physician fee for a follow-up visit (table 13.1)[77]

Table 13.7 Cost of concomitant medications

	Drug dosing	# administrations /year	Dose for 40 kg (1.3 m^2)	Cost of presentation	Cost / dose	$ / year
Corticosteroids ¶	5 mg/day	365	5 mg/day	$0.022 / 5mg	$0.022	$8

Assumes no pharmacy preparation costs or physician visits for infusion since drug is administered at home.
¶ Prednisone

Table 13.8 Annual productivity and non-healthcare costs

	# infusions / year	School-days missed (# infusions/year)	Parent/ caregivers work days
Infliximab	8	8	$1,071 (8*133.9*)
Abatacept	14	14	$ 1,875 (14*133.9*)

*Based on a 7-hour work day. Average hourly rate in Canada 2007, Statistics Canada.[78]

Appendix 14 Sensitivity analyses: Drug acquisition costs by weight

The tables below show the variation of drug acquisition costs according to body weight. Shaded areas represent the costs without vial re-use. Excludes materials, preparation and administration costs which do not vary (negligible variance) by weight.

Table 14.1 Etanercept SC 0.4mg/kg (maximum 25mg/dose)

Etanercept	Dose	# infusions / year	Cost for presentation	$ / dose	$ / year
10 kg	4mg	104	$170/ 25 mg	$170	$17,680
20 kg	8mg	104	$170/ 25 mg	$170	$17,680
30kg	12mg	104	$170/ 25 mg	$170	$17,680
40 kg	16mg	104	$170/ 25 mg	$170	$17,680
50 kg	20mg	104	$170/ 25 mg	$170	$17,680
60kg	25mg	104	$170/ 25 mg	$170	$17,680
70kg	25mg	104	$170/ 25 mg	$170	$17,680

*Assumes vial re-use
In cases of vial re-used a 20% drug waste is factored into the drug cost in order to account for circumstances where the vial cannot be entirely used. However, if the portion leftover in the vial is ≤ 20% the use of the entire vial is assumed.

Table 14.2 Infliximab IV 3-5 mg/kg (every 8 weeks after week 6)

Infliximab	Dose	# infusions / year	Cost for presentation	$ / dose	$ / year
10 kg		8	$940/100mg		
3 mg/kg	30mg			$940	$7,520
5 mg/kg	50mg			$940	$7,520
20 kg		8	$940/100mg		
3 mg/kg	60mg			$940	$7,520
5 mg/kg	100mg			$940	$7,520
30kg		8	$940/100mg		
3 mg/kg	90mg			$940	$7,520
5 mg/kg	150mg			$1,880	$15,040
40 kg		8	$940/100mg		
3 mg/kg	120mg			$1,880	$15,040
5 mg/kg	200mg			$1,880	$15,040
50 kg		8	$940/100mg		
3 mg/kg	150mg			$1,880	$15,040
5 mg/kg	250mg			$1,880	$16,920
60kg		8	$940/100mg		
3 mg/kg	180mg			$1,880	$15,040
5 mg/kg	300mg			$2,820	$22,560
70kg		8	$940/100mg		
3 mg/kg	210mg			$2,820	$22,560
5 mg/kg	350mg			$3,760	$30,080

*Assumes vial re-use
In cases of vial re-used a 20% drug waste is factored into the drug cost in order to account for circumstances where the vial cannot be entirely used. However, if the portion leftover in the vial is ≤ 20% the use of the entire vial is assumed.

Table 14.3 Adalimumab subcutaneous 24mg/m² (maximum 40mg)

Etanercept	Dose	# infusions / year	Cost for presentation	$ / dose	$ / year
10 kg (0.49 m²)	12mg	26	$668/40mg	$668	$17,368
20 kg (0.79m²)	19mg	26	$668/40mg	$668	$17,368
30kg (1.1m²)	26mg	26	$668/40mg	$668	$17,368
40 kg (1.3m²)	31mg	26	$668/40mg	$668	$17,368
50 kg (1.5m²)	36mg	26	$668/40mg	$668	$17,368
60kg (1.7m²)	40mg	26	$668/40mg	$668	$17,368
70kg (1.8m²)	40mg	26	$668/40mg	$668	$17,368

*Assumes vial re-use
In cases of vial re-used a 20% drug waste is factored into the drug cost in order to account for circumstances where the vial cannot be entirely used. However, if the portion leftover in the vial is ≤ 20% the use of the entire vial is assumed.

Table 14.4 Abatacept intravenous 10 mg/kg (maximum 1,000mg)

Abatacept	Dose	# infusions / year	Cost for presentation	$ / dose	$ / year
10 kg	100mg	14	$440/250mg	$440	$6,160
20 kg	200mg	14	$440/250mg	$440	$6,160
30kg	300mg	14	$440/250mg	$880	$12,320
40 kg	400mg	14	$440/250mg	$880	$12,320
50 kg	500mg	14	$440/250mg	$880	$12,320
60kg	600mg	14	$440/250mg	$1,320	$18,480
70kg	700mg	14	$440/250mg	$1,320	$18,480

*Assumes vial re-use
In cases of vial re-used a 20% drug waste is factored into the drug cost in order to account for circumstances where the vial cannot be entirely used. However, if the portion leftover in the vial is ≤ 20% the use of the entire vial is assumed.

Table 14.5 Anakinra subcutaneous 2mg/kg (maximum 100mg)

Etanercept	Dose	# infusions / year	Cost for presentation	$ / dose	$ / year
10 kg	20mg	365	$51.5/100mg	$51.5	$18,798
20 kg	40mg	365	$51.5/100mg	$51.5	$18,798
30kg	60mg	365	$51.5/100mg	$51.5	$18,798
40 kg	80mg	365	$51.5/100mg	$51.5	$18,798
50 kg	100mg	365	$51.5/100mg	$51.5	$18,798
60kg	100mg	365	$51.5/100mg	$51.5	$18,798
70kg	100mg	365	$51.5/100mg	$51.5	$18,798

*Assumes vial re-use
In cases of vial re-used a 20% drug waste is factored into the drug cost in order to account for circumstances where the vial cannot be entirely used. However, if the portion leftover in the vial is ≤ 20% the use of the entire vial is assumed.

Table 14.6 Methotrexate intramuscular 15 mg/m²/week (single-use vials)

Methotrexate	Dose	# administrations/year	Cost for presentation	$ / dose*	Drug costs/year
10 kg (0.49 m²)	7.35mg	52	$12.5/20mg	$12.5	$650
20 kg (0.79m²)	11.85mg	52	$12.5/20mg	$12.5	$650
30kg (1.1m²)	16.5mg	52	$12.5/20mg	$12.5	$650
40 kg (1.3m²)	19.5mg	52	$12.5/20mg	$12.5	$650
50 kg (1.5m²)	22.5mg	52	$12.5/20mg	$25	$1,300
60kg (1.7m²)	25.5mg	52	$12.5/20mg	$25	$1,300
70kg (1.8m²)	27mg	52	$12.5/20mg	$25	$1,300

Appendix 15 Probabilistic sensitivity analyses varying body weight

Tables 15.1 and 15.2 show the change in the results of the PSAs for each biologic when patient body weight was varied between 10 kg and 70 kg. For the other variables used in the analysis the base case scenario values were used.

In the case of etanercept and adalimumab, the treatment costs did not change according to body weight assumed that vials would not be re-used by the patients.

Table 15.1 Infliximab results

Model	Mean incremental cost (95% CI)	Mean incremental effectiveness (95% CI)	ICER (C$/additional respondent at 1 year)
10 kg	$4,624 (3,215 , 5,781)	43.2% (18.2%, 61.1%)	$12,113 (5,839 , 27,836)
20 kg	$6,819 (3,585 , 11,149)	43.2% (18.2%, 61.1%)	$17,611 (6,828 , 40,938)
30 kg	$8,550 (3,278 , 16,260)	43.2% (18.2%, 61.1%)	$22,039 (6,362 , 53,864)
40 kg	$12,167 (9,895, 12,550)	43.2% (18.2%, 61.1%)	$31,209 (16,659, 66,220)
50 kg	$15,090 (8,953 , 22,845)	43.2% (18.2%, 61.1%)	$39,396 (19,061 , 81,652)
60 kg	$16,821 (9,617 , 27,893)	43.2% (18.2%, 61.1%)	$42,823 (18,571 , 94,278
70 kg	$23,361 (16,002 , 34,626)	43.2% (18.2%, 61.1%)	$59,180 (31,186 , 122,189)

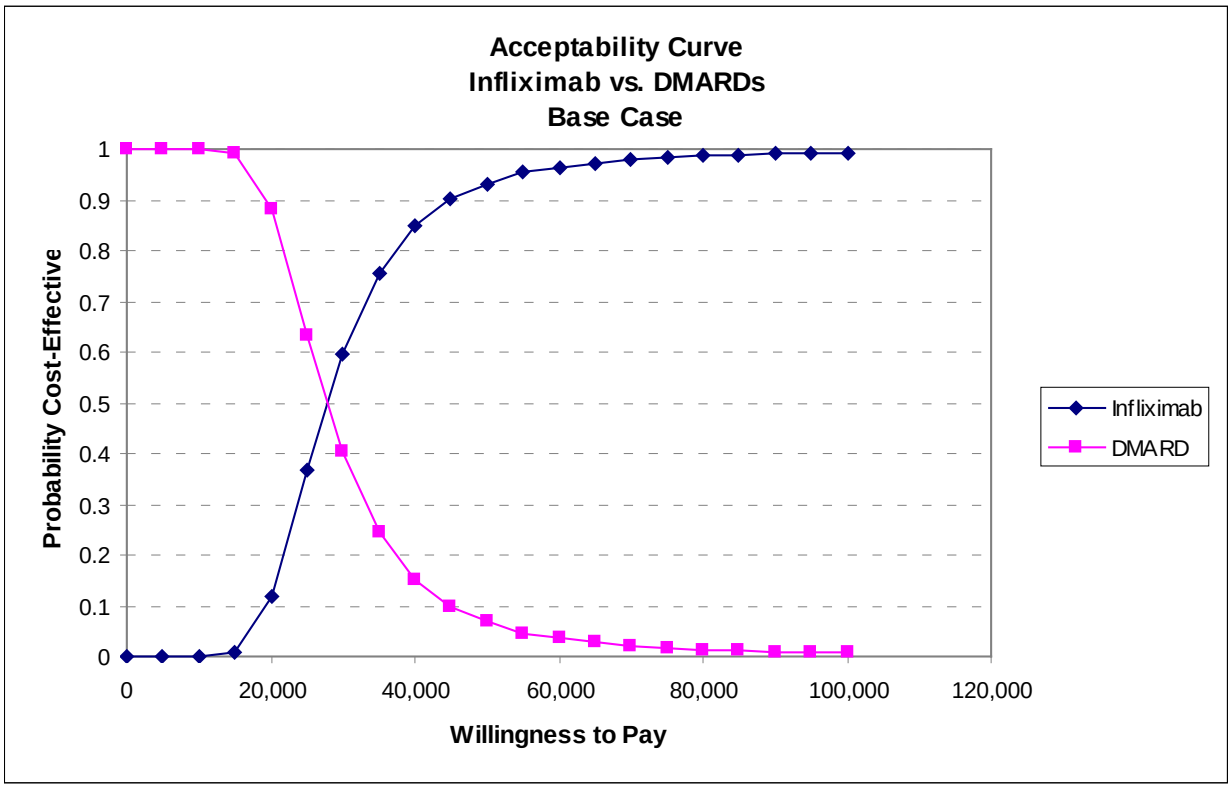
Table 15.2 Abatacept results

Model	Mean incremental cost (95% CI)	Mean incremental effectiveness (95% CI)	ICER (C$/additional respondent at 1 year)
10 - 20 kg	$3,572 (1,955 , 5,092)	49.4% (38.1%, 59.3%)	$7,377 (3,649 , 11,874)
30 - 50 kg	$7,873 (6,226, 9,419)	49.4% (38.1%, 59.3%)	$16,204 (11,393, 22,608)
60 - 70 kg	$13,300 (11,697 , 14,870)	49.4% (38.1%, 59.3%)	$27,353 (21,233 , 35,729)

Appendix 16 Cost-effectiveness acceptability curves

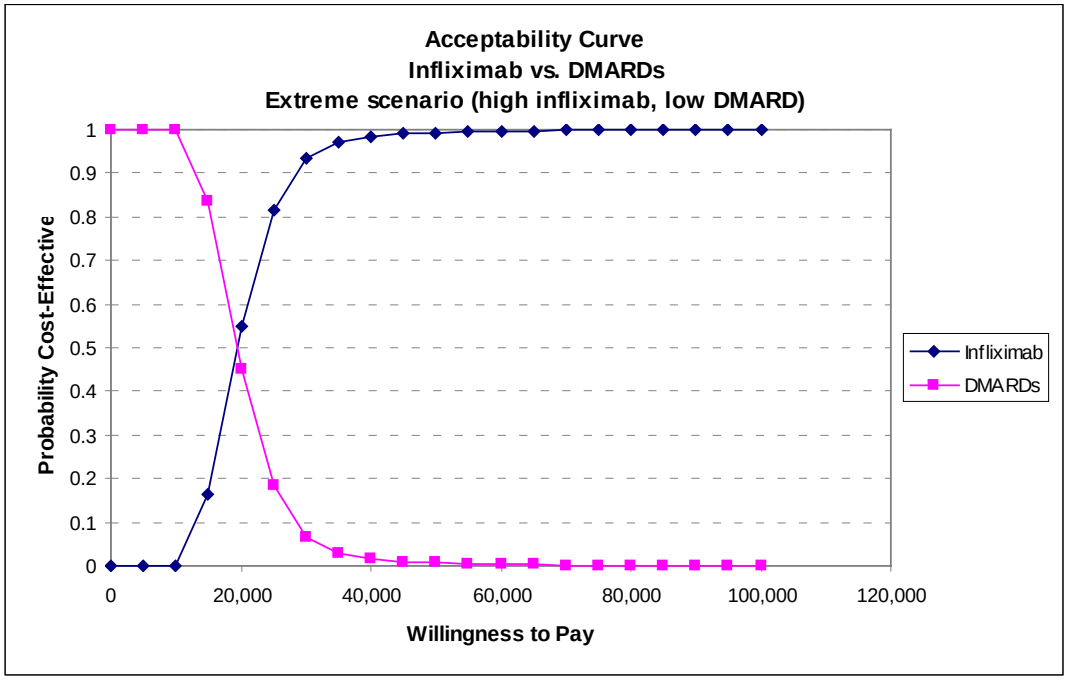
Figures 16.1-16.9 show the cost-effectiveness acceptability curves of the different scenarios used in the probabilistic sensitivity analyses. Etanercept curves are shown in the report. The point at which the two curves cross represents the point at which the two interventions have an equal probability of being cost-effective at the willingness-to-pay threshold shown on the x-axis.

Figure 16.1 Acceptability curve Infliximab vs. DMARDs: Base case



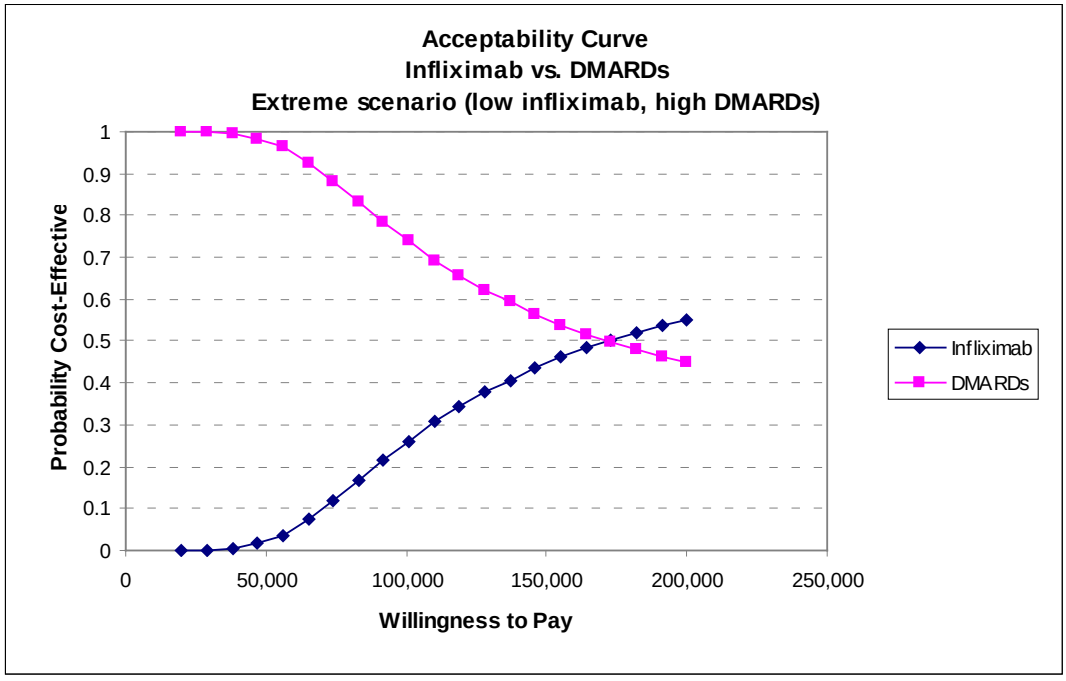
Curves cross at C$30,000

Figure 16.2 Acceptability curve Infliximab vs. DMARDs: Extreme scenario (high infliximab)



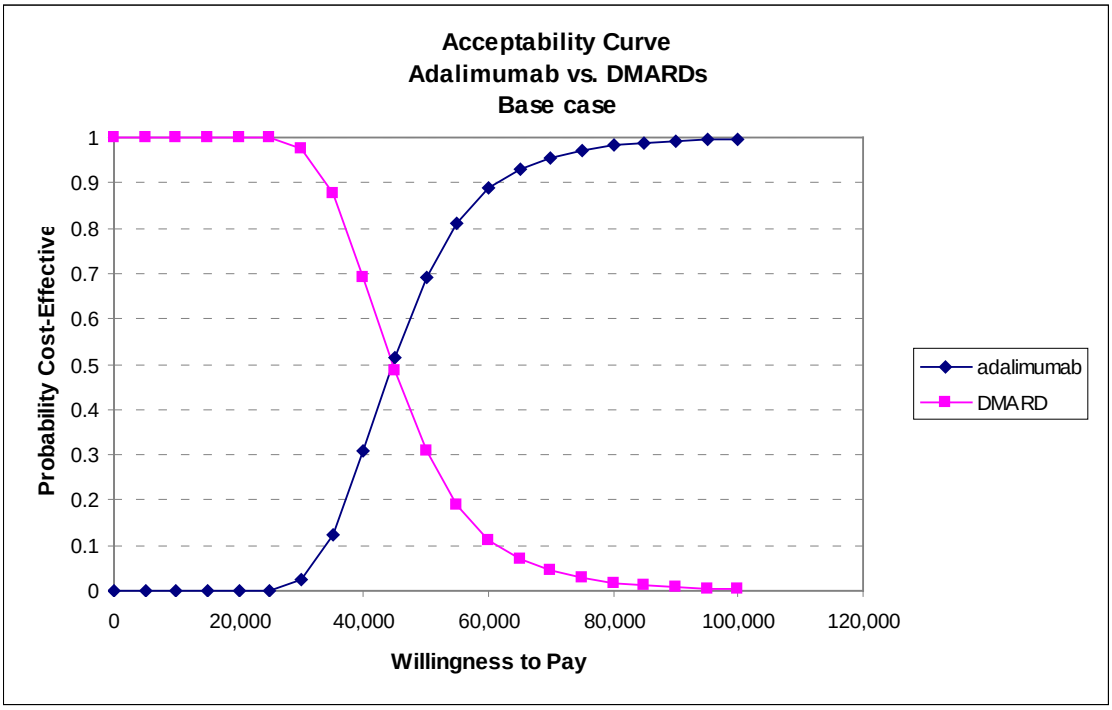
Curves cross at C$20,000

Figure 16.3 Acceptability curve Infliximab vs. DMARDs: Extreme scenario (low infliximab)



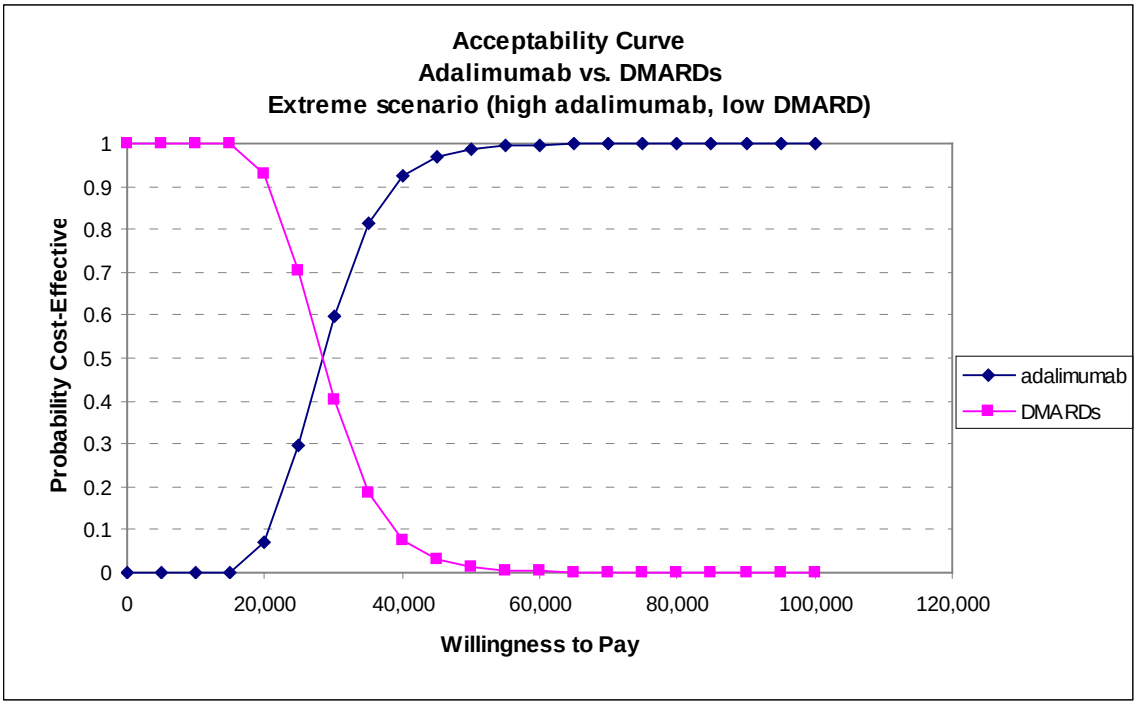
Curves cross at C$173,000

Figure 16.4 Acceptability curve Adalimumab vs. DMARDs: Base case



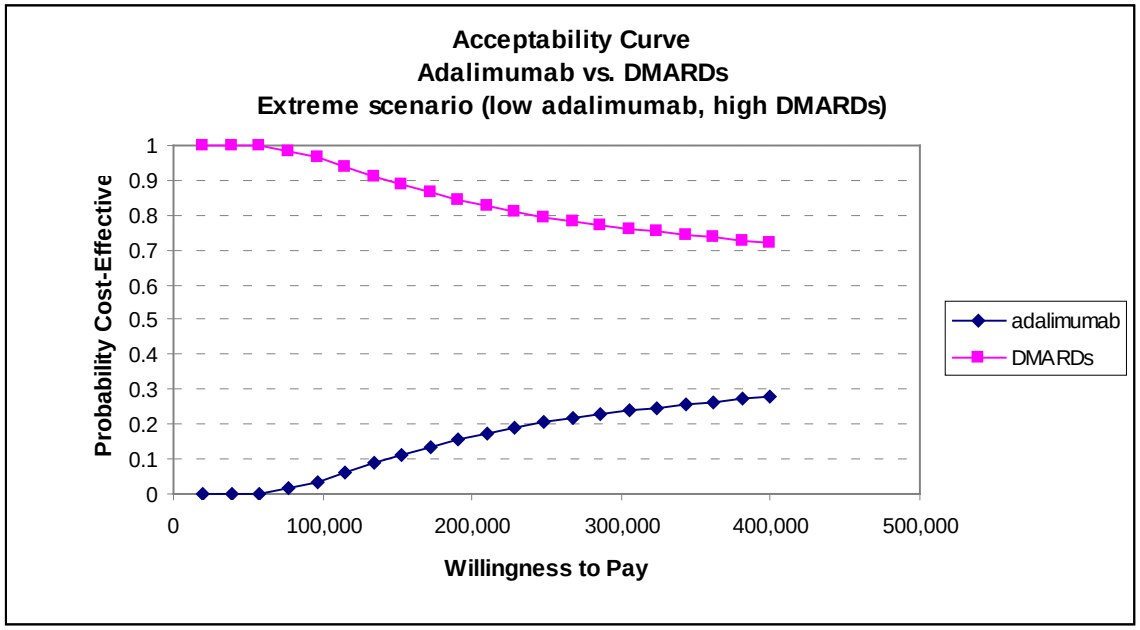
Curves cross at C$45,000

Figure 16.5 Acceptability curve Adalimumab vs. DMARDs: Extreme scenario (high adalimumab)



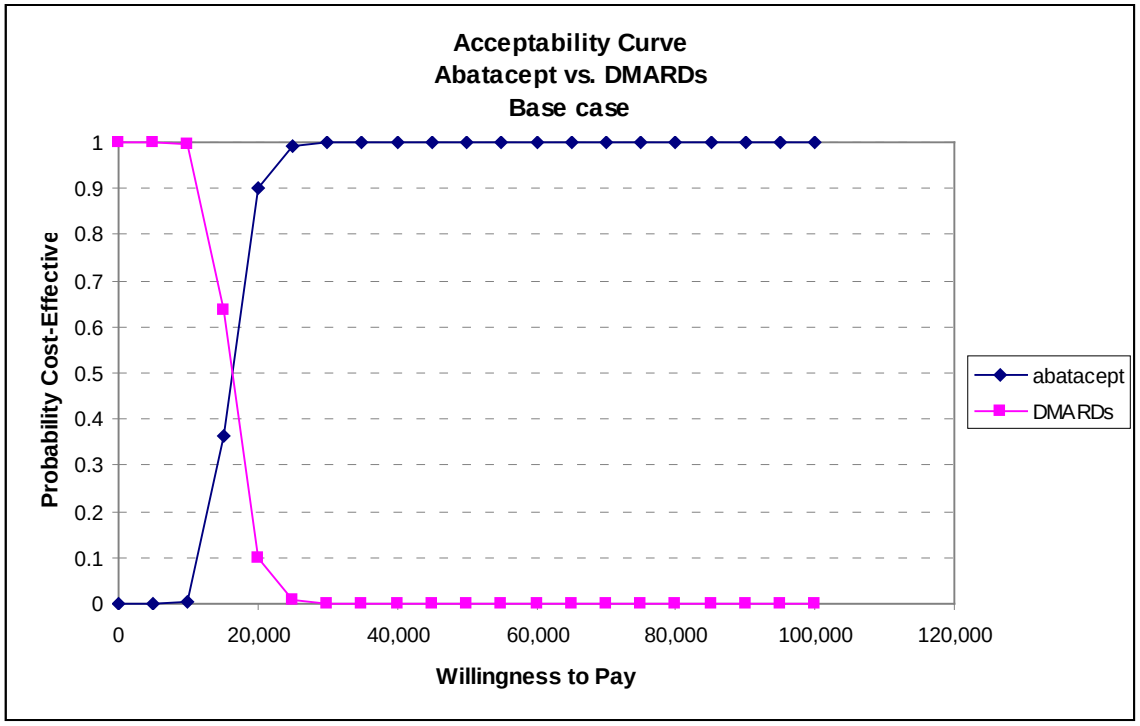
Curves cross at C$30,000

Figure 16.6 Acceptability curve Adalimumab vs. DMARDs: Extreme scenario (low adalimumab)



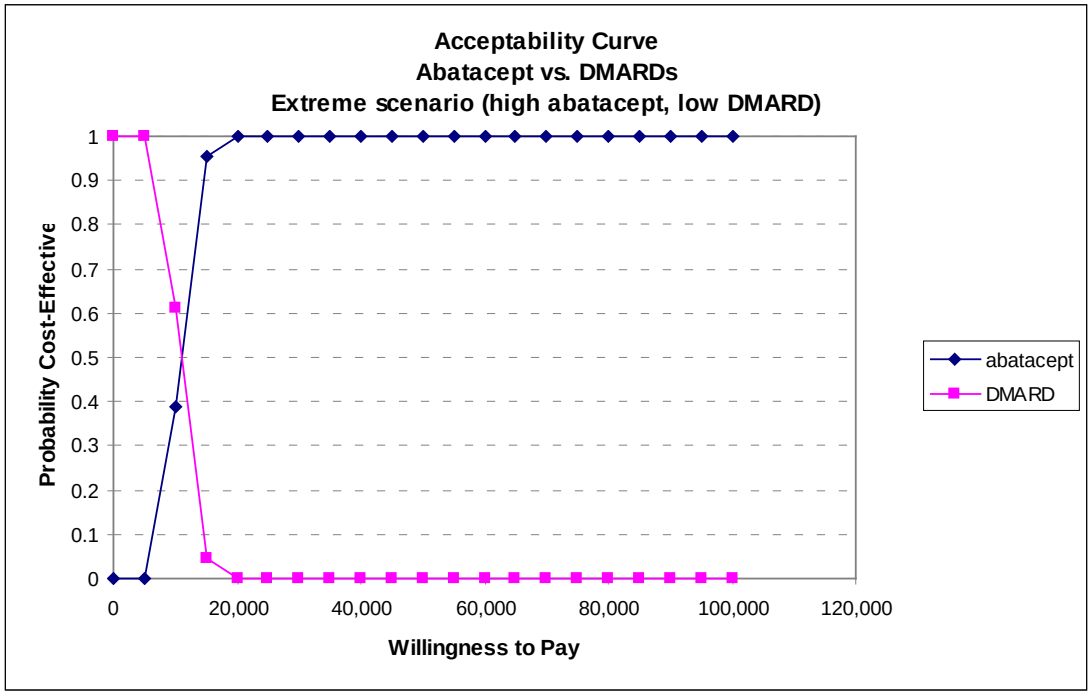
Curves do not cross at thresholds less than $500,000

Figure 16.7 Acceptability curve Abatacept vs. DMARDs: Base case



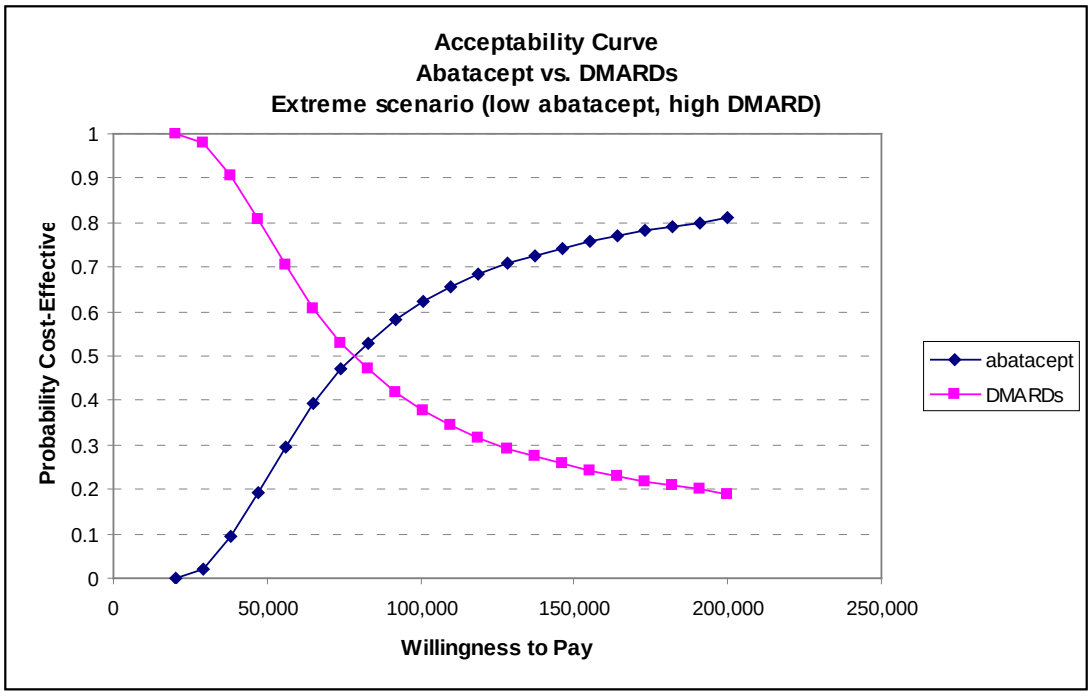
Curves cross at C$20,000

Figure 16.8 Acceptability curve Abatacept vs. DMARDs: Extreme scenario (high abatacept)



Curves cross at C$15,000

Figure 16.9 Acceptability curve Abatacept vs. DMARDs: Extreme scenario (low abatacept)



Curves cross at C$83,000

Appendix 17 Systemic Juvenile Idiopathic Arthritis (JIA)

Studies in JIA patients with systemic disease were identified, as follows:

- Tocilizumab: 1 study that included a double-blind placebo-controlled phase, 2 open-label dose escalation studies, and one open-label study.
- Anakinra: 1 study that included a double-blind placebo-controlled phase, two open-label observational studies.
- Etanercept: 1 publication based on a national US survey.
- Rilonacept: 1 open-label observational study.

Tocilizumab

A study of tocilizumab in patients with systemic JIA has been conducted. [15] It was comprised of three phases: a 6-week open-label lead-in phase, followed by a double-blind, randomized, placebo-controlled 12-week phase, and an open-label extension phase of ≥ 48 weeks. [15]

Patients 2-19 years old who met the ILAR criteria for systemic-onset JIA were eligible for the study. [15] Use of intra-articular corticosteroids and other DMARDs was not permitted in the two weeks preceding randomization. [15] Use of anti-TNF-α was not permitted in the 12 weeks preceding the start of treatment. [15] During the study, use of DMARDs was not allowed, but stable doses of oral corticosteroids were allowed. [15] Patients who both achieved ACR Ped 30 and had CRP < 5 mg/L were eligible to enter the double-blind phase of the study. [15] Patients who either completed the lead-in phase or who were randomized in the double-blind phase were included in the open-label extension phase. The dose of tocilizumab used was 8 mg/kg every two weeks.[15] Weekly administration of tocilizumab was permitted during the extension phase depending on the disease activity. [15] The authors mention that an intention-to-treat method of analysis was used, although it is also mentioned that a LOCF method is used for early withdrawals. [15]

Table 17.1 shows the characteristics of the patients included in the study.

Table 17.1 Baseline characteristics: Patients included in the tocilizumab study by Yokota et al.[15]

	Open-label phase	Double-blind phase	
	Tocilizumab N=56	Tocilizumab N=20	Placebo N=23
Age at the start of the disease (mean, SD)	4.3 (2.6)	3.9 (2.2)	5.1 (3.0)
Age, years			
2-10	20 (36%)	9 (45%)	5 (22%)
6-10	19 (34%)	5 (25%)	11 (48%)
11-15	13 (23%)	5 (25%)	4 (17%)
16-19	4 (7%)	1 (5%)	3 (13%)
Female sex, n (%)	35 (63%)	13 (65%)	15 (65%)
Duration of JIA, years (mean, SD)	4.5 (3.6)	4.6 (3.5)	4.7 (4.0)
N. of active joints, mean (range)	4.0 (0-39)	0 (0-4.0)	0 (0-13)
ESR (mm/hour), mean (range)	44.5 (8-125)	4.0 (0-9)	3.0 (1-13)
CRP (mg/L), mean (range)	43.5 (16-190)	0.1 (0-1)	0.2 (0-1)
Total systemic feature score (0- 8)§, mean (range)	1 (0-3)	1.0 (0-2)	1.0 (0-2)
CHAQ, mean (range)	0.88 (0-3)	0.38 (0-2.63)	0.25 (0-2.75)

SD standard deviation / CHAQ Childhood Health Assessment Questionnaire / JIA juvenile idiopathic arthritis
§ - Includes febrile episode, rheumatoid rash, lymphadenopathy, hepatosplenomegaly, and serositis.

Among the 56 patients included in the open-label phase, 51 (91%) achieved the ACR Ped 30 response criteria at six weeks and 44 (79%) met the criteria for inclusion in the randomized phase of the study (both ACR Ped 30 response and CRP < 5.0 mg/L) [15]. Six (10.7%) patients were withdrawn during the open-label phase: three developed anti-tocilizumab antibodies, two had serious adverse events, and one withdrew due to lack of efficacy. [15] Approximately 90% of the 20 patients randomized to receive tocilizumab and 60% of the 23 patients in the placebo group achieved ACR Ped 30 during the double-blind phase (figures derived from a graph). [15] Sixteen (80%) and four (17%) patients in the tocilizumab and placebo groups, respectively, achieved the response criteria at the end of the double-blind phase[15]. The four respondents in the placebo group had undetectable serum tocilizumab levels at 3-5 weeks after randomization[15]. Ninety-eight percent of the 50 patients included in the open-label extension phase achieved the ACR Ped 30 endpoint, the median follow-up of 61.1 weeks (additional details, table 17.1)[15]. Drug discontinuation details are provided in table 17.2. [15]

Table 17.2 Study outcomes: Patients included in the tocilizumab study by Yokota et al.[15]

	Open-label phase	Double-blind phase		Extension phase
	Tocilizumab N=56	Tocilizumab N=20	Placebo N=23	Tocilizumab N=50
Median duration of treatment	6-week phase	12-week phase		61.1 (8.7-99) weeks
Discontinuations	6 (10.7%) SAE: 2 (3.6%)** Anti-tocilizumab IgE antibodies: 3 (5.4%) Lack of efficacy: 1 (1.8%)	1¶ (5%) – adverse event	1 ¶(4.3%) – adverse event	2 (4%)
Patients who met the response criteria*	44/56 (79%)	16 (80%)	4 (17%)	See ACR Ped response
Childhood Health Assessment Questionnaire	0.38 (0-3)	0.38 (0-2.63)	0.25 (0-2.75)	0.13 (0-2.13)
ACR Ped 30	51 (91%) – at last observation (50 patients completed the lead-in phase)	Approx. 90% From graph	Approx. 60% From graph	47 (98%)
ACR Ped 50	48 (86%)	-	-	45 (94%)
ACR Ped 70	38 (68%)	-	-	43 (90%)
CRP	< 5.0 mg/L 48 (86%)	-	-	Median decrease in CRP (range), from baseline -43.1 (-190 , -16)

CRP C-reactive protein / SAE serious adverse event / ACR Ped American College of Rheumatologists, pediatric criteria
*Patients who reached ACR Ped 30 and with CRP < 5.0 mg/L in the open-label phase, ACR Ped 30 and CRP < 15 mg/L in the double-blind phase
** SAEs: Anaphylactoid reaction (n=1), gastrointestinal hemorrhage (n=1)
¶ Adverse events leading to discontinuation: infectious mononucleosis with liver enzymes increase (n=1, tocilizumab), herpes zoster infection (n=1, placebo).

An open-label phase II tocilizumab study was identified, conducted with 18 pediatric patients with active systemic-onset JIA (ILAR) for more than three months.[81] Patients with active disease for more than three months despite > 0.2 mg/kg/day of prednisolone equivalent were eligible.[81] The patients were divided into three tocilizumab dose groups, 2, 4 or 8 mg/kg, and were further stratified according to age, 2-5 years and 6-18 years. Concomitant use of MTX was permitted at a maximum dose of 20mg/m^2/week.[81] Patients with a history of MAS were excluded.[81] Patients were evaluated at baseline, 48 hours and weekly after the infusion. [81] Patients were followed for four, six, and eight weeks in the 2, 4, and 8 mg/kg groups respectively. [81] Among the 18 patients included, the median age was 6.5 years in the 2 and 4 mg/kg group, and 5.0 years in the 8 mg/kg group. Eight (44%) patients were female across the three groups. [81] It was not clear if randomization was done. Improvement was defined according to the ACR Ped 30.[81]

Fifteen patients were included in the efficacy analysis (three were excluded due to protocol violation)[81]. At week one, 11/15 (73%) patients achieved ACR Ped 30.[81] At week six, 6/9 patients (67%) in the 4 and 8mg/kg groups achieved ACR Ped 30.[81] No withdrawals due to adverse events were reported[81]. There were two (13%) disease flares requiring hospitalization.[81]

An open-label study was identified which included 11 pediatric patients with active systemic-onset JIA despite previous treatment with NSAIDs, corticosteroids, MTX and other DMARDs.[82] It consisted of a dose-escalating study with the objective of evaluating the safety, pharmacokinetics, and efficacy of tocilizumab in this patient population.[82] Patients 2-19 years old with systemic-onset JIA as defined by the ILAR criteria were eligible for the study.[82] Patients with active disease despite treatment with NSAIDs, corticosteroids, cyclosporine, or MTX were observed for four weeks.[82] Dose changes in these agents were not allowed nor was the addition of DMARDs, anti-TNF-α, immunosuppressants, corticosteroids or drugs under investigation.[82] The patients received three doses of tocilizumab 2 mg/kg every two weeks.[82] The dose of tocilizumab could be increased to 4 mg/kg if the CRP levels were greater than 1.5 mg/dl for at least five days after the first and second administrations.[82] A further increase to 8 mg/kg could be done if CRP levels remained > 1.5 mg/dL with the 4 mg/kg dose [82]. Concomitant use of corticosteroids were permitted.[82] The main endpoint was disease response was defined according to the ACR Ped 30 criteria.[82] The median age of the patients was nine years (3-18), and three (27.3%) patients were female.[82] The median duration of the disease was three years (0.5-8.3).[82] At two weeks of treatment, 10 (91.9%) patients achieved ACR Ped 50 (similar to ACR Ped 30 from graph).[82] Eight (72.7%) patients required a dose increase to 4 mg/kg, and three (27.3%) patients required a dose increase to 8 mg/kg due to high levels of CRP.[82] No clinical disease flare (not defined) was reported.[82] No patient had to withdraw from the study.[82] Rescue therapy (methylprednisolone pulses IV) was not required.[82]

A long-term open-label study was identified which included both systemic JIA patients (ILAR) who had an inadequate response to corticosteroids for more than three months and who had been part of phase II and III tocilizumab study, and an additional 61 patients.[45] The tocilizumab dose was 8 mg/kg every two weeks.[45] Endpoints included treatment response according to ACR Ped criteria and exposure-adjusted incidence

rates of adverse events.[45] A total of 128 patients were included with a median age of nine years and a median disease duration of four years.[45] Fifty-five (43%) patients were male.[45] The median dose of corticosteroid was 0.5 mg/kg/day.[45] A total of 73/78 (94%) patients achieved ACR Ped 30 at week 48, 58/58 (100%) at week 96, and 41/41 (100%) at week 144.[45] Four patients achieved remission without tocilizumab or other medications.[45] At a median treatment duration of 78 weeks, 14 (10.9%) patients discontinued treatment due to either adverse events (n=8, 6.3%),[2] presence of anti-tocilizumab IgE antibodies (n=5, 3.9%), or lack of efficacy (n=1, 0.8%).[45] Adverse events are described in a separate section.

Anakinra

The results of a double-blind study comparing anakinra and placebo in children with systematic JIA were published in an abstract format.[42] Twenty-four patients with systemic-onset JIA with insufficient response to corticosteroids were randomized to either anakinra 2 mg/kg subcutaneous / day, maximum 100mg, or matching placebo.[42] Treatment response was defined according to the ACR Ped 30 criteria, resolution of fever and systemic symptoms for more than eight days and a more than 50% decrease of the baseline C-reactive protein and erythrocyte sedimentation rate values.[42] In an intention-to-treat analysis at one month, 8/12 (67%) and 1/12 (8.3%) of patients in the anakinra and placebo groups respectively achieved treatment response.[42] Among 10 patients who switched from placebo to anakinra at the end of month one, nine (90%) exhibited treatment response at month two.[42] Ten patients discontinued the treatment, one due to a diagnosis of Crohn's disease, four due to serious adverse events, one due to an adverse event, and four due to lack of efficacy or disease flare.[42]

A retrospective non-comparative study including 20 pediatric patients with systemic-onset JIA (ILAR) treated with anakinra (start dose: 1-2 mg/kg/day, maximum 100mg/day) was published.[48] Disease improvement was defined according to the ACR Ped 30 criteria[48]. An ITT analysis was used.[48] The arthritis was active in 19 (95%) patients and all patients were receiving corticosteroids when anakinra was started (mean corticosteroid treatment duration: 5.7 years) and DMARDs (except one patient).[48]

[2] Adverse events leading to drug discontinuation: macrophage activation syndrome, anaphylactoid reaction (n=2), cardiac amyloidosis, duodenal perforation, gastrointestinal hemorrhage, infusion reaction (n=2) [45].

Fourteen (70%) patients had used previously used the biologic drugs etanercept, rituximab, or infliximab.[48] Previous treatments were considered either not effective or not very effective.[48] The median age of the patients was 11 years (2.9-22.9), and 12 (60%) patients were female.[48] The median duration of the disease was six years (0.8-15.8). Use of corticosteroids was permitted.[48] The median duration of follow-up was 15 months (2-27).[48] ACR Ped 30 was achieved in 55% of the patients at three months, 50% at six months, and 45% at last follow-up (12-27 months).[48] Complete response (no systemic symptoms and ACR Ped response) was observed in six (30%) patients at three months and four (20%) at the end of follow up.[48] At the end of follow-up (mean 16 months), the authors reported that mean improvements were observed for most disease variables following anakinra treatment.[48] Although the mean difference at last follow-up compared to baseline was statistically significant ($p < 0.05$) for most disease variables, the standard deviation was very wide[48] (table 17.3), which leads us to believe that not all patients experienced improvement. The proportion of patients with ACR Ped disease improvement was not provided. Five (25%) patients discontinued the treatment with anakinra due to lack of efficacy (n=4) and intolerance (n=1). [48] The mean dose of corticosteroids (prednisone) used decreased from 0.5 (SD 0.32) mg/kg/day at treatment start to a mean of 0.24 (SD 0.22) mg/kg/day at the end of follow-up ($p=0.05$).[48] Additionally, corticodependency was reduced in 9/20 (45%) patients.[48]

A study including 16 patients (adult and pediatric) with systemic JIA who received anakinra combined with MTX after not responding to MTX and other anti-TNF drugs was presented at a conference.[83] The median age of the patients was 16 years (9-47), 12 (75%) were females, and the median disease duration was 14.5 (0.5-44.3) years.[83] After a mean duration of treatment of one year (0.8-4.3), 11 (69%) patients were considered respondents according to the EULAR (DAS) criteria. Five (31%) patients discontinued the treatment due to adverse events or lack of efficacy.[83] The authors reported that the most important adverse events were intense pain in the site of injection and severe cutaneous reaction however the number of patients experiencing these outcomes were not provided.[83] The authors concluded that the use of anakinra combined with MTX showed a good efficacy and safety in the short-medium term in patients with refractory systemic JIA. [83]

Table 17.3 Changes in response variables in 20 systemic JIA patients treated with anakinra (source: Lequerre et al.[48])

Variables	Baseline (mean ± SD)	Latest follow-up (15 months, 2-27) (mean ± SD)	p-value
Tender joint count	20.5 ± 14.7	9.9 ± 22.5	0.02
Swollen joint count	18.1 ± 15.1	10.7 ± 19.7	0.01
Pain assessment (VAS, 0-10)	4.4 ± 3.0	4.1 ± 34.3	0.3
Parents global disease activity assessment (VAS, 0-10)	4.1 ± 3.3	3.5 ± 31.9	0.16
Physicians global assessment of disease activity (VAS 0-10)	4.3 ± 2.6	3.8 ± 30.6	0.02
Erythrocyte sedimentation rate, mm/hour	51.9 ± 28.8	24.4 ± 20.2	< 0.0001
C-reactive protein, mg/l	78.9 ± 42.3	25.5 ± 29.9	0.0006
Ferritinaemia, ng/ml	2672 ± 5640	-	-
Leukocyte counts (*10^9/l)	15.4 ± 4.7	10.7 ± 4.2	0.004
CHAQ	1.4 ± 1.0	0.6 ± 1.0	0.01
Corticosteroid doses, mg/kg/day	0.5 ± 0.32	0.24 ± 0.22	0.05

Etanercept

A lower efficacy with etanercept (anti-TNF-α) in patients with the systemic versus other subtypes of JIA[1, 84, 85] suggests that cytokines other than TNF-α, such as interleukin (IL) -1, -6, and -18 may be involved in this disease subtype.[84]

A survey that included data on 82 patients with systemic JIA treated with etanercept SC at a start dose of 0.4 mg/kg (maximum 25 mg) twice a week was identified.[39] Data was collected through questionnaires sent to 122 pediatric rheumatologists in the United States. From the 100 patients for which data was collected, 82 were deemed to have data that could be included in the analysis by the investigators.[39] Disease improvement was measured, however, the ACR Ped score was not used since not all the variables used to define improvement according to the ACR Ped criteria were available.[39] The occurrence of disease flares, defined as the development of systemic features (fevers,

rash, serositis) was reported.[39] Among the 82 patients included in the analyses, the mean age at disease onset was 4.25 (SD 3.73) years, and the mean age at baseline was 9.44 (SD 5.04) years.[39] Among the 29 (35%) patients for which the etanercept dose was increased, the mean dose was 0.83 (0.6 – 1.4) mg/kg/dose.[39] At baseline, 45 (54%) patients presented with systemic symptoms compared to 21 (26%) (p=0.612) at last follow-up (mean treatment duration approximately 23 months).[39] A total of 29 (35.4%) patients discontinued the treatment with etanercept due to disease flare (n=21, 25.6%), poor compliance (n=4, 4.9%), remission (n=3, 3.7%), and adverse event (n=1, 1.2%).[39] One or more episodes of disease flares were observed in 37 (45%) patients at a mean follow-up of 24.8 months (3-70).[39] The mean dose of prednisolone significantly decreased during the follow-up, from 0.47 mg/kg/day at baseline to 0.26 mg/kg/day at last follow-up (p=0.01).[39] A decrease in the number of patients taking prednisolone was also observed, from 59 (72%) at baseline vs. 32 (39%) at last follow-up. [39] The authors believe that the drop in the number of patients with systemic symptoms from baseline to last follow-up may have been due to the disease course rather than the drug treatment[39].

A prospective non-comparative study was identified which included children with systemic JIA who had not responded to MTX.[86] The inclusion criteria was persistent active polyarthritis under treatment with MTX, more than 20 mg/m^2/week for more than three months.[86] Patients were treated with etanercept 0.4mg/kg SC 2x/week concomitantly with MTX and followed between December 1999 and September 2001.[86] The dose of etanercept and MTX could be increased during the study.[86] Other medications such as corticosteroids (≤0.8 mg/kg/day prednisone) and NSAIDs were permitted.[86] Disease improvement was measured through the ACR Ped criteria 30.[86] A total of 15 patients were included in the study with a mean age of 9.3 and a mean disease duration of 3.8 years.[86] The proportion of patients who achieved ACR Ped 30 was 11/15 (73%) at month three, 10/15 (67%), 8/15 (53%), 3/15 (20%) at months five, seven, and 12 respectively.[86] One patient (6.7%) discontinued the drug due to inefficacy before six months, and 7/15 (47%) patients before month 12.[86] Three patients (20%) achieved sustained remission without relapses after 12 months of follow-up.[86] The authors concluded that etanercept combined with MTX was initially effective in most MTX-refractory patients included, but flares and loss of efficacy was observed in most patients after five months.[86] The authors believe that the sudden (sharp) decrease in corticosteroid and MTX doses may have contributed to the drug failures, and suggest

that decreases of doses of these drugs should be done “slowly and gradually”.[86] The authors also suggested that etanercept may need to be combined with MTX in systemic JIA patients.[86]

Rilonacept

A study on rilonacept in patients with both systemic and articular symptoms aged 5-20 years was presented at a conference.[87] The results for the 21 patients included in the open-label phase showed that 76.2% of the patients reached the ACR Ped 30 criteria after four weeks.[87]

References

1. Hashkes PJ, Laxer RM. Medical Treatment of Juvenile Idiopathic Arthritis. JAMA 2005;294(13):1671-84.
2. Quarta L, Corrado A, Melillo N, Cantatore FP. Juvenile idiopathic arthritis: an update on clinical and therapeutic approaches. Ann Ital Med Int 2005;20(4):211-7.
3. McCann LJ, Wedderburn LR, Hasson N. Juvenile idiopathic arthritis. Arch Dis Child Educ Pract Ed 2006;91(2):ep29-ep36.
4. Ravelli A, Martini A. Juvenile idiopathic arthritis. Lancet 2007;369(9563):767-78.
5. Woo P, Wedderburn LR. Juvenile chronic arthritis. Lancet 1998;351:969-73.
6. Johnson CJ, Reilly KM, Murray KM. Etanercept in juvenile rheumatoid arthritis. The Annals of Pharmacotherapy 2001;35:464-71.
7. Paul-Pletzer K. Tocilizumab: Blockade of interleukin-6 signaling pathway as a therapeutic strategy for inflammatory disorders. Drugs of Today 2006;42(9):559-76.
8. Hashkes PJ, Laxer RM. Update on the medical treatment of juvenile idiopathic arthritis. Curr Rheumatol Rep 2006;8(6):450-8.
9. Jadad AR, Moore RA, Carrol D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary ? Controlled Clinical Trials 1996;17:1-12.
10. Lovell DJ, Giannini EH, Reiff A, et al. Etanercept in children with polyarticular juvenile rheumatoid arthritis. Pediatric Rheumatology Collaborative Study Group. N Engl J Med 2000;342(11):763-9.
11. Ruperto N, Lovell DJ, Cuttica R, et al. A randomized, placebo-controlled trial of infliximab plus methotrexate for the treatment of polyarticular-course juvenile rheumatoid arthritis. Arthritis Rheum 2007;56(9):3096-106.
12. Lovell DJ, Ruperto N, Goodman S, et al. Adalimumab with or without methotrexate in juvenile rheumatoid arthritis. N Engl J Med 2008;359(8):810-20.
13. Ruperto N, Lovell DJ, Quartier P, et al. Abatacept in children with juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled withdrawal trial. Lancet 2008;372(9636):383-91.
14. Ilowite N, Porras O, Reiff A, et al. Anakinra in the treatment of polyarticular-course juvenile rheumatoid arthritis: safety and preliminary efficacy results of a randomized multicenter study. Clin Rheumatol 2008.
15. Yokota S, Imagawa T, Mori M, et al. Efficacy and safety of tocilizumab in patients with systemic-onset juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled, withdrawal phase III trial. Lancet 2008;371(9617):998-1006.

16. Lovell DJ, Ruperto N, Li T, et al. Abatacept treatment improves health-related quality of life, pain, and sleep quality in juvenile idiopathic arthritis patients. Presented at the ACR/ARHP Annual Scientific Meeting 2008.
17. Li T, Lovell DJ, Ruperto N, et al. Reduction in missed school days and improvement in parent activity participation in children with juvenile idiopathic arthritis treated with abatacept. Presented at the ACR/ARHP Annual Scientific Meeting 2008.
18. Hyrich KL, Lunt M, Watson KD, Symmons DPM, Silman AJ. Outcomes after switching from one anti-tumor necrosis factor alfa agent to a second anti-tumor necrosis factor alfa agent in patients with rheumatoid arthritis. Results from a large UK national cohort study. Arthritis & Rheumatism 2007;56(1):13-20.
19. Lovell DJ, Ruperto N, Cuttica R, et al. Long-term efficacy and safety of infliximab plus methotrexate for the treatment of polyarticular course juvenile rheumatoid arthritis: findings from an open-label treatment extension. Presented at the ACR/ARHP Annual Scientific Meeting 2008.
20. Gerloni V, Pontikaki I, Gattinara M, et al. Efficacy of repeated intravenous infusions of an anti-tumor necrosis factor alpha monoclonal antibody, infliximab, in persistently active, refractory juvenile idiopathic arthritis: results of an open-label prospective study. Arthritis Rheum 2005;52(2):548-53.
21. European Medicines Agency. Assessment report for Humira. Procedure No EMEA/H/C/II/39 2008.
22. Lovell DJ, Giannini EH, Reiff A, et al. Long-term efficacy and safety of etanercept in children with polyarticular-course juvenile rheumatoid arthritis: interim results from an ongoing multicenter, open-label, extended-treatment trial. Arthritis Rheum 2003;48(1):218-26.
23. Food and Drug Administration. Supplemental biological license application review for Enbrel (recombinant human tumor necrosis factor receptor Fc fusion protein, rhu TNFR:Fc), BLA no.98-1296 (Initial submission November 24, 1998; IND 5088). Center for Biologics Evaluation and Research office of Therapeutics Research and Review 2008.
24. Quartier P, Taupin P, Bourdeaut F, et al. Efficacy of etanercept for the treatment of juvenile idiopathic arthritis according to the onset type. Arthritis Rheum 2003;48(4):1093-101.
25. Horneff G, Schmeling H, Biedermann T, et al. The German etanercept registry for treatment of juvenile idiopathic arthritis. Ann Rheum Dis 2004;63(12):1638-44.
26. Mori M, Takei S, Imagawa T, et al. Pharmacokinetics, efficacy, and safety of short-term (12 weeks) etanercept for methotrexate-refractory polyarticular juvenile idiopathic arthritis in Japan. Mod Rheumatol 2005;15(6):397-404.
27. Prince FH, Twilt M, Ten Cate R, et al. Long-term follow-up on effectiveness and safety of etanercept in JIA: the Dutch national register. Ann Rheum Dis 2008.

28. Horneff G, De Bock F, Foeldvari I, et al. Safety and efficacy of combination of Etanercept and Methotrexate compared to treatment with Etanercept only in patients with juvenile idiopathic arthritis (JIA). Preliminary data from the German JIA Registry. Ann Rheum Dis 2008.
29. Cochino A, Grigorescu S, Miu N, et al. Combination therapy with etanercept and methotrexate in children with juvenile idiopathic arthritis. Ann Rheum Dis 2008;67(Suppl II):266.
30. Southwood T, Cummins C, Cotter C, Rahman J. Duration of etanercept treatment and reasons for discontinuation in a cohort of juvenile idiopathic arthritis (JIA) patients. Presented at the ACR/ARHP Annual Scientific Meeting 2008.
31. Giannini EH, Ilowite N, Lovell DJ, et al. Safety data from over 1,200 patient-years of methotrexate and/or etanercept treatment in children with polyarticular or sytemic juvenile rheumatoid arthrits. Presented at the ACR/ARHP Annual Scientific Meeting 2008.
32. Nielsen S, Ruperto N, Gerloni V, et al. Preliminary evidence that etanercept may reduce radiographic progression in juvenile idiopathic arthritis. Clin Exp Rheumatol 2008;26(4):688-92.
33. Tynjala P, Vahasalo P, Honkanen V, Lahdenne P. Drug survival of the first and second course of anti-TNF agents in juvenile idiopathic arthritis. Ann Rheum Dis 2008.
34. Saurenmann RK, Levin AV, Feldman MB, Laxer RM, Schneider R, Silverman ED. Risk of new-onset uveitis in patients with juvenile idiopathic arthritis treated with anti-tnf alpha agents. J Pediatr 2006;149:833-6.
35. Gerloni V, Pontikaki I, Gattinara M, Fantini F. Focus on adverse events of tumour necrosis factor alpha blockade in juvenile idiopathic arthritis in an open monocentric long-term prospective study of 163 patients. Ann Rheum Dis 2008;67(8):1145-52.
36. De Marco G, Gerloni V, Pontikaki I, et al. [Long-term evaluation of infliximab in the treatment of persistently active juvenile idiopathic arthritis refractory to conventional therapy.]. Reumatismo 2007;59(1):50-6.
37. Alexeeva E, Alexeeva A, Bzarova T, et al. Efficacy and safety of infliximab therapy in patients with various variants of juvenile idiopathic arthritis. Ann Rheum Dis 2008;67(Suppl II):265.
38. Lovell DJ, Reiff A, Jones OY, et al. Long-term safety and efficacy of etanercept in children with polyarticular-course juvenile rheumatoid arthritis. Arthritis Rheum 2006;54(6):1987-94.
39. Kimura Y, Pinho P, Walco G, et al. Etanercept treatment in patients with refractory systemic onset juvenile rheumatoid arthritis. The Journal of Rheumatology 2005;32(5):935-42.
40. Salmaso A, Gerloni V, Lurati A, et al. Efficacy of a second tnfalpha blocker when the first one failed in patients with juvenile idiopathic arthritis (JIA) treated with infliximab, etanercept and adalimumab. Ann Rheum Dis 2008;67(Suppl II):274.

41. Ruperto N, Lovell D, Cuttica R, et al. Long-term efficacy and safety of infliximab plus methotrexate for the treatment of polyarticular course juvenile rheumatoid arthritis. Findings from an open-label treatment extension. Ann Rheum Dis 2008;67(Suppl II):135.
42. Quartier P, Allantaz P, Cimaz R, et al. Anakinra in systemic-onset juvenile idiopathic arthritis: results of a multicenter double-blind trial (ANAJIS). Ann Rheum Dis 2008;67(Suppl II):68.
43. Quartier P, Cimaz R, Pillet P, et al. Anakinra in systemic-onset juvenile idiopathic arthritis (ANAJIS trial): Preliminary results. Presented at the American College of Rheumatology Meeting 2007. http://www.abstractsonline.com/viewer/viewAbstractPrintFriendly.asp?CKey={4E077A6C-C245-4F3B-9033-0753C8C0F34B}&SKey={2A1FDF5A-337D-48B7-9EDB-2667A0BCBC65}&MKey={4B645B61-3963-4802-8A7D-FFE86D8DE308}&AKey={AA45DD66-F113-4CDD-8E62-01A05F613C0D} (accessed March 2009) 2007.
44. Lovell DJ, Reiff A, Ilowite NT, et al. Safety and efficacy of up to eight years of continuous etanercept therapy in patients with juvenile rheumatoid arthritis. Arthritis Rheum 2008;58(5):1496-504.
45. Yokota S, Imagawa T, Miyamae T, Mori M, Nishimoto N, Kishimoto T. Long-term safety and efficacy of tocilizumab in patients with systemic juvenile idiopatic arthritis (JIA) under the extension and long-term trials. Presented at the ACR/ARHP Annual Scientific Meeting 2008.
46. Horneff G. Biologics for treatment of juvenile idiopathic arthritis - update 2007. Akt Rheumatol 2007;32:128-35.
47. Pontikaki I, Gerloni V, Gattinara M, et al. [Side effects of anti-TNFalpha therapy in juvenile idiopathic arthritis]. Reumatismo 2006;58(1):31-8.
48. Lequerre T, Quartier P, Rosellini D, et al. Interleukin-1 receptor antagonist (anakinra) treatment in patients with systemic-onset juvenile idiopathic arthritis or adult onset Still disease: preliminary experience in France. Ann Rheum Dis 2008;67(3):302-8.
49. Bloom BJ. Development of diabetes mellitus during etanercept therapy in a child with systemic-onset juvenile rheumatoid arthritis. Arthritis & Rheumatism 2000;43(11):2606-8.
50. Peek R, Scott-Jupp R, Strike H, Clinch J, Ramanan AV. Psoriasis after treatment of juvenile idiopathic arthritis with etanercept. Ann Rheum Dis 2006;65:1259.
51. Fathalla BM, Goldsmith DP, Pascasio JMC, Baldridge A. Development of autoimmune hepatitis in a child with systemic-onset juvenile idiopathic arthritis during therapy with etanercept. Journal of Clinical Rheumatology 2008;14(5):297-8.
52. Elwood RL, Pelszynski MM, Corman LI. Multifocal septic arthritis and osteomyelitis caused by group A *streptococcus* in a patient receiving immunomodulating therapy with etanercept. Pedatric Infectious Disease Journal 2003;22(3):286-8.
53. Foeldvari I, Kruger E, Schneider T. Acute, non-obstructive, sterile cholecystitis associated with etanercept and infliximab for the treatment of juvenile polyarticular rheumatoid arthritis. Ann Rheum Dis 2003;62:908-9.

54. Armbrust W, Kamphuis SSM, Wolfs TWF, Fiselier TJW, Kuis W, Wulffraat NM. Tuberculosis in a nine-year-old girl treated with infliximab for systemic juvenile idiopathic arthritis. Rheumatology 2004;43:527-9.
55. Manadan AM, Block JA, Sequeira W. Mycobacteria tuberculosis peritonitis associated with etanercept therapy. Clin Exp Rheumatol 2003;21(4):526.
56. Fitch PG, Cron RQ. Septic abscess in a child with juvenile idiopathic arthritis receiving anti-tumor necrosis factor-alpha therapy. J Rheumatol 2006;33(4):825.
57. Holl-Wieden A, Beer M, Marx A, Bonfig R, Tappe D, Girschick HJ. Infection of an urachal cyst during etanercept therapy in juvenile idiopathic arthritis. Rheumatol Int 2008;28:819-22.
58. Yildirim-Toruner C. Hodgkin's lymphoma and tumor necrosis factor inhibitors in juvenile idiopathic arthritis. Journal of Rheumatology 2008;35(8):1680-1.
59. Imundo L. Hodgkin's lymphoma associated with anti-tumor necrosis factor use in juvenile idiopathic arthritis: supplemental case report. Journal of Rheumatology 2008;35(8):1681-2.
60. Tutar E, Ekici F, Nacar N, Arici S, Atalay S. Delayed maculopapular, urticarial rash due to infliximab in two children with systemic onset juvenile idiopathic arthritis. Rheumatology 2004;43(5):674-5.
61. Tyler LN, Harville TO, Blackall DP. Multiple antibodies after transfusion in an infant treated with infliximab. N Engl J Med 2007;357(20):2092-3.
62. Sari I, Binicier O, Birlik M, et al. Thymic enlargement in a patient with juvenile idiopathic arthritis during etanercept therapy. Rheumatol Int 2009;29:591-3.
63. Mor A, Bingham CO, Barisoni L, Lydon E, Belmont HM. Proliferative lupus nephritis and leukocytoclastic vasculitis during treatment with etanercept. Journal of Rheumatology 2005;32:740-3.
64. Bout-Tabaku S, Rivas-Chacon R. Systemic lupus erythematosus in a patient treated with etanercept for polyarticular juvenile rheumatoid arthritis. The Journal of Rheumatology 2007;34(12):2503-4.
65. Lepore L, Marchetti F, Facchini S, Leone V, Ventura A. Drug-induced systemic lupus erythematosus associated with etanercept therapy in a child with juvenile idiopathic arthritis. Clin Exp Rheumatol 2003;21(2):276-7.
66. Kunzmann S, Warmuth-Metz M, Girschick HJ. Cerebral demyelination in association with TNF-inhibition therapy in a 5-year-old girl with aseptic meningitis as the first symptom of Still's disease. Scandinavian Journal of Rheumatology 2005;34(1):76-8.
67. Sukal SA, Nadiminti L, Granstein RD. Etanercept and demyelinating disease in a patient with psoriasis. J Am Acad Dermatol 2006;54:160-4.
68. Tauber T, Turetz J, Barash J, Avni I, Morad Y. Optic neuritis associated with etanercept therapy for juvenile arthritis. J AAPOS 2006;10:26-9.

69. Ramanan AV, Schneider R. Macrophage activation syndrome following initiation of etanercept in a child with systemic onset juvenile rheumatoid arthritis. J Rheumatol 2003;30:401-3.
70. Hashkes PJ, Shajrawi I. Sarcoid-related uveitis occuring during etanercept therapy. Clin Exp Rheumatol 2003;21(5):645-6.
71. Ontario Ministry of Health and Long-Term Care. Exceptional Access Program. http://wwwhealthgovonca/english/providers/program/drugs/odbf/odbf_except_accesshtml (Accessed Jan 4, 2010) 2010.
72. Regie de l'Assurance Maladie du Quebec. List of Medications 2009. http://www.ramq.gouv.qc.ca/en/regie/lois/liste_med.shtml. Accessed Jan. 8, 2010.
73. Ontario Ministry of Health and Long-Term Care. Drugs Funded by Ontario Drug Benefit (ODB) Program. http://wwwhealthgovonca/english/providers/program/drugs/odbf_eformularyhtml (Accessed Jan 4, 2010) 2010.
74. Ontario Ministry of Health and Long-Term Care. Schedule of Benefits. Laboratory Services. http://wwwhealthgovonca/english/providers/program/ohip/sob/lab/lab_mnhtml (Accessed Jan 4, 2010) 2010.
75. Vera-Llonch M, Massarotti E, Wolfe F, et al. Cost-effectiveness of abatacept in patients with moderately to severely active rheumatoid arthritis and inadequate response to methotrexate. Rheumatology 2008;47:536-41.
76. Coyle D, Judd M, Blumenauer B, et al. Infliximab and etanercept in patients with rheumatoid arthritis: a systematic review and economic evaluation [Technology report no 64]. Ottawa:Canadian Agency for Drugs and Technologies in Health; 2006 2006.
77. Ontario Ministry of Health and Long-Term Care. Schedule of Benefits. Physician Services. http://wwwhealthgovonca/english/providers/program/ohip/sob/physserv/physserv_mnhtml (Accessed: April 17th 2008) 2008.
78. Statistics Canada. Earnings, average hourly by hourly paid employees, by province and territory. www40statcangcca/101/cst01/labr80-enghtm (Accessed: Jan 27th 2009) 2008.
79. Brunner HI, Kim KN, Ballinger SH, et al. Current medication choices in juvenile rheumatoid arthritis II--update of a survey performed in 1993. J Clin Rheumatol 2001;7(5):295-300.
80. Santos MJ, Fonseca JE, Canhao H, et al. Consensos para inicio e manutencao de terapeutica biologica na artrite idiopatica juvenil. Acta Reumatol Port 2007;32:43-7.
81. Woo P, Nicholas W, Prieur AM, et al. Open label phase II trial of single, ascending doses of MRA in caucasian children with severe systemic juvenile idiopathic arthritis: proof of principle of the efficacy of IL-6 receptor blockade in this type of arthritis and demonstration of prolonged clinical improvement. Arthritis & Rheumatism 2005;7:R1281-R8.

82. Yokota S, Miyamae T, Imagawa T, et al. Therapeutic efficacy of humanized recombinant anti-interleukin-6 receptor antibody in children with systemic-onset juvenile idiopathic arthritis. Arthritis & Rheumatism 2005;52(3):818-25.
83. Pontikaki I, Gerloni V, Gattinara M, Hila A, Donati C, Fantini F. Anakinra in systemic juvenile idiopathic arthritis (SOJIA) non responsive to anti-TNF. Ann Rheum Dis 2008;67(Suppl II):271.
84. Borchers AT, Selmi C, Cheema G, Keen CL, Shoenfeld Y, Gershwin ME. Juvenile idiopathic arthritis. Autoimmunity Reviews 2006;5:279-98.
85. Quartier P. When should we use TNF antagonists in children with rheumatic disease? Joint Bone Spine 2007;74(1):1-3.
86. Russo RA, Katsicas MM, Zelazko M. Etanercept in systemic juvenile idiopathic arthritis. Clin Exp Rheumatol 2002;20(5):723-6.
87. Lovell D, Giannini E, Kimura Y, et al. Preliminary evidence for sustained bioactivity of IL-1 Trap (Rilonacept), a long acting IL-1 inhibitor, in systemic juvenile idiopathic arthritis (SJIA). Presented at the 2007American College of Rheumatology conference. 2007.