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

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CONFLICTS OF INTEREST

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ABBREVIATIONS

ABMT	autologous bone marrow transplantation
ACR	American College of Rheumatology
AE	adverse event
ANA	anti-nuclear antibodies
C$	Canadian dollar
CHAQ	child health assessment questionnaire
CHF	congestive heart failure
CI	confidence interval
DARE	Database of Abstracts of Reviews of Effects
DB	double blind
DMARD	disease-modifying anti-rheumatic drug
EMEA	European Medicines Agency
ESR	erythrocyte sedimentation rate
EULAR	European League against Rheumatism
FDA	Food and Drug Administration
HTA	health technology assessment
HSC	The Hospital for Sick Children
ICER	incremental cost-effectiveness ratio
ILAR	International League of Associations of Rheumatology
IL	interleukin
INAHTA	International Network of Agencies for Health Technology Assessment
ITT	intention-to-treat
IV	intravenous
JIA	juvenile idiopathic arthritis
Kg	kilogram
LOCF	last observation carried forward
LOM	limitation of motion
MAS	macrophage activation syndrome
mg	milligram
MTX	methotrexate
NHS EED	National Health Services Economic Evaluation Database
NSAID	non-steroidal anti-inflammatory drug
PEDE	Paediatric Economic Database Evaluation
PSA	probabilistic sensitivity analysis
QALY	quality-adjusted life year
QoL	quality of life
RCT	randomized controlled trial
RF	rheumatoid factor
RR	rate ratio

SC	subcutaneous
SD	standard deviation
TNF	tumour necrosis factor
UK	United Kingdom

EXECUTIVE SUMMARY

Introduction

Juvenile idiopathic arthritis (JIA) is one of the most common chronic rheumatic diseases in children. The estimated prevalence of the disease varies considerably, ranging from 7 to 400 per 100,000 children. JIA is divided into different disease subtypes including systemic, polyarticular, oligoarticular, psoriatic, and enthesis-related. Polyarticular JIA is one of the more severe subtypes, where five or more joints are affected within the first six months of illness.

Prognosis and outcome vary according to the disease subtype. Patients with more severe disease experience chronic pain and stiffness, irreversible joint damage, growth abnormalities, and functional disability. In approximately 40 to 50% of JIA patients the disease will remain active into adulthood.

Treatment of JIA is not curative and includes pharmacological therapy, physical and occupational therapy, and psychosocial support. Pharmacological treatments available include non-steroidal anti-inflammatory drugs (NSAIDS), glucocorticoids and disease modifying anti-rheumatic drugs (DMARDs). DMARDs can be non-biologic, such as the anti-inflammatory methotrexate (MTX), or they can be biologic, indicating that they are made from a living organism or its products, such as an antibody. Biologics are newer drugs, some of which have been recently approved for use in pediatric patients. Biologic agents used in the treatment of JIA belong to different classes based on their mechanism of action. Tumour Necrosis Factor (TNF)-α blockers include etanercept, infliximab, and adalimumab. Other biologics include the interleukin-1 blockers anakinra and rilonacept, and the interleukin-6 blocker tocilizumab. Other biologics include abatacept, an inhibitor of the T-cell mediated immune response, and rituximab, an anti CD20 antibody. The most common side-effects reported with biologic agents are injection site reactions and an increased incidence of infections. Concerns have been raised about a possible association between the use of anti-TNF-α drugs and the development of lymphoma, however this association has not yet been proven.

Objectives

The primary objective was to evaluate the clinical efficacy and safety evidence available for biologic drugs used in the treatment of the polyarticular subtype of JIA. The secondary objectives were to compare costs and cost-effectiveness of treatment with each biologic drug to conventional

treatment, comprised of an optimized non-biologic DMARD regimen. This report focuses on patients with the polyarticular-course JIA subtype. Results of studies conducted exclusively in children with systemic JIA are reported separately.

Methods

Systematic literature review

The peer-reviewed literature (Pubmed, Embase, Cochrane databases) and grey literature were searched for studies of biologic drugs used in the treatment of polyarticular JIA.

Study population

The study population consisted of pediatric patients with polyarticular-course JIA who presented with a suboptimal response to an optimized DMARD regimen.

Interventions

The report included biologic agents for which there are studies that met the inclusion criteria: etanercept, infliximab, adalimumab (TNF-α blockers), abatacept (T-cell inhibitor), and anakinra (interleukin-1 inhibitor). These biologic agents were compared to non-biologic DMARDs.

Study outcomes

The main outcome evaluated in most of the identified studies was disease improvement defined according to the American College of Rheumatology (ACR) core set response variables. Disease improvement was defined according to the ACR criteria for pediatrics, the ACR Ped 30, which is defined by an improvement ≥ 30% in at least three of the core variables[a] and the absence of ≥ 30% worsening in more than one variable. Other outcomes included disease flare, drug discontinuation, development of antibodies, and safety.

Cost analysis

The annual cost of treatment with each biologic drug was calculated (2008 C$). The primary cost analysis adopted a health care system perspective and included healthcare resources consumed in drug administration and routine patient monitoring. A secondary cost analysis adopted a societal perspective and included non-healthcare costs consisting of parent/caregiver productivity

[a] Global assessment of the severity of disease by the physician, global assessment of overall well-being by the patient or parent, number of active joints (joints with swelling or joints with limitation of motion and with pain, tenderness or both), number of joints with limitation of motion, erythrocyte sedimentation rate / C-reactive protein (measure of inflammation), Functional assessment (Child Health Assessment Questionnaire, CHAQ)

losses. In the base case analysis a 40 kg patient was assumed, approximating the mean weight in the two pediatric RCTs that reported patient weight. Univariate sensitivity analyses were conducted varying weight/body surface area and medication dose when applicable.

Economic evaluation

The incremental cost-effectiveness of biologics compared to non-biologic DMARDs in patients with polyarticular-course JIA was evaluated. A separate decision model was created for each biologic: etanercept, infliximab, adalimumab, and abatacept. Anakinra was not included as it is used mostly in patients with systemic JIA in our institution. The effectiveness measure used was the proportion of patients who responded to biologics at one year according to the ACR Ped 30 criteria, which was derived from the systematic review as the most commonly used measure of effectiveness in the field. The time horizon was one year. In the base case analysis, it was assumed that in patients with optimized doses of non-biologic DMARDs approximately 30% would respond for a period of six months. Due to the absence of data beyond this point, it was assumed that the rate of responders would remain stable for the remainder of the first year.

Costs were derived from the cost analysis and included those associated with serious adverse drug events. The base case analysis assumed a 40 kg patient.

The incremental cost-effectiveness ratios (ICERs) and their 95% confidence intervals (CIs) were calculated through probabilistic sensitivity analysis (PSA). Further PSAs were carried out by varying approaches used to estimate the effectiveness, and by varying treatment costs using a patient weight range from 10 to 70 kg.

Results

Systematic literature review

Five RCTs in patients with polyarticular JIA were identified, one for each of the following biologic drugs: etanercept, infliximab, adalimumab, abatacept, and anakinra. Several non-controlled observational studies with etanercept and infliximab were also identified.

All the RCTs except infliximab had a withdrawal study design and were divided into three phases. In the open-label lead-in phase (phase 1), the active biologic drug ± MTX was administered to all eligible patients. Patients who had a treatment response in phase 1 were then randomized in the double-blind phase (phase 2) to receive either the active drug ± MTX or its matching placebo ±

MTX for a period of 4-8 months depending on the study. Phase 2 was followed by an open-label non-comparative extension phase (phase 3) where the active drug was administered to patients who were enrolled in the double-blind phase.

In the infliximab RCT, patients were initially randomized to receive either infliximab 3 mg/kg + MTX or matching placebo + MTX for 14 weeks. After this period, patients received infliximab 3 or 6 mg/kg + MTX until week 52. Patients could continue into an open-label extension phase.

Study results

During the open-label phase (phase 1) of the RCTs, ACR Ped 30 criteria were met by 74%, 84%, 65%, and 58% of the patients who received etanercept, adalimumab, abatacept, and anakinra, respectively (the infliximab results are reported separately below). ACR Ped 70 criteria were met by 36%, 59% and 28% in the etanercept, adalimumab and abatacept studies respectively. (The anakinra study did not report the ACR Ped 70 response rates.) At the end of a 4-8-month double-blind phase, the percentage of patients without a disease flare with the active drug (biologic ± MTX) compared to placebo (± MTX) was 72% vs. 19%, 80% vs. 47%, and 84% vs. 60% respectively, in the etanercept, abatacept, and anakinra studies. The difference was not statistically significant in the anakinra study. In the adalimumab study, results were reported separately for those who had been on MTX. In the adalimumab + MTX group the results were 63% vs. 35%; in the adalimumab alone group the results were 57% vs. 29%.

In the infliximab study, the difference in the percentage of ACR Ped 30 responders between infliximab 3 mg/kg + MTX and placebo + MTX was not statistically significant at 14 weeks (64% and 49% respectively). After 14 weeks, all patients received infliximab 3 or 6 mg/kg + MTX. At the end of 52 weeks approximately 75% of the patients met the criteria for ACR Ped 30 responders.

Long-term follow-up results from the open-label extension of RCTs are available for etanercept (eight years), adalimumab (two years), and infliximab (three years). At two years, 69% of the etanercept ± MTX patients met the ACR Ped 30 criteria (intention-to-treat analysis). Analyses including only available patients found response rates of 90% (32 patients) and 100% (11 patients) at four and eight years, respectively. In the adalimumab study, at two years (104 weeks) into the extension phase, approximately 90% of 128 patients were ACR Ped 30 responders. Infliximab follow-up found that a total of 78 (64%) of the 122 patients who were initially included in the RCT went on to enter the open-label extension phase. Among 36 patients who completed

three years of follow-up in the extension phase, ACR Ped 30, 50, 70, or 90 was achieved by 33 (92%) patients at week 204.

Drug discontinuation during phase 1 was 26%, 22%, 36%, and 42% in the etanercept, adalimumab, abatacept, and anakinra studies, respectively. During the double-blind phase, six (24%), four (6%), 11 (18%), and six (24%) of the patients discontinued treatment, respectively. In the infliximab RCT, 13 (11%) patients withdrew between weeks six and 52, mostly due to lack of efficacy or adverse events. In long term studies, discontinuation occurred in 10-66% of etanercept patients (1-8 years), and in 43-71% of patients treated with infliximab (1-5 years).

The evaluation of safety included the agents studied in the RCTs listed above and tocilizumab. During the 2-4-month open-label phase of the biologics RCTs, serious adverse events occurred in 3-7% of the patients treated with etanercept, adalimumab, abatacept, and tocilizumab. Most of the events consisted of serious infections, urticaria/anaphylactoid reaction, and one case of depression and personality disorder. During the double-blind phase, no serious adverse event was reported with the active drugs etanercept, adalimumab, abatacept, or tocilizumab. Serious infections were reported in the placebo group of the abatacept (n=2) and adalimumab (n=1) RCTs.

In the double-blind phase of the infliximab study, six (6/122, 5%) serious infections and six (6/122, 5%) serious infusion reactions were reported in infliximab-treated patients over a 9-12 month period. In the placebo arm of the initial phase, two (3%) serious infections were reported over a 3.5-month period. There were two deaths in the infliximab study. One was due to cardiac arrest following hospitalization for a severe disease flare which occurred six months after the patient discontinued infliximab 3mg/kg in the open-label extension phase. The second occurred in the placebo arm, after the patient was hospitalized due to septic shock, with cardiac function deterioration leading to death.

Cost analysis

Annual treatment costs including drug acquisition and administration, monitoring, healthcare professionals' fees, and concomitant medications were $18,966, $17,259, $18,654, $14,733, and $20,084 with etanercept, infliximab (3-5 mg/kg), adalimumab, abatacept and anakinra, respectively. Annual treatment costs with MTX were estimated at $952.

Economic evaluation

In the base case scenario, at one year the additional costs (95% CI) per additional ACR Ped 30 responder were $26,061 (17,070, 41,834), $31,209 (16,659, 66,220), $46,711 (30,042, 75,787), and $16,204 (11,393, 22,608) with etanercept, infliximab, adalimumab, and abatacept, respectively.

Budget impact

Assuming a prevalence of 100 JIA cases per 100,000 children, there would be approximately 3,000 children with JIA in Ontario, 60% of whom may present with the polyarticular subtype (1,800). If 10% of these children require treatment with biologics (n=180), assuming drug costs of C$15,000 per year, the annual cost in the province would be estimated as C$2.7 million. The 10% estimate is based on patients with no response to conventional treatment. It is possible that the actual proportion of polyarticular JIA patients who would use biologics is higher than 10%, as this has not been previously studied. Assuming that 20% of polyarticular JIA patients receive biologics, the cumulative budget impact to payers in Ontario may rise to approximately C$5.4 million per year.

Discussion

The studies in patients with JIA showed that the use of etanercept, infliximab, adalimumab, abatacept, and anakinra may result in short-term disease improvement (ACR Ped 30) in approximately 80% of patients with active disease following a non-optimal response to treatment with non-biologic DMARDs. The studies found, however, that up to approximately one-third of the patients may need to discontinue the biologic in the first 3-4 months of treatment due to either lack of efficacy or intolerance. The study with the longest follow-up (eight years) reported a 66% rate of discontinuation (excluding disease remissions). The long-term results currently available (up to eight years) show that biologics may remain effective for many years in those who tolerate them.

Although biologic drugs demonstrated large improvements in the treatment of JIA, their long-term safety still needs to be established. Safety concerns with biologic drugs have been raised by health authorities and in the literature. These include development of malignancies and autoimmune disorders, and an increased risk of opportunistic infections.

The long-term impact of biologics compared to non-biologic DMARDs on functional disability and quality of life has not yet been established. The short-term clinical outcomes currently available do

not permit extrapolations to the longer term. Given the potential for a large budget impact as well as the potential for improvement in long-term patient outcomes, more comprehensive economic analyses should be undertaken once long-term outcomes that are clinically relevant such as functional disability/social impact have been accurately estimated. Long-term safety concerns with biologics should also be taken into account in future analyses.

Annual treatment costs with biologics are in the range of C$14,000 to C$19,000 depending on the drug and dose used (40 kg patient). Payers of biologics vary by drug and patient and may include the hospital, the Ministry of Health or other publicly-funded programs, private drug insurance plans or the patient's family. The use of biologics has the potential for considerable cumulative budget impact, possibly as high as C$5 million per year in Ontario.

The economic models were based on the best evidence currently available. Extensive sensitivity analyses were conducted to account for uncertainty in the data. An important limitation was the use of a short-term time horizon of one year. The uncertainty in parameter estimates beyond this time frame was too great to allow for further meaningful extrapolations. As utility estimates for health states were not available, ICERs were based on the incremental cost per additional treatment responder, which poses a challenge in the interpretation and comparison to other studies and thresholds for resource allocation decisions.

Conclusions

The current evidence shows a short-term improvement in disease status following treatment with biologics in patients with polyarticular JIA who had previously had an inadequate response to conventional treatment. It is believed that better control of the disease may result in improvement in important long-term clinical outcomes, such as functional disability, which may affect social life, employment, and quality of life. Long-term treatment outcomes data, however, are not presently available. Disease registries may provide additional evidence on clinical benefits and safety issues in patients treated with these drugs.

Along with a potential for improvement in important long-term clinical outcomes in some patients comes a potential for a considerable health care payer budget impact given the number of patients that may need treatment and the length of treatment. Moreover, important long-term safety concerns have also been raised. All these factors need to be taken into account and should be further evaluated in allocation decisions.

INTRODUCTION

Juvenile idiopathic arthritis (JIA) is one of the most common chronic conditions in childhood and may result in disabilities that are carried into adulthood. Estimates of rates of non-response to the standard drugs available such as non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids or disease-modifying rheumatoid arthritis drugs (DMARDs) such as methotrexate (MTX) vary from five to ten percent[1] to as high as 30%.[2] Non-response may be higher in patients with the polyarticular subset of JIA.[1] Patients with no response or suboptimal response to non-biologic DMARDs are candidates to receive biologic agents.

Biologic drugs have been recently developed based on an enhanced understanding of inflammatory diseases. Classes of biologics include anti-tumour necrosis factor α blockers, interleukin blockers, t-cell blockers, and anti-CD20 antibodies. The introduction of biologic drugs in rheumatology has resulted in an improvement in the outcomes of treatment of rheumatoid arthritis, permitting the control of the disease in patients refractory to pharmacological agents previously available.[3, 4]

The use of biologics has the potential for a high budget impact to payers given the cost of treatment (greater than C$14,000/year), the number of patients that may require the use of these drugs, and the fact that treatment is needed for long periods, or even a lifetime.

Several economic evaluations of biologics have been conducted in adults. To date, however, none have been performed in pediatrics. JIA is different from adult rheumatoid arthritis. Moreover, the fact that pediatric patients receive the medications during a period of physiological and psychological development, and the fact that patients may need to be treated for long periods if not a lifetime, illustrate the importance of evaluating the use of biologics specifically in children.

This report aims to study the evidence available on the use of biologic drugs in children with JIA with inadequate response to non-biologic DMARDs, with respect to safety, efficacy, and cost.

1.1 Background

Juvenile idiopathic arthritis consists of a group of heterogeneous forms of arthritis characterized by persistent joint inflammation that develops in pediatric patients younger than 16 years, lasts longer than six weeks and has no known cause.[5, 6] It is one of the most common chronic rheumatic disease in children.[5] The disease may affect the development of bone and joints and

can affect growth.[5] It is estimated that in approximately 50% of the cases, symptoms such as inflammation and disability due to the disease are carried into adulthood.[7]

The incidence of JIA is estimated to be between 7 to 21 per 100,000 population in the US and Northern Europe.[8] Other studies have reported varying prevalence rates, ranging from 132 to 220 per 100,000,[8] to16 to 113 per 100,000,[9] or 100 per 100,000 children.[10] A review of 34 epidemiological juvenile arthritis studies published between 1966 and 1998 revealed a tremendously wide variation in reported prevalence, varying from 7-400 per 100,000 children.[11] The authors speculated that reasons for the disparities include where the study was undertaken (for example, community or hospital based), differences in diagnostic criteria used and small sample sizes which may also have resulted in less precise estimates.[11] In Canada, a study published in 1996 observed an incidence of 3.14 cases of juvenile rheumatoid arthritis per 100,000 children.[12] A publication based on estimates from children referred to a rheumatology clinic in Saskatchewan revealed a juvenile rheumatic arthritis clinical point prevalence of 35 per 100,000 children and a mean annual clinic referral incidence of 4.7 per 100,000.[13]

1.2 Disease classifications

Different classifications of JIA using different terminology exist, including the ones from the American College of Rheumatology (ACR) and the European League against Rheumatism (EULAR).[5, 8] The International League of Associations of Rheumatology (ILAR) was developed to standardize the classification criteria (table 1).[5, 8]

This report is focused on the polyarticular-course JIA subtype, including both rheumatoid factor (RF) negative and RF positive. Polyarticular JIA is one of the more severe subtypes, where five or more joints are affected within the first six months of illness.[14] Results of studies exclusively in children with systemic JIA subtype are presented separately.

Table 1 Juvenile arthritis classification

Classification of juvenile arthritis Onset subtype		
American College of Rheumatology JRA	**European League Against Rheumatism (EULAR) JCA**	**International League of Associations of Rheumatology (ILAR) JIA**
Systemic	Systemic	Systemic
Polyarticular	Polyarticular rheumatoid factor negative (RF-)	Polyarticular rheumatoid factor negative (RF-)
-	Polyarticular rheumatoid factor positive (RF+)	Polyarticular rheumatoid factor positive (RF+)
Pauciarticular	Pauciarticular	Oligoarticular Persistent Extended
-	Juvenile psoriatic	Psoriatic
-	Juvenile ankylosing spondylitis	Enthesis-related
-	Arthritis associated with inflammatory bowel disease	-
-	-	Undifferentiated arthritis

Source: Borchers et al.,[8] Kulas et al.[6]

Each of these disease subtypes is heterogeneous in their presentation, clinical characteristics, and age of onset.[15] Juvenile idiopathic arthritis (JIA) occurs more frequently in females than in males in most disease subtypes with the exception of systemic arthritis, where there is an equal distribution between both sexes, and enthesitis-related arthritis, where the frequency is higher in males than in females.[5, 8]

The incidence, prevalence and distribution of JIA and its subtypes vary according to the world region, which may be explained by ethnicity, environmental and genetic factors.[16] Oligoarthritis is the most common onset type of JIA in the North America,[8, 12] accounting for approximately 40-60% of the cases.[8, 17] Polyarticular-onset subtype represents approximately 20-25% of the cases at onset,[7, 8] however, patients with systemic-onset[14, 18] and approximately 50% of the patients with oligoarticular-onset subtypes may evolve into a polyarticular-course of the disease.[8, 19] The distribution of JIA types and their characteristics is provided in Appendix 1. A survey performed at The Hospital for Sick Children (HSC) in Toronto showed that all JIA subtypes, with the exception of rheumatoid factor-positive polyarticular and systemic JIA, were more common in children of

European origin than in those of non-European origin.[16] Children of Chinese, Indian subcontinent, or black origin had a higher risk of developing rheumatoid factor-positive polyarticular JIA.[16]

1.3 Pathogenesis

The cause of JIA is not very well understood but may include genetic and environmental factors.[5, 20] It is believed that JIA has an autoimmune etiology as the presence of auto-antibodies has been identified in some patients with JIA such as rheumatoid factor and antinuclear antibodies (ANA),[8] rheumatoid factor (RF), and anti-single-stranded DNA.[15] Studies have found that the presence of ANA may be associated with a longer duration of active disease and/or disability.[8] Approximately 2-12% of JIA patients have a rheumatoid factor antibody, which has also been associated with disability and difficulty in achieving remission.[8]

The inflammatory process involved in the development of rheumatoid arthritis is mediated by macrophages that release inflammatory cytokines such as tumour necrosis factor-α (TNF-α) and interleukins (IL-1, IL-6).[6] These cytokines cause the release of proteinases that cause joint damage and lead to bone and cartilage destruction.[6]

1.4 Disease course and prognosis

The overall prognosis of pediatric patients with chronic arthritis is considered good, however, up to one third of cases may be refractory to conventional therapy with NSAIDs, glucocorticoids, and non-biologic DMARDs.[2] This is mainly the case with systemic and polyarticular onset subtypes.[1]

Prognosis and outcome vary according to the disease subtype.[5] It is believed that patients with a more severe or more extensive disease at onset, polyarticular subtype, symmetrical disease, early wrist or hip involvement, rheumatoid-factor positive disease, and early radiological changes have a worse prognosis.[5, 7]

Patients with more severe disease experience chronic pain and stiffness, irreversible joint damage that may require joint replacement, growth abnormalities, and functional disability.[10] Growth retardation and osteoporosis may occur as a consequence of either the disease or treatment with glucocorticoids.[5, 15] In addition to limitations in school activities, [21] children may also miss school days either due to their disease symptoms or medical appointments. The disease may also have an impact on the life of family members caring for the child due to work absenteeism; in some cases one of the parents may not be able to work at all.[22]

In approximately 40-50% of JIA patients the disease will remain active into adulthood.[7, 19] In the long-term, joint replacement is necessary in 25%-50% of the patients.[17] Even when the disease is not active, disability due to long periods of JIA activity can still be carried into adulthood.[7] This includes joint deformity and destruction, growth abnormalities, osteoporosis, pain, and psychological problems[1, 6, 7] which may affect the patient's quality of life and employment.[7, 8, 10, 23]

The mortality in patients with JIA has been estimated to be three to five times higher than the general population.[8] This may be due to JIA-associated conditions such as macrophage activation syndrome (MAS) and secondary amyloidosis, which are more common in the systemic JIA subtype, but a higher mortality could also be due to treatment complications, and complications of other autoimmune diseases.[8]

Disease remission may occur, however, it is not clear for how long it can be sustained and its occurrence varies according to disease subtype.[24] Studies have shown that fewer than 10% of the clinical remissions last longer than five years.[5, 24] Remission may also be part of the natural disease course.[24, 25]

1.5 Treatments available

1.5.1 Non-biologic agents

Treatment of juvenile idiopathic arthritis is not curative and includes pharmacological therapy, physical and occupational therapy, and psychosocial support.[5, 24] Treatment aims at controlling joint pain and inflammation, reducing joint damage, and avoiding long-term complications such as disability and loss of function.[5, 20] Pharmacological treatments available include non-steroidal anti-inflammatory drugs (NSAIDS), glucocorticoids and disease modifying anti-rheumatic drugs (DMARDs) which include biologic agents. Autologous bone marrow transplantation (ABMT) is an option in patients who are refractory to pharmacological therapy.[8] The experience with the procedure is still limited[26, 27] and the risks involved, including infection and mortality should be weighed against the potential benefits.[7, 8, 17, 27, 28]

Given the differences in clinical presentation of the different JIA subtypes, different treatment steps are recommended for different subtypes, as proposed in the guidelines by Hashkes & Laxer[29] summarized in Appendix 2.

NSAIDs such as naproxen, ibuprofen, and indomethacin are generally used as the initial treatment for juvenile idiopathic disease[5] and are able to control it in approximately one-third of the patients depending on the sub-type.[14] NSAIDs act primarily on the symptoms of the disease and are not able to modify the underlying disease process or improve long-term outcomes.[14, 30]

Intra-articular steroid injections are used at disease onset and during the course of the disease as they prevent contractures that lead to deformities.[5] If disease control cannot be achieved with either NSAIDs or intra-articular steroid injections, other more aggressive treatments are used such as systemic glucocorticoids.[5] Systemic glucocorticoids are usually restricted to patients where the benefits outweigh the risks, which include growth retardation, weight gain, and bone demineralization.[5, 31] Increasingly, practitioners may view MTX as an appropriate first line therapy for any child with polyarthritis.

Disease-modifying anti-rheumatic drugs (DMARDs) are agents that slow the radiological progression of damage to joints.[32] DMARDs are used in an attempt to control the disease before irreversible damage occurs.[30] Non-biological DMARDs are used in the treatment of JIA uncontrolled by NSAIDs and include methotrexate, sulphasalazine, cyclosporine, azathioprine, cyclophosphamide, gold, hydroxychloroquine, penicillamine, chlorambucil, and leflunomide.[8, 31, 33]

Methotrexate (MTX) is the main non-biologic DMARD used in JIA.[6, 34] It has been shown to slow down cartilage injury.[35] Consequences of long-term MTX treatment include hepatic fibrosis (rarely) and osteopathy, although the latter has been reported in children with leukemia using a higher dose (30 mg/m^2) than the one used in rheumatology.[31] Long-term immunosuppression with MTX may also be associated with the development of malignancies (lymphoproliferative diseases), however a causative association between MTX use and the development of the malignancy has not been proven.[31] Over the long-term, treatment with MTX results in 60-70% of JIA patients achieving an improvement of 30% or more in at least three of core clinical endpoints (ACR Ped 30).[2] Treatment with MTX, however, may not be effective in achieving complete disease control, even at high doses.[2] Complete disease control remains elusive for many JIA patients; one study found that in a cohort of polyarthritis patients examined over a five year period, disease was active for a median of 63% of that time.[36] Higher doses of MTX may be necessary in non-responders, however they may not be well tolerated by some children, which may preclude the continuation of treatment.[37, 38]

1.5.2 Biologic agents

More recent findings that proinflammatory cytokines such as tumour necrosis factor α (TNF-α) and interleukins (IL-1, IL-6) are involved in the pathogenesis of JIA[39, 40] led to the development of biologic drugs.[23, 30, 40]

Drugs that block TNF-α (thereby preventing its pro-inflammatory actions[41]) include etanercept, infliximab, and adalimumab.[26] Etanercept is a recombinant fusion protein.[14] Infliximab and adalimumab are monoclonal antibodies.[30, 41] These drugs differ in terms of their structure and pharmacokinetics, as well as dosing interval and administration, efficacy and safety.[42, 43]

Other biologic drugs used to treat JIA are the interleukin-1 blockers, anakinra and rilonacept, and the interleukin-6 blocker tocilizumab.[26] Abatacept, an inhibitor of the T-cell mediated immune response, [26] and rituximab, an anti-CD20 antibody, are also used in JIA. Table 2 provides information on the biologics currently used in JIA.

Table 2 Biologic drugs currently available to treat juvenile idiopathic arthritis

Biologic drug	Class/Mechanism of action	Dosing and treatment regimen – pediatrics (JIA)	Mode of administration
Etanercept	Genetically engineered dimeric fusion protein that inhibits the binding of TNF-α to its receptors[14]	0.4 mg/kg 2x/ wk or 0.8mg/kg 1x/wk Max: 25 mg/dose or 50mg/wk[30]	Subcutaneous injections can be administered at home
Infliximab	Chimeric (mouse-human) anti-TNF-α monoclonal antibody[44]	3-10 mg/kg[30] ; q 2 wks at first, q 4-6 wks thereafter*	Intravenous infusion
Anakinra	Recombinant human IL-1 receptor antagonist [32]	1 mg/kg/day (max 100 mg/day)[30]	Subcutaneous injection Once a day[30]
Adalimumab	Monoclonal anti-TNF-α antibody[41]	24 mg/m^2 or 40 mg[45] Every other wk[46]	Subcutaneous injection
Abatacept	T-cell activation inhibitor [26]	10 mg/kg (maximum 1,000 mg) Every 2 wks for 1 month, q 28 days thereafter [47]	Intravenous infusion [47]
Tocilizumab	Monoclonal chimeric anti-IL-6 receptor antibody[48]	2-8 mg/kg[49] Every 2 wks[49]	Intravenous infusion[48]
Rituximab	Anti-CD20 monoclonal antibody[50]	Under investigation in JIA	Intravenous infusion [50]

IL interleukin / IV intravenous / JIA juvenile idiopathic arthritis / TNF tumour necrosis factor / q every / wk week
*Personal communication, Dr. Brian Feldman, September 2009.

Biologic agents decrease the patient's immune response by interacting with cytokines and T-cell receptor-major histocompatibility complex antigen.[30] Due to their potential immunosuppressive effects, infections are a concern in patients treated with anti-TNF-α agents.[51]

The most common side-effects reported with biologic agents are injection site reactions which are often mild and transient[3, 41, 52] and an increased incidence of infections, sometimes serious, mostly of the upper respiratory tract.[3, 15, 30, 50] Other side-effects reported mainly with anti-TNF-α agents include neurologic/psychiatric disturbances, cutaneous vasculitis, and pancytopenia.[17, 46 53] Infliximab-related anaphylaxis due to the drug's murine component has been reported as well.[30] Transient increases in hepatic enzymes and cholesterol levels which may increase the risk of cardiovascular diseases in patients treated with tocilizumab have been reported.[54]

Infusion-related reactions with anti-TNF-α agents may manifest early, less than 24 hours after the infusion, or late, such as 24 hours to 14 days after the start of drug administration.[55] Although infusion-related reactions tend to start early in the course of treatment, studies have shown that approximately one-fifth of the reactions first manifest later, up to 15 months after the start of treatment,[55] and they have been reported to appear five years after the start of treatment.[55] Early infusion-related reactions include pruritus, edema, urticaria, hypertension, bradycardia, tachycardia, headache, fever, and anaphylactic shock.[55] Late occurring infusion-related reactions may include arthralgia, myalgia, urticaria, eruption, fever or headache.[55]

Concerns have been raised about a possible association between the use of anti-TNF drugs and the development of lymphoma.[41, 46] This association hasn't been proven and it's not clear if patients with rheumatic diseases are at an increased risk in general, especially since patients receiving these drugs tend to have more severe disease.[56 57] It may also be associated with use of other immunosuppressive treatment,[56] genetics, and inflammatory activity.[58] On the other hand, TNF-α has a complex interaction with tumour development and can act as a suppressor or promoter.[56, 57] Longer follow-up is needed in order to evaluate the long-term risk.[10]

Reactivation of infectious diseases such as hepatitis B[41] and tuberculosis, as well as the occurrence of opportunistic infections are a concern in patients treated with anti-TNF- α drugs.[33, 59] It is recommended that patients be tested for tuberculosis before starting treatment with an anti-TNF-α drug and annually thereafter.[9] Other concerns with the TNF-α blockers etanercept,

infliximab, and adalimumab include worsening of congestive heart failure (CHF).[59] Neurological effects such as seizures have been reported with the use of anti-TNF-α.[53]

Regulatory agencies in Canada and US have issued warnings related to the occurrence of malignancies and opportunistic fungal infections in adult and pediatric patients treated with biologic drugs (table 3).

Table 3 Regulatory agency warnings (US and Canada) pertaining to lymphoma and opportunistic fungal infections

Regulatory Agency / Date Drug	Information
Health Canada / July 24th 2006 Infliximab	A Dear HCP Letter issued by the manufacturer in Canada warned of a possible association between the use of infliximab & the development of hepatosplenic T-cell lymphoma (HSTCL, a rare type of lymphoma with a very aggressive & fatal course) in pediatric & young adults with Crohn's disease (six cases reported with the drug).[60] In all six cases of HSTCL, concomitant or previous use of other drugs considered as mutagens/carcinogens such as azathioprine & 6-mercaptopurine (6-MP) occurred which does not allow the establishment of a causal association between infliximab & HSTCL, however, it cannot be ruled out that the drug has caused or exacerbated the disease.[60]
US Food and Drug Administration (FDA) / September 4th 2008 Etanercept, infliximab, adalimumab, cerolizumab	A letter warned of the possibility of histoplasmosis & other fungal infections in patients being treated with anti-TNF-α drugs (etanercept, infliximab, adalimumab, and certolizumab).[61] It was warned that a delay in the diagnosis of these infections & the consequent delay in starting therapy may result in death.[61]
Health Canada, Amgen / April 21st 2009 Etanercept	A letter to HCPs advised of reports of serious pulmonary and disseminated histoplasmosis, coccidiomycosis, and blastomycosis infections sometimes with fatal outcomes in patients using anti-TNF-α agents including etanercept.[62]
US FDA / August 2009 Etanercept, infliximab, adalimumab, and cerolizumab	The U.S. FDA issued a black box warning in the prescribing information for TNF blockers in August, 2009[63] which included an updated boxed warning, highlighting the increased risk of cancer in children & adolescents who receive them. The FDA had reports of 30 cases of malignancies[b] in children & young adults from 1998-April 2008.[64] The patients were taking one of these drugs concomitantly with MTX, azathioprine or 6-MP for the treatment of JIA or Crohn's disease.[64] HCPs were advised to discuss with patients & families the increased risk of developing cancer in children & adolescents, taking into account the benefits of TNF blockers, the risks/benefits of other immunosuppressive therapies, & the risks of untreated illness.
European Medicines Agency (EMEA) / 2009 Adalimumab label	The adalimumab product label was updated in order to include three cases of HSTCL reported in adalimumab-treated adult patients with rheumatoid arthritis and IBD[65].

TNF tumour necrosis factor / 6-MP 6-mercaptopurine / HCP Health care professional / IBD Irritable Bowel Disease

[b] Half of the malignancies were lymphomas including both Hodgkin's and non-Hodgkin's lymphoma, but also included leukemia, melanoma, and solid organ cancers.[64]

The development of antinuclear antibodies (ANA) and anti-double strand DNA with the use of TNF-α blockers has been reported[53] and may be associated with autoimmune diseases.[66] Drug-induced autoimmune diseases such as lupus erythematosus, vasculitis[15, 33, 50, 67] and the occurrence of demyelinating diseases such as multiple sclerosis, optic neuritis,[33, 41, 46, 50, 56, 68-70] paresthesias, visual disturbances and confusion[69] have been reported with the use of anti-TNF-α drugs, however a causal association has not been established.[70] In the case of lupus, anti-TNF-α drugs may act as either a trigger for an underlying disease, or may be the cause of the disease (drug-induced lupus).[67] The development of anti-etanercept, infliximab, and adalimumab antibodies has been reported[46, 53] which may result in decreased drug efficacy and/or increase the risk of adverse events.[71]

1.5.3 Biologics regulatory approval

Table 4 presents the pediatric indications for which each biologic has been approved in Canada.

Table 4 Biologic drugs: Pediatric rheumatology indications approved by Health Canada (current to January 15th 2009)

Biologic Drug	Pediatric rheumatology indications (brief)
Etanercept	Moderate to severely active JIA in patients 4-17 years old with an inadequate response to ≥ 1 DMARDs.
Infliximab	Moderately or severely active Crohn's disease and an inadequate response to conventional therapy. The safety and efficacy has not been established in children < 9 years.
Adalimumab	Canada – not approved in pediatrics. FDA - Reducing signs and symptoms of moderately to severely active polyarticular JIA in patients ≥ 4 years old.
Anakinra	-
Abatacept	JIA of moderately to severely active polyarticular subtype in pediatric patients ≥ 6 years with an inadequate response to one or more DMARDs such as MTX.
Tocilizumab	-
Rituximab	-

DMARD disease-modifying anti-rheumatic drug / FDA Food and Drug Administration / JIA juvenile idiopathic arthritis / MTX methotrexate
Sources: Compendium of Pharmaceutical Specialties (CPS) online version[72]

1.6 Objectives

There are uncertainties regarding the long-term clinical benefits and safety outcomes of biologics in JIA. Biologics have a high treatment cost, which, allied with the potential number of patients that may be eligible for treatment, may have a considerable budget impact.

The primary objective was to evaluate the long-term clinical efficacy and safety evidence available for biologic drugs used in the treatment of the polyarticular subtype of JIA. The secondary objectives were to compare costs and cost-effectiveness of treatment with each biologic drug to conventional treatment, comprised of an optimized non-biologic DMARD regimen.

This report focuses on patients with polyarticular-course JIA subtype. Studies conducted exclusively in children with systemic JIA are reported separately in Appendix 17.

2 METHODS

2.1 Systematic literature search

The peer-reviewed literature (Pubmed, Embase, Cochrane databases) and health technology assessment or health economics databases - The International Network of Agencies for Health Technology Assessment (INAHTA) database including the HTA, NHS EED, and DARE databases, and Paediatric Economic Database Evaluation (PEDE) - were searched in order to identify the following types of publications:

- Comparative or non-comparative clinical studies with biological drugs in patients with JIA (≥ 20 patients).
- Health technology assessment reports, meta-analyses, systematic reviews evaluating the use of these drugs in patients with JIA.
- Economic evaluations with these drugs in JIA.

The websites of regulatory agencies comprising Health Canada, the United States Food and Drug Administration (FDA), and the European Medicines Agency (EMEA) were searched for clinical information that may complement data published in the peer-reviewed literature. Additionally, the reference lists of articles identified were searched for additional eligible publications. Conference proceedings in the area such as the EULAR and the American College of Rheumatology were also searched for the two most recent years 2007 and 2008.

In the case of multiple publications of the same study/cohort of patients, only the most recent results for each outcome were maintained unless a different study population or results at different follow-up times were provided.

Non-clinical studies and those that did not report at least one of the outcomes of interest were excluded from the report (see section 2.5 for a description of the study outcomes used). Studies also had to have reported results with individual drugs rather than a group of drugs, for example, different anti-TNF-α drugs evaluated as one group would not have been eligible.

Given the safety concerns with biologics, case-reports of adverse events following treatment with biologics were also summarized.

There were no restrictions for language, however, only articles in English, French, Portuguese, German, Spanish, and Italian were reviewed due to availability of translation.

Abstracts of articles identified through the systematic literature search were reviewed and the full-texts of articles considered eligible were reviewed. Data from eligible articles were entered into pre-tested data collection forms.

Keywords used in the systematic review are provided in Appendix 3.

2.2 Study population

The study population comprises patients with polyarticular-course JIA who presented with an inadequate response to optimized non-biologic DMARDs regimens.

2.3 Interventions

The report includes biologic agents for which there are studies that met the inclusion criteria: etanercept, infliximab, adalimumab, abatacept, and anakinra. As no efficacy evidence in polyarticular JIA was reported for tocilizumab, only safety data are reported for this agent.

2.4 Comparators

Currently biologic agents are prescribed in JIA patients with inadequate or insufficient response to non-biologic DMARDs. Methotrexate is the first line and most commonly used non-biologic DMARD in treating polyarticular JIA and was used as the standard treatment comparator.[6, 34]

2.5 Study outcomes

The main outcomes evaluated in most identified studies were disease improvement and disease flare and were defined according to the core set response variables set by the American College of Rheumatology (ACR).[73] Disease improvement was defined according to the ACR criteria for

pediatrics, i.e. ACR Ped 30 is defined by an improvement ≥ 30% in at least three of the core variables listed in the box below and the absence of ≥ 30% worsening in more than one variable.[17] ACR Ped 50 (≥ 50% improvement) and ACR Ped 70 (≥ 70% improvement) were also measured in the studies.

Disease flares were defined as worsening ≥ 30% in three of six of the core variables listed in table 5, and ≥ 30% improvement in a maximum of one response variable from baseline.[45, 47, 74, 75] In the etanercept study patients were additionally required to have two active joints in order to be classified as a disease flare.[39]

Table 5 ACR Ped core variables used in the ACR Ped disease improvement and disease flare definitions

ACR Ped core variables used in the ACR Ped disease improvement and disease flare definitions [73]
❖ Global assessment of the severity of disease by the physician
❖ Global assessment of overall well-being by the patient or parent
❖ Number of active joints (joints with swelling or joints with limitation of motion and with pain, tenderness or both)
❖ Number of joints with limitation of motion
❖ Erythrocyte sedimentation rate / C-reactive protein (measure of inflammation)
❖ Functional assessment (Child Health Assessment Questionnaire, CHAQ)

The ACR Ped criteria were validated and have shown reliability in discerning between drug treatments and placebo in studies using NSAIDs, MTX, and biologic drugs.[76] Other outcomes evaluated in the studies are listed in table 6.

Table 6 List of additional outcomes evaluated in the JIA studies identified

Outcomes evaluated in JIA studies
❖ Drug withdrawal
❖ Disease remission*
❖ Development of anti-biologic agent antibodies
❖ Need for biologic drug discontinuation due to intolerance, lack of efficacy, or patient preference
❖ Adverse drug reactions (serious, non-serious) associated with these drugs
❖ Changes in concomitant DMARDs and glucocorticoids with biologic drugs, discontinuation, re-start
❖ Quality of life measured by the Children's Health Questionnaire
❖ Days lost from school or daily activities (parents/caregivers)
❖ Radiographic progression measured according to the Poznanski score

* Disease remission as defined by Wallace et al.: no active joints, no systemic symptoms, no uveitis, normal erythrocyte sedimentation rate, no disease activity according to the physician's global assessment for at least six continuous months[24]

2.6 Data analysis

The report includes the results of the outcomes listed in Table 6. If not provided in the publication, 95% confidence intervals were calculated as indicators of precision of the point estimates.

Short and long-term data with each drug were included in the analysis depending on data availability. Information on outcomes was recorded with the first biologic drug as well as with biologic drug switches.

Since systemic JIA has distinct disease features compared to other JIA subtypes and since the literature suggests that patients with systemic JIA may have a lower response to etanercept,[37, 77] publications including exclusively systemic JIA patients were evaluated separately in appendix 17.

2.7 Cost analysis

The annual cost of treatment was calculated for each biologic drug. The primary cost analysis was performed from the health care system perspective and included health care resources incurred in the drug administration and routine disease-related patient monitoring (table 7) as well as health resources consumed during adverse events. A secondary cost analysis from the societal perspective included non-healthcare costs consisting of parent/caregiver time losses (table 7). Resource utilization was based on a combination of data from the literature and expert opinion.

The doses of biologics used in pediatric patients are based on the patient weight or body surface area. In the base case analysis a 40 kg patient was assumed, approximating the mean weight in the two pediatric RCTs that reported patient weight.

Table 7 lists the healthcare resources include in the cost analysis of biologic agents.

Table 7 Resources included in the cost analysis

	Biologics administered in hospital	Biologics administered at home
Healthcare resources (primary analysis)	❖ Biologic drug acquisition costs ❖ Drugs administered as pre-medications* ❖ Concomitant anti-rheumatic drugs ❖ Materials (IV solutions and IV bags) ❖ Nursing time during drug infusion and pre and post-infusion observation periods ❖ Pharmacy costs in-hospital ❖ Pharmacist dispensing fee ❖ Physician costs in-hospital ❖ Laboratory tests performed in-hospital before each infusion ❖ Physician costs for routine outpatient visits ❖ Routine monitoring outpatient and laboratory tests¶	❖ Biologic drug acquisition costs ❖ Concomitant anti-rheumatic drugs ❖ Materials (IV solutions and IV bags) ❖ Nursing time (training and consulting**) § ❖ Pharmacist dispensing fee ❖ Physician costs for routine outpatient visits ❖ Routine monitoring laboratory and tests¶
Non-healthcare resources to receive treatment	❖ Parent/caregiver time costs ❖ School-days missed to receive treatment (not costed)	Assumed to be nil since the drug is administered at home and not associated with a time loss

* Pre-medications such as acetaminophen, diphenhydramine, and hydrocortisone are administered if patients experienced infusion-related reactions during previous infusions. In patients receiving infliximab, pre-medications are administered routinely (personal communication, Karen Queffelec, Oct. 29, 2009).
**Occasional phone calls to answer parents' questions
§Other administration costs were not considered as it was assumed that it was done by the parents at no additional cost.
¶ Routine monitoring includes tuberculosis screening (X-ray and skin test) before start of biologics, blood tests, and physician visits.

Treatment with MTX included drug acquisition costs, concomitant drugs (folic acid, glucocorticoids) and routine outpatient laboratory tests and physician visits.

Since other pain medications and NSAIDs are generally used only when necessary by the patients, it is difficult to accurately estimate the frequency of their use, therefore these drugs were excluded from the analysis.

In general the commercially available preparations of biologic agents match the doses used in adults. Since pediatric patients use doses that are generally lower than adult doses (depending on patient weight), not all of each medication vial is used at each infusion. Given that re-use of unused portion of the vials is not always possible depending on the drug, no vial re-use was assumed in the cost analyses.

Although some of the biologic agents can be administered at home by parents/caregivers, intravenous administration of biologics requires that the child be brought to the hospital/clinic for the drug infusion. The parent/caregiver's time to bring the child to the hospital/clinic in order to receive intravenous biologics (infliximab, abatacept) is included in the cost analysis. The time in-hospital/clinic varies between 3-7 hours depending on the biologic and comprises the time for drug preparation, pre-infusion laboratory tests and medications, the time for drug infusion and post-infusion monitoring. For this reason, it was assumed that the child would miss a school day in order to receive the treatment in-hospital and that a parent/caregiver would miss a day of paid or unpaid labour. The number of school-days missed was quantified in the analyses, however, this cost was not included due to a lack of consensus in the economic literature on how to cost missed school days.

Resource use was based on the literature and expert opinion. Unit costs were based on hospital or provincial estimates. For parent/caregiver time, the costs were based on the average hourly earnings in Canada assuming a 7-hour working day (statistics Canada 2007).

The economic analysis included costs of treatment of complications such as serious adverse events associated with each biologic agent.

All costs were calculated by multiplying the level of resource use by its unit cost. Costs are reported in 2008 Canadian dollars.

2.7.1 Sensitivity analyses

Parameters that were expected to affect treatment costs were varied in univariate sensitivity analyses. These parameters included patient weight/body surface area and medication dose in case different doses may be used.

2.8 Economic Evaluation

The cost-effectiveness of biologics compared to non-biologic DMARDs in patients with polyarticular-course JIA was evaluated.

The biologic agents included were etanercept, infliximab, adalimumab, and abatacept. Anakinra was not included as it is used mostly in patients with systemic JIA in our institution. Tocilizumab

was not included since there were no studies in patients with polyarticular JIA. The comparator used was non-biologic DMARDs. Each biologic was modeled separately in a decision analysis.

With regard to effectiveness measures, most studies use the ACR-30 scoring system[73] although this may not reflect the goals of treatment. Many providers may not consider a 30% improvement to be clinically significant. Even the ACR-70, which evaluates for a 70% improvement, may not reflect the common desire to achieve complete disease control or remission. Nevertheless, the effectiveness measure used in the economic evaluation was the proportion of patients who had a reduction in symptoms at one year according to the ACR Ped 30 criteria, as this was the most commonly and consistently used outcome measure in the systematic review. The inverse variance method[78] was used in the base-case analysis to pool data from different studies where they existed.

Different DMARDs are used in patients with polyarticular JIA, the main one being MTX.[6, 34] Once a patient does not respond to a DMARD, the dose may be increased (depending on the drug) or a switch to a different DMARD or combination of different drugs may occur. JIA patients are candidates for biologics once their response to an optimized DMARD regimen becomes suboptimal. Therefore the patient population of the model was assumed to be polyarticular-course JIA patients who have had a suboptimal response (with suboptimal response defined as not achieving ACR Ped 30) to an optimized DMARD regimen.

For the comparator arm, the estimates derived from most RCTs of biologic agents could not be used since 1) not all patients in the control group received a DMARD, and 2) many trials used the randomized withdrawal design; patients had received and responded to the biologic drug in the preceding 3-4 months and there was a possibility of a carry-over effect from the previous phase, which is dependent on the biologic drug pharmacokinetics and length of control period. In the infliximab RCT, the group of patients with a suboptimal response to MTX who continued treatment with MTX + placebo (concomitant low dose glucocorticoids and one NSAID) presented a higher than expected response rate of 49.2% (ACR Ped 30) at 14 weeks, possibly due to a placebo effect or regression to the mean in the group.[76] The expected response rate in this group was 20-30%.[76] Due to the scarcity of comparative data on which to base the estimates for the comparative group certain assumptions were made. For instance, it can be expected that some of the patients with a suboptimal response to DMARDs may appear to respond to these drugs for a period of time either because of a placebo effect[76] which may be due to the fluctuating nature of

the disease or to regression to the mean. A meta-analysis that pooled the results in the placebo group of JIA RCTs yielded a 28.5% (95% CI: 24%, 34.2%) rate of ACR Ped 30 response at six months. [79] This is corroborated by the 20-30% placebo response expected by the authors of the infliximab RCT.[76] Therefore, for the base-case model it was assumed that in patients with optimized doses of non-biologic DMARDs, approximately 30% of the patients will still respond for a period of six months. Due to the absence of data beyond this point, it was assumed that the rate of responders would remain stable for the remainder of the first year[c].

The costs included were the same as those in the cost analysis as well as those associated with serious adverse drug reactions and safety monitoring. The base case analysis assumed a 40 kg patient as this was the approximate mean weight provided in three studies.

A one-year time horizon was used in the economic analysis. Extrapolation using data from adult studies was done where necessary. Beyond one year the current available evidence in JIA is sparse for most biologic drugs, especially for controlled studies. Therefore, it was decided that the magnitude of uncertainties beyond one year did not justify further extrapolations.

The incremental cost-effectiveness ratio (ICER) was calculated as the incremental cost per additional responder with biologics compared to current therapies.

2.8.1 Probabilistic sensitivity analyses

The ICERs and their 95% CIs were calculated through probabilistic sensitivity analysis (PSA) using 10,000 Monte Carlo simulations. The PSA simultaneously incorporates the imprecision in estimates of different parameters into the results. This provides an estimate of the variation of the expected cost-effectiveness of each drug. The results were also shown graphically through acceptability curves.

Further PSAs were carried-out by varying approaches used to estimate the effectiveness, such as using data from studies that used alternative analytical approaches such as intention-to-treat (ITT) or last observation carried forward (LOCF). Treatment costs were also varied using a patient weight range from 10 to 70 kg.

[c] Based on adult biologic RCTs (studies of biologics in patients with late rheumatoid arthritis with insufficient response to MTX/DMARDs) which showed that the rate of responders in the MTX arm remained constant during the first year of treatment (based on approximately 1,000 patients).

3 RESULTS

3.1 Systematic literature review results

The systematic review identified 494 publications. There were five RCTs with biologic drugs (etanercept, infliximab, adalimumab, abatacept, and anakinra) in patients with polyarticular JIA.[45, 47, 74-76] The RCTs were of good quality according to the Jadad criteria (Appendix 4).[80]

Non-controlled observational studies with etanercept[81-91] and infliximab[89, 92-94] in polyarticular JIA were also identified. Some publications were based on data reported to national registries in JIA patients treated with etanercept in Germany,[83, 84] Netherlands,[87] and the United States.[81] No rituximab studies in JIA were identified. One tocilizumab study in polyarticular JIA was identified, however, since it included fewer than 20 patients it did not meet the eligibility criteria.

Two studies evaluated the use of a second biologic drug after the first drug was discontinued due to either lack of efficacy or intolerance in patients with JIA.[89, 95] One study at HSC evaluated the risk of new-onset uveitis in patients treated with etanercept or infliximab.[90]

In addition, one systematic review,[96] one full text etanercept HTA report,[97] and four brief HTA reports, one with tocilizumab,[98] one with abatacept,[99] one with adalimumab,[100] and one with etanercept for which only a 1-page summary was available in English[101]were identified. The results of these studies are summarized in the next sections.

Five studies evaluated the use of biologics exclusively in patients with systemic JIA. Two studies included a double-blind placebo-controlled portion, one with tocilizumab[49] and one with anakinra.[102] Three studies were non-comparative and evaluated the use of etanercept,[103] anakinra,[104] and tocilizumab[105] in systemic JIA. These studies are summarized separately in the report since the current evidence suggests that may have different outcomes compared to other non-systemic JIA (Appendix 17).

3.2 Randomized controlled trial study results

RCTs on etanercept,[39] infliximab,[76] adalimumab,[45] abatacept,[47] and anakinra[75] in JIA were identified. With the exception of the infliximab study,[76] the other studies had a withdrawal study design and were divided into three phases. In the open-label lead-in phase (phase 1), the active biologic drug ± MTX was administered to all eligible patients. Patients who had a treatment

response in phase 1 were then randomized in the double-blind phase (phase 2) to receive either the active drug ± MTX or its matching placebo ± MTX for a period of 4-8 months depending on the study. Phase 2 was followed by an open-label non-comparative extension phase (phase 3) where the active drug was administered to patients who were enrolled in the double-blind phase (table 8). Patients who did not respond to the drug during the double-blind phase or who did not complete phase 2 were given the option to continue into the open-label extension.

In the infliximab RCT, patients were randomized to receive either infliximab 3 mg/kg + MTX or matching placebo + MTX for 14 weeks.[76] After this period, patients in the placebo group received infliximab 6 mg/kg + MTX whereas patients in the infliximab 3mg/kg + MTX group continued with the same regimen until week 52.[76] Patients could continue into an open-label extension phase.[76]

Table 8 Characteristics of RCTs evaluating the use of biologic drugs in the treatment of JIA

RCT	Etanercept [39, 74, 106, 107]	Adalimumab ± MTX [45]	Abatacept ± MTX [47]	Anakinra ± MTX [7]	Infliximab + MTX [76]
Follow-up	8 years	2 years	5 years	19 months	4 years
Phase I **Length** **n**	Etanercept alone 3 months n=69	Adalimumab ± MTX 4 months n=171	Abatacept ± MTX 4 months n=190	Anakinra ± MTX 3 months n=86	Infliximab 3mg/kg +MTX vs. Placebo + MTX 3.5 months n=122 (62 drug, 60 placebo)
Phase II **Length** **n (active / control)**	Etanercept vs. placebo 4 months n=51 (25/26)	Adalimumab vs. placebo ± MTX 8 months n=133 (68/65)	Abatacept ± MTX vs. placebo ± MTX 6 months n=122 (60/62)	Anakinra vs. placebo ± MTX 4 months n=50 (25/25)	Infliximab 3mg/kg + MTX vs. Infliximab 6mg/kg + MTX 7.5 months n=112 (62 on 3mg/kg dose / 60 on 6mg/kg dose)
Phase III **F-up available** **n**	Etanercept ± MTX 8 years n=58	Adalimumab ± MTX 1 year n=96	Abatacept ± MTX 0	Anakinra ± MTX 0	Infliximab + MTX 3 years n=36

F-up follow-up / MTX methotrexate

Most RCTs included patients with active polyarticular-course JIA, regardless of onset subtype.[39, 45, 75, 76] The abatacept study included patients with active oligoarticular, polyarticular, or systemic subtypes without systemic manifestations.[47] Eligible patients had inadequate response to MTX and/or other non-biologic DMARDs.[39, 45, 76] Additionally, the abatacept[47] and anakinra[75] studies allowed the inclusion of patients with prior use of anti-TNF-α drugs. Patients intolerant or refractory

to other biologic drugs may present a higher risk of failure or intolerance with a subsequent biologic.[108] The biologic drugs were used alone or in combination with MTX.[39, 45, 47, 75, 76]

Table 9 summarizes the drug dosages, concomitant mediations used in the RCTs and table 10 shows the main study outcomes. Please refer to Appendix 5 for the RCTs' inclusion and exclusion criteria.

Table 9 Study drugs and concomitant therapies (RCTs of biologic drugs in JIA)

	Etanercept [39, 74, 106, 107]	Adalimumab ± MTX [45]	Abatacept ± MTX [47]	Anakinra ± MTX [75]	Infliximab + MTX [76]
Active drug dosage	Etanercept SC 0.4mg/kg (max.25mg) 2x/wk	Adalimumab , 24 mg/m^2 (max.40mg) every other wk ± MTX Randomization stratified according to MTX use	Abatacept IV 10 mg/kg on days 1, 15, 29 every 28 days thereafter (max 1000mg/dose) ± MTX (10-30 mg/m^2/wk)	Anakinra 1 mg/kg/day (max.100 mg/day) ± MTX	Infliximab 3 & 6 mg/kg + MTX 10-15mg/m2/wk at wks 0, 2, 6, 14, 16, 20 & every 8 wks
Comparator (double-blind phase length)	Placebo 4-month (mo) double-blind (DB) phase	Placebo ± MTX (use as above) 8-mo DB phase	Placebo ± MTX (10-30 mg/m^2/wk) 6-mo DB phase	Placebo ± MTX 4-mo DB phase	Placebo + MTX (3.5-mo DB phase) Infliximab 3mg/kg vs. Infliximab 6mg/kg (wks 14-44)
Concomitant medications allowed	**Open-label/double-blind phases** NSAIDs in stable doses, low* doses of glucocorticoids, pain medications** **Extension phase** MTX allowed after 1st year Intra-articular & soft-tissue corticosteroid injections¶ after 12 continuous wks on etanercept	**Open-label/double-blind phases** MTX use as above. NSAIDs in stable doses, low* doses of glucocorticoids, pain medications**	**Open-label/double-blind phases** MTX was allowed but not mandatory. Oral glucocorticoids at stable doses ≥ 4 wks before enrollment (10 mg/day). NSAIDs/analgesics for pain. Other DMARDs not allowed	MTX allowed – dose was maintained stable NSAIDs & low* doses of glucocorticoids allowed, both in stable doses	1 NSAID, low* doses of glucocorticoids, pain medications**, 1 analgesic, narcotic or opioid analgesics. Acetaminophen & antihistamine if mild/moderate infusion reaction was observed in a previous administration

DMARD disease-modifying anti-rheumatic drug / IV intravenous / JIA juvenile idiopathic arthritis / max maximum / MTX methotrexate / NSAIDs non-steroidal anti-inflammatory drugs / SC subcutaneous / wk week / mo month / DB double-blind
* ≤ 2mg of prednisone/kg/day, maximum of 10mg/day
** Not allowed during the 12 hours preceding the joint assessment
¶ Joints injected with glucocorticoids in the previous 24 hours were excluded from assessments.

Table 10 Primary outcomes for each phase of RCTs of biologic drugs in JIA

		Etanercept	Adalimumab ± MTX	Abatacept ± MTX	Anakinra ± MTX	Infliximab + MTX
Primary out-comes	**Open-label phase**	**Modified*** disease improvement, ACR Ped 30	Disease improvement, ACR Ped 30	Disease improvement, ACR Ped 30	Disease improvement, ACR Ped 30	-
	Double-blind phase	Disease flares (worsening ≥ 30% in ≥ 3/6 ACR Ped core response variables **and a minimum of 2 active joints** & ≥ 30% improvement in ≤ 1 core variable)	Time to disease flares (worsening ≥ 30% in ≥ 3/6 ACR Ped core response variables & ≥ 30% improvement in ≤ 1 core variable) **Patients with a flare were considered as ACR Ped non-respondents**	Disease flares (worsening ≥ 30% in ≥ 3/6 ACR Ped core response variables & ≥ 30% improvement in ≤ 1 core variable)	Disease flares (worsening ≥ 30% in ≥ 3/6 ACR Ped core response variables & ≥ 30% improvement in ≤ 1 core variable) Adverse events drug-related	Disease improvement – ACR Ped 30 (week 14)
	Open-label extension	Disease improvement – ACR Ped 30§	Disease improvement ACR Ped 30§	Disease improvement – ACR Ped 30§	Disease improvement – ACR Ped 30§	Disease improvement – ACR Ped 30§
Statistical analysis method for dealing with missing data		**Open-label/double-blind phases** LOCF method for disease improvement in DB phase, **withdrawals without flare considered respondents** **Open-label extension** Modified ITT (year 2) Available pts thereafter	**Open-label /double-blind phases** ITT ¦ **Patients with missing data were considered as non-responders (ACR Ped 30 or disease flare.** **Open-label extension** **LOCF for missing values** [10]	**Double-blind phase** Imputation of missing values using the LOCF method Results stratified according to use of MTX and previous biologics	**Double-blind phase** Not specified for the rates of disease flares. ITT method used for time-to-flare outcome	**Double-blind phase** Modified ITT analysis - missing data/not available pts considered as non-responders

DB double-blind / DMARD disease-modifying anti-rheumatic drug / IV intravenous / ITT intention-to-treat / JIA juvenile idiopathic arthritis / LOCF last observation carried forward / LOM limitation of motion / max maximum / MTX methotrexate / NSAIDs non-steroidal anti-inflammatory drugs / pts patients

* One of the core variables used in the ACR Ped criteria for disease improvement was modified by the investigators for the etanercept study, i.e., "the number of joints with limitation of motion and with pain, tenderness or both" instead of "the number of joints with limitation of motion".

§ Disease improvement compared to baseline measurements from the beginning of the study.

¦ Patients who received at least one dose of the study drug during the phase of the study being analysed.

Table 11 shows the baseline characteristics of the patients included in the first phase of each RCT. Appendix 5 shows the characteristics of the patients included in the double-blind phase.

Table 11 Baseline characteristics of patients included in the JIA RCTs: Start of the lead-in open-label phase

Baseline characteristics	Etanercept [39] n=69	Adalimumab[45] n=171	Abatacept [47] n=190	Anakinra [75] n=86	Infliximab [76] n=60
Mean age, years	10.5	11.2*	12.4	12 (3-17)	11.3 ± 4
Female sex, n (%)	43 (62%)	135/133 (79%)*	137 (72.1%)	63 (73)	
Type of onset of JRA, n (%)		-	JIA course		
Oligoarthritis	7 (10%)		30 (16%)	9 (10)	13 (21.7%)
Polyarticular	40 (58%)		122 (64%)	62 (72)	36 (60%)
Systemic	22 (32%)		37 (20%)	15 (17)	11 (18.3%)
Mean duration of JRA, years	5.9	MTX / No MTX 4.0±3.7 / 3.6±4.0	4.4 ±3.8*	4.7 (1-16)	4.2 ±3.6
Positive for rheumatoid factor, n (%)	15 (22%)	37 (22%)	41 (22%)	-	13 (21.7%)
ESR mm/hour, median (normal: 1-30 mm/hour females, 1-13 males),	35	-	32 ± 26.8	-	-
C-reactive protein (mg/dL) (normal 0-79)	3.5	-	3.2 ± 4.4	-	-
Previous therapy, n (%)					
Glucocorticoids	25 (36%)			50 (58)	26 (43.3%)
NSAIDs	66 (96%)		140 (74%)	2 (2)	-
MTX	50 (72%)	103 (60%)	57 (30%)	67 (78)	60 (100%)
DMARDs	51 (74%)	16 (9%)	anti-TNF-α	25 (29)	24 (40%) prior
Antinuclear antibodies, positive, n (%)	-	-	55 (29%)	-	-
Anti-double-stranded DNA, positive, n (%)	-	-	26 (14%)	-	-

DMARD disease modifying antirheumatic drug / ESR erythrocyte sedimentation rate / JRA juvenile rheumatoid arthritis / MTX methotrexate / NSAIDs non-steroidal anti-inflammatory drugs / TNF tumour necrosis factor
*Information from the double-blind phase

3.2.1 Disease Improvement

The etanercept, adalimumab, abatacept, and anakinra study results are summarized separately from the infliximab study due to differences in study design.

3.2.2 Lead-in open-label phase

The lead-in open-label phase lasted between 12 and 16 weeks depending on the study (table 9). Definitions of the treatment respondents and disease flares are provided in table 10.

During the lead-in phases, ACR Ped 30 criteria were met by 84%, 65%, and 58% of the patients who received adalimumab,[45] abatacept,[47] and anakinra,[75] respectively. In the etanercept study, ACR Ped 30 was reached by 74% (investigator-modified criteria, table 10)[39] or 70%[110] (Giannini criteria[73]) of the patients. In the abatacept study, among 133 patients without prior anti-TNF-α use, 101 (76%) achieved ACR Ped 30 criteria whereas 22/57 (39%) patients with prior anti-TNF-α use achieved ACR Ped 30.[47] ACR Ped 70 criteria were met by 36%,[39] 59%[45] and 28%[47] in the etanercept, adalimumab and abatacept studies respectively. The anakinra study did not report the ACR Ped 70.[75]

3.2.3 Double-blind phase

The double-blind phase includes patients who responded to the biologic drug during the lead-in phase. Some patients who responded to the drug but withdrew due to adverse events or withdrew consent did not continue into the double-blind phase of the study.[39, 45, 47, 75]

At the end of a 4-8-month double-blind phase, the percentage of patients without a disease flare was higher among patients who received biologic drugs ± MTX compared to placebo ± MTX. The difference was not statistically significant in the anakinra study (figure 1).

The etanercept, abatacept, and adalimumab studies reported a higher proportion of respondents according to the ACR Ped 30 criteria compared to placebo.[39, 45, 47] The difference was statistically significant in both etanercept and adalimumab studies (figure 2).[39, 45, 47]

Both the European Medicines Agency (EMEA) and the US Food and Drug Administration (FDA) reported a continuous decline in the number of patients with ACR Ped 30 response in patients treated with adalimumab alone or combined with MTX during the 32-week double-blind phase of the study.[111, 112] Whereas all patients were ACR Ped 30 responders (as per study design) at the beginning of the double-blind phase, an analysis performed by the FDA shows that 8 weeks after the start of the double-blind phase (24 weeks of the study), the percentage of responders dropped to approximately 80% in both groups, and less than 70% at week 16 of the double-

blind phase (from a graph).[112] At the end of the 32-week double-blind phase 63% and 57% met the same criteria in the MTX and non-MTX groups, respectively, as per the RCT results published in the peer-reviewed literature.[45] This decline was more pronounced in the placebo group.[112] In contrast to the other biologics' RCTs, in the adalimumab RCT patients who experienced a disease flare or who dropped out of the study for any reason were considered ACR Ped non-responders regardless of ACR Ped status.[45, 112] This may help explain the lower response rate in the adalimumab study compared to other biologics' RCTs (Figures 1 and 2). The other biologic RCTs used different approaches to impute missing data (table 10).

Figure 1 Percentage of patients without flares: Double-blind phase of the RCTs

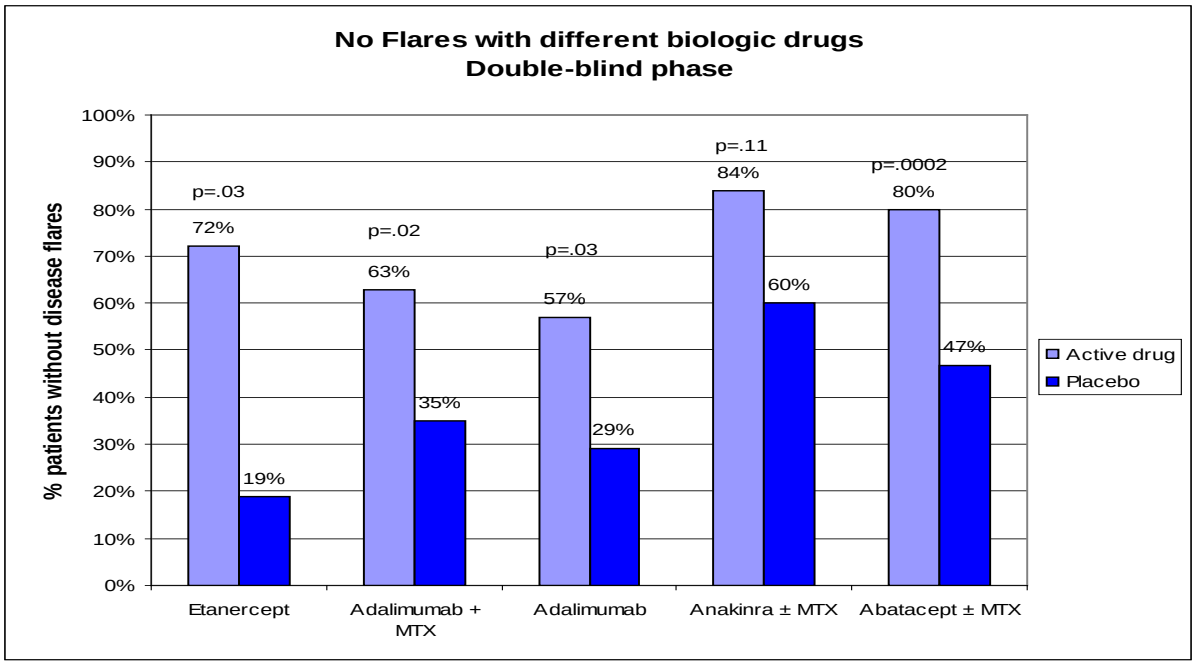
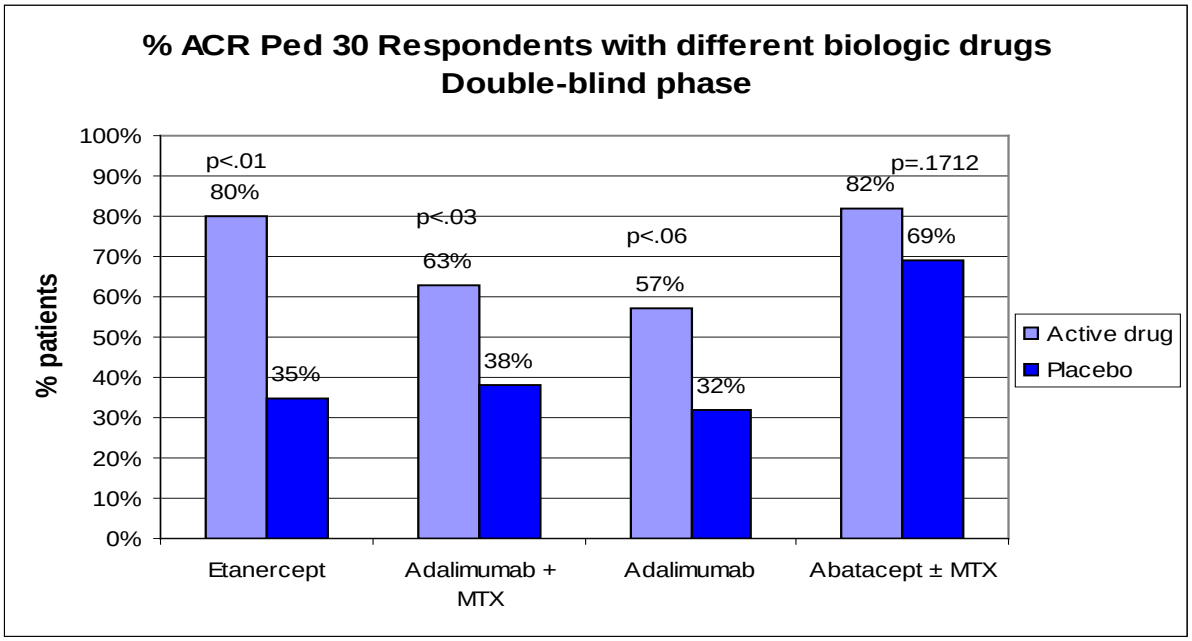


Figure 2 Percentage of patients with ACR Ped 30 response: Double-blind phase of the RCTs



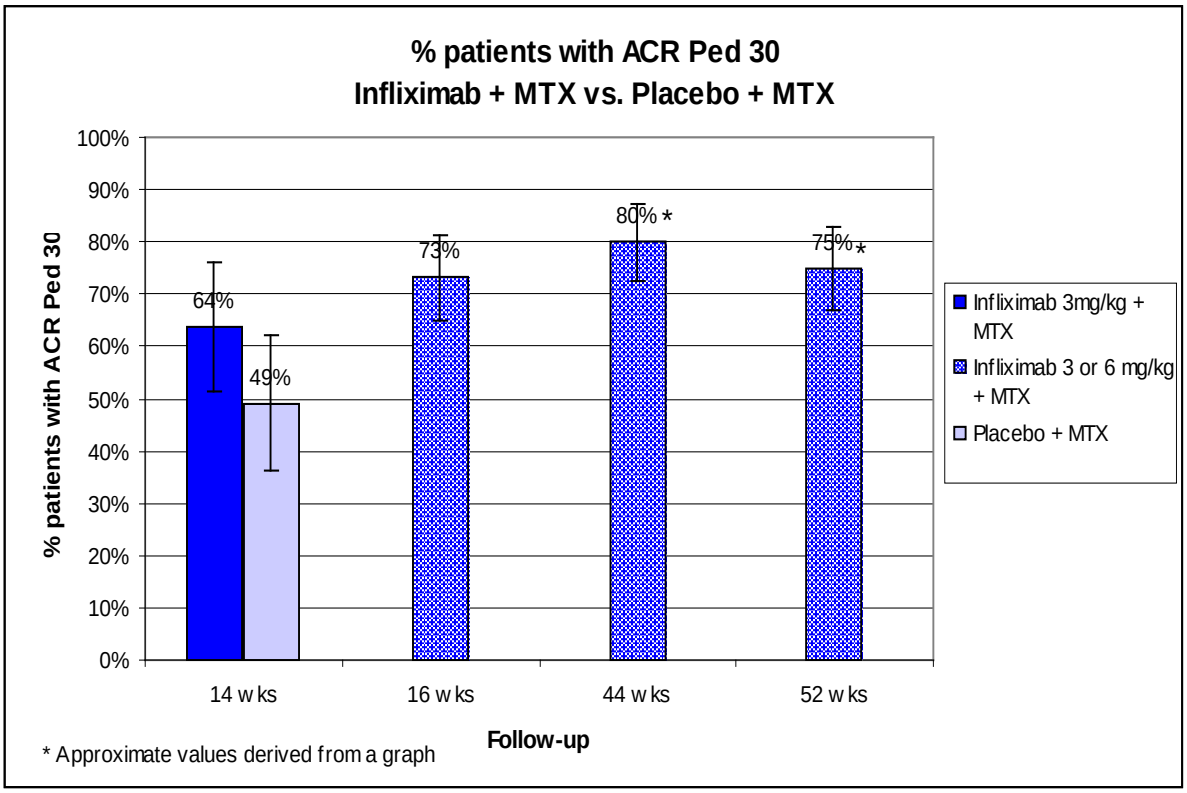
Patients with a disease flare were considered as non-responders (ACR Ped) criteria at the end of the double-blind phase in the adalimumab study regardless of ACR Ped status.

3.2.3.1 Infliximab study

The infliximab study is being reported separately due to its different study design. As opposed to the other trials, the double-blind phase of the study was not restricted to those who responded during the lead-in open-label phase. There was a trend towards a higher rate of ACR Ped 30 respondents in patients receiving infliximab + MTX compared to patients receiving placebo + MTX (figure 3).[76] The authors believe that part of the lack of statistically significant differences between infliximab and placebo may be due to a higher than expected placebo response (actual: 49%, expected: 25-30%) at 14 weeks.[76]

As seen in Figure 3, at one year, approximately 75% of the patients receiving infliximab 3 or 6 mg/kg + MTX met the ACR Ped 30 response criteria, 70% achieved ACR Ped 50, and 50% achieved ACR Ped 70.[76]

Figure 3 Results of the infliximab RCT



MTX methotrexate / wks weeks
* Frequency of ACR Ped 30 responders at weeks 44 and 52 are approximate figures since they were derived from a graph. The error bars refer to the 95% CI calculated based on the number of patients and % of respondents reported in the study.

Although two different dosages of infliximab were used in the study, 3 and 6 mg/kg, the investigators observed that both groups had a similar drug response.[76] Patients in the 3 mg/kg group had lower median drug serum concentrations (especially at trough) and a higher incidence of infliximab antibodies (38% vs. 12%, respectively) compared to the 6 mg/kg group.[76] Presence of anti-infliximab antibodies was associated with a 3-fold higher incidence of infusion-related reactions than those without antibodies.[76] Anti-infliximab antibodies may also be associated with a poorer response since their presence may result in faster drug elimination.[76]

A disparity was observed in the frequencies of disease flares and ACR Ped 30 response among both the placebo and active drug groups of the different studies during the double-blind phase. Some reasons that may help explain this disparity are listed in table 12.

Table 12 Differences in study characteristics

Heterogeneity in baseline characteristics	The percentage of patients with systemic-onset JIA varied between studies (17-32%) It is believed that anti-TNF-α drugs may have a lower efficacy in patients with systemic disease[17, 44]
Length of double-blind phase	May affect the response in the placebo group Double-blind phase length varied between 4-8 months among the studies, which influences a placebo effect as it is expected to weaken with time and may favour the biologic drug arm Possibility of carry-over effect from the use of the biologic drug during the lead-in phase[113] May depend on drug pharmacokinetics as pointed out by Lehman et al[113]
Methotrexate use	In some studies the use of MTX was permitted in combination with placebo (and active drug) while it wasn't permitted in other studies
Blinding issues	A previous HTA report mentions that it is possible that investigators could distinguish between the vials that contained placebo and the active drug during the double-blind phase of the etanercept study[97] Lack of blinding may play an important role in studies with a withdrawal design,[97] which could lead to a higher number of patients being withdrawn from the placebo arm, consequently resulting in an overestimation of the response with the active drug
Prior biologic drug use	The etanercept, infliximab, and adalimumab studies included patients who had never used any biologic anti-rheumatic drug, whereas the abatacept and anakinra studies allowed prior use of anti-TNF-α drugs (etanercept, infliximab, and adalimumab)[47, 75] Patients with prior intolerance/failure to other biologic drugs may be more susceptible to intolerance/failure with a second biologic drug[108]
Definition of response	In some studies patients with a flare were considered as ACR Ped 30 non-responders regardless of ACR Ped status Definitions of disease flare also varied (table 10)
Method of imputation for missing values	As per table 10

3.2.4 Open-label extension phase

Open-label extension results are available for etanercept (eight years),[74, 106, 107] adalimumab (two years),[45 112] and infliximab (four years).[114, 115]

At two years, 69% of the etanercept ± MTX[d] patients met the ACR Ped 30 criteria and 57% met the ACR Ped 70 criteria (ITT analysis).[74] After this period only patients who continued on etanercept treatment were included in the analyses, which may lead to an overestimation of the

[d] MTX could be added to the etanercept regimen after the 1st year and the doses of glucocorticoids, NSAIDs, and pain medications could be adjusted without restriction.

response rate since patients who did not tolerate or did not respond to the drug were excluded. At four years, approximately 90% (derived from a graph) of the 32 patients available had a positive response based on the ACR Ped 30 criteria and 78% met the ACR Ped 70 criteria. [107] At eight years 100% of the 11 patients available met the ACR Ped 70 criteria.[106]

In the adalimumab study, at two years (104 weeks) in the extension phase, approximately 90% and 70% of 128 patients met the ACR Ped 30 and 70 response criteria respectively (LOCF analysis).[45] An ITT analysis reported to the FDA shows that at the beginning of the open-label extension phase, and at week 72, 55/71 (77%) and 46/59 (78%) patients receiving adalimumab + MTX were ACR Ped 30 responders.[112] Thereafter, there was a decline in the numbers of responders, i.e., 30/50 (60%) patients met the same criteria at week 88, continuing through week 120 (data from graph).[112] Similarly, in the adalimumab monotherapy stratum, 46/57 (80%), 30/46 (65%), and 20/34 (59%) patients met ACR Ped 30 criteria at baseline and week 88 respectively.[112] According to the FDA report, although treatment response was maintained in the majority of patients throughout the open-label extension phase, a drop in the response rate after week 72 may be due to a loss of treatment response, but the authors point out that fewer patients continued in the study beyond week 72,[112] which may lead to less precise estimates.

The open-label extension phase data for infliximab is for a four-year period.[114] A total of 78 (64%) of the 122 patients initially included in the RCT entered the open-label extension phase.[114] The reasons for not entering the extension phase were not provided.[114] Among 65 patients who had efficacy data after four years of follow-up in the extension phase, ACR Ped 30 and 70 responses were achieved by 33 (44%) and 18 (24%) patients at week 204 respectively.[114] An earlier abstract based on this data presented at a scientific meeting reported that remission[e] was observed in 14/36 (39%) patients.[115]

3.2.5 Quality of life and missed school days

The impact of abatacept in the quality of life and in the number of school days missed due to the disease were presented at a conference (information in Appendix 6).[116]

3.2.6 Drug discontinuations

Table 13 shows the percentages of patients who discontinued treatment during the 3-4 months lead-in open-label phase of the RCTs.

[e] Definition of remission: no joints with active arthritis, normal erythrocyte sedimentation rate, and physician's global assessment of disease activity ≤ 10 mm on a 10-cm visual analogue scale.

Table 13 Treatment withdrawal: Lead-in open-label phase

	Etanercept [39]	Adalimumab* [45]	Abatacept [47]	Anakinra [75]
Total drug withdrawal, n (%)	18 (26.1%)	38 (22.0%)	67 (35.6%)	36 (41.9%)
Lack of efficacy	15 (21.7%)	11 (6.4%)	64 (33.7%)	27 (31.4%)
Adverse events	1 (1.4%)	6 (3.5%)	1 (0.5%)	-
Patient / parent refusal	2 (2.9%)	3 (1.8%)	-	-
Lost to follow-up	0	1 (0.6%)	1 (0.5%)	-
Protocol violation	-	2 (1.2%)	-	-
Other reasons	-	15 (8.8%)*	1 (0.5%)	-

* Reason for withdrawal of the 15 (8.8%) of the patients in the adalimumab study was not specified.

During the double-blind phase, six (24%), four (5.9%), 11 (18%), and six (24%) of the patients discontinued the etanercept,[39] adalimumab,[45] abatacept,[47] and anakinra[75] treatments, respectively, due to lack of efficacy, adverse events, withdrawal of consent among other reasons. In the placebo group, discontinuations occurred in 19 (73%),[39] one (1.5%),[45] 31 (50%),[47] and 13 (52%)[75] respectively.

In the infliximab study, three (5.1%) patients in the placebo group were excluded from the 6-week efficacy analysis due to either withdrawal of consent (n=1) or potential unblinding (n=2), whereas two (3.4%) in the infliximab 3 mg/kg group were excluded from the same analysis due to potential unblinding.[76] Between weeks 6-52, 13 (10.7%) patients withdrew from the study.[76] The reasons for withdrawal included lack of efficacy, adverse events, withdrawal of consent, and start of alternative therapy among other reasons.[76]

Patients discontinued due to lack of efficacy or intolerance during the double-blind phase of the studies were offered to continue to receive the drug during the open-label extension.[39, 45, 47] Some of these patients responded to the drug during the extension phase.[39, 45, 47]

3.2.6.1 Drug discontinuation during the open-label extension

During the open-label extension phase, 66% of the 58 patients enrolled discontinued etanercept over eight years (17% of the patients in the first 2 years).[106] Reasons provided for discontinuation included, among others, lack of efficacy or adverse events, physician, patient or guardian decision, and did not seem to include discontinuations due to disease remission.[106] In the infliximab study, 14.1% of the patients discontinued the drug between weeks 52 and 204

due to adverse events (discontinuation for other reasons not provided).[117] No information was available for adalimumab, abatacept and anakinra.

3.2.7 Anti-biologic drug antibody and autoantibody detection

The detection of anti-biologic drug antibodies may result in loss of efficacy or pose an increased risk of adverse events.[71] The development of autoantibodies may be associated with autoimmune diseases.[66] Results of the antibody detection tests from the etanercept, infliximab, adalimumab, anakinra, and tocilizumab clinical trials are summarized in Appendix 7.

3.2.8 Comments on the randomized controlled trials

The biologic drug RCTs generally concluded that the drugs improved patient outcomes after an insufficient response to non-biologic DMARDs [76] and that the drugs were well tolerated.[39, 47, 75]

The comparative double-blind phase of the studies was short (4-8 months), therefore, long-term comparisons of the effects of biologic drugs versus non-biologics are not available.

With the exception of the infliximab study, the RCTs had a withdrawal design, which aims to determine how well the response is maintained in those who continue treatment.[113] The RCTs compared the active drug to placebo in patients who were pre-selected to be respondents and tolerate[f] the active drug, with the exception of the infliximab study. This may result in an overestimation or underestimation of the treatment effects compared to the control arm and precludes generalization of the results of the controlled phase of the study. Lehman also argues that the withdrawal design does not provide strong evidence of efficacy or safety since only those patients who responded to the drug were included in the controlled part of the study. [113]

A large proportion of patients (58-84%) with insufficient response to non-biologic DMARDs responded to the biologic drugs in the initial 3-4 month open-label phase. Of these, 18-43% did not respond to the treatment with the same biologic agent in the subsequent double-blind phase (4-8 months), even when considering a minimal 30% improvement[22] in the five core variables that compose the ACR Ped criteria. In those patients who continued to respond, however, response was maintained for long periods, up to eight years in the etanercept study.

[f] As per study publications, patients who met the criteria for improvement were eligible to enter the randomized double-blind phase of the study.[39, 45, 47, 75] However, according to the publications, some patients who experienced adverse events were not enrolled in the double-blind period.[39, 45, 47, 75] Some patients/guardians also refused treatment continuation.

3.3 Non-comparative study results

Non-comparative studies with etanercept and infliximab in JIA patients are described below. No observational studies were identified with abatacept adalimumab, or anakinra. The characteristics of the patients included in these studies are summarized in Appendix 8. Results from the open-label extension phase of the RCTs (etanercept, infliximab, and adalimumab) are also included due to their non-comparative nature.

3.3.1 Non-comparative studies identified in the literature search

3.3.1.1 Etanercept non-comparative studies

Twelve open-label, non-comparative studies of etanercept in pediatric patients intolerant or refractory to MTX, glucocorticoids, and/or other DMARDs were identifed.[74, 81-91] In most studies etanercept was administered twice a week at a dose of 0.4mg/kg (maximum 25mg). Some of the publications consisted of reports from national registries from Germany,[52, 83, 84] Holland,[87] US,[81] and Britain.[82] Some of the studies were presented as abstracts in conferences.[81, 82, 91]

Concomitant use of MTX and/or other DMARDs was allowed in nine studies.[74, 81-83, 86-89, 91] Active polyarticular-course JIA was the main disease subtype in some studies, although other JIA subtypes were also included. The main outcome measure was disease improvement according to the ACR Ped 30.[38, 74, 83, 84, 86, 87, 91] Other outcomes reported included drug discontinuation,[38, 74, 82-84, 86, 87, 89] adverse events,[81-87, 91, 118] disease flares,[86] and radiographic progression.[88] One study from HSC evaluated the risk of new-onset uveitis in patients treated with etanercept or infliximab.[90] Patient follow-up on the studies varied from three months to up to eight years.

3.3.1.2 Infliximab non-comparative studies

Five open-label non-comparative studies of infliximab in patients with JIA with inadequate response to other DMARDs were identified.[89, 92-94, 117] The measure of response used was the ACR Ped 30 or ACR20[g] in most studies.[92-94, 117] Drug discontinuation was also reported[89, 92, 93] but disease flare was not included in the studies. One study reported safety results, treatment discontinuations, and treatment response, however the criterion for treatment response wasn't reported and this endpoint was therefore not used.[120] Patients were allowed to use other DMARDs such as MTX and glucocorticoids concomitantly with infliximab.

[g] ACR20 definition: At least 20% improvement in morning stiffness, erythrocyte sedimentation rate, joint tenderness score, and joint swelling score, and improvement by at least two of five grades (or going from grade two to one) for physician and patient global assessments of current disease severity.[119]

3.3.1.3 Adalimumab non-comparative studies

No observational study on adalimumab was identified, however, the results of the long-term extension of the adalimumab RCT are included here as this phase was non-comparative.[45, 112]

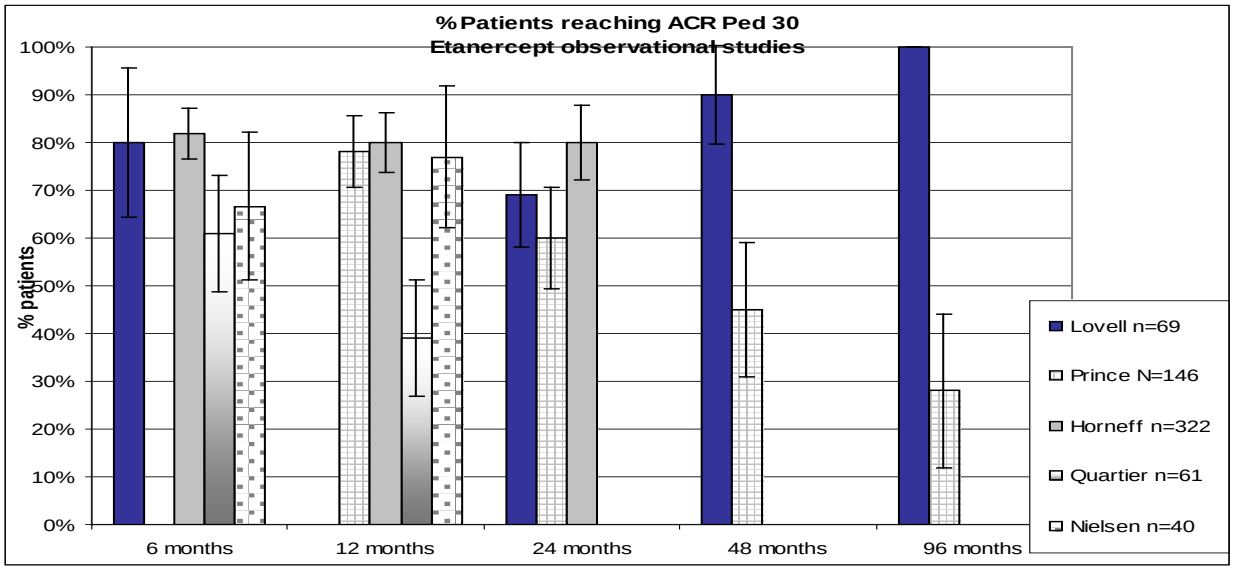
3.3.2 Disease improvement in the non-comparative studies

3.3.2.1 Etanercept non-comparative studies

Baseline characteristics of the patients included in these studies are summarized in Appendix 8. Figure 4 shows the percentage of patients who met the criteria for ACR Ped 30 in each study.

Only the studies that reported ACR Ped 30 in more than one time point were included in the graph. Additionally, in the German registry, 47/67 (70%) and 338/419 (81%) patients treated with etanercept alone and concomitantly with MTX, respectively, achieved ACR Ped 30 at one year.[83] ACR Ped 30 response after three months of treatment with etanercept was observed in 20/22 (90.9%)[38] and 20/51 (39%)[91] patients in two studies, respectively.

Figure 4 Disease Improvement with etanercept: Non-comparative studies



Concomitant use of MTX allowed in all studies with 2 exceptions: 1. Horneff (2008) in which patients were divided into etanercept monotherapy (n=67) & etanercept + MTX (n=419);[83] 2. Horneff (2004) did not clarify if concomitant use of MTX was permitted.[84] Error bars represent the 95% CI calculated based on the number of patients included in the analysis at the different time points.

Differences in rates of respondents among the studies may have been due to heterogeneities in patient baseline characteristics, such as disease duration and JIA subtype, but also due to the approach used in the data analysis. Both ITT and LOCF approaches were used. In general, there was a trend towards a decrease in the rate of ACR Ped 30 response with time in the

studies that used an ITT method of analysis[74, 84, 86, 87] whereas the rate of respondents tended to either be maintained or increase with time in the studies that used either a LOCF approach or in studies that only included patients who remained in the studies in the analyses.[74, 88, 106, 107] As previously discussed, different approaches to handling missing data may affect the results.

3.3.2.1.1 Disease flares in etanercept non-comparative studies

In the study by Quartier et al., nine (15.8%) patients experienced a disease flare within the first year of etanercept treatment, and an additional 2/24 (8.3%) patients with follow-up longer than 15 months experienced a disease flare.[86]

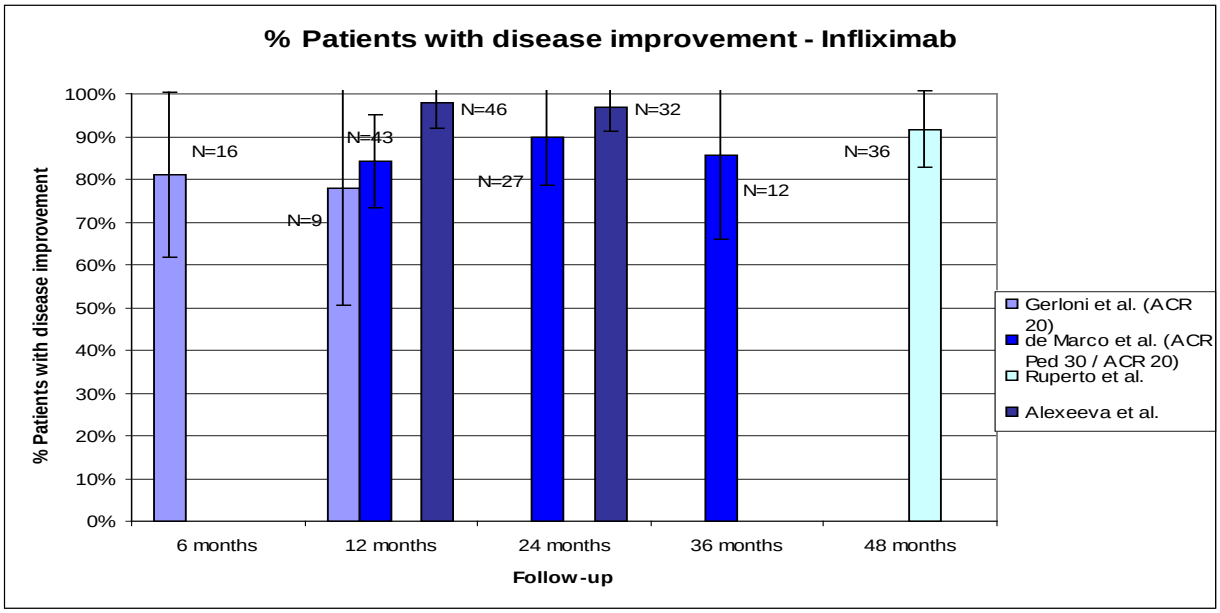
3.3.2.2 Infliximab non-comparative studies

Three open-label non-comparative studies of infliximab in patients with JIA with inadequate response to other DMARDs were identified.[92-94] Results of the long-term extension phase of the infliximab RCT were also included.[117] The measure of response used was the ACR Ped 30 or ACR20. Drug discontinuation was also reported but disease flare was not reported in the studies. One study reported safety results, treatment discontinuations, and treatment response, however the criterion for treatment response wasn't reported and this endpoint was therefore not used.[120] Patients were allowed to use other DMARDs such as MTX and glucocorticoids concomitantly with infliximab. The characteristics of the patients included in these studies are summarized in Appendix 8.

The percentage of treatment respondents to infliximab is shown in figure 5. The dose of infliximab for each administration varied between 3-10 mg/kg.

Within each study, the percentage of responders did not seem to decline with increased follow-up duration, however, it appears that the studies only included the available patients at each time point in the analyses, which may result in an overestimate of treatment response since some patients were previously excluded due to non response or intolerance. The number of patients included in the analyses was small, which results in less precise estimates.

Figure 5 Percentage of patients with disease improvement in open-label infliximab studies



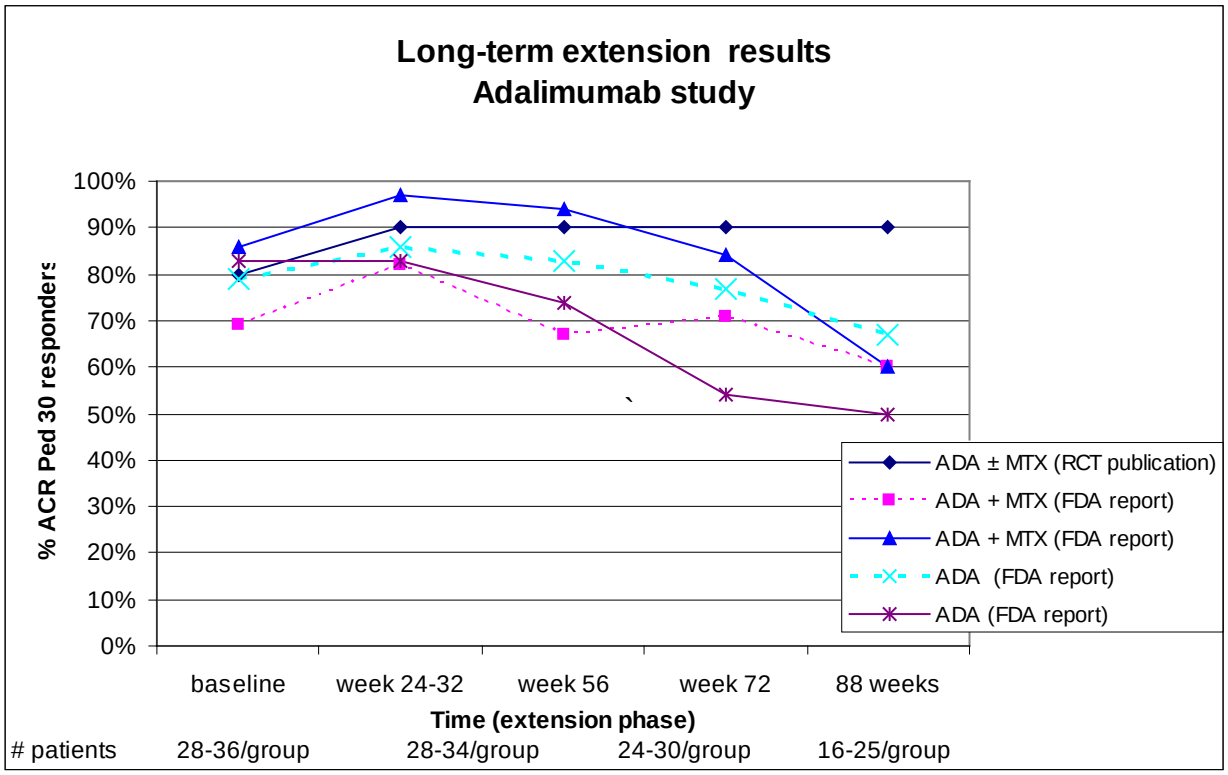
Includes 48-month data from the open-label extension phase of the infliximab RCT (Ruperto et al.).[76]
It was assumed that the per cent of patients with ACR Ped 30 was a sum of patients with ACR Ped 30, 50 & 70 (Alexeeva et al).[94]

3.3.3 Adalimumab open-label extension phase (non-comparative)

The results of the open-label extension phase of the adalimumab are shown in figure 6.

Results obtained using a LOCF approach to missing values imputation showed that approximately 90% of patients responded to adalimumab monotherapy or in combination with MTX (figure 6, dark blue line).[45] Results reported to the FDA used the same data but a different analysis approach, where there was no imputation for missing values. These results showed a decline in per cent responders after weeks 56-72 (figure 6).[112] Dashed lines represent patients who were in the placebo group during the preceding double-blind phase whereas continuous lines represent patients who were in the active group. According to the authors of the FDA report, the decline in per cent respondents may be due to a drop in number of participants after weeks 56-72 and also due to a loss of response.[112]

Figure 6 ACR Ped 30 respondents: Open-label extension phase of the adalimumab study



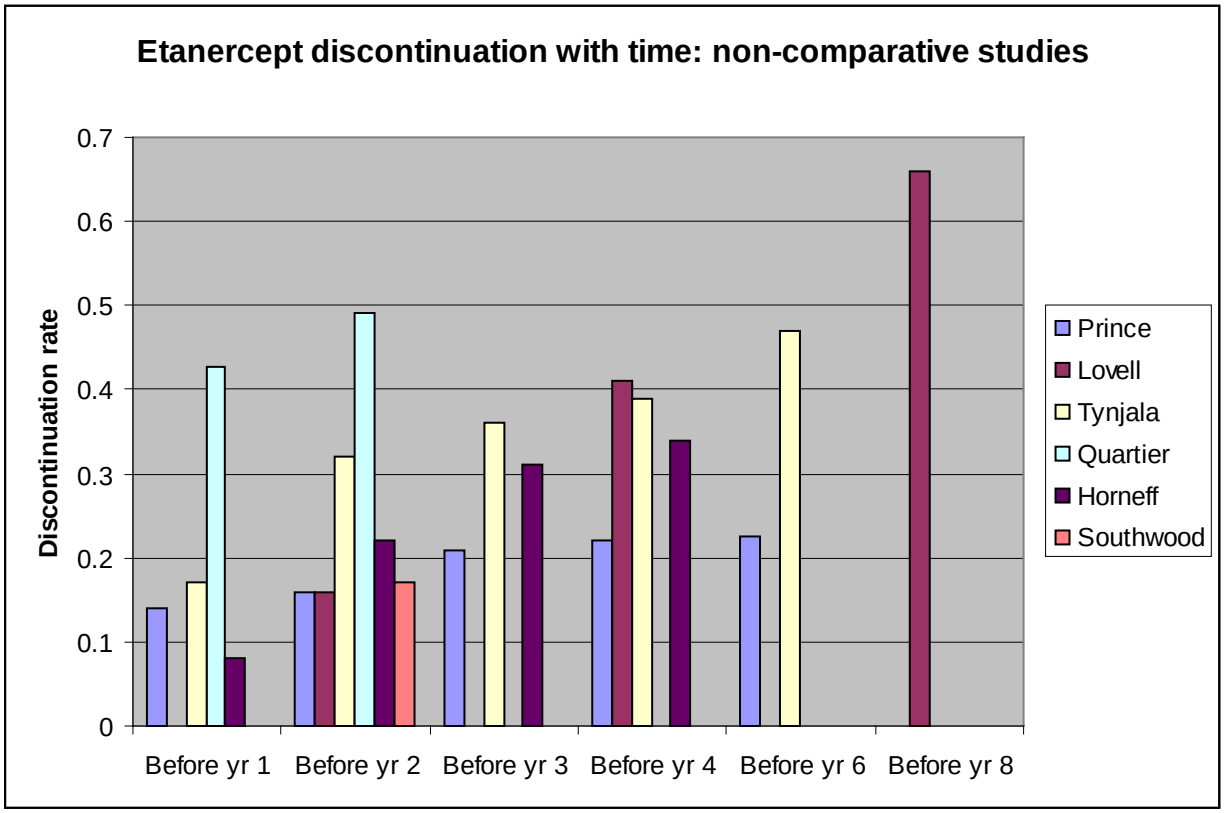
ADA adalimumab / FDA Food and Drug Administration / MTX methotrexate / RCT randomized controlled trial

3.3.4 Treatment discontinuation in non-comparative studies

3.3.4.1 Etanercept

The rate of etanercept discontinuation varied between 10% and 66% in the identified open-label studies. The rates of discontinuations tended to increase with follow-up time (see Figure 7).[74, 81-84, 86, 87, 89, 106, 107] The study with the longest follow-up, eight years, reported a 66% cumulative discontinuation rate.[106] The discontinuations due to disease remission were excluded from the graph if possible. Nevertheless it is not clear if disease remission was part of the reasons for discontinuation, as discontinuations classified as “physician decision” and “others” were both included in the analysis.

Figure 7 Etanercept discontinuation with time: Non-comparative studies



Study by Prince et al.[87], 15-month, 27-month, 39-month, 51-month, and 75-month results were used for 12, 24, 36, 48, 72 months of follow-up respectively.
Study by Tynjala et al.[89], 5-year results were used for the "before year 6" point.
In the initial open-label and double-blind phases of the study by Lovell et al.[107], 5/69 (7.2%) and 6/25 (24%) patients discontinued etanercept due to either lack of efficacy, adverse events or patient refusal, an arithmetic average of these two percentages was used as an estimate for the rate of discontinuation during the first year. These discontinuations were not included in the cumulative figures of the extension phase since some of the patients who withdrew from the study during the initial and double-blind phase of the study may have been re-introduced into the open-label extension phase.

The reasons for drug discontinuation in the different studies are shown in table 14. Most of the discontinuations (30%-100%) were due to adverse events or lack of or suboptimal response. Sample size and baseline characteristics may explain differences in the obtained results.

Table 14 Reasons for discontinuation: Etanercept non-comparative studies

Reason for discontinuation	Lovell[106]	Horneff[84]	Horneff[83]		Quartier[86]	Prince[87]	Tynjala[89]	Southwood[82]	Giannini[81]
Follow-up	**8 years**	**Median: 1 year (1-48 months)**	**1 year**		**2 years**	**Up to 6.3 years**	**Up to 5 years**	**Mean 23 months (1-86)**	**12% of patients followed for 3 years**
Total number of discontinuations	**38/58 (66%)**	**57/334 (17%)**	**14/69* (20.3%)**	**51/427** (11.9%)**	**26/61 (42.6%)**	**47/146 (32.2%)**	**46/105 (44%)**	**74/434 (17%)**	**85/404 (21%)**
Adverse events, n (%)	4 (7%)	11 (3.3%)	3 (4.3%)	14 (3.3%)	26 (42.6%)	6 (4.1%)	7 (6.7%)	Adverse event ¶ or intolerance 30 (6.9%)	3 (0.7%)
Lack of /suboptimal treatment response, n (%)	7 (12%)	27 (8%)	8 (11.6%)	22 (5.2%)		33 (22.6%)	29 (27.6%)	44 (10.1%)	63 (15.6%)
Disease remission	-	14 (4.2%)	-	6 (1.4%)	-	8 (5.5%)	10 (9.5%)	-	19 (4.7%)
Non-compliance	-	-	-	-	-	-	-	10 (2.3%)	
Patient/parental request	8 (14%)	-	-	-	-	-	-	-	
Physician decision	5 (9%)	-	-	-	-	-	-	-	
Loss to follow-up	3 (5%)	-	1 (1.5%)	3 (0.7%)	-	-	-	-	
Other / protocol issue	11 (19%)	5 (1.5%)	2 (2.9%)	6 (1.4%)	-	-	-	-	

* Etanercept monotherapy
** Etanercept + methotrexate
¶ Adverse events that lead to discontinuation: optic neuritis, reduced vision, uveitis flare, macrophage activation syndrome, low mood (n=2), low white cell count, meningoencephalitis, infections (n=3), eczema flares, menorrhagia, anxiety, vaccine administration, headache, pregnancy, sepsis and hallucinations.

3.3.4.2 Infliximab

Drug discontinuation was reported in three studies.[89, 92, 93] Rates of drug discontinuation ranged from 42%-70%. Reasons for discontinuation were mostly due to adverse events or lack of treatment response (table 15).

Table 15 Drug discontinuations in infliximab non-comparative studies

Reason for discontinuation	Gerloni[93] n=24	De Marco[92] n=78	Tynjala[89] n=104
Follow-up	**12 months (n=14)**	**Median: 14 months**	**Up to 60 months**
Total number of discontinuations	**6/14 (42.9%)**	**55 (70.5%)**	**61 (58.7)**
Adverse events, n (%)	5 (35.7%) – infusion-related	26 (33%) mostly infusion-related or hypersensitivity	23 (22%)
Lack of /suboptimal treatment response, n (%)	1 (7.1%)	19 (24.3%)	21 (20%)
Non-compliance	-	1 (1.3%)	-
Disease remission	-	9 (11.5%) – remission or improvement (ACR criteria)	17 (16%)

3.4 Change in concomitant use of other DMARDs

The long-term use of glucocorticoids may affect the child's growth, among other side-effects.[3] A few etanercept studies reported the changes in the use of concomitant DMARDs and glucocorticoids following the introduction of biologic agents.[84, 86, 103, 107] The results of these studies are summarized in Appendix 9.

3.5 Switch to a second biologic

Studies in adults have shown that once a first biologic agent needs to be discontinued due to either lack of efficacy or intolerance, a switch to a second drug may result in a favourable response,[42, 108] especially if there was an initial response to the first drug.[42]

Two studies that evaluated the use of a second biologic agent after the first agent had to be discontinued due to inefficacy or intolerance were identified.[89 95] Appendix 10 summarizes the results of these studies.

In general, the authors found that although patients who discontinue their first anti-TNF-α drug due to a lack or loss of efficacy or intolerance have a higher risk of encountering the same issue with a second anti-TNF-α, this does not hinder a good favourable response with the second drug.[89 95] This is corroborated by the adult literature[108]

In cases of lack of response from the beginning of the treatment with an anti-TNF-α, it has been suggested that a switch to a second drug with a different mechanism of action would be more appropriate.[42] Publications about switches between anti-TNF-α and biologic agents with a different mechanism of action in children with JIA were not identified. The abatacept RCT was not designed to study drug switches but it reported disease response in JIA patients with prior use of anti-TNF-α agents.[47] Among 133 patients without prior anti-TNF-α use, 101 (76%) achieved ACR Ped 30 criteria whereas 22/57 (39%) patients with prior anti-TNF-α use achieved ACR Ped 30 in the 4-month open-label lead-in period.[47]

3.6 Safety

Adverse events reported in the studies identified are summarized below. Results from RCTs are reported separately from observational studies.

Concomitant use of MTX or other DMARDs, and corticosteroid was allowed in the studies included. Most studies included patients with polyarticular-course JIA. RCTs were available which evaluated tocilizumab in the treatment of systemic JIA, and these studies were also included in the safety review (as specified).

The association between the occurrence of adverse events and the biologic agent was not always clearly stated by the authors. Appendix 11 shows the adverse events reported in the biologics RCT and observational studies.

3.6.1 Serious adverse events

During the 2-4-month open-label phase of the biologics RCTs, serious adverse events occurred in 3%-7% of the patients treated with etanercept, adalimumab, abatacept, and tocilizumab.[39, 45, 47, 49] Most of the events consisted of serious infections,

urticaria/anaphylactoid reaction, and one case of depression and personality disorder. There was one (0.5%) case of acute leukemia diagnosed on day 89 in the abatacept study.[47] The authors reported that the patient had been anemic since the start of the study with progressively declining hemoglobin levels.[47]

During the double-blind phase of the RCTs, no serious adverse event was reported with the active drugs etanercept, abatacept, or tocilizumab.[39, 45, 47, 49] One serious infection occurred during the double-blind phase of the adalimumab study.[45] Serious infections were reported in the placebo group of the abatacept (n=2, 3.2%)[47] and adalimumab (n=1, 1.5%)[45] trials. In the anakinra RCT conducted in patients with systemic JIA, three serious infections (3/12, 25%) and one vertebral collapse (1/12, 8.3%) were reported during the double-blind phase.[102, 121] It is not clear if the events occurred in the anakinra or placebo treatment arm.

In the double-blind period of the infliximab study, six (6/122, 4.9%) serious infections and six (6/122, 4.9%) serious infusion reactions were reported in infliximab-treated patients over a 9-12 month follow-up period.[76] In the placebo arm two (3.3%) serious infections were reported over a 3.5-month period.[76] There were two deaths in this study. One was due to cardiac arrest following hospitalization for a sever disease flare which occurred six months after the patient discontinued infliximab 3mg/kg in the open-label extension phase.[76] The second occurred in the placebo arm, after the patient was hospitalized due to septic shock, with cardiac function deterioration leading to death.[76]

During the long-term extension phase of the RCTs 0.02-0.37 serious adverse events per patient-year were reported depending on the study.[45, 49, 106] With the exception of the etanercept study, with a follow-up of up to eight years, the other studies had a follow-up of approximately one year. The most common events were serious infections, 0.02-0.15/patient-year.[45, 49, 106] Two events of rash/anaphylactoid reactions were reported, one (1.7%) with etanercept [106] and one (2%) with tocilizumab.[49] There were two events of abdominal pain, one with etanercept (1.7%),[106] and one (0.004/patient-year) with adalimumab.[45] One serious adverse event of each of the following was reported: hematochesia, arthralgia, dental abscess, and hydrocephalus in the etanercept and adalimumab studies,[45, 106] and one event of gastrointestinal hemorrhage (on tocilizumab).[49]

There were two deaths (1.6%) in patients with systemic JIA treated with tocilizumab, one due to machrophage activation syndrome and the other due to cardiac amyloidosis.[122]

Observational studies with etanercept reported 0.03-0.08 serious adverse events per patient-year.[81, 83-85, 87, 91, 103, 118] One study reported serious adverse events in 12 (20%) patients.[86] Among the serious adverse events across the observational studies, three malignancies were reported, two thyroid (0.2%[83, 84] and 1.1%,[85] respectively) and one yolk sac (0.14%)[85] carcinoma. One case of Hodgkin lymphoma (0.16%) was reported in a patient treated with etanercept and a history of MTX, azathioprine and cyclosporine A use.[83]

Crohn's disease was diagnosed in eight etanercept-treated patients included in different studies (0.2%-3.9%).[83, 85-87, 118] One patient with systemic JIA included in the anakinra RCT developed ileocolic symptoms three months after starting treatment with anakinra, which lead to the diagnosis of Crohn's disease.[102, 121] The investigators reconsidered the systemic JIA diagnosis in this case.[121]

Lupus-like syndrome was diagnosed in two (2.8%) patients with systemic JIA treated with etanercept, one of which was associated with demyelinating neuropathy.[91] In two patients (0.5%) treated with etanercept plus MTX, optic nerve papillitis was reported.[123] Demyelinating disease was diagnosed in one patient but this had already been previously reported.[123, 124] Other neuropsychological adverse events reported in this study included two cases of seizures, two patients experiencing frequent feelings of revulsions, one patient with white matter lesions visualized by MRI, one patient with optic and acoustic hallucinations, one patient with tinnitus and one patient with depression.[123] Another case of optic neuritis following etanercept therapy has been reported.[82] In most cases, the association of adverse events with the biologics was not discussed by the authors. Additional details are provided in Appendix 11.

3.6.2 Non-serious adverse events

The most common non-serious adverse events were infusion-site reactions and infections, mostly of the upper respiratory tract. In most cases, the association of adverse events with the biologics was not discussed by the authors (additional details shown in Appendix 11).

During the 3-4-month lead-in open-label phase of RCTs, infusion-site reactions, occurred in 27 (39%) patients with etanercept,[39] 64 (74%) with anakinra,[75] and eight (4%) with abatacept.[47] In the adalimumab study, there were 1.8 infusion-site reactions per patient.[45] Infections occurred in 35%-41% of the patients in the etanercept, abatacept, and anakinra studies, mostly of the upper respiratory tract.[39, 47, 75] There were 0.12 upper respiratory tract infections per patient in the adalimumab study.[45] Rash occurred in seven (10%)[39] and nine (11%) [75] patients in the etanercept and anakinra study, respectively.

In etanercept-treated patients, there were 50 neuro-psychological events reported in two non-comparative studies, leading to rates of 0.012 and 0.14 events per patient-year, respectively.[83, 85] One study reported 17 neuropsychological events (0.121/patient-year) in patients treated with infliximab.[85] The most common manifestation was headache or severe headache, but also included psychosis, depression, anxiety, nervousness/hyperactivity, aggressiveness, fatigue, and vertigo.[85] One study reported that one in 434 patients (0.2%) treated with etanercept had hallucinations.[82]

There was one case of tuberculosis (1.3%) in the long-term extension of the infliximab study in a patient who had a negative tuberculosis skin test at study entry.[76]

A study from HSC observed two cases (4.4%) of new-onset uveitis among 45 patients treated with either etanercept or infliximab over 2.2 years of follow-up.[90]

3.6.3 Case reports of adverse events

Reports of adverse events in JIA patients for which the authors believed there was a temporal or causal association to etanercept and/or infliximab (table 16) were identified.[125-146] Additional information is provided in Appendix 12.

No definitive causal relationship between the events and biologic agents was established. Case reports do not permit an estimation of the rate of occurrence in patients treated with biologics, however, they provide information regarding each of these rare events.

Some authors raised the possibility that in case of autoimmune events, anti-TNF-α agents may unmask or induce the appearance of the event or symptoms (lupus, diabetes mellitus, psoriasis), in patients predisposed to the disease.[125, 126, 139] Sukal et al. points out that

patients with autoimmune diseases may be more susceptible to other autoimmune diseases such as multiple sclerosis.[143]

Table 16 Case reports identified

Adverse event	Number of cases reported
Optic neuritis	4[144]
Hodgkin's lymphoma	4[134, 135] (+ 8 reported to the FDA)
Macrophage activation syndrome (systemic JIA)	1[145]
Maculopapular rash	2[136]
Systemic lupus erythematosus	2[140, 141]
Lupus nephritis and leukocytoclastic vasculitis	1[139]
Demyelinating events	2[142, 143]
Tuberculosis	1[131] + 1 case of fatal opportunistic pulmonary infection where tuberculosis could not be confirmed.[130]
Uveitis (sarcoid-related)	1[146]
Diabetes mellitus	1[125]
Osteomyelitis (group A streptococcus)	1[128]
Hemolytic transfusion reaction	1[137]
Septic abscess	1[132]
Psoriasis	1[126]
Urachal cyst infection	1[133]
Thymic enlargement	1[138]
Autoimmune hepatitis	1[127]
Acute obstructive cholecystitis	1[129]

FDA: Food and Drug Administration

3.7 Systematic reviews

A systematic review of the use of biologics for the treatment of JIA was published in 2007.[96] The review included comparative and non-comparative studies published as full text.[96] One etanercept RCT and three non comparative infliximab studies were included.[96] No studies on other biologic agents were available in the peer-reviewed literature at the time.[96] The authors concluded that the evidence available on the efficacy and safety of these drugs was not substantial and therefore the benefits and risks of treating pediatric patients with these drugs needed to be weighed.[96]

3.8 Technology assessment reports

A technology assessment report published in 2002 in the UK evaluated the effectiveness and costs of etanercept in JIA.[97] The report was based on the etanercept RCT[39] and included data up to the second year of the study. The authors concluded that the results of the study were congruent with the results in adults with rheumatoid arthritis and that etanercept is an effective treatment for patients with JIA.[97] The authors also pointed out that "the safety profile of etanercept is acceptable at present despite some reports of blood dyscrasias", but that it is important to continue to monitor its safety.[97] The annual drug cost of etanercept assuming single-use vials were used was £8,996 (C$16,000), based on a dose of 0.4 mg/kg (maximum 25mg) twice weekly.[97] The costs includes drug vials, syringes and swabs for the administration of the drug at home assuming no vial re-use.[97] If a multiple-use vial is available, the annual cost was estimated as £2,407 (C$4,280) for a 4-year old and 6.7 mg/dose to £8,996 (C$16,000) for an 18-year old and 25mg/dose. The authors assumed no additional costs for support services, clinic visits, and monitoring.[97] Lack of data did not permit a long-term evaluation of the drug.

An HTA report from Hungary published in 2006 was also identified, however only the abstract was available in English.[101] According to the information in the abstract, the authors concluded that "etanercept can improve the symptoms of JIA", however, ongoing safety monitoring was suggested.[101] The cost per quality-adjusted life year (QALY) gained was estimated as €36,600 (C$57,800) with etanercept compared to MTX.[101]

Brief technology assessment reports from the National Horizon Scanning Centre at the University of Birmingham on adalimumab (2007),[147] abatacept (2007),[148] and tocilizumab (2006)[149] were identified. Based on JIA RCTs, the authors believe that adalimumab and abatacept may be effective in reducing morbidity and improving the patients' quality of life.[147, 148] The authors could not determine the clinical benefits of tocilizumab in JIA due to lack of data.[149] Treatment costs were also not calculated due to lack of data.

3.9 Cost analysis

Tables 17-19 provide the annual treatment costs associated with use of biologic drugs in hospital and at home and with MTX in patients with JIA. Additional details are available in Appendix 13. As drug doses depend on weight, in order to be able to estimate annual drug costs at different dosing regimens, the child's weight was set at 40 kg.

Table 17 Annual drug costs for biologics administered in-hospital

Drug	Drug dosing	# infusions / year	Dose for 40 kg	Biologic drug costs		Costs including drug preparation and administration		Cumulative total costs/year	
				Drug costs / infusion	Drug costs / year	Costs / infusion	Costs / year	With concomitant medication and monitoring§	With productivity costs¶
Infliximab	3-7.5 mg/kg* weeks 0, 2, 6, and every 8 weeks thereafter	8	120 mg/dose (3 mg/kg) 200 mg/dose (5 mg/kg) 300 mg/dose (7.5 mg/kg)	$1,880 (3-5mg/kg) $2,820 (7.5 mg/kg)	**$15,040** **$22,560**	$2,034 $2,974	**$16,274** **$23,794**	**$17,259** **$24,779**	**$18,330** **$25,850**
Abatacept	10 mg/kg days 1, 15, 29, and every 4 weeks thereafter	14	400 mg/dose	$880	**$12,320**	$982	**$13,748**	**$14,733**	**$16,608**

* In the infliximab RCT, doses of 3 or 6 mg/kg were used during the double-blind period,[76] and a mean dose of 4.4 mg/kg was used during the open-label extension.[117] In the study by Alexeeva et al., mean doses varied between 6.2-7.3 mg/kg depending on the study group. The study by de Marco et al. used doses ranging from 3-10 mg/kg.
¦ Includes pharmacy costs for materials for drug preparation, as well as pharmacy technician to prepare the infusion, nursing costs for patient monitoring and drug administration, pre-medications (infliximab), laboratory tests performed before the infusion, and physician costs (Appendix 13)
§ Concomitant medications: it was assumed that patients would use concomitant MTX and glucocorticoids (Appendix 13).
Monitoring includes TB screening (tuberculin test and chest X-ray) before biologic treatment starts, blood work & physician visits every 3 months. More details in Appendix 13.
¶ Productivity costs assume that 1 parent/caregiver will miss 1 day of work for each drug infusion in order to accompany the child to the hospital/clinic. Attributable to IV biologics (infliximab, abatacept, rituximab) that require that the drug be administered at a hospital/clinic. Also includes monitoring and concomitant medication costs.

Table 18 Annual drug costs for biologics received at home

Drug	Drug dosing	# infusions / year	Dose for 40 kg / 1.3 m^2	Drug costs / infusion	Drug costs / year	Costs/year including pharmacy and nursing	Costs/year with annual monitoring and concomitant drugs§	Costs/year with productivity costs¶
Etanercept¦	0.4 mg/kg 2x/week** max 25mg)	104	16 mg/dose	$170	**$17,680**	**$17,981**	**$18,966**	**Not applicable for biologic drugs administered SC**
Adalimumab	24 mg/m^2 or 40mg /2 weeks	26	31.2 mg/dose	$668	**$17,368**	**$17,669**	**$18,654**	
Anakinra	2mg/kg (max.100mg) / day	365	80 mg / dose	$51.5	**$18,798**	**$19,099**	**$20,084**	

SC subcutaneous / max maximum
* Includes 1-hour training with nurse before 1st administration, physician costs, & nursing time for phone calls by the patient's family for clarifications on drug use (details Appendix 13).
**May also be administered once a week, 0.8 mg/kg/administration
§ Concomitant medications: it was assumed that patients would use concomitant MTX and glucocorticoids (Appendix 13).
Monitoring includes TB screening (tuberculin test and chest X-ray) before biologic treatment starts, blood work and physician visits every 3 months. More details in Appendix 13.
¶ Since patients receive the therapy at home, no missed work days for parents/caregivers were assumed.
¦ Etanercept may be administered once a week at a dose of 0.8mg/kg (maximum 50mg) without changes in cost

Table 19 Annual costs of treatment with methotrexate

Drug	Drug dosing	# administrations / year	Dose for 40 kg / 1.3 m^2	Drug costs / infusion	Drug costs / year
Methotrexate	15 mg/m^2/wk	52	19.5mg/wk	$12.5	$650
Folic acid	1 mg/day	365	1mg/day	$0.0259	$9
Corticosteroid	5mg/day	365	5mg/day	$0.022	$8
Treatment costs					**$667**
Treatment costs including annual monitoring§					**$952**

Wk week
§ Includes blood work and physician visits every three months. More details can be found in Appendix 13.

The estimated costs of treatment with each biologic agent are shown in tables 17 and 18. In general the annual treatment costs varied between C$14,000-19,000, including administration costs. The dose of infliximab may be increased in case of insufficient response. The dose of infliximab used in the studies varied between 3-10 mg/kg/dose.[76, 92, 94, 117] The mean infliximab doses varied between 4.4-7.3 mg/kg/dose.[93, 94, 117]

Given that the infliximab treatment costs vary considerably with the dose administered, costs of doses ranging from 3 to 7.5 mg/kg were estimated, which were assumed to be the most common based on the studies above. If higher doses are used, treatment costs will also rise.

Patients who need to receive treatment in the hospital (or rheumatology clinics) need to stay at the hospital for a period of 4-7 hours for drug infusion and for pre and post-infusion periods, and therefore may need to miss a school day for each drug infusion. This accounts for eight and 14 days/year for infliximab and abatacept, respectively. Due to lack of consensus in the economic literature on how to cost a missed school day, no cost has been assigned. The cost of missing one work day for parents/caregivers was included in the analyses as productivity costs.

It was assumed that any portion of the medication left in vials would be discarded and would not be re-used. However if formulations allowing the re-use of medication vials are available, treatment costs may be lower depending on the drug and patient's weight.

3.9.1 Sensitivity analysis of costs according to patient weight

Results of a sensitivity analysis of annual drug costs varying patient weight is provided in table 20. Only drug acquisition costs were included since preparation, administration and healthcare personnel time were not considered to vary by patient weight. Since pediatric patients use doses that are generally lower than adult doses (depending on weight), not all of each medication vial is used at each infusion. Given that re-use of the unused portion of the vials is not always possible depending on the drug, no vial re-use was assumed in the cost analyses and the annual costs therefore do not always vary by weight (additional details in Appendix 14).

Table 20 Annual drug acquisition costs by patient weight

Patient weight	Etanercept 0.4 mg/kg (max. 25 mg)	Infliximab 3 mg/kg	Infliximab 5 mg/kg	Adalimumab 24 mg/m² (max. 40 mg)	Abatacept 10 mg/kg (max. 1000 mg)	Anakinra 2 mg/kg (max.100 mg)	MTX 15 mg/m²/ week
10 kg	$17,680	$7,520	$7,520	$17,368	$6,160	$18,798	$650
20 kg	$17,680	$7,520	$7,520	$17,368	$6,160	$18,798	$650
30 kg	$17,680	$7,520	$7,520	$17,368	$12,320	$18,798	$650
40 kg	$17,680	$15,040	$15,040	$17,368	$12,320	$18,798	$650
50 kg	$17,680	$15,040	$15,040	$17,368	$12,320	$18,798	$1,300
60 kg	$17,680	$15,040	$22,560	$17,368	$18,480	$18,798	$1,300
70 kg	$17,680	$22,560	$30,080	$17,368	$18,480	$18,798	$1,300

Max maximum / MTX methotrexate

3.10 Economic evaluation

The cost-effectiveness of biologic agents compared to non-biologic DMARDs was calculated. Biologic agents included in the economic analyses were etanercept, infliximab, adalimumab, and abatacept. The incremental cost-effectiveness ratio (ICER) was expressed as the incremental cost per additional patient responder (ACR Ped 30) with each biologic drug compared to DMARDs. The time horizon of the analyses was one year.

Treatment costs were derived from the cost analysis. Additionally, costs of serious adverse events such as serious infections were also included. Patients who discontinued the biologic agent or DMARDs at six months due to lack/loss of efficacy or intolerance were assumed to switch a different biologic agent. These patients were considered as non-responders to the first biologic agent or DMARDs. Since there is presently no consensus on the sequence of biologics

that should be used, the costs of the second drug prescribed were assumed to be an average cost of the other biologic agents available.

Table 21 shows the variables used in the base case probabilistic sensitivity analyses. Figure 8 shows a summary of the decision model used in the economic analyses.

Figure 8 Schematic of decision models used in the economic analyses

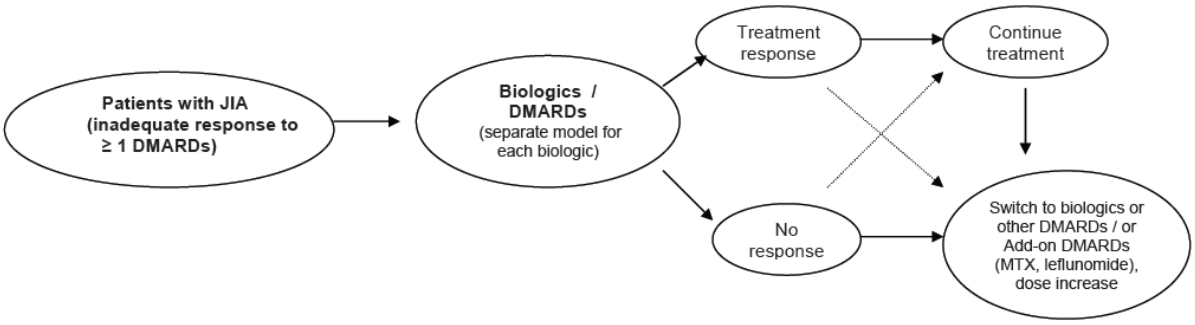


Table 21 Input variables used in the probabilistic sensitivity analyses

Variable	Value (mean, SD)	Distribution	Source
Etanercept			
% ACR Ped 30 6 months	0.79, 0.10	Beta distribution	Pediatric RCT and observational studies [39, 74, 107] (non-systemic onset JIA where possible)
% ACR Ped 30 12 months	0.79, 0.08		
% serious infections	0.04, 0.02		
% discontinuations AE	0.03, 0.05		
Infliximab			
% ACR Ped 30 6 months	0.80, 0.10	Beta distribution	Pediatric RCT [76] and observational studies
% ACR Ped 30 12 months	0.79, 0.05		
% serious infections	0.08, 0.04		
% discontinuations AE	0.08, 0.11		
Adalimumab			
% ACR Ped 30 6 months	0.80, 0.05	Beta distribution	Pediatric RCT[45]
% ACR Ped 30 12 months	0.63, 0.06		
% serious infections	0.04, 0.02		
% discontinuations AE	0.07, 0.02		
Abatacept			
% ACR Ped 30 6 months	0.82, 0.05	Beta distribution	Pediatric RCT [47] Adult RCTs (weighted average)
% ACR Ped 30 12 months	0.82, 0.05		
% serious infections	0.02, 0.03		
% discontinuations AE	0.04, 0.03		
DMARDs			
% ACR Ped 30 6 months	0.30, 0.03	Beta distribution Log-normal distribution	Meta-analyisis[79] Adult meta-analyses[150-153]
% ACR Ped 30 12 months	0.30, 0.03		
% serious infections	RR range: 0.49-1.43		
% discontinuations AE	RR range: 0.68-1.23*		
Drug acquisition costs	See tables 17 and 18		
Costs of serious infections	$6,065 (1,814 – 11,277)	Triangular distribution	Canadian Institute for Health Information (in-hospital costs of various infections ages <1-14 years)

AE adverse events / SD standard deviation / RR rate ratio
* Rate ratio specific for each drug comparison

The effectiveness of each biologic drug was derived from the systematic literature search. For the biologic agents, both RCTs and observational studies were used sources. In cases where

more than one study was available, a weighted average (inverse variance) was used to pool the effectiveness results of different studies.[78] The same sources were used for serious adverse events and treatment discontinuations.

Patients were eligible for the RCTs if they had previously failed to respond to other DMARDs. The study protocols, however, allowed patients to continue taking other DMARDs. It is challenging to estimate these patients' responses to DMARDs over the course of one year (the time horizon for the economic evaluation). In the infliximab RCT, 49.2% of patients with suboptimal response to MTX who continued treatment with MTX + placebo (concomitant low dose glucocorticoids and one NSAID) had an ACR Ped 30 response rate at 14 weeks.[76] The authors commented that this response was higher than the expected 20-30% response and may be due to a placebo effect.[76] Data from the other biologics' RCTs cannot be used since the there is a risk of carry-over effect as all patients received a biologic agent for three to four months before being randomized, and the placebo periods were short.[39, 45, 47] It can be expected that some patients with a suboptimal response to DMARDs may still respond to these drugs for a period of time either because of a placebo effect or due to the fluctuating nature of the disease. For the model it was therefore assumed that in patients with optimized doses of non-biologic DMARDs approximately 30% of the patients still respond to these DMARDs for a period of six months. This is corroborated by the 20-30% response expected by the authors of the infliximab RCT,[76] and by the results of a meta-analysis that pooled the 6-month response rate in the placebo group of JIA RCTs which determined a pooled response rate in the placebo group at six months of 28.5% (95% CI: 24%, 34.2%).[79]

In the sensitivity analyses, the high response rate of 49.2% obtained in the control group of the infliximab study and a low estimate of 20.0% were used to test the robustness of the assumptions. These estimates are for the first six months of treatment. Due to the absence of data beyond this point, it was assumed that the per cent responders would remain stable for the remainder of the first year. This was based on the adult biologic RCTs that showed that the rate of responders in the MTX arm remained constant during the first year of treatment (based on approximately 1,000 patients). These adult studies consisted of studies of biologics in patients with late rheumatoid arthritis with insufficient response to MTX/DMARDs.

No study in the peer-reviewed literature described the long-term MTX outcomes in JIA patients with insufficient response to MTX.

The percentage of patients who achieved ACR Ped 30 in the etanercept studies varied considerably, for instance, from 61%-82% at six months. The small sample sizes of the studies, different approaches to deal with missing data (ITT, LOCF), and possible heterogeneities in patient populations may have contributed to these differences in study results. Therefore, in addition to using the weighted average effectiveness as the base case scenario of the models, sensitivity analyses were carried out in which different sources were used for effectiveness estimates in separate models. For instance the lowest and highest efficacy estimates available from the etanercept studies (RCT/observational) were used in sensitivity analyses. Less evidence is available with the other biologics, in that efficacy estimates came from a single study for each biologic (except etanercept and infliximab). For this reason, a similar increase or decrease in treatment response used in the etanercept models was applied for the other biologics (there was no variation in the results of infliximab studies). Table 22 lists the additional sensitivity analyses performed using different efficacy estimates.

The base case assumed a 40 kg/1.3m² child. Since treatment costs change with patient weight, in the sensitivity analyses, the incremental cost-effectiveness was calculated varying weight from 10 kg to 70 kg (Appendix 15).

Table 22 Additional probabilistic sensitivity analyses varying parameter estimate approaches

Variable	Value (mean, SD) / distribution	Source
EFFICACY LOW ESTIMATE Methotrexate ACR Ped 30 (%, SD)	0.20, 0.05 / beta distribution	Estimate from authors of infliximab RCT[76]
EFFICACY HIGH ESTIMATE Methotrexate ACR Ped 30 (%, SD)	0.49, 0.06 / beta distribution	Response in control group of infliximab pediatric RCT[76]
EFFICACY LOW ESTIMATES Biologics ACR Ped 30 (%, SD) Etanercept Infliximab Adalimumab 6 months Adalimumab 12 months Abatacept	 0.61[86], 0.07 / beta distribution 0.62, 0.07 / beta distribution 0.62, 0.04 / beta distribution 0.49, 0.04 / beta distribution 0.63, 0.04 / beta distribution	 Pediatric observational study etanercept [86] The same relative decrease in estimate was applied to other biologics due to lack of data
EFFICACY HIGH ESTIMATES Biologics ACR Ped 30 (%, SD) Etanercept Infliximab Adalimumab 6 months Adalimumab 12 months Abatacept	 0.84[87], 0.03 / beta distribution 0.85, 0.10 / beta distribution 0.85, 0.05 / beta distribution 0.67, 0.04 / beta distribution 0.87, 0.05 / beta distribution	 Pediatric observational study[87] (etanercept, non-systemic disease) The same relative decrease in estimate was applied to other biologics due to lack of data
Patient weight	10 – 70 kg	-

Tables 23 - 26 show the results of the PSAs using different scenarios with each biologic agent. In cases where some of the simulations showed a lower efficacy of the biologic compared to MTX, the ICER was not provided due to difficulties in interpretation under such circumstances.

Table 23 Etanercept probabilistic sensitivity analyses

Model	Mean incremental cost (95% CI)	Mean incremental effectiveness (95% CI) Absolute difference in ACR Ped 30 responders	% simulations where etanercept had lower efficacy	ICER (C$/additional respondent at 1 year)
Base case	$11,090 (10,261, 11,863)	47.6% (26.7%, 63.6%)	0	$26,061 (17,070, 41,834)
Extreme scenario etanercept high DMARDs low estimate	$10,191 (9,121, 11,350)	62.1% (39%, 79.7%)	0	$17,062 (11,914, 27,026)
Extreme scenario etanercept low, DMARDs high estimate	$12,833 (11,478, 14,145)	12% (-9.7%, 32.7%)	14%	NA

CI confidence interval / NA not applicable / ICER incremental cost-effectiveness ratio
Estimates and ICER based on 10,000 simulations
Negative values indicate higher efficacy with MTX compared to etanercept

Table 24 Infliximab probabilistic sensitivity analyses

Model	Mean incremental cost (95% CI)	Mean incremental effectiveness (95% CI) Absolute difference in ACR Ped 30 responders	% simulations where infliximab had lower efficacy	ICER (C$/additional respondent at 1 year)
Base case	$12,167 (8,959, 12,550)	43.2% (18.2%, 61.1%).	0	$31,209 (16,659, 66,220)
Extreme scenario Infliximab high estimate, DMARDs low estimate	$11,297 (7,897, 15,798)	57.4 (33%, 71.9%)	-	$20,688 (12,121 , 36,034)
Extreme scenario Infliximab low, DMARDs high estimate	$13,951 (10,157, 18,969)	8.1% (-8.4%, 23.8%)	16%	NA

CI confidence interval / NA not applicable / ICER incremental cost-effectiveness ratio
Estimates and ICER based on 10,000 simulations
Negative values indicate higher efficacy with MTX compared to infliximab

Table 25 Adalimumab probabilistic sensitivity analyses

Model	Mean incremental cost (95% CI)	Mean incremental effectiveness (95% CI) Absolute difference in ACR Ped 30 responders	% simulations where adalimumab had lower efficacy	ICER (C$/additional respondent at 1 year)
Base case	$13,107 (10,818, 15,491)	29.41% (17.3%, 41.0%)	0	$46,711 (30,042 , 75,787)
Extreme scenario adalimumab high, DMARDs low estimate	$12,252 ($9,297, $15,249)	43.4 (29.5%, 58.0%)	0	$29,298 (18,071, 46,412)
Extreme scenario adalimumab low, DMARDs high estimate	$12,647 ($11,747 , 13,477)	-1.6% (-17.2% , +14.3%)	58%	NA

CI confidence interval / NA not applicable / ICER incremental cost-effectiveness ratio
Estimates and ICER based on 10,000 simulations
Negative values indicate higher efficacy with MTX compared to adalimumab

Table 26 Abatacept with or without methotrexate probabilistic sensitivity analyses

Model	Mean incremental cost (95% CI)	Mean incremental effectiveness (95% CI) Absolute difference in ACR Ped 30 responders	% simulations where abatacept had lower efficacy	ICER (C$/additional respondent at 1 year)
Base case	$7,873 (6,226, 9,419)	49.4% (38.1%, 59.3%)	0	$16,204 (11,393, 22,608)
Extreme scenario abatacept high estimate, DMARDs low estimate	$6,792 (4,907, 8,610)	63.9% (50.2%, 75.5%)	0	$10,822 (6,964, 15,890)
Extreme scenario abatacept low, DMARDs high estimate	$9,978 (8,154, 11,751)	12.7% (-4.1%, 29.5%	7%	NA

CI confidence interval / NA not applicable / ICER incremental cost-effectiveness ratio
Estimates and ICER based on 10,000 simulations
Negative values indicate higher efficacy with MTX compared to etanercept

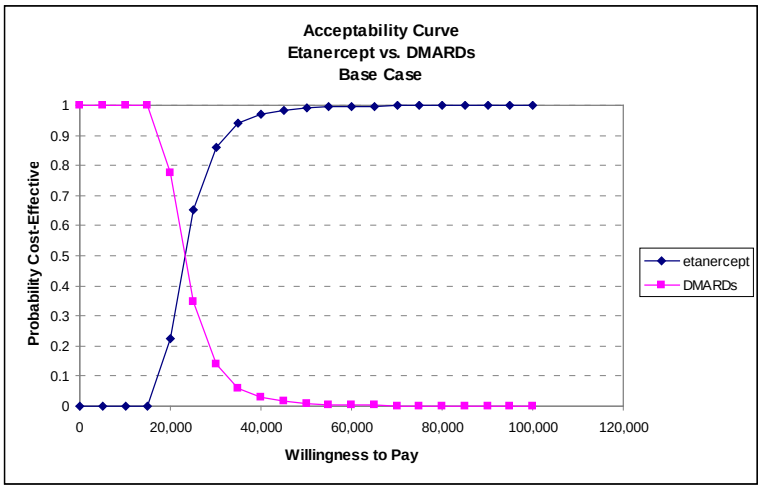
ICER values that fall below US$50,000 per QALY or per life year gained have been presented in the literature as below the threshold for rejection in resource allocation, although the choice of threshold is subject to local budget constraints and other factors. The presentation of ICERs

using unique effectiveness outcomes such as in the present analyses creates difficulties in interpretation and limits comparisons to other studies.

Figure 9 shows the etanercept acceptability curves obtained through the PSAs under different scenarios. The acceptability curves show the probability that biologics are cost-effective (incremental net benefit > 0) at different willingness-to-pay values. The point where the two curves meet shows a 50% probability that either treatment (the biologic or non-biologic DMARD) is cost-effective. The results with other biologics did not differ substantially and are shown in Appendix 16. There is no evidence of difference in efficacy among the biologics and differences in results obtained may be due to sample variation, imprecision or different analytic approaches such as imputation methods for missing values. Costs are always higher with biologics compared to DMARDs.

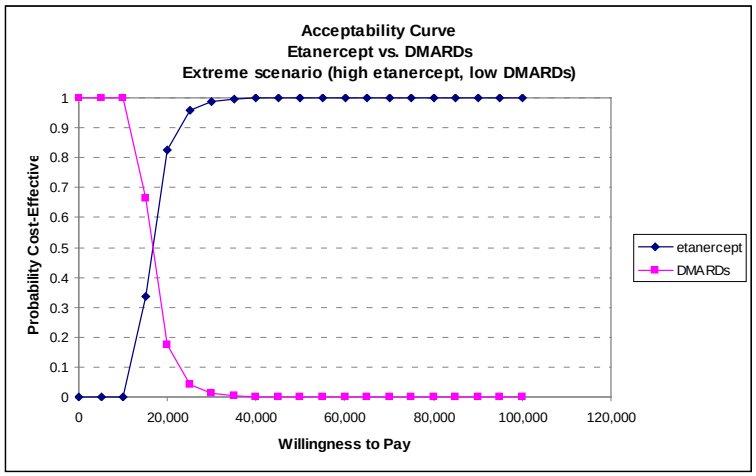
Figure 9 Etanercept probabilistic sensitivity analyses scatterplots

A – Base case analysis



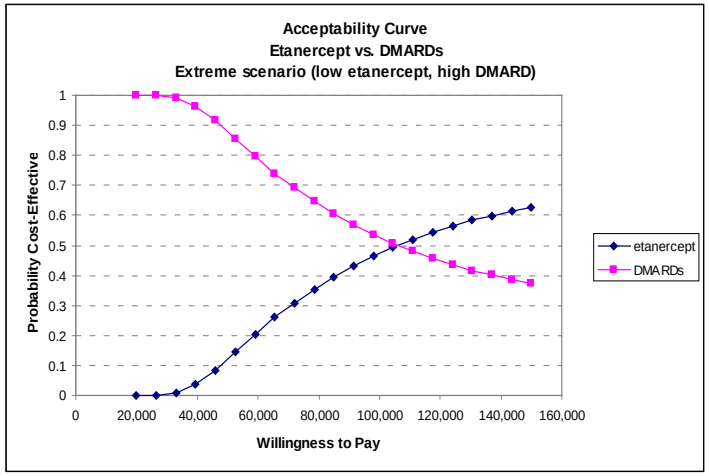
Curves cross at $25,000

B – Extreme analysis (high etanercept, low DMARD estimates)



Curves cross at $20,000

C – Extreme analysis (low etanercept, high DMARD estimates)



Curves cross at $100,000

DMARD disease-modifying anti-inflammatory drug

3.10.1 Comments on the economic analyses

The short-term cost-effectiveness of biologics compared to DMARDs in patients with polyarticular JIA with inadequate response to DMARDs was evaluated. Given the current uncertainty, extrapolating the evidence beyond one year would not result in meaningful estimates.

An important limitation of the economic analyses was that long-term controlled studies in this patient population are not available and short-term outcomes cannot be extrapolated over the long-term with confidence. Thus the long-term costs and consequences of disability remain unknown. In addition, preferences for health states (utilities) were not measured in the current studies, making it impossible to conduct a cost-utility analysis examining differences in quality-adjusted life years. This hinders the interpretability and comparability of the results since willingness-to-pay thresholds are typically based on an incremental cost per QALY gained. The use of incremental cost per additional responder limits comparison to within this patient population but may nevertheless be of value to clinical decision-makers.

There were other limitations of this analysis related to costing. The costs of uncontrolled arthritis were likely under-estimated, as other treatment costs such as physical therapy were not included. As well, productivity losses incurred by parents who must miss work were included for health care appointments but not for prolonged uncontrolled disease. The costs of NSAIDs and other pain medications were also not included as it was difficult to predict their use accurately. These omissions lead to a relative under-estimate of the costs of the less effective comparator intervention (MTX), slanting the cost analysis against the biologics.

Despite high levels of uncertainty in the evidence currently available in pediatrics, cost-effectiveness analyses were undertaken given the high cost of biologics and their potential impact on patient outcomes. In order to partially address these uncertainties, extensive sensitivity analyses were carried out.

3.11 Budget impact of biologics in polyarticular-course JIA

The upper limit for the incremental cost of using biologics was estimated at approximately C$15,000 per patient compared to non-biologic DMARDs. Assuming that 150 patients are treated with biologics at HSC, the upper limit of the total additional annual cost at the institutional level would be C$2,250,000.

Estimates of the prevalence of JIA vary widely, from seven to 400 per 100,000 children.[8, 10, 11] Assuming a prevalence of 100 JIA cases per 100,000 children, there would be approximately 3,000 children with JIA in Ontario, 60% of whom may present with the polyarticular-course disease subtype (1,800). If 10% of these children require treatment with biologics[1] (n=180), assuming additional drug costs of C$15,000 per child, the additional annual cost in the province across payers would be estimated as C$2.7 million. The 10% estimate is based on patients with no response to conventional treatment. It is believed that the proportion of users may extend beyond the 5-10% completely refractory patients to include those patients with an insufficient response to non-biologic treatment (Dr. Brian Feldman, personal communication). The actual number of children who receive biologics has not been estimated, but if it is assumed that 20% of polyarticular-course JIA patients may receive biologics, the cumulative budget impact across payers in Ontario may rise to approximately C$5.4 million per year.

Assuming a mid-point prevalence of 200 JIA cases per 100,000 children, the cumulative budget impact would be C$5.4 to C$10.8 million annually in Ontario if 10-20% of polyarticular-course JIA patients receive biologics. These estimates may be conservative, however more precision requires more accurate estimates of the use of biologics in JIA patients.

Biologics may be paid for by the provincial government, the hospital, or by the patient through private insurance or out-of-pocket, depending on the drug and on the family situation. Even with subscription to a drug plan, families may face out-of-pocket costs in the form co-payments and deductibles which may impede access or affect use.

4 DISCUSSION

The studies in patients with JIA showed that the use biologic drugs (etanercept, infliximab, adalimumab, abatacept, anakinra) may result in some initial short-term disease improvement (ACR Ped 30) in approximately 80% of patients with active disease despite the previous use of non-biologic DMARDs. However, the studies showed that up to approximately 1/3 of the patients may need to discontinue the biologic within the first 3-4 months of treatment due to either lack of efficacy or intolerance. The study with the longest follow-up of eight years reported a 66% rate of discontinuation (excluding disease remissions). The long-term results that are available show that those patients who are able to stay on the biologic may continue to have a favourable response for many years (maximum follow-up of eight years).

While the ACR Ped 30 was used as the primary measure of effectiveness in the economic evaluation for pragmatic reasons, it is acknowledged that a 30% improvement in disease symptoms may be inadequate as a treatment goal. The economic evaluation was, however, designed as an incremental analysis and the difference in effectiveness between the biologic agent and comparator was varied widely, from approximately 12% to 67%, depending on the biologic drug. The sensitivity analysis may thus provide insight into the incremental cost-effectiveness using other measures of effectiveness. For example, if the ACR Ped 70 had been used, the response rate in the MTX comparator may be reduced less than in the biologic arm if relatively more of the total response in the control group was attributable to a placebo effect or regression to the mean. The response rate for biologics would certainly be reduced if the more restrictive ACR Ped 70 were used. If the result of using the ACR Ped 70 as an outcome measure is a decreased incremental effectiveness in the denominator of the ICER, some insight may be gained from the worst case scenarios depicted in tables 23-26, whereby the mean incremental effectiveness of the biologic compared to the comparator ranged from -1.6% to 12.7%. These results show that even with highly conservative effectiveness estimates for the biologics, a net benefit is demonstrated, on average, albeit at a higher cost. If the incremental effectiveness remained unchanged with the ACR Ped 70, the same ICERs would result, but would have greater relevance for clinical practice which aims to achieve higher levels of improvement than observed with the ACR Ped 30.

Patients who discontinue a biologic may be prescribed another biologic. The evidence available on switches between biologics is sparse, but shows that patients who failed or did not tolerate a first choice biologic may respond to a second biologic, especially if there was an initial response to the first drug. Nevertheless, the risk of discontinuing the second drug for a similar reason is higher in patients who switched than in patients who didn't. Most studies on drug switches in JIA were done between anti-TNF-α agents as they were first on the market. There is less data on switches between anti-TNF-α agents to another biologic with a different mechanism of action.

Although biologic drugs demonstrated large improvements in the treatment of JIA, their long-term safety still needs to be established.[154] The safety concerns with biologics raised by health authorities and in the literature include development of malignancies and autoimmune disorders. There is also concern of an increased risk of opportunistic infections. It is believed that reducing the structural lesions that affect functional status may reduce disability and its impact on

activities of daily living, the need for knee/hip replacement surgery, the need for stem cell transplantations and other future events.[1, 6, 7, 10, 17] As previously mentioned, however, long term benefits still need to be established. These are important to determine in order to better predict long-term outcomes for those who can tolerate and respond to therapy, as well as to understand the long-term consequences for those patients that may not be able to continue the treatment with the drug for long periods due to loss of efficacy or intolerance. The short-term clinical outcomes measured in the studies to date do not permit extrapolations to the longer-term.

For most biologics (except etanercept and infliximab), only one study is available and in a relatively small sample of patients, which means that the results have not yet been confirmed in other studies. The evidence was nevertheless reviewed, as treatments that may avoid or reduce future functional disability with their social and quality of life implications are very important.

Annual treatment costs with biologics are high and in the range of C$14,000 to C$19,000 depending on the drug and dose used (a 40 kg patient was used in the base case). Payers of biologics vary by drug and patient and may include the hospital, the Ministry of Health or other publicly-funded programs (such as the Trillium program), private drug insurance plans or the patient's family. Given the high annual costs, a co-payment as low as 10% is not negligible to families, especially given the additional burden of caring for a child with JIA. For example, in the more severe cases, one of the parents may not be able to work, or may have to work less.[22] In the cost analyses it was assumed that unused portions of the medication vials would be discarded. The use of formulations that permit vial reuse may reduce treatment costs.

The use of biologics has the potential for a considerable budget impact across payers at the provincial level. Approximations indicate a C$2 million to C$10 million annual cost for Ontario, depending on prevalence.

The economic models were based on the best evidence currently available. In order to account for the uncertainties involved, extensive sensitivity analyses were conducted using different scenarios. The economic evaluation was limited by the use of a short-term time horizon (one year). The magnitude of uncertainties in parameter estimates beyond this time frame was too great to allow for further meaningful extrapolations. Due to a lack of measurement of utilities in children and of reliable ways to derive utilities from other clinical outcomes, a cost-utility analysis was not possible. ICERs were therefore based on the incremental cost per additional treatment

responder. Although meaningful for clinical decision-makers in this field, this outcome poses a challenge in the comparison to other studies and thresholds for resource allocation decisions.

Given the potential for a significant cumulative budget impact as well as the potential for improvement in long-term patient outcomes with these drugs, more comprehensive economic evaluations should be undertaken once long-term clinically relevant outcomes such as functional disability and quality of life can be more accurately estimated. Concerns with long-term safety of biologics have been raised and should also be taken into account in future analyses.

Economic analyses in pediatric patients are generally more challenging than in adult patients in that there is less clinical evidence, the evidence applies to shorter time-frames and has greater imprecision (small sample sizes) compared to adult studies. Clinical studies in children are challenging as there is generally only a small number of patients available for study, and chronic diseases are relatively rare. Innovative methods recently designed for evaluating treatment effects in rare diseases include Bayesian designs,[155, 156] randomized placebo phase designs,[157] and 'n of 1' trials[158-160] which may improve the quality of data available for pediatric research.

5 CONCLUSIONS

The current evidence shows that a short-term improvement in treatment response is achieved when patients with polyarticular JIA with an inadequate response to conventional treatment are treated with biologic agents. It is believed that better control of the disease may result in improvement in important long-term clinical outcomes, such as functional disability, which may affect social functioning, employment, and quality of life. Such long-term data, however, is not presently available. Disease registries may provide additional evidence on clinical benefits and safety issues in patients treated with these drugs.

Along with a potential for improvement in important long-term clinical outcomes in some patients comes a potential for a substantial budget impact for payers given the cost of treatment, the number of patients that may need treatment and the length of treatment. Moreover, important long-term safety concerns have also been raised. All these factors need to be taken into account and should be further evaluated.

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