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

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CONFLICTS OF INTEREST
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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 (see report appendices).

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 and the absence of ≥ 30% worsening in more than one variable. Other

1 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-
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 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

reactive protein (measure of inflammation), Functional assessment (Child Health Assessment Questionnaire, CHAQ)
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.