Access to Biologic Therapies in Canada for Children with Juvenile Idiopathic Arthritis

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ABSTRACT. ***Objective.*** To compare access to biologic therapies for children with juvenile idiopathic arthritis (JIA) across Canada, and to identify differences in provincial regulations and criteria for access.

Methods. Between June and August 2010, we compiled the provincial guidelines for reimbursement of biologic drugs for children with JIA and conducted a multicenter Canada-wide survey of pediatric rheumatologists to determine their experience with accessing biologic therapies for their patients.

Results. There were significant difficulties accessing biologic treatments other than etanercept and abatacept for children. There were large discrepancies in the access criteria and coverage of biologic agents across provinces, notably with age restrictions for younger children.

Conclusion. Canadian children with JIA may not receive optimal internationally recognized "standard" care because pediatric coverage for biologic drugs through provincial formularies is limited and inconsistent across the country. There is urgent need for public policy to improve access to biologic therapies for these children to ensure optimal short-term and longterm health outcomes. (First Release Aug 1 2012; J Rheumatol 2012;39:1875–9; doi:10.3899/jrheum.120089)

Key Indexing Terms:
JUVENILE IDIOPATHIC ARTHRITIS
DRUG ACCESSIBILITY
BIOLOGIC PRODUCTS
CANADA

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Supported by the Canadian Rheumatology Association summer student scholarship program.

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Accepted for publication June 18, 2012.

Juvenile idiopathic arthritis (JIA) can be associated with short-term and longterm morbidity. While many children respond to standard therapies [nonsteroidal antiinflammatory drugs (NSAID), corticosteroids, and disease-modifying antirheumatic drugs (DMARD)], some do not, and risk joint damage, functional limitations, and lower quality of life. As with adults, treatment with newer biologic agents may provide an effective alternative for children with recalcitrant arthritis.

Trials in JIA demonstrate efficacy for anti-tumor necrosis factor (TNF) agents (etanercept, infliximab, adalimumab), anti-interleukin 1 (IL-1; anakinra), anti-IL-6 (tocilizumab), and T cell co-stimulation inhibitor (abatacept)[1,2,3,4,5,6,7,8,9,10]. In Canada, healthcare and financial reimbursement for formulary drugs is a provincial responsibility. For new drugs to be covered, Health Canada's Health Products and Food Branch must first license them. The Canadian Expert Drug Advisory Committee evaluates each medication, and provides recommendations to provincial governments under the Common Drug Review (www.cadth.ca). Each province has a separate authorization system for drug formulary approval and financial coverage; consequently, there can be variations in availability. First Nations/Inuit children are covered through a separate federal program called Non-Insured Health Benefits (NIHB) for First Nations and Inuit, which can lead to discrepant coverage for those children.

Our aims were to compare access to biologics for JIA

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across Canada, and to identify provincial access criteria regulation differences.

MATERIALS AND METHODS

From June–August 2010, we assessed provincial guidelines for biologic reimbursement and conducted a Canada-wide survey of pediatric rheumatologists to determine JIA-specific access. Data were collected regarding access to biologics for other rheumatic diseases but not presented.

A standardized questionnaire (Appendix 1) was used to document criteria for biologics coverage from provincial drug reimbursement programs. We retrieved information from 11 provincial/territorial Websites and contacted a respective Ministry of Health consultant for data verification.

A second questionnaire (Appendix 2) was completed by telephone interview or e-mail by a representative pediatric rheumatologist from 12 Canadian academic hospitals with a pediatric rheumatology service to obtain center-specific data. For each biologic agent, respondents were asked under what circumstances provincial reimbursement was available, and the success rate and ease of application. Each completed questionnaire was returned to the corresponding center for data verification. Most provinces were represented by 1 center (British Columbia, Saskatchewan, Manitoba, Nova Scotia, and Newfoundland and Labrador); Alberta and Quebec each had 2; Ontario had 3. Nova Scotia reported for the Maritimes (Nova Scotia, New Brunswick, Prince Edward Island), and British Columbia for Yukon. Because patient-specific information was not required, the study was not submitted for ethics approval. The questionnaires were not beta-tested, but were approved by the steering group (CL, AB, BL, LT).

Analysis. Data were summarized by province; descriptive statistics were calculated as appropriate.

RESULTS

Provincial government information. Provincial drug advisory committees include 1–16 members with expertise primarily in pharmacology, health economics, and medicine. Few committees consult rheumatologists; none consult pediatric rheumatologists. Once approved, a biologic enters the provincial formulary under Special Authorization Status designated "Listed-Case by Case" (Listed-CBC). Accessing an approved biologic involves completion of a province-specific standard application form by prescribing rheumatologists. Biologics not Listed-CBC may be approved on a case-by-case basis, which frequently requires a supportive comprehensive letter and written and verbal lobbying.

Table 1 summarizes provincial formulary coverage of biologics for JIA across Canada. Those most frequently approved were etanercept and abatacept. Etanercept was approved for JIA in 9 provinces, but 5 were limited to polyarticular subtypes. Five provinces restricted approval to patients older than 5 years, and 4 provinces approved initial treatment for only 6 months. Although 8 provinces approved abatacept, 5 limited initial treatment to 16 weeks, 6 required a minimum age of 6 years and prior etanercept failure, and 3 approved treatment of only polyarticular JIA. Infliximab was approved in 2 provincial formularies. Other biologics coverage was either unavailable or reviewed after special application. Reimbursement was terminated in all cases if the patient left the province. The percentage of cost covered varied by province, drug plan, and family socioeconomic status.

Pediatric rheumatology center survey. Twelve of 13 pediatric rheumatology centers in Canada participated, representing all provinces and 1 territory. Center-specific biologics coverage for JIA and JIA-related uveitis is presented in Table 2. Etanercept was reimbursed across all rheumatology centers, but only for polyarticular JIA in 8 centers. Applications for coverage of infliximab (8 provinces) and adalimumab (6 provinces) were approved, primarily for JIA and JIA-associated uveitis, in 7 and 5 provinces, respectively.

Nine centers in 6 provinces reported successful access to anakinra, primarily for systemic JIA. No center applied for certolizumab pegol, golimumab, or tocilizumab.

Overall, the application process was believed to be acceptable, but approval took 1 week to 1 year and many application forms were designed for adult rheumatic diseases, making pediatric applications challenging.

DISCUSSION

We provide evidence of difficulty in accessing biologics for Canadian children with JIA, and considerable differences in provincial access criteria. Although biologics are now part of standard care for JIA, only 2, etanercept and abatacept, have a specific indication listing for JIA (Health Canada approval). Not surprisingly, those 2 biologics were most commonly approved on most but not all provincial formularies, and access was often restricted based on a child's age and JIA subtype (polyarticular JIA). We found minimal availability of other biologics for JIA, despite extensive evidence supporting their use[4,5,6,7]. The American College of Rheumatology recently published JIA treatment recommendations based on all published evidence, not only placebo-controlled studies[8]. According to those recommendations, 1 or more anti-TNF agents should be considered for any JIA subtype refractory to standard therapies; abatacept for children failing other biologics; and anakinra for systemic JIA unresponsive to corticosteroids. We found no province listing anakinra for JIA, and 40% refused coverage even by special request.

We discovered significant discrepancies in biologic coverage between provinces, including differences in approved agents, and criteria for coverage. In several provinces, children under age 6 years were not approved for biologics; in most provinces etanercept and/or abatacept were approved only for polyarticular JIA. Children with few, severely affected joints were ineligible. Additional discrepancies included duration of initial coverage and percentage of costs covered (data not included). Several provincial guidelines used "juvenile 'rheumatoid' arthritis," which is not currently accepted international terminology.

Similar to findings for adult patients with ankylosing spondylitis (AS), research shows anti-TNF agents are safe and effective for enthesitis-related arthritis (ERA) refractory to NSAID and DMARD[9,10]. Arthritis Consumer Experts (ACE; www.jointhealth.org), a Canadian patient advocacy

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Table 1. Biologics coverage for pediatric rheumatic disease: provincial government regulations. No disease other than juvenile idiopathic arthritis (JIA) was covered.

Province	Etanercept Status	Etanercept Disease Approved	Infliximab Status	Infliximab Disease Approved	Abatacept Status	Abatacept Disease Approved	Adalimumab Status	Anakinra Status	Rituximab Status	Tocilizumab Status
BC	Listed-CBC	All JIA	Listed-CBC	All JIA	Listed-CBC	All JIA	CBC	CBC	CBC	No
YK	CBC		CBC		CBC		CBC	CBC	CBC	No
AB	Listed-CBC	PJRA	No		Listed-CBC	PJIA	No	No	No	No
SK	Listed-CBC	JIA	CBC		Listed-CBC	JIA	CBC	CBC	CBC	No
MB	CBC		CBC		CBC		CBC	CBC	CBC	No
ON	Listed-CBC	PJIA	CBC		CBC		CBC	CBC	CBC	CBC
QC	Listed-CBC	PJIA or SJIA	Listed-CBC	PJIA or SJIA	Listed-CBC	PJIA or SJIA	CBC	No	CBC	CBC
NB	Listed-CBC	PJRA	CBC		Listed-CBC	PJIA	CBC	No	CBC	No
NS	Listed-CBC	PJRA	CBC		Listed-CBC	JIA	CBC	CBC	CBC	No
PEI	Listed-CBC	JRA	No		Listed-CBC	JIA	No	No	No	No
NFLD	Listed-CBC	PJRA	CBC		Listed-CBC	PJIA	CBC	CBC	CBC	CBC

Listed-CBC: listed in provincial formulary and reviewed on a case-by-case basis; CBC: not listed but considered by special request on a case-by-case basis; No: not listed and not considered on case-by-case basis; PJIA/PJRA: polyarticular subtype of juvenile idiopathic arthritis; SJIA: systemic-onset juvenile arthritis; BC: British Columbia; YK: Yukon; AB: Alberta; SK: Saskatchewan; MB: Manitoba; ON: Ontario; QC: Quebec; NB: New Brunswick; NS: Nova Scotia; PEI: Prince Edward Island; NFLD: Newfoundland and Labrador.

Table 2. Biologics for juvenile idiopathic arthritis (JIA) and uveitis: pediatric rheumatology centers' experience.

Center Province	Etanercept Applied	Etanercept Approved	Infliximab Applied	Infliximab Approved	Adalimumab Applied	Adalimumab Approved	Abatacept Applied	Abatacept Approved	Anakinra Applied	Anakinra Approved	Rituximab Applied	Rituximab Approved
BC	Yes	Yes: All JIA; U	Yes	† Yes: All JIA; U	Yes	Yes: JIA, U	No		Yes	Yes: SJIA	Yes	Non-JIA†
YK	Yes	Yes: PA	No		No		No		No		No	
Edmonton, AB	Yes	Yes: PJIA	Yes	No: PJIA, U, ERA	Yes	No: PJIA, U	No		Yes	No: SJIA	Yes	No†
Calgary, AB	Yes	Yes: PJIA	Yes	No: U	No		No		Yes	No: SJIA	Yes	No
SK	Yes	Yes: All JIA	Yes	Yes: OJIA, PJIA, U	Yes	Yes: PJIA	Yes	Yes: PA	Yes	Yes: SJIA	No	
MB	Yes	Yes: PJIA SJIA, U	Yes	Yes: U	Yes	Yes: U	No		Yes	Yes: SJIA	No	
Toronto, ON	Yes	Yes: PA ERA, refractory OJIA	Yes	Yes: PA, ERA, U	Yes	Yes: PJIA, ERA*	Yes	Yes: PA	Yes	Yes: SJIA	Yes	Yes: PJIA**
Ottawa, ON	Yes	Yes: PA	Yes	Yes: U	Yes	Yes: U	No		Yes	Yes: SJIA	Yes	Non-JIA
Hamilton, ON	Yes	Yes: All JIA	Yes	Yes: JIA, ERA, U	No		No		Yes	Yes: SJIA	No	
Montreal, QC	Yes	Yes: PA OJIA* ERA*	Yes	Yes: PA, U	Yes	Yes††: PA & U	No		Yes	Yes: SJIA#	No	†
Quebec, QC	Yes	Yes: EOJIA PsJIA, PA	Yes	Yes: PJIA	Yes	Yes: EOJIA, PA, U	No		Yes	Yes: SJIA	No	
NB	Yes	Yes: PA	Yes	Yes: JIA	No		No		Yes	Yes: SJIA	No	†
NS	Yes	Yes: PA	Yes	Yes: JIA	No		No		No		No	†
PEI	Yes	Yes: PA	No		No		No		No		No	†
NFLD	Yes	Yes: PJIA	No		No		Yes	Yes: RF PJIA	No		No	

* Difficult to get coverage for OJIA and ERA. † Admitted patient, children's hospital covers infusion. †† Patient must also have uveitis. ** Sometimes approved. # Difficult application process. PA: polyarticular arthritis; PJIA: polyarticular JIA; OJIA: oligoarticular JIA: EOJIA: extended oligoarticular JIA; SJIA: systemic JIA; PsJIA: psoriatic JIA: ERA: enthesitis-related arthritis; U: uveitis; Non-JIA: other rheumatic diseases.

organization, annually produces a biologics formulary report for rheumatoid arthritis, AS, and psoriatic arthritis. The November 2011 ACE report listed etanercept, adalimumab, and infliximab for AS in almost all provinces. We noted that children with ERA or juvenile AS were rarely eligible for these medications, and a laborious approval process was involved.

Treatment of chronic primary or JIA-associated uveitis with biologics can be very effective[11,12]. No Canadian province listed infliximab or adalimumab for this indication

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and less than half the provinces covered these case by case. In other serious childhood rheumatic diseases, biologics can be lifesaving[13,14,15,16]. We noted limited biologics coverage for these conditions (data not shown).

There are limitations to our study. We did not explore biologics coverage for First Nations people, Inuit, or those living in the Northwest Territories or Nunavut. Surveyed pediatric rheumatologists (data not included) suggested the NIHB approval process was difficult. We did not assess contributions from private insurance plans, research studies, compassionate release, hospitals, or charitable foundations. Our study dealt specifically with drug access in Canada, which may limit generalizability; however, limited access is likely in other countries based on the orphan status of JIA and biologic drug expense.

The high costs of biologics are likely a primary disincentive for provinces to provide better biologics access for children with JIA. Research demonstrating cost-benefits from biologics-related early remission of JIA may be necessary to convince provincial payers of their importance. Pediatric rheumatologists and provincial health authorities should collaborate to develop suitable biologic access criteria.

Biologics coverage through provincial formularies is limited and inconsistent across Canada. There is an urgent need for public policy to improve access to biologics to ensure pediatric rheumatologists in Canada can provide what is considered the international standard of care for JIA and to optimize health outcomes.

APPENDIX 1. Access to biologics coverage in Canada for pediatric rheumatology study:
Provincial Government Questionnaire

Part A: Application process
1. Are pediatric rheumatologists provided with specific application forms to request financial reimbursement for their patients requiring biologic agents?
   a. Is the form generic for all ages (adult and youth) or is it specific for the pediatric age group?
      i. [If generic:] Have you considered creating a pediatric form?
   b. Is the form electronic?
      i. [If no] Have you considered creating an electronic form?
2. For patients with extended health benefits, is provincial government approval required first before receiving private insurance coverage?
3. Is there a panel of experts that is commissioned to review all rheumatology requests for biologic agents?
4. If so, how many people are on this panel?
5. What is the professional make up of the personnel sitting on the panel?
      i. If there are physicians, what (if any) is their specialty?

Part B: Official provincial policy regarding drug and disease-specific coverage
1. Does your province provide coverage for each of the biologic drugs listed below for pediatric rheumatology patients?
abatacept (Orencia); etanercept (Enbrel); tocilizumab (Actemra); adalimumab (Humira); infliximab (Remicade); golimumab (Simponi); anakinra (Kineret); rituximab (Rituxan); certolizumab pegol (Cimzia)
2. [If yes] What criteria must be met in granting such coverage?
   a. Of the pediatric rheumatic diseases listed below, which biologic agent is granted coverage? JIA: Oligoarticular, Polyarticular, Psoriatic, Enthesitis-related, systemic; Lupus; Inflammatory myopathies; Systemic sclerosis; Vasculitis; Autoinflammatory conditions
   b. Is there an age limitation associated with coverage?
   c. Is there a minimum number of affected joints required in order to receive coverage of a specific biologic medication?
   d. Are prior treatment failures required before provincial government coverage is granted? If so please specify.
   e. Are there any other conditions required before coverage is granted?
3. When coverage for a biologic agent is granted, for a particular rheumatic diagnosis:
   a. What percentage of the total drug cost is covered?
   b. What is the duration for which the biologic agent is reimbursed without requiring an application renewal?

4. What is the renewal process for biologic coverage?
   a. Is the process similar to the first application? If not, how does it differ?
5. Are there criteria for terminating biologic coverage, such as becoming an adult or relocating to another province? If so:
   a. What are the criteria for termination?
   b. For which diagnoses do these criteria apply?

APPENDIX 2. Access to biologics coverage in Canada for pediatric rheumatology study: Rheumatologists' questionnaire
1. What types of documents are required for application to your provincial government for biologic coverage (e.g.: generic government form, individual patient letters, other)?
2. Is the required document specific and appropriate for pediatric rheumatology patients? Please explain.
3. What format is used to submit these documents (e.g.: fax, e-mail, mail, electronic form, other)?
   a. Is this your/your group's preferred format? If not which format would be better?
4. If your provincial government does not cover a certain biologic for a particular rheumatic disease, what other sources (other than private insurance) can be accessed to provide coverage for your patients?
5. For patients with extended health benefits, is provincial government application required first before private insurance coverage is considered?
   YES ? NO ? DON'T KNOW ?
6. Please add any other suggestions to improve the application form or process
7. Of the following biologics, which would you most like to be reimbursed by your provincial government that is not already covered? Abatacept (Orencia); etanercept (Enbrel); tocilizumab (Actemra); adalimumab (Humira); infliximab (Remicade); golimumab (Simponi); anakinra (Kineret); rituximab (Rituxan); certolizumab pegol (Cimzia); Other: ____
8. When your provincial government does grant coverage:
   a. What percentage of the total drug cost is covered?
   b. What is the duration of time for which the biologic agent is covered without requiring a renewal application? If the answer varies for different biologics, please specify this variation.
9. What is the renewal process for biologic coverage in your province?
   a. Is the amount of work involved similar to the first application? If not, how does it differ?
10. Does your provincial government have criteria for terminating biologic coverage, such as becoming an adult or relocating to another province?
   YES ? NO ? DON'T KNOW ?
If yes, what are the criteria for termination?

Part B: Your/your pediatric rheumatology group's experience requesting provincial coverage for biologics
Biologic agents: abatacept (Orencia); adalimumab (Humira); anakinra (Kineret); etanercept (Enbrel); infliximab (Remicade); rituximab

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(Rituxan); tocilizumab (Actemra); golimumab (Simponi); certolizumab pegol (Cimzia)

Rheumatic diseases: Juvenile Idiopathic Arthritis: oligoarthritis, RF-negative polyarthritis, RF-positive polyarthritis, psoriatic arthritis, enthesitis-related arthritis, systemic onset JIA, undifferentiated JIA; Chronic uveitis; Systemic lupus erythematosus; Juvenile dermatomyositis; Polymyositis; Systemic sclerosis; Other connective tissue diseases; Vasculitis; Other diseases (e.g.: periodic fever syndromes, chronic inflammatory disorders)

1. For which of the listed biologic agents have you/your group ever requested provincial government coverage?

a. For each biologic, for which of the listed diseases were the applications submitted? For JIA applications, please indicate the JIA subtype(s) if known.

2. For each biologic and for each disease selected in question 1

a. Please estimate if applications are approved for provincial coverage: a. None of the time; b. Rarely or under exceptional circumstances; c. Some of the time; d. Most of the time; e. All of the time

b. Where the answer is not "all of the time," please explain why.

3. For each biologic agent selected in question 1, are any subtypes of JIA not covered in the same way as other subtype(s)?

YES ? NO ? DON'T KNOW ?

If yes: a. Which subtypes are not similarly covered? b. Have you ever been able to get coverage for these subtypes? c. How does the application process differ for these subtypes? That is, what extra work is required in order to apply for and/or receive coverage for these patients?

4. Please estimate the amount of time required to complete the first application to your provincial government. a. Outline what processes are included in this time estimate. b. If the answer varies for different biologic agents and/or different diseases, please specify this variation.

5. Please estimate how many written communications (besides the first application form or letter) you/your group have sent to the provincial government per patient before coverage was granted (or, if coverage is never granted, how many are sent before the final decision is rendered). a. If the answer varies for different biologic agents and/or different diseases, please specify this variation

6. Please estimate how many phone calls you/your group have placed to your provincial government before coverage was granted (or, if coverage was never granted, how many calls were placed before the final decision was rendered).

a. If the answer varies for different biologic agents and/or different diseases, please specify this variation

7. Please estimate how much time is taken from submission of the first application to acceptance (or, if coverage was never granted, please estimate the duration before the final decision was rendered.)

a. If the answer varies for different biologic agents and/or different diseases, please specify this variation.

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