The Hospital for Sick Children

Technology Assessment at SickKids (TASK)

THE ECONOMIC EVALUATION OF EARLY INTERVENTION WITH ANTI-TUMOR NECROSIS FACTOR-α TREATMENTS IN PEDIATRIC CROHN'S DISEASE

Report No. 2019-01

Date: February 26, 2019

REPORT HIGHLIGHTS

The Report Highlights consists of a summary of the full report with the same name and should be evaluated in conjunction with the full report. Full documents are available for download at:

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Acknowledgements

This research was generously supported by the Hospital for Sick Children Restracomp Doctoral Scholarship, the University of Toronto, Institute of Health Policy, Management and Evaluation Graduate Fellowship, Eugene Vayda Award, Dr. Robert Duff Barron Graduate Scholarship in Public Health Policy Award, Doctoral Completion Award, the IHPME Travel Award, the Canadian Federation of University Women (CFUW) Dr. Alice B. Wilson Award, the Canadian Institutes of Health Research (CIHR) operating grant (#137137) to W. Ungar, the Ontario Ministry of Health Drug Innovation Fund Grant No. 2010-001, the CIHR Travel Award, and the Genome Canada Conference Travel Award.

Thanks to the RISK Cohort Study in Crohn's Disease Consortium for the use of the RISK-PROKIIDS dataset. Thanks to Dr. Mary-Ellen Hogan, Mr. Austin Nam, Dr. Petros Pechlivanoglou, Dr. Peter Austin, Dr. Jan Barnsley and Dr. Eleanor Pullenayegum for their help and suggestions in tackling this project. Thanks also to Dr. David Naimark, Dr. Lusine Abrahamyan, Dr. Beate Sander, Dr. Walter Wodchis, Dr. Wanrudee Isaranuwatchai, Dr. Murray Krahn, Dr. Myla Moretti, and Ms. Kate Tsiplova for their insight.

Introduction

Crohn's disease (CD) is a chronic gastrointestinal disorder affecting children and adults, in which sections of the gastrointestinal tract become inflamed and ulcerated through an abnormal response of the body's immune system.[1] The incidence of CD among children is increasing in Canada[2], but there is a lack of high quality studies comparing treatments. There is a keen interest to introduce effective treatment as early as possible and to maintain remission for as long as possible because of the lifelong burden of disease and its sustained impact on quality-of-life for children and their families.[3-6] In pediatric CD, costly anti-tumor necrosis factor-α (anti-TNF-α) biological treatments are indicated only after other treatments have not worked. However, several studies suggest that treatment with anti-TNF-α early in the treatment course may be better at achieving remission than traditional strategies.[7, 8] and therefore have been proposed as first line therapy due to their effectiveness. One review concluded that there was insufficient evidence to draw any conclusions on the cost-benefits of a top-down or early treatment strategy[9] while another found that biological treatments were cost-effective in certain situations[10]. To date there have been no economic evaluations comparing the early use of anti-TNF-α treatments to the traditional "step-up" strategy (standard care) in pediatric CD.

Key Messages

- From a public healthcare perspective, early anti-TNF-α intervention was on average more costly than the standard care intervention over three years by CAD$31,112(95%CI: 2,939, 91,715). Early anti-TNF-α intervention was also on average more effective with 11.3 (95%CI: 10.60, 11.59) more weeks in steroid-free medical remission. The incremental cost per steroid-free remission week gained was CAD$2,756 for the early anti-TNF-α intervention.

- From a societal perspective, the incremental cost per additional steroid-free remission week was $2,968 for the early anti-TNF-α intervention. The societal perspective had the same outcome measures and only a marginal increase in cost than the healthcare public payer perspective.

- While unknown, if a willingness-to-pay threshold was assumed to be $2,500 per week in steroid-free remission, early intervention with anti-TNF-α would not be cost-effective from a healthcare payer perspective. Above a willingness to pay threshold of CAD$3,500, the early anti-TNF-α intervention becomes increasingly cost-effective compared to standard (step-up) care and above a willingness-to-pay of CAD$6,000 per week in steroid-free remission, the early anti-TNF-α intervention becomes the dominant strategy. There is considerable uncertainty in the incremental cost-effectiveness ratio and many patients escalate to anti-TNF-α eventually. Therefore, restrictive policies and delays in anti-TNF-α treatment access for pediatric Crohn's patients may want to be re-visited by decision makers.

Objectives

The primary objective of this study will be to determine the incremental cost-effectiveness of early intervention with anti-TNF-α treatment with or without concomitant immunomodulators and with or without steroid induction (top-down approach), compared to the conventional step-up strategy consisting of corticosteroid (or enteral nutrition) induction followed by maintenance treatment with immunomodulators and the introduction of anti-TNF-α treatment after 3 months in moderate-to-severe pediatric CD from public healthcare and societal payer perspectives over a three-year time horizon.

Methods

A two-dimensional probabilistic microsimulation Markov model with seven health states was constructed for children with moderate to severe Crohn's disease (Figure 1). Newly-diagnosed children with Crohn's disease aged 4-17 years who received anti-TNF-α treatment and other concomitant treatments, such as steroids and immunomodulators, within the first three months of diagnosis were compared to children with newly-diagnosed Crohn's disease who received standard care of steroids and/or immunomodulators with the possibility of anti-TNF-α treatment only after three months of diagnosis. The primary outcome measure was weeks in steroid-free remission. The secondary outcome was weeks in remission irrespective of steroid use. The time horizon was three years. A public healthcare payer perspective (Ontario, Canada) and a societal payer perspective were taken. A scenario analysis examined variation in costs of anti-TNF-α treatment. A large, North American multi-centre, observational study of 573 children with Crohn's disease (the RISK-PROKIIDS Study)[11] provided input into clinical outcomes and health care resource use. To reduce selection bias, propensity score matching was used to create comparator groups with 237 standard care subjects and 123 early anti-TNF-α intervention subjects. The health state for each patient visit was based on the determined weighted Pediatric Crohn's Disease Activity Index (wPCDAI) score, or on Physician Global Assessment (PGA) values if wPCDAI was indeterminable. These data were supplemented by other published literature. A one-week cycle length was modelled to reflect the approximate minimum time within a health state. Transition probabilities of moving between health states are shown in Table 1. Direct healthcare costs, assumed by the public healthcare payer, included all intervention costs, physician services, and hospitalizations (Table 2). Costs from a societal perspective included all healthcare payer costs and costs associated with caregiver time losses (indirect costs). Cost-effectiveness acceptability curves (CEACs) reflected uncertainty in the model. The model was validated against other small studies using the parameters of number of remissions at one year and number of surgeries in three years.

Results

Characteristics and Outcomes in the Matched Patient Population

Patient and disease characteristics at diagnosis are listed in Table 3. Health status at 6, 12, 18, 24, and 36 months post diagnosis was determined for each comparator group in the propensity matched RISK-PROKIIDS population and is shown in Table 4. At six months, in the matched early anti-TNF-α group, 52.8.0% were in steroid-free remission at six months and in the standard care group, 39.2% were in steroid-free remission (p=0.019). Patients in the early anti-TNF-α group had a mean number of 3.98 steroid-free remission semesters and 3.61 consecutive steroid-free remission semesters over 36 months compared to the patients in the standard care group who had a mean number of 3.59 steroid-free remission semesters (p=0.036) and a mean number of 3.02 consecutive steroid-free remission semesters (p=0.003). The proportion of RISK-PROKIIDS patients within each comparator group taking each class of medication over the three-year period informed the total cost of drugs for each comparator group at a given time and are shown in Figure 2 (for the early anti-TNF-α biologic group) and Figure 3 (for the standard care group). In the standard care group 54% of patients were taking an anti-TNF-α by the end of the third year post-diagnosis.

Cost-effectiveness Analysis

The results of the cost-effectiveness analysis are summarized in Table 5. In the reference case, from a public healthcare perspective, early anti-TNF-α intervention was on average more costly than the standard care intervention over three years by CAD$31,112. Early anti-TNF-α intervention was also on average more effective with 11.3 more weeks in steroid-free medical remission. The incremental cost per steroid-free remission week gained was CAD$2,756 for the early anti-TNF-α intervention for the reference case from a healthcare payer perspective. The wide confidence interval for the incremental cost in Table 5 reflects the large range of costs incurred by individuals in each comparator arm. Higher costs were accrued by individuals that experienced surgeries, or multiple adverse events in either comparator group.

The cost-effectiveness analysis from the societal perspective was identical to the healthcare public payer perspective except for the addition of costs associated with caregiver productivity time losses. Therefore, the ICER from the societal perspective was slightly higher than that of the healthcare public payer perspective at CAD$2,968 per additional week gained in steroid-free remission for the early anti-TNF-α intervention group. From a societal perspective, early anti-TNF-α intervention was on average more costly

than the standard care intervention over three years by CAD$33,508 and on average more effective with 11.3 more weeks in steroid-free medical remission.

The cost-effectiveness model was also run comparing the two strategies using weeks in medical remission irrespective of steroid use as the outcome. Early anti-TNF-α intervention was more costly than the standard care intervention over three years by CAD$31,112 (95% CI: 2,939, 91,715) and more effective with an additional 6.65 (95% CI: 5.02, 7.00) weeks in medical remission. The incremental cost per additional medical remission week gained was CAD$4,679 for the early anti-TNF-α intervention from a healthcare payer perspective. This suggests that the early anti-TNF-α intervention may be steroid-sparing since there were additional steroid-free remission weeks gained with the early anti-TNF-α as opposed to just remission weeks.

Uncertainty Analysis

The cost-effectiveness acceptability curve from the 2-D microsimulation for the reference case from a healthcare payer perspective (Figure 4) is reflective of uncertainty in the ICER, and represents the proportion of microsimulations wherein each strategy is cost-effective (the dollar value of effectiveness exceeds the costs) over a range of willingness-to-pay thresholds. While an actual willingness-to-pay for a week in steroid-free remission is unknown, at a willingness-to-pay threshold of approximately CAD$3,500 per week in steroid-free remission, neither strategy is dominant over the other as both strategies are cost-effective 50% of the time. Above a willingness to pay threshold of CAD$3,500, the early anti-TNF-α intervention becomes increasingly cost-effective compared to standard care. Above a willingness-to-pay of CAD$6,000 per week in steroid-free remission, the early anti-TNF-α intervention becomes the dominant strategy. From a societal perspective, at a willingness-to-pay threshold of approximately CAD$5,000 per week in steroid-free remission, neither strategy was dominant over the other as both strategies were cost-effective 50% of the time.

The incremental cost of early anti-TNF-α treatment per additional steroid-free remission week gained compared to the standard care intervention using discount rates of 0% and 3% from a healthcare public perspective were CAD$2,740 and CAD$2,771 respectively, and from a societal perspective were CAD$2,954 and CAD$2,982 respectively. Varying the discount rates did not have a major effect on the ICER since the time horizon was only three years.

Scenario Analysis

Scenario analyses were conducted to examine how the cost of infliximab, the anti-TNF-α adoption rate in the step-up group, and the cost of immunomodulators affected the incremental cost-effectiveness ratio (ICER). It was hypothesized that the cost of anti-TNF-α treatment, particularly the cost of infliximab, could be a major source of the uncertainty in the ICER. Based on our model, an increase in the price of infliximab to 150% of its current price increased the ICER to CAD$4,782. Reducing the price of infliximab to 50% and 37.5% of its current price reduced the ICER to CAD$659 and CAD$143, respectively. Reducing the price of infliximab to 25% of its current price resulted in a savings of CAD$372 per additional steroid-free remission week gained. A similar one-way sensitivity analysis demonstrated that doubling or halving the costs of immunomodulators had a negligible effect on the ICER. Reducing the rate of switching to anti-TNF-α in the standard care group by 0.5x increased the ICER for the early anti-TNF-α strategy to CAD$3,175 and increasing the rate of switching to anti-TNF-α by increased the ICER only slightly to CAD$2,750. As expected, not switching to anti-TNF-α in the step-up group increased the ICER to CAD$6,291. The ICER was most sensitive to the price of infliximab compared to the other factors.

Discussion

This study represents the first cost-effectiveness analysis examining early intervention with anti-TNF-α treatment in treatment-naïve pediatric CD compared to standard care defined as traditional step-up therapy with biologics from both societal and healthcare system payer perspectives. It was found that from a public healthcare perspective, early anti-TNF-α intervention was on average more costly than the standard care intervention over three years by CAD$31,112, but more effective, with 11.3 more weeks in steroid-free medical remission resulting in an incremental cost per steroid-free remission week gained of CAD$2,756. From a societal perspective, the ICER was CAD$2,968 per additional week gained in steroid-free remission for the early anti-TNF-α intervention group.

This economic evaluation is novel in that it represents the current standard care of step-up therapy in which pediatric patients can be placed on anti-TNF-α treatment later in their course of treatment after trying other non-biologic treatments. Another unique feature was the use of steroid-free remission weeks rather than the number of patients in remission at a certain time as the primary outcome measure. Steroid-free remission weeks is particularly relevant for a pediatric population since steroids have been shown to affect growth and brain development in children.[12, 13] Our results suggested a steroid-sparing benefit, which is

particularly relevant for a pediatric population, with early anti-TNF-α treatment since there were 11.3 more weeks in steroid-free remission and only 6.7 more weeks in remission over three years compared to standard care.

In a review of economic evaluations in adult and pediatric inflammatory bowel disease, Jean et al., 2018 observed that no studies comparing biologic treatments to standard care in CD resulted in an ICER below a CAD$100,000 per quality adjusted life year (QALY) willingness-to-pay threshold in the Canadian setting which make it difficult to deem biologic treatments as cost-effective at this threshold despite clinical effectiveness.[14] Recent reviews of cost-effectiveness studies, predominantly in adults, of biological agents for the treatment of inflammatory bowel disease showed a wide range of costs per QALYs owing to the diverse outcomes, treatment paradigms and patient populations.[14-16] A review examining the efficacy of early anti-TNF-α treatment versus a step-up strategy for the treatment of Crohn's disease concluded that for pediatric patients, early treatment (top-down) demonstrated positive clinical outcomes in larger studies but were inconclusive in smaller studies, however only six studies were reviewed.[9] The only economic evaluation of biological treatments in pediatric CD, taking a public payer perspective, found that scheduled maintenance therapy with 5 mg/kg of infliximab was cost-effective, assuming a £30,000 per QALY willingness-to-pay threshold, compared to standard care in refractory pediatric CD patients.[17] In an adult study, from a Canadian perspective, comparing infliximab or adalimumab to non-anti-TNFα usual care in refractory adult CD patients over a five-year time horizon found that the cost per QALY gained for infliximab therapy compared with usual care was $222,955 with a 0.166 QALY gain.[18] Overall, research and evidence supporting top-down therapy remain limited in adult and pediatric CD, and further studies are needed to determine the most appropriate CD patients to receive a top-down treatment approach.[9]

The present study used a large multi-centre North American observational study with a comparatively large number of pediatric patients to inform model inputs to increase generalizability. The data were pragmatic and reflected actual clinical practice as opposed to a randomized controlled trial (RCT). The use of patient-level data in an individual microsimulation model allowed the sampling of a wide range of patient ages and health experiences over time as opposed to a cohort model.

A major research gap identified by our study is the lack of health utilities for the calculation of QALYs in children with CD resulting in the use of surrogate measures, such as adult CD utilities[19, 20] being used in cost-utility analyses in children.[9, 17] This points to the critical need to ascertain utilities for pediatric CD

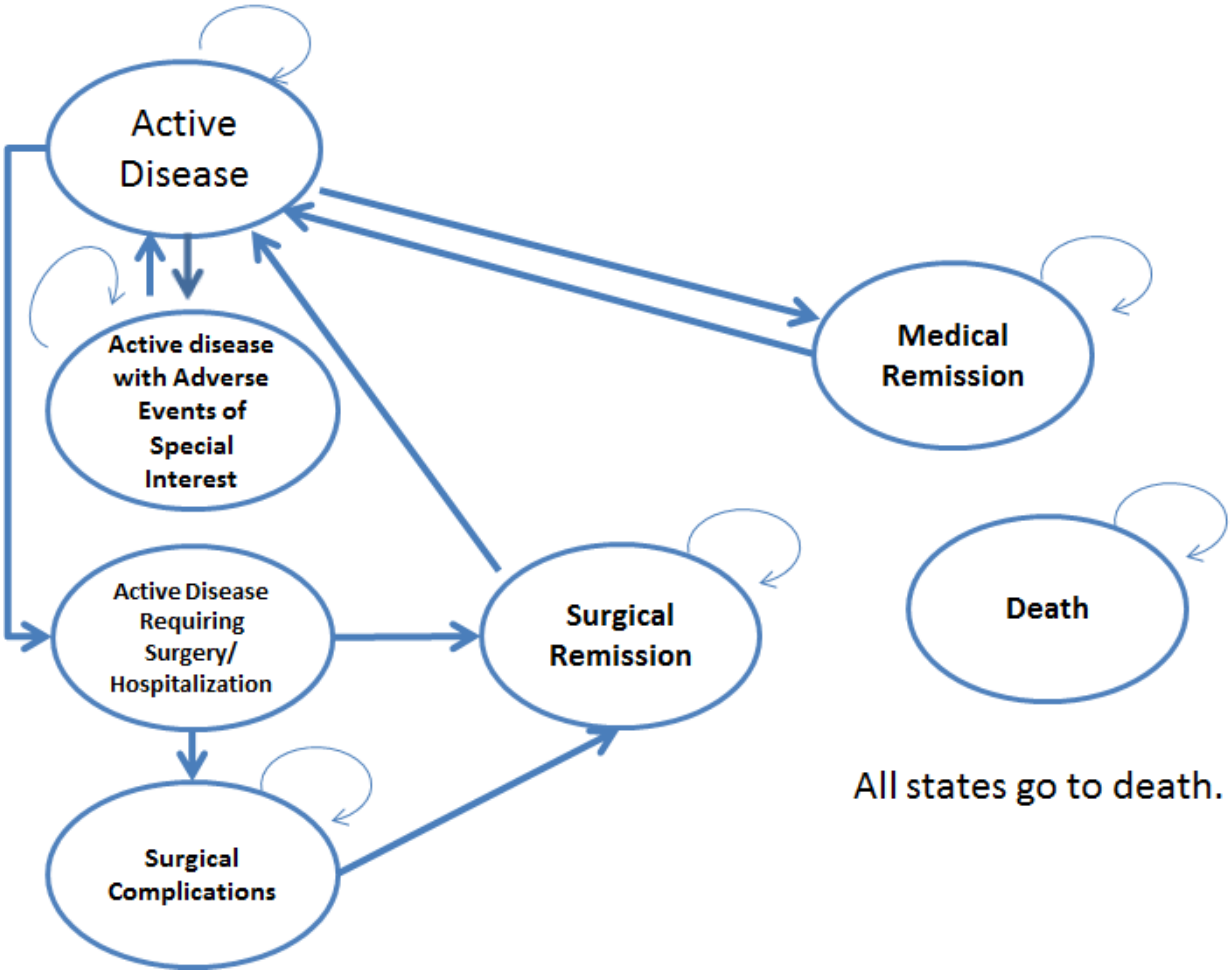
particularly since the disease can manifest itself slightly differently in adults and children as children are developing.[21] Eliciting generic pediatric health utilities can be a challenge in children since completing a standard gamble or time trade off task is limited by their developing cognitive abilities.[22] Nevertheless the determination of QALYs specific for children in CD will allow the comparison of CD treatments to treatments for other diseases so that treatments in pediatric CD can be evaluated more effectively in economic evaluations by policy makers making decisions about treatment coverage.[23]

A limitation of the study was that the study population may not reflect community or rural CD patients since all the recruiting sites were in major urban centers and mainly in academic teaching hospitals. While this study took a Canadian healthcare payer perspective, practice patterns may have been skewed towards U.S. practice since most of the sites were in the U.S. Upon close examination, there was no major difference between the health states and treatment patterns of Canadian and American RISK-PROKIIDS study patients. The entry of new biologics and biosimilars into the market was not included in the study and may affect the external validity of the study. However, the impact of changes in the prices of these agents was tested in the scenario analysis. Similarly, newer practices such as therapeutic drug monitoring were not included in the study, but these are not yet considered standard practice. The RISK-PROKIIDS patients moved frequently and unpredictably between active and remission phases of diseases. Hence, the number of people in steroid-free remission at any one time could vary and may not be an adequate endpoint on its own to measure efficacy of treatment. Multiple clinical endpoints should be considered and reported to avoid reporting bias. The absence of QALY's as the primary effectiveness measure limits the comparability of the treatments to other treatments. A limitation of this study may be that for a chronic life-long illness, a three-year time horizon is too short and a life time horizon would be more suitable. However, data beyond three years in newly-diagnosed children with CD prescribed anti-TNF-α treatments as first line therapy is very limited to reasonably inform a longer term model.

From a clinical management perspective, our results are supportive of the use of anti-TNF-α treatments within the first three months of diagnosis to improve clinical outcomes. However, due to public payer drug formularies, such as in Canada and the United Kingdom, restricting anti-TNF-α use to second line therapy and according to their licensed indications, it may be difficult to implement such a strategy since it would be considered off-label use. Nevertheless, policies should ensure that once treatment with anti-TNF-α is warranted, that it is accessed quickly and that administrative delays in processing and approving applications for special access and reimbursement are avoided as delays have been observed in Ontario.[24]

The purpose of this study was to provide additional rigorous evidence to support policy decision making regarding the use and timing of anti-TNF-α treatments for the treatment of moderate to severe pediatric CD. Cost-effectiveness analyses from both the public healthcare payer and societal perspectives provide a more comprehensive analysis of the costs and consequences involved in the management of pediatric CD with anti-TNF-α therapy. The uncertainty surrounding the ICER made it difficult to state unequivocally that early anti-TNF-α strategy was cost-effective compared to standard care particularly since the willingness-to-pay for a week in steroid-free remission is unknown. The results are nevertheless of value to drug plan decision makers since they show that early anti-TNF-α intervention can be clinically beneficial to children with CD and that the cost of anti-TNF-α is a major driver in its cost-effectiveness. Based on our model, infliximab would likely be cost-effective at 25% of its current Ontario price. Biosimilar infliximab (Inflectra®) is 53% of the cost of originator infliximab (Remicade®) in the Ontario Drug Formulary. Negotiating much lower costs for these treatments could ultimately benefit patients and payers.

Figure 1. The Health State Transition Diagram for Crohn's Disease.



Health states are shown in the ovals. Arrows show the direction of moving from one health state to another. The curved arrows indicate remaining in the same health state from one cycle to the next.

Table 1. Health State Transition Probabilities.

Event (Strategy)	Probability	SD	Time	Source (Reference)	Distribution for Probabilistic Analysis
Active Disease to Medical Remission (Early anti-TNF-α)	0.553	0.003	0 to 6 months	[11]	Beta
	0.396	0.004	6 to 12 months		
	0.500	0.005	12 to 18 months		
	0.400	0.006	18 to 24 months		
	0.355	0.007	24 to 30 months		
	0.529	0.007	30 to 36 months		
Active Disease to Medical Remission (Standard Care)	0.515	0.001	0 to 6 months	[11]	Beta
	0.452	0.002	6 to 12 months		
	0.495	0.002	12 to 18 months		
	0.526	0.003	18 to 24 months		
	0.467	0.003	24 to 30 months		
	0.507	0.004	30 to 36 months		
Continued Medical Remission (Early anti-TNF-α)	0.794	0.002	6 to 12 months	[11]	Beta
	0.747	0.002	12 to 18 months		
	0.899	0.001	18 to 24 months		
	0.828	0.002	24 to 30 months		
	0.843	0.002	30 to 36 months		
Continued Medical Remission (Standard Care)	0.680	0.002	6 to 12 months	[11]	Beta
	0.644	0.002	12 to 18 months		
	0.781	0.001	18 to 24 months		
	0.835	0.001	24 to 30 months		
	0.850	0.001	30 to 36 months		
Active Disease to Active Disease Requiring Surgery or Hospitalization (Early anti-TNF-α)	0.046	0.000	3 years	[11]	Beta
Active Disease to Active Disease Requiring Surgery or Hospitalization (Standard Care)	0.030	0.000	3 years	[11]	Beta
Surgical Remission to Active Disease (Early anti-TNF-α)	0.001	0.001	3 years	[11]	Beta
Surgical Remission to Active Disease (Standard Care)	0.000	0.000	3 years	[11]	Beta
Serious infection on corticosteroid	0.070	0.014	1 year	[25]	Beta
Serious infection on immunomodulator	0.033	0.007	1 year		
Serious infection on anti-TNF-α	0.032	0.006	1 year		
Lymphoma on anti-TNF-α	0.00021	0.000042	1 year		
Lymphoma on immunomodulator	0.00045	0.000090	1 year		
Antibody reaction on infliximab	0.00036	0.001	1 week	[26]	Beta
Surgical complications	0.058	0.002	1 week	[27]	Beta
Death from lymphoma (female)	0.000053	0.000011	1 year	[28]	Beta
Death from lymphoma (male)	0.000084	0.000017	1 year		

Table 2. Direct Costs of Treatments and Services.

Drug Generic Name (Brand name)	Price per Unit (CAD$), (SD)	Source (Reference)	Distribution for Probabilistic Analysis
Infliximab (Remicade®)	987.56 per 100 mg	[29]	Gamma
Adalimumab (Humira®)	769.97 per 40mg	[30]	Gamma
Azathioprine	0.24/50 mg	[30]	Gamma
Methotrexate oral 15mg/m2	0.63/2.5 mg	[30]	Gamma
Methotrexate subcutaneous or intramuscular 15mg/m2	8.92/50 mg	[30]	Gamma
6-mercaptopurine 1.125 mg/kg	2.86/50 mg	[30]	Gamma
Folate supplement	0.03/ 5 mg	[30]	Gamma
Methylprednisone	0.46/ 4 mg	[30]	Gamma
Hydrocortisone	0.36/ 20 mg	[30]	Gamma
Prednisone/Prednisolone	0.02/5 mg	[30]	Gamma
Budesonide	1.90/3mg	[31]	Gamma
Ciprofloxacin	0.62/ 250 mg	[30]	Gamma
Rifaxamin	7.76	[30]	Gamma
Metronidazole	0.06	[30]	Gamma
Mesalazine	0.40/ 400 mg	[30]	Gamma
Sulfasalazine	0.28/ 500 mg	[30]	Gamma
Olsalazine	0.53/250 mg	[30]	Gamma
Gastroenterologist initial consultation	165.50/visit	[32]	Fixed
Gastroenterologist assessment	79.85/visit	[32]	Fixed
Gastroenterologist subsequent visits	31.00/visit	[32]	Fixed
Physician services (supervision of intravenous administration of biologic agents)	54.25/session	[32]	Fixed
Lab Tuberculosis test (IGRA blood test)	90/test	[33]	Fixed
Chest X-ray (screening for tuberculosis in hospital ambulatory care)	162/procedure (101)	[34]	Gamma
Surgery (surgical resection)	22,889/procedure (23,751)	[34]	Gamma
Non-surgical hospitalization	8,172/procedure (7,506)	[34]	Gamma
Colonoscopy	1,488/procedure (824)	[34]	Gamma
Gastroscopy	1,823/procedure (848)	[34]	Gamma
Lymphoma treatment	51,713/treatment (85,454)	[34]	Gamma
Opportunistic infection treatment	5,174/treatment (14,414)	[34]	Gamma
Sepsis treatment	14,168/treatment (29,050)	[34]	Gamma
Infusion labour, nursing time, 170 minutes	48.06/session (16.39)	[35]	Gamma
Infusion supplies	47.91/session	[35]	Fixed

Abbreviations: CAD$ = Canadian dollars; SD=standard deviation

Table 3. Patient Characteristics in Propensity Matched RISK-PROKIIDS Comparator Groups.

Characteristic	Standard Care n=237 (%)	Early Intervention with Biologics n=123 (%)	P value
Sex = Female (%)	75 (31.6)	41 (33.3)	0.837
Age at diagnosis (years) (mean (sd))	12.27 (2.65)	12.28 (2.70)	0.964
Albumin g/dL (mean (sd))	3.46 (0.59)	3.43 (0.62)	0.717
Height Z score (mean (sd))	-0.38 (1.08)	-0.45 (1.21)	0.577
Family history of IBD (%)			0.164
No 1st degree relative	185 (78.1)	107 (87.0)	
One 1st degree relative	41 (17.3)	14 (11.4)	
Two 1st degree relatives	3 (1.3)	0 (0.0)	
Unknown	8 (3.4)	2 (1.6)	
Ethnicity (%)			0.335
Caucasian	176 (74.3)	88 (71.5)	
African	21 (8.9)	12 (9.8)	
Mixed	18 (7.6)	7 (5.7)	
Other	10 (4.2)	9 (7.3)	
Unknown	12 (5.1)	7 (5.7)	
Presence of Perianal Disease (%)			0.048*
No	169 (71.3)	72 (58.5)	
Yes	66 (27.8)	50 (40.7)	
Unknown	2 (0.8)	1 (0.8)	
Disease activity at diagnosis (Physician Global Assessment) (%)			0.235
None	3 (1.3)	0 (0.0)	
Mild	59 (24.9)	23 (18.7)	
Moderate	121 (51.1)	74 (60.2)	
Severe	54 (22.8)	26 (21.1)	
Disease location (%)			0.962
No L1 to L3 disease	0 (0.4)	1 (0.8)	
L1	33 (13.9)	17 (13.8)	
L2	48 (20.3)	23 (18.7)	
L3	136 (57.4)	70 (56.9)	
Unknown	19 (8.0)	12 (9.8)	

Chi-squared tests, t-tests, and Kruskal-Wallis Rank Sum Test were used for comparisons between groups depending on the nature (continuous or non-continuous) of the variables.

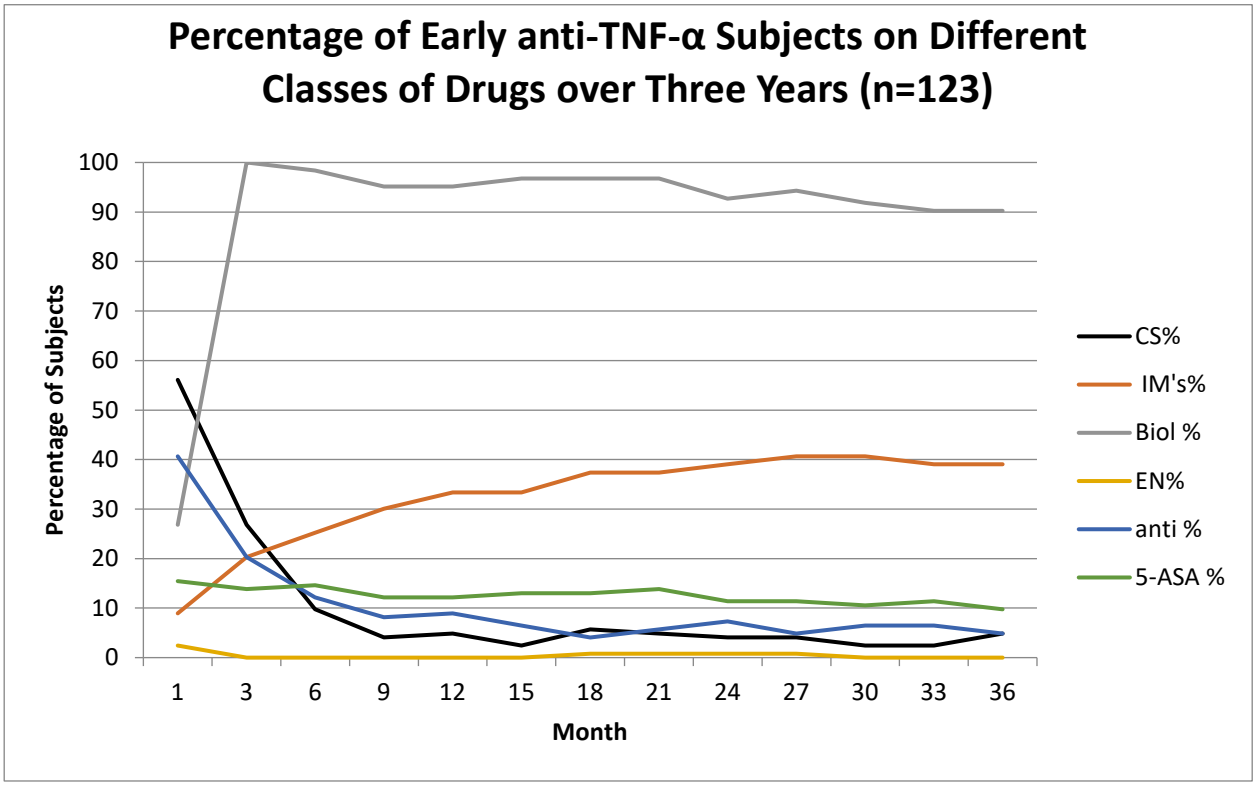
* indicates $p<0.05$. Abbreviations: IBD= inflammatory bowel disease; sd= standard deviation; g/dL= grams per decilitre

Table 4. The Health Status at 6, 12, 18, 24, 30, and 36 Months Post-diagnosis in the Matched RISK-PROKIIDS Comparator Groups.

Health Status	Standard Care n= 237	Early Intervention with Biologics n=123	P value
Number in steroid-free remission at 6 months (%)	93 (39.2)	65 (52.8)	0.019*
Number in steroid-free remission at 12 months (%)	125 (52.7)	75 (61.0)	0.168
Number in steroid-free remission at 18 months (%)	132 (55.7)	82 (66.7)	0.058
Number in steroid-free remission at 24 months (%)	154 (65.0)	92 (74.8)	0.075
Number in steroid-free remission at 30 months (%)	167 (70.5)	87 (70.7)	1
Number in steroid-free remission at 36 months (%)	177 (74.7)	88 (71.5)	0.607
Number of steroid-free remission semesters in 36 months (mean (sd))	3.59 (1.61)	3.98 (1.86)	0.036*
Greatest number of consecutive steroid-free remission semesters in 36 months (mean (sd))	3.02 (1.66)	3.61 (1.97)	0.003*
Total days in hospital at 36 months (mean (sd))	3.76 (10.51)	3.97 (13.37)	0.872
Hospitalized Yes = 1, No =0 (%)	84 (35.4)	45 (36.6)	0.922

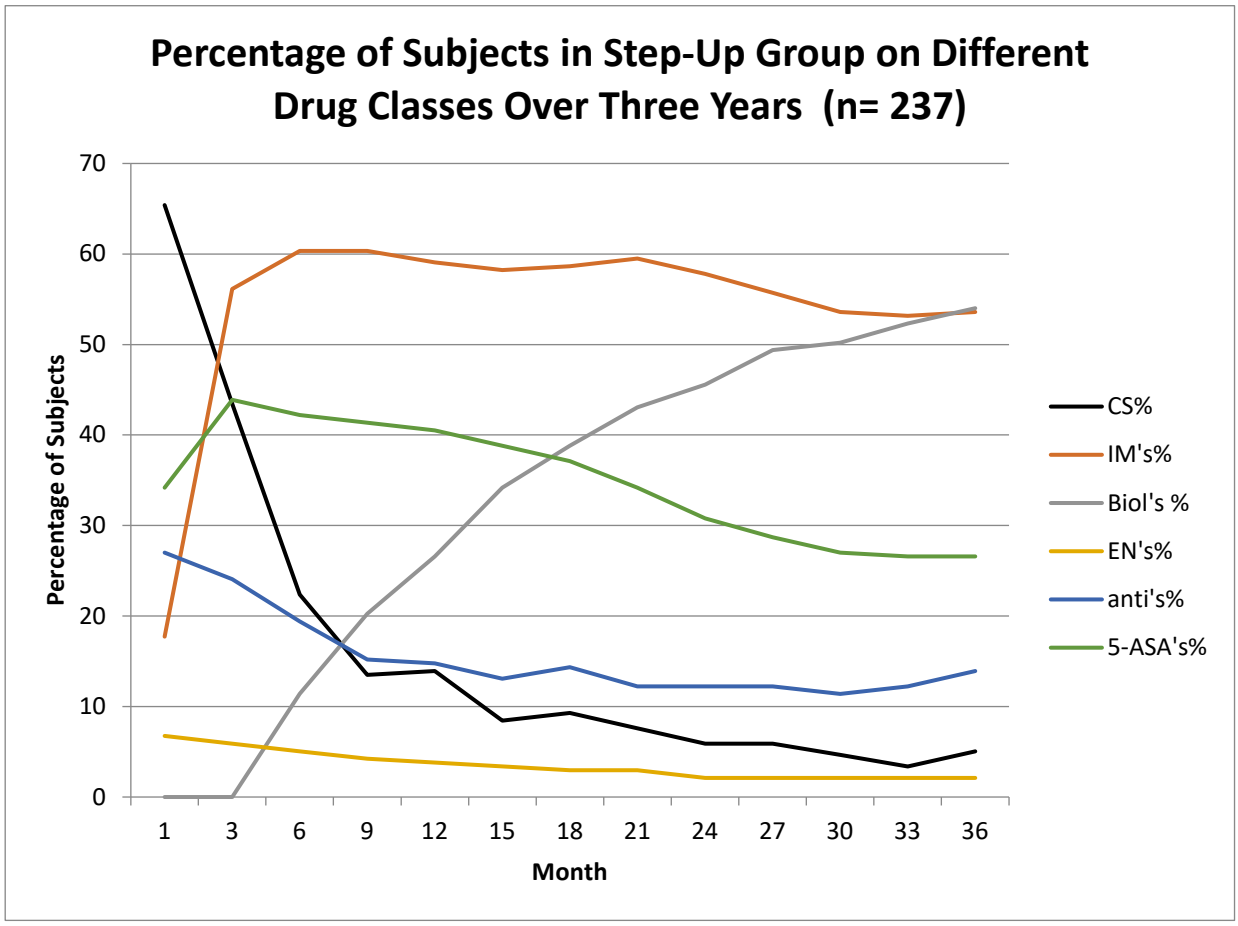
The current health state at diagnosis was based on the weighted Pediatric Crohn's Disease Activity Index (wPCDAI) and the steroid state of the patients; * $p<0.05$; Abbreviations: sd= standard deviation

Figure 2. The Change in Treatment Over Three Years in the Early anti-TNF-α Intervention Group.



Abbreviations: CS =corticosteroids; IM's= immunomodulators; Biol's = anti-TNF-α biologics, EN's =enteral nutrition; anti's =antibiotics; 5-ASA's = Oral 5-aminosalicylate. The graph does not distinguish between monotherapy and concomitant treatments.

Figure 3. The Change in Treatment Over Three Years in the Standard Care (step-up) Group.



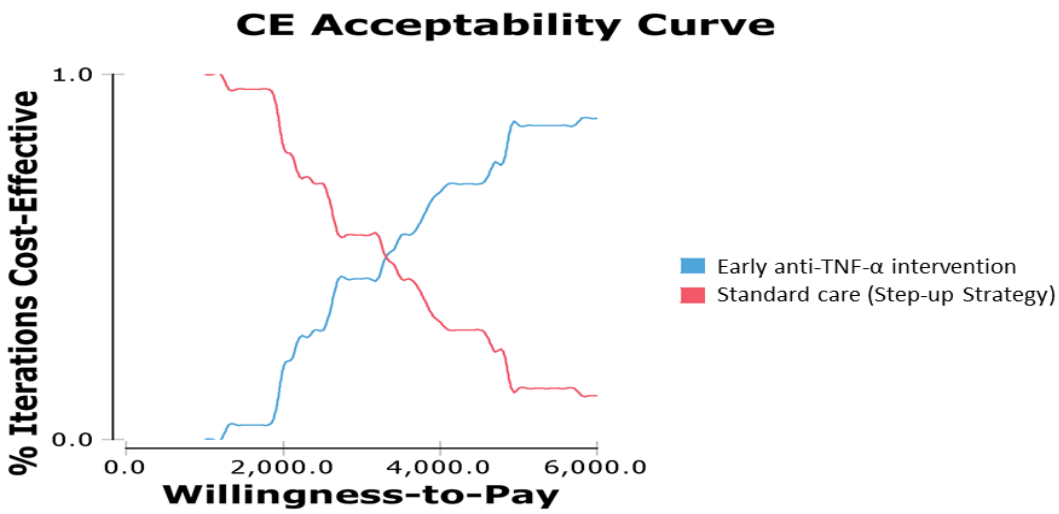
Abbreviations: CS =corticosteroids; IM's= immunomodulators; Biol's =biologics, EN's =enteral nutrition; anti's =antibiotics; 5-ASA's = Oral 5-aminosalicylate. The graph does not distinguish between monotherapy and concomitant treatments.

Table 5. Cost-effectiveness Analysis Results Summary.

Perspective	Strategy	Mean Cost (CAD$)	Incremental Cost (CAD$) (95%CI)	Mean Effectiveness (weeks in steroid-free remission)	Incremental Effect (95%CI)	Incremental Cost-effectiveness Ratio (ICER)
Public Healthcare Payer	Standard Care (Step-up)	96,516		83.07		
	Early anti-TNF-α Intervention	127,628	31,112 (2,939, 91,715)	94.36	11.29 (10.60,11.59)	**2,756**
Societal	Standard Care (Step-up)	100,956		83.07		
	Early anti-TNF-α Intervention	134,464	33,508 (5436, 94,308)	94.36	11.29 (10.60,11.59)	**2,968**

Probabilistic analysis of a two-dimensional microsimulation model with 50 samples of 10,000 microsimulations. Costs are presented in 2017 Canadian dollars.

Figure 4. Cost-effectiveness Acceptability Curve of the Probabilistic (2-D) Cost-effectiveness Analysis of Early anti-TNF-α Intervention vs. Standard Care from a Public Healthcare Payer Perspective.



The willingness-to-pay is presented in Canadian dollars.

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