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Trends of Utilization of Tumor Necrosis Factor Antagonists in Children With Inflammatory Bowel Disease: A Canadian Population-Based Study

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Background: Population-based studies examining the prevalence of anti–tumor necrosis factor (anti-TNF) antagonist utilization in children and young adults with inflammatory bowel disease (IBD) are lacking. We aimed to describe the trend of anti-TNF utilization in pediatric IBD over time.

Methods: Survival analyses were performed for all patients diagnosed with IBD before age 18 years in the province of Manitoba to determine the time from diagnosis to first anti-TNF prescription in different time eras (2005–2008, 2008–2012, 2012–2016).

Results: There were 291 persons diagnosed with IBD (157 with Crohn's disease [CD] and 134 with ulcerative colitis [UC]) over the study period. The likelihood of being initiated on an anti-TNF by 1, 2, and 5 years postdiagnosis was 18.4%, 30.5%, and 42.6%, respectively. The proportion of persons aged <18 years utilizing anti-TNFs rose over time; in 2010, 13.0% of CD and 4.9% of UC; by 2016, 60.0% of CD and 25.5% of UC. For those diagnosed after 2012, 42.5% of CD and 28.4% of UC patients had been prescribed an anti-TNF antagonist within 12 months of IBD diagnosis. Initiating an anti-TNF without prior exposure to an immunosuppressive agent increased over time (before 2008: 0%; 2008–2012: 18.2%; 2012–2016: 42.8%; $P < 0.001$). There was a significant reduction in median cumulative dose of corticosteroids (CS) in the year before anti-TNF initiation (2005–2008: 4360 mg; 2008–2012: 2010 mg; 2012–2016: 1395 mg prednisone equivalents; $P < 0.001$).

Conclusions: Over a period of 11 years, anti-TNFs are being used earlier in the course of pediatric IBD, with a parallel reduction in the cumulative CS dose.

Key Words: anti-TNF, colitis, Crohn, IBD, infliximab

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INTRODUCTION

Since their introduction >20 years ago, anti–tumor necrosis factor alpha (anti-TNF) agents have revolutionized the treatment of inflammatory bowel disease (IBD). Several anti-TNF agents such as infliximab (IFX) and adalimumab (ADA) have been proven effective in inducing and maintaining corticosteroid (CS)-free remission in both adults and children with Crohn's disease (CD) and ulcerative colitis (UC).[1–9] For decades, CS, despite their multiple serious adverse events, especially on growth and development, have been the main agent for induction of remission in persons with IBD.[10] However, CS-free remission and reduced CS dosing have become key targets of quality improvement in IBD programs.[11] In addition, immunosuppressive (IM) agents such as azathioprine (AZA) and methotrexate (MTX) have been utilized for many years to maintain remission in IBD.[12, 13] Nonetheless, their suboptimal efficacy and potential adverse events have encouraged many practitioners to gradually adopt a "top-down" approach, using anti-TNF agents early on, especially in children with IBD where the disease is usually severe and extensively distributed throughout the gastrointestinal tract.[14] Although several randomized controlled and observational studies have documented the efficacy of anti-TNF agents in children

with IBD,[6–9, 15] there are currently no population-based studies documenting the pattern of utilization of anti-TNFs in children with IBD. Understanding the changing utilization pattern of ant-TNF agents over time among children with IBD and their effects on pre-anti-TNF CS exposure will provide insights as to whether clinicians are improving in providing these medications in a manner that reduces cumulative CS exposure. In addition, this could help in appreciating expected costs associated with changing utilization patterns of anti-TNFs. In a population-based analysis, we aimed to examine the utilization pattern of anti-TNFs in Manitoban children with IBD.

METHODS

Data Source

Data were extracted from the University of Manitoba IBD Epidemiology Database, which contains data on all children in the Canadian Province of Manitoba (population 1.3 million in 2016) meeting a validated administrative case definition of IBD between 1984 and 2016. Manitoba is a Canadian province with a relatively stable migration pattern. All residents have access to comprehensive universal health insurance with minimal nonparticipation, as residents do not pay a premium to register for insured benefits.

A full description of the methodology utilized to identify persons with IBD has been previously published.[16] Data on all outpatient medications such as anti-TNFs dispensed to Manitoban children with IBD, including medication name, doses dispensed, and time period of treatment, have been obtained. The database does not contain data on inpatient medications, disease phenotype or severity, personal behaviors, or nutritional habits.

Study Population

All persons with IBD who were under the age of 18 years and received at least 1 dose of IFX and/or ADA between September 2005 and April 2016 were identified. For prevalence of use estimates, patients were deemed current utilizers of anti-TNFs if they had a dispensation of an anti-TNF in the previous 90 days. Time to first use of an anti-TNF agent was calculated only for incident cases who were diagnosed with IBD after September 2005, when IFX became formally available for Manitoban children with CD. To be considered an incident case, there had to be at least 3 years of continuous registration before the first IBD-related health care contact, or continuous registration since birth for children under age 8 years at the time of the first related health care contact.

Outcome Definitions

The prevalence of current anti-TNF use and any history of anti-TNF exposure among all participants over the study period was determined for those who are younger than age 18 years. Survival analyses were conducted for all persons diagnosed with IBD before the age of 18 years to determine the time from diagnosis to first anti-TNF exposure in different time eras (2005–2008, 2008–2012, 2012–2016). Subjects were censored at transition of care to adult service (their 18th birthday), outmigration, death, or the end of data availability (March 31, 2016). We also assessed the percentage of anti-TNF users who were dispensed IM medications either in the year before or during anti-TNF initiation. We calculated the cumulative dose of CS in the 12 months before starting an anti-TNF agent and compared this over the aforementioned eras. Different doses of CS were converted to prednisone equivalents using a conversion table.[17]

Statistical Analysis

We used nonparametric Kaplan-Meier estimators to perform survival analyses for IBD overall, CD, and UC. Comparisons within these survival analyses were performed using other stratifications, including sex, age at diagnosis (<10, 10–18 years), and growth failure. Differences in time from diagnosis to first anti-TNF dispensation were compared using the log-rank test, with Sidak's adjustment for multiple comparisons.

ETHICAL CONSIDERATIONS

The study protocol was approved by the Manitoba Health Information Privacy Committee and the Health Research Ethics Board of the University of Manitoba.

RESULTS

There were 291 persons diagnosed with IBD (157 CD, 134 UC) younger than age 18 years over the study period. One hundred thirty-one children and young adults (90 [69%] with CD and 41 [31%] with UC, 75 boys) received anti-TNF agents, with 32 (24%) children aged <10 years. The majority of participants who received anti-TNFs received IFX (76% of those with CD, 90% with UC). The treatment details are summarized in Table 1.

The prevalence of active anti-TNF use gradually rose over the study period for both CD and UC (Fig. 1); from 13.0% of CD and 4.9% of UC in 2010 to 60.0% of CD and 25.5% of UC by March 2016 ($P < 0.0001$). Within each group (CD vs UC), there was no significant difference in the prevalence of anti-TNF use between sexes or age groups (<10 years vs 10–18 years).

Time from IBD diagnosis to dispensing the first anti-TNF agent by era of diagnosis was significantly shorter in the recent era (2012–2016) compared with earlier eras (before 2008 and 2008–2012) (Fig. 2). For those diagnosed after April 2012, 42.5% of CD and 28.4% of UC had been started on an anti-TNF agent within 12 months of IBD diagnosis, compared with 15.5% with CD and 11.8% of UC of those diagnosed between April 2008 and March 2012. Children with CD were more likely

TABLE 1. Treatment Details of Participants on Anti-TNF Agents Between 2005 and 2016

	CD, No. (%)[a]	UC, No. (%)
IFX	69 (52.7)	37 (28.2)
ADA	25 (19.1)[b]	
Era of starting anti-TNF		
Before 2008	17 (13.0)	
2008–2012	44 (33.6)	
2008–2016	70 (53.4)	
Prior IM in the 12 mo before anti-TNF	76 (58.0)	28 (21.4)
AZA/MP	70	28
MTX	6	0
Active IM with anti-TNF	59 (45.0)	15 (11.5)
Active AZA/6 MP use between diagnosis of IBD and starting anti-TNF		
2005–2008	13 (9.9)	
2008–2012	36 (27.5)	
2008–2016	46 (35.1)	
Median cumulative dose in mg of corticosteroids in the 12 mo before starting anti-TNF		
2005–2008	4360	
2008–2012	2010	
2008–2016	1395	
Mean cumulative dose in mg of corticosteroids		
2005–2008	8553.14	
2008–2012	3600.38	
2008–2016	1772.17	
IBD-related hospitalization in the 12 mo before starting anti-TNF	33 (25.2)	25 (19.1)
IBD-related surgery between diagnosis until starting anti-TNF	9 (6.9)	

[a]Percentage of the total cohort (131 participants).
[b]Details are not provided, as sample size was <6 people, to protect confidentiality.

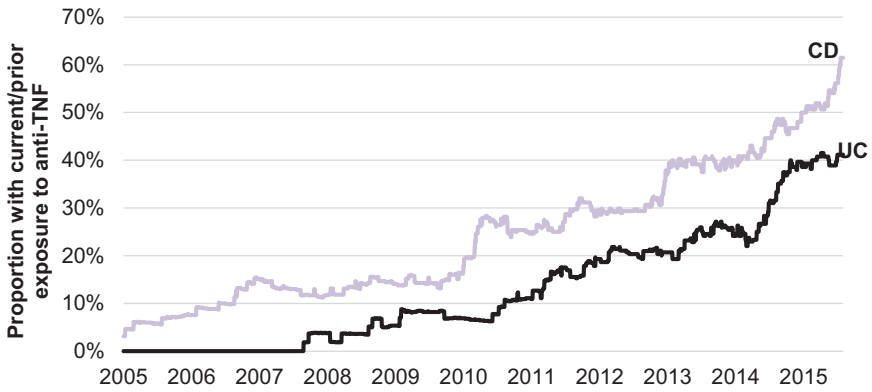

FIGURE 1. Cumulative prevalence of anti-TNF utilization over the study period for persons with Crohn's disease and ulcerative colitis.

to start on an anti-TNF agent earlier in their disease course compared with those with UC (P = 0.002). The overall likelihood of starting an anti-TNF by 1, 2, and 5 years after IBD diagnosis was 19.0%, 36.9%, and 51.0% for CD, and 16.7%, 24.0%, and 30.7% for UC. Among incident cases of IBD who received at least 1 dose of an anti-TNF, 82% of those with CD and 68% of those with UC had an IM dispensed before anti-TNF initiation. The likelihood of initiating anti-TNF therapy in those who were IM naïve increased over time (2008–2012: 14.0%; 2012–2016: 28.3%; P = 0.029). In the 12 months before starting an anti-TNF, 98 children were on AZA and 6 were on MTX. The majority of those children were boys (61%).

Overall, 50% of children with CD and 92% of those with UC had CS exposure in the 12-month period before starting an

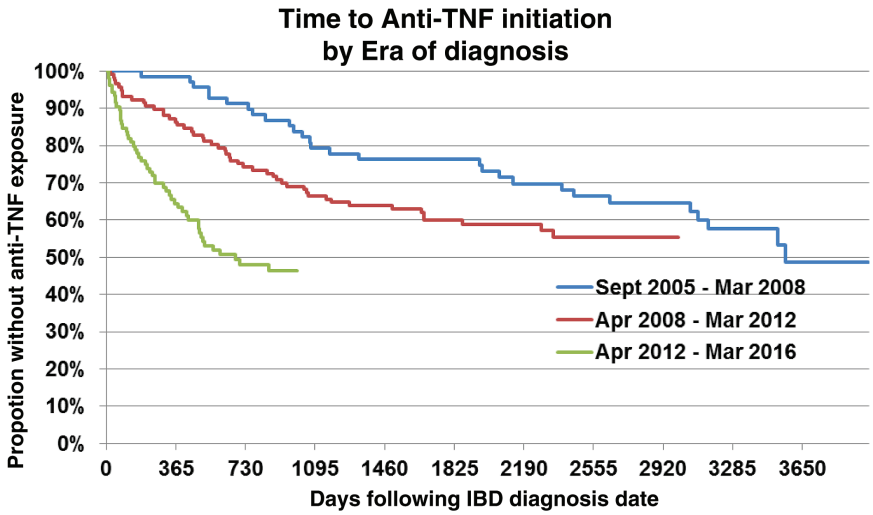

FIGURE 2. Time to anti-TNF initiation by era of diagnosis.

anti-TNF agent. Age and sex were not significantly different between those who utilized CS and those who did not in the year before starting anti-TNFs. The proportion of children with CS exposure in the year before anti-TNF exposure significantly decreased over the study period for children with CD ($P < 0.0001$) but not for those with UC ($P = 0.2$). The median cumulative dose of CS in the year before anti-TNF initiation significantly decreased over time (2005–2008: 4360 mg; 2008–2012: 2010 mg; 2012–2016: 1395 mg prednisone equivalents; $P < 0.001$).

The median time from anti-TNF institution to discontinuation was 4.0 years; 72.9% of children who were started on anti-TNF therapy remained on therapy at 1 year after initiation. Duration of anti-TNF treatment did not significantly differ between boys and girls, or those with CD vs those with UC. There was a trend toward a lower risk of anti-TNF discontinuation among persons who were initiated on anti-TNFs after April 2011 compared with those who started therapy before this date ($P = 0.069$).

DISCUSSION

In this population-based study with up to 11 years of longitudinal data, we found a significant increase in the utilization of anti-TNF agents and a reduction in the gap between the initial diagnosis of IBD and starting an anti-TNF agent. This likely reflects awareness of the advantages of using these medications early in the course of IBD. This increase was paralleled by a reduction in the overall cumulative exposure to CS before anti-TNF initiation, though only significantly among those with CD, and a greater likelihood of starting anti-TNF therapy without a prior trial of immunomodulators.

Population-based studies reporting anti-TNF utilization in pediatric IBD are scarce. In 1 population-based study from France (EPIMAD) that enrolled children with CD, 120 persons received IFX over 6 years, with 82% of participants on CS, 38% on AZA, and 7% on MTX within 1 year of diagnosis. Of those who received IFX, 24% were started on IM when IFX was initiated and 69% continued on the same IM after IFX initiation.[18] The study did not report the prevalence of IFX utilization over time. Using the Stanford Translational Research Integrated Database (STRIDE), Park et al.[19] examined anti-TNF utilization among children and adults with IBD between 2006 and 2012. Concordant with our study, IFX utilization was significantly higher than ADA utilization. There was a significant increase in utilizing anti-TNF agents in both pediatric and adult cohorts between 2006 and 2008, followed by modest declines by 2012. Nonetheless, the proportion of the pediatric population prescribed anti-TNFs was significantly higher than that of the adult population. Using a clinical database, Ashton et al.[20] reported a significant increase in the prevalence of children with IBD treated with anti-TNF agents, from 5.1% in 2007 to 27.1% in 2017. This increase paralleled a significant reduction in surgical resection rates, mainly in children with CD, whereas colectomy rates for UC remained the same. Several observational pediatric studies indicated the benefits of early introduction of anti-TNF agents, such as the RISK observational study, which reported the significant superiority of early introduction of anti-TNF agents over IM in inducing clinical remission in children with CD.[21]

It is not clear why pediatric utilization of anti-TNF agents is higher than that of the adult population. It may reflect the nature of pediatric IBD having worse disease severity, more extensive locations within the gastrointestinal tract, and higher acuity.[22, 23] Nonetheless, a recent study showed that CD in children and young adults, although more phenotypically extensive, is not more aggressive compared with adult-onset CD.[24] Another possible explanation is the fact that anti-TNF agents provide an attractive alternative to CS, which may have a negative effect on actively growing children compared with adults who have already established their final growth status. This was reflected in

our study by the significant reduction of the cumulative CS dose over time. Previously, our group showed a steady use of CS, with 56% of children and young adults with IBD exposed to CS within 1 year of their IBD diagnosis and no significant decrease over eras of follow-up between 2002 and 2010.[25] This has clearly changed recently, with a significant reduction in CS use from 2010 to 2016. Our results likely indicate that pediatric gastroenterologists are willing to use anti-TNF agents earlier in the disease course to reduce the impact of adverse events related to CS exposure. Crohn's disease has a greater negative effect on growth compared with UC,[26, 27] and this may have encouraged greater anti-TNF utilization in children with CD compared with those with UC.

Our study has several points of strength. There are hardly any population-based studies in children with IBD with data extending from the initial diagnosis of IBD to the first utilization of anti-TNF agents followed by several years of longitudinal observation. As such, an accurate description of anti-TNF dispensation and changes in prescribing practice over a relatively long period were thoroughly examined and reported. This study, however, has limitations. Because this data set contains only outpatient drug dispensations, it is possible that the reported CS exposure has been undermeasured, as prescribed inpatient CS utilization would not have been estimated. We could not report on certain characteristics such as number of surgeries for CD vs UC when the sample size was <6 persons to protect patient confidentiality. We were also unable to report on the exclusive enteral nutrition program that has been utilized in our center as a primary therapy for CD or other dietary habits and that may have influenced CS exposure or anti-TNF dispensation. The database does not contain data on disease severity, phenotype, or indications of medications.

CONCLUSIONS

Utilization of anti-TNF agents has been rising, and more recently they are being used early in the course of pediatric inflammatory bowel disease, especially in those with Crohn's disease. It was reassuring to document the decline of cumulative CS use in recent years, especially in children with Crohn's disease, suggesting that 1 trade-off to the increased costs of increasing anti-TNF use will be reduced ill effects from CS. More studies on the long-term costs associated with increased utilization of anti-TNF medications in children and young adults with IBD are warranted.

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