Title: Top-down versus Step-up Prescribing Strategies for Tumor Necrosis Factor Alpha Inhibitors in Children and Young Adults with Inflammatory Bowel Disease

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ABSTRACT

Background: Early initiation of tumor necrosis factor-alpha inhibitor (TNFI) therapy for children and young adults with inflammatory bowel disease (IBD) is not well described.

Methods: We conducted a retrospective cohort study of children and young adults (≤24 years) newly diagnosed with IBD using health insurance claims from 2009 to 2013. The conventional "step-up" approach was defined as TNFI initiation >30 days after first IBD medication prescription, whereas the "top-down" approach was defined as new TNFI prescription within 30 days of first IBD medication prescription. Switching rates, time to initiation, discontinuation, and adherence to TNFIs were compared between the two strategies.

Results: A total of 11,962 IBD patients were identified. Among 3,300 TNFI users, 1,298 (39.3%) were treated with the top-down approach, while 2,002 (60.7%) were treated with the step-up approach. Top-down approach use increased from 31.4% to 49.8% during the 5-year period, and under this approach, most patients were treated with TNFIs alone. Time to TNFI initiation was shorter for patients diagnosed in more recent years. Patients treated with the top-down strategy had lower rates of corticosteroid use (32.5% vs 94.2%) compared to step-up treatment but presented a higher rate of TNFI discontinuation. The two strategies both exhibited high adherence (mean proportion of days covered: 83.7% to 95.4%).

Conclusions: Early TNFI initiation increased over time for children and young adults with IBD and was related to lower rates of corticosteroid use compared to the conventional approach. However, the higher rate of TNFI discontinuation under the top-down approach requires further examination.

Key Words: Inflammatory bowel disease, pediatric inflammatory bowel disease, biologic therapies, medication patterns, tumor necrosis factor-alpha inhibitors.

INTRODUCTION

Inflammatory bowel disease (IBD) is an immune-mediated disorder characterized by chronic inflammation in the gastrointestinal tract and includes both Crohn's disease (CD) and ulcerative colitis (UC).[1] Children account for about 30% of all cases of IBD.[2] The incidence of IBD in children aged 1 to 17 years is 4.6 per 100,000 for CD[2,3] and 2.1 per 100,000 for UC and has been increasing globally.[4] In most cases, children with IBD carry the disease into later adulthood. Notably, adolescents and young adults aged 15 to 29 years have the highest incidence of both CD and UC.[5] Childhood-onset IBD typically has more extensive symptoms and more frequent and severe episodes than adult-onset IBD.[6,7] In addition, children with IBD are more likely to experience anxiety and depression, poor school functioning, and lower quality of life than children without IBD.[8]

Drug treatment for IBD includes corticosteroids, 5-aminosalicylates, thiopurines, methotrexate, immunosuppressants (e.g., cyclosporine and tacrolimus), and tumor necrosis factor-alpha inhibitors (TNFI). Among these drugs, TNFIs are generally considered the most effective, and as a result, use of TNFIs for IBD has increased over time.[9-11] However, some controversy exists about when in the disease course TNFIs should be used.

According to the recommendations of the North American Society for Pediatric Gastroenterology Hepatology and Nutrition (NASPGHAN), the European Crohn's and Colitis Organisation (ECCO), and the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN), TNFIs can be considered in both the induction and maintenance phases of treatment.[12-14] Under the conventional step-wise treatment approach, or the "step-up" approach, the use of systemic corticosteroids and/or immunomodulators is recommended before initiating TNFIs. However, a newer treatment strategy called the "top-down" approach has recently emerged. In this approach, patients are treated more aggressively by using TNFIs, often combined with immunomodulators, as initial therapy. Recent evidence suggests that use of TNFIs earlier in the disease course may improve clinical outcomes.[15-19] The "top-down"

approach may be particularly beneficial to children because early use of TNFIs may decrease or avoid the use of corticosteroids, which are associated with adverse effects on pubertal growth.

The rate of adoption of the top-down treatment approach in current clinical practice has not been examined in children and young adults with IBD. In addition, little is known about how the step-up and top-down treatment strategies differ in terms of switching, adherence, and persistence with TNFI therapy in real-world settings. Therefore, this study aimed to examine the use of the top-down approach for children and young adults with IBD and more specifically to compare medication utilization between the step-up and top-down strategies.

MATERIALS AND METHODS

Data Source

Health insurance claims from January 1, 2009, to December 31, 2013, were obtained from the Truven Health MarketScan® Commercial Claims and Encounters (CCAE) databases. These databases contain health care claims for about 180 million people across the U.S. who were commercially insured, mainly through employer-based coverage. All data were de-identified and include information on health plan enrollment, medical service utilization, and prescription records. Each claim contained longitudinal information on patient demographics, type of encounter (e.g., outpatient, inpatient, or emergency room visits), date of encounter, physician specialties, disease diagnoses (using International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] code), medical procedures, and expenditures.[20]

Study Population

Patients were eligible to be included in the study if they had a new diagnosis of IBD (ICD-9-CM code 555.xx or 556.xx) at an age of ≤24 years during the study period. The algorithm for identification of confirmed IBD was two diagnoses within 1 year or at least one IBD diagnosis coded by a pediatrician or gastroenterologist.[21] A new diagnosis was defined as the absence of an IBD diagnosis in the 6-month period prior to the first confirmed IBD identified.

The date of the new diagnosis was marked as the index date. For eligible subjects, at least 6 months of continuous enrollment was required before and after the index date. In addition, eligible patients had to have received at least one IBD medication during the follow-up period. However, we excluded patients with a history of tuberculosis and/or medications for tuberculosis, which is a contraindication for TNFI use. The study cohort was followed from the index date until the health plan disenrollment date or the end of the study period, whichever came first.

Medications used for IBD consisted of systemic corticosteroids, 5-aminosalicylates (sulfasalazine, mesalazine), thiopurines (azathioprine and 6-mercaptopurine), methotrexate, TNFIs (infliximab, adalimumab, certolizumab, and golimumab), and other immunosuppressants (tacrolimus, cyclosporine, rituzumab, and vedolizumab). Patients who used TNFIs in the follow-up period were further categorized as having received the top-down or step-up approach based on the order of their treatment regimen. The top-down approach was defined as a dispensing of a new TNFI prescription within 30 days of the first medication prescription for IBD (i.e., 5-aminosalicylates, systemic corticosteroids, thiopurines, and/or immunosuppressants), while the step-up approach was defined as TNFI initiation more than 30 days after the first IBD medication prescription.[19]

Study Outcomes

We assessed the use of IBD medications during the follow-up period in the study cohort. The time from IBD diagnosis to first TNFI prescription was calculated. Any switch from the initial TNFI (the first TNFI agent) to another TNFI within 1 year was identified, and the pattern of switching was described.

Persistence and adherence with TNFI therapy was also assessed. Persistence was defined as continuous use of TNFIs among patients who had at least two prescriptions and who did not switch from their initial TNFI. Any gap between two consecutive TNFI claims was calculated, and a gap of ≤90 days was defined as continuous use. The period of continuous use

(or time to discontinuation) was calculated as the time from the first TNFI prescription date to the last prescription date before a gap >90 days plus half the days supply for the last prescription. Adherence to TNFI was defined as the proportion of days covered (PDC) over a 180-day period among patients who continuously took TNFIs for ≥180 days. The total number of days supply of TNFIs was calculated, with adjustment of overlapping days due to early refills. PDC was calculated as adjusted total days of supply of TNFIs divided by 180 days and multiplied by 100.[22]

Statistical Analyses

We described baseline demographic information and medication use patterns for the overall study cohort, the top-down approach, and the step-up approach as well as for non-TNFI users. Use of individual TNFI agents by age group (<12, 12-17, and 18-24 years) was compared between the top-down and step-up approaches using chi-square tests.

Among TNFI users, the time from IBD diagnosis to first TNFI prescription was compared by year of diagnosis using a log-rank test. A Kaplan-Meier plot was used to illustrate the proportion of patients prescribed a TNFI by the time followed from the diagnosis. We also used Cox hazard models to examine the hazard ratios (HR) and 95% confidence interval (CI) of TNFI use for patients in different year of diagnosis, compared to year of 2009.

We assessed the time from first TNFI use to discontinuation by individual TNFI agent. The proportions of patients who continuously took TNFIs for 1, 3, 6, 12, 18, and 24 months were then compared between the top-down and step-up approaches using a log-rank test. As a sensitivity analysis for persistence, we varied the gap from 90 days to 30, 60, and 120 days in order to define continuous use of TNFIs. Adherence was described in mean PDC with quartile, minimum, and maximum values. A stratified analysis was conducted to examine whether the adherence varied by age group. In addition, we performed a sensitivity analysis of the PDC using a 365-day period.

The statistical software SAS version 9.4 (Cary, North Carolina, USA) and STATA 12 (College Station, Texas, USA) were used for data cleaning, extraction, and analysis. A university Institutional Review Board (IRB) determined that this study did not involve human subject research, and thus no IRB application and review were necessary.

RESULTS

A total of 11,962 patients with incident IBD were followed for a median of 657 days (interquartile range 409-1,000 days); their mean age was 17.3 years (standard deviation 5.0), and 51% were males. Of the overall cohort, 3,300 (27.6%) used TNFIs and 8,662 (72.4%) were treated with other agents (Table 1). No differences were found in the proportions of geographic location and corticosteroid use between TNFI and non-TNFI users. However, TNFI users included a greater proportion of patients who were in the 12-17 year age group (38.7% vs 29.6%, $p<0.0001$), males (54.1% vs 49.8%, $p<0.0001$), methotrexate users (11.7% vs 2.3%, $p<0.0001$), and thiopurine users (38.6% vs 25.4%, $p<0.0001$) compared to non-TNFI users but exhibited a lower rate of 5-aminosalicylate use (52.4% vs 79.3%, $p<0.0001$).

Among patients taking TNFIs, 1,298 (39.3%) were treated with the top-down and 2,002 (60.7%) with the step-up approach. Under top-down treatment, TNFI therapy was the first treatment in 76.7% of patients (i.e., there was no prior use of other IBD medications prior to TNFI initiation). The proportion of patients receiving top-down treatment increased over the study period (31.4%, 37.5%, 39.0%, 42.2%, and 49.8% for the years 2009 to 2013, respectively; p for trend <0.0001). Patients who received top-down treatment were less likely to use corticosteroids (32.5% vs 94.2%, $p<0.0001$), 5-aminosalicylates (17.3% vs 75.1%, $p<0.0001$), methotrexate (7.2% vs 14.6%, $p<0.0001$), or thiopurines (13.5% vs 54.8%, $p<0.0001$) compared to step-up patients.

Infliximab was the most commonly used TNFI across different age groups (Table 2). However, the proportion of patients administered infliximab as their initial TNFI therapy was

lower among those 18-24 years of age (55.1%) compared to those <12 years old (89.2%) and 12-17 years old (82.3%) while a contrasting pattern was observed for adalimumab (37.9%, 16.6%, and 10.6% among those 18-24, 12-17, and <12 years of age, respectively). In addition, a consistent pattern of infliximab and adalimumab use was observed between the top-down and step-up strategies across the three age groups: the rate of infliximab use was higher in the top-down strategy, while the rate of adalimumab use was higher in the step-up strategy.

The time from IBD diagnosis to TNFI initiation was shorter for patients who were diagnosed more recently (log-rank test $p<0.001$), as shown in Figure 1. For example, among those diagnosed with IBD in 2009, it took almost 2 years for 20% of the patients to start TNFI therapy, while for those diagnosed in 2010, 2011, 2012, and 2013, it took about 1.5, 1, 0.6, and 0.5 years, respectively. Compared to the 2009 diagnosis group, the HR (95% CI) for receiving TNFIs was 1.18 (1.05-1.32), 1.35 (1.20-1.52), 1.76 (1.56-1.99), and 2.01 (1.72-2.35) for patients diagnosed in 2010, 2011, 2012, and 2013, respectively.

Among TNFI users overall, the rate of switching from one TNFI to another within 1 year was 6.7% (Table 3). The one-year switching rate was similar between the top-down (5.7%) and step-up strategies (7.4%). The mean time to switching after the initial TNFI prescription was 172 days for the step-up strategy and 191 days for the top-down strategy. When switching occurred, switching from infliximab to adalimumab was the most common pattern.

As for patients who did not switch their initial TNFIs, their persistence with TNFI therapy is shown in Table 4. The median time to discontinuation was about 300 days for infliximab, adalimumab, and certolizumab. Depending on the individual TNFI used, a range of 77.8% to 86.1% of patients persistently received TNFI therapy for 6 months, and 67.8% to 74.8% underwent continuous 12-month TNFI therapy. However, discontinuation of TNFI therapy was higher in patients receiving the top-down compared to the step-up strategy (log-rank test $p=0.034$). The results did not change substantially when the gap used to define continuous use was varied from 90 days to 30, 60, or 120 days.

Among patients who continuously took their TNFIs without switching their initial TNFI therapies, the adherence to TNFIs was high (Table 5). The mean PDC was highest for infliximab (95.4%), followed by adalimumab (91.0%) and certolizumab (83.7%). No patients in the golimumab group could be followed for ≥180 days. We found no differences in the PDC estimates between the top-down and step-up strategies. Adherence to individual TNFIs did not vary by age group. The results were similar when PDC was calculated using a 365-day period.

DISCUSSION

In this analysis, we examined the employment of the top-down and step-up strategies in children and young adults with IBD. This study followed IBD children and young adults for 5 years and found that 27.6% were treated with TNFIs. Childhood-onset IBD usually has more extensive symptoms and more severe disease progression than adult-onset IBD.[6,7] As a result, children have been reported to require pharmacotherapy more often than adults. For example, Goodhand and colleagues analyzed 200 adolescents and adults with IBD in a case-control study and found that biological therapy (i.e., infliximab) was used more frequently in adolescents (20%) than in adults (8%).[23] Similarly, we found that 27.6% of children and young adults used TNFIs. Our study provided additional detail on the types of TNFIs used (including the newer agents adalimumab, certolizumab, and golimumab) and the use of these agents within age groups. While infliximab was the dominant agent used across patients aged <12, 12-17, and 18-24 years, the use of adalimumab increased with age.

Infliximab and adalimumab have similar efficacy and safety profiles in adults with IBD.[24,25] In addition, a recent network meta-analysis of 17 randomized controlled trials involving adults with moderate to severe CD reported that infliximab and adalimumab were the most effective therapies for inducing remission in the induction and maintenance phases, respectively.[26] Moreover, in the Gauging Adalimumab efficacy in Infliximab Non-responders (GAIN) trial, adalimumab induced remission in 21% of adults with CD who were either intolerant

of or nonresponsive to infliximab.[27] Thus, adalimumab is often used as a second-line treatment for patients who stop responding to infliximab. However, we found that 28.0% of IBD patients aged 18-24 were prescribed adalimumab as the initial treatment in the top-down strategy. Similarly, using the Stanford Translational Research Integrated Database, Park and colleagues found a trend of increasing adalimumab use between 2007 and 2012 for both adult and pediatric patients with IBD.[11] One reason for this finding may be that the costs of infliximab as the first-line therapy were significantly higher than the costs of adalimumab, with the higher infliximab costs driven by both a higher drug cost and the additional cost of administration.[28] In addition, factors such as availability, patient preference, route of administration (subcutaneous for adalimumab and intravenous infusion for infliximab), and the reimbursement policies of individual insurance companies may have affected the prescribing decisions made by physicians.

We found that children and young adults with IBD were treated with TNFIs more aggressively during the time period we studied. Specifically, of TNFI users, 42.6% were treated earlier with TNFIs (the top-down strategy), and this proportion increased from 31.4% to 49.8% from 2009 to 2013. In addition, the time from IBD diagnosis to TNFI initiation became shorter for patients diagnosed in more recent years. In clinical studies, the top-down strategy was associated with a higher remission rate in both adults and children with CD.[15-17] Furthermore, Rubin and colleagues found that the top-down strategy was associated with lower concomitant use of corticosteroids and discontinuation or switching of TNFIs in adults.[19] Our findings also revealed lower rates of corticosteroid use in children and young adults under the top-down strategy. However, we did observe a higher rate of discontinuation of TNFIs in patients treated with the top-down strategy. Reasons for this are unknown. ECCO and ESPGHAN guidelines do not specify a duration for TNFI use in patients with IBD. It is possible that the top-down strategy, a more aggressive treatment approach, is related to some causes for discontinuation, such as occurrence of adverse events or development of anti-drug antibodies (which leads to

ineffectiveness of TNFIs), and thus more studies are needed to confirm our findings and identify the reasons for discontinuation.

Among IBD patients treated with the top-down strategy, we found that most used TNFI monotherapy; only 25.8% initiated 5-aminosalicylates or thiopurines, either concomitantly or as augmentation to TNFIs. In the Study of Biologic and Immunomodulator Naive Patients in Crohn's Disease (SONIC) trial, the combination of infliximab and azathioprine showed a greater corticosteroid-free remission rate (56.8%) than use of infliximab (44.4%) or azathioprine (30.0%) alone.[29] In addition, whereas one study found that up to 61% of CD patients developed antibodies to infliximab,[30] the combination of TNFIs and immunomodulators has been associated with a lower risk of anti-drug antibody development.[29,31] However, TNFIs were reported to be associated with an increased risk of lymphoma in children, especially when combined with thiopurines.[32,33] Prescribing of a TNFI alone as opposed to in combination with other immunomodulators remains controversial. In our study, due to the limitations of the claims data, we were unable to identify the reasons for physicians' prescribing decisions or to examine development of anti-drug antibodies in patients receiving TNFI therapy. Future studies are needed to evaluate the effectiveness of TNFI monotherapy as opposed to combined therapy as well as the associated clinical consequences in children and young adults with IBD.

Several limitations of our study merit discussion. First, included patients may have been misclassified as having IBD if the disease diagnoses were coded inaccurately. However, we made every effort to identify the IBD cohort by using an algorithm that was validated previously[21]. In addition, any misclassification that may have occurred was likely nondifferential between the top-down and step-up strategies, and would bias our results toward to the null. Second, due to the absence of some clinical information in the claims database, such as gastrointestinal symptoms and endoscopy results, we were unable to accurately account for the effect of disease severity on TNFI utilization. Third, our findings for TNFI adherence should be interpreted with caution. The claims data provided only the dates and days supply of

prescription fills, and thus we could not determine whether patients actually took the medications. However, adherence measurement using prescription records has been validated previously.[34,35] In addition, it may not be appropriate to compare adherence to infliximab (by intravenous infusion) with adherence to other TNFI agents (by subcutaneous injection) because of their different routes of administration. Furthermore, the effect of specialty pharmacy management on adherence to TNFIs was difficult to identify and control for in our analysis.

In summary, this study characterized utilization of TNFIs in children and young adults with IBD. Employment of the top-down strategy increased over time and the time to TNFI initiation became shorter during the study period, indicating that a more aggressive treatment approach has emerged for children and young adults with IBD. However, higher rates of TNFI monotherapy and discontinuation were observed with the top-down strategy. Future studies should evaluate the long-term benefits and risks of the top-down treatment approach to ensure the effectiveness and safety of this emerging aggressive treatment approach for children and young adults.

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REFERENCES

1. Epidemiology of pediatric inflammatory bowel disease. pp 45-59 In: Pediatric Inflammatory Bowel Disease. Ed: 2nd. Editors: Petar mamula, Jonathan E Markowitz, Robert N Baldassano. Springer, New York, 2013.

2. Pappa HM, Semrin G, Walker TR, et al. Pediatric inflammatory bowel disease. *Curr Opin Gastroenterol.* Jul 2004;20:333-340.

3. Kugathasan S, Judd RH, Hoffmann RG, et al. Epidemiologic and clinical characteristics of children with newly diagnosed inflammatory bowel disease in Wisconsin: a statewide population-based study. *J Pediatr.* Oct 2003;143:525-531.

4. Malaty HM, Fan X, Opekun AR, et al. Rising incidence of inflammatory bowel disease among children: a 12-year study. *J Pediatr Gastroenterol Nutr.* Jan 2010;50:27-31.

5. Johnston RD, Logan RF. What is the peak age for onset of IBD? *Inflammatory bowel diseases.* Oct 2008;14 Suppl 2:S4-5.

6. Leung Y, Heyman MB, Mahadevan U. Transitioning the adolescent inflammatory bowel disease patient: guidelines for the adult and pediatric gastroenterologist. *Inflammatory bowel diseases.* Oct 2011;17:2169-2173.

7. Lemberg DA, Day AS. Crohn disease and ulcerative colitis in children: an update for 2014. *J Paediatr Child Health.* Mar 2015;51:266-270.

8. Qualia CM, Bousvaros A. Advances in Pediatric IBD. *Curr Pediatr Rep.* 2013;1:206-213.

9. Rutgeerts P, Sandborn WJ, Feagan BG, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. *N Engl J Med.* Dec 8 2005;353:2462-2476.

10. Hyams J, Crandall W, Kugathasan S, et al. Induction and maintenance infliximab therapy for the treatment of moderate-to-severe Crohn's disease in children. *Gastroenterology.* Mar 2007;132:863-873; quiz 1165-1166.

11. Park KT, Sin A, Wu M, et al. Utilization trends of anti-TNF agents and health outcomes in adults and children with inflammatory bowel diseases: a single-center experience. *Inflammatory bowel diseases.* Jul 2014;20:1242-1249.

12. Rufo PA, Denson LA, Sylvester FA, et al. Health supervision in the management of children and adolescents with IBD: NASPGHAN recommendations. *J Pediatr Gastroenterol Nutr.* Jul 2012;55:93-108.

13. Ruemmele FM, Veres G, Kolho KL, et al. Consensus guidelines of ECCO/ESPGHAN on the medical management of pediatric Crohn's disease. *J Crohns Colitis.* Oct 1 2014;8:1179-1207.

14. Turner D, Levine A, Escher JC, et al. Management of pediatric ulcerative colitis: joint ECCO and ESPGHAN evidence-based consensus guidelines. *J Pediatr Gastroenterol Nutr.* Sep 2012;55:340-361.

15. D'Haens G, Baert F, van Assche G, et al. Early combined immunosuppression or conventional management in patients with newly diagnosed Crohn's disease: an open randomised trial. *Lancet.* Feb 23 2008;371:660-667.

16. Kim MJ, Lee JS, Lee JH, et al. Infliximab therapy in children with Crohn's disease: a one-year evaluation of efficacy comparing 'top-down' and 'step-up' strategies. *Acta paediatrica.* Mar 2011;100:451-455.

17. Lee YM, Kang B, Lee Y, et al. Infliximab "Top-Down" Strategy is Superior to "Step-Up" in Maintaining Long-Term Remission in the Treatment of Pediatric Crohn Disease. *J Pediatr Gastroenterol Nutr.* Jun 2015;60:737-743.

18. Lee YS, Baek SH, Kim MJ, et al. Efficacy of Early Infliximab Treatment for Pediatric Crohn's Disease: A Three-year Follow-up. *Pediatric gastroenterology, hepatology & nutrition.* Dec 2012;15:243-249.

19. Rubin DT, Uluscu O, Sederman R. Response to biologic therapy in Crohn's disease is improved with early treatment: an analysis of health claims data. *Inflammatory bowel diseases.* Dec 2012;18:2225-2231.

20. Danielson E. White Paper. Health Research Data for the Real World: The MarketScan® Databases. 2011. Available at: http://truvenhealth.com/portals/0/assets/PH_11238_0612_TEMP_MarketScan_WP_FINAL.pdf Accessed on March 23, 2016.

21. Liu L, Allison JE, Herrinton LJ. Validity of computerized diagnoses, procedures, and drugs for inflammatory bowel disease in a northern California managed care organization. *Pharmacoepidemiol Drug Saf.* Nov 2009;18:1086-1093.

22. Peterson AM, Nau DP, Cramer JA, et al. A checklist for medication compliance and persistence studies using retrospective databases. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research.* Jan-Feb 2007;10:3-12.

23. Goodhand J, Dawson R, Hefferon M, et al. Inflammatory bowel disease in young people: the case for transitional clinics. *Inflammatory bowel diseases.* Jun 2010;16:947-952.

24. Osterman MT, Haynes K, Delzell E, et al. Comparative effectiveness of infliximab and adalimumab for Crohn's disease. *Clin Gastroenterol Hepatol.* May 2014;12:811-817 e813.

25. Zorzi F, Zuzzi S, Onali S, et al. Efficacy and safety of infliximab and adalimumab in Crohn's disease: a single centre study. *Aliment Pharmacol Ther.* Jun 2012;35:1397-1407.

26. Singh S, Garg SK, Pardi DS, et al. Comparative efficacy of biologic therapy in biologic-naive patients with Crohn disease: a systematic review and network meta-analysis. *Mayo Clinic proceedings.* Dec 2014;89:1621-1635.

27. Sandborn WJ, Rutgeerts P, Enns R, et al. Adalimumab induction therapy for Crohn disease previously treated with infliximab: a randomized trial. *Annals of internal medicine.* Jun 19 2007;146:829-838.

28. Choi GK, Collins SD, Greer DP, et al. Costs of adalimumab versus infliximab as first-line biological therapy for luminal Crohn's disease. *J Crohns Colitis.* May 2014;8:375-383.

29. Colombel JF, Sandborn WJ, Reinisch W, et al. Infliximab, azathioprine, or combination therapy for Crohn's disease. *N Engl J Med.* Apr 15 2010;362:1383-1395.

30. Vincent FB, Morand EF, Murphy K, et al. Antidrug antibodies (ADAb) to tumour necrosis factor (TNF)-specific neutralising agents in chronic inflammatory diseases: a real issue, a clinical perspective. *Ann Rheum Dis.* Feb 2013;72:165-178.

31. Miele E, Markowitz JE, Mamula P, et al. Human antichimeric antibody in children and young adults with inflammatory bowel disease receiving infliximab. *J Pediatr Gastroenterol Nutr.* May 2004;38:502-508.

32. Cucchiara S, Escher JC, Hildebrand H, et al. Pediatric inflammatory bowel diseases and the risk of lymphoma: should we revise our treatment strategies? *J Pediatr Gastroenterol Nutr.* Mar 2009;48:257-267.

33. Diak P, Siegel J, La Grenade L, et al. Tumor necrosis factor alpha blockers and malignancy in children: forty-eight cases reported to the Food and Drug Administration. *Arthritis Rheum.* Aug 2010;62:2517-2524.

34. Choo PW, Rand CS, Inui TS, et al. Validation of patient reports, automated pharmacy records, and pill counts with electronic monitoring of adherence to antihypertensive therapy. *Medical care.* Sep 1999;37:846-857.

35. Grymonpre R, Cheang M, Fraser M, et al. Validity of a prescription claims database to estimate medication adherence in older persons. *Medical care.* May 2006;44:471-477.

Figure legend:
Figure 1. Kaplan-Meier plot of percentage of children and young adults with incident IBD who initiated TNFI therapy, by the time from disease diagnosis to the start date of TNFI use

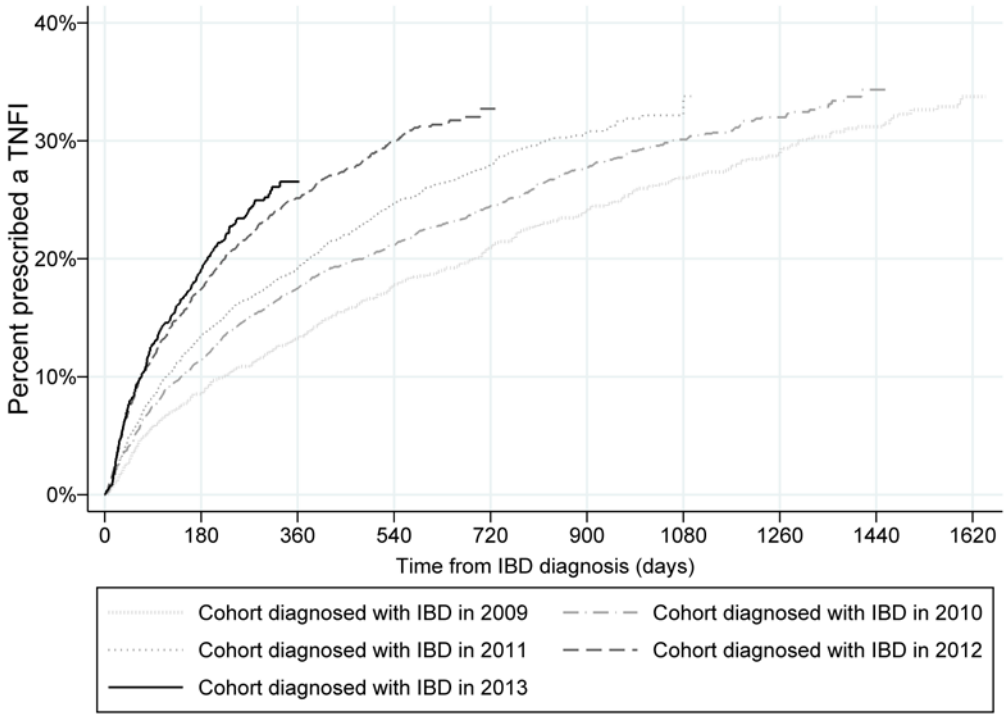

Table 1. Demographic characteristics and medication utilization among children and young adults with incident IBD

	Overall cohort (N=11,962)		Non-TNFI users (N=8,662)		TNFI users					
					Overall TNFI users (N=3,300)		Top-down strategy [a] (N=1,298)		Step-up strategy [a] (N=2,002)	
	n	%	n	%	n	%	n	%	n	%
Patient characteristics at baseline										
Age group										
Age <12	1,594	13.3%	1,188	13.7%	406	12.3%	155	11.9%	251	12.5%
Age 12-17	3,839	32.1%	2,563	29.6%	1,276	38.7%	533	41.1%	743	37.1%
Age 18-24	6,529	54.6%	4,911	56.7%	1,618	49.0%	610	47.0%	1,008	50.4%
Male	6,096	51.0%	4,310	49.8%	1,786	54.1%	730	56.2%	1,056	52.8%
Region										
Northeast	2,941	24.6%	2,175	25.1%	766	23.2%	322	24.8%	444	22.2%
Midwest	2,894	24.2%	2,050	23.7%	844	25.6%	316	24.4%	528	26.4%
South	3,974	33.2%	2,869	33.1%	1,105	33.5%	413	31.8%	692	34.6%
West	1,916	16.0%	1,386	16.0%	530	16.1%	215	16.6%	315	15.7%
Unknown	237	2.0%	182	2.1%	55	1.7%	32	2.5%	23	1.2%
Medication use [b]										
Corticosteroids	8,300	69.4%	5,992	69.2%	2,308	69.9%	422	32.5%	1,886	94.2%
Thiopurines	3,471	29.0%	2,199	25.4%	1,272	38.6%	175	13.5%	1,097	54.8%
Azathioprine	1,777	51.2%	1,114	50.7%	663	52.1%	98	7.6%	565	28.2%
6-mercaptopurine	1,694	48.8%	1,085	49.3%	609	47.9%	77	5.9%	532	26.6%
5-aminosalicylates	8,599	71.9%	6,871	79.3%	1,728	52.4%	224	17.3%	1,504	75.1%
Methotrexate	588	4.9%	201	2.3%	387	11.7%	94	7.2%	293	14.6%
TNFIs	3,300	27.6%	NA	NA	3,300	100.0%	1,298	100.0%	2,002	100.0%
Infliximab	2,303	69.8%	NA	NA	2,303	69.8%	1,034	79.7%	1,269	63.4%
Adalimumab	869	26.3%	NA	NA	869	26.3%	220	17.0%	649	32.4%
Certolizumab	123	3.7%	NA	NA	123	3.7%	44	3.4%	79	4.0%
Golimumab	5	0.2%	NA	NA	5	0.2%	0	0.0%	5	0.3%
Other immunosuppressants	55	0.5%	44	0.5%	11	0.3%	0	0.0%	11	0.6%

[a] The top-down treatment approach was defined as new TNFI prescription within 30 days of first IBD medication prescription; the step-up approach was defined as new TNFI prescription more than 30 days after first IBD medication prescription.
[b] Medication use was defined as presence of prescription claims during the follow-up period.
IBD: inflammatory bowel disease; NA: not applicable; TNFI: tumor necrosis factor-alpha inhibitor.

Table 2. Percent of children and young adults with incident IBD prescribed a TNF inhibitor, by age and agent

	Overall TNFI users		Top-down strategy [a]		Step-up strategy [a]		P value [b]
	n	%	n	%	n	%	
Age <12							
New TNFI use	406	100.0%	155	100.0%	251	100.0%	
By agent							
Infliximab	362	89.2%	146	94.2%	216	86.1%	0.010
Adalimumab	43	10.6%	9	5.8%	34	13.5%	0.014
Certolizumab	1	0.2%	0	0.0%	1	0.4%	1.000
Golimumab	0	0.0%	0	0.0%	0	0.0%	N/A
Age 12-17							
New TNFI use	1,276	100.0%	533	100.0%	743	100.0%	
By agent							
Infliximab	1,050	82.3%	490	91.9%	560	75.4%	<0.0001
Adalimumab	212	16.6%	40	7.5%	172	23.1%	<0.0001
Certolizumab	13	1.0%	3	0.6%	10	1.3%	0.258
Golimumab	1	0.1%	0	0.0%	1	0.1%	1.000
Age 18-24							
New TNFI use	1,618	100.0%	610	100.0%	1008	100.0%	
By agent							
Infliximab	891	55.1%	398	65.2%	493	48.9%	<0.0001
Adalimumab	614	37.9%	171	28.0%	443	43.9%	<0.0001
Certolizumab	109	6.7%	41	6.7%	68	6.7%	0.985
Golimumab	4	0.2%	0	0.0%	4	0.4%	0.304

[a] The top-down treatment approach was defined as new TNFI prescription within 30 days of first IBD medication prescription; the step-up approach was defined as new TNFI prescription more than 30 days after first IBD medication prescription.
[b] P value was generated from chi-square test for top-down versus step-up strategy.
IBD: inflammatory bowel disease; NA: not applicable; TNFI: tumor necrosis factor-alpha inhibitor.

Table 3. One-year TNFI switch rate by treatment strategy in children and young adults with incident IBD

	Overall TNFI users			Top-down strategy [c]			Step-up strategy [c]			
Initial TNFI therapy [a]	Total users	No. patients switched [b]	Switch rate	Total users	No. patients switched [b]	Switch rate	Total users	No. patients switched [b]	Switch rate	P-value [d]
Any TNFI	3,300	222	6.7%	1,298	74	5.7%	2,002	148	7.4%	0.0581
Infliximab	2,303	140	6.1%	1,034	54	5.2%	1,269	86	6.8%	0.1204
Adalimumab	869	64	7.4%	220	15	6.8%	649	49	7.6%	0.7195
Certolizumab	123	17	13.8%	44	5	11.4%	79	12	15.2%	0.7859
Golimumab	5	1	20.0%	0	0	NA	5	1	20.0%	NA

[a] Initial TNFI is the first prescribed TNFI.
[b] Only patients who switched their TNFIs in the first year after initiation were included.
[c] The top-down treatment approach was defined as new TNFI prescription within 30 days of first IBD medication prescription; the step-up approach was defined as new TNFI prescription more than 30 days after first IBD medication prescription.
[d] P value was generated from chi-square test for top-down versus step-up strategy.

TNFI: tumor necrosis factor-alpha inhibitor. NA: Not applicable.

Table 4. Time to discontinuation and persistence with first prescribed TNFI among children and young adults with incident IBD

	Duration (days), mean (median)	Persistence (%) [a]					
		1 month	3 months	6 months	12 months	18 months	24 months
Overall TNFI users							
Infliximab	405 (320)	98.2%	93.2%	82.4%	71.0%	64.1%	59.7%
Adalimumab	400 (307)	98.5%	92.3%	86.1%	74.8%	68.5%	63.3v
Certolizumab	413 (316)	97.8%	94.4%	77.8%	67.8%	61.7%	60.0%
Golimumab [b]	167 (167)	100.0%	100.0 %	NA	NA	NA	NA
Top-down strategy [c]							
Any TNFIs	418 (338)	97.3%	92.5%	80.8%	70.2%	61.5%	56.8%
Infliximab	411 (336)	97.3%	92.3%	80.1%	69.2%	60.1%	55.6%
Adalimumab	442 (349)	97.3%	93.4%	85.7%	73.7%	66.7%	60.0%
Certolizumab	471 (454)	97.1%	91.2%	71.9%	79.2%	70.6%	66.7%
Golimumab [b]	NA	NA	NA	NA	NA	NA	NA
Step-up strategy [c]							
Any TNFIs	393 (301)	98.9%	93.5%	85.0%	73.0%	67.7%	63.9%
Infliximab	399 (308)	98.9%	94.1%	84.6%	72.7%	67.9%	64.0%
Adalimumab	385 (289)	98.9%	91.9%	86.3%	75.3%	69.2%	64.8%
Certolizumab	380 (298)	98.3%	96.4%	81.6%	60.0%	56.7%	53.8%
Golimumab [b]	167 (167)	100.0%	100.0 %	NA	NA	NA	NA

NA: Not applicable.
[a] Persistence was defined as continuous claims with a gap less than 90 days.
[b] Only four patients (zero in the top-down strategy and four in the step-up strategy) were included in the analysis and none of them had enough follow-up for more than 3 months.
[c] The top-down treatment approach was defined as new TNFI prescription within 30 days of first IBD medication prescription; the step-up approach was defined as new TNFI prescription more than 30 days after first IBD medication prescription.

Table 5. Adherence with first prescribed TNFI among children and young adults with incident IBD

	Overall TNFI users				Top-down strategy [b]				Step-up strategy [b]			
	N	Mean	Median (IQR)	Min-Max	N	Mean	Median (IQR)	Min-Max	N	Mean	Median (IQR)	Min-Max
Infliximab [a]	1323	95.4%	99.5% (95.6-100.0)	51.4-100.0%	625	95.5%	99.4% (95.6-100.0)	51.4-100.0%	698	95.3%	99.4% (95.0-100.0)	53.0-100.0%
Adalimumab	497	91.0%	95.0% (86.2-99.5)	48.6-100.0%	144	90.2%	95.0% (85.9-99.7)	50.8-100.0%	353	91.3%	95.6% (86.7-99.4)	48.6-100.0%
Certolizumab	63	83.7%	84.5% (77.4-92.8)	43.1-100.0%	23	83.4%	81.2% (77.3-95.6)	55.8%-100.0%	40	83.9%	85.4% (77.1-92.8)	43.1-100.0%

[a] The adherence of infliximab was assessed using the service date for infliximab intravenous infusion.
[b] The top-down treatment approach was defined as new TNFI prescription within 30 days of first IBD medication prescription; the step-up approach was defined as new TNFI prescription more than 30 days after first IBD medication prescription.
IQR: interquartile range; PDC: proportion of days covered.