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Effectiveness of Anti-TNF α for Crohn Disease: Research in a Pediatric Learning Health System

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WHAT'S KNOWN ON THIS SUBJECT: Studies on adult patients who have Crohn disease have shown a comparative benefit of anti-TNF α versus placebo and thiopurines. These same studies have not been done in children, because of time, cost, and ethical (withholding an efficacious treatment) challenges.



WHAT THIS STUDY ADDS: Anti-TNF α therapy administered in routine practice to children with Crohn disease was more effective than usual care at achieving clinical and corticosteroid-free remission. Using data from the ImproveCareNow learning health system for observational research is feasible and produces valuable evidence.

abstract

OBJECTIVES: ImproveCareNow (ICN) is the largest pediatric learning health system in the nation and started as a quality improvement collaborative. To test the feasibility and validity of using ICN data for clinical research, we evaluated the effectiveness of anti-tumor necrosis factor- α (anti-TNF α) agents in the management of pediatric Crohn disease (CD).

METHODS: Data were collected in 35 pediatric gastroenterology practices (April 2007 to March 2012) and analyzed as a sequence of non-randomized trials. Patients who had moderate to severe CD were classified as initiators or non-initiators of anti-TNF α therapy. Among 4130 patients who had pediatric CD, 603 were new users and 1211 were receiving anti-TNF α therapy on entry into ICN.

RESULTS: During a 26-week follow-up period, rate ratios obtained from Cox proportional hazards models, adjusting for patient and disease characteristics and concurrent medications, were 1.53 (95% confidence interval [CI], 1.20–1.96) for clinical remission and 1.74 (95% CI, 1.33–2.29) for corticosteroid-free remission. The rate ratio for corticosteroid-free remission was comparable to the estimate produced by the adult SONIC study, which was a randomized controlled trial on the efficacy of anti-TNF α therapy. The number needed to treat was 5.2 (95% CI, 3.4–11.1) for clinical remission and 5.0 (95% CI, 3.4–10.0) for corticosteroid-free remission.

CONCLUSIONS: In routine pediatric gastroenterology practice settings, anti-TNF α therapy was effective at achieving clinical and corticosteroid-free remission for patients who had Crohn disease. Using data from the ICN learning health system for the purpose of observational research is feasible and produces valuable new knowledge. *Pediatrics* 2014;134:37–44

Over the last several decades, therapeutic advances in the treatment of pediatric Crohn disease (CD) have included the widespread use of immunomodulators such as 6-mercaptopurine, azathioprine, and methotrexate.^{1–3} More recently, the anti-tumor necrosis factor α (anti-TNF α) biological agents (eg, infliximab and adalimumab) have been adopted as a treatment of moderate to severe pediatric CD.⁴ Although several studies on adult patients who have CD have shown a comparative benefit of anti-TNF α versus placebo⁵ and thiopurines,⁶ these same studies have not been done in children because of practical (time and cost) and ethical (withholding an efficacious treatment) challenges.

The cost of anti-TNF α is in the range of tens of thousands of dollars per year, and the long-term direct and indirect costs are substantial.⁷ Administration of anti-TNF α has been associated with serious infections, hepatic T-cell lymphomas, systemic lupus, and blood disorders.⁸ Variation in the management of pediatric patients who have CD results in part from a paucity of evidence on how to best treat patients who have this disorder.^{9–11} The costs, risks, and treatment variability of anti-TNF α therapy are key reasons it was selected as 1 of the Institute of Medicine's top 25 comparative effectiveness research priorities.¹²

To address the lack of information on the effectiveness of anti-TNF α therapy for moderate to severe pediatric CD, we conducted a study to evaluate use of these agents to induce remission among children managed in pediatric gastroenterology practices. Similar to pragmatic clinical trials, which assess the effectiveness of therapies in unselected patients,¹³ our study contrasted initiation of biologic therapy among pediatric patients who had moderate to severe CD with usual care, which may involve any combination of thiopurines, methotrexate, corticosteroids, 5-aminosalicylates, nutrition therapy, and surgery.

The study was done in ImproveCareNow (ICN), which started as a quality improvement collaborative and is becoming a national, distributed learning health system. A learning health system is organized around communities of patients, clinicians, and researchers who work together to purposefully integrate knowledge generation (research) with knowledge dissemination and implementation at the point-of-care (quality improvement).^{14–19}

ICN has included a chronic disease registry since 2007. Initially, it was used expressly for quality improvement. We sought to test the feasibility and validity of using these data for comparative effectiveness research. In addition to estimating treatment effects, we contrasted our results with those reported in 2 controlled trials: an anti-TNF α efficacy study done with pediatric patients (the REACH study⁴) and a comparative study of anti-TNF α versus thiopurines done with adult patients (the SONIC study⁶).

METHODS

Study Setting

ICN was established in 2007 to improve the health and health care of children who have inflammatory bowel disease (IBD).^{20,21} Participating pediatric gastroenterology practices enrolled patients in an IBD registry, collected data at each outpatient visit, conducted quality improvement activities, and participated in research. Although sites worked to provide highly reliable care through the use of quality improvement methodology adapted to local circumstances, specific therapeutic choices were at the discretion of physicians.

We created a research dataset from the ICN registry by encrypting patient, physician, and practice identifiers and offsetting dates by a patient-specific randomly generated constant. The Children's Hospital of Philadelphia's Institutional Review Board deemed this

research exempt from continuing review. The registry comprised longitudinal records of clinical care and health status collected during outpatient encounters and entered via a web-portal into a central database. Data elements included symptoms, results of physical examinations, laboratory values, physician assessments, and prescribed therapies. To standardize data collection, all sites were trained in the use of the case report form. Select data issues were reviewed at semi-annual in-person meetings, monthly webinars, and via listserv.

This study used ICN registry data collected from April 2007 to March 2012. A total of 35 pediatric gastroenterology practices enrolled 6402 patients who had IBD; of these, there were 4130 (65%) patients who had CD who made 20 456 visits.

Disease Activity

For each visit, clinicians recorded the components of the Short Pediatric Crohn's Disease Activity Index (sPCDAI)²² and a Physician Global Assessment rating of disease severity (from 1 [inactive] to 4 [severe disease]). The sPCDAI used 6 of the 11 components from the full PCDAI,²³ including abdominal pain, stools, weight loss, abdominal examination, extra-intestinal manifestations, and general well-being. The sPCDAI has comparable discriminatory accuracy for categorizing disease severity as the full PCDAI.²² Based on the scoring conventions for the full PCDAI, we defined moderate to severe disease as a sPCDAI score ≥ 30 , and clinical remission as a score < 10 . A remission was considered corticosteroid-free if a visit satisfied the clinical remission criterion and the patient was not taking oral corticosteroids at any dose. We did not evaluate whether corticosteroid-free remission was sustained.

Missing Data

Across the full dataset 8% of the sPCDAI components were missing; 41% of visits

had at least 1 missing component. To address this problem, we implemented multiple imputation (MI) using the SAS procedure MI (SAS Institute, Inc, Cary, NC). MI provides a range of reasonable predictions for missing data. Inferences obtained from multiply imputed data account for both the missing data and the uncertainty of the imputations.^{24–26}

We implemented MI by creating 100 replicates of the dataset. The imputation procedure fit a discriminant model, which is appropriate for categorical data such as the sPCDAI components.²⁷ The independent variables in the discriminant models were age, gender, race (white, black, other), disease phenotype (inflammatory, stricturing, or penetrating), disease location (ileum, colon, and upper tract), concurrent medications (thiopurines, methotrexate, 5-aminosalicylates, and oral corticosteroids), Physician Global Assessment of disease severity, practice site, and duration of disease. Once missing components were imputed, we computed the sPCDAI score. The trials were formed and statistical models run separately for each replicate, and then results were pooled to obtain single treatment estimates.

Trial Formation

We conceptualized the registry dataset as a sequence of nonrandomized trials in which anti-TNF α therapy was initiated or not initiated.²⁸ This sequential-trials strategy allows a patient to contribute >1 trial to the analysis, which makes greatest use of available data.^{28,29} To be eligible as a first visit in an initiator trial (ie, the baseline visit), the patient had to be a new user of anti-TNF α (either infliximab or adalimumab) therapy. All visits made by patients who never used biologic therapy were potential non-initiator baseline visits. Among users of biologic therapy, visits that occurred before the start of biologic initiation

were potential starting points for non-initiator trials.

Eligibility criteria for baseline visits for all trials were age <21 years and moderate to severe disease severity (sPCDAI score ≥ 30). Trials also included a visit during the follow-up period, which began at 2 weeks and concluded at 26 or 52 weeks, and at least 1 visit before the start of the trial.

We applied the trial selection criteria to the 100 replicates of the dataset. Because some of the sPCDAI components were imputed by using MI, the sPCDAI values varied across replicates; thus, trials could meet the inclusion criteria of sPCDAI ≥ 30 in some but not other replicates. The number of trials ranged from 232 to 252 per replicate, with a mean of 241 for initiators, and 1147 to 1210 per replicate, with a mean of 1182 for non-initiators. Across the 100 replicates, patients contributed 1.9 trials on average.

Statistical Analyses

Outcomes for trials (clinical remission or corticosteroid-free remission) were evaluated regardless of whether patients subsequently altered therapy. This approach makes use of the intention-to-treat principle. We conducted bivariate analyses to test the comparability between initiator and non-initiator trials on patient, disease, and pharmacological treatment characteristics measured at baseline. These were implemented with logistic (categorical covariates) or linear (continuous covariates) regression models that regressed type of trial (initiator versus non-initiator) on 1 covariate and obtained robust variance estimates, accounting for clustering of trials within a patient, for the differences in proportions or means.

We computed the unadjusted probability of achieving remission during 26 or 52 weeks of follow-up. We adjusted the probability of achieving remission

by using the generalized estimating equation (GEE), clustering on patients, with a logit link function, and adjusted for patient age in years, gender (male, female), race (white, black, other), disease phenotype (inflammatory, stricturing, penetrating), location of disease (ileum, colon, upper tract; all yes/no indicators), time since CD diagnosis (<1 year vs ≥ 1 year), and medication use (thiopurines, methotrexate, 5-aminosalicylates, and corticosteroids; all yes/no indicators).

We estimated rate ratios by fitting a Cox proportional hazards model, with time since the start of the trial as the time variable, and adjusted for the covariates used in the GEE models. Separate models were fit with 26- and 52-week durations of follow-up.

To evaluate the timing of the effect of biologics on induction of remission, we plotted the cumulative probability of remission and corticosteroid-free remission as a function of time. We estimated the cumulative probability of the outcomes by week of follow-up for the 100 imputed replicates and averaged these values to create the plots.

To estimate a number needed to treat (NNT), we extended the trials to include a 26-week pre-trial observation period. This longitudinal analysis contrasted the within-subjects pre–post change between the 2 treatment groups. We fit the generalized estimating equation, clustering on patient, and regressed the outcome on covariates and a 4-category variable for treatment group (initiator or non-initiator) by time period (pre or post). The treatment effect estimate contrasted the average trial-level probability of remission from the pre- to the post-period in the initiator versus non-initiator groups. The NNT was computed as the reciprocal of the absolute percentage difference between the 2 groups³⁰; we also computed 95% confidence intervals (CI) for the NNTs.³¹

Some trials were censored at their last visit because the treatment outcome was not achieved during the observation period. Among these right-censored trials, we identified those with a visit 27 to 52 weeks after the start of the trial and used linear interpolation to assign a sPCDAI score at 26 weeks and then re-estimated treatment effects. We also re-estimated treatment effects using the single-item Physician Global Assessment, which was present for 96% of pediatric CD visits.

Comparison With REACH and SONIC

We applied the REACH selection criteria to initiator trials,⁴ which involved restricting the sample to those who started anti-TNF α >3 months after diagnosis and were receiving thiopurines and/or methotrexate at the time of trial initiation. Although REACH assessed remission at 10 weeks, we allowed assessment to occur as late as 16 weeks to account for variation in visit frequency.

We reanalyzed the SONIC study of adult CD patients⁶ by combining its anti-TNF α treatment arms (anti-TNF α only and anti-TNF α with thiopurine), computing the 26-week corticosteroid-free remission rate, and estimating a rate ratio using the thiopurine-only group as the referent. We contrasted these results with our study's estimates.

RESULTS

Among the pediatric patients who had CD in our sample, 1814 received anti-TNF α therapy, and of these, 603 started therapy during the time of the study. There were 2316 patients who never used anti-TNF α therapy.

Patient and disease characteristics and concurrent medications at the baseline visit of trials are shown in Table 1. Non-initiator trials were more likely to begin with thiopurines, 5-aminosalicylates, and corticosteroids. Physicians rated disease severity as higher for the initiator

trials, despite sPCDAI scores comparable to the non-initiator trials.

By 26 weeks, initiator trials had a 54.4% chance of achieving remission, whereas non-initiators had a 41.2% chance (Table 2). Also, by 26 weeks, initiators had a 47.3% chance of achieving corticosteroid-free remission vs 31.2% for non-initiators. Adjusting for patient and disease characteristics and baseline medications produced comparable remission rate estimates to unadjusted analyses.

The remission rate ratios for 26 and 52 weeks of follow-up were similar in unadjusted and adjusted analyses (Table 3). Initiator trials were ~50% more likely to achieve clinical remission and 70%

more likely to achieve corticosteroid-free remission compared with non-initiator trials.

Figure 1 shows the cumulative probability of remission and corticosteroid-free remission among the initiator and non-initiator trials. The biologic treatment effect emerged as early as 6 weeks of follow-up, which was when the curves began to separate.

Analyses replacing the sPCDAI with Physician Global Assessment of disease severity produced a 26-week rate ratio of 1.46 (95% CI, 1.16–1.85) for clinical remission and 1.82 (95% CI, 1.41–2.35) for corticosteroid-free remission, which were similar to the estimates obtained from the sPCDAI.

TABLE 1 Baseline Characteristics (ie, First Visit for Each Trial) for Anti-TNF α Initiator and Non-Initiator Trials

Characteristic	Initiator Trials	Non-Initiator Trials	P
	% (95% CI)		
Patient gender			
Male	51.4 (44.9–57.9)	50.8 (45.9–55.8)	.88
Female	48.6 (42.1–55.1)	49.2 (44.2–54.1)	
Patient race			
White	82.3 (77.1–87.4)	84.2 (80.7–87.7)	.27
Black	13.6 (8.9–18.2)	10.2 (7.4–13.0)	
Other	4.2 (1.4–6.9)	5.6 (3.3–7.9)	
Disease phenotype			
Inflammatory	89.0 (84.7–93.2)	87.1 (83.4–90.8)	.63
Strictureing	3.9 (1.2–6.6)	5.4 (3.0–7.8)	
Penetrating	7.1 (3.7–10.6)	7.5 (4.4–10.5)	
Disease locations			
Ileum	72.0 (66.1–77.8)	71.5 (66.9–76.0)	.87
Colon	86.9 (82.5–91.2)	83.7 (80.2–87.1)	.19
Upper tract	51.2 (44.7–57.7)	52.4 (47.4–57.4)	.74
Medications			
Thiopurine	33.8 (27.7–39.9)	59.6 (55.6–63.5)	<.01
Methotrexate	10.1 (6.2–13.9)	6.8 (4.8–8.8)	.12
5-Aminosalicylate	35.3 (29.1–41.5)	49.5 (45.2–53.8)	<.01
Corticosteroid	27.2 (21.5–33.0)	43.4 (39.6–47.1)	<.01
	Mean (95% CI)		
Age (y)	14.9 (14.5–15.4)	14.6 (14.3–15.0)	.24
Weight (kg)	51.3 (49.0–53.5)	49.9 (48.1–51.7)	.30
Height (cm)	157.9 (155.6–160.2)	155.9 (154.0–157.8)	.14
Disease duration (y)	2.8 (2.4–3.1)	2.7 (2.5–3.0)	.75
sPCDAI score	41.9 (40.4–43.4)	41.1 (40.4–41.8)	.36
Physician Global Assessment	2.7 (2.6–2.8)	2.4 (2.3–2.4)	<.01
C-reactive protein (mg/L) ^a	4.8 (3.2–6.4)	5.3 (4.1–6.4)	.64
Erythrocyte sedimentation rate (mm/h) ^a	28.5 (25.2–31.9)	24.5 (22.6–26.5)	.03
Albumin (g/dL) ^a	3.9 (3.8–3.9)	3.9 (3.9–4.0)	.13
Hematocrit (%) ^a	36.1 (35.4–36.9)	36.9 (36.5–37.2)	.07

^a On average across the 100 replicates, C-reactive protein values were available for 54% of initiator and 50% of non-initiator trials, erythrocyte sedimentation rate for 77% of initiator and 68% of non-initiator trials, albumin for 77% of initiator and 73% of non-initiator trials, and hematocrit for 81% of initiator and 78% of non-initiator trials.

TABLE 2 Percentage of Trials Achieving Remission and Corticosteroid-Free Remission During 26- And 52-Week Follow-up Periods

Outcome	Duration of Follow-up	Initiator Trials	Non-Initiator Trials
		% Achieving Outcome (95% CI)	
Unadjusted			
Clinical remission	26 wk	54.4 (47.7–61.1)	41.2 (38.2–44.2)
	52 wk	66.6 (60.3–72.8)	56.2 (53.2–59.3)
Corticosteroid-free remission	26 wk	47.3 (40.6–53.9)	31.2 (28.4–34.0)
	52 wk	60.1 (53.7–66.5)	47.5 (44.5–50.5)
Adjusted ^a			
Clinical remission	26 wk	54.8 (47.2–62.4)	40.7 (36.5–45.0)
	52 wk	67.3 (60.1–74.4)	55.6 (51.1–60.1)
Corticosteroid-free remission	26 wk	45.6 (38.1–53.1)	30.8 (26.8–34.7)
	52 wk	58.8 (51.5–66.2)	47.0 (42.5–51.5)

^a Proportions were adjusted for patient age, gender, and race, disease location, duration, and phenotype, and concurrent medications, all measured at baseline of the trial.

On average across the 100 imputed replicates, 110 initiator and 695 non-initiator trials were right-censored because they did not achieve remission and did not have a visit at 6 months. We interpolated a sPCDAI value at 26 weeks for these trials and re-estimated the rate ratio for remission, which was 1.54 (95% CI, 1.23–1.93).

There were an average of 159 initiator and 897 non-initiator trials in the 100 imputed replicates for analyses that involved a 26-week observation period before trial initiation and 26-week follow-up interval (ie, post-period). On average, the chances of remission for initiators were 32.6% higher in the post-period compared with the pre-period, whereas the post-pre change for non-initiators was just 13.2%. The difference-in-difference treatment effect estimate adjusts the change in the initiator group for the change in the

non-initiator group and was 19.4% (95% CI, 9.0–29.8) for clinical remission, an NNT of 5.2 (95% CI, 3.4–11.1). The corticosteroid-free remission difference-in-difference estimate was 19.9% (95% CI, 10.0–29.8) with an NNT of 5.0 (95% CI, 3.4–10.0).

Contrast With REACH and SONIC

Applying REACH selection criteria⁴ to the ICN sample yielded an average of 75 initiator trials across the 100 replicates. The clinical response rates (to be consistent with REACH, defined for ICN as sPCDAI score <30 and a minimum decrease of 15) were: REACH 88% (95% CI, 82%–94%)⁴ vs ICN 82% (95% CI, 72%–91%). The clinical remission rates were: REACH 59% (95% CI, 50%–68%)⁴ vs ICN 49% (95% CI, 38%–61%).

Combining the infliximab-only with the infliximab plus thiopurines treatment arms from the SONIC trial⁶ yielded a 26-week corticosteroid-free remission rate

of 51%, which contrasts with our study's estimate of 47%. The unadjusted corticosteroid-free remission rate ratios for the contrast with the comparison groups were 1.69 (95% CI, 1.31–2.17) for SONIC and 1.73 (95% CI, 1.38–2.16) for ICN.

DISCUSSION

This study provides evidence that anti-TNF α therapy given to pediatric patients who have moderate to severe CD in real-world settings is effective at achieving remission at rates comparable to single-group, open-label clinical trials, such as REACH,⁴ with pediatric patients and comparative controlled studies done with adults, such as SONIC.⁶ The treatment effect emerged as early as 6 weeks after initiation of therapy. In our analyses the outcome was achieved once a visit satisfied either the clinical or corticosteroid-free remission criteria, even if subsequently the patient may have experienced a worsening in disease activity. Thus, our results provide evidence on induction but not maintenance of remission.

There are important differences between our observational study and REACH and SONIC. Although we applied the REACH selection criteria to initiator trials, not all patients in our study were assessed at 10 weeks; instead, we allowed a patient to be assessed as late as 16 weeks to account for variation in visit frequency, which was at the discretion of patients and clinicians. Neither REACH nor our study were masked. The SONIC study was done with an adult sample, randomized and double-blinded, and enrolled patients naïve to thiopurines.

Like an open-labeled randomized trial, the effect of treatment initiation in our nonrandomized trials tests the combination of pharmacological and behavioral effects induced by treatment awareness among clinicians and participants. Both patients and clinicians

TABLE 3 Rate Ratios For Initiator Trials Versus Non-Initiator Trials at 10, 26, and 52 Weeks of Follow-up

Outcome	Duration of Follow-up	Unadjusted Rate Ratios (95% CI)	Adjusted Rate Ratios ^a (95% CI)
		Initiator versus Non-Initiator Trials	
Clinical remission	26 wk	1.44 (1.17–1.77)	1.53 (1.20–1.96)
	52 wk	1.46 (1.22–1.74)	1.52 (1.23–1.89)
Corticosteroid-free remission	26 wk	1.73 (1.38–2.16)	1.74 (1.33–2.29)
	52 wk	1.63 (1.35–1.97)	1.62 (1.28–2.04)

^a Rate ratios were adjusted for patient age, gender, and race, disease location, duration, and phenotype, and concurrent medications, all measured at baseline of the trial.

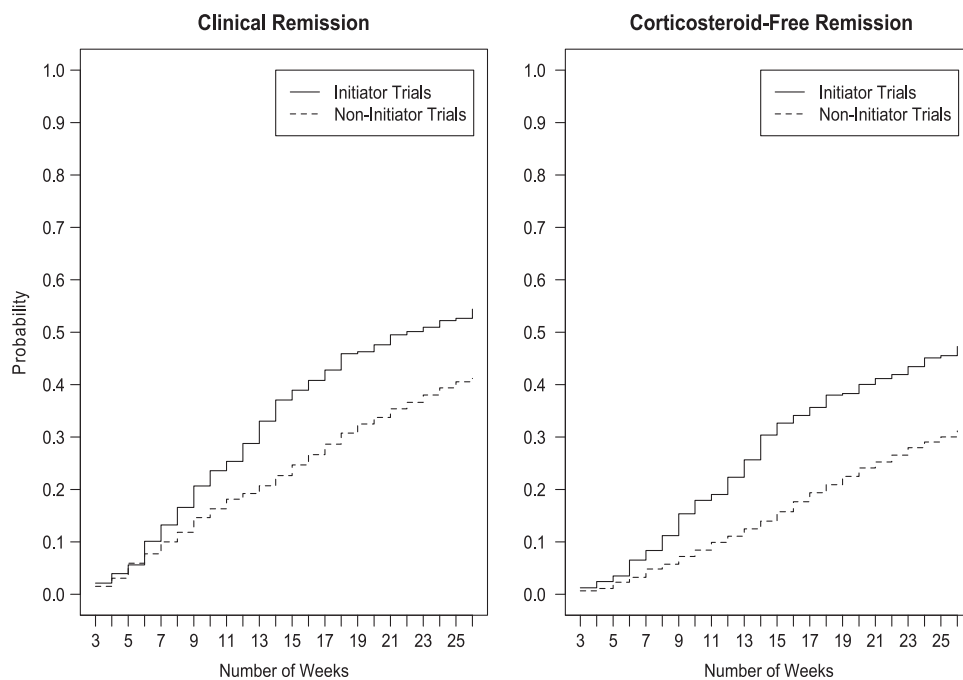


FIGURE 1 Cumulative probability of remission and corticosteroid-free remission for initiator and non-initiator trials during a 26-week follow-up period.

were aware of the decision to use biologic therapy. For this reason, we preferred the use of the sPCDAI over the Physician Global Assessment of disease severity. The sPCDAI provided a more objective assessment of disease activity, whereas the Physician Global Assessment may have been subject to information bias, in which physicians factored use of biologics into their summary assessment of disease severity. It was reassuring that analyses using the Physician Global Assessment, which had less missing data, produced the same treatment effect estimates as the sPCDAI.

As the demand for comparative effectiveness evidence increases, new strategies for estimating treatment effects using observational data will be needed. This is particularly true for pediatrics, which frequently imports results of adult studies into its evidence base. The approach we used in this study to examine observational registry data as a sequence of nonrandomized trials is a promising methodology that can be extended to other clinical

questions.^{28,29} The method allows generalization of likely benefits to patients as it avoids overly strict selection criteria that characterize explanatory clinical trials, which test efficacy and are not representative of real-world practice.³²

One of our biggest concerns regarding the repurposing of the ICN registry data for research was missing data. We used MI, which assumes that data are missing at random and missingness is not informative.²⁶ This assumption may not hold in our study, because it is possible that clinicians were less likely to perform some examinations in patients who had low disease activity. The similarity in treatment effects obtained with the sPCDAI and Physician Global Assessment of disease severity, which was present for nearly every visit, was reassuring. Unmeasured confounders, such as mucosal inflammation observed by endoscopy, may have positively influenced both the decision to initiate treatment and the level of disease activity; if this were the case, biologic treatment effectiveness would be underestimated. A fi-

nal limitation is the potential for bias introduced by loss to follow-up. If this occurred at a greater frequency among anti-TNF α users in remission (less frequent follow-up among patients doing well) this would further underestimate treatment effectiveness.

CONCLUSIONS

Our findings suggest that anti-TNF α agents are comparatively more effective than usual care for treating children who have moderate to severe CD who are managed in routine clinical practice settings. We have demonstrated that prospectively collected data from a large pediatric learning health system can be used to answer important clinical questions that cannot be addressed with controlled trials because of practical or ethical challenges. The study's methodology offers advantages relative to conventional clinical trials in terms of time, cost, recruitment, and the capacity to forgo use of placebo. Our results are remarkably consistent with those of single-group efficacy studies among

children⁴ and comparative controlled clinical trials done among adults,^{4,6} but they expand the evidence base by providing new information on the comparative effectiveness of anti-TNF α for CD managed in routine pediatric gastroenterology settings.

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KEY WORDS

Crohn disease, comparative effectiveness research, anti-tumor necrosis factor- α , child

ABBREVIATIONS

anti-TNF α —anti-tumor necrosis factor- α

CD—Crohn disease

CI—confidence interval

IBD—inflammatory bowel disease

ICN—ImproveCareNow

MI—multiple imputation

NNT—number needed to treat

sPCDAI—Short Pediatric Crohn Disease Activity Index

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Effectiveness of Anti-TNF α for Crohn Disease: Research in a Pediatric Learning Health System

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