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INFLAMMATORY BOWEL DISEASE

Comparative Effectiveness of Anti-TNF in Combination With Low-Dose Methotrexate vs Anti-TNF Monotherapy in Pediatric Crohn's Disease: A Pragmatic Randomized Trial

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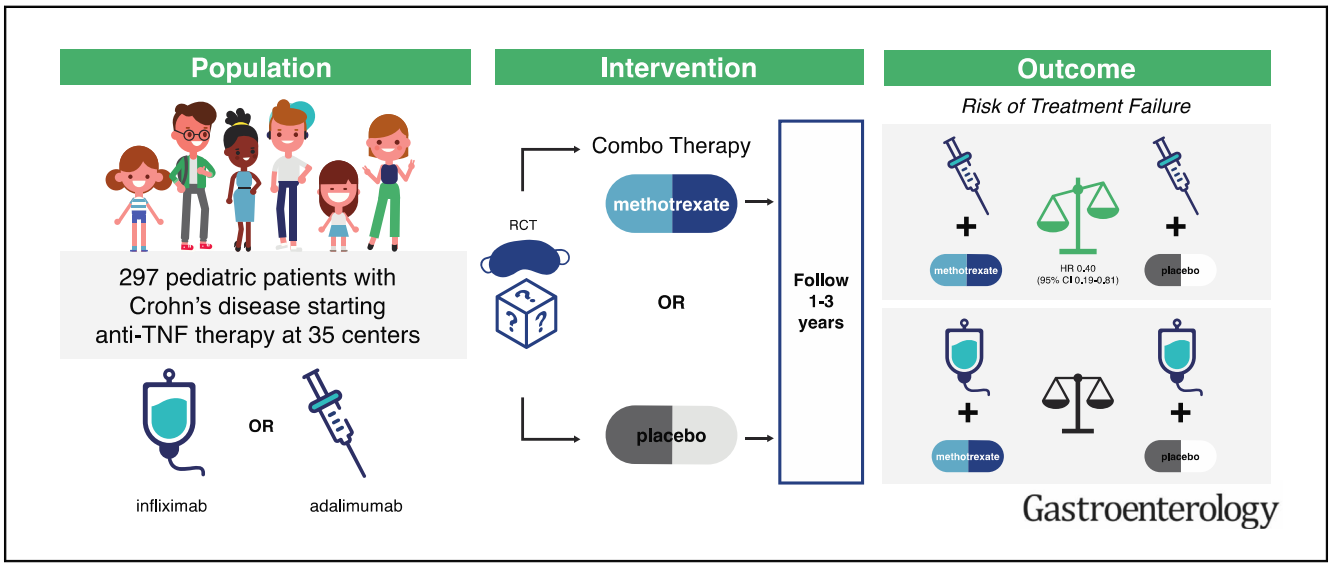

BACKGROUND & AIMS: Tumor necrosis factor inhibitors, including infliximab and adalimumab, are a mainstay of pediatric Crohn's disease therapy; however, nonresponse and loss of response are common. As combination therapy with methotrexate may improve response, we performed a multicenter, randomized, double-blind, placebo-controlled pragmatic trial to compare tumor necrosis factor inhibitors with oral methotrexate to tumor necrosis factor inhibitor monotherapy. **METHODS:** Patients with pediatric Crohn's disease initiating infliximab or adalimumab were randomized in 1:1 allocation to methotrexate or placebo and followed for 12–36 months. The primary outcome was a composite indicator of treatment failure. Secondary outcomes included anti-drug antibodies and patient-reported outcomes of pain interference and fatigue. Adverse events (AEs) and serious AEs (SAEs) were collected. **RESULTS:** Of 297 participants (mean age, 13.9 years, 35% were female), 156 were assigned to methotrexate (110 infliximab initiators and 46 adalimumab initiators) and 141 to placebo (102 infliximab initiators and 39 adalimumab initiators). In the overall population, time to treatment failure did not differ by study arm (hazard ratio, 0.69; 95% CI, 0.45–1.05). Among infliximab initiators, there were no differences between combination and monotherapy (hazard ratio, 0.93; 95% CI, 0.55–1.56). Among adalimumab initiators, combination therapy was associated with longer time to treatment failure (hazard ratio, 0.40; 95% CI, 0.19–0.81). A trend toward lower anti-drug antibody development in the combination therapy arm was not significant (infliximab: odds ratio, 0.72; 95% CI, 0.49–1.07; adalimumab: odds ratio, 0.71; 95% CI, 0.24–2.07). No differences in patient-reported outcomes were observed. Combination therapy resulted in more AEs but fewer SAEs. **CONCLUSIONS:** Among adalimumab but not infliximab initiators, patients with pediatric Crohn's disease treated with methotrexate combination therapy experienced a 2-fold reduction in treatment failure with a tolerable safety profile. ClinicalTrials.gov, Number: NCT02772965.

Keywords: Crohn's Disease; Children; Anti-Tumor Necrosis Factor–α; Infliximab; Adalimumab; Methotrexate.

[§] **Authors share co-senior authorship.**

Abbreviations used in this paper: **ADA, anti-drug antibody; AE, adverse event; CD, Crohn's disease; HR, hazard ratio; PRO, patient-reported outcome; PROMIS, Patient Reported Outcome Measurement and Information System; SAE, serious adverse event; SPCDAI, Short Pediatric Crohn's Disease Activity Index; TDM, therapeutic drug monitoring; TNF, tumor necrosis factor.**

Most current article

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Crohn's disease (CD) is a chronic inflammatory bowel disease that affects approximately 600,000 Americans[1] and 1.1 million Europeans,[2] costs $3.6 billion annually,[3] and results in substantial morbidity,[4] absenteeism,[5] and diminished quality of life.[6] Pediatric CD (PCD) is often more severe,[7] impacting psychosocial and physical development substantially.[8]

Anti–tumor necrosis factor (TNF) biologics (infliximab and adalimumab) have revolutionized the treatment of PCD. However, despite robust efficacy, not all patients achieve remission, and many lose response over time.[9] Combination therapy with a second immunosuppressive agent can improve response and prevent anti-drug antibody (ADA) development,[10] which may contribute to loss of response.[11] The risks of combination therapy include further immune suppression and a low, but well-described, risk of malignancy.[12]

In a landmark trial of adult CD, patients receiving combination therapy with infliximab and azathioprine had higher rates of remission and less frequent ADA development than those treated with infliximab monotherapy.[13] In PCD, methotrexate is generally used in combination therapy, due to malignancy concerns with azathioprine. However, evidence to support oral methotrexate is lacking. A randomized trial of subcutaneous methotrexate with infliximab in adult CD[14] found no differences in clinical outcomes. However, patients receiving combination therapy were less likely to develop ADA, raising the possibility that the trial was too short to observe differences resulting from ADA development.

Maximizing anti-TNF response is particularly important in PCD, as second-line treatments for adults are not US Food and Drug Administration–approved in children. Yet, the benefits and risks of anti-TNF combination therapy have not been well-established. We conducted a randomized, double-blind, multicenter, pragmatic clinical trial to compare the effectiveness and safety of anti-TNF in combination with low-dose, oral methotrexate vs monotherapy. We hypothesized that combination therapy would be more effective with tolerable safety.

WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

Anti-tumor necrosis factor (TNF) inhibitors, including infliximab and adalimumab, are a mainstay of pediatric Crohn's disease (PCD) therapy; however, nonresponse and loss of response is common. Combination therapy with methotrexate may improve response.

NEW FINDINGS

We conducted a randomized, double-blind, multicenter, pragmatic clinical trial to compare anti-TNF in combination with low-dose oral methotrexate to anti-TNF monotherapy in children with PCD. Among infliximab initiators, there were no differences between combination and monotherapy. Among adalimumab initiators, combination therapy was associated with longer time to failure. Combination therapy resulted in more adverse events, but fewer serious adverse events.

LIMITATIONS

Slow recruitment compounded by the COVID-19 pandemic prevented us from reaching our recruitment target. Thus, some of our analyses were underpowered. As a pragmatic trial, we prioritized inclusion of outcomes routinely assessed in clinical care. Therefore, we could include endoscopy or other measures of mucosal healing (ie, calprotectin or imaging) as trial end points.

CLINICAL RESEARCH RELEVANCE

These findings suggest strong consideration of using methotrexate combination therapy for patients with PCD initiating adalimumab but not infliximab. Future research evaluating other strategies to optimize anti-TNF therapy and focusing on outcomes of mucosal healing are necessary.

BASIC RESEARCH RELEVANCE

This randomized controlled trial found that combination therapy with adalimumab and methotrexate results in fewer treatment failures than adalimumab monotherapy. Future research to identify clinical, genetic, immunologic, and microbiome-related predictors of response and loss of response to anti-TNF therapy will further inform precision medicine approaches to guide care.

Methods

Study Setting

We recruited participants at 35 US centers participating in the ImproveCareNow Network[15] between October 2018 and December 2021. The Institutional Review Board at Cincinnati Children's Medical Center approved the study protocol.

Participants

Participants were younger than 21 years, ≥20 kg, diagnosed with PCD by standard criteria,[16] and initiating infliximab or adalimumab (or biosimilars). Exclusion criteria were prior anti-TNF treatment for PCD, anti-TNF use for postoperative prophylaxis without active disease, abdominal or pelvic abscess, other methotrexate contraindications, lack of stable address, anticipated short follow-up, and inability to provide assent and/or consent.

Intervention and Comparator

Our primary intervention was oral methotrexate or an identically matched placebo manufactured and tested by Temple CGMP Services (Philadelphia, PA), in addition to the anti-TNF agent. Selection and dosing of the anti-TNF agent was at the discretion of the treating physician in accordance with pragmatic trial design.[17] Therapeutic drug monitoring (TDM) and dose and interval adjustment were allowed.

For those in the active arm, oral methotrexate was administered with a weekly dose of 15 mg for children ≥40 kg, 12.5 mg for children 30 to <40 kg, and 10 mg for children 20 to <30 kg. All participants received pretreatment with ondansetron 4 mg (or placebo) to prevent nausea and folic acid (1 mg/d).

Study medications were dispensed by mail and refilled quarterly by a central investigational pharmacy (McKesson, Irving, TX).

Randomization and Masking

Randomization occurred within 42 days of anti-TNF initiation. We randomized participants with a computer-generated 1:1 allocation ratio, stratified by site and anti-TNF agent using constrained block sequences with a maximum imbalance of 3.[18] On randomization, the treatment assignment was sent electronically to the study pharmacy directly. By necessity, the study central study pharmacy was unblinded. Participants, caregivers, study teams, the overall study principal investigator, and the lead statistician were blinded until completion of analysis.

Prior and Concomitant Medications

Immunomodulators were discontinued before randomization, if applicable. Patients treated with corticosteroids were initiated on a taper at the discretion of the treating physician. Other immunosuppressants or biologics were not permitted.

Study Outcomes

Primary outcome. The primary outcome, an indicator of failure to achieve or maintain steroid-free remission, was defined by occurrence of any of the following: failure to achieve remission (Short Pediatric Crohn's Disease Activity Index [SPCDAI] <15) by week 26; failure to complete a steroid taper by week 16; SPCDAI ≥ 15, attributed to active CD, at 2 or more consecutive visits beyond week 26; hospitalization or surgery for CD beyond week 26; use of corticosteroids for CD for ≥ 10 weeks cumulatively, beyond week 16; and discontinuation of anti-TNF and/or study drug for lack of effectiveness or toxicity.

Treatment de-escalation or discontinuation of anti-TNF or study medication for nonmedical reasons was not considered a treatment failure.

Secondary outcomes. We conducted a multistakeholder process to identify and prioritize a set of previously validated patient-reported outcomes (PROs) from the National Institutes of Health Patient Reported Outcome Measurement and Information System (PROMIS) that were most relevant to patients with PCD. In an initial phase, 42 children with CD, 70 parents, and 26 expert clinicians rated the importance of available PROMIS item banks. The domains of Pain Interference and Fatigue emerged as the highest priority. We next conducted semi-structured interviews with 37 patients and cognitive interviews with 14 patients to further explore their experiences with fatigue and pain. Based on concepts that participants identified as important, item understandability, psychometric evaluation of precision and coverage, and balance across different facets of each domain, we constructed 8-item short forms composed of items selected from the PROMIS Fatigue and Pain Interference item banks.[19] Prior data demonstrated that these PROs are reliable, valid, and responsive.[20,21] Prespecified measurement time points were approximately 1 and 2 years after randomization.

Serum was collected at approximately 26 and 91–104 weeks after randomization for measurement of ADAs. Samples were analyzed at 2 reference laboratories using both drug-sensitive (Progenika Biopharma, Derio, Spain) and drug-tolerant (LabCorp, Calabasas, CA) assays[22] (Supplementary Methods).

Adverse events (AEs) and serious adverse events (SAEs), as described in the Supplementary Methods, were reported by site investigators. Exacerbations of PCD were captured as treatment failures and were not required to be submitted as separate AEs.

Covariates

We recorded the following covariates, as assessed at baseline: participant age, gender, race, ethnicity, the anti-TNF agent used, SPCDAI score, Physician Global Assessment of disease activity, disease location, current and prior perianal disease, current or prior use of prednisone and other steroid medications, prior use of methotrexate, prior use of 6-mercaptopurine or azathioprine, time from diagnosis (<2 or ≥ 2 years), height, weight, body mass index, albumin, hemoglobin, C-reactive protein, and erythrocyte sedimentation rate.

Participant Follow-up and Data Collection

Consistent with pragmatic trial design, follow-up occurred in the context of routine clinical care. Guidance for suggested follow-up intervals and assessments was included in the study protocol.

Participants were followed for 104 weeks or until study termination (April 2021), after the last enrolled participant completed 52 weeks of follow-up. Participants were given the option to participate for an additional year.

Study data were collected through the ImproveCareNow registry,[15,23] described further in the Supplementary Methods. In addition, electronic case report forms were used to capture trial-specific data not already included in the registry. Site investigators provided oversight to ensure the accuracy, completeness, and timeliness of the data collection. In the event of incomplete or inconsistent data, correction and/or clarification was requested from the site. Sites ascertained individual components of the composite end point during routine office visits, at the time of hospitalization or surgery, or between encounters. When sites identified that a participant met 1 or more components of the primary end point, they indicated the outcomes met and date on a separate case report form that was reviewed and signed by the site principal investigator. In addition, the study monitor and research project manager queried the ImproveCareNow Registry data and COMBINE case report forms regularly to identify any possible outcomes that were not yet identified by sites and asked the sites to confirm (or not) whether an end point had been met. In addition, at each visit, site principal investigators were asked to confirm that the participant had not yet met a component of the primary end point and would continue on study treatment. Finally, at the end of each participant's follow-up or at the time or at the time of loss to follow-up or disenrollment, site principal investigators also confirmed participants who had not met a study end point.

Statistical Analysis

All analyses were based on a modified intent-to-treat population, including participants who received at least 1 shipment of medication from the study pharmacy. We first described and compared the distributions of patient characteristics within

treatment arms overall, and stratified by anti-TNF agent, using standard bivariate statistics.

To compare the distribution of time to treatment failure in the 2 arms, we computed log-rank tests stratified by anti-TNF agent prescribed (infliximab and adalimumab). In addition, we developed a Cox model adjusting for anti-TNF (infliximab and adalimumab), site census region, and covariates that differed between treatment groups using a threshold of $P < .2$.

We compared the average of PROMIS Pain Interference and Fatigue scores between treatment groups at week 52 and 104. We estimated the difference in mean PROMIS scores at 52 and 104 weeks by fitting mixed model for repeated measures to PROMIS scores at all available time points, adjusted for covariates used in our primary outcome analyses.

We next compared the proportion of positive ADA between treatment groups overall, and stratified by anti-TNF, using the χ^2 test. We considered patients with ADA detected at either or both time points on either or both assays as positive.

For all 3 secondary end points, we prespecified a threshold of $P < .05/3$ for determining statistical significance based on Bonferroni correction.

Finally, we summarized investigator-reported AEs and SAEs using standard descriptive statistics.

Prespecified Subgroup Analyses

We explored heterogeneity of treatment effects by conducting a number of prespecified subgroup analyses of our primary study end point. Subgroups considered included time from diagnosis (<2 or ≥ 2 years), elevation of baseline C-reactive protein $>2\times$ normal (include only if non-missing), elevation of baseline sedimentation rate or erythrocyte sedimentation rate using a cutoff of >18 mm/h, non-White vs White race, Hispanic vs non-Hispanic, disease location (ie, ileum only, colon only, and ileocolonic), and whether dose adjustment was performed over the course of follow-up (a surrogate for proactive TDM).

Missing Data

There were no missing data on the primary study end point, as we confirmed whether and when participants met (or not) 1 or more components of the primary composite end point as described above. Regarding the secondary end points of PROMIS measures, missing data were handled by fitting a mixed model for repeated measures. To analyze the average of the PRO reported at week 52 and week 104, if the week-52 PRO was missing, we analyzed only the week-104 value and vice versa. For analyses of ADA, not all participants were able to provide a sample at both time points. Analyses were limited to provided samples. For all adjusted analyses, missing covariates were imputed using multiple imputation. We used SAS software (SAS Institute) for all analyses.

Sample Size

We estimated a necessary sample size of 353 participants (Supplementary Methods) and set a recruitment target of 425 participants to explore heterogeneity of treatment effects. Due to slow recruitment, exacerbated by the COVID-19 pandemic, the study was discontinued before full enrollment, with a final sample size of 297 participants. Based on the actual sample size our statistical power was 73% to detect a 15% difference in the primary outcome.

Patient and Stakeholder Engagement

Two parents (D.W. and L.P.) served as co-investigators from the time of proposal development through all phases of project implementation and were provided financial support for their time and effort. In addition, the larger ImproveCareNow Parent Working Group served as a study advisory board, affirming the importance and patient- and family-centeredness of the overall study question, and providing input for the overall study design. All key design decisions were informed by stakeholder input, including the preference for individual-level vs cluster randomization, and the incorporation of a placebo-controlled design. After funding, the final study protocol was developed using a similar process of co-production.

As described above, we used a multistakeholder process to identify PROs most relevant to patients with PCD to serve as secondary outcomes for the trial.

We also incorporated meaningful patient and parent engagement in the development of recruitment materials. Parent co-investigators led the design of paper and web-based recruitment materials, including an animated video. Recruitment materials were also reviewed by parents and patients not associated with the research to assure balance and appeal. To further support recruitment, we developed shared decision-making tools to improve knowledge about the study, lower decisional conflict, and increase decisions that are congruent with patients' values.[24] Importantly, we elicited and incorporated the perspectives of patients, parents, and clinicians to iteratively refine components of the shared decision-making process and related training materials, as reported previously.[25]

Role of the Funding Sources

The study sponsors had no role in study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Results

Study Population

Across 35 centers, we prescreened 1905 patients, enrolled 321, and randomized 306, with 297 included in our modified intent-to-treat analysis. In total, 156 patients were assigned methotrexate (110 infliximab initiators and 46 adalimumab initiators) and 141 were assigned placebo (102 infliximab initiators and 39 adalimumab initiators). Median follow-up in the methotrexate and placebo arms was 751 and 737 days, respectively (Figure 1).

Demographic and clinical characteristics of the study population overall and stratified by anti-TNF are provided in Table 1 and Supplementary Tables 1 and 2. The mean age was 13.9 years, 35% were female, and 82% were White. Median time from diagnosis was 2 months. Median SPCDAI at enrollment was 15 (mild disease activity); 41% were on steroids at randomization. Participant characteristics were generally well-balanced between study arms.

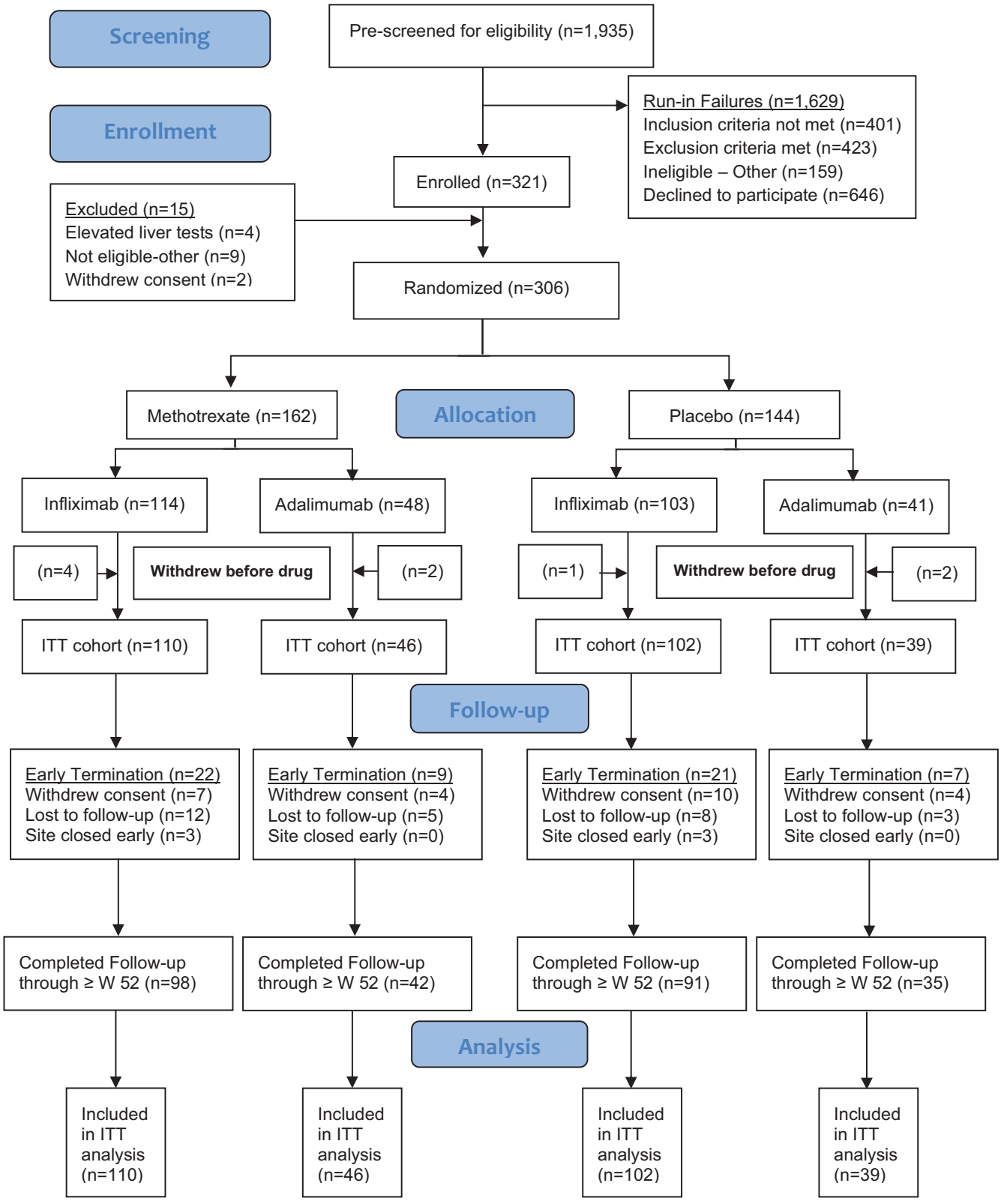

Figure 1. Participant flow diagram. ITT, intent-to-treat.

Table 1. Demographic and Clinical Characteristics of the Overall Study Population

Characteristic	All patients	Combination therapy (active)	Monotherapy (placebo)	*P* value
Demographic				
Total no. of patients, n (%)	297 (100)	156 (53)	141 (47)	—
Female, n (%)	104 (35)	53 (33)	51 (36)	.72
Age, *y*, mean (SD)	13.9 (2.6)	13.8 (2.5)	14.0 (2.8)	.49
Race, n (%)				
Asian	4 (1)	2 (1)	2 (1)	1.0
Black/African American	32 (11)	13 (8)	19 (13)	.15
White	244 (82)	131 (84)	113 (80)	.45
Multiracial or other	13 (4)	8 (5)	5 (4)	.51
Ethnicity, n (%)				.73
Hispanic or Latino	8 (3)	5 (3)	3 (2)	
Not Hispanic or Latino	285 (97)	150 (97)	138 (98)	
Clinical				
Height, *z* score, mean (SD)	–0.24 (1.07)	–0.21 (1.08)	–0.28 (1.07)	.61
Weight, *z* score, mean (SD)	–0.25 (1.12)	–0.27 (1.14)	–0.23 (1.10)	.74
Body mass index, *z* score, mean (SD)	–0.20 (1.17)	–0.25 (1.21)	–0.14 (1.14)	.44
Time from diagnosis, *mo*, mean (SD)	8.9 (15.6)	8.1 (16.0)	9.7 (19.2)	.46
Disease location, n (%)				
Lower GI				
None	5 (2)	5 (3)	0 (0)	
Ileum only	67 (24)	32 (22)	35 (26)	.03
Colon only	48 (17)	19 (13)	29 (21)	
Ileocolonic	161 (57)	88 (61)	73 (53)	
Upper GI				
Proximal	140 (52)	74 (53)	66 (51)	.72
Distal	70 (28)	36 (28)	34 (28)	.99
Perianal disease at enrollment, n (%)	31 (21)	17 (22)	14 (21)	.86
History of perianal disease, n (%)	85 (29)	43 (28)	42 (30)	.72
SPCDAI score at randomization, mean (SD)	17.0 (15.6)	17.2 (16.4)	16.9 (14.6)	.86
Physician Global Assessment at randomization, n (%)				.53
Quiescent	69 (23)	37 (24)	32 (23)	
Mild	100 (34)	48 (31)	52 (37)	
Moderate	80 (27)	41 (26)	39 (28)	
Severe	8 (3)	6 (4)	2 (1)	
Baseline PROMIS fatigue score, mean (SD)	47.6 (15.2)	47.4 (15.5)	47.8 (14.9)	.83
Baseline PROMIS pain score, mean (SD)	46.9 (14.3)	46.5 (14.5)	47.4 (14.1)	.60
Prior treatment, n (%)				
Prior azathioprine or mercaptopurine therapy	36 (12)	18 (12)	18 (13)	.75
Prior methotrexate	47 (16)	26 (17)	21 (15)	.70
Current treatment, n (%)				
Any steroid at randomization	120 (41)	64 (41)	56 (40)	.90
Anti-TNF				.73
Infliximab	212 (71)	110 (71)	102 (72)	
Adalimumab	85 (29)	46 (29)	39 (28)	
Baseline laboratory tests				
Erythrocyte sedimentation rate, *mm/h*, highest within 42 d of randomization, mean (SD)	18.6 (18.4)	20.4 (19.3)	16.6 (17.3)	.11
Albumin, *g/dL*, worst within 42 d of randomization, mean (SD)	3.8 (0.6)	3.8 (0.5)	3.9 (0.6)	.40
Hemoglobin, *g/dL*, lowest within 42 d of randomization, mean (SD)	12.1 (2.2)	11.8 (1.8)	12.4 (2.7)	.06
C-reactive protein at randomization >2× upper limit of normal, n (%)	47 (19)	27 (21)	20 (16)	.34

GI, gastrointestinal.

Primary End Point

Overall, 88 of 297 participants (30%) experienced study-defined treatment failure (57 of 212 [27%] of infliximab initiators and 31 of 85 [36%] of adalimumab initiators). A total of 40 of 156 participants (26%) in the combination therapy group and 48 of 141 participants (34%) in the monotherapy group experienced treatment failure (Table 2). The most common component of the

Table 2. Treatment Failure in Participants Treated With Anti-TNF in Combination With Methotrexate vs Anti-TNF Monotherapy

Variable	Treatment failures, n (%)	Unadjusted HR (95% CI)	Adjusted HR[a] (95% CI)
Overall (n = 297)	88 (30)	0.69 (0.45–1.05)	0.69 (0.45–1.07)
Infliximab (n = 212)	57 (27)	0.93 (0.55–1.56)	0.85 (0.50–1.45)
Adalimumab (n = 85)	31 (36)	0.40 (0.19–0.81)	0.42 (0.19–0.90)

[a]Overall analyses adjusted for baseline C-reactive protein (CRP) more than twice upper limit of normal and race. Infliximab analyses adjusted for baseline CRP more than twice upper limit of normal, erythrocyte sedimentation rate >20 mm/h, region, and race. Adalimumab analyses adjusted for baseline SPCDAI.

composite end point experienced by study participants was hospitalization for active inflammatory bowel disease after week 25. A breakdown of the number of participants who experienced each component of the composite end point, stratified by treatment assignment and anti-TNF agent used is provided as Supplementary Table 3.

Kaplan-Meier analysis of the overall population (Figure 2*A*) showed a nonsignificant trend toward lower event rates in the combination therapy (hazard ratio [HR], 0.69; 95% CI, 0.45–1.05; $P = .08$). Figure 2*B* and *C* show Kaplan-Meier curves after stratification by anti-TNF (infliximab and adalimumab). Among infliximab initiators, there was no difference between combination therapy and monotherapy (HR, 0.93; 95% CI, 0.55–1.56; $P = .78$). Among adalimumab initiators, combination therapy significantly outperformed monotherapy (HR, 0.40; 95% CI, 0.19–0.81; $P = .01$). Effect estimates were essentially unchanged after adjustment (Table 2).

Prespecified Subgroup Analyses

The results of prespecified subgroup analyses are shown in Supplementary Table 4. We observed a larger magnitude of treatment effect in participants with colonic CD and elevated sedimentation rate at baseline and a similar trend among those with elevated baseline C-reactive protein. In

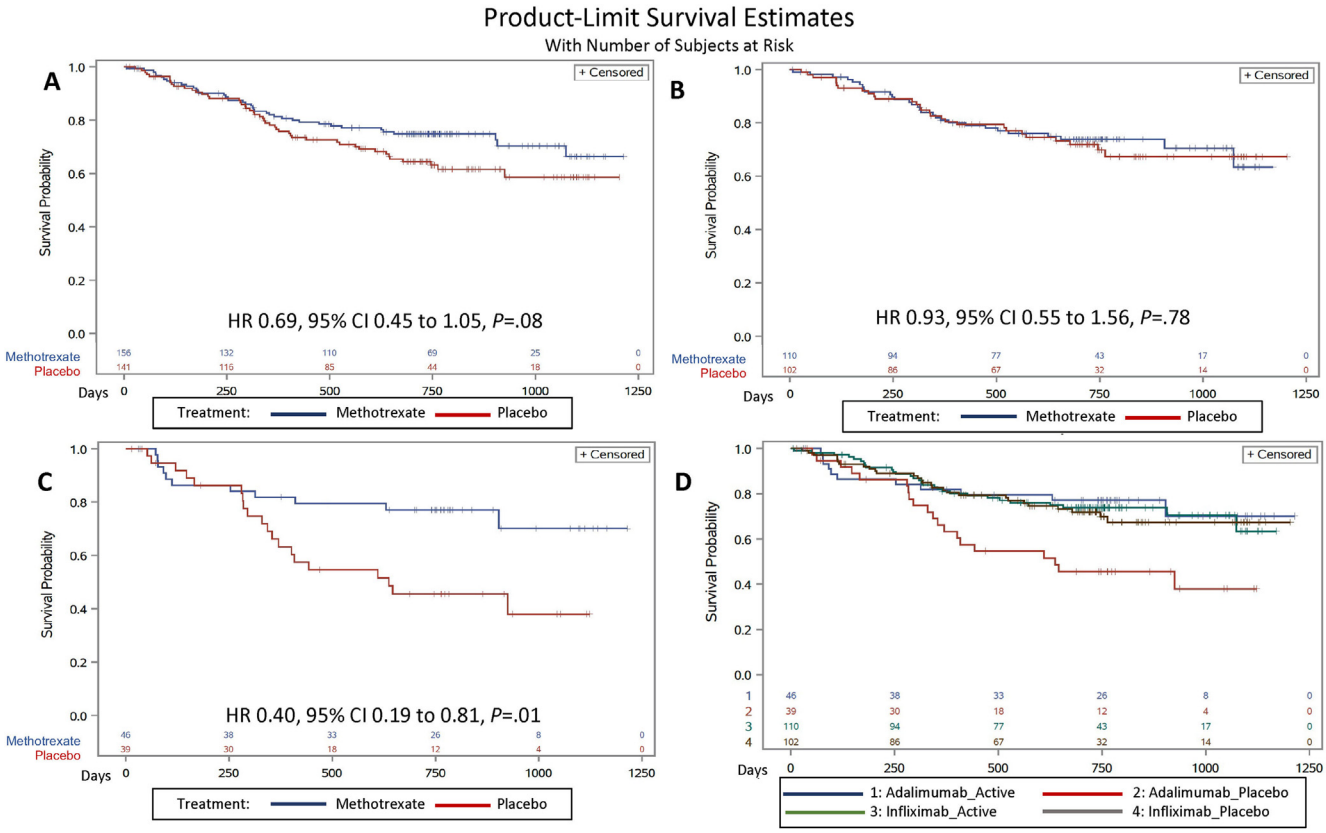

Figure 2. (*A*) Kaplan-Meier analysis of the time-to-event in the overall population. (*B*) Kaplan- Meier analysis among infliximab initiators. (*C*) Kaplan-Meier analysis among adalimumab initiators. (*D*) Kaplan-Meier curves broken out by both anti-TNF agent and combination vs monotherapy.

addition, we observed a trend toward a smaller magnitude of treatment benefit in patients who underwent anti-TNF dose adjustment.

Post-Hoc Analyses

In a per-protocol analysis where patients who discontinued study methotrexate or placebo for nonmedical reasons were censored after 30 days, effect estimates were stronger and statistically significant in the overall study population (HR, 0.65; 95% CI, 0.43–0.99) and among adalimumab users (HR, 0.35; 95% CI, 0.17–0.73). In an analysis only events due to lack of effectiveness including (66 of 88 participants with treatment failure), effect estimates were also stronger and statistically significant overall (HR, 0.56; 95% CI, 0.3–0.9) and among adalimumab users (HR, 0.23; 95% CI, 0.09–0.57). Discontinuations due to toxicity were no different overall, and after stratification by anti-TNF.

Figure 2*D* shows Kaplan-Meier curves broken out by both anti-TNF agent and combination vs monotherapy. Among participants treated with monotherapy, patients treated with adalimumab had higher event rates than those receiving infliximab (HR, 2.19; 95% CI, 1.23–3.89; $P = .008$). Event rates in the infliximab combination therapy group or adalimumab combination therapy group were no different than infliximab monotherapy.

Secondary End Points

We observed no clinically or statistically significant differences in PROMIS measures of Pain Interference and Fatigue domain when weeks 52 and 104 were averaged, or at either time alone (Table 3).

Of 151 infliximab users (71%) with available serum, 61 (40%) had positive ADA. Differences between groups (47% monotherapy vs 34% combination therapy) did not reach statistical significance (relative risk, 0.72; 95% CI, 0.49–1.07). Infliximab users with positive vs negative ADA were no more likely to experience treatment failure (44% vs 39%; $P = .71$). Of 61 adalimumab users (72%) with available serum, 11 (18%) had positive ADAs. This proportion was higher in the monotherapy group (21% vs 15%) but did not reach statistical significance (relative risk, 0.71; 95% CI, 0.24–2.07) (Supplementary Table 5). Adalimumab users with positive ADAs were more likely to experience treatment failure compared with those with negative ADAs (64% vs 36%; $P = .03$).

Table 3. Differences in PROMIS Pain Interference and Fatigue Between Combination Therapy and Monotherapy Groups

	Pain interference		Fatigue	
Variable	Effect estimate	*P* value	Effect estimate	*P* value
Overall				
Week 52	−1.36	.33	0.59	.64
Week 104	−0.70	.69	0.88	.64
Infliximab				
Week 52	−1.29	.43	0.52	.79
Week 104	−1.40	.52	0.05	.98
Adalimumab				
Week 52	−1.56	.55	0.82	.79
Week 104	0.81	.78	2.93	.34

NOTE. Effect estimate is mean difference in *T* scores between the active and placebo groups. Negative values indicate lower levels of the measured domain in active vs placebo groups. Minimally important differences in PROMIS measures are in the range of 3–5 based on studies in other populations.

Safety

A total of 118 (76%) combination therapy patients experienced 1 or more AEs, compared with 96 of 141 (68%) monotherapy patients. Forty-four percent of patients receiving combination therapy experienced an AE that was possibly or definitely related to treatment, compared with 33% of monotherapy patients. However, participants in the monotherapy arm were more likely to experience an SAE (16% vs 12%) (Table 4).

Supplementary Tables 6–9 describe categories of AEs observed in >2% of the study population, all SAEs, and laboratory abnormalities. Nausea and vomiting, elevated liver enzymes, and infection SAEs were more commonly reported in patients receiving combination therapy. Conversely, gastrointestinal symptoms were more prevalent in the monotherapy arm.

Discussion

In the largest double-blind, randomized trial to date in PCD, we found that anti-TNF combination therapy with low-dose oral methotrexate outperformed monotherapy for adalimumab-treated patients, but not infliximab-treated patients, resulting in a 2-fold reduction in the occurrence of events indicating treatment failure. We observed slightly more AEs in the combination therapy group, as expected, but fewer SAEs. Overall, these findings suggest improved effectiveness of combination therapy in patients treated with adalimumab and a tolerable safety profile.

Our findings reinforce and extend those of prior trials in adult patients. Although the SONIC (Study of Biologic and Immunomodulator Naive Patients in Crohn's Disease) trial suggested that combination therapy with infliximab and azathioprine was more efficacious than infliximab monotherapy,[13] COMMIT (Combination of Maintenance Methotrexate-Infliximab Trial) showed no clinical benefit of combination therapy with methotrexate.[14] Our pediatric study confirms the absence of a clinical benefit of combination therapy with infliximab and methotrexate. Our pragmatic design allowed proactive TDM and higher doses of infliximab rather than the fixed dosing (5 mg/kg) used in prior adult studies. Thus, it is possible that with optimized use of infliximab, we have reached a ceiling of effectiveness above which combination therapy does not add benefit.

The improved effectiveness of combination therapy among adalimumab-treated patients was notable. Prior studies of adalimumab combination therapy were less

Table 4. Summary of Adverse Events (at Participant Level)

	All patients (n = 297)		Combination therapy (active) (n = 156)		Monotherapy (placebo) (n = 141)	
Event	n	%	n	%	n	%
AE	214	70	118	73	96	67
SAE	40	13	18	11	22	15
Related AE						
Possibly related	113	37	68	42	45	31
Definitely related	9	3	6	4	3	2
Possibly or definitely related	115	38	69	43	46	32

rigorous and inconclusive. A single-center, open-label, randomized trial of adalimumab with and without azathioprine in adult patients with CD showed no benefit of combination therapy.[26] In a post-hoc analysis of a small (n = 78) pediatric trial that compared proactive vs reactive TDM, investigators reported a numeric trend toward longer steroid-free remission among patients treated with combination therapy, although only 7 patients receiving combination therapy received methotrexate.[27] Our multicenter, double-blind, placebo-controlled trial provides robust and compelling data in favor of adalimumab and methotrexate combination therapy.

Our study was not designed to compare infliximab with adalimumab; nor was it designed to evaluate the role of proactive TDM. However, proactive TDM is endorsed in the ImproveCareNow Mode Care Guidelines[16] and was considered standard of care at study sites during the time of our study. In our study population, 54% of infliximab patients and 44% of adalimumab patients had 1 or more recorded anti-TNF doses or interval changes during follow-up and 45% of infliximab and 40% of adalimumab patients had 1 or more standard of care TDM tests in the first year since randomization (Supplementary Table 10). Thus, the observed benefit of combination therapy among adalimumab users was demonstrated in the setting of standard of care TDM. Of note, anti-TNF dose or interval adjustment and TDM were more frequent in infliximab-treated patients than adalimumab-treated patients, likely due to ease of obtaining trough levels during infusions and more flexible dosing. It is possible that lower rates of treatment failure among infliximab users in our study may be related to more intensive TDM. Indeed, prior studies have suggested a benefit of proactive TDM in patients treated with adalimumab,[28] although more definitive studies are needed. Although not statistically significant, we observed a trend toward a smaller magnitude of treatment benefit in patients who underwent anti-TNF dose adjustment, raising the possibility that more aggressive TNF dosing may have similar effectiveness to combination therapy.

Among both infliximab and adalimumab users, we observed nonsignificantly lower rates of immunogenicity in the combination vs monotherapy groups. This trend is consistent with prior adult studies[14] and adds substantially to the pediatric literature on this topic.[27] Prevention of ADA may partially explain the benefits of combination therapy among adalimumab users. However, our study and the prior adult study showed no clinical benefit of infliximab and methotrexate, despite lower rates of ADA development. Therefore, preventing immunogenicity cannot fully account for the benefits of combination therapy.[9] Indeed, some patients in our study who developed ADA continued to maintain steroid-free remission, and other patients who experienced treatment failure did so in the absence of ADAs. Future research to evaluate the significance of ADAs, including neutralizing and non-neutralizing antibodies, especially in pediatric populations, will be important.

We did not observe any differences in PROs of Pain Interference or Fatigue. Prior data demonstrated these PROs are reliable, valid, and responsive.[20,21] We speculate that failure to observe differences between treatment groups may be related to analyzing these PROs at fixed time points rather than at the time of treatment failure. Patients experiencing treatment failure likely switched therapy and improved by the predefined time points in our study. In a prior blinded analysis of PROs assessed closer to the time of treatment failures, we observed higher Pain Interference and Fatigue in those who experienced treatment failure compared with those who remained outcome-free.[21] Although PRO measurement at fixed time points limited our ability to observe treatment-related differences, it reassuringly indicates that patients experiencing treatment failure with anti-TNF may improve with subsequent therapy. Future studies of PCD that use PROs should focus on analyzing PRO trajectories over multiple time points rather than focusing on prespecified time points.

Key strengths of our study include the rigorous randomized, double-blind design and the pragmatic nature of our trial, including broad eligibility criteria, flexible and adaptive dosing of anti-TNF and study medications, and inclusion of a diverse group of study centers. Thus, our study findings should be broadly generalizable to real-world care of patients facing the treatment decision of combination or monotherapy. We also incorporated robust input from parents and patients throughout all phases of the study, ensuring that the study question, design, and outcomes were all patient- and family-centered (Supplementary Methods).

The most notable study limitation is that slow recruitment compounded by the COVID-19 pandemic prevented us from reaching our recruitment target. Thus, failure to detect a difference between combination and monotherapy in our overall study population may reflect type 2 error. However, stratified analyses by specific TNF provide compelling data that even with a larger sample size, it is unlikely there would have been a significant difference among infliximab initiators, and treatment effects among adalimumab initiators were readily apparent, even with a smaller sample size. Consistent with pragmatic trial design,[17] adherence was encouraged but not strictly monitored. Thus, our intent-to-treat results reflect real-world effectiveness rather than optimal efficacy. Had we excluded those with poor adherence, the effect size among adalimumab users would likely be similar to the per-protocol analysis. In an effort to include all patients initiating anti-TNF, we did not require colonoscopy before enrollment and thus could not confirm active intestinal inflammation in all participants. We also recognize that baseline measures of disease activity are imperfect and there were missing data for some participants. Nevertheless, randomization should have accounted for any differences between treatment groups. There is also the possibility that use of infliximab vs adalimumab may vary by site and that site case mix and/or other practices may be associated with patient outcomes. We did not include endoscopy or other measures of mucosal healing (ie, calprotectin or imaging) as trial end points. As a pragmatic trial, we prioritized inclusion of outcomes assessed routinely in clinical care. Emerging data indicate that evaluation of mucosal healing at a prespecified time point is not yet standard of care, even in adult patients.[29] In our study, only 38% of participants underwent colonoscopy during follow-up (41% had calprotectin measurement). To the extent that such testing was differentially performed in symptomatic patients, the use of available data would have introduced substantial bias. However, our primary end point indirectly reflects mucosal healing. Among 66 participants with loss of effectiveness, 39 (59%) underwent colonoscopy, of which 85% were found to have active intestinal inflammation and 31 (47%) had fecal calprotectin measurement with a median value of 814 μg/g.

In conclusion, our study findings suggest strong consideration of using combination therapy for patients with PCD initiating adalimumab but not infliximab. Dissemination and implementation of these findings should lead to improved outcomes in this patient population, including consideration of de-implementation of combination therapy in patients treated with infliximab. The evaluation and comparison of additional strategies to further optimize response to adalimumab, including proactive TDM, warrant additional research.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://doi.org/10.1053/j.gastro.2023.03.224.

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Conflicts of interest

These authors disclose the following: Michael D. Kappelman has consulted for Abbvie, Janssen, Pfizer, Takeda, and Lilly, is a shareholder in Johnson & Johnson, and has received research support from Pfizer, Takeda, Janssen, Abbvie, Lilly, Genentech, Boehringer Ingelheim, Bristol Myers Squibb, Celtrion, and Arenapharm. Hans H. Herfarth has consulted for Alivio, BMS, Boehringer, ExeGi Pharma, Finch, Fresenius Kabi, Gilead, Janssen, Otsuka, Pfizer, Pure Tech, and Ventyx and has received research support form Allakos, Artizan, NovoNordisk, and Pfizer. William B. Brinkman has common stock holdings in the following publicly traded companies: Pfizer, Merck, Abbott Laboratories, Viatris, and Johnson & Johnson. Richard B. Colletti has consulted for Janssen Research & Development and is a member of the scientific advisory board for Janssen Biotech. Traci W. Jester has received research support from Abbvie. Ellen A. Lipstein has received research support from Pfizer, Inc. Jonathan Moses is on the Speaker's Bureau for Abbvie and on the scientific medical advisory board for PSI Inc. Dinesh S. Pashankar has received research support from Janssen and Abbvie. Shehzad A. Saeed is a member of the advisory board for Abbvie, Inc. Athos Bousvaros has consulted for Takeda, Best Doctors, Eli Lilly, Fresenius Kabi, and has received research support from Janssen, Abbvie, Takeda, Buhlmann, Arena, Eli Lilly, Bristol Myers Squibb, and PROCISE diagnostics. The remaining authors disclose no conflicts.

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Data Availability

De-identified study data, data dictionary, study protocol, statistical analysis plan, and informed consent form will be made available within 12 months of publication in accordance with the Patient-Centered Outcomes Research Institute's (PCORI) data sharing policy. Information regarding the PCORI-designated repository and submission of data requests can be found at https://www.pcori.org/about/governance/policy-data-management-and-data-sharing

Supplementary Methods

Anti-Drug Antibodies

A drug-sensitive assay was performed by Progenika Biopharma.[22] ADAs were determined by enzyme-linked immunosorbent assay using Promonitor-ANTI-IFX-1DV or Promonitor-ANTI-ADL-1DV, following package insert instructions, and Triturus Analyzer for an automatic processing of 96-well enzyme-linked immunosorbent assay plates. ADA concentrations were interpolated from corresponding standard curve generated with each assay. The lower limit of quantification was 5 AU/mL and 10 AU/mL for ANTI-IFX and ANTI-ADL, respectively.

A drug-tolerant assay was performed by Labcorp. ADAs were quantified using Labcorp-developed electrochemiluminescence-based immunoassays with a lower limit of quantification of 22 ng/mL for infliximab and 25 ng/mL for adalimumab.[22] Labcorp's ADA assays' high drug tolerance is achieved by pretreatment of samples that displaces circulating drug in patient serum that would otherwise cause falsely low or false-negative ADA results. Furthermore, all ADA-positive results are confirmed for drug specificity by an additional analytic step.

ImproveCareNow Registry

Study data were collected through the ImproveCareNow (ICN) patient registry and supplemented by trial-specific electronic case report forms. In 2007, ICN established a standardized, web-based clinical registry that enabled collection of standardized, inflammatory bowel disease–specific data about processes and outcomes of care (eg, disease characteristics, patient well-being, laboratory results, and medications). Participating collected routine clinical data at office visits and hospitalizations as part of the ICN registry described above.[15] In 2010, with Agency for Healthcare Research and Quality funding, ICN developed a modular, open-source registry that can be linked to an electronic health record to minimize the burden of manual data entry. This allows for a significant portion of registry data to be transferred electronically via a secure web portal to the registry, and stored for re-use in quality improvement, chronic care delivery, and comparative effectiveness research.[23]

Changes to the Original Study Protocol

Changes to the study protocol were made with input from study methodologists, the clinical committee, and parent co-investigators. Early in the study, we identified that eligibility criteria were too strict and that we were excluding some participants who site investigators would have considered candidates for combination therapy. We therefore broadened our eligibility criteria to allow our trial population to more closely represent the population of patients facing the treatment decision. We also lengthened the window of time allowed between initiation of the anti-TNF treatment and trial enrollment from 4 weeks to 6 weeks, as this was the window of time in which clinicians and families were often discussing the decision of whether to pursue anti-TNF combination or monotherapy. Another small change in the study protocol was made when we observed that a few participants withdrew from the study within a day or 2 after randomization and before study medication was shipped from the pharmacy. As these patients reflect those who may change their mind before picking up a prescription from the pharmacy in the real world, we modified our protocol to use a modified intent-to-treat analysis only, including participants who received at least 1 shipment of medication from the study pharmacy.

We made a slight deviation to our planned analyses of ADA before beginning data analysis. We originally planned to compare the proportion of patients with positive ADAs measured in the second year of the trial; however, our final analyses included those with positive ADAs between 6 and 12 months after randomization, as well as in the second year of follow-up. We made this change as a positive ADA at an earlier time point is an important marker of immunogenicity, and not all patients provided blood samples during the second year of follow-up, particularly during the pandemic.

Other changes to the study protocol were made due to challenges with recruitment. Specifically, we shortened the minimum follow-up period to 1 year rather than 2 years to allow more patients to be recruited before study closure. We also extended study follow-up for up to 3 years to collect additional data and allow more time for patients to experience primary study outcomes.

Sample Size

Our sample size calculation assumed treatment failure would occur in 50% of the monotherapy arm and in 35% of the combination arm. This was based on the 2 adult trials of anti-TNF combination vs monotherapy that observed 1-year treatment success rates of 40% and 56% in the monotherapy groups.[13,14] We considered an absolute difference of 15% as the minimum clinically important difference, below which the benefits of combination therapy would not outweigh the risks. Assuming an exponential distribution for time to treatment failure, a total of 140 events would be required to achieve a power of 80% with a 2-sided type I error rate of 0.05. After accounting for variable follow-up, we estimated a necessary sample size of 353 participants and a goal recruitment of 425 participants to allow exploration of heterogeneity of treatment effects.

Adverse Events and Serious Adverse Events

Our study protocol defined SAEs as events that were fatal; life-threatening; required or prolonged a hospital stay; or resulted in persistent or significant disability or incapacity, congenital anomaly, birth defect (in the offspring of a study participant), or other important medical events as determined by the site investigator. AEs not meeting any of the criteria for serious were regarded as nonserious AEs.

Supplementary Table 1. Demographic and Clinical Characteristics of the Study Population: Infliximab Only

Characteristic	All patients	Combination therapy (active)	Monotherapy (placebo)	*P* value
Demographic				
Total no. of patients, n (%)	212 (100)	110 (52)	102 (48)	—
Female, n (%)	81 (38)	39 (35)	42 (41)	.39
Age, *y*, mean (SD)	13.7 (2.6)	13.6 (2.5)	13.7 (2.8)	.89
Race, n (%)				
Asian	4 (2)	2 (2)	2 (2)	.94
Black/African American	27 (13)	13 (12)	14 (14)	.68
White	169 (80)	88 (80)	81 (79)	.92
Multiracial or other	10 (5)	5 (4)	5 (5)	.90
Ethnicity, n (%)				.45
Hispanic or Latino	7 (3)	5 (5)	2 (2)	
Not Hispanic or Latino	203 (97)	104 (96)	99 (98)	
Clinical				
Height, *z score*, mean (SD)	–0.28 (1.08)	–0.28 (1.09)	–0.28 (1.07)	.99
Weight, *z score*, mean (SD)	–0.27 (1.13)	–0.31 (1.24)	–0.23 (1.02)	.58
Body mass index, *z score*, mean (SD)	–0.18 (1.17)	–0.24 (1.29)	–0.12 (1.04)	.48
Time from diagnosis, *mo*, mean (SD)	8.7 (17.6)	8.3 (16.9)	9.1 (18.4)	.74
Disease location, n (%)				
Lower GI				
None	5 (2)	5 (5)	0 (0)	
Ileum only	46 (23)	22 (22)	24 (24)	.06
Colon only	34 (17)	13 (13)	21 (21)	
Ileocolonic	115 (58)	61 (60)	54 (55)	
Upper GI				
Proximal	98 (52)	51 (54)	47 (51)	.67
Distal	45 (26)	22 (25)	23 (27)	.76
Perianal disease at enrollment, n (%)	23 (22)	12 (22)	11 (21)	.93
History of perianal disease, n (%)	63 (30)	29 (27)	34 (33)	.31
SPCDAI score at randomization, mean (SD)	18.7 (16.2)	19.8 (17.0)	17.4 (15.3)	.34
Physician Global Assessment at randomization, n (%)				
Quiescent	42 (23)	22 (23)	20 (23)	.50
Mild	74 (41)	35 (37)	39 (44)	
Moderate	58 (32)	31 (33)	27 (31)	
Severe	8 (4)	6 (6)	2 (2)	
Baseline PROMIS fatigue score, mean (SD)	48.1 (14.7)	47.5 (14.7)	48.7 (14.8)	.56
Baseline PROMIS pain score, mean (SD)	47.6 (14.5)	46.9 (14.5)	48.3 (14.5)	.48
Prior treatment, n (%)				
Prior azathioprine or mercaptopurine therapy	23 (11)	11 (10)	12 (12)	.68
Prior methotrexate	30 (14)	17 (15)	13 (13)	.59
Current treatment, n (%)				
Any steroid at randomization	83 (40)	45 (41)	38 (38)	.67
Baseline laboratory tests				
Erythrocyte sedimentation rate, *mm/h*, highest within 42 d of randomization, mean (SD)	18.9 (18.6)	21.7 (20.9)	15.8 (15.3)	.03
Albumin, worst within 42 d of randomization, *g/dL*, mean (SD)	3.8 (0.6)	3.8 (0.5)	3.8 (0.6)	.28
Hemoglobin, lowest within 42 d of randomization, *g/dL*, mean (SD)	12.0 (1.7)	11.7 (1.8)	12.3 (1.5)	.006
C-reactive protein at randomization >2× upper limit of normal, n (%)	29 (15)	18 (19)	11 (13)	.22

GI, gastrointestinal.

Supplementary Table 2. Demographic and Clinical Characteristics of the Study Population: Adalimumab Only

Characteristic	All patients	Combination therapy (active)	Monotherapy (placebo)	*P* value
Demographic				
Total no. of patients, n (%)	85 (100)	46 (54)	39 (46)	—
Female, n (%)	23 (27)	14 (30)	9 (23)	.45
Age, *y*, mean (SD)	14.4 (2.6)	14.1 (2.5)	14.8 (2.6)	.24
Race, n (%)				
Asian	0 (0)	0 (0)	0 (0)	—
Black/African American	5 (6)	0 (0)	5 (13)	.02
White	75 (88)	43 (93)	32 (82)	.18
Multiracial or other	3 (3)	3 (7)	0 (0)	.50
Ethnicity, n (%)				.45
Hispanic or Latino	1 (1)	0 (0)	1 (3)	
Not Hispanic or Latino	82 (99)	46 (100)	36 (97)	
Clinical				
Height, *z score*, mean (SD)	–0.15 (1.06)	–0.05 (1.04)	–0.27 (1.09)	.35
Weight, *z score*, mean (SD)	–0.19 (1.07)	–0.16 (0.86)	–0.22 (1.30)	.82
Body mass index, *z score*, mean (SD)	–0.23 (1.18)	–0.27 (0.99)	–0.18 (1.39)	.75
Time from diagnosis, *mo*, mean (SD)	9.3 (17.5)	7.7 (13.5)	11.2 (22.0)	.39
Disease location, n (%)				
Lower GI				
None	0 (0)	0 (0)	0 (0)	
Ileum only	21 (26)	10 (23)	11 (29)	.49
Colon only	14 (17)	6 (14)	8 (21)	
Ileocolonic	46 (57)	27 (63)	19 (50)	
Upper GI				
Proximal	42 (52)	23 (52)	19 (51)	.93
Distal	25 (34)	14 (36)	11 (31)	.68
Perianal disease at enrollment, n (%)	8 (21)	5 (22)	3 (19)	1.0
History of perianal disease, n (%)	22 (26)	14 (30)	8 (21)	.30
SPCDAI score at randomization, mean (SD)	13.3 (13.4)	11.3 (13.4)	15.6 (13.1)	.17
Physician Global Assessment at randomization, n (%)				.78
Quiescent	27 (36)	15 (39)	12 (32)	
Mild	26 (35)	13 (34)	13 (35)	
Moderate	22 (29)	10 (26)	12 (32)	
Severe	0 (0)	0 (0)	0 (0)	
Baseline PROMIS fatigue score, mean (SD)	46.4 (16.4)	47.3 (17.4)	45.3 (15.2)	.61
Baseline PROMIS pain score, mean (SD)	45.2 (13.6)	45.5 (14.6)	44.7 (12.6)	.81
Prior treatment, n (%)				
Prior azathioprine or mercaptopurine therapy	13 (15)	7 (15)	6 (15)	.98
Prior methotrexate	17 (20)	9 (20)	8 (21)	.91
Current treatment, n (%)				
Any steroid at randomization	37 (44)	19 (41)	18 (46)	.65
Baseline laboratory tests				
Erythrocyte sedimentation rate, *mm/h*, highest within 42 d of randomization, mean (SD)	17.6 (17.9)	16.2 (12.2)	19.0 (22.3)	.55
Albumin, *g/dL*, worst within 42 d of randomization, mean (SD)	3.9 (0.6)	4.0 (0.6)	3.9 (0.6)	.90
Hemoglobin, *g/dL*, lowest within 42 d of randomization, mean (SD)	12.4 (3.2)	12.3 (1.5)	12.6 (4.5)	.77
C-reactive protein at randomization >2× upper limit of normal, n (%)	18 (29)	9 (29)	9 (29)	1.0

GI, gastrointestinal.

Supplementary Table 3. Number of Participants Meeting a Primary Outcome and Number of Participants Who Experienced Each Component of the Composite End Point, Stratified by Treatment Assignment and Anti-TNF Agent

	Adalimumab		Infliximab		Overall		
Variable	Active	Placebo	Active	Placebo	Active	Placebo	Total
No. of patients meeting 1 or more component of the primary outcome	11	20	29	28	40	48	88
Hospitalization (IBD-related) after wk 25	1	1	7	7	8	8	16
Discontinuation of the anti-TNF agent for lack of effectiveness	3	7	0	5	3	12	15
Discontinuation of the study drug for toxicity	3	1	6	6	9	7	16
Discontinuation of the anti-TNF agent for toxicity	2	2	3	3	5	5	10
Discontinuation of the study drug for lack of effectiveness	0	3	5	4	5	7	12
Abdominal surgery for active IBD after wk 25	0	1	6	2	6	3	9
Use of (steroid) for a period of over 10 wk cumulatively, beyond wk 16	0	4	2	1	2	5	7
SPCDAI $\geq$15 without non-IBD cause at 2+ consecutive visits beyond wk 26	1	1	4	1	5	2	7
Failure to achieve remission (SPCDAI $<$15) by the wk 26 visit	0	2	2	1	2	3	5
Failure to taper steroids by wk 16	1	0	0	2	1	2	3
No. of outcomes	11	22	35	32	46	54	100

IBD, inflammatory bowel disease.

Supplementary Table 4. Prespecified Subgroup Analyses

Subgroup analysis	Interaction *P*	Group name	HR (95% CI)	Group name	HR (95% CI)	Group name	HR (95% CI)
Race	.67	White	0.63 (0.39–1.02)	Non-White	0.78 (0.34–1.81)	NA	NA
Ethnicity	.99	Hispanic	NA	Non-Hispanic	0.59 (0.30–0.91)	NA	NA
Time since diagnosis	.49	$<$2 y	0.68 (0.44–4.51)	$\geq$2 y	0.49 (0.10–1.67)	NA	NA
Disease location	.08	Ileum only	0.60 (0.01–0.55)	Colon only	0.07 (0.01–0.55)	Ileocolonic	0.78 (0.44–1.37)
C-reactive protein $>2\times$ normal	.33	Yes	0.50 (0.19–1.31)	No	0.86 (0.53–1.45)	NA	NA
Erythrocyte sedimentation rate $>$18 mm/h	.02	Yes	0.33 (0.14–0.78)	No	1.15 (0.65–2.04)	NA	NA
TNF dose change	.55	Yes	0.73 (0.42–1.27)	No	0.56 (0.29–1.07)	NA	NA

NA, not applicable.

Supplementary Table 5. ADAs in Participants Treated With Anti-TNF Monotherapy and Combination Therapy

	Participants with sample for ADA measurement				
	Monotherapy		Combination therapy		
Anti-TNF	n	ADA-positive, n (%)	n	ADA-positive, n (%)	OR (95% CI)
Infliximab	72	34 (47.2)	79	27 (34.0)	OR 0.72 (0.49–1.07)
Adalimumab	28	6 (21.4)	33	5 (15.2)	OR 0.71 (0.24–2.07)

OR, odds ratio.

Supplementary Table 6. Adverse Events (Serious and Nonserious) Reported in >2% of Study Population

	All patients (n = 297)		Combination therapy (active) (n = 156)		Monotherapy (placebo) (n = 141)	
Event	n	%	n	%	n	%
Infection	79	26	45	28	34	24
Nausea/vomiting	53	17	35	22	18	13
Abdominal discomfort	46	15	24	15	22	15
Rash	36	12	17	10	19	13
Headache	30	10	12	7	18	13
Elevation of liver enzymes (AST, ALT)	29	9	21	13	8	6
Fever	21	7	13	8	8	6
Diarrhea	20	7	7	4	13	9
Fatigue	16	5	8	5	8	6
Anti-TNF infusion-related reaction	9	3	4	2	5	3
Alopecia	8	3	4	2	4	3
Dizziness	7	2	3	2	4	3

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Supplementary Table 7. Subjects With Laboratory Abnormalities

	All patients (n = 297)		Combination therapy (active) (n = 156)		Monotherapy (placebo) (n = 141)	
Abnormalities in laboratory values	n	%	n	%	n	%
Elevated AST (2× ULN)	19	6	15	9	4	3
Elevated ALT (2× ULN)	31	10	21	13	10	7
Low WBC (<3.5× 10^9/L)	11	4	6	4	5	3

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal; WBC, white blood cells.

Supplementary Table 8. Serious Adverse Events Among Participants Assigned to Combination Therapy (n = 27)

SAE description	No. of events
Infection	5
Nausea/vomiting	2
Tenosynovitis of right ankle	1
Anti-TNF infusion reaction	1
Diarrhea	1
Intentional ingestion	1
PCD flare and pharyngitis (Group A streptococcal)	1
Headache	1
Gastric tube placement	1
Major depression	1
Back pain	1
Colon perforation, colostomy creation	1
CD exacerbation with ileitis and small bowel obstruction	1
Fever	1
Bowel obstruction	1
Suicide attempt	1
Tonsillectomy and adenoidectomy	1
Perirectal abscess	1
Suicidal ideation, depression, anxiety	1
Nausea/infection	1
CD with intestinal obstruction	1
Anemia	1

Supplementary Table 9. Serious Adverse Events Among Participants Assigned to Monotherapy (n = 29)

AE description	No. of events
Abdominal discomfort	6
Anti-TNF infusion reaction	2
Kidney stone	2
Constipation	1
Nausea/vomiting	1
Bowel microperforation	1
Decreased stools, abdominal pain	1
Suicidal ideation	1
Abdominal pain, fecal impaction	1
Nausea/vomiting, abdominal pain	1
Ileocecectomy	1
Bloody diarrhea	1
Acute pancreatitis	1
Paranoia and mental status change	1
Acute cellulitis	1
PCD exacerbation	1
Acute depression with suicidal ideation	1
Postoperative infection from ileocecectomy	1
Infection	1
Perianal abscess	1
Facial flushing	1
Facial abscess	1

Supplementary Table 10. Anti-TNF Dosing, Dose Adjustment, and Use of Therapeutic Drug Monitoring in Study Population

Measure	Infliximab	Adalimumab
Initial maintenance dose, *mg*, median	300	40
Initial maintenance dose, *mg/kg*, median	6.2	0.68
Initial maintenance interval, *wk*, median	7.2	2
Proportion of participants with 1 or more recorded dose and/or interval change, %	53	33
No. of recorded dose changes, mean	0.90	0.39
Final maintenance dose, *mg*, median	500	40
Final maintenance dose, *mg/kg*, median	8.5	0.63
Final maintenance interval, *wk*, median	6.8	1.4
Proportion of patients with 1 or more standard of care TDM test in the first year since randomization, %	45	40