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Long-Term Outcomes With Adalimumab Therapy in Pediatric Crohn Disease: Associations With Adalimumab Exposure

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ABSTRACT

Background/Aims: Pediatric Crohn disease (CD) treatment goals have evolved. Among children receiving adalimumab (ADA) we examined long-term durability of clinical remission, linear growth, and associations of trough concentration (TC) with biomarker, endoscopic and imaging outcomes.

Methods: Single-center retrospective study. Pediatric CD activity index, C-reactive protein, fecal calprotectin, and height measured longitudinally. Discontinuation due to secondary loss of response (LOR) was assessed using Cox proportional hazards model. Associations between TC and clinical and biomarker remission, endoscopic and magnetic resonance imaging (MRI) improvements were assessed using Cox regression with time-dependent covariates.

Results: Between January 2007 and June 2018, 213 children (median age 14.1 years (interquartile range [IQR] 12.5–15.7) 65% males) initiated ADA. One hundred and seventy-four (82%) achieved clinical remission (PCDAI < 10). During 24.8 (IQR 15.6–38.4) months follow-up, 26 (15%) discontinued ADA due to LOR, and 10 (6%) due to adverse events. Being anti-tumor necrosis factor (TNF) naïve and inflammatory behavior associated with increased likelihood of clinical remission (odds ratio [OR] 2.39, $P = 0.033$, and 3.13, $P = 0.013$, respectively) and with decreased LOR (hazard ratio [HR] 0.3, $P = 0.002$, and HR 0.35, $P = 0.01$, respectively). Cumulative LOR among 135 anti-TNF naïve patients: 0%, 8%, 15% within 1, 2, 3 years, similarly durable with mono- and immunomodulator combination therapy. Among pre-/early pubertal children mean height (−0.82) normalized to −0.07. TC consistently >7.5 ug/mL was associated with durable clinical remission (HR = 17.24, $P < 0.001$); TC >10 ug/mL with durable biomarker remission (HR = 6.56, $P < 0.001$) and endoscopic (OR 10.4, $P = 0.002$) and MRI (OR 7.6, $P = 0.001$) improvements.

Conclusion: ADA monotherapy maintains durable clinical remission. Biomarker remission, mucosal and transmural improvements were associated with greater ADA exposure.

Key Words: adalimumab, Crohn disease, pediatrics

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What Is Known

- Adalimumab induces and maintains clinical and biomarker remission in children with Crohn disease.
- Remission rates are greater among previously anti-tumor necrosis factor naïve children.
- PAILOT study demonstrated benefit of pro-active versus reactive therapeutic drug monitoring with adalimumab.

What Is New

- Clinical remission is durable beyond one year and associated with normalization of height if initiated before advanced puberty.
- Remission is sustained without concomitant immunomodulation.
- Adalimumab trough concentrations during maintenance >10 ug/mL are associated with greater likelihood of biomarker remission, resolution of mucosal ulceration, and transmural improvement in children.

Multi-center clinical trials of open-label induction followed by randomized dose-ranging maintenance regimens have demonstrated the efficacy of both infliximab and adalimumab (ADA) in children with Crohn disease (CD) (1,2). Durability of response is of great importance in young patients, given their long lives ahead during which effective therapy is needed. Real-world experience with infliximab in children treated for luminal CD demonstrates that preservation of responsiveness is enhanced by concomitant immunomodulation (IM) (3,4). Comparable pediatric

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data comparing ADA durability with and without IM are lacking (5). Moreover, the beneficial effects of ADA on linear growth past one year have been infrequently examined (6). Limited pediatric data exist concerning optimal ADA exposure and rates of endoscopic or magnetic resonance (MR) imaging improvement (7). In a single-center pediatric cohort, we retrospectively reviewed the efficacy, and durability of ADA therapy for luminal CD. We sought to determine the real-world effectiveness of monotherapy versus concomitant IM in preventing secondary loss of responsiveness (LOR); to identify variables associated with treatment failure; and to evaluate the association of ADA exposure with clinical and biomarker remission and improvement in endoscopic and cross-sectional imaging findings.

METHODS

Patients initiating ADA within the IBD program at SickKids Hospital, Toronto between January 2007 (date of first access to ADA) and June 2018 for treatment of luminal CD were identified from a prospectively maintained database of biologic therapy. All patients with suspected new onset IBD systematically undergo upper endoscopy, ileocolonoscopy and imaging of the small intestine by magnetic resonance enterography (MRE), to thereby assess CD macroscopic localization and behavior according to the Paris Classification (8). Patient demographics, ethnicity, age at diagnosis, duration of diagnosed CD, anatomic location of CD, previous and concomitant treatments, and anthropometric data were extracted from electronic medical records. Indications for treatment with ADA were specified as either chronically active steroid-dependent CD despite prior IM use, loss of response/intolerance to infliximab, or presence of risk factors for severe disease warranting early biologic therapy without a trial of IM (9). ADA patient support programs established by Abbvie Canada provide regular reports of administered doses to physicians. Labeled regimens, as used in the IMAGINE licensing trial (2), suggest doses of 160 mg/80 mg/40 mg for children weighing >40 kg, and 80 mg/40 mg/20 mg if <40 kg, to be given at baseline/week 2/alternate weekly from week 4. CD patients initiating ADA are seen 8–12 weeks post-induction and then followed routinely every 4–6 months. Weights (using Scale-Tronix, Wheaton, IL) and heights (using wall-mounted stadiometer) are measured and pubertal development assessed by Tanner staging. Standardized clinic forms capture the pediatric CD activity index (PCDAI) (10) and physician global assessment (PGA) of disease activity as ''inactive,'' ''mild,'' ''moderate,'' or ''severe''. Laboratory measures assessed as standard clinical care include complete blood count (CBC), erythrocyte sedimentation rate (ESR), serum albumin, and C-reactive protein (CRP). Fecal calprotectin (FCal) measurement using a standard ELISA technique (Calpro AS, Lysaker) began in 2014.

Outcomes Assessment

Initial response to induction was assessed at weeks 8–12. Clinical remission at clinic visits was defined as steroid-free PGA of inactive disease and PCDAI <10, partial response by categorical improvement in PGA to ''mild'' and PCDAI remaining >10, and non-response as PGA of ongoing active ''moderate'' or ''severe'' disease and PCDAI remaining >10. Biomarker remission was defined as CRP <1 mg/L and FCal <250 ug/g. Patients were followed until discontinuation of therapy or until transfer to adult care at age 18 years. Reason for ADA discontinuation as specified by treating physician was recorded. Secondary LOR was defined as active disease leading to ADA discontinuation after achieving steroid-free clinical remission. For analysis of linear growth, anthropometric parameters were expressed as z scores, using chronologic age- and sex-matched reference standards published by the Center for Disease Control (CDC) National Center for Health Statistics (NCHS) in 2000 (11). Macroscopic appearances at reassessment endoscopic or MR examination among patients in clinical remission were classified as complete healing, substantial improvement, partial improvement, or no change/worsening using predetermined definitions (Table 1, Supplemental Digital Content, *http://links.lww.com/MPG/C611*). Adverse events as noted in the patient chart were recorded.

ADA and anti-ADA antibody (ATA) levels were measured using Immundiagnostik monitor enzyme-linked immunosorbent assay (ELISA). The assay detects drug levels >0.8 μg/mL and total ATA >10 AU/mL in the absence of drug. ADA trough concentration (TC) measured at least 24 weeks after initial induction or after any dose escalation was considered to reflect maintenance exposure. Based on existing literature, patients with TC consistently >7.5 and >10 were considered to have adequate drug exposure for the endpoints of clinical and biomarker remission, respectively (12–15).

Statistical Analyses

Depending on data distribution, continuous variables are reported as mean ± standard deviation (SD) or medians with interquartile ranges (IQR), and categorical variables as frequencies and percentages. Differences between groups were assessed using the Student t-test for normally distributed variables and the Mann-Whitney U test for non-normally distributed variables. Univariate and multivariable associations between independent variables and initial response to ADA, endoscopic remission or transmural remission were tested for significance using logistic regression. Variables found to have univariate associations with $P < 0.1$ were eligible for inclusion in the multivariable model. Durability of clinical response was assessed by recording time to secondary LOR using survival analysis via a Cox proportional hazards model. Patients were censored at LOR or last follow-up (16). Unadjusted and adjusted Cox proportional hazards models were performed to compare predictive factors and time to secondary LOR. Cox regression operationalizing TC as a time-dependent covariate and using time-dependent coefficients was performed to determine the association between serial ADA TCs during maintenance and clinical/biomarker remission and endoscopic/transmural healing. Differences in mean height z scores from baseline to subsequent follow-up were compared by paired samples t-test. For all analyses, the statistical significance level was defined as $P < 0.05$. All statistical analyses were performed using SPSS (IBM SPSS Statistics for Windows, version 25, IBM Corp., Armonk, NY, USA, 2017) and R (R: a language and environment for statistical computing, version 3.6.1, R Foundation for Statistical Computing, Vienna, Austria, 2019).

Ethical Considerations

This study was approved by the Research Ethics Board at SickKids Hospital.

RESULTS

Patients

Between January 2007 and June 2018, 213 children and adolescents with luminal CD (median age 14.1 years (IQR 12.5–15.7 years) 65% males) initiated ADA. Only two patients were lost to follow-up before transfer to adult care at age 18 years. Median duration of pediatric follow-up while receiving ADA was 24.3 (IQR

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TABLE 1. Patient characteristics at the time of adalimumab initiation

	All cohort (n = 213)
Male	138 (65)
Caucasian ethnicity	158 (74)
At adalimumab initiation: age (y)	14.1 (12.5–15.7)
Tanner stage: 1 or 2	90 (45%)
4 or 5	81 (41%)
Age at diagnosis (y)	11.9 (9.9–13.8)
Duration of diagnosed CD at ADA initiation (mo)	17 (1.8–25.9)
Disease location* L1	65 (31)
L2	30 (14)
L3	117 (55)
L4a	56 (26)
L4b	20 (9)
L4ab	27 (13)
Perianal fistulizing disease**	52 (24)
Disease behavior*** B1	175 (82)
B2	27 (13)
B3	6 (3)
B2B3	5 (2)
Positive family history in any relative	68 (32)
In first degree relative(s)	33 (16)
EIMs, N (%)	34 (16)
Baseline hs-CRP (mg/dL)	10.8 (2.6–30)
Baseline albumin (mg/mL)	37 (4)
Baseline PCDAI	17.5 (10–27.5)
Indication for adalimumab	
Failed immunomodulator	77 (36)
Failed infliximab (± prior immunomodulator)	56 (26)
Without immunomodulator trial (risk for severe disease)	80 (38)
Prior treatments none	18 (9)
Thiopurine monotherapy	35 (16)
Methotrexate monotherapy	77 (36)
Prednisone	134 (63)
EEN	62 (29)
Budesonide	18 (8)
Treatment at time of adalimumab initiation: Prednisone	59 (28)
EEN	53 (25)

Continuous variables presented as median (IQR) and categorical variables as N (%). IQR = interquartile range; PCDAI = pediatric Crohn disease activity index; CRP = C-reactive protein; SD = standard deviation; EEN = exclusive enteral nutrition. *Disease location by Paris Classification. L1 = distal 1/3 ileum ± limited cecal disease, L2 = colonic disease, L3 = ileocolonic disease, L4a = upper disease proximal to ligament of Treitz, L4b = upper disease distal to ligament of Treitz and proximal distal 1/3 ileum. L4a and L4b as per Paris classification are designated in addition to distal ileal and/or colonic disease. **Based on Paris classification perianal disease was defined as presence of fistula or abscess. ***Disease behavior by Paris Classification. B1 = inflammatory, B2 = stricturing, B3 = penetrating, B2B3 = stricturing and penetrating.

13.2–37.3) months. Table 1 summarizes patient demographic and CD phenotypic data. One hundred and fifty-seven patients (74%) were anti-TNF naïve; the remainder had prior secondary LOR and/or intolerance to infliximab related to anti-infliximab antibody development. None had previous intestinal surgery. The proportion of patients for whom ADA was the first anti-TNF increased over the years of study. Median disease duration at ADA initiation was 17 months for the whole cohort and 8.6 months among anti-TNF naïve patients. At ADA initiation, 53% were receiving corticosteroids or EEN for short-term control of symptoms. Eighty patients (38%) initiated ADA without prior trial of IM, including 18 (9%) who received ADA without exposure to either steroids or EEN.

Treatment Regimens

One hundred and eighty-three patients (86%), including 34 weighing between 30 and 40 kg, received standard adult ADA induction with 160 mg/80 mg. Thirty (14%), all weighing less than 35 kg, received lower induction doses (120 mg/80 mg or 80 mg/40 mg). Maintenance dosing initiated was 40 mg every 2 weeks for all except three patients weighing less than 30 kg, who initially received 20 mg every 2 weeks. ADA maintenance was initiated as monotherapy (without concomitant IM) in 79% overall, including 85% of anti-TNF naïve patients, and 60% of those with prior infliximab failure.

Efficacy of Induction Therapy

Patient disposition is shown in Figure 1. Among all 213 patients, steroid-free clinical remission was achieved in 174 (82%) and partial response in 27 (13%), whereas 12 patients (5%) had primary non-response. Steroid-free clinical remission was achieved more often in patients naive to anti-TNF versus those with prior infliximab exposure (86% vs 70%, $P = 0.008$). Table 2, Supplemental Digital Content, *http://links.lww.com/MPG/C611* lists covariates tested for significant association with clinical remission. In multivariable analysis, two factors were significantly associated with increased likelihood of steroid-free clinical remission: being anti-TNF naïve and inflammatory (non-stricturing, non-penetrating) behavior (odds ratio [OR] 2.39, 95% confidence interval [CI] 1.07–5.31, $P = 0.033$, and OR 3.13, 95% CI 1.27–7.69, $P = 0.013$, respectively). Oral prednisone use at initiation of ADA was associated with a lower likelihood of steroid-free clinical remission (OR 0.42, 95% CI 0.19–0.94, $P = 0.034$).

Durability of Clinical Remission

As shown in Figure 1, 138 (79%) of 174 patients achieving steroid-free clinical remission were continuing ADA at transfer to adult care or last follow-up. Their median follow-up on ADA under pediatric care was 24.8 (IQR 15.6–38.4) months, with 61 (35%) and 32 initial remitters (18%) having completed 3 and 4 years of follow-up, respectively. The 36 (21%) initial remitters who discontinued therapy did so after median 22.4 (IQR, 18.2–32.6) months because of adverse events (n = 10) or secondary LOR (n = 26). Following initial attainment of steroid-free clinical remission, secondary LOR necessitating ADA discontinuation was encountered in only 14 (10%) of 135 anti-TNF naïve patients at rates of 0%, 8% and 15% in the first, second and third years respectively, but in 12 (31%) of 39 infliximab-experienced patients at rates of 3%, 22% and 52% in the first, second and third years respectively, $P = 0.001$. ADA regimen was intensified during follow-up in 56, by interval shortening (n = 50), dose escalation (n = 1), both (n = 3) or by re-loading (n = 2). The majority of escalations occurred during year 1 (n = 24) or within the first 2 years (n = 45), as prompted by return of symptoms (n = 28), and/or low ADA levels (n = 12), and/or failure to achieve biomarker remission (n = 34) or endoscopic/transmural remission (n = 15).

In contrast to the durability of ADA therapy among clinical remitters, when response to initial induction was only partial, subsequent discontinuation of therapy was very common (Fig. 1) due to initial treatment partial response ultimately being deemed unsatisfactory.

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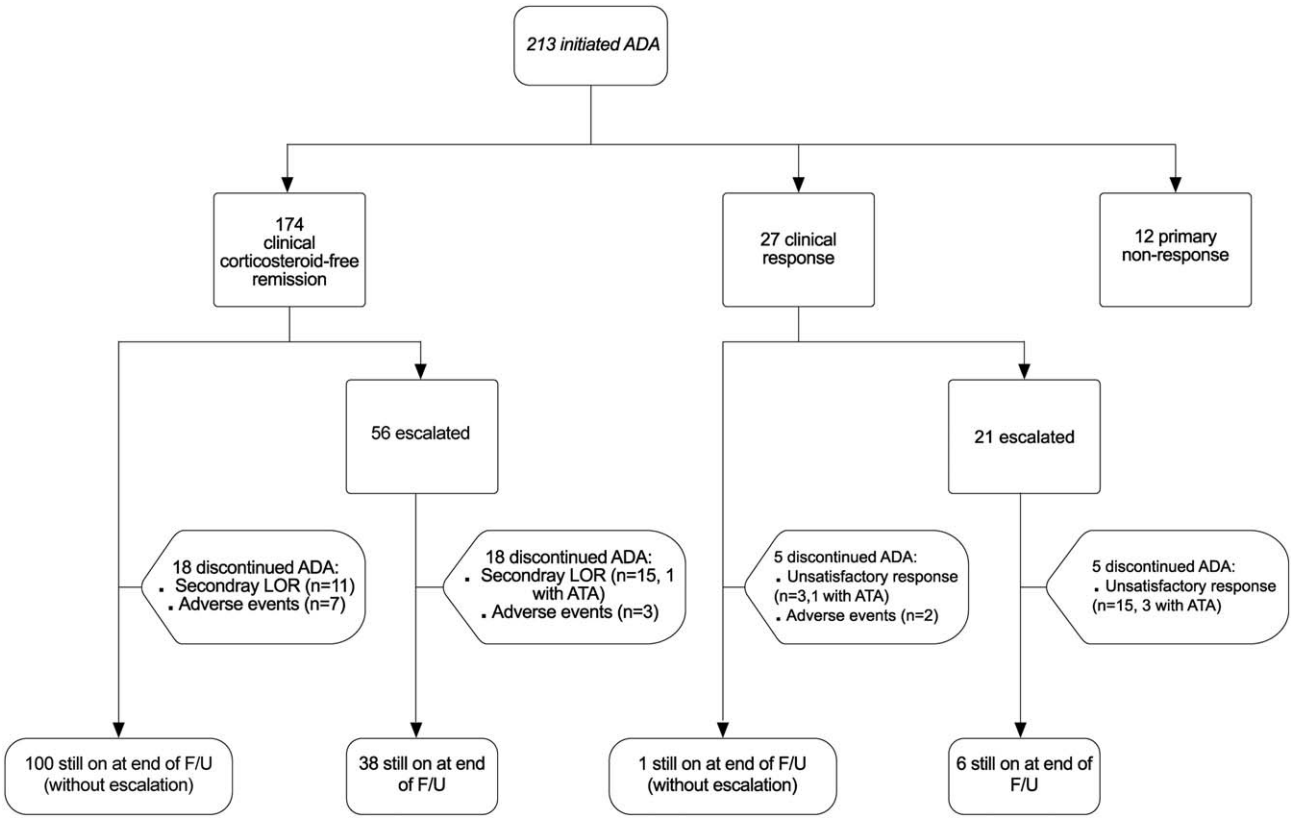

FIGURE 1. The disposition of included patients over time.

Factors Associated With Secondary Loss of Responsiveness

Table 3, Supplemental Digital Content, *http://links.lww.com/MPG/C611* lists covariates tested for significant association with LOR among clinical remitters (n = 174). In multivariable analysis, only two factors were significantly associated with decreased likelihood of LOR: being anti-TNF naïve and inflammatory (non-stricturing, non-penetrating) behavior (HR 0.3, 95% CI 0.14–0.65, $P = 0.002$, and HR 0.35, 95% CI 0.15–0.78, $P = 0.01$, respectively). Overall, 49 of 174 (28%) patients achieving clinical remission received concomitant IM therapy: two azathioprine; 47 methotrexate (weekly low oral dose in 43, subcutaneous injection in 4) during at least the first year. Secondary LOR leading to ADA discontinuation occurred in overall 8 (16%) of 49 patients treated with ADA in combination with IM compared to 18 (14%) of 125 receiving ADA monotherapy ($P = 0.853$). Time to secondary loss of response with mono- versus combination therapy among patients previously anti-TNF naïve and infliximab-experienced is displayed in Figure 2. Secondary LOR with ADA monotherapy versus with concomitant IM occurred, respectively, in 11 of 107 (10%) versus 3 of 28 (11%) of anti-TNF naïve patients ($P = 0.881$), and in 5 of 21 (24%) versus 7 of 18 (39%) of those with prior infliximab use ($P = 0.764$). One hundred and twelve patients had ADA TC tested at least 24 weeks post induction or dose escalation. By using time-dependent covariates and time-dependent coefficients in a Cox model, we found that maintenance TC consistently >7.5 μg/mL (achieved in 93/112 patients) was associated with increased likelihood of durable clinical remission (HR 17.24, 95% CI 6.33–45.45, $P < 0.001$).

Biomarker Remission

Among initial remitters (n = 174) remaining in clinical remission at 1 year (n = 162) and at end of follow-up (n = 138), respectively 74 and 70 had both CRP and Fcal measured. Likelihood of biomarker remission at one year and at end of follow-up was 70% (52/74) and 56% (42/70), respectively. By using time-dependent covariates and time-dependent coefficients in a Cox model, consistently maintaining TC >10 μg/mL, observed in 42 of 70 patients, was associated with an increased likelihood of biomarker remission (HR 6.56, 95%CI 2.27–10.28, $P < 0.001$).

Growth

Among children who were Tanner stage 1–2 at ADA initiation, mean height *z* scores were lower at ADA initiation than at diagnosis, but improved significantly during ADA therapy (Fig. 3). Mean height *z* scores remained unchanged for children initiating ADA in advanced puberty (Tanner stage 4/5).

Endoscopic and Magnetic Resonance Enterography Re-evaluations in Clinical Remitters

Among 138 patients maintaining clinical remission, 62 underwent colonoscopic reassessment and 87 repeated MRE when in clinical remission after median, respectively, 24.2 (IQR 16–34.4) and 20 (IQR, 12.8–32.8) months (Table 1, Supplemental Digital Content, *http://links.lww.com/MPG/C611*). Mucosa was normal

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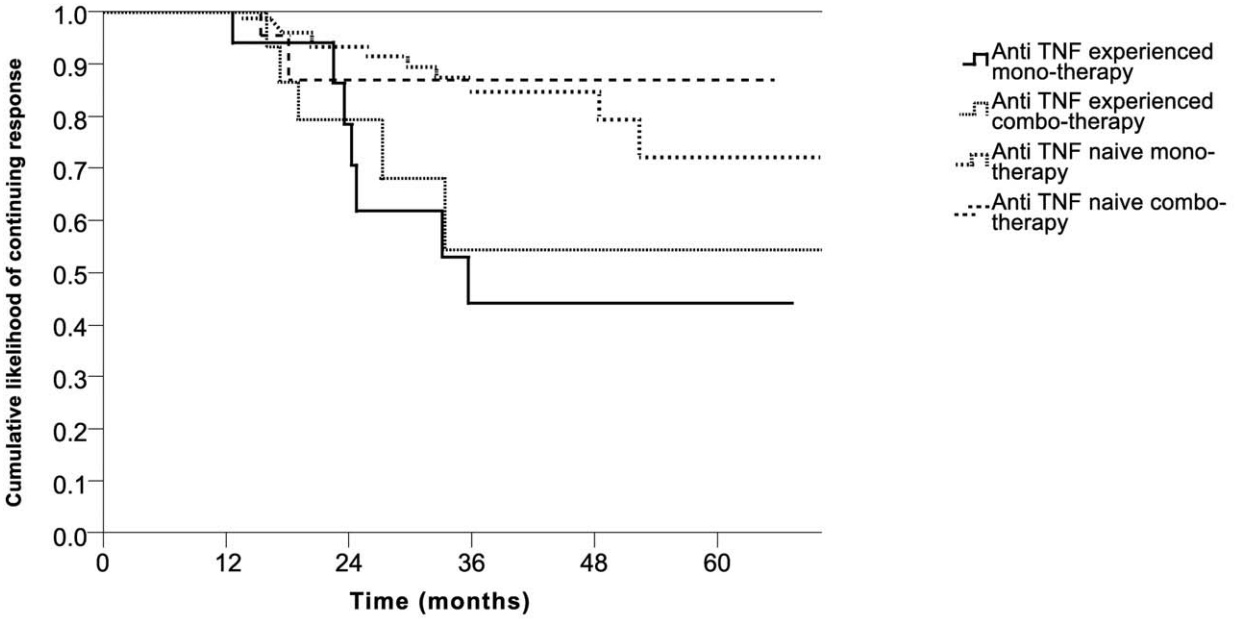
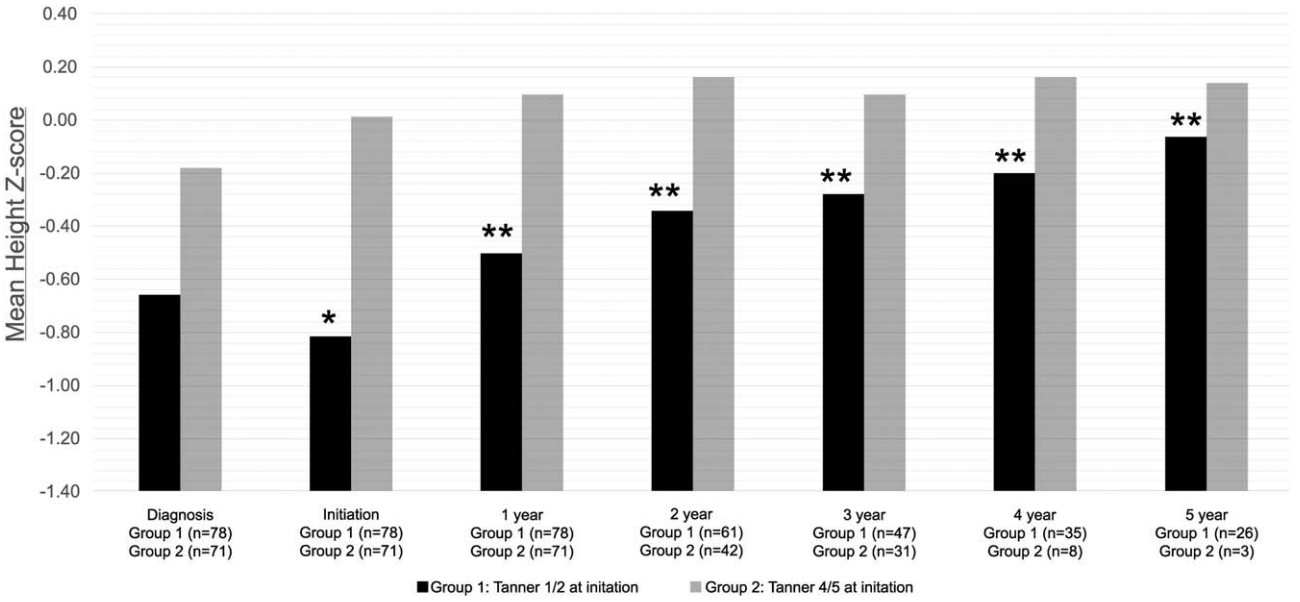


Number at risk	At ADA initiation	12 months	24 months	36 months	48 months	60 months
Anti TNF experienced mono-therapy	18	18	10	10	6	6
Anti TNF experienced combo-therapy	21	21	9	9	6	6
Anti TNF naive mono-therapy	107	107	66	41	25	10
Anti TNF naive combo-therapy	28	28	18	9	6	7

FIGURE 2. Time from adalimumab induction to secondary loss of response necessitating drug discontinuation is plotted for initial clinical remitters controlling for previous infliximab use and concomitant immunomodulator therapy.



***Mean height Z score was lower at ADA initiation compared to diagnosis (p=<0.001)**

**** Mean height Z score was improved compared to time of ADA initiation (p=<0.001)**

FIGURE 3. Longitudinal mean height z-scores during follow-up on adalimumab therapy in patients grouped according to Tanner stage at adalimumab initiation. Data are shown for patients who achieved clinical remission post-induction.

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endoscopically in 32 (52%), of whom 20 also had no histologic inflammation; another 10 met criteria for substantial endoscopic improvement. 39 clinical remitters had ADA TC consistently >10 during maintenance before endoscopy, while 17 had levels <10 μg/mL at least once (ADA levels not measured in 6). Thirty two of 38 (84%) with normal mucosa or substantial endoscopic improvement consistently maintained ADA levels >10 μg/mL compared to 7 of 18 (39%) of clinical remitters lacking endoscopic improvement. In multivariate logistic regression, maintaining ADA levels >10 μg/mL was associated with increased likelihood of endoscopic improvement (OR 10.4, 95% CI 2.4–25, $P = 0.002$) (Table 4, Supplemental Digital Content, *http://links.lww.com/MPG/C611*). On repeat MRE 43 patients (50%) had significant transmural response (25 with substantial improvement and 18 with complete normalization of MRE). Seventy one of 87 had ADA TC measured before MRE. ADA levels during maintenance were consistently >10 ug/mL in 35 of 41 (85%) and 13 of 30 (43%), respectively, of those with and without complete or substantial transmural healing. In multivariate logistic regression, maintaining ADA levels >10 μg/mL was associated with increased likelihood of transmural healing (OR 7.6, 95%CI 2.2–26.5, $P = 0.001$) (Table 5, Supplemental Digital Content, *http://links.lww.com/MPG/C611*).

Drug Safety

Adverse events with ADA therapy are shown in Table 6, Supplemental Digital Content, *http://links.lww.com/MPG/C611*. There were no serious infections, malignancies or deaths. Adverse events leading to ADA discontinuation were: severe psoriasis in five patients, vasculitis in three patients, and neurologic symptoms in two patients.

DISCUSSION

Treatment targets in pediatric CD have evolved beyond alleviation of symptoms and facilitation of normal growth to include deeper remission (17). As new biologics or oral small molecules enter the therapeutic armamentarium, it is important that their efficacy be benchmarked against real world outcomes with optimized anti-TNF.

Our observed post-induction clinical remission rate with ADA was high, likely reflecting the short disease duration, particularly when ADA was initiated as first anti-TNF. Rates of clinical response are consistently inversely related to disease duration in post-hoc analyses of anti-TNF clinical trials, and have been highest with disease duration less than 2 years (18,19). The lower likelihood of success with prior infliximab secondary failure or intolerance, as was observed much earlier among adult CD patients (20), highlights the importance of maintaining durability of response to the first anti-TNF.

Clinical remission was very durable in our cohort, with nearly 80% of the previously anti-TNF naïve cohort remaining on therapy during follow-up throughout pediatric care. Importantly, ADA response was durable even given as monotherapy. These observations stand in contrast to infliximab, where the benefit of concomitant immunomodulator use in preventing secondary loss of response has been clearly evident in real-world pediatric experience (3,4). Although not confirmed in our data, but supporting what has been our clinical practice, a recent prospective trial in adults has shown benefit to starting azathioprine with second anti-TNF in case of immune-mediated LOR to the first anti-TNF (21).

In the Personalizing Anti-TNF Therapy in Crohn's Disease (PANTS) study (22), rates of anti-drug antibodies measured with a drug-tolerant assay were higher with infliximab than with ADA, respectively 62.8% and 28.5% at 1 year. Concomitant IM mitigated the risk with both (hazard ratio 0.39 [95% CI 0.32–0.46] for infliximab; 0.44 [0.31–0.64] for adalimumab; $P < 0.0001$). As recently reported by Sazonovs, HLA-DQA∗1 carriage was an additional factor influencing anti-drug antibody development in the PANTS study, an observation that might pave the way for personalized anti-TNF regimen (23).

Given the importance of TNFα and other pro-inflammatory cytokines in the pathophysiology of linear growth impairment in CD (24), it would be anticipated that effective anti-TNF therapy should facilitate linear growth, provided its initiation is not delayed until close to the time of epiphyseal fusion. Our findings in patients Tanner stages 1 and 2 are particularly encouraging, as stature improves steadily, such that heights are normally distributed in comparison to age-and gender-matched healthy peers by 5 years.

Current pediatric practice targets clinical remission and intestinal healing (17), but data regarding the likelihood of achieving endoscopic and cross-sectional imaging targets have been hitherto lacking. Our cohort included patients initiating ADA over a span of 11.5 years, during which time treatment targets gradually evolved. In the early years of the study, colonoscopic or MR imaging reassessments were undertaken when patient progress on therapy was unsatisfactory, in order to guide next step of therapy. Only in recent years has it been common to repeat MR imaging or colonoscopy to assess intestinal healing in well-appearing, asymptomatic patients, who are growing normally. Based on data available in such patients, complete normalization of MR imaging was uncommon with ADA therapy, even among clinical remitters. Endoscopic healing or substantial improvement was observed in 68% of children re-examined when in clinical remission. Among adult patients treated with ADA in the ''tight control'' arm of the CALM study, 56 (46%) of 122 achieved CDEIS <4 and no deep ulcers by week 48 (25).

TDM is increasingly used as a tool for optimizing biologic therapy (26). Proactive versus reactive TDM enhanced rates of sustained clinical remission and biomarker response with ADA in the prospective, randomized PAILOT study, albeit with a conservative target ADA TC of 5 ug/mL (27). Plevris et al (28) reported ADA TC >8.5 ug/mL to be associated with biomarker remission. We demonstrated an association between sustained maintenance TC >10 ug/m and biomarker remission, resolution of ulcers at endoscopy, and improvement in transmural inflammation. These analyses, however, were retrospective and based on data from TDM performed either reactively or proactively. In a prospective study of ADA TC measured prospectively early following induction, our group reported week 8 ADA TC of >12.5 ug/mL to be associated with clinical/biomarker remission at week 24 (29).

Although data ascertainment was aided by use of standardized clinic forms and by ADA patient support program, this was a retrospective study with inherent limitations. Clinical practice changed over the years of the study; during the early years TDM was reactive rather than proactive. Repeat endoscopic and MR examinations were not performed among all clinical remitters and were not scored prospectively by validated multi-item measures. The lack of access to a drug-tolerant assay significantly limits understanding of rate of ATA development, and identifies only patients where ATA increases clearance in the extreme. Nevertheless, our study confirms the efficacy of anti-TNF therapy, as used early following diagnosis in pediatric CD. Remission is durable even with ADA monotherapy, allowing growth to normalize if initiated before advanced puberty. Clinical remission is frequently associated with resolution of endoscopic ulceration, but normalization of MR imaging is uncommon. Consistently higher TCs during maintenance are associated with biomarker remission, endoscopic healing and transmural imaging improvement. Prospective studies are needed to investigate whether dose

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intensification in a treat-to-target fashion improves rates of endoscopic and transmural remission.

REFERENCES

1. 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* 2007;132:863–73.
2. Hyams JS, Griffiths A, Markowitz J, et al. Safety and efficacy of adalimumab for moderate to severe Crohn's disease in children. *Gastroenterology* 2012;143:365–74.
3. Grossi V, Lerer T, Griffiths A, et al. Concomitant use of immunomodulators affects the durability of infliximab therapy in children with Crohn's disease. *Clin Gastro Hepatol* 2015;13:1748–56.
4. Church PC, Guan J, Walters TD, et al. Infliximab maintains durable response and facilitates catch-up growth in luminal pediatric Crohn's disease. *Inflamm Bowel Dis* 2014;20:1177–86.
5. Matar M, Shamir R, Turner D, et al. Combination therapy of adalimumab with an immunomodulator is not more effective than adalimumab monotherapy in children with Crohn's disease: a post hoc analysis of the PAILOT Randomized Controlled Trial. *Inflamm Bowel Dis* 2020;26:1627–35.
6. Walters TD, Faubion WA, Griffiths AM, et al. Growth improvement with adalimumab treatment in children with moderately to severely active Crohn's disease. *Inflamm Bowel Dis* 2017;23:967–75.
7. Faubion WA, Dubinsky M, Ruemmele FM, et al. Long-term efficacy and safety of adalimumab in pediatric patients with Crohn's disease. *Inflamm Bowel Dis* 2017;23:453–60.
8. Levine A, Griffiths A, Markowitz J, et al. Pediatric modification of the Montreal classification for inflammatory bowel disease: the Paris classification. *Inflamm Bowel Dis* 2011;17:1314–21.
9. Mack DR, Benchimol EI, Critch J, et al. Canadian association of gastroenterology clinical practice guideline for the medical management of pediatric luminal Crohn's disease. *Gastroenterology* 2019;157:320–48.
10. Hyams JS, Ferry GD, Mandel FS, et al. Development and validation of a pediatric Crohn's disease activity index. *J Pediatr Gastroenterol Nutr* 1991;12:439–47.
11. Kuczmarski RJ, Ogden CL, Grummer-Strawn LM, et al. CDC growth charts: United States. *Adv Data* 2000;314:1–27.
12. Feuerstein JD, Nguyen GC, Kupfer SS, et al. American gastroenterological association institute guideline on therapeutic drug monitoring in inflammatory bowel disease. *Gastroenterology* 2017;153:827–34.
13. Ungar B, Levy I, Yavne Y, et al. Optimizing anti-TNF-alpha therapy: serum levels of infliximab and adalimumab are associated with mucosal healing in patients with inflammatory bowel diseases. *Clin Gastro Hepatol* 2016;14:550–7.
14. Yarur AJ, Jain A, Hauenstein SI, et al. Higher adalimumab levels are associated with histologic and endoscopic remission in patients with Crohn's disease and ulcerative colitis. *Inflamm Bowel Dis* 2016;22:409–15.
15. Gibson DJ, Ward MG, Rentsch C, et al. Review article: determination of the therapeutic range for therapeutic drug monitoring of adalimumab and infliximab in patients with inflammatory bowel disease. *Alim Pharmacol Ther* 2020;51:612–28.
16. Clark TG, Bradburn MJ, Love SB, et al. Survival analysis. Part I. Basic concepts and first analyses. *Br J Cancer* 2003;89:232–8.
17. Turner D, Ricciuto A, Lewis A, et al. STRIDE-II: an update on the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) initiative of the International Organization for the Study of IBD (IOIBD): determining therapeutic goals for treat-to-target strategies in IBD. *Gastroenterology* 2020.
18. Colombel JF, Sandborn WJ, Rutgeerts P, et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. *Gastroenterology* 2007;132:52–65.
19. Ungaro RC, Aggarwal S, Topaloglu O, et al. Systematic review and meta-analysis: efficacy and safety of early biologic treatment in adult and pediatric patients with Crohn's disease. *Aliment Pharmacol Ther* 2020;51:831–42.
20. Sandborn WJ, Rutgeerts P, Enns R, et al. Adalimumab induction therapy for Crohn disease previously treated with infliximab: a randomized trial. *Ann Intern Med* 2007;146:829–38.
21. Roblin X, Williet N, Boschetti G, et al. Addition of azathioprine to the switch of anti-TNF in patients with IBD in clinical relapse with undetectable anti-TNF trough levels and antidrug antibodies: a prospective randomised trial. *Gut* 2020;69:1206–12.
22. Kennedy NA, Heap GA, Green HD, et al. Predictors of anti-TNF treatment failure in anti-TNF-naive patients with active luminal Crohn's disease: a prospective, multicenter, cohort study. *Lancet Gastroenterol Hepatol* 2019;4:341–53.
23. Sazonovs A, Kennedy NA, Moutsianas L, et al. HLA-DQA1∗05 carriage associated with development of anti-drug antibodies to infliximab and adalimumab in patients with Crohn's disease. *Gastroenterology* 2020;158:189–99.
24. Walters TD, Griffiths AM. Mechanisms of growth impairment in pediatric Crohn's disease. *Nat Rev Gastroenterol Hepatol* 2009;6:513–23.
25. Colombel JF, Panaccione R, Bossuyt P, et al. Effect of tight control management on Crohn's disease (CALM): a multicenter, randomised, controlled phase 3 trial. *Lancet* 2018;390:2779–89.
26. Ricciuto A, Dhaliwal J, Walters TD, et al. Clinical outcomes with therapeutic drug monitoring in inflammatory bowel disease: a systematic review with meta-analysis. *J Crohns Colitis* 2018;12:1302–15.
27. Assa A, Matar M, Turner D, et al. Proactive monitoring of adalimumab trough concentration associated with increased clinical remission in children with Crohn's disease compared with reactive monitoring. *Gastroenterology* 2019;157:985.e2–96.e2.
28. Plevris N, Lyons M, Jenkinson PW, et al. Higher adalimumab drug levels during maintenance therapy for Crohn's disease are associated with biologic remission. *Inflamm Bowel Dis* 2019;25:1036–43.
29. Rinawi F, Ricciuto A, Church PC, et al. Association of early post-induction adalimumab exposure with subsequent clinical and biomarker remission in children with Crohn's disease. *Inflamm Bowel Dis* 2021;27:1079–87.

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