

# Difficult-to-treat-pediatric Crohn's disease: focus on adalimumab

Bella Zeisler  
Jeffrey S Hyams

Division of Digestive Diseases,  
Hepatology, and Nutrition,  
Connecticut Children's Medical  
Center Hartford, University of  
Connecticut School of Medicine,  
Department of Pediatrics, Farmington,  
CT, USA

**Abstract:** Adalimumab is a fully humanized anti-tumor necrosis factor alpha monoclonal antibody that was recently granted regulatory approval in the USA for the treatment of moderate to severe Crohn's disease (CD) in children. Like infliximab, the first biologic agent used to treat pediatric CD, regulatory approval was secured many years following approval for adults. The long delay between adult and pediatric approval has led to many years of off-label use of adalimumab, although it is anticipated that the use of adalimumab may further increase with official regulatory approval. To date, pediatric literature on the use of adalimumab for treatment of CD is limited, and pediatric practitioners have mostly extrapolated from research and experience provided by the adult literature. The aim of this paper is to review the literature regarding adalimumab for the treatment of pediatric CD, and includes a review of landmark adult studies as well as the pivotal pediatric study that facilitated regulatory approval. We also discuss the role of anti-tumor necrosis factor alpha agents including adalimumab in the current treatment paradigm for pediatric CD.

**Keywords:** pediatrics, Crohn's disease, adalimumab, biologic agent

## Introduction

While the precise etiology of Crohn's disease (CD) remains unknown, current evidence suggests that intestinal inflammation arises due to an abnormal response of the intestinal immune system to the fecal microbiome in genetically predisposed individuals.<sup>1</sup> This inflammation can lead to significant gastrointestinal symptoms, including abdominal pain, diarrhea, and bleeding, resulting in weight loss and nutritional compromise. Complicated disease, including stricturing and perforation, as well as abscess formation, often results in the need for surgical intervention. Poor bone health, growth failure, delayed puberty, and a variety of extra-intestinal manifestations, such as arthritis and liver disease, as well as impaired psychosocial development, are commonly observed.<sup>2-7</sup>

The incidence of pediatric CD is estimated to be about four to seven per 100,000<sup>8,9</sup> and is likely to be on the rise.<sup>10,11</sup> Approximately 25% of newly diagnosed cases of CD occur in individuals younger than 20 years of age, and in general, this younger population often has a more severe clinical phenotype.<sup>12,13</sup> Further, compared with adult patients, a higher frequency of corticosteroid and immunomodulator use has been reported in newly diagnosed children.<sup>14</sup> However, despite relatively frequent use, it is not clear that use of immunomodulators and corticosteroids, often referred to in the literature as "conventional therapy", changes the natural history of the disease

Correspondence: Bella Zeisler  
Connecticut Children's Medical  
Center, Division of Digestive Diseases,  
Hepatology, and Nutrition  
282 Washington Street, Hartford,  
CT 06106, USA  
Tel +1 860 545 9560  
Fax +1 860 545 9561  
Email bzeisler@connecticutchildrens.org

or ameliorates progression to intestinal stricturing and perforation. Moreover, “conventional therapies” have not been shown to reverse CD-associated growth delay.<sup>2</sup>

Biologic therapy is the newest class of medication indicated for the treatment of CD. A biologic agent is a medication that specifically targets immune or genetic mediators of disease. The first drugs in this class approved for inflammatory bowel disease were anti-tumor necrosis factor alpha (TNF- $\alpha$ ) agents. Infliximab, a mouse-human chimeric monoclonal anti-TNF- $\alpha$  antibody, was the first biologic agent approved for inflammatory bowel disease in adults, initially for CD in 1998 and then subsequently for ulcerative colitis (UC) in 2005.<sup>15–20</sup> It was then approved for pediatric CD and UC in 2006 and 2011, respectively.<sup>21–29</sup> It is currently also approved for rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and plaque psoriasis. It is administered by infusion generally every 8 weeks following induction.

Adalimumab, the focus of this paper, is a fully humanized anti-TNF- $\alpha$  monoclonal antibody. It is administered via subcutaneous injection typically by the patient at home. The most common dosing schedule is every other week following a loading dose. It was approved for adult CD and UC in 2007 and 2012, respectively. Additional indications for adalimumab approved by the US Food and Drug Administration (FDA) in adults include rheumatoid arthritis as of 2002, psoriatic arthritis as of 2005, ankylosing spondylitis as of 2006, and plaque psoriasis as of 2008. In 2008, adalimumab was also approved for use in pediatric patients aged 4 years and older with juvenile inflammatory arthritis. Finally, in late 2014, it was approved for CD, its second pediatric indication, for children aged 6 years and older.

Prior to the recent FDA approval, pediatric inflammatory bowel disease care providers have used adalimumab off-label for patients refractory to other therapeutic options, and specifically as a next line for patients who have lost response to or cannot tolerate infliximab. Its new regulatory status will likely stimulate broader use of this drug, thereby prompting further interest and increased knowledge and understanding of its use.

The aim of this paper is to review the literature supporting the 2014 approval of adalimumab for the treatment of pediatric CD, and includes the landmark studies in adults that have led the way for pediatric medical decision-making and investigation. We also discuss the role of anti-TNF- $\alpha$  agents in the current treatment paradigm for pediatric CD.

The following case is illustrative of situations in which adalimumab might be considered in pediatric CD.

## Case vignette

A 14-year-old female presents with a 6-month history of abdominal pain, loose stools with occasional blood, decreased growth velocity, and primary amenorrhea. Physical examination reveals a pale Tanner I teenager who appears younger than her chronologic age. Her abdomen is soft but mildly tender in the right lower quadrant. Two small anal tags are noted, without any evidence of fistula or abscess. Mild pre-tibial edema is seen as well as marked clubbing. Laboratory evaluation reveals anemia and elevation of markers of inflammation, including a hemoglobin of 9.8 g/L and an erythrocyte sedimentation rate of 65 mm/hour. Additional testing reveals a low albumin of 2.4 g/dL and a bone age consistent with an 11-year-old. Upper gastrointestinal endoscopy reveals no visual or microscopic inflammation in her esophagus, stomach, or duodenum. Ileocolonoscopy reveals marked ulceration of her terminal ileum and cecum as well as scattered aphthous lesions throughout her colon. Magnetic resonance enterography reveals 25 cm of diseased terminal ileum with marked wall thickening and mural enhancement.

One week later the physician meets with the patient and family to discuss possible therapeutic options that included: initial prednisone followed by a thiopurine for maintenance therapy; exclusive enteral nutrition followed by a thiopurine for maintenance therapy; and primary anti-TNF- $\alpha$  therapy with or without a concomitant immunomodulator

Until recently, per the prevailing algorithm of care, the patient described in the above vignette would likely receive initial prednisone or exclusive enteral nutrition for induction of remission, followed by an immunomodulator for maintenance therapy. Anti-TNF- $\alpha$  agents were reserved for rescue therapy only after “conventional therapy” failure. However, since regulatory approval of infliximab in the late 1990s, which as mentioned above was the first anti-TNF- $\alpha$  agent approved for CD, evidence continues to mount in both the adult and pediatric literature supporting its safety, as well as its often superior efficacy in controlling symptoms, improving growth parameters, closing fistulae, decreasing the need for surgery, and possibly improving the natural history of the disease.<sup>15–17,22,23,30–33</sup> Thus, the role of anti-TNF- $\alpha$  agents as primary therapy given soon after diagnosis for patients with moderate to severe CD has gained traction. In current pediatric clinical practice, infliximab continues to be the

first anti-TNF- $\alpha$  used for most patients with moderate to severe CD, likely because it was the first anti-TNF- $\alpha$  agent approved for CD as well as enhanced dosing flexibility on a mg/kg basis. Adalimumab has to date been most often used as a second line anti-TNF- $\alpha$  agent when there has been a loss of response to infliximab because of development of neutralizing antibodies or when other infliximab-specific side effects have developed.

## Landmark studies of adalimumab in adult CD

The major studies leading to approval of adalimumab for adults with CD include CLASSIC I and II, GAIN, EXTEND, and CHARM, including its open-label extension study ADHERE, which at this time includes 4 years of follow-up data.<sup>34-41</sup> CLASSIC I was a randomized, double-blind, placebo-controlled trial that investigated induction of remission over a 4-week period. This study enrolled 299 adult patients with moderate to severe CD and naïve to anti-TNF- $\alpha$  therapy. The patients were randomized to receive adalimumab at varying doses or placebo. The primary endpoint of this study was remission at week 4. There was a linear dose response across dose groups; patients receiving the highest dosing schedule were three times more likely to achieve remission than those receiving placebo (36% versus 12%, respectively) which was statistically significant. There were no increased adverse events seen among patients receiving adalimumab compared with placebo.<sup>34</sup> CLASSIC II, the follow-up study that investigated maintenance of remission enrolled 276 patients from CLASSIC I. Patients received open-label adalimumab at weeks 0 and 2. At week 4, 55 patients were in remission. These patients were then rerandomized to receive adalimumab or placebo every other week or weekly. Maintenance of remission at week 56 was achieved in 79% and 83% of these 55 patients who received the alternate-week or weekly dosing schedule, respectively, compared with 44% of those who received placebo ( $P < 0.05$ ). In this study, there was no significant increase in adverse events among patients receiving the active drug compared with placebo.<sup>35</sup>

GAIN was a 4-week, randomized, double-blind, placebo-controlled trial that enrolled 325 patients across 52 sites in the USA, Canada, and Europe to evaluate induction of remission in patients receiving adalimumab versus placebo for patients previously exposed to infliximab. In this study, patients had stopped infliximab due to continued symptoms or adverse events. GAIN showed that induction of remission

with adalimumab in patients previously failing infliximab was observed in 21% compared with 7% in the placebo group ( $P < 0.0001$ ),<sup>36</sup> suggesting a role for adalimumab even in patients for whom previous anti-TNF- $\alpha$  therapy has failed.

EXTEND was a randomized, double-blind, placebo-controlled trial evaluating adalimumab for induction and maintenance of mucosal healing in 135 adults with moderate to severe ileocolonic CD. Concomitant therapy with immunomodulators, mesalazine compounds, and CD-related antibiotics was permitted provided that patients were at a stable dose as defined by the study protocol. Ileocolonoscopy was performed at weeks 12 and 52. Mucosal healing was observed in 27% versus 13% at week 12 (not statistically significant) and 24% versus 0% at week 52 ( $P < 0.001$ ) for patients who all received induction therapy and who were then randomized to receive adalimumab versus placebo, respectively.<sup>38</sup>

As a follow-up to CLASSIC II, CHARM, now the largest prospective study to date evaluating the safety and efficacy of adalimumab for the treatment of CD in adults, was a randomized, double-blind, placebo-controlled multicenter study evaluating the safety and efficacy of adalimumab. This study enrolled 854 patients at 92 sites across North America, Europe, Australia, and South Africa. A total of 505 patients completed the 56-week study. First, patients received open-label induction therapy with adalimumab at weeks 0 and 2. At week 4, they were randomized to receive placebo or adalimumab weekly or every other week through week 56. The primary endpoint was clinical remission at weeks 26 and 56. At weeks 26 and 56, remission rates were 47%/41%, 40%/36%, and 17%/12% for patients receiving drug weekly, every other week, or placebo, respectively. Differences between weekly and every other week dosing schedules were not significant. However, differences between patients receiving drug versus placebo were significant. In this study, no significant increase in adverse events was seen in patients receiving drug versus placebo.<sup>37</sup> Patient data collection continued in an open-label extension study, ie, ADHERE, and 4 years of data are now published.<sup>39-42</sup> Of note, after 4 years, 54% of patients who were in remission at 1 year following study enrollment, remain in remission and no new safety signals have emerged.<sup>41</sup>

## Pediatric literature on adalimumab in CD

As is the case across many areas of medicine, investigation and drug approvals in pediatric CD have lagged behind those in adults. At present, pediatric-specific data on the

use of adalimumab for the treatment of CD are limited, and pediatric practitioners tend to extrapolate heavily from adult investigation and clinical experience.

Other than a single case report,<sup>43</sup> there were no published pediatric data prior to 2008. Between 2008 and 2010, some pediatric data began to emerge, including additional case reports and small retrospective single-center studies.<sup>44-48</sup> In 2008, a small, open, prospective evaluation of the short-term and long-term efficacy and safety of adalimumab in children with moderate to severe CD was reported.<sup>49</sup> In this study, a total of 23 pediatric CD patients received subcutaneous adalimumab during a 48-week period. At baseline, 13 patients also received immunomodulators. Data were recorded at weeks 2, 4, 12, 24, and 48 weeks. Remission (response) rates at these time points were 36.3 (87%), 60.8 (88%), 30.5 (70%), 50 (86%), and 65.2 (91%), respectively. No serious adverse events were reported in this study.<sup>49</sup>

A larger chart review study in 2009 looked at data across 12 sites participating in the Pediatric Inflammatory Bowel Disease Collaborative Research Group. In total, 115 patients with CD received at least one dose of adalimumab. Ninety-five percent of patients in the study had been previously treated with infliximab. Reasons for discontinuation of infliximab were loss of response (47%), intolerance (45%), or preference for subcutaneous medication (9%). Clinical response/corticosteroid-free remission rates documented at 3, 6, and 12 months were 65/22%, 71/33%, and 70/42%. No serious adverse events were recorded.<sup>50</sup>

An additional relatively larger chart review study published in 2011 summarizes the pediatric experience using adalimumab for patients living in the UK and Republic of Ireland.<sup>51</sup> Of the 72 patients (70 with CD, one with UC, and one with indeterminate colitis) studied across 19 pediatric centers, 94% of whom had previously received infliximab, remission rates were 24%, 58%, and 41% at 1, 6, and 12 months, respectively. The authors reported that 61% of all study subjects went into remission at some time during the study. Of the 46 patients treated with a concomitant immunomodulator, 34 (74%) went into remission during the study versus 9/24 (37%) patients who were not treated with a concomitant immunomodulator. Thirty-five percent of patients in the study required dose escalation. By the end of the study, 22 patients had discontinued adalimumab due to non-response, loss of response, an allergic reaction, or a prolonged drug holiday. There were 15 adverse events reported in this study, including four serious events, two of which resulted in death. Both deaths were in children receiving concomitant immunomodulator therapies who also had central

venous catheters for total parenteral nutrition. Both deaths were attributed to catheter-related sepsis. Although notable, the downward trend in remission seen in the study between 6 and 12 months is difficult to interpret, especially without data points extending beyond 1 year.

In line with previous studies demonstrating positive effects of infliximab on growth and bone health in pediatric patients with CD,<sup>25,31,52</sup> a small 2012 study looked at the effects of adalimumab on growth among 36 children with CD. Catch-up growth was seen in 42% of patients, and was more likely to be seen in patients who achieved remission, were on concomitant immunomodulators, or whose indication for using adalimumab was an allergic reaction to infliximab.<sup>53</sup>

The largest and most conclusive pediatric study to date addressing the safety and efficacy of adalimumab for CD, which led to approval of adalimumab by the FDA for pediatric CD, was IMaGINE 1 study, published in 2012.<sup>27</sup> This study prospectively enrolled 192 pediatric patients with moderate to severe CD for whom conventional therapy was unsuccessful. Patients received open-label induction therapy with subcutaneous adalimumab at weeks 0 and 2. Patients weighing  $\geq 40$  kg received 160 mg followed by 80 mg, and patients weighing  $< 40$  kg received 80 mg followed by 40 mg. At week 4, patients were assigned to groups based on clinical response and prior exposure to infliximab. The groups were then given double-blind maintenance therapy with adalimumab at high or low doses (40 mg versus 20 mg for patients  $\geq 40$  kg and 20 mg versus 10 mg for patients  $< 40$  mg) every 2 weeks for 48 weeks. Clinical remission at week 26 was the primary endpoint. At week 26, 33.5% of patients were in clinical remission, with no significant differences between the high-dose and low-dose groups. In this study, no new safety signals were detected. Twelve patients did experience a serious infection. No deaths, malignancies, or demyelinating disease events occurred during the study period.

Following IMaGINE 1, a retrospective study in 2013 looked at short-term and long-term follow-up of 120 pediatric patients with inflammatory bowel disease (101 with CD and 19 with UC) from three sites in Israel who were treated with anti-TNF- $\alpha$  therapy (either adalimumab [18%] or infliximab [82%]).<sup>54</sup> Response rates to infliximab and adalimumab did not differ and were thus compiled together. In this study, 89% of patients achieved a short-term response following induction. The cumulative probability of losing response to treatment was 17%, 38%, and 49% after 1, 3, and 5 years, respectively.

The most recent pediatric study of adalimumab for CD, published in 2014, was a retrospective, observational Dutch

cohort investigation of the efficacy of adalimumab in pediatric patients previously treated with infliximab. The efficacy of adalimumab was compared in patients who had non-response versus loss of response to infliximab. Fifty-three patients were studied. Twelve patients received monotherapy, and the remaining patients received combination therapy with immunomodulators, corticosteroids, or exclusive enteral nutrition. Median follow-up was 12 months. Remission was achieved in 64% and an additional 21% achieved a response. Further, remission was maintained by 50% of patients for 2 years. Adalimumab failures occurred in 34% during the observation period due to non-response, loss of response, or adverse events. More infliximab non-responders failed adalimumab treatment compared with patients who lost response to infliximab. There was one serious adverse event recorded in this study.<sup>55</sup>

## Discussion

Regulatory approval of adalimumab for the treatment of moderate to severe pediatric CD in children removes a potential obstacle to its use and now offers clinicians another approved choice in the use of anti-TNF- $\alpha$  therapy. A key question is whether one of the two approved agents, infliximab or adalimumab, offers advantages over the other. In head-to-head adult studies, response and remission rates as well as other outcome measures, such as need for hospitalization or surgery and fistula or abscess formation appear similar, particularly in anti-TNF- $\alpha$ -naïve patients.<sup>56</sup>

Regarding the use of a concomitant immunomodulator along with anti-TNF- $\alpha$  therapy, a landmark study in 2010 showed that infliximab plus a thiopurine significantly improves efficacy at 1 year compared with infliximab monotherapy or azathioprine monotherapy.<sup>57</sup> Efficacy data on adalimumab monotherapy versus combination therapy with adalimumab has been somewhat less clear.<sup>58,59</sup> From a safety point of view, while studies have shown that monotherapy with anti-TNF- $\alpha$  agents (either infliximab or adalimumab) is not associated with an increased risk for malignancy,<sup>60,61</sup> with the possible exception of some skin cancers,<sup>60,62,63</sup> immunomodulator therapy either alone or in combination with anti-TNF- $\alpha$  therapy has been linked to an increased chance of developing various malignancies,<sup>60,64,65</sup> including hepatosplenic T-cell lymphoma, an extremely rare but universally aggressive and fatal tumor that has almost exclusively affected only young males.<sup>66</sup> Although the safety and efficacy of concomitant immunomodulator therapy has been studied for both infliximab and adalimumab, head-to-head data are presently not available.

On a practical level, adalimumab may be easier to administer because it can be given at home as a subcutaneous injection by the patient or parent. It does not require a child to take time off school or the parent to miss work to travel to a health facility for an intravenous infusion of infliximab. However, injections of adalimumab are noted to be quite uncomfortable for some patients, and dosing is fixed by 20 mg and 40 mg syringes. In addition, adherence cannot generally be directly observed. On the other hand, infliximab, given as an intravenous infusion, often necessitates disruption of work and school schedules. However, there is greater dose flexibility on a mg/kg basis, and administration can be monitored.

Recent data suggest that monitoring serum trough levels of either agent may facilitate improved efficacy by ensuring adequate drug is being administered as well as by identifying patients who have developed loss of response because of development of antibodies to the drug.<sup>67-69</sup> Both drugs are immunogenic and are associated with development of antibodies.<sup>67</sup>

The central question moving forward is whether anti-TNF- $\alpha$  therapy should be positioned differently in pediatric patients with moderate to severe disease and used earlier in the disease course as first-line rather than as “rescue” following failure of “conventional” therapy. In other words, should the so-called top-down approach become the new “conventional therapy” for selected pediatric patients? A recent comparative effectiveness study of children newly diagnosed with CD convincingly demonstrated that early anti-TNF- $\alpha$  therapy (in the first 3 months following diagnosis) was superior to early immunomodulator therapy alone for the first 3 months in achieving clinical remission as well as improving growth parameters at 1 year in children with moderate to severe disease. The effect was noted despite a large number of patients receiving immunomodulator therapy early in the course of treatment who were then subsequently treated with anti-TNF- $\alpha$  agents between 3 and 12 months.<sup>30</sup> This paper did not purport to support the use of early anti-TNF- $\alpha$  therapy in all newly diagnosed children with CD. However, it did suggest that biologic therapy should be considered early on for children identified as being at “high risk” for poor outcomes. A recent consensus statement suggested the following features as conferring high risk: extensive disease, deep ulcerations on colonoscopy, marked growth retardation, osteopenia, penetrating or stricturing disease at diagnosis, and severe perianal disease.<sup>70</sup> In adults, predictors of disabling disease include age <40 years, an initial requirement for corticosteroids to control symptoms, and perianal disease.<sup>71</sup> Clearly, many children meet these last criteria as well.

Other biologic agents may also be of value in the treatment of children with moderate to severe CD, but require further study. Certolizumab pegol (an additional anti-TNF- $\alpha$  agent approved in 2008 for adults with CD)<sup>72</sup> is a PEGylated antigen binding fragment (Fab') of a humanized monoclonal antibody to TNF- $\alpha$ . This agent is also currently indicated for the treatment of rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. Certolizumab pegol is administered subcutaneously every 4 weeks after induction. Data on its use in children are currently sparse. There are some data published in abstract form from NURTURE, an ongoing pediatric trial aiming to recruit 160 patients for evaluation of the safety, efficacy, pharmacokinetics, and immunogenicity of certolizumab pegol in children.<sup>73</sup> Preliminary data suggest that plasma concentrations of certolizumab pegol during the 6-week induction period are similar to those observed in adults when body weight is taken into account.

Natalizumab, a humanized monoclonal antibody against the cell adhesion molecule  $\alpha 4$ -integrin, is approved for adult CD (as well as multiple sclerosis). This medication, which is administered by intravenous infusion every 4 weeks, works by inhibiting leukocyte migration from blood vessels to sites of inflammation. Natalizumab was initially approved by the FDA in 2004, but was subsequently withdrawn from the market due to cases of progressive multifocal leukoencephalopathy, a rare neurologic condition caused by the John Cunningham virus. Natalizumab was then reintroduced in the USA in 2006 under a restricted distribution program.<sup>74</sup> A single small pediatric cases series published in 2007 suggested utility in children, although the dosing schedule used in that study was likely suboptimal.<sup>74</sup> The fear of progressive multifocal leukoencephalopathy has likely limited its use in children.

Vedolizumab, approved in 2013 for the treatment of adult CD and UC, is a monoclonal antibody that demonstrates gut-selective anti-inflammatory activity by binding to the  $\alpha_4\beta_7$  integrin. It does not appear to be associated with progressive multifocal leukoencephalopathy, but there are currently no pediatric data and clinical trials in children have not been started.

Thus, in reference to the clinical vignette presented earlier in this paper, given current data from the pediatric and adult literature regarding the safety and efficacy of anti-TNF- $\alpha$  agents and the natural history of moderate to severe CD in children, we would advocate cautious consideration of anti-TNF- $\alpha$  as a first-line treatment for this patient, who presents with high-risk features of disease, including growth retardation. Either infliximab or adalimumab could be

used, although the only published data on early use is with infliximab.<sup>30</sup> Concomitant use of an immunomodulator, such as 6-mercaptopurine/azathioprine or methotrexate, would be considered in our patient, although the latter option would be potentially problematic if the patient was sexually active or planned to become sexually active, due to the known teratogenic effects of methotrexate. Data have shown that while concomitant 6-mercaptopurine/azathioprine along with anti-TNF- $\alpha$  therapy may provide increased efficacy as well as increased durability due to suppression of anti-TNF- $\alpha$  neutralizing antibodies,<sup>57,75,76</sup> there are limited data on the utility of methotrexate in the same role. However, at this time, the data do show that concomitant methotrexate may improve trough levels of TNF- $\alpha$ , possibly leading to increased durability of effect.<sup>75</sup>

Over the last 2 decades, primarily through addition of biologic therapies to the clinical armamentarium, there has been considerable progress in our ability to help patients with CD achieve remission, avoid corticosteroid use, and other disease complications, including surgery. At this time, as discussed, there are only two biologic agents approved for pediatric CD, ie, infliximab and adalimumab. Going forward, in order to further optimize the use of biologic agents for pediatric CD, continued investigation will be needed to demonstrate safety and efficacy for newer agents not yet approved for pediatric use, and to optimize dosing schedule guidelines and monitoring of drug levels.

## Disclosure

JH has acted as a consultant for Janssen Biotech, Abbvie, Celgene, Avaxia, Receptos, Salix, and UCB. BZ has no conflicts of interest to report.

## References

1. Abraham C, Cho JH. Inflammatory bowel disease. *N Engl J Med*. 2009;361:2066–2078.
2. Pfefferkorn M, Burke G, Griffiths A, et al. Growth abnormalities persist in newly diagnosed children with Crohn disease despite current treatment paradigms. *J Pediatr Gastroenterol Nutr*. 2009;48:168–174.
3. Kanof ME, Lake AM, Bayless TM. Decreased height velocity in children and adolescents before the diagnosis of Crohn's disease. *Gastroenterology*. 1988;95:1523–1527.
4. Griffiths AM, Nguyen P, Smith C, MacMillan JH, Sherman PM. Growth and clinical course of children with Crohn's disease. *Gut*. 1993;34:939–943.
5. Sawczenko A, Ballinger AB, Savage MO, Sanderson IR. Clinical features affecting final adult height in patients with pediatric-onset Crohn's disease. *Pediatrics*. 2006;118:124–129.
6. Motil KJ, Grand RJ, Davis-Kraft L, Ferlic LL, Smith EO. Growth failure in children with inflammatory bowel disease: a prospective study. *Gastroenterology*. 1993;105:681–691.
7. Savage MO, Beattie RM, Camacho-Hubner C, Walker-Smith JA, Sanderson IR. Growth in Crohn's disease. *Acta Paediatr Suppl*. 1999;88:89–92.

8. Kugathasan S, Judd RH, Hoffmann RG, et al. Epidemiologic and clinical characteristics of children with newly diagnosed inflammatory bowel disease in Wisconsin: a statewide population-based study. *J Pediatr*. 2003;143:525–531.
9. Muller KE, Lakatos PL, Arato A, et al. Incidence, Paris classification, and follow-up in a nationwide incident cohort of pediatric patients with inflammatory bowel disease. *J Pediatr Gastroenterol Nutr*. 2013;57:576–582.
10. Malaty HM, Fan X, Opekun AR, Thibodeaux C, Ferry GD. Rising incidence of inflammatory bowel disease among children: a 12-year study. *J Pediatr Gastroenterol Nutr*. 2010;50:27–31.
11. Barton JR, Gillon S, Ferguson A. Incidence of inflammatory bowel disease in Scottish children between 1968 and 1983: marginal fall in ulcerative colitis, three-fold rise in Crohn's disease. *Gut*. 1989;30:618–622.
12. Kelsen J, Baldassano RN. Inflammatory bowel disease: the difference between children and adults. *Inflamm Bowel Dis*. 2008;14 Suppl 2: S9–S11.
13. Vasseur F, Gower-Rousseau C, Vernier-Massouille G, et al. Nutritional status and growth in pediatric Crohn's disease: a population-based study. *Am J Gastroenterol*. 2010;105:1893–1900.
14. Goodhand J, Dawson R, Heffernon M, et al. Inflammatory bowel disease in young people: the case for transitional clinics. *Inflamm Bowel Dis*. 2010;16:947–952.
15. Targan SR, Hanauer SB, van Deventer SJ, et al. A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor alpha for Crohn's disease. Crohn's Disease cA2 Study Group. *N Engl J Med*. 1997;337:1029–1035.
16. Sands BE, Anderson FH, Bernstein CN, et al. Infliximab maintenance therapy for fistulizing Crohn's disease. *N Engl J Med*. 2004;350:876–885.
17. Hanauer SB, Feagan BG, Lichtenstein GR, et al. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet*. 2002;359:1541–1549.
18. Sandborn WJ, van Assche G, Reinisch W, et al. Adalimumab induces and maintains clinical remission in patients with moderate-to-severe ulcerative colitis. *Gastroenterology*. 2012;142:257–265. e1–e3.
19. Reinisch W, Sandborn WJ, Hommes DW, et al. Adalimumab for induction of clinical remission in moderately to severely active ulcerative colitis: results of a randomised controlled trial. *Gut*. 2011;60:780–787.
20. Colombel JF, Sandborn WJ, Ghosh S, et al. Four-year maintenance treatment with adalimumab in patients with moderately to severely active ulcerative colitis: data from ULTRA 1, 2, and 3. *Am J Gastroenterol*. 2014;109:1771–1780.
21. Baldassano R, Braegger CP, Escher JC, et al. Infliximab (Remicade) therapy in the treatment of pediatric Crohn's disease. *Am J Gastroenterol*. 2003;98:833–838.
22. 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;132:863–873.
23. Hyams JS, Lerer T, Griffiths A, et al. Long-term outcome of maintenance infliximab therapy in children with Crohn's disease. *Inflamm Bowel Dis*. 2009;15:816–822.
24. Cezard JP, Nouaili N, Talbotec C, et al. A prospective study of the efficacy and tolerance of a chimeric antibody to tumor necrosis factors (Remicade) in severe pediatric Crohn disease. *J Pediatr Gastroenterol Nutr*. 2003;36:632–636.
25. Borrelli O, Bascietto C, Viola F, et al. Infliximab heals intestinal inflammatory lesions and restores growth in children with Crohn's disease. *Dig Liver Dis*. 2004;36:342–347.
26. Hyams JS, Lerer T, Griffiths A, et al. Outcome following infliximab therapy in children with ulcerative colitis. *Am J Gastroenterol*. 2010;105:1430–1436.
27. Hyams JS, Griffiths A, Markowitz J, et al. Safety and efficacy of adalimumab for moderate to severe Crohn's disease in children. *Gastroenterology*. 2012;143:365–374. e2.
28. Fanjiang G, Russell GH, Katz AJ. Short- and long-term response to and weaning from infliximab therapy in pediatric ulcerative colitis. *J Pediatr Gastroenterol Nutr*. 2007;44:312–317.
29. Cucchiara S, Romeo E, Viola F, et al. Infliximab for pediatric ulcerative colitis: a retrospective Italian multicenter study. *Dig Liver Dis*. 2008;40 Suppl 2:S260–S264.
30. Walters TD, Kim MO, Denson LA, et al. Increased effectiveness of early therapy with anti-tumor necrosis factor-alpha vs an immunomodulator in children with Crohn's disease. *Gastroenterology*. 2014;146:383–391.
31. Walters TD, Gilman AR, Griffiths AM. Linear growth improves during infliximab therapy in children with chronically active severe Crohn's disease. *Inflamm Bowel Dis*. 2007;13:424–430.
32. Sands BE, Blank MA, Patel K, van Deventer SJ; ACCENT II Study. Long-term treatment of rectovaginal fistulas in Crohn's disease: response to infliximab in the ACCENT II Study. *Clin Gastroenterol Hepatol*. 2004;2:912–920.
33. Hyams J, Walters TD, Crandall W, et al. Safety and efficacy of maintenance infliximab therapy for moderate-to-severe Crohn's disease in children: REACH open-label extension. *Curr Med Res Opin*. 2011;27:651–662.
34. Hanauer SB, Sandborn WJ, Rutgeerts P, et al. Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: the CLASSIC-I trial. *Gastroenterology*. 2006;130:323–333.
35. Sandborn WJ, Hanauer SB, Rutgeerts P, et al. Adalimumab for maintenance treatment of Crohn's disease: results of the CLASSIC II trial. *Gut*. 2007;56:1232–1239.
36. 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;146:829–838.
37. 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.
38. Rutgeerts P, Van Assche G, Sandborn WJ, et al. Adalimumab induces and maintains mucosal healing in patients with Crohn's disease: data from the EXTEND trial. *Gastroenterology*. 2012;142:1102–1111. e2.
39. Panaccione R, Colombel JF, Sandborn WJ, et al. Adalimumab sustains clinical remission and overall clinical benefit after 2 years of therapy for Crohn's disease. *Aliment Pharmacol Ther*. 2010;31:1296–1309.
40. Kamm MA, Hanauer SB, Panaccione R, et al. Adalimumab sustains steroid-free remission after 3 years of therapy for Crohn's disease. *Aliment Pharmacol Ther*. 2011;34:306–317.
41. Panaccione R, Colombel JF, Sandborn WJ, et al. Adalimumab maintains remission of Crohn's disease after up to 4 years of treatment: data from CHARM and ADHERE. *Aliment Pharmacol Ther*. 2013;38:1236–1247.
42. Schreiber S, Reinisch W, Colombel JF, et al. Subgroup analysis of the placebo-controlled CHARM trial: increased remission rates through 3 years for adalimumab-treated patients with early Crohn's disease. *J Crohns Colitis*. 2013;7:213–221.
43. Mian S, Baron H. Adalimumab, a novel anti-tumor necrosis factor-alpha antibody in a child with refractory Crohn's disease. *J Pediatr Gastroenterol Nutr*. 2005;41:357–359.
44. Noe JD, Pfefferkorn M. Short-term response to adalimumab in childhood inflammatory bowel disease. *Inflamm Bowel Dis*. 2008;14:1683–1687.
45. Wyneski MJ, Green A, Kay M, Wyllie R, Mahajan L. Safety and efficacy of adalimumab in pediatric patients with Crohn disease. *J Pediatr Gastroenterol Nutr*. 2008;47:19–25.
46. Rosenbach Y, Hartman C, Shapiro R, Hirsch A, Avitzur Y, Shamir R. Adalimumab treatment in children with refractory Crohn's disease. *Dig Dis Sci*. 2010;55:747–753.
47. Hadziselimovic F. Adalimumab induces and maintains remission in severe, resistant paediatric Crohn disease. *J Pediatr Gastroenterol Nutr*. 2008;46:208–211.
48. Martin-de-Carpi J, Pociello N, Varea V. Long-term efficacy of adalimumab in paediatric Crohn's disease patients naive to other anti-TNF therapies. *J Crohns Colitis*. 2010;4:594–598.

49. Viola F, Civitelli F, Di Nardo G, et al. Efficacy of adalimumab in moderate-to-severe pediatric Crohn's disease. *Am J Gastroenterol*. 2009;104:2566–2571.
50. Rosh JR, Lerer T, Markowitz J, et al. Retrospective Evaluation of the Safety and Effect of Adalimumab Therapy (RESEAT) in pediatric Crohn's disease. *Am J Gastroenterol*. 2009;104:3042–3049.
51. Russell RK, Wilson ML, Loganathan S, et al. A British Society of Paediatric Gastroenterology, Hepatology and Nutrition survey of the effectiveness and safety of adalimumab in children with inflammatory bowel disease. *Aliment Pharmacol Ther*. 2011;33:946–953.
52. Thayu M, Leonard MB, Hyams JS, et al. Improvement in biomarkers of bone formation during infliximab therapy in pediatric Crohn's disease: results of the REACH study. *Clin Gastroenterol Hepatol*. 2008;6:1378–1384.
53. Malik S, Ahmed SF, Wilson ML, et al. The effects of anti-TNF-alpha treatment with adalimumab on growth in children with Crohn's disease (CD). *J Crohns Colitis*. 2012;6:337–344.
54. Assa A, Hartman C, Weiss B, et al. Long-term outcome of tumor necrosis factor alpha antagonist's treatment in pediatric Crohn's disease. *J Crohns Colitis*. 2013;7:369–376.
55. Cozijnsen M, Duif V, Kokke F, et al. 2014. Adalimumab therapy in children with Crohn's disease previously treated with infliximab: a Dutch nationwide cohort study. *J Pediatr Gastroenterol Nutr*. 2015;60(2):205–210.
56. Osterman MT, Haynes K, Delzell E, et al. Comparative effectiveness of infliximab and adalimumab for Crohn's disease. *Clin Gastroenterol Hepatol*. 2014;12:811–817. e3.
57. Colombel JF, Sandborn WJ, Reinisch W, et al. Infliximab, azathioprine, or combination therapy for Crohn's disease. *N Engl J Med*. 2010;362:1383–1395.
58. Kopylov U, Al-Taweel T, Yaghoobi M, et al. Adalimumab monotherapy versus combination therapy with immunomodulators in patients with Crohn's disease: a systematic review and meta-analysis. *J Crohns Colitis*. 2014;8:1632–1641.
59. Reenaers C, Louis E, Belaiche J, Seidel L, Keshav S, Travis S. Does co-treatment with immunosuppressors improve outcome in patients with Crohn's disease treated with adalimumab? *Aliment Pharmacol Ther*. 2012;36:1040–1048.
60. Osterman MT, Sandborn WJ, Colombel JF, et al. Increased risk of malignancy with adalimumab combination therapy, compared with monotherapy, for Crohn's disease. *Gastroenterology*. 2014;146:941–949.
61. Lichtenstein GR, Rutgeerts P, Sandborn WJ, et al. A pooled analysis of infections, malignancy, and mortality in infliximab- and immunomodulator-treated adult patients with inflammatory bowel disease. *Am J Gastroenterol*. 2012;107:1051–1063.
62. Long MD, Herfarth HH, Pipkin CA, Porter CQ, Sandler RS, Kappelman MD. Increased risk for non-melanoma skin cancer in patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol*. 2010;8:268–274.
63. Long MD, Martin CF, Pipkin CA, Herfarth HH, Sandler RS, Kappelman MD. Risk of melanoma and nonmelanoma skin cancer among patients with inflammatory bowel disease. *Gastroenterology*. 2012;143:390–399. e1.
64. Kandiel A, Fraser AG, Korelitz BI, Brensinger C, Lewis JD. Increased risk of lymphoma among inflammatory bowel disease patients treated with azathioprine and 6-mercaptopurine. *Gut*. 2005;54:1121–1125.
65. Beaugerie L, Brousse N, Bouvier AM, et al. Lymphoproliferative disorders in patients receiving thiopurines for inflammatory bowel disease: a prospective observational cohort study. *Lancet*. 2009;374:1617–1625.
66. Kotlyar DS, Osterman MT, Diamond RH, et al. A systematic review of factors that contribute to hepatosplenic T-cell lymphoma in patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol*. 2011;9:36–41. e1.
67. Yanai H, Lichtenstein L, Assa A, et al. Levels of drug and antidrug antibodies are associated with outcome of interventions after loss of response to infliximab or adalimumab. *Clin Gastroenterol Hepatol*. July 25, 2014. [Epub ahead of print.]
68. Singh N, Rosenthal CJ, Melmed GY, et al. Early infliximab trough levels are associated with persistent remission in pediatric patients with inflammatory bowel disease. *Inflamm Bowel Dis*. 2014;20:1708–1713.
69. Paul S, Del Tedesco E, Marotte H, et al. Therapeutic drug monitoring of infliximab and mucosal healing in inflammatory bowel disease: a prospective study. *Inflamm Bowel Dis*. 2013;19:2568–2576.
70. Rummelle FM, Veres G, Kolho KL, et al. Consensus guidelines of ECCO/ESPGHAN on the medical management of pediatric Crohn's disease. *J Crohns Colitis*. 2014;8:1179–1207.
71. Beaugerie L, Seksik P, Nion-Larmurier I, Gendre JP, Cosnes J. Predictors of Crohn's disease. *Gastroenterology*. 2006;130:650–656.
72. Sandborn WJ, Feagan BG, Stoinov S, et al. Certolizumab pegol for the treatment of Crohn's disease. *N Engl J Med*. 2007;357:228–238.
73. Hussain SZ, Feagan BG, Samad A, Forget S, Sen DL, Lacroix B. Use of certolizumab pegol in children and adolescents with active Crohn's disease: pharmacokinetics over 6 weeks in the NURTURE study. *Gastroenterology*. 2011;140 Suppl 1:S-265.
74. Hyams JS, Wilson DC, Thomas A, et al. Natalizumab therapy for moderate to severe Crohn disease in adolescents. *J Pediatr Gastroenterol Nutr*. 2007;44:185–191.
75. Feagan BG, McDonald JW, Panaccione R, et al. Methotrexate in combination with infliximab is no more effective than infliximab alone in patients with Crohn's disease. *Gastroenterology*. 2014;146:681–688. e1.
76. Sokol H, Seksik P, Carrat F, et al. Usefulness of co-treatment with immunomodulators in patients with inflammatory bowel disease treated with scheduled infliximab maintenance therapy. *Gut*. 2010;59:1363–1368.

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