Biologics for the treatment of moderate-to-severe ulcerative colitis in pediatric patients

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Abstract: Ulcerative colitis (UC) is a chronic, inflammatory disease of the large intestine. In pediatric patients, UC is associated with significant morbidity including persistent symptoms affecting quality of life, hospitalizations, and surgery, and therapeutic strategies are limited. The advent of biologics, specifically anti-tumor necrosis factor-α medications, has been very beneficial for pediatric patients suffering from UC. Since the introduction of these therapies, there has been improvement in the rates of both remission as well as colectomy-free survival. However, there has been concern regarding the adverse events associated with these medications including the risk of infection and malignancy. The efficacy and safety of infliximab, the most frequently used biologic medication in pediatric patients with UC, will be the focus of this review.

Keywords: ulcerative colitis, biologics, anti-TNF-α, infliximab, adalimumab

Introduction
Ulcerative colitis (UC) is a form of chronic, inflammatory bowel disease (IBD) characterized by relapsing inflammation of the large intestine including the rectum. Both of the inflammatory bowel diseases, Crohn disease (CD) and UC, are associated with significant morbidity. The etiology of these diseases is unclear, but appears to involve an abnormal immune response to environmental factors in a genetically susceptible host. While the diagnosis of IBD can occur at any age, up to 25% of patients will become symptomatic during childhood or adolescence.¹ The pediatric literature suggests that the highest age-related occurrence of UC occurs in patients greater than 10 years of age.² In North America, for example, the incidence of UC in patients 10–19 years of age is thought to be approximately two cases per 100,000 persons.³ Similar incidences have been described in Europe.⁴,⁵ In terms of prevalence, population-based studies suggest that IBD, in general, is unevenly distributed throughout the world, with the highest disease rates occurring in industrialized nations.⁷,⁸ Also, it has been demonstrated that people who immigrate to Westernized countries have a higher rate of developing IBD, especially UC.⁹ UC affects the rectum with contiguous proximal involvement that can include the entire large intestine. Patients typically present with chronic symptoms of abdominal pain, diarrhea, and rectal bleeding. Rectal bleeding is the most frequently observed symptom and is thought to occur in approximately 83%–95% of pediatric patients with UC.¹⁰ In the pediatric population, the presentation of symptoms is variable. However, children frequently present with more extensive disease as compared to adults and thus are more likely to experience acute, severe symptoms at the time of diagnosis.¹¹ A statewide epidemiological study in Wisconsin¹² evaluating pediatric...
patients newly diagnosed with IBD found left-sided colitis in only 10% of children with UC at the time of presentation. Conversely, 90% of children presented with pancolitis.\textsuperscript{12}

There are clear phenotypic differences between adult and pediatric patients with UC. In addition, in pediatric UC, the disease extent often changes with time.\textsuperscript{13} In a cohort of 113 pediatric patients newly diagnosed with UC, for example, proximal disease extension according to Montreal Classification occurred in 49% of patients with a median follow-up time of 6 years.\textsuperscript{14} Because pediatric patients with UC represent a unique population, the Montreal Classification was recently modified and renamed the Paris Classification.\textsuperscript{13} In terms of disease extent, a fourth category was added to the Montreal Classification and thus disease extent can be classified as patients with proctitis (E1), patients with left-sided colitis distal to the splenic flexure (E2), patients with extensive colitis distal to the hepatic flexure (E3), or patients with pancolitis (E4). To designate severity (S0 or S1), the Paris Classification incorporates the Pediatric Ulcerative Colitis Activity Index (PUCAI) score. The PUCAI score is a validated, noninvasive tool developed to measure disease activity in pediatric UC and will be discussed in more detail later in this review.\textsuperscript{15}

In general, the symptoms of UC reflect the extent of colonic inflammation. Patients with proctitis present with diarrhea and hematochezia and there are no systemic findings such as fever, weight loss, or hypoalbuminemia. There is usually good response to therapy. In left-sided colitis, patients present with abdominal cramping and tenderness, bloody diarrhea, and urgency to defecate. Associated systemic findings may be present and the treatment of the left-sided disease may be more challenging. Finally, the presentation of extensive colitis or pancolitis involves abdominal pain and tenderness, multiple bloody stools per day, nocturnal bowel movements, urgency, and tenesmus. Systemic manifestations are common such as fever, leukocytosis, anemia, and hypoalbuminemia. Patients who present with extensive, severe UC are at risk for life-threatening complications including severe hemorrhage, toxic megacolon, and intestinal perforation. Severe UC may be refractory to medical management and in some patients, surgical removal of the colon may be required. In fact, it is believed that there is a relationship between disease severity at presentation and a need for colectomy within 5 years of diagnosis.\textsuperscript{16}

The goals for managing UC are to eliminate symptoms of disease, improve quality of life, and avoid hospitalization and surgery (colectomy). In pediatric patients, some of the additional aims are to promote and allow normal, unrestricted activity (ie, attending school) and to ensure optimal nutrition, bone health, and growth. Maintenance of corticosteroid-free remission is also critical. Therapies are generally targeted at key positions in the inflammatory pathway. However, with growing knowledge regarding the pathogenesis of UC, a more individualized approach, which takes into account a person’s genetics and gut microbiota, is imminent.

For many years, well-established therapies such as aminosalicylates and immunomodulators 6-mercaptopurine have been used in a step-up fashion in the treatment of pediatric UC. However, the more recent development and use of biologic agents that target key inflammatory molecules, such as TNF-\(\alpha\), has transformed the approach to the medical management of UC. Multiple studies, in adults as well as in children with IBD, have demonstrated that biologic medications are effective in the induction and maintenance of symptomatic remission. Although clinical improvement is an obvious goal of the therapy, the literature currently suggests that in order to increase the chance of lasting remission and decrease the potential for adverse effects of long-standing inflammation, it is important to attain mucosal healing.\textsuperscript{17} Biologic therapy has the ability to induce and maintain mucosal healing and, therefore, has led to more valiant treatment goals.\textsuperscript{18}

\section*{The role of TNF-\(\alpha\) in inflammatory bowel disease}

Tumor necrosis factor-\(\alpha\) (TNF-\(\alpha\)) is an important pro-inflammatory cytokine in the development of IBD. It is produced by macrophages and T-lymphocytes and is responsible for the induction of many additional cytokines, which further perpetuate the inflammatory process. Interestingly, TNF-\(\alpha\) has been found in increased concentrations in the blood, colonic tissue, and stool of patients with UC.\textsuperscript{19} Biologic medications that target the TNF-\(\alpha\) molecule are effective therapies for both CD and UC. The most intensively studied anti-TNF-\(\alpha\) medication is infliximab, a chimeric IgG1 monoclonal antibody to TNF-\(\alpha\). Infliximab neutralizes TNF-\(\alpha\) by binding with high affinity to both soluble and transmembrane forms of the molecule. Infliximab also inhibits the ability of TNF-\(\alpha\) to bind to its receptor. Twenty-five percent of the infliximab molecule consists of murine protein. More recently, alternative anti-TNF-\(\alpha\) medications such as adalimumab, certolizumab, and golimumab have been developed that consist of fully humanized protein. Several other biologic medications, including antibodies and small molecules, have also been investigated in the treatment of IBD. This includes antileukocyte adhesion molecules and inhibitors of the IL-23 inflammatory pathway. However, the
anti-TNF-α medications, infliximab and adalimumab, are the most commonly used biologic medications in the treatment of pediatric UC and thus will be the focus of this review.

**Anti-TNF-α therapy in pediatric patients**

Over the years, multiple studies in both adult and pediatric patients have demonstrated that anti-TNF-α medications are effective in the treatment of CD.\(^{20-25}\) For example, the REACH trial, a prospective, multicenter, randomized, open-label trial, was a landmark pediatric study, which established that infliximab is effective in the treatment of pediatric patients with moderately to severely active CD.\(^{22}\) However, the early literature evaluating the efficacy of anti-TNF-α medications in UC yielded conflicting results; thus, the effectiveness of anti-TNF-α medications in UC was initially uncertain. The definitive evidence for the efficacy of infliximab in UC was provided by the adult Active Ulcerative Colitis Trials 1 and 2 (ACT 1 and ACT 2) in 2005.\(^{19}\) These were randomized, double-blind, placebo-controlled trials examining the efficacy of infliximab for the induction and maintenance of remission in patients with moderately to severely active UC. Both ACT 1 and ACT 2 included 364 patients who received infliximab or placebo at weeks 0, 2, and 6. In ACT 1, patients continued therapy every 8 weeks, through week 46 and were followed for a total of 54 weeks. In ACT 2, patients received therapy every 8 weeks, through week 22 and were followed for 30 weeks. Infliximab was found to be superior to placebo in the induction of and maintenance of both clinical and histological response in adult patients who had failed conventional therapy. Recently, the ACT 1 and 2 Extension Study was published.\(^{20}\) Patients from the original cohort, who achieved benefit with infliximab, were eligible to participate for 3 additional years of therapy. Infliximab was found to be effective and well tolerated as a long-term maintenance therapy.

The first pediatric studies evaluating the efficacy of infliximab in UC were generally small, single-center reports (see Table 1).\(^{27-33}\) One of the larger retrospective studies was a multicenter study by Cucchiara and colleagues, which evaluated the efficacy of infliximab, based on the Lichtiger Colitis Activity Index (LCAI), in 22 pediatric patients with UC refractory to or dependent upon corticosteroids.\(^{28}\)

### Table 1 The first pediatric studies evaluating the efficacy of infliximab in ulcerative colitis

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>Design</th>
<th>n</th>
<th>Subjects</th>
<th>Outcome measures</th>
<th>Short-term response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serrano et al(^{27})</td>
<td>2001</td>
<td>Retrospective</td>
<td>3</td>
<td>Patients not responding to conventional therapy</td>
<td>Subjective clinical improvement, ESR, prednisone dosage</td>
<td>Clinical improvement 3/3 (100%)</td>
</tr>
<tr>
<td>Mamula et al(^{28})</td>
<td>2002</td>
<td>Retrospective</td>
<td>9</td>
<td>Hospitalized patients unresponsive to 2 wks of iv corticosteroid or ambulatory patients on an immunomodulator with no response or incomplete response to corticosteroid</td>
<td>LCAI and PGA at 2 days and 2 weeks post-infusion</td>
<td>Decreased PGA in 7/9 (77%); inactive disease by LCAI in 6/9 (66%) at 2 weeks</td>
</tr>
</tbody>
</table>
| Russell et al\(^{22}\) | 2004 | Retrospective | 14  | Group 1: newly diagnosed, fulminant colitis refractory to 7–10 d of iv corticosteroid  
Group 2: relapsed UC refractory to 710 d of iv corticosteroid  
Group 3: steroid dependent UC not responding to conventional therapy | LCAI                                                                            | Group 1: 5/5 (100%)  
Group 2: 3/4 (75%)  
Group 3: 1/5 (20%) |
| Eidelwein et al\(^{20}\) | 2005 | Retrospective | 12  | Fulminant colitis (n = 3), acute exacerbation of colitis (n = 3), steroid-dependent colitis (n = 5), steroid-refractory colitis (n = 1) | Physician assessment of abdominal pain, stool frequency, rectal bleeding          | Short-term response in 12/12 (100%); complete resolution of symptoms in 9/12 (75%), partial improvement in symptoms in 3/12 (25%) |
| Cucchiara et al\(^{27}\) | 2008 | Retrospective | 22  | Severe UC refractory to corticosteroid (n = 4), steroid-dependent colitis (n = 16), steroid-refractory colitis (n = 2) | LCAI                                                                            | Response in 12/22 (55%), partial response in 6/22 (27%), no response in 4/22 (18%) |
| McGinnis et al\(^{21}\) | 2008 | Retrospective | 46  | Steroid-resistant or dependent UC                                         | Post-treatment recategorization into Truelove and Witts “mild” category or better | Clinical response in 28/40 (70%) |

**Abbreviations:** ESR, erythrocyte sedimentation rate; IV, intravenous; LCAI, Lichtiger Colitis Activity Index; PGA, Physician global assessment; UC, ulcerative colitis.
Response or partial response was seen in the majority of patients (55% and 27%, respectively). A small, prospective study of Brazilian children with IBD treated with infliximab demonstrated improvement in clinical manifestations in all patients.33 Of the seven patients with UC, five (71%) experienced a significant reduction in the PUCAI score. The remainder of the initial studies is summarized in Table 1. The majority of these studies demonstrated clinical improvement, at least in the short term. However, long-term outcomes of infliximab therapy in pediatric UC were initially uncertain.

In 2004, we reported 2-year follow-up data to our initial case series,28 which demonstrated that infliximab treatment was associated with both short-term and long-term benefit in pediatric patients with UC who were refractory to conventional therapy.34 Short-term improvement was seen in 82% of patients35 and prolonged improvement was seen in 63% of patients.34 More recently, Hyams and colleagues performed a multicenter, prospective, observational cohort study of 332 pediatric patients with UC.35 In this study, 61% of patients who had failed intravenous corticosteroids and had been prescribed infliximab as a second-line therapy, avoided colectomy at 24 months. In addition, at 12 and 24 months, 28% and 21% of patients were in remission and off corticosteroids, respectively.35 These data were consistent with a recent large, multicenter, retrospective study in adults with UC, which demonstrated long-term (greater than 1 year) maintenance of mucosal healing as well as improved rates of colectomy-free survival.36

Adalimumab is a fully humanized monoclonal antibody, which also binds TNF-α. Generally, adalimumab is used in patients who either lose response or become intolerant to infliximab. The time to remission for adalimumab may be slower as compared to infliximab, which makes it somewhat less suitable for the treatment of acute, severe exacerbations.37 The Retrospective Evaluation of the Safety and Effect of Adalimumab Therapy (RESEAT) study was a large, multicenter description of adalimumab therapy in pediatric CD.25 Adalimumab was found to be well tolerated and effective in the treatment of moderately to severely active CD. More recently, adalimumab was studied in a prospective fashion and was demonstrated to be safe and effective in the treatment of pediatric CD.38 Adalimumab has been used in the treatment of ulcerative colitis, although it is currently not US Food and Drug Administration (FDA)-approved for this indication. Recently, the efficacy of adalimumab was evaluated in adult patients with UC.39 In a controlled and double-blinded study by Sandborn and colleagues, adalimumab was found to be safe and more effective than placebo for the induction and maintenance of remission in patients with moderate-to-severe UC refractory to conventional therapy.39 Very little data, however, exist regarding the use of adalimumab in pediatric UC and there have been no prospective trials. In a small, retrospective study of ten pediatric patients with IBD treated with adalimumab because of either lack of or loss of response to infliximab, three patients with UC achieved improvement in the LCAI in the short term.40 However, one of these patients later failed adalimumab and required colectomy.40 This study included a very small number of UC subjects and, clearly, larger studies are required to determine the efficacy of adalimumab in pediatric UC. There are no reports on the use of certolizumab pegol and golimumab in the pediatric population with UC.

Taken together, the available pediatric literature supports the use of anti-TNF-α medications in the treatment of ulcerative colitis. In fact, in 2011, the FDA approved infliximab for the treatment of moderately to severely active UC in children older than 6 years in the setting of inadequate response to conventional therapy. The infliximab dose used in pediatric patients is 5 mg/kg. Similar to the adult population, intravenous infusions are given at 0, 2, and 6 weeks for induction. Infusions are then administered every 8 weeks for maintenance of remission. However, when there is inadequate response, especially in the setting of subtherapeutic infliximab trough levels, the dosage may be increased (up to 10 mg/kg) or the dosing interval may be decreased.

As mentioned in the introduction, the inflammatory bowel diseases are associated with significant morbidity and this high morbidity has led to a substantial public health burden.41 A recent study describing the direct health care costs of CD and UC in US children and adults42 demonstrated significantly increased annual healthcare costs for patients with CD and UC as compared to non-IBD controls. Not surprisingly, in IBD patients, pharmaceuticals accounted for the largest proportion of direct costs and infliximab was the most costly medication. In this study, as compared to prior studies, pharmaceutical costs had increased while IBD-related hospitalization costs had decreased. This study and others43,44 have suggested that in the era of expensive anti-TNF medications, at least some of the increased pharmaceutical costs may be offset by a subsequent decrease in hospitalizations and surgeries.

Immunogenicity and safety of biologic medications

One of the most frequently encountered side effects of infliximab is the formation of antibodies (ATI) to the murine
portion of the drug. ATIs can be associated with acute infusion reactions, delayed hypersensitivity, and loss of response. ATIs develop in approximately 35% of pediatric patients. The prevalence of acute infusion reactions varies between studies; however, it ranges between 15%–20%. Similar to the adult data, infusion reactions in the pediatric population were detected in 15% of all 432 infusions. In the REACH study, 16.1% of patients developed infusion reactions.

In the largest series of pediatric patients reported to date, 1,652 infliximab infusions were administered at six centers and a similar 16.5% rate of infusion reactions was seen. Acute infusion reactions are clinically manifested by shortness of breath, chest pain, palpitations, hypotension, urticaria, and headache. In cases of mild reactions, these situations can be controlled by decreasing the rate of the infusion, followed by administration of antihistamines and/or hydrocortisone if needed. In severe cases, the infusion is often stopped followed by the administration of epinephrine and the above medications. Subsequent infusions are then frequently preceded by corticosteroids and/or antihistamines. The most efficient method to prevent development of ATIs is systematic therapy rather than episodic treatment. Development of infusion reactions and ATIs do not completely preclude further use of this agent, but is often the reason therapy is changed to a humanized version of this antibody such as adalimumab.

Delayed infusion reactions, or serum sickness reactions, typically occur 4–9 days following an infusion. These reactions usually occur with episodic therapy and long treatment intervals. Standard induction therapy including three doses at the beginning of treatment with infliximab has been shown to reduce the incidence of delayed hypersensitivity reactions.

The formation of autoantibodies such as antinuclear antibodies (ANA) and antibodies to double-stranded DNA (anti-dsDNA) has also been associated with the use of anti-TNF-α therapy. Drug-induced lupus is a rare occurrence and in general, the development of autoimmunity has not been associated with adverse outcomes. Discontinuation of therapy with infliximab usually resolves most complications. There are currently no guidelines to routinely screen for autoantibodies.

Biologic therapy is associated with an increased risk of infection. Specifically, there is an increased risk of reactivation of latent tuberculosis (TB) associated with anti-TNF-α therapy. It is currently recommended that all patients who are to begin treatment with an anti-TNF-α medication are screened for latent TB. In terms of the risk of other infections associated with biologic therapy, the majority of the pediatric data comes from the REACH study. In the REACH study, depending on the arm, the infliximab dosing interval was either q8 week or q12 week. There appeared to be a greater risk of infection in the q8 week arm compared to the q12 week arm (73% versus 38%, respectively). The infections included abscess, pneumonia, enterocolitis, and herpes zoster. Similar infections were also reported in a recent study of the efficacy and safety of adalimumab in pediatric patients with CD. Aside from infections, biologic therapy has also been associated with neutropenia, psoriasis, and vasculitis in pediatric patients with UC.

Malignancies reported in children using ant-TNF-α medications have raised concerns of a potential increased risk. In 2010, the FDA’s Adverse Event Reporting System was searched to identify malignancies associated with anti-TNF-α medications in children 0–18 years of age. There were 48 reports of malignancy and 31 of these cases occurred following infliximab therapy while the remainder occurred following adalimumab or etanercept use. Of the 31 malignancies associated with infliximab, hepatosplenic T-cell lymphoma (n = 9) was the most common followed by non-Hodgkin’s lymphoma (n = 5), Hodgkin’s lymphoma (n = 3), and leukemia (n = 3). Patients with IBD accounted for 24 of the 31 cases and included all of the cases of hepatosplenic T-cell lymphoma (HSTL). The authors concluded that there may be an increased risk of cancer in children treated with anti-TNF medications. However, because many of the patients were being treated with concomitant medications, including immunosuppressive medications, a causal relationship could not be established. Kotlyar and colleagues later described 36 cases of hepatosplenic T-cell lymphoma in patients with IBD. The majority of cases occurred in male patients younger than 35 years. Interestingly, there were no cases of HSTL in patients who were treated with an anti-TNF-α medication alone. All patients were either treated with an immunomodulator as monotherapy or with a combination of an immunomodulator and an anti-TNF-α medication. There were no malignancies reported in the REACH study, although follow-up may have been too short. Presently, there appears to be an increased risk of malignancies associated with anti-TNF-α therapy. However, studies to date are limited by confounding factors including concomitant use of other immunosuppressive medications.

The use of infliximab in fulminant disease

As discussed previously, pediatric patients with UC often present with acute, severe disease and in these situations,
the treatment options are limited. Corticosteroids are considered to be first-line therapy in acute, severe exacerbations. However, approximately 1/3 of pediatric patients with severe UC will not have a complete response to corticosteroids. There are several indices used early on in the course of therapy in the adult population to help predict which patients will fail to respond to corticosteroids. In these patients, “rescue” therapies, such as biologics, can then be promptly instituted. Until recently, no such tool existed in pediatrics. In 2007, the PUCAI was developed. The PUCAI uses non-invasive items such as degree of abdominal pain, amount of rectal bleeding, and number of stools per 24 hours to measure disease activity in pediatric UC. The PUCAI was initially validated by means of a prospective cohort of 48 pediatric patients with ulcerative colitis undergoing colonoscopy. The PUCAI correlated well with established indices including the Beattie index, Physician global assessment (PGA), and Mayo score. More recently, the PUCAI was prospectively evaluated in 215 children with UC. This study confirmed the validity of the PUCAI as a primary outcome measure in determining disease activity in pediatric UC.

The PUCAI score is now used commonly to direct therapeutic decisions in pediatric patients presenting with severe, acute UC. For example, a PUCAI of greater than 45 on day 3 can be used to predict nonresponse to IV corticosteroids. In addition, patients who have a calculated PUCAI of greater than 70 on day 5 of corticosteroids should be regarded as steroid refractory and rescue therapy with infliximab should be considered.

Recently, a multicenter, prospective, observational study was designed in order to evaluate outcomes in severe pediatric UC, in which pediatric patients hospitalized for severe UC were enrolled. The PUCAI, calculated on days 3 and 5 of IV corticosteroid treatment, was able to predict patients who would require rescue therapy. Of the patients (29%) who required rescue treatment with infliximab, 76% responded and 52% remained well 1 year following initiation of therapy. Clearly, there is a role for biologics early in the course of therapy in certain pediatric UC patients with severe disease.

The effect of infliximab on UC outcomes

At some point during the course of the illness, surgical removal of the colon may become a necessity for patients with UC. In pediatrics, 40% of patients require colectomy 10 years after diagnosis. The most commonly performed procedure in children with UC is the ileal pouch-anal anastomosis (IPAA). Because, in UC, the disease is limited to the colon, IPAA is considered a curative procedure. However, postoperative surgical, inflammatory, and functional complications are relatively common and thus medical management is favored when feasible. In 2005, Jarnerot and colleagues published the first randomized, placebo-controlled study of infliximab as a rescue therapy to prevent colectomy in hospitalized adult patients with severely active UC. In this study, 45 patients who did not respond to IV corticosteroids on day 4 of hospitalization were randomized to receive either one dose of infliximab (5 mg/kg) or placebo. At 3 months, 67% of patients treated with infliximab avoided colectomy compared to 29% of patients in the placebo group. Subsequently, in a follow-up evaluation of the ACT-1 and ACT-2 cohort, the incidence of colectomy through 54 weeks was 10% for infliximab and 17% for placebo (P = 0.02).

It appears that infliximab therapy is also effective for the prevention of colectomy in pediatric patients with UC. For example, in the era of infliximab, Turner and colleagues reported short-term and 1-year colectomy rates of 9% and 19% respectively in pediatric patients with acute, severe UC. This 1-year colectomy rate was significantly lower than the rate reported in a historical cohort, of 42%. In terms of moderately to severely active UC, in patients treated with maintenance infliximab, the Hyams et al. study demonstrated that 61% of patients had remained colectomy-free at 2 years. There have been no studies in pediatric patients with UC evaluating long-term outcomes with infliximab therapy and this should be a focus of future research.

Conclusion

Infliximab has revolutionized the approach to the medical management of children and adolescents suffering from UC. In pediatric patients with UC treated with anti-TNF-α medications, response and remission rates are high. Additionally, it appears that anti-TNF-α medications improve colectomy-free survival. The biologic medications discussed in this review appear to be safe, but are not devoid of risk. It is important to screen for latent TB and patients must be followed closely to evaluate for evidence of other infections. Finally, there is an increased risk of certain types of cancers associated with anti-TNF-α therapy, thus careful monitoring including frequent physical examinations is required. Of course, it is critical that the benefits and the risks of biologic medications are discussed with the patient and family prior to the initiation of therapy.

Disclosure

The authors report no conflicts of interest in this work.

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