

Loss of response to biologics versus increased risk of lymphoma in children with inflammatory bowel disease: the clinician's conundrum

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Inflammatory bowel disease in children can be marked by aggressive disease both at presentation and over time. Risk stratification of individual patients may help identify when early biologic therapy is justified. Currently, combination biologic and immunomodulator therapy for moderate-to-severe Crohn's disease is the most effective treatment regimen. The clinician's conundrum arises from the recent understanding that rare but serious adverse events do occur with use of these strong immune suppressive drugs and may be more prevalent with combination therapy. An understanding of the natural history of Crohn's disease and ulcerative colitis and the benefits and risks of the current medical armamentarium is essential to provide optimal care for each child with inflammatory bowel disease.

KEYWORDS: 6-mercaptopurine • anti-tumor necrosis factor • antibodies to infliximab • azathioprine • children • Crohn's disease • immunomodulators • inflammatory bowel disease • infliximab • loss of response • lymphoma • methotrexate • pediatric • ulcerative colitis

In the past decade, the medical armamentarium to treat inflammatory bowel disease (IBD) has continued to expand such that clinicians and patients have more choices to treat Crohn's disease (CD) and ulcerative colitis (UC). However, with more options for therapy comes the need to choose responsibly, weighing the benefits and risks of each therapy in an individualized manner for every patient. The clinician needs to control the disease to prevent morbidities that can arise from poorly controlled IBD, while understanding the known rare risks of therapy which can have an equally devastating impact on patients. In the future, surrogate markers may be used in predicting the course of disease. Such risk stratification in individual patients with IBD may help identify when a 'top down' approach with early biologic therapy is justified.

In this article, the authors will review both the adult and pediatric literature to provide a context for the potential role of biologic therapy in children with IBD. The authors will begin with a review of the natural history of CD and

UC, examining the potential complications that are associated with poorly controlled IBD. The predictors of disease progression and disability will be briefly discussed. The reader should be convinced of the critical importance of achieving remission for the child with IBD. The authors will then review the supporting evidence to argue that combination biologic and immunomodulator therapy for moderate-to-severe CD in children is the most effective treatment regimen to date. The clinician's conundrum arises from the recent understanding that rare but serious adverse events do occur with use of these strong immune suppressive drugs and may be more prevalent with combination therapy (TABLE 1).

What are the complications associated with poorly controlled IBD & the known predictors of disease progression & disability?

Population-based studies have shown that the clinical course of CD is heterogeneous and varies over time with more aggressive disease often

Table 1. Anti-TNF monotherapy versus combination therapy: clinical options.

Option	Benefits	Risks
Anti-TNF monotherapy	Increased efficacy (compared to immunomodulators)	Loss of response, immunogenicity
Long-term combination therapy (e.g., azathioprine with infliximab)	Increased efficacy (compared to immunomodulators AND to anti-TNF monotherapy) Decreased likelihood of loss of response	Increased risk of lymphoma (e.g. hepatosplenic T-cell lymphoma)
Short-term combination therapy (e.g., azathioprine and infliximab for 6 months, then discontinue azathioprine)	Increased efficacy (at least for first 6 months) Unknown if this approach reduces long-term loss of response	Unknown
Anti-TNF plus methotrexate	Effects on efficacy unknown	Unknown

noted in children [1,2]. In adults, Veloso *et al.* observed that disease activity in CD in the year following diagnosis predicts future disease activity for over 10 years [3]. Patients with quiescent disease within that first year had a 77% probability of maintaining clinical remission in the subsequent year with a gradual decline until reaching a plateau at 58% still in remission after 6 years of disease. However, among patients whose CD remained active through the first year following diagnosis, only 16% were in a clinical remission in the subsequent year, gradually rising to a plateau of 38% in clinical remission at year 6 [3,4]. In a referral-based population of 2000 adults with CD using the Vienna Criteria, Cosnes *et al.* noted that after 5 and 20 years of having CD respectively, 48 and 12% of patients had active inflammatory disease; 12 and 18% of patients had strictures; and 40 and 70% of patients had fistula or abscesses [5].

The natural history of CD in children is often more aggressive than in adults. In a median follow-up of 84 months (range: 52–124 months), Vernier-Massouille *et al.* followed 404 children with a new diagnosis of CD [6]. Between diagnosis and last follow-up, inflammatory phenotypes decreased from 71 to 41%, whereas strictures and penetrating phenotypes (presence of fistula and abscesses) increased from 25 to 44% and 4 to 15%, respectively. Perianal disease (abscess and fistula) progressed from 9% at diagnosis to 27% at last follow-up. Ileal and ileocolonic disease posed a higher risk for requiring surgical resection as compared with isolated colonic disease. Based on Kaplan–Meier analysis, the cumulative incidence of surgery from the time of diagnosis were 20% at 3 years and 34% at 5 years [6].

Similar to CD, the literature supports a tendency toward more aggressive disease in UC in children compared with adults, both at presentation and over the course of the disease. The prevalence of extensive disease or pancolitis at presentation in prospective studies is reported to be 24–48% in adults [2,7,8] compared with 74–90% in children [2,9,10]. In a comparison prospective

study, Van Limbergen *et al.* reported that at 5-year follow-up, 26.1% of childhood-onset UC patients had undergone colectomy versus 15.5% of adult-onset UC patients [2]. By 10-year follow-up, 40% of childhood-onset UC patients and 19.9% of adult-onset UC patients had had a colectomy. Examining the Kaplan–Meier survival analysis, the median time to surgery was 11.1 years in childhood-onset UC compared with >50 years in adult-onset UC [2,11]. Extensive colonic involvement in children carries the risk of significant morbidity; however, distal uncontrolled disease is sometimes difficult to control and can be very disabling [12].

The natural history of CD and UC can often be described as dynamic, particularly in children. There is frequent extension and more aggressive involvement of the GI tract over time. An additional goal of control-

ling disease activity in IBD is ultimately to prevent long-term complications that are often seen in adults with a long-standing history of suboptimally and often poorly controlled IBD including osteoporosis, venous thrombosis and bowel malignancy. The risk of bone fracture in adults with CD and UC is increased up to 40% relative to controls [13–16]. Adults with IBD have a three-fold increased risk of deep venous thrombosis and pulmonary embolism [16–18]. Recent meta-analyses of several adult cohorts with IBD suggest the risk of colorectal cancer is approximately 8% after 20 years of disease, and 18% after 30 years of disease. The risk of small bowel cancer also markedly increases in patients with active small bowel CD [19]. However, many of the studies examining morbidity of IBD were performed prior to the more common use of anti-TNF therapy and the therapy's potentially improved rate of mucosal healing.

Risk stratification using clinical features, genetics & serology

The serious complications that can result from IBD highlight the need to develop prognostic factors that will identify those patients who would benefit from early intervention with biologic therapy. In a review, Blonski *et al.*, noted that characteristics of patients at risk for more complicated CD included younger age at initial diagnosis, the presence of perianal lesions, ileal involvement, smoking and the need for therapy with corticosteroids [4]. The pediatric literature suggests that female gender, older age at diagnosis and ileal or ileal-colonic disease are associated with increased risk of complicated disease behavior and hence subsequent need for surgery [20,21]. In CD, findings on index ileocolonoscopy, including deep and extensive ulcerations of greater than 10% of the mucosal area of at least one segment of the colon, may be a valuable component for risk stratification [22]. In UC, the current literature is not conclusive about which factors are associated with disease that is more aggressive. In a review

of prognostic factors, Blonski *et al.* suggested that patients with primary sclerosing cholangitis tended to have a lower relapse rate, whereas those patients who were ex-smokers, female or of younger age exhibited an elevated risk of relapse [4].

Ultimately, a better understanding of the interaction between an individual's genotype, effector and regulatory immune response, intestinal microbiome and environmental triggers may enable us to incorporate risk stratification to provide optimal personalized therapy. Genetic markers and serological immune responses are beginning to help identify high-risk patients with CD [23,24]. In CD patients with the genetic marker for innate immunity NOD2, three major single nucleotide polymorphisms (SNPs), namely R702w (SNP8), 6908r (SNP12) and 1007fs (SNP13), are responsible for the majority of clinically aggressive phenotypes [25,26]. Furthermore, immune responses to the antigens of certain intestinal microorganisms have been found in CD patients with complicated disease including *Pseudomonas fluorescens* (I2), porin protein C from *Escherichia coli* (Ompc), bacterial flagellin (Cbl1r1) and *Saccharomyces cerevisiae* (Asca). The magnitude of the immune response seems to correlate with rapid disease progression [23,24]. Dysbiosis, characterized by a reduction in bacterial diversity and an altered ratio of beneficial and deleterious bacterial species in the enteric microbiome, may play a key role in the development of chronic intestinal inflammation [27,28]. Furthermore, the human diet and possibly antibiotic exposure early in life may alter enteric bacterial composition and related gene expression and metabolic activity [29–33].

Role of mucosal healing in assessing response

Currently, mucosal healing is to date the best predictor of sustained corticosteroid remission in patients with early stage CD and UC, and has been associated with reduced risk of hospitalization and surgery [1,34–39]. The benefits of mucosal healing in adults with CD are well described by Baert *et al.* [35]. The authors observed stable, steroid-free remission through years 3 and 4 in 17 out of 24 (70.8%) CD adults achieving complete mucosal healing at year 2, compared with only six (27.3%) out of 22 patients with endoscopic activity. Mucosal healing was the sole determining predicting factor for clinical outcome with no impact from initial disease management. Furthermore, mucosal healing was a predictive marker irrespective of the Crohn's disease activity index (CDAI); CDAI at year 2 did not correlate with mucosal healing [35]. Similarly, in newly diagnosed adults with UC treated with corticosteroids, lack of mucosal healing was the only factor associated with negative outcomes. The rates of hospitalization (25 vs 48.7%) and colectomy (3.3 vs 18.0%) at 5-year follow-up in complete and partial responders, respectively, were significantly different [34]. However, when using the term mucosal healing, the following questions arise: What is the degree of intestinal healing that is required to change the disease course? What is the correlation between transmural and mucosal healing in CD? Would transmural healing be a superior end point to mucosal healing in CD?

In summary, the adult and pediatric literature demonstrate the serious morbidity that can be associated with poorly controlled

IBD including strictures and the need for bowel resections, abscess and related infectious complications, vascular thrombosis, osteoporosis, malignancy and diminished quality of life. Children are faced with the same morbidities as adults but with the additional impact on pubertal development and growth compounding the lifetime complications. Furthermore, children and adolescents with IBD are at risk for psychosocial distress including depression, anxiety, social isolation and altered self-image, which can all negatively affect their health-related quality of life [40]. It is important to note that most of the natural history studies to date were conducted prior to the prevalent use of anti-TNF agents and consequently prior to the ability to achieve mucosal healing in many patients. Currently, there is no standardized and consistent definition of disabling or aggressive disease [41]. However, bowel preservation and mucosal healing are becoming achievable goals with the use of TNF antagonists. Thus, through the judicious use of medical therapies with proven efficacy, development of indices for risk stratification and creation of standardized definitions of disease activity and bowel healing, the clinician may have the tools to modify the natural history of CD and UC [42].

Review of biologic & immunomodulator therapy

Our prior article provided an overview of therapy for pediatric IBD [43]. The authors now focus on the update of therapy utilizing immunomodulators and anti-TNF agents for children with more severe CD and UC. The balance of optimal medical care in the wake of known, rare, drug-related complications becomes essential in the care of these children.

Crohn's disease

The landmark SONIC trial in adults by Colombel *et al.* [44] now serves as the benchmark by which new therapies and their outcomes should be measured. This study demonstrated that in immunomodulator-naïve adult patients, the combination of azathioprine (AZA) and infliximab (IFX) was superior at inducing and maintaining remission during the 50-week trial. The study was a double-blinded, randomized, controlled trial with adults with CD for a median of 2.3 years with CDAI 220–450, naïve to immunomodulators but excluded patients heterozygous to thiopurine S-methyltransferase. The patients were randomized to one out of the three groups: AZA 2.5 mg/kg, IFX 5 mg/kg or combination of AZA and IFX. IFX was given at 0, 2, 6 weeks and then every 8 weeks. The primary outcome was corticosteroid-free clinical remission at 26 weeks defined as CDAI <150. Secondary outcomes included mucosal healing at week 26 and corticosteroid-free clinical remission at week 50. Corticosteroid-free clinical remission in the three groups at week 26 was as follows: AZA 30%, IFX 44% and combination 56.8% ($p < 0.001$ for comparison with combination therapy). Furthermore, mucosal healing was reported at week 26 with AZA 16.5%, IFX 30%, combination 43.9% ($p < 0.001$ for the comparison with combination therapy). At week 50, the corticosteroid-free clinical remission was AZA 24%, IFX 34.9%, combination 46.2%. Antibodies to IFX (ATI) were detected at week 30 in one out of 116 patients (0.9%) receiving combination therapy and 15 out of 103 patients (14.6%) receiving IFX [44].

In the SONIC trial, the authors concluded that adults with moderate-to-severe CD were most likely to enter and maintain a corticosteroid-free clinical remission with mucosal healing with dual therapy. AZA monotherapy was demonstrated to be the least effective agent to induce clinical and endoscopic remission. In this study, it is important to note that all patients were naive to immunomodulators, which differed from traditional clinical practice at the time, where biologics were considered in a step-up approach with failure of immunomodulator monotherapy. Furthermore, AZA was prescribed with a fixed dosing for all patients [44]. Although controversial, it is possible that efficacy may have improved in both AZA groups if AZA dosing had been amenable to change based on individual 6-thioguanine levels [45]. The markedly lower level of detected ATIs in the combination group compared with IFX monotherapy suggests the possibility that immunomodulators reduce the likelihood of ATIs and that in return may improve biologic efficacy [44].

The study of alternative anti-TNF antibody therapies (adalimumab and certolizumab) has demonstrated similar rates of efficacy in adults with CD; patients who have not previously received IFX and who were diagnosed more recently are more likely to respond to adalimumab and certolizumab. Furthermore, unlike the SONIC trial, many patients in these trials were not naive to immunomodulator therapy at study entry [46–50].

The use of methotrexate (MTX) as an immunomodulator with anti-TNF therapy is less well studied than combination AZA/IFX for the treatment of CD. In an abstract report, Feagan *et al.* describe a double-blind, randomized, placebo-controlled trial evaluating IFX 5 mg/kg with placebo versus IFX 5 mg/kg plus MTX 25 mg subcutaneous in adults with CD (63 patients per arm) [51]. Following induction, IFX was administered every 8 weeks. The treatment failure rates at week 50 were comparable (IFX monotherapy group 29.8% treatment failure, IFX/MTX group 30.69% treatment failure). The author's conclusion that there was no significant difference in outcomes between biologic monotherapy and combination therapy with MTX remains preliminary at the time this review is being written, as only the abstract is available [51]. However, there is evidence that concomitant MTX can reduce ATI formation. In a prospective cohort study of patients receiving episodic on-demand infliximab by Vermeire *et al.*, the incidence of ATIs was comparable in patients receiving combination therapy with MTX and IFX versus AZA and IFX [52]. Both of these groups had ATI rates of approximately 45%, compared with 73% on IFX monotherapy. In this study, it is important to note that the adults were given on-demand infusions of IFX with a median of three infusions per patient (interquartile range: 2–5) over a median period of 42 (interquartile range: 25–74) weeks. Given our current understanding that reduced antibody formation often correlates with improved biologic efficacy, further study of combination therapy with MTX and anti-TNF therapy using scheduled dosing is warranted.

Biologic therapy is also promising for children with CD. In the REACH study, Hyams *et al.* examined children with CD with median disease duration of 1.9 years and Pediatric Crohn's Disease Activity Index >30 in a randomized, multicenter, open-label

trial [53]. Unlike the adult SONIC trial, all patients had been on immunomodulators for at least 8 weeks prior to enrollment with continued use through the duration of the trial and no placebo arm or control group was included. All patients were given IFX 5 mg/kg at 0, 2 and 6 weeks. Following the induction regimen of infliximab 5 mg/kg at week 10, 66 of 112 (58.9%) treated patients were in clinical remission (95% CI: 49.8, 68.0%). Furthermore, 103 patients who responded to induction were then randomized to obtain IFX 5 mg/kg every 8 weeks or IFX 5 mg/kg every 12 weeks. At week 54, clinical remission was higher in IFX every 8 weeks (55.8%) compared with IFX every 12 weeks (23.5%) [53]. Unlike the SONIC trial, the REACH trial did not directly compare monotherapy with combination therapy [44,53]. Furthermore, mucosal healing was not examined in the REACH study [53].

Adalimumab can serve as an alternative option to infliximab in children with moderate-to-severe CD. In an open-label study, Hyams *et al.* reported no significant difference in the rate of clinical remission at week 26, between high- and low-dose groups (36 out of 93, 38.7% vs 27 out of 95, 28.4%; $p = 0.075$) [54]. However, in subgroup analysis at week 26, IFX-naïve patients treated with high-dose adalimumab exhibited a significantly higher rate of clinical remission compared with the low-dose group (56.9 vs 35.2%; $p < 0.026$). Furthermore, among patients on high-dose adalimumab, at 52-week follow-up, IFX-naïve patients exhibited a significantly higher rate of clinical remission than IFX-exposed patients (45.1 vs 19%; $p = 0.008$). Approximately two-thirds of patients were on immunomodulator therapy during the study [54]. Adalimumab can serve as a rescue therapy in some children with CD no longer responsive to IFX but is more effective in children without prior exposure to IFX.

Ulcerative colitis

Combination therapy is less well studied in UC. The ACT I/II trials demonstrated that anti-TNF therapy could be used for induction and maintenance of remission in moderate-to-severe UC. In a double-blinded randomized placebo-controlled trial, Rutgeerts *et al.* demonstrated that in adults with moderate-to-severe UC, treatment with IFX 5 mg/kg at 0, 2 and 6 weeks and then every 8 weeks was as effective as IFX 10 mg/kg [55]. In ACT I, clinical remission was significantly more common at week 8 in both IFX 5 and 10 mg/kg groups (38.8 and 32%, respectively) compared with the placebo group (14.9%) and at week 54 in IFX 5 mg/kg (34.7%; $p = 0.001$) compared with IFX 10 mg/kg (34.4%, $p = 0.001$) and the placebo group (16.5%). Furthermore, mucosal healing at week 54 was described in approximately 45% of the IFX group compared with 18.2% of the placebo group ($p < 0.001$). Of note, approximately half of the enrolled patients remained on concurrent thiopurine therapy throughout the study. However, the small number of patients with positive tests for antibodies to IFX precluded interpretation of the role of combination therapy and immunogenicity in this trial [55]. Anti-TNF therapy with adalimumab has also recently been shown to be efficacious in some adults with UC both for induction and maintenance therapy [56,57].

Hyams *et al.* performed a randomized, multicenter, open-label trial in children with UC (median disease: 1.4 years). Upon

enrollment, patients had a median Mayo score of 8.0 and median Pediatric Ulcerative Colitis Activity Index (PUCAI) score of 55. Fifty three percent of enrolled children received thiopurines prior to and during the trial. All patients were given IFX 5 mg/kg at 0, 2 and 6 weeks. Patients who responded to induction IFX were then randomized to obtain IFX 5 mg/kg every 8 weeks or IFX 5 mg/kg every 12 weeks until week 54. At 8-week follow-up, clinical remission was noted in 40% of children by Mayo score and 33.3% by PUCAI score. Mucosal healing was observed in 68% of the 60 evaluable patients at week 8. In follow-up at week 54, among those who responded to induction IFX, PUCAI clinical remission was seen in 38.1% on IFX every 8 weeks compared with 18.2% on IFX every 12 weeks ($p = 0.146$) [58]. Of note, this study was not powered to look at combination therapy.

Summary of efficacy studies in IBD

In summary, IFX maintenance therapy given in a scheduled interval every 8 weeks with concomitant thiopurine therapy has been shown to provide the most effective treatment for both children and adults with moderate-to-severe CD. Clinical remission persists in approximately half of these children and adults at 1 year. Furthermore, in the adult studies, mucosal healing has been shown to often accompany clinical remission [44,53]. Peer-reviewed data are not available to date to assess the efficacy of MTX as an immunomodulator in combination with biologic therapy. In adults and children with UC, IFX at a dose of 5 mg/kg induces a clinical remission at 8 weeks in approximately 40% of adults and children. Approximately a third of adults and children sustain clinical remission at 1 year on scheduled 8-week IFX therapy. It is noteworthy that corticosteroid-free clinical remission occurred less commonly [55,58]. It is not known whether remission rates would have improved if thiopurines had been used in the rest of the adults and children in the UC trials and if the thiopurines had been individually tailored based on achieving therapeutic 6-thioguanine levels [45]. Based on the current literature, the authors conclude that anti-TNF agents with or without immunomodulators are more effective than conventional immunomodulator therapy alone for adult and pediatric CD and UC with greater long-term efficacy in CD as compared with UC. Achievement of mucosal healing is believed to provide the best indicator for subsequent long-term clinical remission and potentially reducing the known complications associated with CD and UC. However, to date only the studies in adults with both CD and UC have confirmed that anti-TNF therapy does in fact provide simultaneous mucosal healing. There is a suggestion that mucosal healing occurs concomitant with clinical remission in children with UC but studies have not been powered to examine this outcome measure.

Dose escalation for anti-TNF therapies has been well incorporated into clinical practice for children and adults with waning of clinical efficacy of anti-TNF therapy over time. In the ACCENT I 54-week trial, among adults with CD who lost response to IFX while on 5 mg/kg scheduled treatment, almost 90% responded with dose escalation to 10 mg/kg. The 80% who subsequently lost

response on 10 mg/kg regained response on IFX 15 mg/kg [59,60]. In the ACCENT II 46-week study, 57% adult patients with fistulizing CD who lost response on the 5 mg/kg dose subsequently responded to a 10 mg/kg dose [61]. In the Pediatric REACH study, the authors described successful dose escalation in 75% of the 32 children who lost response during the study trial but the study was not powered to examine this transition [53]. Although clinical efficacy following anti-TNF drug dose escalation can often be achieved, it is not known if these modifications translate into prolonged clinical efficacy.

Combination therapy may prevent loss of response to anti-TNF therapy

At this point, there are two hypotheses for why combination therapy works; these hypotheses are not mutually exclusive. The first is that two drugs acting on two different immune mechanisms provide a more effective control of inflammation in IBD. The second is that anti-TNF monotherapy is more commonly associated with development of antibodies to the anti-TNF biologic. Onset of immunogenicity is often manifested by rapid clearance of the anti-TNF agent and consequent loss of clinical response. Infusion reactions are a common manifestation of this antibody development and can have severe symptoms (e.g., shortness of breath and anaphylaxis).

Over the past few years, investigators have attempted to identify and reduce factors that contribute to the development of immunogenicity in patients on anti-TNF therapy. Several recent changes in medical practice have reduced the risk of onset of immunogenicity including use of humanized monoclonal antibody, scheduled dosing of the biologic therapy, pretreatment with corticosteroid and addition of concomitant immunomodulator therapy.

IFX, the original and most studied anti-TNF, is a hybrid molecule containing both human and murine portions. The human portion involves the Fab fragment, which binds to human TNF. The Fc portion of the molecule is murine [43,62]. The immunogenicity can be reduced but is still present using fully humanized anti-TNF antibody as seen in adalimumab and certolizumab [46,47,62].

Several studies have demonstrated the reduction in development of immunogenicity and improved long-term efficacy with the change of administration of anti-TNF therapy from on-demand dosing to scheduled interval dosing. It is believed that the improved long-term response to IFX with scheduled 8-week interval dosing is at least partly related to a decreased likelihood of development of ATIs; however, there may also be other contributing factors such as the rate of clearance of the drug unrelated to immunogenicity. It is also important to note that some patients with low titers of ATI still benefit from IFX and that loss of response can still occur over time even on strict scheduled interval dosing. Gisbert *et al.* evaluated loss of response in 16 studies of patients with CD on primarily scheduled interval dosing of IFX [63]. With 6284 patient-years of follow-up, the mean percentage of patients with loss of IFX response was 37% with annual risk of loss of IFX response 13% per patient-year of uninterrupted therapy [53,60,63,64].

Concomitant immunomodulator therapy significantly reduces antibody formation to IFX and improves the pharmacokinetics of IFX. In a prospective cohort study of adults with refractory luminal or fistulizing CD, on-demand IFX was given with a median of three IFX infusions over 42 weeks. Thirty seven percent were on AZA and 28% were on MTX (subcutaneous). Forty six percent of patients on immunomodulator therapy exhibited ATIs with a median IFX level of 6.45 µg/ml compared with 73% not on immunomodulator therapy with median IFX titer of 2.42 µg/ml [52]. The role of ATIs persists in fixed long-term therapy but probably to a lesser degree as noted in the SONIC trial, where ATIs were detected at week 30 in 0.9% receiving combination therapy and 14.6% receiving IFX [44]. Furthermore, in a single study to date, pretreatment with hydrocortisone reduced formation of drug antibodies [65].

Based on the adult data, we can infer that in children with CD and UC, the accepted starting dose of IFX 5 mg/kg should be given in a fixed schedule every 8 weeks following induction therapy. Furthermore, concomitant therapy with immunomodulators and pretreatment with hydrocortisone should be considered in children with CD and UC on IFX. The long-term efficacy in adult studies demonstrates the relationship between reduction of ATIs and sustained higher IFX levels, improved clinical and endoscopic efficacy and reduction in potentially harmful infusion reactions.

Administration of combination therapy

Understanding how to give biologic therapy has raised new questions about the duration of therapy needed, including: when can we discontinue concomitant immunomodulator therapy? How long do we need to continue anti-TNF therapy? Van Assche *et al.* performed an open-label, randomized study examining the influence of discontinuation of immunomodulators in patients in remission with combination therapy [66]. Patients with controlled disease >6 months after the start of IFX (5 mg/kg intravenously) combined with an immunomodulator were randomized to continue or to discontinue the immunomodulator, while all patients received scheduled IFX 5 mg/kg every 8 weeks for 104 weeks. Mucosal ulcers were absent at week 104 in 64% (continued) and 61% (discontinued) of evaluated patients with ongoing response to IFX. Although the IFX trough levels were higher in the continued group, ATIs were similarly infrequent in both groups (continued 5% and discontinued 12.5%) [66]. The authors concluded that continuation of immunomodulators beyond 6 months offered no clear benefit over scheduled IFX monotherapy for the first 2 years of therapy. However, it is important to note that the SONIC trial clearly demonstrated superior efficacy with combination therapy at 1 year and increased development of ATIs in the exclusive monotherapy group [44,66]. We currently do not know the degree to which short-term, 6-month combination therapy, compared with initial exclusive monotherapy with anti-TNF, will affect the long-term development of immunogenicity to anti-TNF therapy.

Once patients with CD have achieved a state of remission, can the anti-TNF agent be discontinued with maintenance of an immunomodulator agent? In a prospective cohort study,

Louis *et al.* examined adults with luminal CD with a median disease duration of 7.8 years [67]. The median duration of administration of IFX and an immunomodulator was 2.2 and 2.8 years, respectively. All participants were in a clinical corticosteroid-free remission with CDAI <150 for at least 6 months and 77% in endoscopic remission with Crohn's Disease Endoscopic Index of Severity ≤3. The study examined the timing of relapse after withdrawal of IFX up to a 30-month follow-up. During the study, there were 52 confirmed relapses (52.2%): 44 patients relapsed within the first year and seven within the second year. Forty patients were then retreated with the same IFX dose and frequency, in addition to pretreatment hydrocortisone. Ninety three percent (37 out of 40) responded with clinical remission defined as CDAI <150. This study demonstrated that approximately half of CD adult patients in a deep clinical and endoscopic remission on IFX and an immunomodulator would relapse within 1–2 years of stopping IFX despite continuation of the immunomodulator. It is promising that retreatment with IFX in the short term seemed to be effective. The authors propose characteristics that stratify patients with a lower risk of flaring (i.e., hemoglobin level >145 g/l; white blood cell count ≤6.0 × 10⁹/l; CRP 5 mg/l and fecal calprotectin 300g/g). Further study is needed in view of the size of the study cohort and the large number of predictors examined [67]. In most patients with luminal CD on long-term IFX, continuing IFX seems prudent, given the high likelihood of relapse upon discontinuation. However, it is reassuring that, at least for the short term, restarting IFX following a hiatus has been shown to be safe and successful as long as concomitant immunomodulator therapy is provided.

Risks of immunomodulator/biologic therapies

Individuals with IBD do not seem to incur an intrinsic risk of developing lymphoma. However, there is evidence to suggest that either alone or in combination with anti-TNF, the use of thiopurines increases the risk of lymphoma, albeit rarely. Many of these reported lymphomas occur concomitantly with primary EBV infection. Furthermore, hepatosplenic T-cell lymphoma (HSTCL) is a rare but concerning issue in young adult males with IBD who have been exposed to at least 2 years of thiopurines. Examining the rheumatoid arthritis (RA) literature, it is interesting to note that exposure to anti-TNF therapy with or without MTX does not seem to carry the same risk of development of lymphomas [68–70].

Lewis *et al.* concluded that the relative risk of lymphoma for CD/UC compared with matched controls was 1.2 with standardized incidence ratio 1.32 (0.78–2.10) and that there was no evidence of increased risk of lymphoma in patients with IBD compared with the general population. In this study cohort, immunomodulators (AZA or 6-mercaptopurine) were only used by 13% of CD patients and 6% of UC patients [71].

Several studies have suggested that there is an increased risk of lymphoma in IBD patients both on thiopurine alone and in combination with anti-TNF [72,73]. Beaugerie *et al.* studied a large prospective cohort of adults with IBD with median follow-up of 35 months [74]. The three groups included: thiopurine continued

(5867) with 9% also on anti-TNF; thiopurine discontinued (2809) with 12% also on anti-TNF; and never on thiopurines (10,810) with <1% on anti-TNF. Duration of disease ranged from 7.5 to 10.5 years among the three groups. Twenty three lymphomas were reported (14 non-Hodgkin's lymphoma [NHL] and one Hodgkin's lymphoma) on continued thiopurines compared with two NHL in discontinued thiopurines and six NHL in never thiopurines. The youngest case was in a 20-year-old male. The multivariate adjusted hazard ratio was 5.26 (2.2–12.6) in those continuing thiopurines compared with others. Furthermore, ten out of 15 lymphoma cases in the continuing thiopurine group exhibited post-transplant lymphoproliferative disorder with EBV positivity. Only two out of eight cases were EBV positive in the naive thiopurine group. The authors concluded that the thiopurines increased the risk of developing lymphoproliferative disease with risk factors including EBV presence, older age, male gender and longer duration of IBD [74].

Dayharsh *et al.* described a similar association between EBV and the risk of lymphoma [75]. In a retrospective review of adults at the Mayo clinic, 18 patients with lymphoma were identified: EBV infection was found in five out of six patients on thiopurine for a median of 3.5 years, versus two out of 12 patients never receiving thiopurines. The authors hypothesized that post-transplant lymphoproliferative disorder probably occurs because of reduced cell-mediated immune surveillance allowing EBV-infected lymphocytes (especially B cells) to proliferate [75].

In the pediatric literature, Ashworth *et al.* performed a retrospective review at a single pediatric hospital to examine the relationship between IBD and lymphoma [76]. Among the 1374 patients, 58% had CD, 34% had UC and 3% were IBD undetermined. Two lymphoma cases were observed among 2574 patient-years of taking thiopurine (2 per 4441 past years of ever taking thiopurine). Both patients were male, aged 12 and 18 years old, with CD and UC, respectively. Both patients had been taking thiopurines (22 and 28 months thiopurine use) but were EBV negative. A third patient had hemophagocytic lymphohistiocytosis on thiopurines. Compared with the Surveillance Epidemiology and End Results Program data (0.58 per 10,000 patient-years) the rate of lymphoma was three out of 10,000 patient-years in total and 4.5 lymphoma per 10,000 patient-years on thiopurines. Interestingly, no malignancies were observed in 1140 patient-years of combination anti-TNF and thiopurine therapy or 694 patient-years of MTX therapy [76].

HSTC lymphoma is a rare but concerning issue for medical teams caring for young adults and children with IBD. Parakkal *et al.* examined the US FDA adverse event reporting system database for lymphomas and use of biologic agents [77]. They found 25 cases of HSTCL. Twenty two (88%) had IBD; 19 had CD and three had RA. Ninety six percent (24/25) were on anti-TNF and immunomodulation. Seventeen out of the 25 patients were less than 35 years old, on combination thiopurine and anti-TNF therapy and 16 out of 17 were male. Three elderly patients were never exposed to thiopurine (two on anti-TNF and MTX and one on anti-TNF alone) [77]. Kotlyar *et al.* reviewed published reports and MedWatch for reports of HSTCL. Thirty six patients were

identified with HSTCL; 20 were on IFX and thiopurine and 16 were on thiopurine alone. The median duration of thiopurine was 5.5 years in the combination group and 6 years in the thiopurine monotherapy group. Twenty seven out of 30 were less than 35 years old and 28 out of 30 were male. All but one of the IBD patients with HSTCL had been taking thiopurines for at least 2 years before developing lymphoma [78]. HSTCL is a very rare but concerning issue particularly in young adult males with IBD, most commonly with at least a 2-year exposure to thiopurines and often in combination with anti-TNF therapy.

An alternative practice, substituting the immunomodulator MTX for a thiopurine in combination with biologic therapy, warrants consideration. In a recent review examining the long-term safety of MTX therapy in RA, Salliot and van der Heijde concluded that there did not seem to be an increased risk of lymphoma in adults receiving MTX monotherapy with mean dose of 10.5 mg weekly (range: 4.6–18 mg) [79]. The majority of experience of combination biologic therapy with MTX arises from the rheumatology literature, where a biologic is almost always used in combination with MTX. Although the clinical trial literature has suggested a potential link between anti-TNF therapy and lymphoma [80], longer-term RA studies suggest there is no association. Wolfe and Michaud led a large observational study of lymphoma in 19,562 adult patients, which included over 89,710 person-years of follow-up including anti-TNF exposure in 10,815 patients. This study found no evidence supporting a link between anti-TNF therapy, MTX or combination therapy and the risk of lymphoma in routine clinical practice [70]. This study is in agreement with an analysis of the linked cancer registry reports from adults with RA in Sweden by Askling *et al.* [68]. Pediatric juvenile idiopathic arthritis (JIA) observational studies provide further reassurance [69,81]. Beukelman *et al.* observed 7812 children with JIA with 12,614 person-years follow-up. The standardized incidence ratio (SIR) for probable and highly probable malignancies was 4.4 (95% CI: 1.8–9.0) in children with JIA versus children without JIA. The treatment for JIA, including MTX monotherapy (SIR: 3.9 [95% CI: 0.4–14]) and TNF inhibitors (SIR: 0 [95% CI: 0–9.7]) did not appear to be significantly associated with the development of malignancy [69]. Most of the studies in the rheumatologic literature do not account for RA severity. This could be important because natural history studies in RA have exhibited an increased risk of lymphoma in comparison with the general population, primarily thought to be linked to high levels of disease activity [68–70,80,82–84]. In summary, large recent population-based studies primarily in adults with RA provide us with reasonable reassurance of the lack of an association between MTX and anti-TNF and lymphoma. However, analyses controlling for disease severity in adults and children with RA and JIA have been more difficult to conduct.

Expert commentary & five-year view: weighing benefits & risks of therapeutic options in CD & UC

In the child with moderate-to-severe CD, the option to utilize anti-TNF therapy may save the child from a lifetime of disabling

morbidity, which can occur in the face of undertreatment of their CD. If the clinician chooses to use anti-TNF therapy, it is important to maximize the efficacy of anti-TNF therapy with use of scheduled dosing, pretreatment hydrocortisone and consideration of upfront, concomitant therapy with an immunomodulator agent.

Here arises the clinician's conundrum for the child with CD who is failing long-term maintenance monotherapy with thiopurines. Four options for clinical therapy should be considered:

- The clinician can switch to anti-TNF monotherapy with the understanding that immunogenicity is more likely to occur over the long term;
- The clinician can opt for dual therapy with anti-TNF therapy and long-term thiopurine. This approach will more likely improve the long-term efficacy of the anti-TNF agent but also expose the child to a rare but real risk of lymphoma (in particular hepatosplenic T-cell lymphoma);
- The clinician can add an anti-TNF agent with continuation of a thiopurine for 6 months, and then switch to anti-TNF monotherapy. This option seems to reduce the risk of immunogenicity without seriously increasing the risk of developing lymphoma;
- Finally, the clinician can switch the patient to dual therapy with anti-TNF and long-term low-dose MTX. This approach may reduce the risk of immunogenicity and may prolong efficacy of the anti-TNF agent.

The rheumatologic literature provides some reassurance regarding the safety of combination therapy with an anti-TNF agent and MTX. However, there may be unique additional factors contributing to the development of malignancy in patients with IBD on combination therapy. These factors include the inflammatory process itself and/or the potentially large exposure to abdominal radiation. The literature does tell us that combination therapy with an anti-TNF agent and thiopurine is more effective, but can carry a cost on safety, especially in children [85]. Data on the efficacy and safety of MTX in combination with anti-TNF therapy in patients with CD is not fully known and should be studied with a particular focus on safety in children.

In children with UC, biologic therapy may prove to be more efficacious as a short-term bridge to surgical or immunomodulator therapy, although this has not been studied to date. One must weigh the risk–benefit ratio of long-term biologic therapies versus surgical treatment with colectomy.

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Key issues

- The clinical course for Crohn's disease in children is often marked by an aggressive natural history with surgery required in up to 34% of patients at 5 years from diagnosis.
- Ulcerative colitis in children is often characterized by extensive colitis with a cumulative rate of colectomy up to 40% at 10 years.
- Scheduled combination therapy with anti-TNF (and pretreatment hydrocortisone) and thiopurines will improve efficacy and extend the duration of clinical remission in Crohn's disease.
- Long-term Infliximab therapy is effective in a subset of children with severe ulcerative colitis, but loss of response may also occur.
- Thiopurines, either alone or in combination with an anti-TNF agent, increase the risk of lymphoma, albeit rarely. Concomitant primary EBV infection is a risk factor for lymphoma.
- Hepatosplenic T-cell lymphoma is a very rare but concerning issue particularly in young adult males with inflammatory bowel disease; most commonly with at least a 2-year exposure to thiopurines and often in combination with anti-TNF therapy.

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