The Role of Combination Therapy in Pediatric Inflammatory Bowel Disease: A Clinical Report from the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition

*Andrew S. Day, †Ajay S. Gulati, ‡Nishaben Patel, §Brendan Boyle, ||K.T. Park, and ¶Shehzad A. Saeed

ABSTRACT

The treatment goal for children suffering from inflammatory bowel disease has been evolving with biologic therapies like anti-tumor necrosis factor agents assuming a more central role in treatment of more aggressive and extensive phenotype. Earlier introduction of anti-tumor necrosis factor agents have shown to be more effective and may even alter the natural history of inflammatory bowel disease. Development of anti-drug antibodies, however, limits long-term usage and leads to dose adjustment in almost half of patients treated with these medications. One of the strategies to minimize the development of anti-drug antibodies has been concomitant use of immunomodulator medications, resulting in fewer infusion reactions and sustained trough levels, potentially lowering the need for dose adjustments. Balanced with these benefits of optimized dosing and likely more sustained response, however, is the concern about increased risk of complications, such as infections and malignancies. The current manuscript reviews the available pediatric literature regarding efficacy, safety, and side effect profile of combination (immunomodulator and biologics) therapy in pediatric Crohn disease and ulcerative colitis, with particular emphasis on cost constraints, and recommendations for selection of patients who would benefit most from combination therapy.

Key Words: biologic therapy, combination, Crohn Disease, immunosuppressive, inflammatory bowel disease, ulcerative colitis

(*JPGN* 2018;66: 361–368)

During the last 2 decades, the management of inflammatory bowel disease (IBD) has evolved considerably with the development and introduction of novel biologic therapies, especially those directed against tumour necrosis factor (TNF)-α. In more recent years, there is increasing support for the earlier introduction of these therapies (a so-called top-down approach), rather than a step-up strategy (1). In addition, there is increasing awareness of the importance of optimizing dosage, and dosing frequency to achieve sustained response and remission rates along with improved quality of life in selected patient populations.

These issues are especially relevant in children and adolescents with severe IBD, who face numerous hurdles in the short and long term. These include nutritional, growth, pubertal development, and daily functioning. Although the short-term goals of management in pediatric IBD include clinical remission, the long-term goal of therapy in children is to achieve corticosteroid and surgery-free sustained remission, while optimizing quality of life, bone density, and growth velocity and minimizing side-effects of medications. Furthermore, mucosal healing is increasingly recognized as an optimal outcome, superior to clinical remission alone, as this results in changes in the trajectory of the course of disease (2).

One particular aspect of the delivery of the anti-TNF therapies is the consideration for sole use of a TNF inhibitor (monotherapy) or the combined use with another immunomodulator drug, as so-called ''combination therapy'' (3). These immunomodulators (IMs) include the thiopurines (azathioprine [AZA] or 6-mercaptopurine [6-MP]) or methotrexate (MTX). Combination therapy may include the addition of a biologic to current use of an immunomodulator, as well as the simultaneous commencement of both components. A third scenario is the addition of an IM to an existing biologic to reestablish control or reduce anti-drug antibodies (ADA).

The demonstrated benefits of combination therapy include enhanced durability of biologic response and reduction of the formation of antibodies to the TNF-α inhibitor: together leading to superior response and remission rates with consequent reduction in disease complications (3). Although these benefits have been delineated, concerns have arisen as to the potential for higher rates of adverse events such as infectious complications and lymphoma (3). These benefits and risks of combination therapy are especially relevant to the pediatric population with IBD. This review summarizes and highlights key aspects of combination therapy for children and adolescents with IBD.

COMBINATION THERAPY FOR THE MANAGEMENT OF PEDIATRIC CROHN DISEASE

Various studies, with differing levels of evidence, have evaluated the outcomes of combination therapy in adults and children with Crohn disease (CD). These data come from

Received June 28, 2016; accepted November 17, 2017.

From the *Department of Paediatrics, University of Otago (Christchurch), Christchurch, NZ, the †Department of Pediatrics, Division of Gastroenterology, University of North Carolina at Chapel Hill, Chapel Hill, NC, the ‡Division of Pediatric Gastroenterology/Nutrition, Golisano Children's Hospital, Rochester, NY, the §Division of Gastroenterology, Hepatology, Nutrition, Nationwide Children's Hospital, Columbus, OH, the ||Department of Pediatrics, Division of Gastroenterology, Hepatology and Nutrition, Stanford University School of Medicine, Palo Alto, CA, and the ¶Division of Gastroenterology, Hepatology, and Nutrition, Cincinnati Children's Hospital Medical Center, Cincinnati, OH.

Address correspondence and reprint requests to Professor Andrew S. Day, MD, FRACP, Department of Paediatrics, University of Otago, Christchurch, P.O. Box 4345, Christchurch 8140, New Zealand (e-mail: andrew.day@otago.ac.nz).

The authors report no conflicts of interest.

DOI: 10.1097/MPG.0000000000001850

TABLE 1. Evaluation of combination therapy in children with Crohn disease

Reference	Type of study	Patient no.	Drug regimen	Outcomes
4	Multicenter RCT	99	10-wk IFX + AZA or MTX then combo or IFX alone	PCDAI and SES similar at 54 wk
5	Post-hoc RCT	188	Combo vs ADA alone	Remission and antibody rates similar at wk 26
6	Retrospective	115	ADA ± IMM	No effect upon response
7	Retrospective	120	IFX or ADA ± IMM	No effect upon biologic failure rate
8	Retrospective	71	IFX ± IMM	Trend to increased loss of response after IMM cessation
9	Retrospective	188	IFX ± MTX (low dose)	CD and UC. Use of MTX did not influence outcomes
10	Retrospective	78	IFX or ADA ± IMM	No benefit of combo on outcomes
11	Retrospective	72	ADA ± IMM	Superior remission in combo group
12	Retrospective	195	IFX ± IMM	More durable response with combo
13	Registry	502	IFX ± IMM	Combo for >6 mo enhanced duration of response

ADA = adalimumab; AZA = azathioprine; IFX = infliximab; IMM = Immunomodulator, MTX = methotrexate.

randomized controlled trials (RCTs), post-hoc analysis of previous RCT, and observational, retrospective studies (3) (summarized in Table 1).

Only 1 RCT has evaluated combination therapy versus monotherapy for pediatric CD (4). This open-label trial included 99 patients who completed combination induction dosing with infliximab (IFX) (5 mg/kg) plus an immunomodulator (AZA or MTX) at a number of centers in Poland. At week 10, the responders (n = 84) were then randomized to 1 of 2 groups. Group 1 continued combination therapy through to week 54, whereas group 2 changed to IFX monotherapy after week 26. Outcomes as assessed by Pediatric CD Activity Index (PCDAI), Simple Endoscopic Score (SES)-CD, and medication escalation at week 54 were similar between the 2 groups. The protocol for this study allowed for intensification of therapy if necessary: this was required in a similar number of subjects in both groups. The protocol did not include assessment of antibody development or analysis of immunomodulator adherence. Furthermore, the follow-up period was relatively short.

A post-hoc analysis of the IMAgINE trial, presented at Digestive Diseases Week (DDW) in 2014, found that remission rates andADAs were similar between 117 patients treated with combination therapy and 71 managed with monotherapy using adalimumab for 26 weeks (5). In addition, responders were similar at both week 26 and week 52.

A number of retrospective studies have evaluated aspects of combination therapy in pediatric CD. Several studies have shown similar outcomes for remission and loss of response, with no clear benefit for combination therapy (6–10). Russell et al (11), however, noted higher remission rates in 72 children treated with adalimumab given in combination with an IM than in those with adalimumab alone (74% vs 37%, $P = 0.003$). This analysis incorporated data from 19 separate sites around the United Kingdom. Follow-up durations varied, with only 29 children assessed after 12 months of therapy limiting further evaluations. In addition, Church et al (12) found an increased duration of response for those treated with combination therapy: this study included 195 children managed with IFX as monotherapy or in combination with an immunomodulator. Another study, evaluating data involving 502 children included in an IBD registry that involved a number of centers, found that patients treated with combination therapy for >6 months had an increased probability of remaining on IFX for 5 years, compared to those on monotherapy or whom received IM for <6 months' duration (13). This was particularly pronounced in males treated with combination therapy, particularly when methotrexate was utilized as the IM.

Further data, including 3 RCTs, come from studies in adult patients with CD. Van Assche et al (14) evaluated 80 patients treated initially successfully with combination therapy (with IFX) for at least 6 months. Patients were then randomized to receive ongoing mono or combination therapy for 104 weeks. At week 104, relapse rates and mucosal healing were similar between groups. Although trough IFX levels were higher in the combination group between 40 and 88 weeks, antibody levels were similar between the 2 groups. These data suggested that combination therapy beyond 6 months did not enhance efficacy. Only 34 of the initial group of 80 patients, however, completed the full period of observation without requiring adjustment of the IFX dose. In addition, the differential effect of the type of immunosuppressive drug was not elucidated.

The 2010 SONIC trial compared outcomes for patients treated with AZA vs IFX monotherapy vs combination IFX/AZA (15). The 508 subjects were all naïve to IFX or AZA at study onset. A greater number of patients treated with combination therapy were in steroid free remission at week 26 than those treated with monotherapy (57% vs 44%, $P = 0.02$). Higher IFX trough levels and lower antibody levels were also found for those treated with combination therapy. Furthermore, mucosal healing was greater in those receiving combination therapy than those with AZA alone. Some of these differences could reflect the delay in the onset of benefit seen with AZA. The COMMIT trial evaluated outcomes comparing IFX monotherapy versus combination IFX/MTX in 126 patients naïve to both drugs (16). Although combination therapy was tolerated well, there was no difference in the primary outcome (disease relapse) at week 50. However, similar to the SONIC trial, IFX trough levels were higher and antibody levels lower in the group treated with combination therapy.

The American Gastroenterological Association (AGA) guidelines currently recommend that for induction therapy, that anti-TNFs are used in combination with thiopurines rather than anti-TNF monotherapy. No recommendation is made for or against combination versus monotherapy for maintenance of remission (17).

COMBINATION THERAPY FOR THE MANAGEMENT OF PEDIATRIC ULCERATIVE COLITIS

Data evaluating combination versus monotherapy in children with ulcerative colitis (UC) are limited to the post-hoc analysis of 1 clinical trial (18). In this evaluation of the outcomes for 32 patients treated with combination therapy and 28 patients with monotherapy, the authors found similar response, remission, and mucosal healing at week 8, along with similar remission rates at week 54.

Just 1 RCT evaluating combination versus monotherapy has been undertaken in adults with UC (19). In this UC-SUCCESS trial, patients were randomized to 1 of 3 arms (AZA monotherapy, IFX monotherapy, or IFX/AZA). At week 16, more patients were in remission with combination therapy, but mucosal healing was similar between groups. Antibody levels were lower in the combination group.

Post hoc analyses of the ACT 1 and 2 trials found similar response and remission rates for combination (n = 227) versus monotherapy (n = 257) (20). Again, antibody levels were lower in the combination therapy group. A retrospective study found that combination therapy leads to higher steroid-free remission at 6 and 12 months (21). Other retrospective studies have found increased IFX duration with combination therapy (22) and increased loss of response with monotherapy (23). This contrasts with the findings of a further study, wherein response for patients treated with adalimumab combination and monotherapy were similar (24).

LIMITATIONS OF AVAILABLE DATA ON COMBINATION THERAPY IN PEDIATRIC CROHN DISEASE AND ULCERATIVE COLITIS

Overall, as highlighted above, the published data evaluating combination therapy in children with IBD are limited by the lack of high-quality studies. Significant variations in study protocols also make interpretation of data difficult. These variations include the duration of combination therapy, the type of IM used, the dose of the IM used, the type of biologic drug utilized, and therapeutic drug monitoring for biologic therapy.

Low-dose IM therapy as part of combination therapy has been proposed as a mechanism to reduce the development of ADA, while reducing the risk of adverse effects of the IM itself. A cross-sectional study including 72 adults receiving combination therapy (as IFX and a thiopurine) evaluated the relationship between 6-thioguanine nucleotide levels and IFX trough levels (25). A 6-thioguanine nucleotide level of 125 pmol/$\geq 8 \times 10^8$ red blood cells was associated with higher IFX levels. These levels are almost half of that required for optimal efficacy with thiopurine monotherapy; this reduced dosing requirement may lead to a reduced concern about thiopurine toxicity.

The required dose for MTX, however, has not been clearly established. For example, Vahabnezhad et al (9) retrospectively evaluated low-dose MTX (defined as <10 mg/week) in their cohort of 188 patients. The authors did not report a differential benefit, but did suggest that the dose of MTX may have been too low.

The timing of commencement of IM as part of combination therapy is of particular relevance. Given that the thiopurines have delayed onset of action, one might expect enhanced benefits if these were commenced before the the biologic agent. Although some reports including subjects already receiving an IM before starting a biologic, others have commenced both agents simultaneously. Furthermore, there may be a role for the secondary introduction of an IM when loss of response occurs in biologic monotherapy.

The type of biologic employed in combination therapy may also be important in the outcomes observed. Although some reports grouped individuals treated with IFX and adalimumab together (7), most have considered them separately.

A further important limitation of the available data is the duration of follow-up and the outcome assessments considered. Given the chronic nature of both CD and UC, long-term benefits are of much greater importance and relevance than short-term effects. Furthermore, outcomes encompassing assessment of mucosal healing are likely of much more relevance then clinical observations, given the importance of mucosal healing in altering the course of disease (2).

Therapeutic Drug Monitoring and Immunomodulator Use in Combination Therapy

As mentioned above, one of the primary considerations of IM use in combination therapy is to reduce immunogenicity and thereby enhance the extent and duration of biologic response. The role of therapeutic drug monitoring (TDM: utilizing drug trough levels and anti-drug antibodies) has become increasingly relevant in this regard.

A post-hoc analysis of the SONIC study further evaluated the relationships between ADA and IFX trough levels (26). The initial SONIC data illustrated that those subjects treated with AZA in combination had higher IFX levels. The further analyses demonstrated that, despite this, within particular IFX level quartiles there was no efficacy advantage for combination therapy in regards steroid-free remission at 26 weeks. There did appear to be benefits in terms of mucosal healing, but these changes did not reach statistical significance with the number of subjects evaluable.

A retrospective assessment of TDM in a series of 73 Canadian children receiving IFX evaluated the outcomes of this approach (27). Although 52 of the 73 children were also receiving an IM, the study did not focus upon the role of TDM in combination therapy as such. The results of IFX trough levels resulted in a change or the addition of an IM in just 7 instances.

THE POTENTIAL RISKS OF COMBINATION THERAPY IN CHILDREN

The primary safety concerns regarding the TNF-α inhibitors relate to the risk of opportunistic infection and malignancy. Given that each of the individual IMs also confers risk, the concern of combination therapy is whether this strategy amplifies risk further. Because these adverse events are relatively rare, individual RCTs are underpowered to estimate risk (28). Therefore, pooled RCT and observational studies constitute the primary data sources. As such, limitations including reporting bias, patient variability across studies, and unmeasured confounders are inherent. Nevertheless, these data provide a framework to discuss the risks of combination therapy with patients and their families.

Infection

Opportunistic infections are caused by microorganisms that are not pathogenic in a healthy host, but are able to induce significant disease in immunocompromised individuals (29). With the exception of certain severe forms of IBD presenting early in life (30), the majority of untreated patients with IBD do not display evidence of systemic immunodeficiency (31). Hence the risk for opportunistic infections in patients with IBD is derived primarily from the immunosuppressive therapies used to treat these individuals. Numerous observational studies have shown that the IMs (ie, thiopurines and methotrexate), anti-TNF agents, and steroids each impart an increased risk of infection in patients with IBD (32,33). Moreover, these studies suggest that the combination of such therapies compounds infectious risk even further. For example, Toruner et al (32) demonstrated that the use of a thiopurine, steroid, or anti-TNF agent individually was associated with an increased risk of infection in patients with IBD (odds ratio, 2.9; 95% confidence interval [CI], 1.5–5.3); however, when 2 or 3 of these drugs were used in combination, the odds ratio increased to 14.5 (95% CI, 4.9–43).

Despite the general observation that combining immunosuppressive agents tends to increased risk of opportunistic infection in

patients with IBD, the precise impact of combination therapy remains controversial. A recent analysis of infectious complications secondary to IBD therapy using the Food and Drug Administration Adverse Event Reporting System showed that monotherapy with an anti-TNF or IM increased the odds of developing a serious infection (34). However, combining these medications did not increase infectious risk over that of monotherapy. Similarly, multiple pooled RCT meta-analyses have suggested that combination therapy does not increase total adverse events, including severe infection, in IBD patients treated with such therapy (20,35).

It is important to highlight additional key risk factors that may predispose patients with IBD to the development of serious infections. The Crohn Therapy, Resource, Evaluation, and Assessment Tool registry, which was established to evaluate IFX safety in patients with CD, found that moderate-to-severe disease activity was the most important factor (hazard ratio [HR], 2.24; 95% CI, 1.57–3.19) associated with serious infection in individuals with CD (36). The use of IFX alone had a lower HR (HR, 1.43; 95% CI, 1.11–1.84). The combination of anti-TNF and IM therapy appears to be associated with a lower risk of infections than coadministration of corticosteroids (32,33).

The Randomized, Multicenter, Open-Label Study to Evaluate the Safety and Efficacy of Infliximab in Pediatric Patients with Moderate to Severe Crohn's Disease assessed infectious complications (37). All children in this study were receiving combination therapy. Patients receiving more frequent IFX infusions had an increased incidence of infections (73.6% of patients receiving every 8 week dosing vs 38% of patients on every 12-week dosing) (37). However, in a follow-up study, the majority of infections in these patients were mild respiratory infections (38).

In summary, the use of multiple immunosuppressive medications in patients with IBD appears to increase infectious risk, particularly if steroids are included. Pediatric data are sparse, although most reported infections in children on combination IM and anti-TNF therapy are mild. Additional studies regarding infectious risk in children on combination therapy are needed, and pediatric registries have been initiated to address these issues. Based on present adult data, the use of combination therapy may have a net effect of reducing infectious risk in select patients by improving disease remission rates and minimizing steroid use, both of which appear to be profound risk factors for the development of serious infection in patients with IBD.

Lymphoma

It is generally believed that IBD alone is not a risk factor for the development of lymphoma (39). However, an increased risk of lymphoma has been linked to immunosuppressive and biologic medications used to treat patients with IBD, and constitutes a major provider and patient concern (40,41). In particular, numerous studies have demonstrated an association between thiopurine usage and the development of lymphoproliferative disorders, although the absolute risk for these malignancies in such patients remains low (42,43). For example, a large, single-center, retrospective study of pediatric IBD patients treated with thiopurine monotherapy reported the incidence of lymphoma to be quite rare (4.5 per 10,000 patient-years) in this population (42). In contrast, the relative risk of lymphoma in patients receiving thiopurines is elevated. A recent meta-analysis describes a 6-fold higher risk of lymphoma in patients with IBD actively taking thiopurines relative to the general population; however, this increased risk occurred primarily in patients exposed to thiopurines greater than 1 year, and reverted back to baseline upon discontinuation of therapy (44). This suggests that the elevated lymphoma risk associated with thiopurine therapy may be related to cumulative drug exposure, and is reversible upon drug cessation.

In contrast, a consistent association of lymphoma with anti-TNF monotherapy has not been reported. Data recently published from the The Crohn Therapy, Resource, Evaluation, and Assessment Tool registry demonstrated no association of malignancy risk with IFX therapy alone (HR = 0.59; $P = 0.16$) (45). Similar findings were shown for adalimumab in a pooled analysis of 6 RCTs, which included 3050 patient-years of exposure to this drug (46). A nationwide cohort study in Denmark that included 56,146 patients with IBD (age $\geq$15 years) showed no increased risk of lymphoma in patients exposed to an anti-TNF medication, when adjusted for factors such as age and IM use (47). Finally, Hyams et al (48) recently reported that IFX is not associated with an increased risk of malignancy in pediatric patients with IBD. Importantly, this study analyzed data from 5766 children with IBD during the course of approximately 10 years.

In regards to combination therapy with both a thiopurine and an anti-TNF agent, numerous pooled RCT, and observational cohort studies have reported lymphoma incidence rates ranging from 2.1 to 19.1 per 10,000 patient-years (49,43,45,46,50,–51). This again suggests that the absolute risk of lymphoma with combination therapy is low. The relative risk of lymphoma, as measured by standardized incidence ratios (SIR), has ranged from 2.0 to 10.2, and was raised in a subset of these analyses [51–3]. Interestingly, the majority of the studies described showed no increased risk of lymphoma with combination therapy when compared to IM treatment alone. (49,45,50) A key exception to this was the CESAME trial, in which patients who continued on thiopurine therapy alone had a lower risk of lymphoma development (SIR, 6.5; CI, 3.48–11.2) than those continued on combination therapy (SIR, 10.2; CI, 1.24–36.9) (43).

In summary, it appears that the majority of lymphoma risk in patients on combination therapy is attributable to the thiopurine component, although there may be some degree of increased risk related to the addition of an anti-TNF agent, the extent of which remains unclear.

Hepatosplenic T-cell Lymphoma

The majority of lymphoproliferative disorders reported in the IBD population are non-Hodgkin lymphomas (43,52). Hepatosplenic T-cell lymphoma (HSTCL) is a very rare form of non-Hodgkin lymphomas (53), but has garnered significant attention because of its aggressive clinical course and predilection for younger patients. In 2011, a systematic review of HSTCL in patients with IBD identified 36 unique cases (54). Twenty of these patients were receiving combination therapy, and 16 were receiving thiopurine monotherapy. The majority were males younger than 35 years, and all but one had been receiving thiopurine therapy for at least 2 years. Subsequent reports have described additional cases of HSTCL in patients with IBD (2 patients in a case series from Australia (55) and 2from the Porto Pediatric IBD working group of the European Society of Paediatric Gastroenterology, Hepatology and Nutrition) (56). Interestingly, each of these 4 individuals were males who had received thiopurines, but no biologic therapies. In summary, because HSTCL is a rare and often fatal condition, assessing causality of specific medications has been difficult (57). Most patients, however, who develop this condition are young males who have been receiving thiopurine therapy for >2 years. Therefore, these drugs should be used with caution in this group, whether as monotherapy or in combination with anti-TNF medications.

Skin Cancer

In contrast to lymphoma, multiple studies have demonstrated an elevated baseline risk for both melanoma and nonmelanoma skin cancers (NMSC) in patients with IBD (58,59). NMSC (which includes basal cell and squamous cell carcinomas) is common, with >3.5 million cases treated in the United States annually (60). Although NMSC is usually benign, surgery can be disfiguring, and its high incidence results in substantial treatment costs (61). Similar to lymphoma, multiple studies have demonstrated an increased risk (ranging from 2- to 6-fold) of NMSC with use of thiopurines (58,62,63).

It has been more difficult to assess risk of NMSC with anti-TNF monotherapy because the majority of patients receiving such treatment have had previous exposure to an IM. Indeed, some studies have suggested that even a past exposure to a thiopurine can increase the risk of NMSC (63), although conflicting reports have demonstrated a return to baseline risk after thiopurine cessation (58,64). At least 1 study has suggested that anti-TNF therapy may increase the risk of NMSC ~2-fold (65). A follow-up study by the same group demonstrated the greatest risk for NMSC was associated with prolonged (>365 days) combination therapy with a biologic and thiopurine (~4-fold), followed by prolonged thiopurine monotherapy (~3-fold), and finally prolonged biologic monotherapy (~1.5-fold) (62). This is similar to the results of a recent meta-analysis examining malignancy risk with the use of adalimumab. However, in this study, adalimumab monotherapy carried no increased NMSC risk, whereas combination therapy with adalimumab and a thiopurine was associated with an NMSC SIR of 4.59 (95% CI 2.51–7.70) (46). Therefore, like lymphoma, the thiopurines seem to be driving the majority of risk for NMSC, although combining these drugs with an anti-TNF medication may slightly increase this risk further.

Although melanoma is less common than NMSC, its global incidence is increasing, and it remains a significant cause of cancer-related mortality (66). A recent meta-analysis reported a 37% increased risk of melanoma in patients with IBD (59). Thus far, a clear association between thiopurine therapy and melanoma risk has not been established. Some studies suggest an increased risk, whereas others do not (62,67). In contrast, there are reports of an increased risk of melanoma with anti-TNF therapy alone (62,68). For example, Long et al (62) reported an odds ratio of 1.88 for the development of melanoma. In summary, although the risk of melanoma does appear to be increased in patients with IBD, additional data are needed to determine the influence of anti-TNF therapy (alone or in combination with a thiopurine) on the development of melanoma in this population.

THE COST OF COMBINATION THERAPY

The cost considerations related to combination therapies include direct and indirect costs. Although the current discussion will focus on direct costs, there is no question that indirect costs (eg, opportunity lost) from pediatric IBD are high among affected patients and families and the extreme variability of these costs between patients makes cross-sectional cost estimations difficult. Regardless, for the practicing pediatric gastroenterologist, an important consideration is that higher out-of-pocket costs are strongly correlated to poorly controlled IBD and greater disease severity, as overall frequency of medical care—especially acute care—invariably increases (69).

In the United States, the Average Wholesale Price (AWP) is the average cost of prescription drugs acquired at wholesale prices. Although AWP prices can vary between hospital pharmacies, it is considered to be a reference price for comparison of pharmaceutical costs across health systems. However, AWP is not defined by law or regulation and reflects the price reported in commercial publications. Therefore, AWP does not account for discounts available to various payers (70). As prescription drug pricing is non-transparent, there is likely high variability and volatility of acquisition costs of prescription drugs such as biologics for pharmacies.

In evaluating drug costs for combination therapies, biologic therapies are the key drivers of costs. In comparison to biologics, AZA, 6-MP, and MTX are extremely affordable. For example, according to Red Book AWP prices, azathioprine 100 mg/day would be <$1500 for an entire year, whereas IFX is $1113.89 per 100 mg unit and adalimumab is $1748.19 per 40 mg syringe (71). The full cost of these biologics will clearly depend on the individual dosing strategies and frequency. For example, although the standard dosing regimen for maintenance IFX involves 5 mg/kg every 8 weeks, increasing the dose amount or frequency will substantially alter drug- and encounter-related costs. In addition to the direct drug-related costs, further consideration must also be made to non-drug costs. Infused drugs are associated with substantial administration costs, such as facility charges, pharmacy supplies, and nursing/personnel costs. Non-drug costs can be higher than the actual drug itself, especially if the infusion is associated with inpatient diagnosis-related groups (72,73).

In real-world clinical practice, one-size does not fit all, as a single cost-effective pharmaco-therapy strategy may not be applicable across all patients. Instead, the pediatric gastroenterologist should focus on improving the value of care, where value is defined as the health benefit gained (eg, length of time in clinical remission) per cost. Outcomes, such as risks of medication versus cost, are also important aspects. When attempting to optimize value, a patient-centered definition of health benefit is important, especially in pediatrics. However, based on the existing literature as a whole, haphazard dose intensification or class switching of biologics based on subjective complaints (eg, abdominal pain) is cost-ineffective. As the role of noninvasive biomarkers (eg, calprotectin) to objectively monitor mucosal inflammation continues to evolve, judicious use of biologics and determination of clear indications for escalating therapies—especially through evidence-based practice, patient education, and adherence—will enhance the value of combination therapy and overall cost-effectiveness.

The utility of therapeutic drug monitoring is an area of ongoing discussion and debate. Although some test-based strategies may reduce costs while achieving comparable or improved clinical effectiveness (74), the major concern and feedback at the practice-level is the high out-of-pocket cost contribution for patients and families when drug levels and antibodies are tracked longitudinally. Finally, the advent of biosimilars is another factor poised to alter the cost-effectiveness of biologic therapy in IBD. Biosimilars, which contain the same molecular property as the original biological agent, are already competing with biologics' market share in Europe and Asia (75). If the US Food and Drug Administration follows suit in the near future, biosimilars such as CT-P13 (trade names Remsima and Inflecta) will likely reduce the acquisition costs of biologics.

In summary, direct costs associated with combination therapy are driven by drug and non-drug costs of biologic therapies. Increasing use of biologics has changed the economic landscape of IBD, wherein outpatient pharmacy utilization costs account for the largest segment of total IBD-related health care costs in the United States (76). Establishing deep remission and tight disease control through combination therapy within a value-based, individualized care model may enhance patients' quality of life, long-term health, and cost-effectiveness.

SELECTING THE PATIENT WHO WOULD BENEFIT FROM COMBINATION THERAPY

Individual patient risk stratification can help healthcare providers identify more severe disease phenotype. This may provide support for the early use of a biologic agent or indeed for the use of a top-down approach (1). However, the factors that influence the indication for, or response to, combination therapy are not yet clear.

Blonski et al (77) noted that characteristics of adult patients at risk for complicated CD included younger age at initial diagnosis, the presence of perianal lesions, ileal involvement, smoking, and the need for therapy with corticosteroids. Although children tend in general to have more aggressive and extensive disease than adults (78), the pediatric literature suggests female sex, older age (6–17 years) compared with a younger age (0–5 years) and ileal or ileocolonic disease are risk factors for developing complications such as strictures, abscesses, and fistulas and subsequent need for surgery (79,80).

Additionally, disease characteristics associated with more debilitating disease include extensive disease, previous surgery, fistulizing phenotype, perianal involvement, significant growth failure, or corticosteroid dependence/refractoriness. Hence, early combination therapy may be more appropriate in a patient with such risk factors, wherein the benefits of altering the disease course outweigh the potential risks of the intervention.

A further patient factor relates to sex. There is no suggestion in the published literature that the benefits of combination therapy differ according to the sex of the patient. However, as noted earlier, the risk of hepatosplenic lymphoma subsequent to use of thiopurines in combination therapy appears to be greater in young males. The risk of other complications, such as hemophagocytic lymphohistiocytosis, does not appear to have sex preference (48). Nonetheless, sex could influence the choice of immunomodulator included in combination therapy.

Another factor for consideration is Epstein–Barr virus (EBV) status. Primary EBV infection in patients with IBD on thiopurines is a risk factor for lymphoproliferative disorders (including lymphoma). Hence, EBV status should be considered in the prescription of thiopurines. In a recent publication, Gordon et al (81) assessed EBV status in 688 children with IBD. Two-thirds of those treated with thiopurines were IgG-negative before commencing therapy. Furthermore, the majority of infections in these children occurred around 2 years after starting thiopurines.

Additional factors that need to be kept in mind when considering combination therapy are the duration of this combination therapy and strategies for treatment after the specific period of combination. Different durations of combination therapy have not been evaluated directly. Grossi et al (13) showed that children who were receiving combination therapy for >6 months tended to maintain a more durable response to IFX than those receiving combination therapy for <6 months. These data suggest that the 6-month combination period maybe an optimum time to achieve long-term benefits with combination therapy, and allowing potential withdrawal of IM thereafter. In patients who have been in clinical remission with combination therapy for >27 months and with C-reactive protein <5 mg/L and platelet count $<298 \times 10^9$ cells/L, the authors considered it reasonable either to continue a low-dose concomitant IM or to discontinue the IM (82).

Beyond the period of combination therapy, the options include continuation of biologic monotherapy or IM monotherapy. The latter was evaluated in a group of 115 patients initially managed with IFX and an IM (83). Patients who were in deep clinical and endoscopic remission for at least 6 months and at low-risk of relapse were continued on IM alone (with cessation of the IFX). These authors concluded that approximately 50% of patients with CD who were treated for at least 1 year with IFX and an IM experienced a relapse within 1 year after discontinuation of IFX. The authors propose characteristics that stratify patients with a higher risk of flaring (male sex, the absence of surgical resection, leukocyte counts $>6.0 \times 10^9$ cells/L, hemoglobin $\leq$145 g/L, C-reactive protein $\geq$5.0 mg/L, and fecal calprotectin $\geq$300 μg/g). In this study, patients with no >2 of these risk factors had a 15% risk of relapse within 1 year. Reassuringly, retreatment with IFX was effective and well tolerated in 88% of patients who experienced a relapse (83).

At present, it would be reasonable to utilize low-dose methotrexate in young men (<35 years) rather than a thiopurine in combination with a biologic and to consider thiopurines in other patients. Work is still required, however, to fully establish the ideal dosage regimen for an IM in this setting. Furthermore, combination therapy should be considered for at least 6 months, with further steps (such as conversion to monotherapy) considered only after full assessment including confirmation of mucosal healing. It is unclear whether this decision is best made based on noninvasive markers (such as fecal calprotectin) or requires endoscopic reassessment (with associated costs and risks). Further data are required to ascertain the most patient-centered approach. The COMBINE trial (Clinical Outcomes of Methotrexate Binary Therapy in Practice) is a randomized, double-blind, placebo-controlled, multicenter pragmatic clinical trial to evaluate the effectiveness of low-dose oral methotrexate in patients with pediatric CD initiating anti-TNF therapy and maybe able to address some of these unanswered questions in pediatric CD.

In summary, consideration of patient-related factors is important to optimize the benefit to risk ratio. While acknowledging the limitations in data, a detailed discussion with the patient and/or family regarding the risks and benefits of combination therapy versus monotherapy is necessary to help them make choices that fit their personal preferences. However, further research and analysis of genetics, serological markers, and the gut microbiome are needed to better establish which markers predict an individuals' disease course and to better elucidate which patients are more likely to benefit from early combination therapy.

CONCLUSIONS

Although various aspects of combination therapy have been considered by investigators in recent years, there remain numerous important gaps in our understanding. Although some data demonstrate improved maintenance of efficacy and durability of response when combination therapy is employed, there are concerns about the health risks particularly with ongoing thiopurine exposure (ie, lymphoproliferative disorders).

A practical approach, however, may be to consider combination therapy in the context of individualization, risk stratification, and an overall ''treat to target'' strategy. Combination therapy may be considered more appropriate in higher-risk individuals, who exhibit greater risk of disease complication or adverse outcomes. Particular factors to consider may include sex, EBV status, penetrating or fistulizing perianal disease, and possibly patients at risk or with a history of autoantibody development to anti-TNF therapy or requiring an individualized drug exposure target to achieve the intended treatment effect. Doses of IM should also be carefully considered with combination therapy, as low-dose AZA or MTX may be adequate to achieve the intended clinical effect than the higher, standard dosing for either medication.

At present, there are insufficient pediatric data to provide more definitive guidelines. Further work is required to clarify the optimal agent(s) to use in combination therapy (and the doses required) and to identify the optimal personalized approach to

maximize benefit and minimize risk at the heterogeneous individual- and population-levels.

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