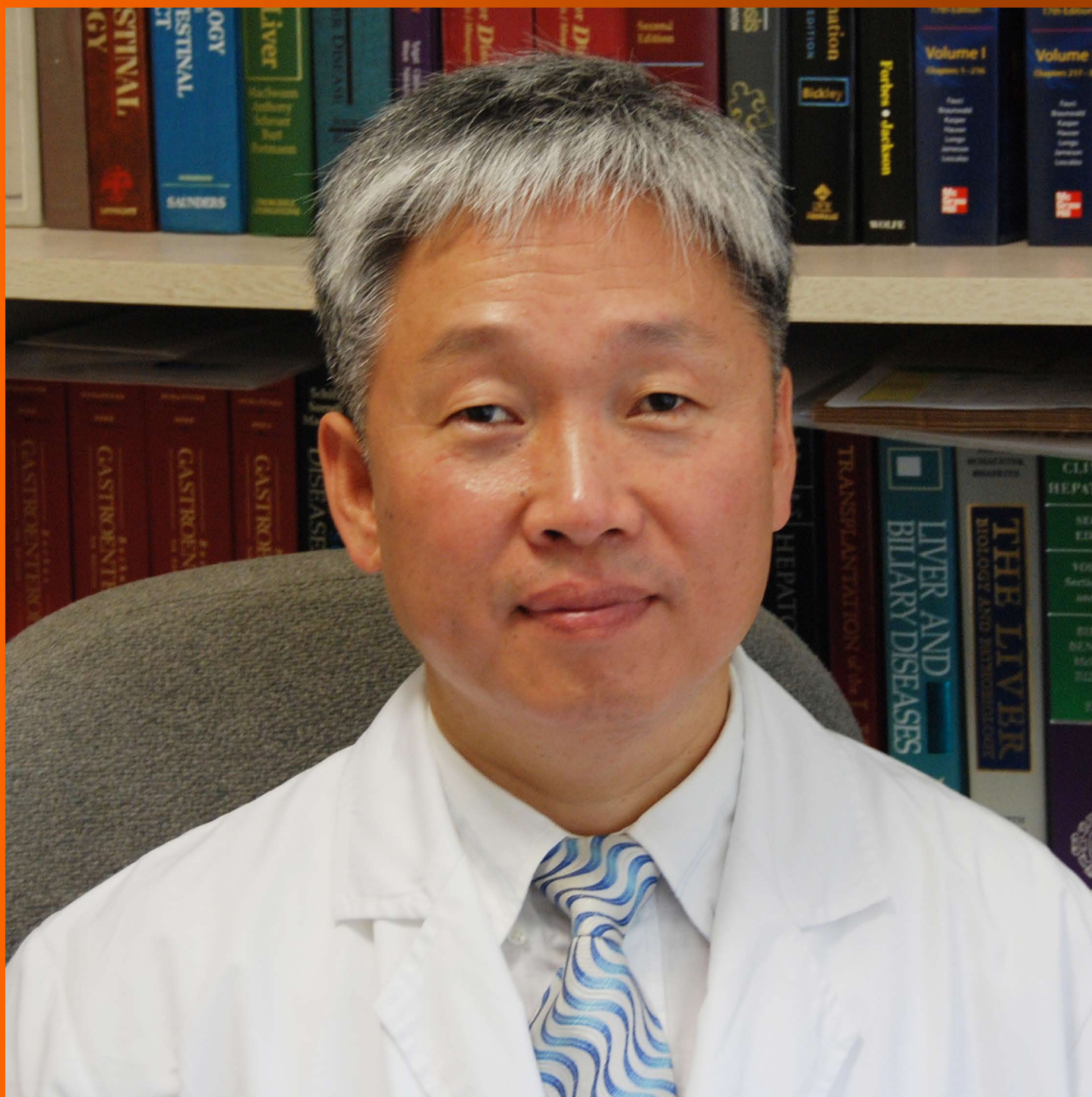


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Contents

Quarterly Volume 8 Number 2 May 6, 2017

EDITORIAL

- 90 Management of esophageal caustic injury
De Lusong MAA, Timbol ABG, Tuazon DJS

FRONTIER

- 99 5-Aminosalicylates to maintain remission in Crohn's disease: Interpreting conflicting systematic review evidence
Gordon M

MINIREVIEWS

- 103 Combination therapy for inflammatory bowel disease
Sultan KS, Berkowitz JC, Khan S
- 114 Inflammatory bowel disease: Efficient remission maintenance is crucial for cost containment
Actis GC, Pellicano R

ORIGINAL ARTICLE

Case Control Study

- 120 Thiol/disulphide homeostasis in celiac disease
Kaplan M, Ates I, Yuksel M, Ozderin Ozin Y, Alisik M, Erel O, Kayacetin E

Observational Study

- 127 Correlation of rapid point-of-care vs send-out fecal calprotectin monitoring in pediatric inflammatory bowel disease
Rodriguez A, Yokomizo L, Christofferson M, Barnes D, Khavari N, Park KT
- 131 Clinical and economic impact of infliximab one-hour infusion protocol in patients with inflammatory bowel diseases: A multicenter study
Viola A, Costantino G, Privitera AC, Bossa F, Lauria A, Grossi L, Principi MB, Della Valle N, Cappello M
- 137 Interferon-free treatments in patients with hepatitis C genotype 1-4 infections in a real-world setting
Ramos H, Linares P, Badia E, Martín I, Gómez J, Almohalla C, Jorquera F, Calvo S, García I, Conde P, Álvarez B, Karpman G, Lorenzo S, Gozalo V, Vázquez M, Joao D, de Benito M, Ruiz L, Jiménez F, Sáez-Royuela F; Asociación Castellano y Leonesa de Hepatología (ACyLHE)

Randomized Controlled Trial

- 147 Low dose oral curcumin is not effective in induction of remission in mild to moderate ulcerative colitis: Results from a randomized double blind placebo controlled trial
Kedia S, Bhatia V, Thareja S, Garg S, Mouli VP, Bopanna S, Tiwari V, Makharja G, Ahuja V

Contents

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Combination therapy for inflammatory bowel disease

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Abstract

Biologic therapies such as infliximab and adalimumab

have become mainstays of treatment for inflammatory bowel disease. Early studies suggested that combination therapy (CT) with infliximab and an immunomodulator drug such as azathioprine may help optimize biologic pharmacokinetics, minimize immunogenicity, and improve outcomes. The landmark SONIC trial in Crohn's disease and the UC SUCCESS trial in ulcerative colitis demonstrated CT with infliximab and azathioprine to be superior to monotherapy with either agent alone at inducing clinical remission in treatment naïve patients with moderate to severe disease. However, many unanswered questions linger. The role of CT in non-naïve patients as well as the optimal duration of CT remains unknown. The effectiveness of CT with alternate biologics and/or alternate immunomodulators is not as clear, and it is unknown whether SONIC's conclusions can be extrapolated beyond infliximab and azathioprine. Also looming are the risks of CT including opportunistic infection and malignancy; specifically, lymphoma. This review lays out the evidence as it pertains to the risks and benefits of CT as well as the areas that require further research. With this information in hand, the practitioner may develop a treatment strategy that best suits each individual patient.

Key words: Crohn's disease; Adalimumab; Vedolizumab; Ulcerative colitis; Infliximab; Inflammatory bowel disease; Methotrexate; Azathioprine

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Core tip: The benefits of combination therapy (CT) with infliximab and azathioprine likely outweigh its risks in treatment naïve patients with moderate to severe Crohn's disease and ulcerative colitis. A similar benefit in patients already failing biologics or immunomodulators is not as well defined. There is a lack of strong prospective evidence demonstrating a benefit for CT with adalimumab and an immunomodulator. While expert guidelines emphasize the use of CT, its use should be preceded by a careful weighing of the risks and benefits by the physician and patient, especially in scenarios where the strongest

evidence for CT may not directly apply.

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INTRODUCTION

Traditional management of inflammatory bowel disease (IBD), both Crohn's disease (CD) and ulcerative colitis (UC), involved the stepwise use of 5-aminosalicylate compounds, followed by steroids and then an immune modulator (IMM) such as 6-mercaptopurine (6MP), azathioprine (AZA) or methotrexate (MTX) in those individuals unable to successfully taper off steroids, or those with rapid disease recurrence once steroids were withdrawn. While the IMMs are generally ineffective agents for induction of response or remission in IBD^[1] the thiopurines 6MP/AZA have proven to be effective for the maintenance of response and remission in CD and UC^[1,2] while the purine analogue MTX appears to offer the same benefit for CD^[3]. Beginning in the 1990's, biologic therapies targeting tumor necrosis factor alpha (TNF- α) entered into this paradigm. The first in class medication infliximab (IFX) was initially shown to be effective both for induction and maintenance of remission for CD, and latter for UC. In the years that followed, IFX was followed by other TNF- α blockers including adalimumab (ADA) for CD and UC, certolizumab pegol for CD, and golimumab for UC. Even more recently we have seen the addition of biologics targeted at different points in the body's inflammatory response, such as the anti-integrins natalizumab and vedolizumab (VDZ) which inhibit the migration of white blood cells, mostly activated T cells to areas of bowel inflammation, as well ustekinumab which blocks the IL 12/23 pathway of inflammation.

Consistently, clinical trials of biologics have involved the use of these newer therapies in combination with IMMs. Initially, the use of this form of combination therapy (CT) was a natural outgrowth of the failure of IMMs to fully control disease in some of the clinical trial population, with the biologic therapy added on to continued IMM treatment. While the initial clinical trials of IFX did not show any improved response with the use of CT over monotherapy with biologic alone, there were some other findings which suggested that the use of both classes of medications together might be superior to one or the other alone. In a way, the potential benefit of CT would seem to be an answer to an obvious question: If one has access to two separate therapies with different mechanisms, each less than 100% effective, can the use of both in combination increase the rates of response over each individually?

In the following review we will address the basic

questions both the clinician and patient will need to have answered before considering the use of CT; (1) Does CT work, and why does it work? (2) Is CT effective for those with either CD or UC? (3) Is CT effective for different combinations of IMM and biologic? (4) Is CT effective at all stages of IBD therapy? (5) Is CT safe? (6) Is CT being utilized? and (7) What do the experts say about CT?

DOES CT WORK/WHY DOES IT WORK?

Though the earliest clinical trials of IFX were not designed to assess the efficacy of CT, study design permitting continued IMM use provided some early data on the effect of CT. Given the few options for alternate therapy available at the time, a majority of patients in the phase 3 trials of IFX for both CD and UC had experienced prior failure of IMM therapy with either 6MP/AZA or MTX. For many, this failure to achieve remission likely involved a partial response rather than a complete lack of efficacy. In either case, large numbers of patients entering these trials continued on prior IMM therapy. This "step up" approach to CT will be discussed in more detail in the following sections. In the case of the CD trials ACCENT 1 and ACCENT 2^[4,5] approximately 50% of study patients, well matched by active treatment and placebo arms, continued on IMMs. In the UC studies of IFX, ACT 1 and 2, approximately 33% of patients were on IMMs at study entry^[6].

Overall, the clinical trials of IFX did not show any improved clinical efficacy associated with the use of CT. These early trials did however give the first hints of how CT might provide a benefit to the IFX patient over monotherapy in the form of decreased immunogenicity. Overall, the development of antibodies to IFX (ATI) were significantly lower in the CT patients, with 4%-20% without CT developing ATI, compared to rates of 4%-6% among those using CT^[7]. This effect was noted to be greatest for those patients using the current standard 5 mg/kg dose of IFX. There was also no observed benefit in terms of higher IFX levels, but neither was there any increase in the rates of infections. Along with the lower ATI levels for those using IMM, were lower overall rates of infusion reactions at 12.5%, compared to 22.0% for those not using IMM.

Following up on these early observations, subsequent investigations began to take a closer look at the interplay between IFX, the development of anti-drug antibodies and possible impact on IFX drug levels, treatment reactions and clinical efficacy. In a prospective non-randomized trial, Baert *et al*^[8] followed 123 patients on IFX, with 47% receiving concurrent IMM. In this study, as was common at that time, patients with luminal disease were treated with episodic rather than scheduled IFX therapy, while those with fistulizing disease received a week 0, 2 and 6 induction regimen followed by episodic treatment. Overall, patients received a mean number of 3.9 infusions. In total, 61% developed ATI. Higher antibody

levels > 8.0 µg/mL predicted shortened clinical response, 35 d vs 71 d ($P < 0.001$), with higher levels of ATI in those without IMM usage ($P < 0.001$) and lower drug levels in those without IMM usage ($P < 0.001$). Infusion reactions were found to be more common among those not using IMM [relative risk (RR) = 2.40; 95%CI: 1.65-3.66; $P < 0.001$]. Vermeire *et al.*^[9] performed similar work using IFX on demand for both luminal and fistulizing CD. They enrolled 174 patients who received IMM (either MTX or AZA) or no IMM in a non-randomized fashion. MTX was given subcutaneously at 25 mg weekly for 12 wk followed by 15 mg weekly, while ASA was given at a weight-based dose of 2-2.5 mg/kg. ATI levels were checked at 4 wk following IFX doses. Again, episodic treatment with IFX resulted in high ATI levels, especially for patients not receiving concomitant IMM. Overall they observed 73% of patients without IMM developing ATI, compared to 46% with IMM, $P < 0.001$. This effect was consistent across IMM types, with 44% of MTX patients developing ATI vs 48% of AZA patients, $P = \text{NS}$. There was a trend towards higher average IFX drug levels with IMM, 2.22 µg/mL vs 6.45 µg/mL, $P = 0.065$, and significantly less infusion reactions with IMM, 16% vs 40%, $P = 0.04$.

Taking into account the two main observations of IFX immunogenicity at the time, the association of lower ATIs with scheduled treatment^[10,11] and concurrent use of IMM, the Study of Biologic and Immunomodulators Naïve Patients in Crohn's Disease (SONIC) trial was designed to answer the question of whether clinical response was superior with CT over monotherapy^[11]. Unlike the earlier clinical trials, patients entering SONIC were entered into one of three treatment arms and followed prospectively. Additionally, given the strong association between episodic dosing, antibody formation and decreasing effectiveness of treatment, all patients in SONIC and future trials of CT were given IFX on a fixed schedule rather than episodically, as is the current practice. In total, 508 patients were randomized to either IFX monotherapy (with oral placebo), AZA monotherapy at 2.5 mg/kg (with IV placebo), and CT with IFX and AZA. All patients in the study were naïve to both IMM and biologics, had a Crohn's Disease Activity Index (CDAI) > 220, and underwent ileocolonoscopy at baseline. The primary study endpoint was steroid free clinical remission at 26 wk, defined by a CDAI < 150. This endpoint was achieved by 30.0% of those on AZA monotherapy vs 44.4% on IFX monotherapy, ($P = 0.006$) and 56.8% of those on CT, which was significantly greater than either AZA ($P < 0.001$) or IFX monotherapy ($P = 0.02$). Though CT achieved higher rates of mucosal healing than IFX alone, 43.9% vs 30.1%, this result was not found to be statistically significant, $P = 0.06$, likely due to the large number of patients without active disease found on baseline ileocolonoscopy. Additional findings again mirrored those of earlier studies, showing higher week 30 IFX trough levels with CT vs IFX monotherapy, 3.5 µg/mL vs 1.6 µg/mL ($P < 0.001$), and lower incidence of ATI, 0.9% vs 14.6%. Notably, serious adverse events

(SAE) were actually lower with CT than IFX monotherapy (15.1% vs 23.9%, $P = 0.04$). Serious infections were similar across treatment groups, with 3.9% of patients on CT, 4.9% of those on IFX monotherapy, and 5.6% of those on AZA alone.

IS CT EFFECTIVE FOR UC?

Though SONIC was notable in regards to the generally short median disease duration of 2.3 years of participants, it did appear to provide an answer to the question of the superiority of CT over monotherapy with IFX, at least for the select group of treatment naïve patients with CD. Following up on these findings the UC SUCCESS trial was designed to answer the same question, and determine if CT with IFX and AZA was also more effective for UC^[12]. With a similar study, 239 patients with active UC confirmed by sigmoidoscopy were enrolled to treatment arms of IFX with oral placebo, AZA with IV placebo, and AZA. Again, all patients were biologic naïve, though prior AZA exposure (discontinued at least 3 mo earlier) was permitted. The primary study endpoint of steroid free remission at week 16, defined by a MAYO score ≤ 2 , was achieved by 39.7% of CT vs IFX monotherapy ($P = 0.017$). Mucosal healing, defined by a subscore of 0 or 1, showed a trend towards greater effect for CT vs IFX monotherapy 62.8% vs 54.6% ($P = \text{NS}$), and complete mucosal healing defined by an endoscopic subscore of 0 was significantly greater for those on CT vs IFX monotherapy, 29.5% vs 11.7%, $P = 0.006$. Again, no increased incidence of SAE was observed with CT. Serious infections were similar in all three groups, (0 in the CT group, 1 in the IFX monotherapy group, and 1 in the AZA monotherapy group).

IS CT EFFECTIVE FOR OTHER IMMS?

Of course thiopurines were not the only IMMs that had shown potential benefits when used with IFX. MTX had demonstrated similar effects of decreasing ATI and increasing IFX trough levels. With that in mind, a prospective study of MTX with IFX, the COMMIT trial, was preformed comparing IFX monotherapy and subcutaneous placebo to IFX with subcutaneous MTX for patients with CD^[13]. Like SONIC the study enrolled biologic naïve patients, but other inclusion criteria and study methods were notably different. There was no need for minimum baseline CDAI, and inclusion only required that patients had required steroids within 6 wk prior to enrollment. Additionally, all IFX infusions were given along with 200 mg of IV hydrocortisone as premedication. The primary study endpoint was failure to achieve steroid free remission at week 16 (defined by a CDAI < 150), or failure to maintain remission through week 50. In total 126 patients were enrolled, with an average disease duration of over 10 years in each treatment arm, as well as a relatively low CDAI of 207 for both CT and monotherapy groups. The week 14 primary endpoint of steroid free remission was not

found to be greater for CT vs monotherapy, 76% vs 78%, and neither was the week 50 endpoint, 56% vs 57%. Critiques of the trial have pointed at the overall low baseline levels of CDAI, suggesting that it is more difficult to detect a significant response to therapy when the disease is less severe. Also, the use of hydrocortisone along with all infusions may have offered additional clinical benefit, again obscuring any distinct MTX effect. Even so, the trial again demonstrated the ability of MTX to modify immune response to IFX, with lower ATI in the MTX arm vs placebo, 4% vs 20% ($P = 0.01$), and a trend towards higher IFX trough levels, 6.35 $\mu\text{g/mL}$ vs 3.75 $\mu\text{g/mL}$ ($P = \text{NS}$).

IS CT EFFECTIVE FOR OTHER BIOLOGICS WITH IMMS?

The next biologic, possessing a similar mechanism of action to IFX, was adalimumab (ADA). ADA differs from IFX not only by its subcutaneous route of delivery, but by its fully humanized protein structure. Given that the main benefit of IMM with IFX appeared to be linked to blunting an immune response, it could not be assumed that ADA would be as immunogenic, or that IMM with ADA would demonstrate the same benefits. In fact, early studies of ADA pharmacokinetics and clinical outcomes did demonstrate a correlation of clinical response to higher ADA trough levels and lower antibody to adalimumab, similar to prior observations with IFX. Unlike IFX however, early investigations did not find that IMM influenced these outcomes^[14]. A retrospective analysis of mixed IBD patients using IFX ($n = 108$) again showed increased drug levels ($P = 0.037$) and decreased antibodies to IFX ($P = 0.001$) among those using IMM. This benefit to IMM was not found among the 109 ADA treated patients, with CT showing similar drug trough levels ($P = 0.496$) and antibody levels ($P = 0.63$)^[15] to those on ADA monotherapy. A recent large meta-analysis of ADA pharmacokinetics of 14 studies included 1941 patients with mixed IBD diagnoses with available clinical outcome, drug trough and antibody data available. Once again, clinical response was associated with higher drug trough and low antibody to ADA, but CT did not appear to influence either antibody or drug trough levels^[16]. The study suggests that antibodies to ADA do occur, they do appear to cause low levels of trough ADA and lessened clinical effect, but there is a lack of evidence suggesting that IMM have the ability to prevent the development of these antibodies.

To the present time there has been no trial of ADA matching the designs of either SOINIC or UC SUCCESS. While not a substitute for a prospectively designed trial, there is still clinical data available addressing the issue of CT with ADA and IMM. Another meta-analysis designed to look specifically at clinical outcomes with ADA monotherapy vs CT among CD patients included 18 studies [randomized control trials (RCT), open-label

prospective, observational studies, cohort and case-control studies] with 2280 ADA monotherapy patients and 2014 CT patients^[17]. Of the 6 studies analyzing induction of remission (960 ADA, 997 CT), the use of CT was associated with greater clinical response OR = 0.79 (0.65-0.96); $P = 0.02$, though this was not found to be the case when the analysis was limited to the RCT, OR = 1.11 (0.72-1.73); $P = 0.64$. There was also no evidence of clinical benefit to CT for induction of response OR = 0.68 (0.37-1.25); $P = 0.22$, 12 mo remission OR = 1.08 (0.79-1.48); $P = 0.61$, or 12 mo response OR = 1.21 (0.74-1.99); $P = 0.44$. At present there is even less data specifically addressing the clinical impact of IMM with ADA for UC. As was the case with the early IFX trials, almost half of the patients in the initial clinical trials were using IMM at enrollment. Though the remission rates were higher with CT, the small absolute number of patients involved and the absence of a specific prospective trial design should caution against any definitive conclusions.

Since IFX and ADA were the first biologics approved for IBD treatment, most of the current data on CT deals with IFX and ADA. Of course, biologic development has continued beyond this class of medications, most recently with the addition of the new integrin inhibitor, VDZ. While not the first in class, with that distinction going to natalizumab, the updated mechanism of action targets $\alpha 4\beta 7$ on circulating white blood cells. Blockade of this gut specific integrin decreases WBC adherence to the vascular endothelial wall, and subsequent migration to areas of inflammation. As is the case for all non-IFX biologics, there is currently no prospectively designed study addressing CT of VDZ with IMM. Review of the results of the large phase 3 clinical trials offers some of the early immunologic data seen with earlier biologics. GEMINI 1, enrolling 895 patients with UC for induction and maintenance, included a third of patients with concurrent IMM use. Overall, antibodies to vedolizumab (AVA) were infrequent, found in 3.7% of patients at "any time" during testing, with a mere 1.0% testing positive on ≥ 2 samples^[18]. GEMINI 2, enrolling 1115 patients with CD for induction and maintenance also included a third with concurrent IMM use^[19]. Overall AVA were again infrequent, 4.1% at "any time", and 0.4% on ≥ 2 samples. The authors of each study commented that "concomitant immunosuppressive therapy was associated with decreased immunogenicity (data not shown)".

More recently an analysis of the phase 2 and 3 trials for both CD and UC has been preformed, addressing the issue of CT^[20]. Among a total of 2830 patients, covering 4811 patient years there was no observed increased risk of adverse events. During active VDZ therapy, CT patients had a 3% risk of AVA, compared to 4% for VDZ monotherapy. As has previously been noted for TNF- α inhibitors, higher levels of anti-drug antibody were seen following completion of VDZ therapy among those patients without IMM as compared to those

Table 1 Author's summary of the evidence for combination therapy

	Crohn's disease		Ulcerative colitis	
	Clinical benefit	Pharmacokinetic/immunogenic benefit	Clinical benefit	Pharmacokinetic/immunogenic benefit
IFX + AZA/6MP (treatment naïve)	+	+	+	+
IFX + AZA/6MP (step-up from immunomodulator monotherapy)	-	NA	NA	NA
IFX + MTX	+/-	+	NA	NA
ADA + IMM	+/-	+/-	NA	NA
VDZ + IMM	NA	+	NA	NA
Ustekinumab + IMM	NA	NA	NA	NA

IFX: Infliximab; AZA: Azathioprine; 6-MP: 6-mercaptopurine; MTX: Methotrexate; ADA: Adalimumab; VDZ: Vedolizumab; IMM: immunomodulatory; +: beneficial; +/-: Possible benefit; NA: No adequate data available.

with ongoing IMM use, 18% vs 3%. Theoretically, this may have implications for issues such as prevention of AVA during VDZ drug holiday, and potential infusion reactions and/or drug effectiveness on resuming therapy. It does not however offer answers to the key question of risks and benefits of CT with VDZ and IMM.

Even more recently Ustekinumab, targeting the p40 subunit of IL-12/23 has obtained regulatory approval for induction and maintenance therapy for CD. In the recently published phase 3 induction and maintenance trials, approximately a third of patients received concurrent IMM with Ustekinumab or placebo^[21]. The investigators have yet to publish data analyzing the effect of CT, though they did report an overall low level of antidrug antibodies at 44 wk of 2.3%. Again, while there is no prospective clinical trial data yet available on CT, a recent retrospective study from the GETAID group analyzed their experience with 122 treated patients^[22]. All 122 patients were prior treatment failures with TNF- α inhibitors, with only 18 using IMM at the time of ustekinumab therapy. Of all factors analyzed, only IMM use was found to be a predictor of 3 mo clinical benefit, OR = 5.43; 95%CI: 1.14-25.77; $P = 0.03$ (See summary of evidence for induction CT, Table 1).

IS CT EFFECTIVE AT ALL STAGES OF IBD THERAPY?

Step up therapy: Adding biologic to failing IMM

As we have seen, most of the available evidence suggesting a benefit to CT involves the use of IFX and IMM begun simultaneously, especially in those naïve to biologic as well as to IMM. In reality, IMM is still widely used as part of a step up algorithm of care, with biologics employed as additional therapy in cases of IMM failure as in the early clinical trials. Given the frequent positioning of IMM as mono-therapy prior to biologic, a specific look is required into the role of continuing IMM as part of a combination step-up therapy.

A recent analysis by Osterman *et al.*^[23] retrospectively analyzed a cohort of CD patients beginning biologic therapy with either IFX or ADA, 1459 and 871 patients

respectively. In total 381 CT patients using IFX and IMM were matched to 912 monotherapy IFX patients, as were 196 CT using ADA and IMM matched to 505 ADA monotherapy patients. In the IFX group, 86% of the CT patients were part of a step-up protocol, adding biologic to existing IMM, as were 89% in the ADA group. These high percentages effectively made the analysis of the effect of CT into an analysis of CT as part of a step-up treatment approach. Thiopurines accounted for 90% of IMM use. Given the retrospective design, the authors were unable to analyze for common clinical trial outcomes such as improvement in CDAI or endoscopic response and remission. Looking at alternate outcomes, they were unable to show any benefit to CT in terms of surgery (HR = 1.20, OR: 0.73-1.96), hospitalization (HR = 0.82, OR: 0.57-1.19), rates of combined biologic discontinuation and surgery (HR = 1.09, OR 0.88-1.34) or serious infections overall (HR = 0.93, OR 0.88-1.34). Rates of opportunistic infections were significantly increased (HR = 2.64, OR: 1.21-5.73), mostly due to increased rates of herpes zoster (HR = 3.16, OR: 1.25-7.97). These findings were consistent across the subgroups for both IFX and ADA. The overall conclusion: there is no apparent benefit to continuing IMM, in cases of IMM failure, once biologic therapy is begun. Similarly, a recent meta-analysis by Jones *et al.*^[24] reviewed the results of 11 randomized trials of anti-TNF- α therapies including IFX, ADA and certolizumab, among 1601 patients of which 40% were on CT. All patients on CT received biologic as part of a step-up approach after failing to achieve remission with IMM. Again, there was no benefit to CT for the outcomes of 6-mo remission (OR = 1.02; CI: 0.80-1.31), 6-mo response (OR = 1.08; CI: 0.79-1.48). Neither however was there any increase risks of adverse events with CT (OR = 0.71; 95%CI: 0.41-1.25).

Step up therapy: Adding IMM to failing biologic

The issue of stepping up to CT by the addition of IMM to failing biologic is less well studied. A small retrospective cohort analysis by Ben-Horin *et al.*^[25] examined the outcomes of 5 patients (3 with CD, 2 with UC) with a secondary loss of response to IFX associated with

high ATI levels and undetectable trough. Two patients were treated with MTX and 3 received either AZA/6MP. In all cases patients experienced a decrease in ATI, an increase in trough, and a recapturing of clinical response. Despite the questionable efficacy of CT when the anti-TNF is ADA, the same group has recently shown a similar result when adding IMM as salvage therapy to failing ADA in 23 patients (21 with CD, 2 with UC) with confirmed antibodies to ADA. Salvage therapy with IMM (14 with thiopurines, 9 with MTX) was associated with elimination of antibodies to ADA, increased ADA levels, and recapturing of response (median time to sero-reversal 5 mo) in 11 patients (48%)^[26].

Optimal duration of successful CT

The final issue to address with regard to effectiveness of CT is the question of duration: For those patients in remission on CT, for how long should they continue to take the IMM? The retrospective data on de-escalation is mixed^[27]. There is very limited prospective controlled data to guide therapy. Van Assche *et al.*^[28] from Belgium reported on a group of 80 CD patients with disease controlled on CT for a minimum of 6 mo, at IFX doses of 5 mg/kg, at intervals of every 8 wk or greater. Patients were randomized to maintenance with IFX and placebo vs continued CT, and followed for 104 wk. The primary outcome was the need to decrease the IFX dosing interval or discontinuation of IFX. Secondary outcomes included IFX trough levels and safety. While those patients discontinuing IMM showed significantly lower IFX trough levels at 54 wk, 1.65 µg/mL vs 2.87 µg/mL ($P < 0.0001$), and a trend towards higher CRP levels, there was no difference at 104 wk with regards to the need for rescue IFX, discontinuation of IFX. The authors concluded that there was no benefit to IMM beyond 6 mo in patients achieving remission with combination IFX and IMM. Another more recent prospective study however suggested a possible benefit to continued CT. Eighty-one patients on CT for at least 1 year were randomized to continuation of CT at the same dose (Cohort A), reduction of azathioprine dose by 50% (Cohort B), or complete cessation of azathioprine (Cohort C)^[29]. While differences in clinical outcomes at one year were not statistically significant ($P = 0.1$), there was a trend towards higher relapse rates in Cohort C (30.7% vs 17.8% and 11.5% in Cohorts A and B). Only in Cohort C were infliximab trough levels significantly decreased at one year as compared to study initiation (4.2 µg/mL vs 2.1 µg/mL, $P = 0.02$). This data also suggests that a reduced dose of maintenance immunomodulator may provide similar benefits as full dose maintenance CT.

IS CT SAFE?

CT and lymphoma

Though most of the additional risk associated with CT relates to an increased risk of infections, particularly

opportunistic infections with Candida and Herpes Zoster^[30] risk of lymphoma casts a long shadow over any discussion of CT. Since CT has typically meant thiopurines with biologic, it is first important to acknowledge that the vast majority of evidence points to a 4 to 5 fold increased risk of lymphoma associated with thiopurine use. This figure has been observed both in a meta-analysis of referral center IBD patients, as well as in the recent CESAME population study from France, which noted that this risk was primarily associated with active thiopurine use^[31,32]. The case for an increased risk of lymphoma with biologic monotherapy is far weaker, particularly for those with IBD^[33]. Most evidence supporting this increased risk is drawn from the larger rheumatoid arthritis population, for which the disease itself is known to carry an increased risk^[34].

In the absence of large population data on lymphoma risk with CT, investigators have employed mathematical modeling incorporating the observed increased risk with thiopurines to predict the risk/benefit of lymphoma with CT. Scott *et al.*^[35] in a recent Markov model analyzed the risk/benefit of IFX monotherapy vs CT at a variety of patient ages, utilizing quality of adjusted life years (QALY) as their primary outcome measure. The analysis accounted for the benefits of CT including increased response and remission rates, decreased surgery and less CD related death, balanced against the risk of death related to lymphoma and infections. They concluded that CT increased QALY for all patients, with that benefit decreasing as the patients aged. A patient 55 years or younger could expect to benefit from CT for at least 7 years. Even for those over 75 years, with the highest background risk of lymphoma, they estimated that it would take almost 5 years for QALY to suffer by continued use of CT. Another recent analysis by Siegel *et al.*^[36] utilized a Monte Carlo Simulation to predict the effects of one year of IFX monotherapy vs CT. in a theoretical population of 100000 thirty-five-year-old modeled on the SONIC trial. Here again the authors predicted that CT would result in an increased numbers of lymphomas for CT vs IFX monotherapy, 60 vs 40 cases respectively. However, since most infections observed in CD are related to the underlying disease activity rather than opportunistic infections, they also predicted that the more effective treatment of CD with CT would result in far fewer serious infections with CT vs IFX monotherapy, 3892 vs 4884, ultimately resulting in fewer deaths (399 vs 446). The authors concluded that the benefits of CT would continue to outweigh the risks unless serious infections occurred in over 20% of CT patients—a rate 5 fold greater than predicted, or if lymphoma occurred in over 3.9% of CT patients—a rate 65 fold higher than predicted.

No review, however, of CT can be complete without addressing the rare, but frightening complication of hepatosplenic T-cell lymphoma (HSTL), an aggressive and almost uniformly fatal disease that has been described

among IBD patients using CT. A recent systematic review of the literature by Kotlyar *et al.*^[37] documented 36 IBD patients who developed HSTCL. Of these, 20 received CT with a thiopurine and a TNF- α inhibitor, and 16 had thiopurine monotherapy. There were no cases reported of HSTCL with TNF- α inhibitor monotherapy. Only 2 (6.5%) were female, and the median age was 22.5 years. Notably only one patient, in the CT group, had a history of less than 2 years of thiopurine use. Overall, the authors concluded that the risk of HSTCL was highest for young men on CT, estimated at 1:3534.

Utilization of CT

Just as the literature addressing CT provides a variety of outcomes depending upon the population analyzed and the question being asked, so too does the real world data on the utilization of CT. In a recent large prospective survey study of seven high volume tertiary referral IBD practices, 1659 patients with CD, 946 with UC, and 60 indeterminate colitis, a wide variation of usage of CT was noted, particularly among those with CD^[38]. While initially only including those with an IBD diagnosis of less than 4 years, the authors ultimately included patients with all disease durations in their cohort. For those with CD, the lowest site utilization rate of CT was 8%, vs 32% at the site with the highest frequency, adjusted OR (95%CI) 3.15 (1.79-5.56). The authors report that the results observed were similar when excluding the site with the lowest frequency from each parameter of analysis.

Among the entire CD cohort, slightly more than half of anti-TNF use was as part of CT, with 47% overall on anti-TNF and 21% on CT. For those with UC, the range of usage of CT was 6% to 13%, OR 1.14 (0.48-2.78). Among the entire UC cohort, less than a third of anti-TNF use was part of CT, with 23% overall on anti-TNF and 9% on CT. It should be noted that the authors did not provide a breakdown of the type of biologic therapy used, so we have no way of knowing if the proportion of CT usage was higher among IFX patients, where the evidence to support CT is significantly stronger. Additionally, the results do not specify rates of CT usage for induction vs maintenance, where we have also seen differing degrees of supporting data.

A recent population wide study from France^[39] prospectively followed all IBD patients affiliated to the French national health insurance, tracking treatment and outcomes over the years 2009-2014. During that time there were 69725 new incident patients with IBD. CT was defined as the concomitant initiation of anti-TNF's and thiopurines in a period of 30 d. Among these newly diagnosed CD patients, the 5-year cumulative probability of CT and anti-TNF monotherapy was 18.3% and 33.8% respectively. For UC, the 5-year cumulative probability of CT and anti-TNF monotherapy was 7.4% and 12.9% respectively, *i.e.*, CT accounted for just slightly more than half of anti-TNF use. The authors report that CT was more frequent with IFX after one

year than with ADA for both CD and UC patients (4.2% vs 3.1% and 1.7% vs 0.6%) respectively. Given that this data arises from a large/general population, it is not surprising to see lower overall rates of biologic use and CT use than in the population from the IBD referral centers. It is noteworthy however that the proportion of CT use among those using anti-TNF is fairly similar.

In a retrospective review of community trends of biologic use from the US, we analyzed referrals to our institution's infusion center which provided IFX infusion services to both the full time teaching faculty, as well as to private practice gastroenterologists^[40]. Overall 247 new IFX referrals (154 CD, 93 UC) started on treatment from 2002 to 2014. Only 23.3% of patients received CT at the time of their first infusion (24% CD, 20.4% UC). These results were similar when analyzing the subgroup of 127 patients receiving IFX as part of a standard 0, 2, 6 wk induction regimen. Again, only 26% of CD and 28% of UC patients were on CT during their first induction IFX infusion. Notably, there was no trend observed of increasing use of CT over the years, despite the accumulating evidence of its benefit.

WHAT DO THE EXPERTS SAY?

Guideline recommendations

Finally, taking into account the available evidence, major GI professional societies have provided their consensus guidelines regarding CT use in the management of IBD. As with any guideline, it is important to note not only the type of recommendation provided, but also the grading of the recommendation based on the quality of supporting evidence and the year in which the guideline appeared (Table 2).

In 2009 the Practice Parameters Committee of the American College of Gastroenterology (ACG) recommended IFX monotherapy or IFX combined with AZA as more effective than AZA in the treatment of patients with moderate to severe CD failing first-line therapy with mesalamine and/or corticosteroid who were naïve to IMM and biologic^[41]. Additional ACG guidelines the following year were unable to support the same recommendation for UC^[42]. The 2011 guidelines from the World Congress of Gastroenterology with the European Crohn's and Colitis Organization concluded that CT of IFX and AZA was superior to induction of remission and mucosal healing over a 1 year time period. The authors further stated that it was uncertain if this was the best strategy beyond one year of treatment, and that it was unknown if this was true for other biologic/IMM combinations^[43]. In 2013 the American Gastroenterological Association (AGA) published its guidelines on the use of thiopurines, MTX and anti-TNF- α drugs for the treatment of CD. The authors suggested using anti-TNF- α in combination with thiopurines over anti-TNF- α monotherapy to induce remission in cases of moderately severe CD (Weak Recommendation, moderate quality evidence), again showing the strong impact of SONIC on clinical thought.

Table 2 Summary: Major society guidelines addressing combination therapy

	CD	UC
American College of Gastroenterology (2009 CD, 2010 UC)	IFX or IFX and AZA superior to AZA	Unknown efficacy of CT
European Crohn's and Colitis Organization and World Congress of Gastroenterology (2011)	IFX and AZA superior to monotherapy (in treatment naïve)	Unknown efficacy of CT
American Gastroenterological Association (CD guidelines (2013)	Anti-TNF- α and AZA superior to monotherapy	
American Gastroenterological Association Clinical Care Pathways (2014 CD, 2015 UC)	Consider IMM with anti-TNF- α or 2 nd /3 rd line biologic	Consider IMM with all anti-TNF- α or VDZ use
Hong Kong IBD Society (2013)	Anti-TNF- α and AZA superior to monotherapy	CT not addressed
Indian Society of Gastroenterology (UC consensus)		CT not addressed
Asian Pacific Association of Gastroenterology (UC consensus)		CT not addressed
Japanese Society of Gastroenterology (CD guidelines)	CT Not addressed	

IFX: Infliximab; AZA: Azathioprine; IMM: Immunomodulator (includes AZA, 6-mercaptopurine, Methotrexate); VDZ: Vedolizumab; CT: Combination therapy; UC: Ulcerative colitis; CD: Crohn's disease.

The authors go on to acknowledge the uncertain benefits of CT in cases of prior IMM failure, CT with other anti-TNF- α drugs, as well as CT using MTX^[44].

More recently in 2015, a panel of IBD experts in association with the AGA published pathways of care to aid clinical decision making. In the UC care pathway, at all steps where treatment with anti-TNF or VDZ is indicated, the authors recommend consideration of the addition of either a thiopurine specifically, or IMM generally. The authors support the use of MTX as an alternate IMM to thiopurine^[45]. A similar AGA pathway for CD in 2014, the "Crohn's Disease Evaluation and Treatment: Clinical Decision Tool", also supports CT as an option for all patients receiving anti-TNF therapy. The pathway emphasizes that the addition of an IMM offers improved efficacy and should be considered in moderate to high risk patients receiving their 2nd or 3rd biologic^[46]. Neither pathway addresses how long CT should be utilized.

Consensus statements from Asian medical societies do not emphasize CT as much as their western counterparts. The Japanese, Indian and Asia-Pacific societies for gastroenterology do not address the potential therapeutic benefits of CT in their respective IBD guidelines nor do they cite the SONIC trial^[47-49]. In contrast, in a guideline issued by the Hong Kong IBD society a class A recommendation states that CT is the most effective way to induce remission in moderate to severe CD^[50]. The guideline goes on to recommend an individualized weighing of risks and benefits of CT for each patient. It is likely that further patient experience and review may lead to increased attention into the role of CT in non-European/North American expert reviews and guidelines. As for now, those studies showing the greatest benefit to CT, specifically SONIC and UC SUCCESS, almost exclusively studied European/North American populations. Patient characteristics with regard to race are not addressed in UC SUCCESS, but the population in SONIC is specifically identified as over 90% "white race". This raises the possibility that our strongest data on CT may not be generalizable to those in other regions.

CONCLUSION

While newer IBD therapies continue to be developed and tested in clinical trials, for the vast majority of patients and their physicians the emphasis remains on the best possible use of currently approved therapies to control disease activity. With the available choices expanding, the definition of CT may eventually broaden to include combinations of multiple biologics, but for now CT is defined by IMM use along with biologic.

The available evidence does suggest a benefit to CT, but this evidence is clearer for the use of IMM with IFX specifically, and especially in those without prior IMM or IFX use. This benefit appears to apply to both patients with CD and UC. The level of evidence for the benefit of IMM with other biologics is not a clear, nor is it certain that this combination if applied sequentially as step up therapy offers the same improved response as starting the two together. The main mechanism of benefit of IMM in the setting of biologic appears to be through the suppression of antibody formation to the biologic treatment. With less inherent immunogenicity to newer biologics, it is perhaps not surprising that the benefit of adding IMM is harder to define with other combinations. To better answer the question would require dedicated prospective studies of each CT as was the case with IFX, which are unlikely to be performed. With regards to the safety of CT, there is valid concern regarding the increased risk of opportunistic infections, though perhaps outweighed by the benefits of better disease control. As for the risks of malignancy with CT, the numbers again suggest that any increased risk is far outweighed by the potential benefits, at least over a "short term" of several years. Even though patients and physicians may understand that this risk is minor in comparison to potential benefits, the observed rates of CT use suggest that fear of this complication is still a strong motivating force away from CT. Overall, GI professional societies have advocated the use of CT when the anti-TNF is IFX, but not explicitly for other combinations. As we have seen, there is evidence to support other forms of CT, but both the physician and

the patient need to be aware of the strength of this evidence, be certain that the risks are understood, and the goals of therapy are achieved if other forms of CT are used.

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