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MINIREVIEWS

Monitoring inflammatory bowel disease during pregnancy: Current literature and future challenges

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Abstract

Inflammatory bowel disease has a high prevalence in women of childbearing age and can have a significant impact on pregnancy, from conceiving to carrying the pregnancy. Active disease during pregnancy is known to have negative effects on pregnancy outcomes; therefore, careful monitoring during this period is an important but challenging aspect of care and is crucial as it affects important management decisions. Recent data seems to suggest that endoscopy is a relatively safe procedure during all trimesters of pregnancy. Serum biomarkers such as C-reactive protein and fecal calprotectin are helpful non-invasive markers, but have shown conflicting results for correlation with disease activity in some initial studies. Further work is necessary to establish standard of care monitoring during pregnancy.

Key words: Inflammatory bowel disease; Crohn's disease; Ulcerative colitis; Pregnancy; Fecal calprotectin

Core tip: This review article fills in the gap in the paucity of literature specifically focusing on the monitoring of inflammatory bowel disease during pregnancy. New and emerging literature on the use of non-invasive biomarkers such as fecal calprotectin is discussed, but classic monitoring techniques such as endoscopy and radiographic imaging are also evaluated within the scope of pregnancy.

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INTRODUCTION

Inflammatory bowel disease (IBD) has a high prevalence in young adults and affects many women of childbearing age. Having IBD has many effects on women who are contemplating having children, ranging from conceiving to carrying the pregnancy, concerns about passing the disease onto children, fetal outcomes, and effects of pregnancy on the disease process itself.

Many women with IBD have poor knowledge about their ability to bear children or the effect that IBD will have on their pregnancy, with a tendency to overestimate the effects of IBD on fertility[1,2]. This has led to the phenomenon of voluntary childlessness, which affects up to 18% of women with IBD as compared to 6% in the general population. Women with IBD have misconceptions about a decreased rate of fertility, fear of passing on the condition onto offspring, and concerns over the effects of the disease on pregnancy outcomes[3]. In fact, multiple studies have shown that overall rates of fertility between the general population and women with IBD in clinical remission are comparable[4]. However, this trend excludes women who had pelvic surgical procedures, and in particular ileal pouch-anal anastomosis (IPAA) procedures for ulcerative colitis (UC), which have a relative risk of infertility of 3.91 as compared to the general population[5].

Most women who have a quiescent disease before pregnancy have normal pregnancy outcomes. However, active disease upon conception or during pregnancy has been shown to increase adverse outcomes such as low birth weight, preterm birth, and fetal loss[6]. In a recent retrospective study following 406 pregnant Indian IBD patients, pregnancies after disease onset were associated with higher number of adverse fetal outcomes and cesarean sections compared to before disease onset[7] . Similarly, a study from Denmark sought to evaluate birth outcomes with a cohort of women on anti-TNF therapy during pregnancy. Disease activity was associated with adjusted odds ratio of 2.05 for low birth weight and 2.64 for preterm birth, with the ratio for preterm birth increasing to 3.60 for patients with clinical moderate to severe disease activity[8]. In addition to disease activity, inadequate gestational weight gain in the IBD population has been shown to have a 2-fold increase in risk of low gestational weight compared with non-IBD patients with inadequate gestational weight gain in a Norwegian cohort study[9]. This finding has been reproduced in a prospective American cohort study for Crohn's disease, but not for ulcerative colitis[10].

Given the adverse effects of active IBD and associated effects on pregnancy outcomes, careful monitoring during this period is an important but challenging aspect of care. Ideally, disease activity should be objectively assessed prior to pregnancy as a part of conception planning. Endoscopy showing histological mucosal healing is an important predictor of clinical outcomes. This is particularly important since the correlation of clinical symptoms and histologic disease can be weak, especially in Crohn's disease. Therefore, having an objective assessment of disease activity during pregnancy is crucial as this directly affects important management decisions, such as medication changes, in order to keep the pregnant patient in remission through the prenatal course.

To this end, the purpose of our review paper is to discuss the current landscape of research on the safety, efficacy and utility of various methods of monitoring IBD activity during pregnancy (Table 1).

LOWER ENDOSCOPY

Endoscopy is the most definitive method of monitoring and evaluating disease activity. However, endoscopic procedures have been theorized to pose a threat to the fetus through the possibility of intra-procedural maternal hypoxia and hypotension, which can cause fetal hypoxia and potential demise[11]. Additionally, sedating medications, prolonged procedure times, and maternal positioning during endoscopy can potentially have significant effects on maternal circulation. Here, we have categorized lower endoscopy into colonoscopy and flexible sigmoidoscopy due to their separate risks and benefits.

Colonoscopy

Colonoscopy may be indicated in a pregnancy state, to evaluate the extent of ulcerative colitis that may determine the need for additional immunosuppressive agents or in small bowel Crohn's disease. A systematic review of lower gastrointestinal endoscopies performed in all three trimesters of pregnancy evaluated any adverse pregnancy outcomes that were noted to be in a temporal or etiological relation with the procedure[12]. This review comprised of 100 endoscopies, with a total of six reported adverse events that were related to the procedure. The authors concluded that colonoscopy is not only a low-risk procedure during pregnancy, but also that there were no significant changes in adverse events between the three trimesters. Furthermore, a prospective study done by de Lima *et al*[13] compared 42 pregnant IBD patients who underwent lower endoscopy (13 colonoscopies and 33 sigmoidoscopies) with case-matched pregnant IBD patients who did not undergo endoscopy. The adverse events were two spontaneous abortions, which were likely related to the endoscopic procedure; however, this was not a statistically significant difference when compared to the control group. There remains a gap of literature on safety of endoscopy in pregnant patients; but early studies appear

Table 1 Overview of various disease monitoring modalities and their pros/cons in pregnant inflammatory bowel disease patients

Monitoring modality	Pros	Cons
Lower endoscopy		
Colonoscopy	Gold standard of disease monitoring	Limited studies
	Early studies show no difference in adverse events between pregnant IBD patients who underwent colonoscopy and who did not undergo colonoscopy	Provider/patient hesitancy due to procedural and anesthetic concerns
Flexible sigmoidoscopy	Can be performed without sedation	Limited studies
	No case reports of any procedure-related complications	
Radiologic studies		
Ultrasound	Safest form of radiologic imaging	Sensitivity in pregnancy unknown
	Contrast-enhanced ultrasound shown to have good results in IBD	
Magnetic resonance imaging	No use of damaging ionizing radiation	Currently no well-controlled studies of the teratogenic effects of gadolinium contrast in pregnant women have been performed and the fetal risk is unknown
	Can detect luminal and extraluminal abnormalities	
	Long-term safety after exposure to MRI trimester of pregnancy showed no increased risk of harm to the fetus or in early childhood	
Biomarkers		
Albumin	Low albumin shown to be predictor of poor outcomes in IBD	Limited utility in pregnancy due to pregnancy-induced hemodilution resulting in lower albumin values
ESR	Generally a good marker of inflammation and reflects disease activity	Limited utility in pregnancy due to physiologic increase in ESR (2-3 x upper limit of normal)
CRP	Levels are only slightly raised in normal pregnancy and are still under the normal limits	May not accurately reflect disease activity in second and third trimester
	CRP higher in clinically active pregnant IBD patients at preconception and first trimester compared to clinically inactive pregnant IBD patients	Limited studies in pregnant IBD population
FCP	Measure of GI mucosal inflammatory activity detected prior to signs of systemic inflammation	Conflicting evidence for utility of FCP in IBD during pregnancy
	Multiple studies showing correlation between FCP levels and non-invasive disease activity scores in CD and UC	Limited studies with actual endoscopic data to evaluate clinical activity

IBD: Inflammatory bowel disease; CD: Crohn's disease; MRI: Magnetic resonance imaging; UC: Ulcerative colitis; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; FCP: Fecal calprotectin.

to suggest that endoscopy when necessary is shown to be a low-risk and safe procedure in any trimester.

Flexible sigmoidoscopy

Unsedated flexible sigmoidoscopy is an alternative approach to evaluate the rectum and left colon, thereby avoiding the risks of anesthesia. It plays an important role in determining the severity of mucosal disease in patients with refractory colitis and to evaluate concomitant infections. Based on reviews of retrospective studies and case series, it seems that performing an unsedated flexible sigmoidoscopy in a pregnant woman is quite safe[14]. None of the studies or case reports indicated any procedure-related complications to either the mother or fetus. In addition, the timing of the procedure did not seem to matter given that sigmoidoscopies were safely performed during all three trimesters.

Safety of anesthetics and colon cleansing agents

According to a joint statement from the American Society of Anesthesiologists and the American College of Obstetrics and Gynecology, none of the currently used anesthetic agents, when used in standard concentrations at any gestational age, have been shown to have any teratogenic effect in humans. There is currently an insufficient amount of data on the safety of colon cleansing agents in the pregnant population. Polyethylene glycol electrolyte isotonic cathartic solutions have not been studied in pregnancy, and are classified as pregnancy category C. Sodium phosphate preparations (category C) may cause fluid and electrolyte abnormalities and should be used with caution. Tap water enemas may be sufficient for flexible sigmoidoscopy in a pregnant patient.

RADIOLOGIC STUDIES

In general, imaging with non-ionizing radiation is preferred over modalities with ionizing radiation in pregnancy. In utero radiation exposure to a developing fetus includes intrauterine growth restriction, microsomia, mental retardation, organ malformation, and childhood cancers. These risks are dependent on the gestational age at the time of exposure and the absorbed radiation dose levels. Traditionally, abdominal plain films and computed tomography (CT) scans are avoided due to their high levels of ionizing radiation. However, consensus statements from the American College of Obstetricians and Gynecologists, American College of Radiology, and International Commission on Radiological Protection have

all concluded that radiation doses less than 50 mGy are shown to have negligible risk to the fetus. Therefore, most properly done diagnostic procedures do not present a measurably increased risk to the fetus and should be performed in cases of diagnostic necessity[15].

Ultrasound

Ultrasound is the safest form of radiologic imaging in pregnancy; it can be used to assess abscess formation along with the location and length of the affected segment of bowel. More recently, contrast enhanced ultrasound has been studied in inflammatory bowel disease with good results. It is an emerging technique to evaluate disease activity, the differentiation between small bowel stricture due to inflammation or mural fibrosis, and for the assessment of response to specific therapies[16]. Its sensitivity in pregnancy needs to be investigated.

Magnetic resonance imaging

The principal advantage of MRI over ultrasonography and CT scan is the ability to image deep soft tissue structures in a manner that is less operator dependent and does not use ionizing radiation. As per the guidelines from the American College of Obstetrics and Gynecologists, there are no precautions or contraindications for MRI specific to the pregnant woman[17]. It is being used now in routine obstetric care. MRI has been used to diagnose terminal ileal CD during pregnancy[18].

Use of gadolinium based contrasts agents (GBCA) in MRI during pregnancy: To date, there have been no known adverse effects to human fetuses reported when clinically recommended dosages of GBCA have been given to pregnant women. A single prospective cohort study of 26 women exposed to gadolinium chelates during the first trimester of pregnancy showed no evidence of teratogenesis or mutagenesis in their progeny[19].

There are no known cases of nephrogenic systemic fibrosis associated to the use of GBCAs in pregnant patients. However, gadolinium chelates may accumulate in the amniotic fluid which has the potential for the dissociation of the toxic free gadolinium ion. This is swallowed by the fetus and enters the fetal circulation possibly conferring risk to the fetus. Currently no well-controlled studies of the teratogenic effects of these media in pregnant women have been performed and the fetal risk is unknown.

Both the American College of Radiology and the American College of Obstetrics and Gynecology conclude that gadolinium contrast with MRI should be used with caution; it may be used as a contrast agent in a pregnant woman only if it significantly improves diagnostic performance and is expected to improve fetal or maternal outcome, outweighing the possible but unknown risk of fetal exposure to free gadolinium ions. Lowest possible dose should be used to achieve diagnostic results. Contrast enhanced MRI may be useful to evaluate for abscess or fistulas.

Abdominal X ray

Traditionally X-rays are avoided in pregnancy due to fear of fetal risks from ionizing radiation. The maximal risk attributed to a 1-rad exposure, approximately 0.003%, is thousands of times smaller than the spontaneous risks of malformations, abortion, or genetic disease[20]. One abdominal X ray results in fetal exposure to radiation to 0.1 rad[21]. Therefore, in diagnosis of toxic megacolon, the risks to the fetus of an abdominal X-ray (1 in 30000) compared to the condition being poorly managed (60% fetal mortality rate) indicate that the patient should be imaged as would a non-pregnant patient. In conclusion, in cases of emergent situation or when other modalities are not available, an abdominal X ray would prove to be an important test.

BIOMARKERS

Serum and fecal biomarkers play an important role in non-invasive monitoring of the disease activity in IBD patients.

Albumin

Albumin is routinely used to assess overall disease activity state and its impact on the body. Patients with active disease may lose protein/albumin from the inflamed mucosa. Low albumin has shown to be a predictor of poor outcomes in inflammatory bowel disease. However, there are normal physiological changes in some laboratory parameters in pregnancy that should not be attributed to disease activity. Pregnancy causes hemodilution, resulting in fall in albumin by about 1 mg/dL by the end of 1st trimester. Hence, albumin of 2 mg/L during the third trimester in a patient with baseline albumin of 3 mg/L may not reflect worsening disease activity.

Erythrocyte sedimentation rate

Erythrocyte sedimentation rate (ESR) is a marker of inflammation and reflects disease activity. Pregnancy causes a physiological increase in ESR from increase fibrinogen levels. The increase is about 2 to 3 times upper limit of normal by the first trimester. Hence an elevated ESR of 40 mm/h may reflect normal health in a third trimester pregnancy female. Thus, ESR values merit careful interpretation in evaluation of the disease activity in pregnant state.

C-reactive protein

C-reactive protein (CRP) is another marker of inflammation and reflects disease activity. Its levels are usually unaltered or possibly only slightly raised in normal pregnancy compared to a non-pregnant state, however the levels are still under the normal limits[22]. In a prospective study, Bal *et al*[23] evaluated the association of elevated CRP with clinical disease activity during pregnancy among women with IBD. The median CRP was numerically higher in women with clinically active disease

compared to those with clinically inactive disease at preconception (6.95 *vs* 2.80 mg/L, *P* = 0.559) and first trimester (24.75 *vs* 6.00 mg/L, *P* = 1.000), respectively. However, surprisingly the median CRP was lower in women with clinically active disease compared to those with clinically inactive disease at second trimester (8.85 *vs* 12.40 mg/L, *P* = 0.5923), and third trimester (5.45 *vs* 11.90 mg/L, *P* = 0.592), respectively. Their study shows that CRP remains a potential tool for assessing IBD disease activity in the early trimesters of pregnancy; however, it may not accurately reflect the disease activity in later trimesters. It is possible that in their study, concomitant minor infections in later trimesters might have increased CRP in healthy pregnancy patients with silent IBD. More research is needed to clearly identify the response of CRP in pregnancy state with IBD. At present, most physicians consider CRP as a useful tool in monitoring disease activity during pregnancy.

Fecal calprotectin

Among various different biological markers, fecal calprotectin (FCP) has emerged as the most superior marker to diagnose or monitor inflammatory bowel disease. Calprotectin is a heterodimer of two S100 proteins (S100A8 and S100A9), which are a family of calcium-binding proteins that are linked to innate immune functions through their expression in macrophages, monocytes, phagocytes, and granulocytes[24]. These proteins are released during periods of inflammation from gastrointestinal epithelial cells. Therefore, fecal calprotectin can be used as a measure of gastrointestinal mucosal inflammatory activity that is detected prior to signs of systemic inflammation, such as elevations in CRP or ESR[25].

Elevation of fecal calprotectin concentrations is shown to predict disease relapse in the next 12 mo in IBD, although this association is stronger in UC than in CD[26,27]. A recent prospective study showed that fecal calprotectin level below 50 ug/g is predictive of histologic remission in quiescent UC[28]. While there are a multitude of studies that have successfully shown the use of fecal calprotectin in monitoring IBD, its utility in pregnancy has not been fully elucidated yet.

Does pregnancy affect FCP levels?

To evaluate the utility of FCP as marker for active IBD disease during pregnancy, the effects of normal pregnancy on FCP need to be established. A recent prospective study involving 135 patients compared the concentrations of FCP in healthy non-pregnant and pregnant women and in patients with inflammatory bowel disease[29]. Stool samples were taken during each trimester, and there were no significant difference ($P < 0.092$) between FCP concentrations during each trimester. The mean FCP concentration between pregnant and non-pregnant health women showed no statistically significant difference, suggesting that pregnancy itself does not cause an elevation in FCP markers. While the FCP concentrations between patients with IBD and healthy controls were statistically different, no pregnant patients with IBD were included in this study; therefore, it is difficult to draw a conclusion on the combined influence of IBD and pregnancy on FCP levels.

Evidence for utility of FCP in IBD during pregnancy

To date, there have been a few recent studies assessing the utility of FCP in IBD during pregnancy. Initial results have been conflicting, with some showing good correlation between FCP levels and non-invasive disease activity score in CD and UC, while others showed that it is a poor predictor of IBD relapse during pregnancy. Huang *et al* enrolled seventeen pregnant IBD patients in a prospective study, in which fecal calprotectin was monitored at pre-conception and at each trimester along with modified Harvey Bradshaw Index (mHBI) for Crohn's disease and partial Mayo score for ulcerative colitis patients. The median FCP values for women with clinically active disease (as measured by mHBI $\geqslant$ 5 and partial Mayo score $\geqslant$ 2) were numerically higher than women with clinically inactive disease, but did not reach statistical significance at all-time points[30].

A prospective study by Shitrit *et al*[31] enrolled 33 pregnant women with IBD, and compared fecal calprotectin levels with partial Mayo and Harvey Bradshaw index scores, along with serum ESR, CRP, and albumin levels. No correlation was noted between FCP and clinical scores, albumin, and inflammatory serum markers, although a subsequent study by the same group using 80 samples from 57 pregnant patients did show a positive correlation between stool calprotectin and Crohn's disease activity index and partial Mayo scores (r = 0.60 and r = 0.77, respectively)[32]. FCP showed a high sensitivity and specificity in the occurrence of disease activity (as determined by the clinician) at 81.8% and 80.7% in a prospective study by Kanis *et al*[33]; however, there was no correlation between an elevated FCP and subsequent disease relapse. Ultimately, there is no clear consensus at this time with these small prospective studies showing conflicting results. FCP should be used in conjunction with clinical judgment, and appears to be an unreliable predictor of IBD relapse in the setting of pregnancy.

DISCUSSION

Monitoring IBD during pregnancy continues to be an important challenge for clinicians. Recent data seems to suggest that endoscopy, both colonoscopy and flexible sigmoidoscopy, is a relatively safe procedure during all trimesters of pregnancy. MRI and ultrasound remain the safest methods of imaging during pregnancy. Serum biomarkers such as CRP and fecal calprotectin are helpful non-invasive markers, but have shown conflicting results for correlation with disease activity in some initial studies. Further investigation into these non-invasive biomarkers is necessary. Careful monitoring during this period remains a crucial component for important management

decisions to keep the patient in remission throughout the prenatal course.

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ORIGINAL ARTICLE

Retrospective Study

Declining use of combination infliximab and immunomodulator for inflammatory bowel disease in the community setting

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Abstract

AIM

To describe trends of combination therapy (CT) of infliximab (IFX) and immunomodulator (IMM) for inflammatory bowel disease (IBD) in the community setting.

METHODS

A retrospective study was conducted of all IBD patients referred for IFX infusion to our community infusion center between 04/01/01 and 12/31/14. CT was defined as use of IFX with either azathioprine, 6-mercaptopurine, or methotrexate. We analyzed trends of CT usage overall, for Crohn's disease (CD) and ulcerative colitis (UC), and for the subgroups of induction patients. We also analyzed the trends of CT use in these groups over the study period, and compared the rates of CT use prior to and after publication of the landmark SONIC trial.

RESULTS

Of 258 IBD patients identified during the 12 year study period, 60 (23.3%) received CT, including 35 of 133 (26.3%) induction patients. Based on the Cochran-Armitage trend test, we observed decreasing CT use for IBD patients overall ($P < 0.0001$) and IBD induction patients, ($P = 0.0024$). Of 154 CD patients, 37 (24.68%) had CT, including 20 of 77 (26%) induction patients.

The Cochran Armitage test showed a trend towards decreasing CT use for CD overall ($P < 0.0001$) and CD induction, ($P = 0.0024$). Overall, 43.8% of CD patients received CT pre-SONIC *vs* 7.4% post-SONIC ($P < 0.0001$). For CD induction, 40.0% received CT pre-SONIC *vs* 10.8% post-SONIC ($P = 0.0035$). Among the 93 patients with UC, 19 (20.4%) received CT. Of 50 induction patients, 14 (28.0%) received CT. The trend test of the 49 patients with a known year of induction again failed to demonstrate any significant trends in the use of CT ($P = 0.6$).

CONCLUSION

We observed a trend away from CT use in IBD. A disconnect appears to exist between expert opinion and evidence favoring CT with IFX and IMM, and evolving community practice.

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

Core tip: In our 13 year experience at a community hospital infusion center, approximately 26% of inflammatory bowel disease patients receiving infliximab infusions received concomitant immunomodulator therapy. This is comparable to rates of combination therapy (CT) at major tertiary referral centers. However, there was a trend of decreased utilization of CT over the study period, even following the publication of SONIC. This suggests a need for further study to define the population with the most favorable risk-benefit ratio from CT, as well as the need for more direct guidelines from major societies.

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INTRODUCTION

Crohn's disease (CD) and ulcerative colitis (UC) together comprise most cases of inflammatory bowel disease (IBD). The prevalence of IBD in the United States appears to be increasing, and it is currently estimated at 1 in 300 individuals, or roughly 1.5 million members of the population[1]. For both CD and UC, treatment of moderate to severe disease often includes the use of corticosteroids for induction of clinical remission, with guidelines recommending transitioning patients off corticosteroids and using an immunomodulator (IM) such as 6-mercaptupurine (6-MP), azathioprine (AZA) for either CD or UC, or methotrexate (MTX) for CD, to maintain remission[2] For those failing to maintain steroid free clinical response or remission with IM, the addition or substitution of the newer biologic therapies comprise the next step in what is now commonly referred to as a "step up" approach to IBD therapy.

Infliximab (IFX) was introduced as the first biologic therapy targeting TNF-α. Initially approved in the United States for CD in 1997, approval for UC followed in 2005[3]. Though IFX has been followed by other TNF-α inhibitors, and newer biologics targeting alternate pathways, IFX is still among the most widely used biologic therapies[4]. IFX and the other biologics are increasingly viewed as an alternative to steroid and IM therapy as part of a "top down" therapeutic approach, which has been shown to reduce patients' steroid exposure as well as potentially improving overall clinical outcomes[5].

Early studies suggested a potential therapeutic benefit to combination therapy (CT) utilizing both IFX and IM, mainly through reduction of antibodies to IFX (ATI), reduced infusion reactions and higher IFX trough levels[6]. A major turning point was the SONIC study. While earlier work examined the role of IM combined with anti TNF-α mostly in those with IM exposure and failure prior to stepping up to IFX, SONIC focused on induction therapy among patients naïve to both biologic and IM with CD. Patients were randomized to receive either IFX, AZA or CT with both agents. CT was found to be superior to monotherapy with either IFX or AZA for the induction of steroid free clinical remission, without any increase in adverse events[7]. More recently the UC SUCCESS trial has demonstrated a similar benefit to combing AZA with IFX in those with UC[8].

Since the publication of SONIC, key thought leaders[9] and major society guidelines[10] have increasingly advocated for the use of CT, but it is unclear to what extent community practice has changed, balanced against reports of opportunistic infections[11], and cases of hepatosplenic T-cell lymphoma (HSTCL) with CT[12,13]. Currently, little is known regarding the adoption of CT in the community setting. Our main goal was to analyze the trends over time of CT usage for IBD overall, CD and UC. As a secondary goal we sought to examine whether the publication of the SONIC trial has had any impact on the proportion of CT use for CD in the community setting.

MATERIALS AND METHODS

The Northwell Health Center for Infusion Medicine, part of the Division of Rheumatology, provides IFX infusion services on behalf of both Northwell Health faculty and community gastroenterologists. Patients referred for IFX include both those beginning therapy at the center, as well as those switching their infusion therapy from another location. Center protocol requires that all physician referrals must include the completed standardized medical history form specifying IBD type, along with signed orders for IFX dose, schedule and pre-infusion medications. The standardized form includes a medication history section which specifically asks the

Table 1 Patient demographics *n* (%)

	IBD[1]	CD	UC
Total	258	154	93
Male	127 (49.2)	78 (50.6)	48 (51.6)
Mean age, yr	40.88 ± 16.67	39.59 ± 16.28	43.66 ± 17.04
IFX Pre-SONIC	111 (43.0)	73 (47.4)	30 (32.2)
6-MP/AZA use	56 (21.7)	35 (22.7)	18 (19.4)
MTX use	4 (1.6)	3 (1.9)	1 (1.1)

[1]The "IBD Total" group includes the "CD Total" and "UC Total" groups, as well as 11 patients with indeterminate colitis. IBD: Inflammatory bowel disease; CD: Crohn's disease; UC: Ulcerative colitis; IFX: Infliximab; 6-MP: 6-mercaptupurine; AZA: Azathioprine; MTX: Methotrexate.

referring physician to record either past or current use of AZA, 6-MP, MTX, without specifying dose, as well as other commonly used IBD medications. Following the initiation of IFX, updated versions of the standardized medical history are not performed.

We conducted a retrospective chart review of all patients receiving IFX infusions at the center from 01/01/2002 until 12/31/2014. Inclusion criteria required a diagnosis of CD, UC or indeterminate colitis (IC), receipt of at least 1 IFX infusion at the center, age of 18 years or greater, and availability of a completed standardized medical history form.

In addition to IBD type, patients were subcategorized as induction or maintenance patients based on the schedule of the infusions they received. Induction patients were those whose first infusion was part of a documented standard week 0, 2, and 6 induction regimen. All other patients were grouped in the maintenance cohort. CT for both induction and maintenance patients was defined by IM use at first IFX dose at the infusion center. Descriptive analysis was performed of the overall group including both induction and maintenance IBD patients, as well as for the subgroup limited to induction patients. Similar analyses were performed by CD and UC subgroups. For the secondary analysis comparing usage of CT therapy pre *vs* post SONIC, a patient was considered a pre-SONIC patient if they presented to the infusion center before April 2010.

The proportions of CT use in the induction and maintenance groups were calculated for all patients as well as for CD and UC separately. In secondary analyses we stratified patients based on years of age (< 35, 35-60, > 60), diagnosis (UC *vs* CD), gender and faculty status of the prescribing physician (faculty *vs* community) to investigate for any disparities in CT utilization between subgroups.

RESULTS

The infusion records of 293 IBD patients were reviewed. Of these, 10 were excluded due to incompleteness of the infusion record, and 25 were excluded due to a missing record of concurrent medications, leaving 258 for analysis. The patients were referred by 57 gastroenterologists (mean and median patients per gastroenterologist of 4.54 and 2 respectively). Patient demographics are detailed in Table 1. 154 (59.7%) had CD, 93 (36.1%) had UC. Eleven patients had IC, and these patients were included in the overall analysis but excluded from the disease-specific analyses. For two subjects, one each with CD and UC, infusion pre *vs* post April 2010 was confirmed without exact date of first dose. These patients were excluded from the analyses of trends in CT use over time.

All IBD patients

Among the total group of 258 patients with IBD, 60 (23.3%) received CT at the time of first IFX infusion at our center. The Cochran-Armitage trend test of the 256 patients with a known year of first infusion demonstrated a significant decrease in the use of CT for all IBD patients over the 13 year period, from 2002 to 2014, $P < 0.0001$ (see Figure 1A). The IBD induction group included 133 patients of whom 35 (26.3%) received CT. The trend test of the 131 subjects in the IBD induction group with a known year of induction again demonstrated a significant decreasing trend in the use of CT, $P = 0.0024$.

For the 258 total IBD group 111 (43.0%) had their induction or maintenance regimen start pre-SONIC compared with 147 (57.0%) post-SONIC. Due to evidence of effect modification (EM) of the patient's IBD diagnosis type on the relationship between induction time period (pre *vs* post-SONIC trial) and use of CT ($P = 0.01$), analyses comparing pre *vs* post-SONIC trial were stratified by disease type. Stratum-specific results for CD are reported below.

CD patients

Among the 154 patients with CD, 37 (24.0%) received CT at the time of first infusion. The Cochran-Armitage trend test of the 153 patients with a known year of first infusion demonstrated a significant decrease in the use of CT over the 13 year period, from 2002 to 2014, $P < 0.0001$ (see Figure 1B). The CD induction group included 77 patients of whom 20 (26.0%) received CT. The trend test of the 76 subjects with a known year of induction again demonstrated a significant decreasing trend in the use of CT, $P = 0.0024$. The proportion of all CD patients receiving CT was greater pre *vs* post-SONIC (43.8% *vs* 7.4%, respectively, $P < 0.0001$) as well as for the induction only group (40.0% *vs* 10.8%, respectively, $P = 0.0035$).

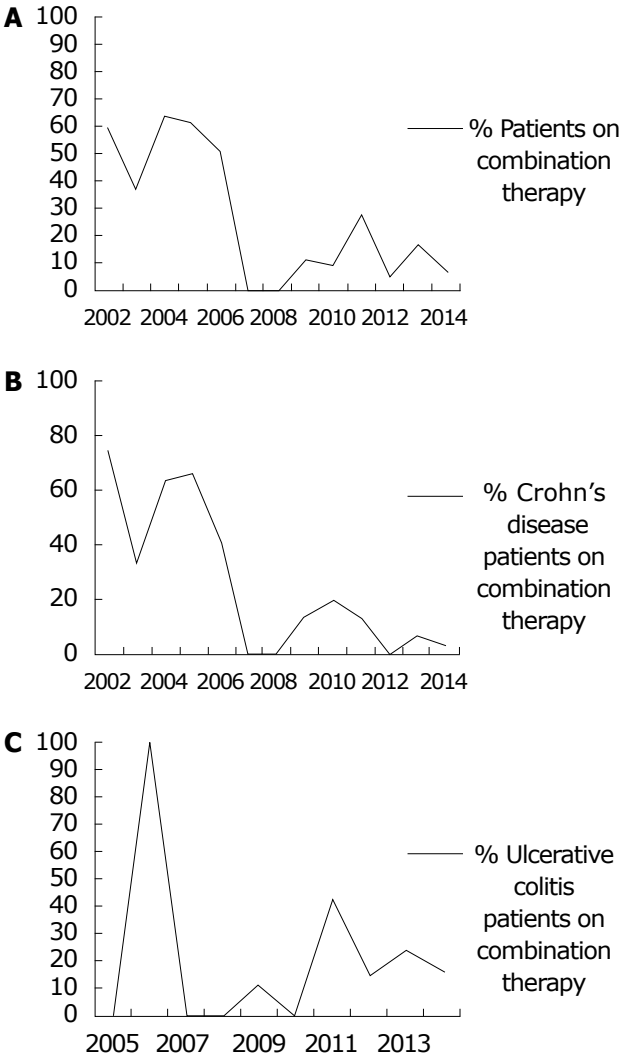

Figure 1 Percentage of inflammatory bowel disease (A), Crohn's disease (B), and ulcerative colitis (C) patients on combination therapy. Y axis: Percentage of infusion patients receiving combination therapy (0-100%); X axis: Year for which data is being reported (2002-2014). A: Percentage of inflammatory bowel disease patients receiving combination therapy over time; B: Percentage of Crohn's disease patients receiving combination therapy over time; C: Percentage of ulcerative colitis patients receiving combination therapy over time.

UC patients

Among the 93 patients with UC, 19 (20.4%) received CT at the time of first infusion. The Cochran-Armitage trend test of the 92 patients with a known year of first infusion did not demonstrate any significant trends in the use of CT over time, $P = 0.9$ (see Figure 1C). The UC induction group included 50 patients of whom 14 (28.0%) received CT. The trend test of the 49 patients with a known year of induction again failed to demonstrate any significant trends in the use of CT, $P = 0.6$.

There were no statistically significant differences in the proportions of CT use across the study period, among CD patients or UC patients, according to age group, gender, faculty status of the referring gastroenterologist, use of other agent or steroid use ($P > 0.05$ for all tests); results not shown.

DISCUSSION

Despite the positive effects offered by CT for CD in the SONIC population, and for UC by UC SUCCESS, it is unclear to what degree the use of CT has been adopted into clinical practice. A recent review from 7 high volume IBD referral centers, comprising 1659 patients with CD and 946 with UC, showed a wide range of adoption of CT. Among CD patients the use CT overall was 21%. There was a significant variation of usage across all centers ranging between 8% and 32%, with a 95%CI: 3.15 (1.79-5.56). Among UC patients the use of CT overall was 9%, with no significant variation of usage seen, ranging between 6% and 13%, CI 1.14 (0.48-2.78)[14].

Our findings offer a different perspective by which to view the question of CT usage, by providing 13 years of follow up data addressing the adoption of CT in the community setting. Examining a mixed cohort of 258 patients of whom 154 had CD, all receiving IFX, we found that CT was employed at the beginning of therapy in 23.3% of patients overall. Notably, we observed a significant trend of decreasing use of CT for IBD generally, in the CD cohort, as well as for the subgroup of CD patients receiving induction therapy.

Much like the findings from the referral center consortium, we suspect that these findings do not reflect a lack of awareness on the part of community gastroenterologists with the SONIC trial. More likely, it reflects a deeper understanding of what the SONIC results specifically support; the value of CT in a subset of treatment naïve patients. It is also likely that persistent concerns regarding adverse events with CT exert a strong pull away from CT even in cases where it may be appropriate. Though it is still uncertain if CT increases Non-Hodgkin's Lymphoma rates overall as compared to thiopurine monotherapy[15], it is now accepted that CT increases the risk of Hepatosplenic T Cell Lymphoma (HSTCL). While exceedingly rare, a recent systematic review found that 20 of 36 documented cases of HSTCL occurred in patients with a history of CT use[13]. Evidence of this association began to accumulate in 2007, which coincides with the temporary disappearance of CT use for our patients at that time[16]. Despite risk-benefit analyses favorable to CT accounting for lymphoma[17] - the preferences of physicians and/or patients have likely been impacted, particularly when faced with a black box warning addressing HSTCL found in the IFX packaging insert. Even if one is to accept the benefit of CT for induction, there is still uncertainty regarding the appropriate duration of IMM for maintenance[18]. This uncertainty may itself serve as a barrier to choosing CT over anti-TNF-α monotherapy.

The main weaknesses of our findings are mainly those which are inseparable from the retrospective study design. While our primary aim was simply observational, examining trends of CT usage over time, we specifically singled out the publication of SONIC as a time point for analysis and comparison. Given the

impact of SONIC on clinical thinking we believe this to be fair, but since we did not have data on disease duration or history of prior IMM use, it is unknown how our study population compared to those in SONIC. Especially for those patients infused during the earlier years of the analysis, it is very likely that many had a longer disease duration and past IMM use, unlike those patients in the SONIC cohort. A history of failure or intolerance to prior IMM could not be accounted for, and would tend to lower the use of CT for those beginning IFX. Also, as we defined induction by a specific schedule of IFX infusions at 0, 2, and 6 wk, we were unable to account for those receiving induction therapy with a non standard regimen, nor were we able to differentiate those receiving a first time induction regimen verses those who may have been receiving re-induction with IFX. Also, our inability to track medication changes other than IFX over time prevents us from observing the rate of CT usage at any time point during IFX therapy. I.e. we have no way of knowing how many of our patients beginning IFX mono-therapy may have "stepped up" to CT over time. Also, while we did a pre *vs* post SONIC analysis for IBD overall, this result of course included patients with UC, which the SONIC trial did not address. Finally, with 57 prescribing gastroenterologists identified it would appear that we have a fair overview of local community practice, but the community itself is narrowly defined and may not be reflective of prescribing trends in other regions.

In summary, we present the results of our analysis of community prescribing trends of CT with IFX and IMM for IBD overall, CD and UC. Over the 13 year period examined we observed a significant trend away from usage of CT with IFX and IMM for IBD overall and for CD patients specifically. It is likely that balanced against the benefit of CT observed in the SONIC cohort are the daily concerns of both patients and their physicians regarding HSTCL risk and the uncertainty of optimal duration of IMM use along with IFX. Further investigation regarding these issues, as well as a clearer demonstration of benefit in non treatment native patients, will be needed to support any future expanded use of CT.

ARTICLE HIGHLIGHTS

Background

The SONIC trial demonstrated the superiority of combination immunomodulator and biologic therapy for Crohn's disease (CD). Further studies evaluated the efficacy of combination therapy (CT) in ulcerative colitis. There are concerns regarding the safety of CT, specifically the risks of infection and malignancy.

Research frontiers

Little is known about the degree of utilization of CT in the community setting. It is also unknown whether the publication of the SONIC trial impacted rates of CT usage.

Innovations and breakthrough

This study demonstrates that the utilization of CT has generally trended down over the past decade. It also demonstrates that the publication of the SONIC study did not lead to an increase in the utilization of CT.

Applications

The decline in CT utilization highlights the need for further studies to define the ideal patient population for CT, as well as the need for more definitive guidelines from professional societies.

Terminology

Combination therapy refers to the concurrent use of an immunomodulator, such as azathioprine, with a biologic drug, such as infliximab, in the treatment of inflammatory bowel disease.

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CORRECTION

Erratum for factors associated with visceral fat accumulation in the general population in Okinawa, Japan (*World J Gastrointest Pharmacol Ther* 2016; 7: 261-267)

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Arakaki S, Maeshiro T, Hokama A, Fujita J. Erratum for Factors associated with visceral fat accumulation in the general population in Okinawa, Japan (*World J Gastrointest Pharmacol Ther* 2016; 7: 261-267). *World J Gastrointest Pharmacol Ther* 2018; 9(1): 14-15 Available from: URL: http://www.wjgnet.com/2150-5349/full/v9/i1/14.htm DOI: http://dx.doi.org/10.4292/wjgpt.v9.i1.14

CORRECTION

Correction to: Arakaki S, Maeshiro T, Hokama A, Hoshino K, Maruwaka S, Higashiarakawa M, Parrott G, Hirata T, Kinjo K, Fujita J. Factors associated with visceral fat accumulation in the general population in Okinawa, Japan. *World J Gastrointest Pharmacol Ther* 2016; 7(2): 261-267 PMID: 27158542 DOI: 10.4292/wjgpt.v7.i2.261[1].

Erratum 1

In the Results and Discussion, the description regarding the relationship between several parameters and VFA is lacking. In the Results (page 263) within the right side column, after "...(P < 0.05, Table 4).", "Although statistically not significant, a univariate analysis also indicated that FPG and HbA1c were slightly higher and HDL-C was slightly lower in males with low VFA group (Table 3)." should be added.

In the Discussion (page 266), after the first sentence (...related diseases[14].) in the left side column, "In the present univariate analysis, in contrast to most prior reports, although statistically not significant, HDL-C was slightly lower and FPG and HbA1c were slightly higher in males with low VFA group. The precise reasons for this discrepancy have not been revealed, however, the lack of data, including medication, lifestyle behaviors, smoking status, and chronic disease status, may have influenced the discrepancy. These characteristics have

been known as strong modifiers to these variables. Further work is needed to clarify this issue." should be added.

Erratum 2

In the Discussion, the description regarding the reason for gender differences in VFA by current drinking is lacking. In the Discussion (page 266), after "….such as beer *vs* liquor." in the left side column, "Other possible factors have been considered, including the differences among ethanol metabolizing enzyme genes, diet factors, smoking, and amount of exercise. These factors need to be further investigated." should be added.

Erratum 3

In the Results (page 263), in the last sentence of right side column, "significant lower" should have been "significantly higher".

REFERENCES

1 **Arakaki S**, Maeshiro T, Hokama A, Hoshino K, Maruwaka S, Higashiarakawa M, Parrott G, Hirata T, Kinjo K, Fujita J. Factors associated with visceral fat accumulation in the general population in Okinawa, Japan. *World J Gastrointest Pharmacol Ther* 2016; **7**: 261-267 [PMID: 27158542 DOI: 10.4292/wjgpt.v7.i2.261]

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