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REVIEW

Azathioprine and Infliximab: Monotherapy or Combination Therapy in the Treatment of Crohn's Disease

Bryan L. Love[1,3], Lisa S. Smith[2], Steedman A. Sarbah[3] and Fred C. Fowler[4]

[1]South Carolina College of Pharmacy, University of South Carolina, Columbia, SC, USA. [2]Wingate University School of Pharmacy, Wingate, NC, USA. [3]Gastroenterology/Hepatology Division, WJB Dorn Veterans Affairs Medical Center, Columbia, SC, USA. [4]Gastroenterology/Hepatology, Carolina Digestive Health Associates, Charlotte, NC, USA.
Corresponding author email: steedman.sarbah@va.gov

Abstract: Crohn's disease is a chronic inflammatory disease of the gastrointestinal tract often resulting in complications resulting in decreased quality of life. Several classes of medications are available to clinicians including mesalamine, budesonide, systemic corticosteroids, thiopurine derivatives, and monoclonal antibodies which target tumor necrosis factor (TNF). Guidelines generally recommend reserving TNF-antagonists for patients who have failed other first-line therapies; however, emerging data suggests there may be some benefit in combining TNF-antagonists, specifically infliximab, with azathioprine. The purpose of this review is to compare the benefits and risks of combination therapy, and identify patients who may benefit most from this approach.

Keywords: inflammatory bowel disease, crohn's disease, infliximab, azathioprine

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Introduction

Crohn's disease (CD) is a chronic inflammatory disorder of unknown etiology characterized by focal, asymmetric, transmural, and often granulomatous lesions predominantly affecting the gastrointestinal (GI) tract. Goals of therapy include inducing a clinical response, reducing the duration of active disease flares, maintaining clinical remission, and preventing surgery and other chronic complications. Disease location, severity, and complications are important considerations when determining the therapeutic approach. Traditionally, treatment algorithms for CD have employed a "step-up" approach to management; using less toxic medications for patients with mild-to-moderate disease and reserving more toxic agents for patients with moderate-to-severe disease activity.[1,2] The approval and success of tumor necrosis factor (TNF) alpha inhibitors in patients refractory to other medical treatments, has created debate as to whether earlier, more aggressive therapies or a "top-down" strategy should be advocated.

Arguments can be made both in support of and against the use of TNF-antagonists for CD as monotherapy or in combination with immunosuppressant medications, azathioprine (AZA) or 6-mercaptopurine (6MP). Evidence refuting combined biologic therapy with immunosuppressant medications include: differences in some clinical outcomes are less apparent with longer observations; combination therapy is associated with more drug related costs; monotherapy with either AZA/6MP or infliximab is potentially safer; and monotherapy is more widely accepted by patients and physicians. In contrast, combination therapy with immunosuppressant anti-TNF biologic agents has proven more effective in prospective randomized trials, demonstrates reduced rates of antibody formation, and results in higher serum concentrations of TNF-antagonists. The decision to use combination therapy is often a difficult decision for the gastroenterologist. The purpose of this review will be to examine the factors required to make an informed decision that is both evidence-based and offers rationale to individualize therapy for CD patients.

Mechanism, Metabolism, PK

Infliximab is a chimeric monoclonal IgG antibody to TNF.[3] TNF, existing in soluble and membrane bound forms, is a pro-inflammatory cytokine produced by macrophages and T lymphocytes.[4] TNF induces other pro-inflammatory cytokines, including IL-1 and IL–6.[5–7] These interleukins are responsible for further inflammation and induction of acute phase reactants such as C reactive protein (CRP). The intestines of patients with IBD have higher levels of TNF compared to healthy subjects, and TNF-induced inflammation occurs in other diseases including psoriasis, rheumatoid arthritis, and ankylosing spondylitis.[8,9]

The mechanism of action for TNF alpha antagonists to treat CD is not completely understood. While TNF alpha antagonists neutralize TNF, this is not the sole mechanism, since etanercept and onercept have no activity in IBD.[4,10] Induction of complement dependent cytotoxicity, antibody dependent cell mediated cytotoxicity, and apoptosis of monocytes may contribute since both infliximab and adalimumab share these features.[5,11] However, certolizumab pegol does not induce apoptosis, yet is effective for treating adults with CD.[12]

Infliximab has a small volume of distribution (4.5–6 L) and is distributed mainly in the intravascular space. In patients with CD, higher peak serum infliximab concentrations do not confer greater efficacy.[13] However, higher serum trough levels are associated with greater efficacy.[14] Slow drug clearance (15 mL/hr) and metabolism by proteases produce a 7–12 day elimination half life. Infliximab drug concentrations exhibit linear pharmacokinetics but accumulation does not occur with either the 5 mg/kg or 10 mg/kg dose.[13]

Azathioprine, prodrug of 6-mercaptopurine, decreases cytotoxic T cells by inhibiting B and T lymphocytes and is indicated for maintenance of remission in patients with moderate to severe CD.[15] There are no dose response studies for AZA or 6-MP to guide dosing. Azathioprine's active metabolite, 6-thioguanine, is responsible for its activity.[16] AZA's slow onset of action, due to slow accumulation of 6-thioguanine in tissues, means it is only useful for treating active disease when combined with corticosteroids.[1] A drug interaction between AZA and infliximab has been reported. When given concomitantly, infliximab increases the blood levels of 6-thioguanine leading to a greater infliximab response and tolerance.[16] AZA is metabolized mainly by thiopurine-S-methyltransferase (TPMT), and in patients with mutations in the TPMT gene, a TPMT

deficiency occurs. A TPMT deficiency causes AZA to be metabolized by two lesser enzymatic pathways resulting in 6-thioguanine accumulation and frequent myelosuppression.[17]

Efficacy

Concomitant infliximab and AZA produce higher infliximab trough levels, lower infliximab antibody formation, and increased rate of clinical response and remission. Lemann, et al a randomized, multi-center, double blind, placebo-controlled trial in 113 patients investigated the combination of an episodic one-time infliximab and AZA vs. AZA alone in AZA naïve or AZA failure patients with steroid dependent luminal CD. The purpose was to determine if infliximab could be used as a bridging agent to compensate for AZA's slow onset of action.[18] The primary endpoint of steroid-free clinical remission at week 24 was significantly higher in the AZA and infliximab combination group compared to AZA in both the AZA naïve and AZA failure patients. Also, steroid consumption was lower in the combination treatment group. The episodic infliximab dose is no longer the standard of care because it is associated with increased antibody formation, higher rate of infusion-related reactions, and lower serum trough infliximab concentrations.[19] The results from Lemann and colleagues cannot be extrapolated to infliximab maintenance therapy or to patients not dependent on or refractory to steroids.

Questions to consider for concomitant therapy include clinical remission resulting from concomitant AZA and maintenance infliximab dosing, clinical response in AZA naïve patients, non-naïve AZA patients, steroid dependent patients, and long term response. The Study of Biologic and Immunomodulator Naïve Patients in Crohn's Disease (SONIC) was a 50 week investigation of 508 steroid dependent patients with moderate to severe luminal CD comparing azathioprine and scheduled infliximab to infliximab or azathioprine alone. Patients had to be immunosuppressant and biologic agent naïve. The primary endpoint was steroid-free clinical remission at week 26. At baseline, approximately 40% of patients were receiving prednisone or budesonide and approximately one-half took 5-aminosalicylates. Patients were stratified by duration of CD (average 2.2 years), and baseline prednisone dose ($<$20 mg or $\geq$20 mg). The combination group had significantly higher steroid free remission (57%) compared to, 44% in the infliximab group and 30% in the AZA group. 65% of patients had mucosal lesions at baseline, and the mucosal healing rate was significantly higher in the combination infliximab and AZA group compared to AZA monotherapy ($P < 0.001$), but not infliximab monotherapy.[20]

In SONIC's voluntary 20 week blinded extension study, the AZA and infliximab combination produced a statistically significant clinical remission at week 50 compared to AZA monotherapy, but not infliximab monotherapy. This study suggests the combination of infliximab and AZA induces more steroid-free clinical remission and mucosal healing than either agent alone for patients who have never received a biologic agent or an immunosuppressant. It is important to note that the data cannot be extrapolated to patients who previously failed azathioprine therapy, and it is unclear if continuing azathioprine in patients who have failed azathioprine therapy will produce additional benefit.[20]

The only data supporting the use of combination therapy with azathioprine and infliximab for fistulizing CD comes from one small pilot study of 16 patients. Patients were required to be AZA naïve and to have a draining fistula for at least 3 months without abscess or significant stricture. Complete fistula closure (primary endpoint) took place in 75% of patients and the average time to fistula closure was 14 days but at week 50 there was no significant difference in clinical remission between the combination group and infliximab. While the pilot study implies azathioprine added to infliximab may provide additional benefit in fistula closure, only a randomized trial in a sufficient number of patients can confirm this.

Data for concomitant AZA and scheduled infliximab treatment for patients who are not naïve to AZA is important to consider. A post-hoc analysis of two Phase 3 randomized placebo controlled trials investigated clinical remission with infliximab and AZA vs. infliximab in UC (ACT 1 and 2) and two Phase 3 randomized controlled trials in patients with CD (ACCENT I luminal CD and ACCENT II fistulizing CD).[21] The post-hoc analysis measured clinical remission for the one-third of CD patients in ACCENT I and II who were receiving immunosuppressants at baseline. AZA doses could not be adjusted during the study. Neither study showed a statistically significant

increase in clinical response or remission rate between concomitant AZA and infliximab therapy to infliximab therapy alone at either the 5 mg/kg infliximab dose (ACCENT I and II) or 10 mg/kg dose (ACCENT I).

Sokol, et al investigated 121 IBD patients (UC 23 patients and CD 98 patients) who had received at least 6 months of infliximab treatment. Approximately 13% of patients were naïve to immunosuppressants (AZA or Methotrexate).[22] Patient treatment was divided into 6-month semesters of concomitant immunosuppressant and infliximab 5 mg/kg or infliximab 5 mg/kg alone. Each semester was analyzed independently for each patient. There were 265 semesters with immunosuppressants and 319 semesters without. Concomitant infliximab and AZA treatment and luminal disease were the only factors associated with a lower risk of IBD flare. Azathioprine treated patients had less IBD flairs than methotrexate but 67% of the patients taking methotrexate were given oral methotrexate. Finally, the benefit of concomitant treatment did not wane over time when 5 semesters were analyzed, and maximum CRP levels and dose of infliximab were lower in the concomitant group.

Durability of concomitant infliximab and AZA is important. A 5 year retrospective cohort study of 123 patients receiving concomitant treatment of infliximab and AZA versus infliximab alone showed improved remission rates and decreased need for surgery for the first year only. In years 2–5 differences were no longer significant in either remission or need for surgery.[23] However, it is important to note that only 58 patients remained in the study by year 5. Taking AZA at infliximab initiation was the only variable associated with remission at 2 years. Continued concomitant therapy during the first 2 years was not associated with improved remission. Clinical remission was not evaluated with the CDAI but from gastroenterologists' clinical judgment. However, this method is more frequently used in clinical practice than CDAI which is primarily a research tool.

High anti-infliximab antibody concentrations and low infliximab serum trough concentrations decrease infliximab's response rate.[24] In ACCENT I,[25] ACCENT II,[26] SONIC,[20] and Lichtenstein, et al[21] participants taking combination infliximab and AZA had lower infliximab antibody concentrations than patients taking infliximab monotherapy. Ten percent of the patients analyzed in the Lichtenstein study developed antibodies to infliximab and 75% of those patients had received infliximab without AZA.[21] In SONIC, antibodies were detected in 0.9% of combination treated patients but was over ten-fold higher with infliximab monotherapy (14.6%). Infliximab trough levels were higher in the combination group, 3.5 mcg/mL, compared with infliximab monotherapy, 1.6 mcg/mL ($P < 0.001$).[20] In Lichtenstein, et al median infliximab serum trough concentrations were similar for infliximab treatment with our without AZA but there was less trough variability for patients receiving 5 mg/kg infliximab.[21]

The "top-down" approach to treating newly diagnosed CD patients has recently received attention for its steroid sparing affects, prevention of early mucosal damage, and improved clinical response. This approach to treatment means using immunosuppressants or biologic agents first instead of 5-aminosalicylates or corticosteroids.[27] D'Haens, et al conducted a "top-down" trial investigating combined infliximab and AZA in comparison with traditional corticosteroid therapy. At week 26, 19% more patients in the combined infliximab and AZA group had achieved clinical remission than the control group ($P = 0.0278$).[27]

Mucosal healing at one year is associated with the reduced need for corticosteroids, lower risk of abdominal surgery, and lower rates of hospitalization.[28–30] Corticosteroids appear to have little impact on mucosal healing which is another reason the "top-down" approach is appealing.[31] In Lehman, et al there was improvement in mucosal lesions in the combined infliximab and AZA treatment group, but the study was not powered to detect a statistical significance.[18] In the Colombel, et al study, 64% of patients had mucosal lesions at baseline.[20] At week 26, statistically significant mucosal healing occurred in 44% of patients on combination therapy, 30% of patients on infliximab, and 17% of patients on AZA. Also, clinical remission was higher in patients with the greatest number of mucosal lesions.

Finally, clinical trials with biologic agents indicate patients with a higher baseline CRP ($\geq$10 mg/dL) may have better clinical response rates than patients with CRP $<$ 10 mg/dL.[24,25] Likewise, in the post-hoc analysis for Colombel, et al patients with a high CRP had a higher rate of steroid free clinical remission at week 26.[32,33]

The optimal duration of combination infliximab and azathioprine therapy is not clear. A study compared discontinuing AZA with continuing AZA in patients whose symptoms were under control for at least 6 months on combination therapy. Infliximab trough concentrations were lower and CRP was higher in patients who discontinued azathioprine therapy, but overall outcomes (discontinuing infliximab or the need to increase the dose) were similar.[14] In the 20 week extension study of SONIC, clinical remission at week 50 in the combination group and infliximab were not significantly different.[20]

Safety

Azathioprine and its metabolite, 6-mercaptopurine, are thiopurine analogs used for their immunosuppressive properties to maintain remission in both Crohn's disease and ulcerative colitis. Additionally, AZA/6MP allows for the reduction or avoidance of systemic corticosteroids, thus avoiding corticosteroid adverse effects. The most common adverse reactions associated with thiopurines include nausea/vomiting, leucopenia, thrombocytopenia, elevation in liver enzymes, and pancreatitis.

Infliximab has been useful in the treatment of IBD for more than a decade and has demonstrated effectiveness in refractory luminal and fistulizing CD. Infliximab produces a rapid clinical response, has steroid-sparing effects, promotes mucosal healing, increases quality of life, and reduces hospitalization rates. The most commonly reported adverse effects with anti-TNF therapy are acute infusion reactions, delayed hypersensitivity reactions, and infectious complications. Although beneficial in most patients, questions still remain regarding its long term safety, which includes the development of serious infections and malignancies. In addition to more common bacterial infections, anti-TNF therapy has been linked to opportunistic infections with bacterial, viral, and fungal pathogens.[34]

In the Lemann, et al trial[18] the frequency and severity of adverse events were not different between patients receiving AZA/6MP with infliximab or AZA/6MP alone. In total, 50% of patients in the monotherapy group compared with 51% in the combination group experienced at least one adverse effect. The incidence of infection was similar with 18 infectious events occurring in infliximab- and 16 cases in AZA/6MP-treated patients (P = NR). No deaths or cases of malignancy were reported.[18]

In the SONIC trial, the overall incidence of adverse effects was similar among AZA, infliximab, or combination groups; however, serious adverse events were less likely in the combination therapy group compared with either AZA ($P = 0.01$) or infliximab monotherapy ($P = 0.04$). Infusion reactions occurred in 16.6% of infliximab patients compared with 5% in the combination group ($P < 0.001$). There were no differences reported in infectious episodes or incidence of malignancy during the trial.[20]

Randomized, double blind clinical trials are generally considered the best measure of efficacy between two or more treatments; however, one of the limitations with these clinical trials is that most are typically too short to determine meaningful conclusions about the long-term safety concerns (cancer, opportunistic infections) of TNF-antagonists. While there are limitations to cohorts, registries, or meta-analysis studies, they may provide a better estimate of some of these long-term risks.

Serious infections

In patients without IBD, certain risk factors predispose patients to opportunistic infections including inherited or acquired immune deficiency states, malnutrition, leucopenia, diabetes mellitus, and target organ diseases such as emphysema. Additionally, immunosuppressive medications have been associated with opportunistic infections depending on their dose and effects on host immune function. A case-control study by Toruner, et al sought to identify risk factors for the development of opportunistic infections in patients with IBD.[35] A total of 100 infections were reported over a 6 year period, and infection with Herpes zoster, *Candida albicans*, Herpes simplex, Cytomegalovirus, and Epstein-Barr virus were reported most frequently. Patients receiving corticosteroid therapy were about 2 to 3 times more likely to develop opportunistic infections when compared with similar patients not receiving corticosteroids. The use of AZA/6MP alone increased the risk of infection by about 2- to 3-fold; however, when AZA/6MP was combined with corticosteroids, the risk increased to about 15-fold.[35] While infliximab use alone or in combination with other immunosuppressive medications resulted in more frequent opportunistic infections, the risk

only reached statistical significance in patients receiving infliximab, AZA/6MP, and corticosteroids in combination.[35] Although there are certainly limitations to this study, it does at least confirm that the use of corticosteroids, AZA/6MP, or infliximab in this study was associated significantly with the development of opportunistic infections. In addition, patients receiving combination therapy were more likely to develop an opportunistic infection. A similar increase in severe infections in meta-analysis of rheumatoid arthritis patients receiving anti-TNF in combination with methotrexate has also been reported previously.[36] Patients receiving anti-TNF antibody therapy (infliximab or adalimumab) were twice as likely to develop severe infection compared with controls.[36]

The Crohn's Therapy, Resource, Evaluation, and Assessment Tool (TREAT) is a prospective, observational, multicenter, long-term registry of North American patients with CD initiated in 1999 to evaluate the safety of therapies for CD. Through August 2004, 6290 patients with CD were enrolled from both academic (18%) and community (82%) centers. Approximately half of all patients (n = 3179) had been treated with infliximab with about 85% of those receiving at least 2 (median = 5, range 1–32) infusions. A total of 106 patients (1.7%) from the TREAT registry met criteria for a serious infection. Before adjusting for other factors, there was a significantly higher rate of infection in patients receiving infliximab versus those who did not. In addition, the rate of infection was higher within three months of receiving infliximab compared with patients who had not received infliximab in the prior three months. However, when compared in a multivariate analysis, infliximab was not associated with an increased risk of serious infection (OR 0.99, $P = 0.97$). Duration of CD, Caucasian race, disease severity, prednisone usage, and narcotic analgesics were identified as independent risk factors for serious infection in the multivariate model. The risk of serious infection was similar for infliximab alone (HR 2.1; CI 1.23–3.66) and infliximab plus immunomodulators (HR 2.2; CI 1.35–3.72).[37–39]

Malignancy

Organ transplant patients receiving thiopurines as part of their immunosuppressant regimen are known to have an increased risk of developing lymphoproliferative disorders;[40,41] however, the risk of developing a lymphoproliferative disorder in patients receiving thiopurines for IBD is controversial. The CESAME study addressed this risk with data from a large prospective cohort of 19,486 French patients with IBD, including 11,759 patients with CD. During 49,713 patient-years of follow-up, there was one case of Hodgkin's lymphoma and 22 cases of non-Hodgkin's lymphoma. Fifteen patients were receiving thiopurines at symptom onset, two had discontinued therapy, and six had never received AZA or 6MP. The adjusted hazard ratio of lymphoproliferative disorder between patients receiving and those who had never received thiopurines was 5.28 (95% CI 2.01–13.9; $P = 0.0007$). This risk appeared to be present regardless of whether anti-TNF therapy was continued, discontinued, or never received by the patient.[42]

Hepatosplenic T cell lymphoma (HSTCL) is a rare disease, aggressive in nature and usually results in a fatal outcome. Patients commonly present with hepatosplenomegaly and systemic symptoms (fever, night sweats, and weight loss). Commonly reported laboratory abnormalities include thrombocytopenia, anemia, leucopenia, and elevations in lactate dehydrogenase (LDH) and liver enzymes. Hepatosplenic T cell lymphoma comprises only 5% of peripheral T cell lymphomas, with over 200 cases reported worldwide. HSTCL typically affects adolescent or young adult men, with a median age of 35 years, ranging from 8 months to 68 years.[43]

Development of HSTCL is not limited to a single class of medications used to treat IBD patients. Immunosuppression with corticosteroids, azathioprine, 6-mercaptopurine, infliximab, and adalimumab has been associated with HSTCL. A total of 36 cases of HSTCL have been reported to-date; 20 patients received combination of infliximab and a thiopurine and 16 received thiopurine monotherapy for IBD.[44] Four patients previously treated with infliximab received adalimumab with a thiopurine. There have been no reported cases in patients with IBD receiving only TNF-antagonists.[44] In total, 15 patients received concomitant therapy with corticosteroids; eight of these patients received TNF-antagonists, and seven received thiopurines only.[44] While cases

Table 1 Summary of studies investigating the benefit of infliximab and azathioprine combination therapy[18–19,21–23]

Study	Trial Design	N	Treatment	Primary Endpoint	Results
Lemann, et al[19]	Randomized double blind, multi-center, placebo controlled	113	AZA 2–2.5 mg/kg orally +placebo or AZA + INF 5 mg/kg IV wk 0, 2, 6 wk		AZA + INF = 57% vs. AZA = 29% (p = 0.02) AZA + INF = 63% vs. AZA = 32% (p = 0.02) in AZA naïve AZA + INF = 50% vs. AZA = 26% (p = 0.08) in AZA failure patients
Colombel, et al SONIC[18]	Randomized double blind placebo controlled	169	INF 5 mg/kg IV wk 0, 2, 6 then every 8 wk or AZA 2.5 mg/kg orally daily or combination INF + AZA	Steroid free remission at week 26	INF 44.4% AZA = 30% (p = 0.006) Combination INF + AZA = 56.8% (p = 0.02 vs. inf, p < 0.001 versus AZA)
Lichtenstein, et al[21]	Post-hoc analysis of ACT 1, ACT 2, ACCENT I, ACCENT II to compare INF or INF + AZA combination	1383	ACT 1 and ACT 2 5 or 10 mg/kg INF or placebo ACCENT I and ACCENT II INF scheduled doses or placebo	Clinical response or remission or fistula response, and safety	No difference in clinical response or remission
Sokol, et al[22]	Open label non-randomized	121	INF or INF + IS	IBD flares, perianal complications and switch to adalimumab in 6 month semesters	IBD flares INF + IS 19.3% INF = 32.0% (p = 0.003) Perianal complications INF + IS 4.1% INF = 11.8% (p = 0.03) Switch to adalimumab INF + IS 1.1% INF = 5.3% (p = 0.006)
Moss, et al[23]	5 year retrospective cohort	123	INF or INF + AZA	Clinical remission	AZA at INF initiation was the only variable associated with remission at 2 years. Continued use of AZA after initiation of INF was not associated with remission

Abbreviations: SONIC, The Study of Biologic and Immunomodulator Naïve Patients in Crohn's Disease; N, number of patients; AZA, azathioprine; IBD, Inflammatory Bowel Disease; INF, infliximab; N/A, not applicable; wk, week; IS, Immunosuppressant; IV, intravenous.

have been reported with thiopurines alone, it does appear that concomitant therapy with multiple immunosuppressant medications may increase the incidence of HSTCL. Other factors that may influence the risk of HSTCL development include the underlying severity of IBD, dose-related or duration of medications used, and each patient's underlying innate immunity.

In addition to hematological malignancies, some reports suggest an increased risk of lung cancer in heavy smokers treated with anti-TNF therapies. A 24-week study of infliximab in COPD patients reported four lung cancers during therapy (plus two additional cancers following study completion) in 157 infliximab treated patients, compared with one in 77 placebo-treated patients.[45]

Place in Therapy

Compared with monotherapy with either agent alone, the combination of infliximab and azathioprine shows some therapeutic benefits; however, there is at least a small increased risk of opportunistic infection and malignancy. Recommending combination therapy in all patients would potentially expose some patients with less extensive disease to unnecessary risks and increase costs; therefore, it is important to consider factors that predict a more aggressive disease course.

Clinical factors, endoscopic findings, serologic testing, and molecular testing have been examined as predictors of more aggressive disease. Beaugerie, et al identified independent factors associated with a disabling disease course in the 5-year period following diagnosis which included age $<$40 years at diagnosis, perianal disease at diagnosis, and steroids required for initial flare-up. The presence of two or more of these risk factors was associated with a 90% chance of developing a disabling disease.[46] Small bowel and anoperineal involvement at initial diagnosis have been identified as predictors of early stricturing and/or penetrating complications.[47] Patients who quit smoking for more than a year have reduced need for steroids and immunosuppressive therapy comparable to nonsmokers unlike CD patients who continue to smoke.[48] The presence of a severe endoscopic lesion, defined as a large coalescent and deep ulceration covering more than 10% of the mucosal area in at least one colonic segment, is a strong predictor of colectomy within 8 years of the index colonoscopy.[49]

Although development of IBD is complex and likely multifactorial, concordance of IBD in siblings and twins is suggestive of a genetic predisposition to develop IBD. In 2001 the nucleotide-binding and oligomerisation domain 2 (*NOD2*) gene was identified as the first susceptibility gene for IBD. Since then, several other susceptibility genes including single nucleotide polymorphisms (SNP) have been strongly associated with the development of IBD. Recent work by Weersma in CD patients identified an increased risk of more severe disease course in patients where more susceptibility genetic mutations were present.[50] Likewise, immune factors may influence disease activity and clinical course. Variable immune responses to microbial antigens including *Escherichia coli* outer-membrane porin C (OmpC), *Pseudomonas fluorescens* CD-related protein (I2), and Anti-*Sacharomyces cerevisiae* antibody (ASCA) and autoantigens, perinuclear anti-neutrophil antibody (pANCA), may also explain differences in CD complications and severity. In one study, both the frequency and magnitude of immune responses to anti-OmpC, anti-I1, ASCA, and anti-CBir1 flagellin were significantly associated with more aggressive disease in children with CD. Internal penetrating and/or stricturing disease was highest in patients positive for all four immune responses (OR 11; 95% CI 1.5–80.4).[51] A commercial test is now available combining serologic immune factors and genetic markers to provide individual probability of complications after CD diagnosis.

Although prospective, randomized clinical trials are not available to definitively guide treatment, patients presenting with one or more of these risk factors for complicated disease course may be ideal candidates for combination therapy with infliximab and azathioprine. The importance of eliminating modifiable risk factors, such as smoking, cannot be overemphasized regardless of whether monotherapy or combination therapy is considered. Patients should be counseled on the impact of smoking on their CD, and provided with access to smoking cessation support, including medications if appropriate.

Conclusion

Based on current research, combination azathioprine and infliximab induces greater steroid-free clinical remission in luminal CD than either agent alone.

Clinical remission may be even greater in patients with more severe disease at onset evidenced by mucosal lesions and higher CRP levels, but additional studies are needed to confirm this. Also, further research is need to delineate the role for combination AZA and infliximab in patients with previous AZA treatment failure and in patients who are not steroid dependent. Safety concerns with combination therapy include increased risk of opportunistic infections and malignancies including hepatosplenic T-cell lymphoma. At this time, it is best to reserve this treatment approach for patients with evidence of more severe CD at diagnosis and to assess the risk and benefit for each patient on an individual basis. Future clinical trials are needed to identify patient populations where early combined immunosuppression would be most beneficial.

Disclosure

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers of this paper report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.

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