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Inflammatory Bowel Disease (G Lichtenstein, Section Editor)

The Evolving Role of Thiopurines in Inflammatory Bowel Disease

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Abstract

Purpose of review With the advent of biologic therapies for the treatment of inflammatory bowel disease, the roles of thiopurines have continued to evolve. This review will focus on recent advances in pharmacology and the safety and efficacy of thiopurines as maintenance therapies for steroid-induced remissions and post-surgical maintenance of remission and as combination therapies to reduce immunogenicities of biologic agents.
Recent findings Due to pharmacogenetics of thiopurine S-methyltransferase, thiopurine dosing is more effectively based on monitoring of thiopurine metabolites rather than weight-based dosing. Thiopurines continue to have a role as maintenance therapy after steroid-induced remissions and in combination with biologics to induce and maintain remission. Safety monitoring includes measurements of blood counts, liver chemistries, and dermatologic evaluations and protection from sun exposure.
Summary Thiopurines appear to be safe during pregnancies and while very uncommon, lymphomas (including hepatosplenic T cell lymphomas) remain a recognized risk, particularly in younger and older males.

Introduction

Thiopurines (azathioprine, AZA; mercaptopurine, 6MP) have been used in the management of ulcerative colitis (UC) and Crohn's disease (CD) for multiple decades. However, with the advent of biologics and introduction of potent small molecules (e.g., Janus Kinase inhibitors), the role of thiopurines in the management of inflammatory bowel disease (IBD) needs to be redefined. In this review, we re-assess the current utilities and appropriate use of thiopurines in management of both UC and CD.

Pharmacology

Thiopurine derivatives, AZA and 6MP, have no intrinsic activity; they undergo a series of multi-step enzymatic process to convert to active metabolites. AZA is a prodrug that is rapidly converted to 6MP in the liver and red blood cells [1, 2]. Further metabolism of 6MP occurs by three competitive enzymatic pathways: xanthine oxidase converts 6MP to 6-thiouric acid (thiourate), an inactive metabolite excreted by the kidneys: hypoxanthine phosphoribosyltransferase, and a subsequent series of constitutive and inducible enzymes that convert 6MP to the metabolically active form 6-thioguanine nucleotides (6-TGN) which are phosphorylated and have antimetabolite and pro-apoptotic properties in bone marrow (primarily white blood cell and platelet lineages); and thiopurine S-methyltransferase (TPMT) that converts 6MP to 6-methyl-mercaptopurine (6MMP) [3], a less clinically effective metabolite that is associated with hepatic transaminitis. TPMT functional activity is determined by genetic polymorphisms such that 0.3% of the population are homozygous for absent TPMT activity, 10% of the population are heterozygotes with intermediate activity, and the remainder of polymorphisms produce more TPMT enzymatic activity that diverts 6MP metabolism to 6-MMP [4]. Therefore, with similar doses of AZA or 6MP, low TMPT functional activity is associated with bone marrow suppression while high functional TPMT activity will divert 6MP metabolism away from 6TG and will be associated with elevated liver transaminases and less therapeutic impact on bone marrow–derived cells. While liver transaminitis does not lead to chronic liver disease, high concentrations of 6TG have been associated with veno-occlusive disease of the liver and nodular regenerative hyperplasia [5]. Therefore, to avoid bone marrow toxicity, it is recommended to check functional TPMT enzyme activity prior to initiating thiopurines and to utilize lower doses in patients with reduced functional activity [6, 7]. Most recently, a genetic polymorphism, NUDT15 that is more common in the Asian population, but also infrequently observed in Caucasians, has been recognized to be associated with an increased risk of myelosuppression [8••].

Trials in childhood leukemia utilized weight-based dosing of thiopurines that led to weight-based studies in IBD. Despite the observation that have correlated AZA and 6MP therapeutic effects (and bone marrow toxicity) with 6-TGN levels (e.g., in one study, 6-TGN levels > 292 pmol/8 × 10^8 RBCs were associated with an 85.7% positive predictive value of clinical response) [9] ironically, most "guidelines" advocate weight-based dosing of 2.5 mg/kg for AZA and 1.5 mg/kg for 6 MP [10]. In contrast, we and others have attempted to optimize thiopurine use by targeting a therapeutic range for 6TGN and assessing 6TGN and 6MMP metabolites in non-responding patients [11••].

Induction therapy in Crohn's disease and ulcerative colitis

Numerous clinical trials as far back as the National Cooperative Crohn's Disease Study have failed to demonstrate an effect of thiopurines, as monotherapy, to induce clinical remissions in either CD or UC; usually attributed to their slow onset of action [12, 13]. In addition, a more recent randomized controlled trial (RCT) in early CD found AZA to be no more effective than placebo at inducing

sustained corticosteroid-free remission in CD [14], and results from a recent Cochrane meta-analysis of thirteen RCTs involving nearly 1200 patients showed no advantage for AZA or 6MP over placebo for induction of remission or clinical improvement in active CD [15]. There is limited but similar data regarding lack of efficacy of thiopurines in inducing remissions in ulcerative colitis [16, 17]. As a result, thiopurines are not recommended as monotherapy for induction of remission in either CD or UC. Their primary role in induction therapy remains in combination with biologic agents (discussed in detail later).

Maintenance therapy in Crohn's disease and ulcerative colitis

In contrast to the lack of efficacy of thiopurine monotherapy for induction remissions in IBD patients, the impact AZA and 6MP on the maintenance of steroid-induced clinical remission has been well established in numerous controlled trials and meta-analyses. Thiopurines have demonstrated significant steroid-sparing effect as well as maintaining mucosal healing in CD [18]. In an observational study in CD patients on AZA monotherapy (mean duration 24.4 ± 13.7 months) complete mucosal healing was achieved in 70% patients with ileitis and 54% of patients with colitis [19]. In addition, recent series have demonstrated evidence that thiopurines decrease surgical rates amongst CD patients [20]. In a cohort of pediatric patients with CD, use of AZA was associated with decrease surgical hazard rates (HR) of 0.51 (95% CI 0.33–0.78), an effect that was more pronounced in patients for whom AZA was introduced earlier in their course of the disease [21]. Similarly, in UC, thiopurines have a more consistent impact as maintenance agents. In a meta-analysis of 30 studies involving 1600 patients, AZA/6MP showed a mean efficacy of 76% for maintenance of remission and an absolute risk reduction (ARR) of 23% (number needed to treat (NNT) of 5 compared to placebo in the prevention of relapse) [22].

Another scenario where thiopurines have been utilized as maintenance therapy is for patients with acute, severe, UC in hospitalized patients following induction therapy with cyclosporine. Cyclosporine, a calcineurin inhibitor, has been shown to be efficacious as a rescue therapy after failure to respond to intravenous corticosteroids in hospitalized patients. Yet, while cyclosporine is an effective inductive agent, its use has not been similarly efficacious as a maintenance agent [23]. Thiopurines have been successfully used for maintaining remission after cyclosporine induction in these patients and thereby decreases colectomy rates in these complex patients [24].

Along the same line, there has been consistent evidence that thiopurines not only maintain clinical remission but also decreases longer-term IBD complications such as hospitalizations and surgeries, thus impacting on the "natural history" of UC and CD [25, 26•]. Nevertheless, in Europe, therapeutic objectives in IBD are evolving such that de-escalation of therapy is an emerging goal. There have been relatively few studies assessing withdrawal of successful thiopurine maintenance therapy. An early trial demonstrated increasing relapse rates after withdrawal of azathioprine maintenance therapy in UC patients [27] and while a retrospective report of CD patients maintained on AZA suggested that, after 4 years of CD maintenance, azathioprine could be discontinued without loss of effectiveness [28], a prospective randomized trial by the same group demonstrated that AZA withdrawal after 4 years of CD maintenance did lead to an

increased risk of clinical relapse [29]. A recent meta-analysis by Boyapati et al. has also confirmed that withdrawal of AZA maintenance therapy in CD leads to an increased risk of clinical relapse in (32% vs 14% RR:0.42) [30].

Combination therapy with biologics

Despite the consistent impact of thiopurines on the pharmacokinetic profiles of biologic agents (increased drug levels and reduced anti-drug antibodies) that was initially observed with infliximab in IBD. Post hoc analyses of phase 3 studies enrolling patients with an "inadequate response" to AZA or 6MP failed to demonstrate a benefit for patients receiving concomitant thiopurines and infliximab [31, 32]. Similar results were noted in trials with adalimumab, certolizumab pegol, natalizumab, vedolizumab, and ustekinumab (see below). However, it must be noted that patients were not randomized according to ongoing immunomodulator therapy, and the trials were not powered to demonstrate a difference between patients receiving concomitant immunomodulators.

In contrast, the pivotal SONIC trial (Study of Biologic and Immunomodulators Naïve Patients in Crohn's Disease) prospectively compared infliximab monotherapy to azathioprine monotherapy and to combination therapy with infliximab and AZA (2.5 mg/kg). In the SONIC trial enrolling immunosuppressive-naïve and bio-naïve patients with earlier Crohn's disease, the results clearly showed superiority for combination therapy with steroid-free clinical remission rates of 30% on AZA monotherapy vs 56.8% receiving combination therapy ($P < 0.0001$) vs 44% for infliximab monotherapy ($P = 0.02$) [33]. Similarly, the UC-SUCCESS trial demonstrated similar superiority with AZA/infliximab combination therapy in immunosuppressive and biologic-naïve UC patients [34]. Whether results with combination therapy were due to medication synergy or increased drug levels of biologics was investigated in a post hoc analysis of SONIC by Colombel et al. that suggest that clinical outcomes were indistinguishable within groups having similar drug concentrations and point to the impact of AZA on infliximab pharmacokinetics and reduced clearance (including immunogenicity) as the mechanism of improved outcomes with combination therapy in IBD [35•]. The optimal dosing of thiopurines used in combination with IFX (and presumably other biologics) also remains to be established. In a cross-sectional analysis by Yarur et al., a 6-TGN of 125 pmol/8×10^8 red blood cells appeared adequate to achieve therapeutic levels of infliximab [36].

To date, there has been only one prospective study of adalimumab assessing mono- vs combination therapy with a thiopurine in CD that demonstrated improvement in endoscopic outcomes (but not clinical remissions) with combination therapy [37]. However, while a meta-analysis of 7 studies assessing induction of remission ($n \approx 1900$) suggested that Adalimumab monotherapy was "mildly" inferior to combination therapy [OR = 0.78 (0.64–0.96), $P = 0.02$] [38], there was no apparent impact on maintenance therapy, and a recent post hoc analysis from a pediatric CD trial similarly failed to confirm a benefit (or harm) with adalimumab combination therapy for induction or maintenance.

The efficacy of combination therapy with vedolizumab and thiopurines in IBD remains uncertain. Similar to trials with anti-TNF agents that enrolled proportions of patients not responding to thiopurines, post hoc analyses of the

Gemini I and II trials showed no apparent clinical benefit of combination with immunosuppressive agents in CD and UC [39, 40]. Post hoc analyses of similarly designed phase 3 trials with ustekinumab did not identify better outcomes for patients on background immunosuppressive therapy [41]. Despite higher blood levels of vedolizumab and ustekinumab in patients receiving thiopurines, the overall rates of anti-drug antibodies were lower than those observed with infliximab suggesting that in the settings of biologics with longer half-lives and less inherent immunogenic properties, thiopurines may have less impact on pharmacokinetics and clinical outcomes [42].

Indeed, loss of response to biologic agents and anti-TNF agents, in particular, is a significant issue [43]. A significant proportion of patients' lose response secondary to immunogenicity and the formation of anti-drug antibodies (ADA) cause faster clearance and sub-therapeutic drug levels [44]. Several recent studies have suggested that the addition of a thiopurine to patients who have developed anti-drug antibodies to anti-TNF biologics may reduce the presence of antibodies and allow improvement in the pharmacokinetics and clinical outcomes [45•, 46, 47]. In a retrospective analysis by Strik et al., the addition of thiopurine leads to suppression of ADAs, increased drug levels, and recaptured clinical response in 77% of patients who had previously developed immunogenic failure to infliximab or adalimumab [48].

A common clinical question related to potential toxicities of thiopurines (see below) pertains to "how long" combination therapies with biologics and thiopurines should be continued. Separate randomized withdrawal trials of infliximab and AZA have assessed the impact of withdrawing one or the other agent. Van Assche et al. found no benefits in clinical outcomes or mucosal healing of continuing thiopurines beyond 6 months, although higher infliximab drug levels and lower CRP levels were found in patients continuing on combination therapy beyond a year [49]. However, the previously mentioned Cochrane analysis did not demonstrate an increased risk of relapse in patients withdrawn from thiopurines during combination therapy with biologics [30]. In contrast, the STORI (infliximab diSconTinuation in CrOhn's disease patients in stable Remission on combined therapy with Immunosuppressors) trial withdrew infliximab from patients receiving combination therapy with azathioprine and demonstrated gradual reductions in clinical remissions over time, particularly in patients who had not achieved "deep remissions." [50] While debate is ongoing regarding the duration of combination therapy with biologics and thiopurines, ultimately, the use of therapeutic drug monitoring provides a rationale means of approaching a patient in a durable remission on combination therapy. Therapeutic biologic levels and low 6TGN would justify stopping the thiopurine, whereas "sub-therapeutic" levels of a biologic and therapeutic 6TGN would logically suggest stopping the biologic. Such an approach has yet to be evaluated in clinical trials.

Special populations

Pregnancy

AZA has been used during pregnancy in transplant and rheumatology patients for some time. In a retrospective study comparing outcomes of 187 IBD patients

on thiopurines with the non-exposed patient, unfavorable pregnancy-related outcomes defined as low birth weight, preterm delivery, congenital malformation, and death were 21.9% vs 31.8% respectively ($P = 0.01$) [51]. A meta-analysis of 7 studies with nearly 3000 patients revealed that thiopurines are not associated with low birth weight or congenital abnormalities but may be associated with preterm delivery [52]. Similar results were confirmed in a prospective study from the Netherlands in which 309 IBD patient (216 CD and 85 UC) were followed during 311 pregnancies. Thiopurines were used during 108 pregnancies and the authors found no difference in pregnancy outcomes or infant health at 1 year between the study and control group [53].

Thiopurines are now generally considered safe in pregnant IBD patients [43]. A 2011 survey of gastroenterologists with > 82,000 IBD patients showed that greater than 90% recommended continuous thiopurine treatment [54, 55•].

Post-operative Crohn's disease

More than half of patients with CD will undergo at least one intestinal resection during the course of their disease and post-operative recurrence (POR) is common [56]. Thiopurines alone or in combination with other agents (imidazoles or Anti-TNF agents) are often recommended for reducing the risk of POR [57•, 58]. In a prospective randomized control trial compared with placebo, 6MP was shown to be more effective at preventing clinical and endoscopic recurrences at 2 years (50% vs 77% and 43% vs 64% respectively $P < 0.05$) [59]. In a retrospective analysis of 326 patients, Papay et al. showed a significant reduction in re-operation rate with long-term AZA use (> 36 months) as compared with the control groups (< 36 months and no treatment) [60]. A meta-analysis of four randomized clinical trials with a total of 433 patients concluded that thiopurines were more effective than placebo for preventing endoscopic recurrence of Rutgeert's i2–4 lesions (mean difference, 23%; 95% CI, 9–37%; $P = 0.0016$; NNT = 4) at 1-year after surgery [61].

Thiopurines and risk prevention of colorectal cancer

Patients with IBD are at increased risk of colorectal cancer (CRC); this risk is related to the duration and the extent of colonic involvement [62]. Since chronic inflammation is the key driver for increased risk [63] of colonic neoplasia in IBD, the anti-inflammatory properties of thiopurines should be protective although evidence to that effect remains inconclusive. In a retrospective population-based study from the Netherlands involving nearly 2500 patients, the use of thiopurines was associated with a decreased risk of neoplasia [HR 0.10 (95% CI 0.01 to 0.75)] [64]. While a meta-analysis performed in 2014 did not find a protective benefit of thiopurines against colonic neoplasia, [65] a more recent systematic review and meta-analysis of 95,000 patients supported a protective effect of thiopurines against CRC cancer in IBD [66].

Thiopurines in patients with a previous history of cancer

The use of thiopurines in patients with a previous history of cancer remains controversial due to insufficient data. While a previous study suggested delaying treatment with thiopurines for three to 5 years after a cancer diagnosis [67], a subsequent meta-analysis of 16 studies with more than 11,000 patients has

shown no difference in cancer recurrence between non-exposed vs exposed patients on immunomodulators [68].

Uninsured/underinsured populations

A substantial proportion of the US population remains uninsured or underinsured. IBD is a relatively low prevalence but a high-cost disease and drugs cost are a significant proportion of that expenditure [69, 70]. Biologics which are considered the most effective therapy for moderate to severe IBD remain expensive [71]. Immunomodulators, including thiopurines, can provide a cost-effective treatment strategy in this population [72].

Side effects

Toxicities from thiopurines, including intolerance and allergic, can be dose-dependent or idiosyncratic [73] and account for the observations that approximately 25% of the exposed patients develop an adverse reaction and 17% discontinue therapy due to adverse events [74].

The most frequent intolerance to thiopurines is nausea, experienced by up to 10% of patients with females and CD patients at most risk [74]. Other common intolerant side effects include arthralgias, malaise, and flu-like illness [75]. Approximately 60–70% of patients who develop intolerance to AZA will tolerate a switch to 6MP, but not vice versa [3].

In contrast, acute pancreatitis is an allergic side effect that can occur in up to 7% of patients started on thiopurines with almost all cases presenting within the first 2 to 3 weeks after initiating therapy. With immediate drug withdrawal, most cases are mild and resolve spontaneously [76]. In the setting pancreatitis or other allergic reactions such as rash, fever, or arthritis, re-challenge or substitution between AZA and 6MP typically induces similar toxicities and can include a septic shock–like syndrome. In contrast, a few small case series have demonstrated that "cautious" challenge or substitution of thioguanine can be successfully tolerated [77].

Dose-dependent reactions

Myelosuppression

The cumulative incidence of bone marrow suppression from thiopurines ranges from 5 to 7% [75] and is related to TPMT functional activity (see above). Leukopenia is the most common presentation although thrombocytopenia or pancytopenia can develop [78]. Bone marrow suppression can develop over weeks or arise during long-term therapy [79]. High 6-TGN levels have been related to leukopenia related to AZA or 6MP [80] justifying recommendations for measuring functional TPMT activity prior to initiating therapy, particularly if introduced in a mg/kg strategy. Reduced dosing (e.g., 50% reduction) is advocated for intermediate functional TPMT activity (approximately 15% of the population) and patients with homozygous low-activity (approximately 1/300 individuals) should either avoid AZA/6MP in favor of 6TG or be initiated at 10% of standard dosing with extremely close monitoring of leukocyte counts. Other correlates with 6TGN levels include leukopenia, itself, as well as elevated erythrocyte mean

corpuscular volume [81]. Common recommendations for therapeutic drug monitoring of include measuring complete blood counts (CBC) every 1 to 2 weeks after initiating therapy to avoid acute bone marrow suppression and then subsequently every 3 months to avoid the risk of late-onset myelosuppression [79]. In Asian populations, and less commonly in Caucasians, genome-wide studies have implicated NUDT15 variants to be associated were associated with increased risk of thiopurine associated myelosuppression, irrespective of dose or the TPMT levels [8••, 82].

Immunosuppression

Even in the absence of neutropenia, viral, bacterial, parasitic, and fungal infections have been associated with the use of thiopurines; with a particular increased risk of viral infections [83]. Risk factors for infections include advanced age, malnutrition, other comorbid conditions (diabetes, chronic lung disease, etc.), and concomitant use of other immunosuppressive therapies (including corticosteroids) [84]. Kirchgesner et al. evaluated serious infections (requiring hospitalization) in large French population database of 200,000 patients. The rate of serious infection was 0.8% (1 in 125) in unexposed as compared to 1.1% (1 in 91) in patients with thiopurine monotherapy. Incidence rates were higher (2.2%) for patients on combination therapy with biologics, particularly in the subgroup patients older than 65 [85]. Thus, it is recommended that patients about to initiate thiopurine or other immunosuppressive therapies (including biologics) receive age-appropriate vaccinations (including influenza, pneumococcus, zoster, hepatitis B, and human papillomavirus) [86].

Malignancies

Lymphomas are the most relevant neoplastic concern associated with thiopurines that usually occur in individuals previously exposed to Epstein-Barr virus [87]. In a recent nationwide cohort study based on the French National Health Insurance databases of 189,000 IBD patients followed for a median of 6.7 years, the absolute risk of lymphoma was low (336 cases). Two hundred twenty cases were in patients without thiopurine exposure (incidence rate [IR] per 1000 person-years, 0.26; 95% CI 0.23–0.29) vs (IR, 0.54; 95% CI 0.41–0.67) for the 70 cases in patients exposed to thiopurine monotherapy with an adjusted hazard ratio [aHR] of 2.60 (95% CI, 1.96–3.44; $P < .001$). The risk was also higher in individuals on combination therapy with anti-TNF agents [aHR, 6.11 (95% CI 3.46–10.8; $P < .001$)] [88••]. A meta-analysis of 18 studies demonstrated that the risk of lymphoma was proportional to duration of therapy; becoming significantly increased after 1 year of use but reverting to baseline after discontinuation of therapy. Subgroup analysis identified males having had approximately twice the relative risk (RR) compared to females with patients younger than 30 years having the highest relative risk (standardized incidence ratio = 7) and younger men having the highest risk (approximately 9-fold). While the RR approximated 6-fold, the magnitude in absolute term remains low with the highest RR being in patients older than 50 years (1:354 cases per patient-year, with a RR of 4.78) [89].

Hepatosplenic T cell lymphoma (HTCL) is the least common, highly aggressive and most lethal lymphoma subtype associated with thiopurine therapy linked to AZA/6MP monotherapy or in combination therapy with anti-TNF agents. This rare, nearly always fatal lymphomas occur primarily in young males under the age of 35 years after a minimum of 2 years [90]. However it is important to point out recent case reports HTCL occurring with the use of anti-TNF combination therapy with Methotrexate, in older patients (> 65) and in females [91]. Another rare, uniformly fatal syndrome, hemophagocytic lymphohistiocytosis (HLH), is a multisystem inflammatory response in which the mononuclear phagocyte system is activated [92]. The risk of this syndrome and other B cell lymphomas are particularly high in individuals who develop a primary Epstein-Barr virus (EBV) infection while on thiopurines [93]. A frequently implied but not yet uniformly recommended strategy is to check EBV status before starting thiopurines and to avoid using these drugs in a patient who are at risk of acquiring a primary EBV infection [94].

Skin Cancer

Thiopurines are known to increase the risk of non-melanotic skin cancer (NMSC). In a study of almost 13,000 IBD patients, of which nearly 3000 patients were on thiopurines, the risk of NMSC was higher in exposed as compared to the unexposed with aHR of 2.1 ($P < 0.0001$) [95]. Though data remain conflicting, in this particular study, the risk decreased to the baseline levels after stopping thiopurines aHR 0.7 ($P = 0.07$). The study also associated the risk linked to the duration of exposure with a significant increase in risk after 2 years of continuous thiopurine exposure. No association was found between melanomas and thiopurine use [95].
In "light" of these studies, it is recommended that patients receiving thiopurines should minimize direct sun exposure, use sun block, and have regular dermatological screening [96•].

Best practice

In this era of personalized medicine thiopurines still have an important but evolving role in the management of IBD. They remain advocated by GI societies in the USA and abroad for maintenance therapy after steroid-induction for both UC [97•, 98, 99] and CD [57•, 100–103]. Thiopurines have a slow onset of action and are not recommend as single agents for induction of remission in either UC or CD [102, 103]. Pretreatment TPMT enzyme testing and weight-based dosing are endorsed; however, response is best correlated with 6TGN levels in RBCs [11••]. Combination therapies with immunomodulators and anti-TNF biologics (primarily IFX) are more effective than either thiopurine or biologic monotherapy in both CD [33] and UC [34] where, based on post hoc analysis, the increased efficacy was associated with reduced immunogenicity and increased drug levels [35•]. It remains to be determined if this advantage is maintained with other anti-TNFs [104, 105] or newer biologic agents.

Close laboratory monitoring for hematologic and hepatic toxicities is recommended. There is increased but uncommon risk of lymphomas and other rare hematological malignancies; the risk increases with age and is higher in

patients on combination therapy. Increased risks for non-melanoma skin cancers with thiopurines warrant sun protection and regular dermatologic examinations. Thiopurines are also associated with an increased risk of viral and other opportunistic infections, thus expansion age-appropriate vaccinations are recommended before initiating and during maintenance therapy with thiopurines and other immune-suppressive therapies.

Thiopurines may provide cost-effective approaches to the treatment of IBD (e.g., compared with biologics) but should demand similar monitoring of clinical and endoscopic end-points currently advocated in "treat to target" strategies for CD and UC [106, 107].

Compliance with ethical standards

Conflict of Interest
Saurabh Kapur declares that he has no conflict of interest. Stephen B. Hanauer declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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