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Update on the risk of lymphoma following immunosuppressive therapy for inflammatory bowel disease

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Abstract

The care of inflammatory bowel disease has changed considerably with the introduction of a number of immunosuppressants including anti-metabolite and anti-TNF therapies. While efficacious, these medications also carry important risks, notably the potential risk of lymphoma. This risk is one of the most worrisome for both patients and physicians. Our current knowledge is still evolving; however, our understanding of what risks these drugs carry, both individually and synergistically, is critical in allowing informed decision making. In this article, we will describe the known lymphoma risks of commonly used immunosuppressant medications in inflammatory bowel disease, with an emphasis on non-Hodgkin's lymphoma and hepatosplenic T-cell lymphoma.

Keywords

hepatosplenic T-cell lymphoma; immunosuppression; inflammatory bowel disease; lymphoma; non-Hodgkin's lymphoma

In the era of increasing immunosuppressant use, one of the more challenging issues in managing patients with inflammatory bowel disease (IBD) is balancing the risks and benefits of medical therapy. Both patients and physicians alike often worry about the risk of lymphoma associated with these therapies. By weakening host immune system surveillance for tumor cells, chronic use of immunosuppressive medications allows proliferation of these malignancies. This article will review the risk of lymphoma associated with immunosuppressants used in IBD and will discuss the implications for both patients and physicians.

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Nonbiologic immunosuppressant therapies

The link between immunosuppression and malignancy is clearly illustrated in the natural history of patients with HIV and AIDS. These patients have an increased risk of lymphoma even before the onset of AIDS, and this risk is inversely correlated to CD4 counts [1–3].

Patients who have undergone solid organ transplantation further illustrate the link between immunosuppression and lymphoma, specifically lymphomas positive for Epstein–Barr virus (EBV), a human herpes virus present in over 90% of the population [4–8]. EBV-infected B lymphocytes are typically controlled by cell-mediated host immunosurveillance. Immunocompromised states, including medically induced immunosuppression, impair host immunosurveillance and allow the emergence of lymphoproliferative disorders. Data from the transplant population also suggest that the risk of lymphoma is correlated with the degree of immunosuppression and that many of these lymphomas regress with cessation of immunosuppressive therapy [4,9–16].

Cyclosporine

Cyclosporine (CsA) is an immunosuppressant drug widely used in the transplant population. It is believed to bind lymphocytes, especially T lymphocytes, inhibiting calcineurin, which in turn leads to a downregulation of transcription of IL-2. There are a number of proposed mechanisms for enhanced tumor progression with CsA use, including direct cellular effects and indirect effects via the induction of TGF- β , angiogenesis stimulation by VEGF and through suppression of DNA repair and reduced p53-induced apoptosis [8,9,17–19].

The fields of dermatology and organ transplantation have some of the most extensive experience with CsA use and risk of lymphoma [5,20–25]. However, especially in the field of organ transplantation, the use of combination therapies makes it difficult to assess the impact of individual immunosuppressive agents. It remains possible that cancer risk in patients treated with CsA is related to general immunosuppression rather than any particular agent, and that in this context CsA promotes, rather than induces, tumor growth. *In vitro* studies have shown dose-dependent reduction in peripheral blood mononuclear cell DNA repair, with an increased overall reduction in DNA repair and subsequent increased cancer incidence when CsA therapy was combined with azathioprine (AZA) and prednisone therapy [19]. CsA-based therapies have shown a higher malignancy rate and lower mean time to tumor development in some studies of post-transplant patients; and in a comparison of low-dose to normal-dose post-kidney transplant CsA regimen, there was a higher cancer incidence in the higher-dose CsA regimen, which the authors attributed to a dose-dependent reduction in DNA repair capability [15,17]. A worldwide study of organ transplant patients found that less than 1% of both men and women developed lymphoma; however, this rate still translated into a nearly 28-times increased risk of lymphoma development in those patients exposed to CsA [26]. Two retrospective studies attempted to examine CsA-associated rates of post-transplant lymphoma compared with other immunosuppressive regimens [16,27]. While both studies found an increased risk of lymphoma overall, there were no differences in populations treated with CsA compared with those treated with steroids/thiopurine-analog therapy, raising the question of whether lymphoma development was related to overall immunodeficiency rather than any single drug [16,27]. Two cases of lymphoma were reported in a prospective cohort of over 1000 psoriatics (standardized incidence ratio [SIR]: 2.0; 95% CI: 0.2–7.2) [28]. This rate was comparable to a previously reported lymphoma rate in a non-CsA-exposed psoriatic population [29].

Referring specifically to CsA-related lymphoma in IBD patients, a hospital-based study of 782 IBD patients at a single hospital reported four cases of non-Hodgkin's lymphoma (NHL) [30]. All cases occurred in patients on immunosuppression. One of these four

patients had received 5 months of methotrexate (MTX) therapy followed by 12 months of CsA and was found at the time of colectomy to have a positive lymph node with large cell diffuse B-cell type lymphoma. No further evidence of lymphoma was found and the patient required no therapy [30]. Two additional case reports of CsA-treated IBD patients have been published, including a case of rectal lymphoma in a patient treated with CsA for 4 years, and a case of B-cell lymphoma found in the lymph nodes and pouch of a ulcerative colitis (UC) patient who had been treated with four-drug combination immunosuppression prior to ileal pouch-anal anastomosis surgery [31,32].

Methotrexate

Methotrexate, a structural analogue of folic acid, irreversibly inhibits dihydrofolate reductase, the enzyme responsible for converting folic acid to folate cofactors that are necessary for *de novo* synthesis of the nucleoside thymidine as well as purine base synthesis. MTX is cytotoxic, induces immunosuppression and leukopenia, and has been implicated in impairment of cellular immune control of tumor proliferation. It has specifically been linked with impairment in immune control of EBV-induced B-cell proliferation.

Like CsA, the majority of experience examining MTX and rates of lymphoma comes from non-IBD studies, specifically the psoriasis and rheumatoid arthritis (RA) populations. In these populations, there have been a number of case reports of lympho-proliferative disorders, including EBV-positive lymphoma, occurring in MTX-treated patients [4,6,10–12,14,33–38]. However, it is important to appreciate the background risk of lymphoma in these populations, specifically in patients with connective tissue disorders, which appears to confer a baseline two-to-threefold increased risk of lymphoma [12,39–46]. Furthermore, confounding by indication may have occurred, with the patients with most severe disease receiving the longest duration or highest dosage of medication, which consequently further complicates interpretation of studies. This is particularly relevant in the case of RA, where disease severity has been strongly associated with the risk of lymphoma independent of immunosuppressant medications use [12,42–44].

When examining the psoriatic literature, studies have shown mixed results (Table 1). A small matched case–control study from 1982 found no increased risk of non-cutaneous cancers in MTX-treated psoriatic patients compared with non-exposed psoriatic patients [47]. However, a more recent study by the same author found an elevated risk of lymphoma in patients treated with MTX for longer than 36 months compared with the general population (incidence rate ratio [IRR]: 3.65; 95% CI: 1.34–9.90) [48]. It is unclear if this risk would have remained elevated if compared with other psoriatic patients with similar disease severity. A cohort study examining MTX use within a cohort of 5000 hospitalized psoriatics found 21 cases of lymphoma in over 77,000 person-years of follow-up time, none of which occurred in MTX-treated patients [29]. To date, no meta-analysis has been performed examining an overall rate of lymphoma associated with MTX use in the psoriatic population. Furthermore, making comparisons between these different studies is difficult given the different baseline severity and comparison populations.

One finds similar limitations when examining the RA literature. In 2004, a large study of 18,572 RA patients found no increased rates of lymphoma in MTX-treated RA patients compared with RA patients with no MTX exposure [45]. There were two conflicting studies in 2008 [49,50]. A nested case–control study of 23,810 RA patients found a nonsignificant adjusted risk of lymphoma in MTX-exposed patients [49]. However, a smaller community-based study of 458 RA patients found a fivefold increased risk of NHL in those patients exposed to MTX compared with the general population, although no comparison with non-MTX-treated RA patients was performed [50].

A recent review examined the long-term safety of MTX therapy in RA [51]. The authors were unable to examine a relationship between MTX exposure and lymphoma in RA patients, in part because most studies compared MTX-treated patients with the general population, and not with RA patients not receiving MTX [51]. In addition, studies often failed to account for RA severity in study designs [42].

There is no well-designed study of MTX-associated lymphoma in IBD, especially with an increasing trend toward thiopurine analog and biologic therapy use in these patients. In a single-center study of 782 IBD patients, two of four reported cases of NHL occurred in patients with exposure to MTX [30]. One of the patients had been exposed for 4 years, the other for 5 months. The overall risk of NHL in this population was significantly high (SIR: 31.2; 95% CI: 2.0–85); however, issues of power and selection bias complicate interpretation of these results [30].

Thiopurine analogs

Azathioprine is a prodrug of 6-mercaptopurine (6-MP). Both drugs are converted to active 6-thioguanine (6-TG) nucleotides, which become incorporated into ribonucleotides and in turn inhibit nucleotide synthesis, protein synthesis and lymphocyte proliferation. Thiopurine analogs may also directly inhibit cytotoxic T-cell and natural killer cell function, inhibiting cell-mediated immunosurveillance. This may facilitate the development of lymphoproliferative disorders, in part due to proliferation of EBV-infected lymphocytes. There is also evidence of another possible mechanism of action involving apoptosis of activated T cells [52].

There are a number of studies examining a link between the development of lymphoma and thiopurine analog use in IBD patients. Unfortunately, many of these have been single-center or hospital-based, raising issues of ascertainment and referral bias. There is also the issue of confounding by indication in which uncertainty exists if the increased incidence of lymphoma in IBD patients receiving thiopurine analog therapy is due to the immunomodulator itself or reflects the more aggressive nature of the disease in these patients.

There have been a number of single-center studies examining the risk of lymphoma in IBD patients treated with thiopurine analogs (Table 2). One of the first to be published was a study in the late 1980s examining 396 IBD patients treated at the center over an 18-year period [53]. They found only one case of lymphoma in a patient treated with 6-MP for approximately 9 months [53]. Two single-center studies of IBD patients treated with thiopurine analog therapy found no cases of lymphoma within their population [54,55]. Five single-center studies have reported cases of lymphoma in their thiopurine analog-treated IBD patients [30,56–59]. A single-center study of 157 Crohn's disease (CD) patients found a single case of lymphoma in a patient treated with AZA for 17 months [56]. A 550-patient study from New York (USA) found two cases of NHL, including one cerebral and one abdominal lymphoma, resulting in an SIR of 4.9 (95% CI: 0.9–14.5) [57]. A retrospective study of 782 IBD patients found four cases of lymphoma, two of which occurred in patients with AZA exposure, resulting in an extremely high SIR, albeit with extremely wide confidence intervals (37.5; 95% CI: 3.5–138) [30]. A retrospective chart review of 626 AZA-treated patients found three cases of NHL, but the risk was not significantly different compared with the rate of lymphoma in non-AZA-treated IBD patients [58]. Likewise, a second retrospective chart review of 285 patients at a single center found a single case of lymphoma [59].

There have been three population-based studies examining lymphoma risk associated with thiopurine use in IBD. Two of these studies have come from the General Practice Research

Database. Lewis *et al.* evaluated 1465 IBD patients treated with thiopurine analog therapy and found only one case of Hodgkin's lymphoma in a patient with UC who had received AZA 10 months earlier [60]. This translated into a nonsignificant SIR (1.57; 95% CI: 0.04–8.75) [60]. Armstrong *et al.* performed a nested case–control study within an IBD cohort in the General Practice Research Database comparing patients with malignancy to those without and examining their exposure to AZA [61]. They examined the use of AZA in two ways: when examining it as a prescription density (dose–response relationship) they found a nonsignificant odds of lymphoma (1.37; 95% CI: 0.79–2.40). However, when examining AZA use as a ever/never binary variable (resulting in an increased power) there was a significantly increased odds of lymphoma associated with the use of AZA, with an odds ratio (OR) of 3.22 (95% CI: 1.01–10.18) [61]. Differences between these two studies may reflect a difference in time period and follow-up time of the populations. The third cohort study was a prospective nationwide study from France evaluating the risk of lymphoproliferative disorders in IBD patients treated with thiopurine analog therapy [62]. In this study of 19,486 patients with 49,713 patient-years of follow-up, 23 patients were diagnosed with lymphoproliferative disorders (22 NHL), 17 of which had some thiopurine exposure. This resulted in a multivariate hazard ratio of 5.26 (95% CI: 2.20–12.6) [62].

A meta-analysis by Kandiel *et al.* of six cohort studies obtained a pooled SIR of 4.18 (95% CI: 2.07–7.51) [63]. Five of the six studies were single-center studies and there was significant heterogeneity among all the studies, although excluding any single study did not appreciably affect the results. Three of the six studies directly compared thiopurine-treated with thiopurine-untreated IBD patients and had a combined SIR of 2.92 (95% CI: 1.1–8.1). A second meta-analysis found a nonsignificant risk of lymphoma in IBD patients treated with thiopurine analog therapy [64]. This meta-analysis differed with respect to two studies compared with the meta-analysis by Kandiel *et al.*, and additionally substituted data from a population-based University of Manitoba (Canada) IBD dataset when a study had no control group, thus introducing an unmeasurable bias to the analysis [64].

Role of EBV in thiopurine-associated lymphoma—A 15-year review from the Mayo Clinic identified all IBD patients who developed lymphoma and evaluated two 8-year time intervals (1985–1992 and 1993–2000) corresponding to the introduction of use AZA/6-MP use [65]. Six cases of lymphoma occurred during the first interval and 12 cases occurred during the second interval. A total of 50% of these latter 12 cases occurred in patients treated with thiopurine analog therapy and the majority of these lymphomas were EBV-positive [65]. Similar results were observed in the Cancers Et Surrisque Associe aux Maladies inflammatoires intestinales En France (CESAME) study where only one of eight patients diagnosed with lymphoma while not receiving thiopurines had EBV lymphoma; by contrast, 12 out of 15 patients receiving thiopurines at the time of diagnosis had EBV-positive lymphoma [62].

Overall, it seems plausible that the thiopurines are associated with an increased risk of lymphoma, with a magnitude of risk ranging from three- to five-times higher than nontreated IBD patients. Several issues still remain to be resolved, including the relationship between cumulative dose and risk, whether the risk remains constant after discontinuation of thiopurine use, and how the risk changes with combination immunosuppressant use. The recent CESAME cohort study has provided some of the first data on these questions. While patients in this study who continued thiopurine therapy had an increased risk of lymphoma, those who had discontinued thiopurines had an incidence of lymphoma similar to patients never treated with thiopurines and similar to the general population (SIR: 1.44; 95% CI: 0.17–5.20). Furthermore, the SIR for patients on combination thiopurine and anti-tumor necrosis factor (TNF) therapy was markedly elevated, with a SIR of 10.2 (95% CI: 1.24–36.9) [62].

Biologics

Currently there are three anti-TNF agents (infliximab, adalimumab and certolizumab) and one anti- $\alpha 4$ integrin (natalizumab) that have been approved for use in IBD. Concerns regarding the risk of lymphoma, and specifically the risk of hepatosplenic T-cell lymphoma (HSTCL), surround all of these agents.

Infliximab

Infliximab is a chimeric monoclonal antibody directed against human TNF. Infliximab is composed of a linkage of variable regions of mouse anti-human TNF monoclonal antibody to human IgG1 with κ light chains. Infliximab binds to and neutralizes soluble TNF *in vitro* and *in vivo*, and also binds to the transmembrane form of TNF, downregulating a number of inflammatory mediators [66]. Infliximab has an extensive history of use in RA. It was approved by the US FDA for treatment of CD in October 1998 and received licensing in the European Union in September 1999. It additionally received FDA approval for UC in September 2005.

At the time of FDA approval in 1998, there were two small open-label studies and two randomized placebo-controlled trials evaluating infliximab efficacy in CD, with no report of incident lymphoma. Following its commercial release, three single-center studies, two multicenter retrospective studies, two randomized efficacy trials and a retrospective population-based cohort study reported no cases of lymphoma in infliximab-treated patients [30,67–73]. Likewise, the Crohn's Therapy, Resource, Evaluation and Assessment Tool (TREAT) registry, a long-term registry set up to assess the safety of infliximab with 3396 patients exposed to infliximab (14,184 patient-years), found no increased risk of lymphoma in infliximab-treated patients (relative risk: 0.74; 95% CI: 0.24–2.29) [74]. This dataset is potentially subject to both selection and ascertainment bias based on the recruitment and follow-up methods. In particular, loss to follow-up or incomplete data could contribute to the lack of an observed association.

By contrast, the A Crohn's disease Clinical study Evaluating infliximab in a New long term Treatment (ACCENT) 1 trial, a large multicenter randomized controlled trial evaluating infliximab for maintenance therapy in CD, reported a single case of lymphoma [75]. A large population-based cohort study found three cases of lymphoma, two of which were fatal, although a large number of those treated were on concomitant thiopurine analog therapy [76]. An additional single-center study of 500 consecutive patients treated with infliximab reported two cases of lymphoproliferative disorders, one NHL and one Hodgkin's lymphoma [77]. Both patients also had prior exposure to thiopurine therapy [77]. A recent review of 207 patients in Edinburgh, UK, treated with infliximab found three hematologic malignancies including one NHL [78]. In 2002, the FDA's MedWatch post-marketing adverse event surveillance system reported a total of 26 cases of lymphoproliferative disorders occurring in patients treated with infliximab for RA and CD, five of which were NHL and three of which were Hodgkin's lymphoma. Concern was also raised about the short temporal relationship between the initiation of medical therapy and lymphoma development [79]. Subsequent 'possible' or 'probable' infliximab-associated lymphoma cases led to the FDA Arthritis Advisory Committee reporting an eightfold increased rate of lymphoma in CD patients treated with infliximab compared with age-, gender- and race-matched populations [80]. In October 2004, the risk of malignancy, including lymphoma, was added to the package insert of infliximab.

There are a number of difficulties in determining the risk of lymphoma in IBD patients treated with infliximab. Lymphoma development is a rare event, making ascertainment of an appropriate number of cases, and thus precision of determining risk, very difficult. There is a

possible elevated predisposition for lymphoma in chronically ill IBD patients which, even if low, confounds interpretation of studies without an appropriate comparison group. Confounding by indication further complicates interpretation: if patients who are most unwell are at highest lymphoma risk by virtue of ongoing inflammation but are also more likely to receive infliximab, interpretation of causality is difficult. In addition, many of these patients had exposure to or are on concomitant immunosuppressive medications, particularly thiopurine analogs, making determination of drug causality challenging. Elucidating the effects of multiple immunosuppressant drug use on lymphoma risk remains an important question.

Adalimumab

Adalimumab, a recombinant human immunoglobulin IgG1 monoclonal antibody that binds human soluble TNF, was approved for RA in 2002 and for moderate-to-severe CD in 2007. Pre- and postmarketing studies consistently found elevated rates of lymphoma in adalimumab-treated RA patients, although baseline rates of lymphoma in RA patients must be taken into account [81–84]. To date, no cases of NHL have been attributed to adalimumab use in IBD patients, either in the initial efficacy trials or in retrospective safety studies [85–88]. However, data in IBD are relatively sparse. Based on the more extensive data in RA, current FDA guidelines report an approximately threefold increased risk of lymphoma in adalimumab patients compared with the general population [89].

Certolizumab

Certolizumab pegol is a Fab fragment of humanized anti-TNF- α monoclonal antibody with polyethylene glycolation to increase the half-life of the antibody and, thus, decrease the dosing frequency. It is approved for use in moderate-to-severe CD in those intolerant to infliximab or those who have lost response to prior anti-TNF therapy [87,90,91]. In the initial efficacy studies, the only case of reported lymphoma occurred in the placebo arm in a patient who was on thiopurine therapy [87].

Pooled data on lymphoma risk—There have been two meta-analyses examining safety and lymphoma risk in the anti-TNF therapies. In 2008, a meta-analysis examining the safety and efficacy of 21 placebo-controlled trials identified no increased risk of cancer among those IBD patients treated with anti-TNF and control groups [92]. However, this study did not report a separate assessment of the risk of lymphoma in the treated populations and only reported a total of 16 malignancies across all the treatment groups [92]. A second meta-analysis specifically analyzed the risk of NHL in CD patients treated with any anti-TNF therapy [93]. The control group in this study included both a population-based registry and a population of CD patients treated with immunomodulators, and included 8905 patients, the majority of whom had prior exposure to immunomodulators. In the 26 studies analyzed, a total of 13 cases of NHL were reported. This was significantly higher compared with the general population (3.23; 95% CI: 1.5–6.9), although it was not significantly elevated when compared with CD patients treated with thiopurine analog therapy alone (SIR: 1.7; 95% CI: 0.5–7.1). Sensitivity analyses using studies with low drop-out rates yielded even higher rates of lymphoma [93].

Natalizumab

Natalizumab is a humanized murine antibody against α 4-integrin. The medication is believed to work by reducing the ability of inflammatory cells to attach and pass through the lining of the intestines and blood–brain barrier, and therefore has been approved for use in multiple sclerosis. In 2004, natalizumab was approved for use in CD but was subsequently withdrawn from the market for a period of time when it was linked with progressive

multifocal leukoencephalopathy, a rare irreversible neurologic condition caused by the JC virus. It is currently on the market again for use in CD, although it is available through a restricted distribution program in which all patients using this drug must be entered into a monitoring registry and cannot be on other concomitant immunosuppressive medications.

In the Efficacy of Natalizumab in Crohn's Disease Response and Remission (ENCORE) trial, a single case of B-cell lymphoma was reported in a patient who had received six total infusions of natalizumab in combination with 6-MP [94]. No other cases of lymphoma to date have been reported in association with natalizumab in IBD. However, a single case of primary CNS lymphoma has been reported in a 37-year-old man with multiple sclerosis who had received 21 infusions of natalizumab [95]. A total of 3 years prior to the diagnosis of high-grade B-cell non-Hodgkin's CNS lymphoma, the patient had been treated with a number of short courses of high-dose corticosteroids, an 8-month course of IFN- β (ending approximately 25 months before the diagnosis of lymphoma) and a 10-month period of AZA (ending approximately 22 months prior to the diagnosis of lymphoma) [95]. The patient had a 4-week washout period following the cessation of AZA and subsequently received natalizumab for 80 weeks until the time of the CNS lymphoma diagnosis [95].

Hepatosplenic T-cell lymphoma

Hepatosplenic T-cell lymphoma is a rare aggressive extranodal T-cell lymphoma that primarily affects young males in the second and third decade of life. Patients typically have hepatosplenomegaly without lymphadenopathy and the clinical course is very aggressive, with a median survival of less than 1 year despite therapy [96].

A recent review of the reported literature identified 28 cases of HSTCL, all of which occurred in patients with CD who had previously had some duration of thiopurine analog exposure [97]. The majority of these patients were men (93%) and the median age of diagnosis was 22 years of age [97]. At least six of these cases had not been exposed to an anti-TNF therapy. Of those cases of HSTCL reported among patients treated with anti-TNF therapies, there have been three cases reported in patients treated with adalimumab [98]. The remainder have occurred in patients treated with infliximab. Among the cases that have been reported following adalimumab exposure, two occurred in IBD patients with prior infliximab exposure and the third occurred in a patient who had no prior anti-TNF exposure. Of note, no cases of infliximab-associated HSTCL have been reported with any other disease state other than IBD [98–102].

The black-box warning for infliximab now includes information regarding HSTCL, especially concerning the risk in adolescent and young adult patients with CD. Given the growing number of cases reported within both anti-TNF and immunomodulator therapy, it is difficult to assign infliximab a primary or even causative role in the pathogenesis. A number of potential confounders complicate assigning causation, including the underlying disease itself, other immunosuppressant use and length of disease duration. While low event rates limit the ability to obtain precise estimates of risk, the increasing number of reported cases certainly demands vigilance when using these medications.

Risks/benefits in early aggressive therapy

When examining the risk of lymphoma in patients with IBD, it is equally important to consider the real risk of active disease in patients, which can be not only very disabling but sometimes lethal [103]. A number of studies to date have demonstrated that patients with IBD are willing to accept the risks associated with medical therapy, sometimes at levels exceeding known levels, in exchange for clinical improvement [104–106]. This appears to be especially true in younger adults [105]. Similarly, decision models have demonstrated

that the potential benefits of thiopurine and TNF therapy appear to outweigh risks in most patients [104,105]. In one decision model, the favorable balance of the trade-off between the risk of lymphoma and therapeutic benefit of thiopurine therapy diminished with increasing age, consistent with an increased baseline risk of lymphoma [105].

Several key questions still remain unanswered. One concerns the issue of what risk (if any) of lymphoma is associated with short exposure to anti-TNF and thiopurine therapy, and if the risk of lymphoma remains after therapy is discontinued. This has important implications in current therapy, for example, in the increasing movement towards early aggressive therapy in CD or in the increasing use of immunosuppressant therapy prior to surgical consideration in UC. If risk resolves upon discontinuation of medication, this may change patient risk-taking behaviors, at least initially. Specifically, if the medication does not prove beneficial, and the patient can discontinue therapy with minimal exposure to lymphoma risk, patients and physicians may be less reluctant to attempt therapy. Likewise, if therapy proves successful, it is likely that risk-taking thresholds may be higher and risk more acceptable to these patients.

A related question is whether to employ initial combination immunosuppressant therapy, or serial therapy where another immunosuppressant medication is added to a current immunosuppressant regimen. In the meta-analysis by Siegel, nearly all patients with NHL were concurrently on or had previously received thiopurine therapy, so their estimated rates of lymphoma at least partially represent that for combination therapy [93]. It is unclear if risk is additive, multiplicative or synergistic in combination therapy. Mixed results regarding efficacy and infectious risks in combination therapy further complicate decisions regarding multiple immunosuppressant use [107–109].

Finally, several limitations must be acknowledged in our current exploration of lymphoma risk related to medical therapy. Most studies published thus far have lacked appropriate control groups (i.e., patients with IBD treated with alternative therapies), making evaluation and comparisons difficult both within and between studies. The latency of cancer development makes studies difficult to carry out. Controlling for drug exposure, both past and present, complicates appropriate assessment of lifetime exposures. Underlying disease severity potentially further confounds assessment of causality regarding lymphoma development.

The risk of lymphoma in medical therapy for IBD is a complicated issue. An open discussion with patients regarding the potential risks as well as our limitations in knowledge is imperative. IBD patients treated with thiopurines appear to have an increased risk for lymphoma, anywhere from three- to five-times higher than IBD patients not exposed to these drugs. While fewer data exist on IBD patients treated with MTX, data suggest that if a risk exists, it is lower than that associated with thiopurine use. Data from anti-TNF therapy are further complicated by concomitant use of other immunosuppressants in most studies, but it appears that there is an increased risk of lymphoma. HSTCL is a separate issue, for which an increased risk appears likely to be associated with both anti-TNF and thiopurine use. Combination therapy probably increases the risk of all types of lymphoma, although further studies are necessary to definitively examine this. Most importantly, however, while the relative risks of lymphoma associated with all therapies may be higher, the absolute risk remains low; all risks need to be weighed against the real risk of untreated IBD and the real benefit these therapies can offer to these patients.

Expert commentary

The risk of lymphoma associated with medical therapy for IBD is a cause of concern for patients and physicians. In the field of dermatology, RA and organ transplant, the data examining CsA and MTX are mixed, although there is a plausible biological mechanism for reduced immunologic surveillance of tumor cells. The paucity of data examining whether these medications increase the risk of lymphoma in IBD makes informed decision counseling a challenge. Data examining the risk of lymphoma with thiopurine analogs demonstrate a three-to-fivefold increased risk of lymphoma in treated patients. The anti-TNF medications have also demonstrated an elevated risk of lymphoma in both RA and IBD. However, the data examining both the immunomodulator and anti-TNF medications are complicated by concomitant use of other immunosuppressants, disease severity and disease duration. Given that more suppressed immune states in other diseases are associated with an increased risk of lymphoma, it is logical to believe that this also holds true for IBD. In addition, both thiopurine analogs and anti-TNF medications have increasingly been reported in association with cases of HSTCL. Further examination of this association is necessary to fully elucidate this risk. However, the risk of lymphoma must be weighed against the very real benefits these medications offer patients with active disease. As we become more informed regarding the risks associated with these medications, we can help our patients make informed decisions regarding their care.

While we await further data, it is important to consider strategies that may improve outcomes while minimizing risk. One strategy that can be used when counseling patients is to explain that the risk–benefit balance becomes clearer once it is evident if a patient will respond to a therapy. Prior to initiating thiopurines or anti-TNF therapies, the expected response and remission rates are well below 100%. However, within approximately 3 months, it becomes clear whether a patient has responded to the therapy and whether this has resulted in a complete remission. The available data for thiopurines suggest that this short-term trial does not result in a lifelong increased risk of lymphoma. While similar data for anti-TNF therapies are lacking, it is logical that the same would hold true. Thus, a several month trial entails a short period of increased lymphoma risk, during which the absolute increased risk is quite small. After the first few months, patients can decide whether the risk associated with continued therapy is acceptable given the outcomes achieved in the first several months of therapy. For those who have failed to achieve adequate disease control, the medication can be discontinued, probably with few long-term consequences.

Five-year view

The next 5 years are likely to be very active in the field of IBD. Current research will focus on developing more specifically targeted medications, including immunosuppressants, drawing upon our growing knowledge of the etiology of IBD. Concurrent with this push for newer drugs will be an increasing bank of experience with our current immunosuppressive therapies. It is hoped that this experience will help illuminate the relationship between immunosuppression in IBD and malignancy risk, answering questions such as how combined immunosuppressive regimens affect risk levels and providing additional data on how risk changes with discontinuation of medications. The majority of research to date has come from single-center studies; however, with the growth of databases of IBD patients across the world, population-based studies will become more prevalent and help shed even more light on the management of IBD. Importantly, sample sizes needed to study rare events such as lymphoma are generally only feasible within multicenter databases and population-based electronic medical records or using administrative data. Finally, a renewed interest in comparative effectiveness research, which considers both the benefits and harms of therapy as used in general practice, will hopefully lead to studies that directly compare different

treatment strategies, thereby reducing the need to extrapolate from multiple unrelated studies.

Key issues

- The link between immunosuppression and malignancy has been shown in a variety of populations and is believed to be due, in part, to a decreased immunosurveillance of tumor cells.
- Studies for cyclosporine mainly come from the dermatology and organ transplant literature, and point to a likely link between cyclosporine use and lymphoma, although it is unclear if this is due to the drug specifically or immunosuppression in general.
- Most evidence examining the association between methotrexate and lymphoma comes from the rheumatoid arthritis and psoriatic populations, where the relative risk of lymphoma, if it exists, is relatively small.
- Several studies have examined the risk of lymphoma associated with the thiopurine analogs (azathioprine and 6-mercaptopurine) and estimate an increased risk in the order of three-to-five-times higher than non-treated inflammatory bowel disease (IBD) patients.
- There have been a number of cases of lymphoma reported in patients exposed to anti-tumor necrosis factor (TNF) therapy, with as much as a threefold elevated risk. However, a large proportion of these patients have also received thiopurines, making specific assessments difficult. Furthermore, data on the anti-TNF medications other than infliximab (i.e., certolizumab and adalimumab) are limited in IBD.
- Although rare, hepatosplenic T-cell lymphoma is a very aggressive form of lymphoma that has increasingly been reported in IBD patients exposed to both thiopurine and anti-TNF therapy.
- While the risk of lymphoma is serious and patients must be counseled regarding the known risks, it should also be weighed against the real benefits these medications can offer appropriately selected patients with IBD.

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Table 1

Selected studies of methotrexate use in psoriasis and rheumatoid arthritis.

Author (year)	Disease	Outcome	Comparison group	RR/OR/SIR/IRR (95% CI)	Ref.
Stern <i>et al.</i> (1982)	Psoriasis	Noncutaneous malignancy	Psoriatic patients	0.96 (0.5–2.0)	[47]
Stern <i>et al.</i> (2006)	Psoriasis	Lymphoma	General population	3.65 (1.34–9.90) [†] 0.85 (0.37–1.67) [‡]	[48]
Hannuksela-Svahn <i>et al.</i> (2000)	Psoriasis	Non-Hodgkin's lymphoma	General population Psoriatic patients	2.2 (1.4–3.4) 0	[29]
Wolfe <i>et al.</i> (2004)	Rheumatoid arthritis	Lymphoma	General population	1.7 (0.9–3.2)	[45]
Bernatsky <i>et al.</i> (2008)	Rheumatoid arthritis	Hematologic malignant neoplasms	Rheumatoid arthritis patients	1.12 (0.93–1.34)	[49]
Buchbinder <i>et al.</i> (2008)	Rheumatoid arthritis	Non-Hodgkin's lymphoma	General population	5.1 (2.2–10.0)	[50]

[†]Based on patients with >36 months exposure to methotrexate.

[‡]Based on patients with <36 months exposure to methotrexate.

IRR: Incidence rate ratio; OR: Odds ratio; RR: Relative risk; SIR: Standardized incidence ratio.

Table 2

Selected studies of azathiopurine/6-mercaptopurine use and lymphoma in inflammatory bowel disease.

Study (year)	Study type	Medication	Patients (n)	Lymphoma cases (n)	SIR/RR/OR (95% CI)	Ref.
Present <i>et al.</i> (1989)	Single center	6-MP	276 CD 120 UC	0 CD 1 UC	Not reported	[53]
Connell <i>et al.</i> (1994)	Single center	AZA	450 CD 282 UC 23 indeterminate colitis	0	0	[54]
George <i>et al.</i> (1996)	Single center	6-MP	90 UC	0	0	[55]
Bouhnik <i>et al.</i> (1996)	Single center	AZA, 6-MP	157 CD	1	Not reported	[56]
Korelitz <i>et al.</i> (1999)	Single center	6-MP	380 CD 170 UC	2 CD 0 UC	4.9 (0.9–14.5)	[57]
Farrell <i>et al.</i> (2000)	Single center	AZA	238 IBD	2 IBD	37.5 (3.5–138)	[30]
Fraser <i>et al.</i> (2002)	Single center	AZA	271 CD 355 UC	0 CD 3 UC	4.6 (0.9–13.7)	[58]
Glazier <i>et al.</i> (2005)	Single center	6-MP	160 CD 125 UC	1 CD 0 UC	Not reported	[59]
Lewis <i>et al.</i> (2001)	Population-based study	AZA, 6-MP	837 CD 628 UC	0 CD 1 UC	1.6 (0.0006–9.0)	[60]
Armstrong <i>et al.</i> (2010)	Population-based study	AZA	15,441 IBD	15 IBD	1.37 (0.79–2.40) [†] 3.22 (1.01–10.18) [‡]	[61]
Beaugerie <i>et al.</i> (2009)	Population-based study	AZA, 6-MP	19,486 IBD	17 IBD	5.26 (2.20–12.6)	[62]
Kandiel <i>et al.</i> (2005)	Meta-analysis	AZA, 6-MP	3891 IBD	11	4.18 (2.07–7.51)	[63]
Masunaga <i>et al.</i> (2007)	Meta-analysis	AZA, 6-MP	4039 IBD	9	0.0 (–0.8–0.7) [§]	[64]

[†]Dose–response relationship.

[‡]Ever/never-use relationship.

[§]Results expressed as weighted mean difference.

6-MP: 6-mercaptopurine; AZA: Azathioprine; CD: Crohn's disease; IBD: Inflammatory bowel disease; RR: Risk ratio; SIR: Standardized incidence ratio; UC: Ulcerative colitis.