Nonmelanoma Skin Cancer Risk in Patients With Inflammatory Bowel Disease Undergoing Thiopurine Therapy: A Systematic Review of the Literature

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BACKGROUND Azathioprine and 6-mercaptopurine (thiopurines) are common adjunct treatments for inflammatory bowel disease (IBD). Although thiopurine therapy in organ transplant recipients is known to increase nonmelanoma skin cancers (NMSCs), dermatologic literature yields less data regarding NMSC risk of thiopurine use in IBD.

OBJECTIVE The aim of this study was to systematically review current literature on NMSC risk in patients with IBD using thiopurine therapy.

METHODS Systematic review of PubMed was performed with keywords “inflammatory bowel disease,” “ulcerative colitis,” “Crohn’s disease,” “thiopurine,” “azathioprine,” “6-mercaptopurine,” “skin cancer,” “non-melanoma,” “squamous cell carcinoma,” and “basal cell carcinoma.” All available publication years were included. Publications were evaluated using PRISMA guidelines.

RESULTS The systematic review yielded 67 articles; 18 met final inclusion criteria.

LIMITATIONS Heterogeneity of study designs limited direct comparisons of thiopurine exposure and NMSC risk.

CONCLUSION Patients with IBD using thiopurines seem to have a moderately increased risk of NMSC that is proportional to therapy duration. Risk of NMSC seems to decrease or return to baseline after discontinuing therapy, although additional data are needed to support this trend. Younger patients with IBD using thiopurines seem to be at greater risk of NMSC. Appreciating NMSC risk in patients with IBD undergoing thiopurine therapy should help direct skin cancer screening recommendations and sun protective measures.

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Inflammatory bowel disease (IBD) is a chronic inflammatory disease of the gastrointestinal tract that is loosely divided into 2 major categories: (1) Crohn disease (CD) which occurs at any location along the gastrointestinal tract, and (2) ulcerative colitis (UC) which is characterized by inflammation localized to the colon. An array of treatments has been described for both conditions, most of which inhibit generalized inflammatory pathways (e.g., sulfasalazine, mesalazine, systemic corticosteroids, thiopurines, methotrexate, and newer monoclonal antibodies to tumor necrosis factor alpha [TNFα], IL-12/17, and alpha-4/beta-7 integrin). Patients who have received immunosuppressive therapies such as those listed above have been noted to present with increased risk of various liquid and solid malignancies.[1–3] The malignancy type and degree of risk varies depending on the specific therapeutic agent used and the dose received.

Among the commonly used immune suppressive agents in the treatment of IBD, azathioprine, and 6-mercaptopurine constitute the thiopurine

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therapeutic family that is frequently used as adjunctive therapy. Pharmacologically, these act as prodrugs that are metabolized to deoxythioguanine-5′-triphosphate, which serves as a purine analogue for DNA polymerases, preferentially blocking DNA synthesis in cells lacking a nucleotide salvage pathway (i.e. activated T- and B-cells).[4] Both azathioprine and 6-mercaptopurine are known photosensitizers that reduce the minimal erythema dose for UV-A radiation and also play a role in generation of reactive oxygen species.[5–7] The risk of solid and liquid malignancies seems to be increased in patients with IBD who have undergone thiopurine therapy.[8] Similar patterns have been frequently observed for solid organ transplant patients who have used thiopurine therapy as part of their immunosuppressive regimen, but these patients are often maintained at a higher level of immune suppression compared with well-controlled patients with IBD.[9,10]

The dermatology and dermatologic surgery literature has devoted significant recent attention to the increased skin cancer risk in solid organ transplant recipients, but few publications exist in the authors' literature to address the extent to which skin cancer risk extends to patients with IBD using similar therapeutic agents, albeit at lower doses. This review aims to address the question of the degree of risk thiopurine therapy confers for development of nonmelanoma skin cancer (NMSC) in patients with IBD.

Materials and Methods

A systematic review was performed using PubMed/Medline to collect publications on risk of developing NMSC in patients with IBD undergoing thiopurine therapy. The keywords used in the search were "inflammatory bowel disease," "ulcerative colitis," "Crohn's disease," "thiopurine," "azathioprine," "6-mercaptopurine," "skin cancer," "non-melanoma," "squamous cell carcinoma," and "basal cell carcinoma". The actual search language string is included in **Supplemental Digital Content 1**, Appendix I, http://links.lww.com/DSS/A86. The search yielded 67 potential publications. Case reports/series and review articles were excluded from final inclusion due to low level of clinical evidence. Remaining publications that were deemed by abstract or full-text review to not address the topic of NMSC risk in the setting of thiopurine use were also excluded. Of the initial 67 publications, 18 met the final inclusion criteria (Figure 1). The reference sections from the selected publications were reviewed thoroughly for evidence of any additional relevant articles that were not captured by the initial search strategy, but no additional relevant publications were discovered. The complete list of publications included for systematic review and their characteristics are provided in Table 1.[11–28] The selected studies were evaluated according to PRISMA guidelines.[29]

Results

Article Selection Process

The Pubmed search strategy (see **Supplemental Digital Content 1**, Appendix I, http://links.lww.com/DSS/A86) produced a total of 67 articles that made some mention of IBD, thiopurine therapy, and skin cancer. The search produced a partial internal validation in the form of a meta-analysis conducted in 2014, which had analyzed all relevant publications up through 2012. The authors' search strategy identified all the articles that were included in that meta-analysis (8 total).[20] Case reports (10 total) and reviews (30 total) were excluded from the final analysis due to low level of evidence (LOE) or lack of novel data synthesis, respectively. One meta-analysis was included for final review due to its novel synthesis of data from previous studies.[20] Review of the abstracts and/or full text of the remaining 27 articles

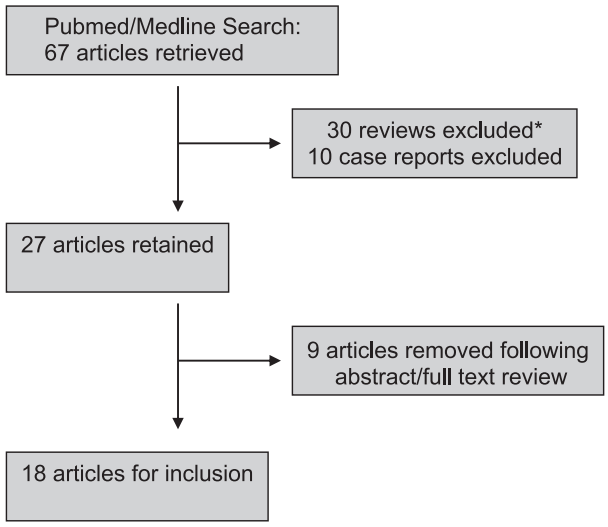

Figure 1. Search strategy for systematic review.

TABLE 1. Summary of Publications Included in Systematic Review

Reference	*Study Type*	*Year*	*Country*	*Drug(s)*	*Exposure*	*Cases*	*Controls*	*Mean Follow-Up*	*LOE (USPSTF/ CEBM)*
Armstrong and colleagues[11]	Nested case control	2010	United Kingdom	AZA	>1 Rx	43	15,398	6.4 yrs	II/2b
Long and colleagues[12]	Retrospective cohort; nested case control	2010	USA	AZA/6MP	≥1 Rx, <90 d from NMSC	742	2,968	1.32 yrs	II/2b
Setshedi and colleagues[13]	Retrospective cohort	2011	South Africa	AZA/6MP	TP use (any duration)	123	691	9.9 yrs	II/2b
Singh and colleagues[14]	Retrospective cohort; case control	2011	Canada	AZA/6MP	2 + Rx	170	680	11.7 yrs	II/2b
Peyrin-Biroulet and colleagues[15]	Prospective observational cohort	2011	France	AZA/6MP	TP use (any duration)	8,676	10,810	2.55 yrs	II/2b
van Schaik and colleagues[16]	Retrospective cohort	2011	Holland	AZA/6MP	≥50 mg AZA/6MP over 6 mo	819	2,068	6.46 yrs	II/2b
Camus and colleagues[17]	Retrospective cohort; case control	2012	France	AZA	2.25 mg/kg AZA × 1 yr	220	440	12.17 yrs	II/2b
Long and colleagues[18]	Retrospective cohort; nested case control	2012	USA	AZA/6MP	≥1 Rx	3,288	12,945	2 yrs	II/2b
Gómez-García and colleagues[19]	Retrospective observational cohort	2013	Spain	AZA/6MP	Any use	429	383	12.19 yrs	II/2b
Ariyaratnam and Subramanian[20]	Meta-analysis (of 8 previous studies)	2014	N/A (United Kingdom)	AZA/6MP	Per included studies	14,081	46,000	3.81 yrs (weighted avg.)	II/2a
Abbas and colleagues[21]	Retrospective cohort; nested case control	2014	USA	AZA/6MP	Person-years of any TP exposure	3,346	14,527	8.1 yrs	II/2b
Beigel and colleagues[22]	Retrospective cohort	2014	Germany	AZA/6MP ± TNFα	2.0–2.5 mg/kg AZA	262	404	5.66 yrs	II/2b
McKenna and colleagues[23]	Database inquiry (adverse event)	2014	USA	AZA/6 MP and TNFα	TP use in TNFα trial (FAERS)	241	752	N/A	III/2c
Osterman and colleagues[24]	Retrospective cohort; nested case control	2014	USA	AZA/6 MP + ADA vs ADA alone	ADA alone, ADA + TP or MTX, ADA + TP only	563	900	1.5 yrs (median)	II/2b
Kopylov and colleagues[25]	Nested case control	2015	Canada	AZA/6MP, MTX and TNFα	≤12 mo, 13–36 mo, or >36 mo exposure	474	4,680	No reported mean (>1 yr, all patients)	II/2b

TABLE 1. (Continued)

Reference	Study Type	Year	Country	Drug(s)	Exposure	Cases	Controls	Mean Follow-Up	LOE (USPSTF/CEBM)
Scott and colleagues[26]	Retrospective cohort	2016	USA	AZA/6MP and TNFα	≥2 Rx in 4 mo, with at least 1 Rx after incident NMSC	381	2,407	2.24 yrs	II/2b
van den Heuvel and colleagues[27]	Retrospective cohort	2016	the Netherlands	AZA/6MP/TG	>365 d of use	456	2,496	8.1 yrs	II/2b
Clowry and colleagues[28]	Retrospective cohort	2017	Ireland	AZA/6MP and TNFα	Any TP use	1,084	874	9.8 yrs	II/2b

6MP, 6-mercaptopurine; ADA, adalimumab; AZA, azathioprine; LOE, level of evidence; NMSC, nonmelanoma skin cancer; TG, thioguanine; TNF, tumor necrosis factor; TP, thiopurine.

identified an additional 9 that did not provide data regarding the question of NMSC risk in patients with IBD using thiopurines. In total, there were 18 articles that met criteria for inclusion in the final review (Figure 1).

Study Characteristics and Level of Evidence

Fourteen of the selected studies were population or patient database cohort studies (13 retrospective design and 1 prospective design). Six of the 14 cohort studies also provided a nested case-control analysis of the data[12,14,17,18,21,24]; 2 additional studies were designed as nested case-control analyses without a population cohort.[11,25] In addition to these, there was 1 adverse event database inquiry[23] and 1 meta-analysis that were included[20] (Table 1).

There was significant heterogeneity in the definition of thiopurine exposure used in each of the studies, with some only requiring history of any thiopurine use during the study period, whereas others defined specific dose and duration of use as inclusion criteria. Some studies were designed to compare use of biologic immunotherapy with and without thiopurines, and therefore did not include a thiopurine-only group (Table 1). The number of cases (or cohort size) is listed along with control population size and the mean follow-up (ranging 1.5–12.19 years) in Table 1.

The LOE was assessed by scales developed by the United States Preventive Services Task Force and the Oxford Center for Evidence-Based Medicine. The LOE ranged from II/2a to III/2c, with most of the included articles assigned to II/2b LOE (n = 16, 89%) (Table 1).

Outcome Measures and Statistical Risk

Most of the studies included in the authors' analysis sought to record any incidence of NMSC during any portion of the follow-up period (n = 15, 83%). A smaller number of studies set time parameters for occurrence of NMSC within the assessment period[21,24] (n = 2, 11%) and 1 study sought to determine the time to incidence of a second NMSC after a primary incident NMSC was identified[26] (Table 2).

TABLE 2. Outcomes, Statistical Measures, and Limitations of Reviewed Publications

Reference	*Outcome*	*Statistical Measure(s)*	*Limitations/Risk of Bias/Comments*
Armstrong and colleagues[11]	NMSC incidence in AZA users	OR: 0.99 (95% CI, 0.35–2.81)	Selection bias in the form of community provider–only database in areas where secondary care centers provide significant portion of AZA Rx's; ascertainment bias is likely; study only analyzes AZA users and not 6MP
Long and colleagues[12]	First NMSC Dx and Tx (claims based) after IBD diagnosis	Cohort study, IRR: 1.64 (95% CI, 1.51–1.78) Case-control study, recent use OR: 3.56 (95% CI, 2.81–4.50); persistent use adjusted OR: 4.27 (3.08–5.92)	Selection criteria limit study population to those aged <64 yrs; retrospective cohort controls were non-IBD (nested case study had IBD controls); exposure assessment was pharmacy claim–based but without dose information; detection/ascertainment bias is not controlled for in cohort analysis; relatively short mean duration of follow-up
Setshedi and colleagues[13]	Any cancer (with NMSC subset) identified by chart review in IBD database	RR, 4.9 (95% CI, 1.1–21.8); white subset, RR 1.4 (2.3–47.7)	Small study population likely to affect risk calculations; study population is mix of white, mixed race, and African patients who have very different NMSC risk susceptibility; small number of patients with NMSC prevented dose–response effect analysis; UV exposure levels do not correspond well to other studies reviewed
Singh and colleagues[14]	SCC and BCC cases occurring in IBD database	Cohort study, SCC HR: 5.40 (95% CI, 2.00–14.56); BCC HR: 1.12 (0.68–1.85) Case-control study, SCC OR: 20.52 (2.42–173.81); BCC OR: 2.07 (1.10–3.87)	Database did not include use of immunosuppressant medications before 1995; coding and capture of NMSC had not been previously validated in the database used; this study was the only study to differentiate between SCC and BCC risk profiles; examined the effect of dose on NMSC risk
Peyrin-Biroulet and colleagues[15]	NMSC Dx during cohort entry period	Ongoing TP, HR: 5.9 (95% CI, 2.1–16.4; $p = .0006$) Past TP, HR: 3.9, (1.3–21.1; $p = .02$)	CESAME cohort included a younger patient population than many other studies reviewed, which may overestimate the HR due to low incidence of NMSC in age-matched controls
van Schaik and colleagues[16]	NMSC Dx during/after TP use	Unadjusted HR: 0.94 (95% CI, 0.58–1.50); adjusted HR: 0.85 (0.51–1.41)	Small study sample size limits conclusions; inclusion criteria more strict than other studies, limiting direct comparisons

TABLE 2. (Continued)

Reference	*Outcome*	*Statistical Measure(s)*	*Limitations/Risk of Bias/Comments*
Camus and colleagues[17]	Incident cancers (w/NMSC subset) occurring in registry of patients with CD	No statistical measure provided; 1.8% of TP responders and 0% of controls developed NMSC	Only analyzes AZA users and only patients with CD (not UC); data collected from single-center tertiary care facility's database; high percentage of patients lost to follow-up (19%); very small number of NMSCs in exposed group and none in control group (limited power); no statistical analysis specific to NMSC risk was provided by authors
Long and colleagues[18]	First NMSC Dx and Tx (claims based) after IBD diagnosis	Cohort study, IRR: 1.46 (95% CI, 1.40–1.53); adjusted HR: 1.34 (1.28–1.40) Case-control study, any TP use, adjusted OR: 1.85 (95% CI, 1.66–2.05); TP use with anti-TNF agent, OR: 3.89 (2.33–6.46)	Selection criteria limit study population to those aged <64 yrs; study has 6 mo lead time or screening time which may underestimate affected cases; study uses administrative claims data that is subject to misclassification of exposure/outcomes; no data on TP dosing are obtainable; relatively short mean duration of follow-up; study is large and has robust statistical power and was controlled for health care utilization
Gómez-García and colleagues[19]	Any malignancy (included NMSC as subset) in TP user	Not provided; post hoc calculation of RR: 1.19 (95% CI, 0.42–3.40, $p = .74$)	Small study, overall study population, and small number of controls; no power calculation performed; imprecise definition of TP exposure; incidence rates on study population may be influenced by UV exposure of study location (Granada, Spain)
Ariyaratnam and Subramanian[20]	NMSC Dx while on TP	Pooled-adjusted HR: 2.28 (95% CI, 1.50–3.45)	Significant heterogeneity of studies included in meta-analysis (population characteristics and duration of follow-up contributed heavily); HR was heavily influenced by hospital-based populations and shorter duration of follow-up; variations in study design within the meta-analysis cannot be controlled for; provides the largest collective dataset and robust external validity
Abbas and colleagues[21]	NMSC Dx (and Tx) at least 6 mo from study start; also measured risk after stopping TP and cumulative incidence by increasing years of exposure	HR: 2.1 (95% CI, 1.6–2.6) (HR 0.7, 95% CI, 0.5–1.0, after stopping TP) IRR: first year, 1.6 ($p = .09$); second year, 2.1 ($p = .005$); third year, 2.2 ($p = .007$); fourth year, 2.1 ($p = .04$); fifth year, 3.6 ($p < .0001$); 5 + year, 2.9 ($p < .0001$)	Patient population limited to VA health care system (older, white, male patient bias) which impacts external validity; did account for ascertainment bias which decreases magnitude of HR; socioeconomic status of study population better matches general population than tertiary care center populations; controlled for relative UV exposure levels across the study population

TABLE 2. (Continued)

Reference	*Outcome*	*Statistical Measure(s)*	*Limitations/Risk of Bias/Comments*
Beigel and colleagues[22]	Any malignancy (with NMSC subset) occurring during study period	8 cases of NMSC in thiopurine subset (vs zero in anti-TNF group); no statistical calculation provided, post hoc OR: 27.0 (1.55–470)	Very small study size limits the statistical power of this analysis; there were no NMSC events in the comparison group (anti-TNF), which does not match trends noted in other studies; no statistical analysis is provided by the authors (our post hoc OR is provided for ease of comparison; confidence interval is wide)
McKenna and colleagues[23]	Incident NMSC while on anti-TNF therapy plus TP compared with anti-TNF alone	PRR, augmented odds of NMSC with concomitant TP and anti-TNF ($N = 51$, $p < .001$) vs with anti-TNF alone ($N = 93$, $p = .036$)	Adverse event database (FAERS) is limited by a spontaneous reporting bias; underreporting and overreporting are not controlled for; does not specify dose or duration of exposure; database was heavily skewed toward patients with CD (not characteristic of IBD population as a whole); statistical measures difficult to compare with other studies
Osterman and colleagues[24]	Incident NMSCs on ADA alone, ADA + any immunomodulator, or ADA + TP, (up to 70 d after last ADA dose), Crohn disease only	TP + ADA vs ADA alone, unadjusted RR: 3.63 (95% CI, 1.14–11.58); adjusted RR: 4.01 (1.24–13.00)	Crohn disease only; no immunomodulator-only group (i.e., TP only); short median follow-up time compared with other studies which may underestimate NMSC in ADA only group; immunomodulator duration was not factored into risk calculations; did not account for relative UV exposure; combined randomized clinical trial data with prospective observational data; study had 2 comparison groups (general population and patients with CD)
Kopylov and colleagues[25]	NMSCs after specified duration of therapies selected	≥3 yrs of TP, OR 1.41 (95% CI, 1.11–1.79) >5 yrs of TP, OR: 2.07 (95% CI, 1.36–3.7) After stopping TP, OR: 1.04 (0.69–1.55)	Younger patients are underrepresented in this study due to database characteristics; no information on disease severity; UV exposure was not controlled for
Scott and colleagues[26]	Second NMSC, 1 + year after incident NMSC	HR: 1.49 (95% CI, 0.98–2.27) (HR 1.35, 95% CI, 0.87–2.70 for short-term TP use)	Older patient population (Medicare only); limited comparability with other studies because outcome was second NMSC 1 + years after incident NMSC. Exclusion criteria may have removed high incidence outliers that would further elevate HR and improve significance calculation
van den Heuvel and colleagues[27]	Any cancer Dx (with NMSC subset) obtained from chart review and Dutch cancer registry cross-reference.	Total IBD cohort, SCC, SIR: 3.83 (95% CI, 1.83–7.04), TP-only exposure group, SCC SIR: 3.88 (1.04–9.93)	Medication analyses were based on prescription data only; HRs were not calculated which limits comparison with other studies; highly reliable cancer diagnoses due to cross-reference strategy

TABLE 2. (Continued)

Reference	*Outcome*	*Statistical Measure(s)*	*Limitations/Risk of Bias/Comments*
Clowry and colleagues[28]	First NMSC of any subtype appearing in cross-reference of IBD database and national cancer registry	OR: 5.26 (95% CI, 2.15–12.93)	No dose or duration of immune suppressive therapy was available in the database; patients older than 85 yrs were excluded; limited by small sample size and use of a hospital-based database (selection and ascertainment bias); not stratified by UV exposure

6MP, 6-mercaptopurine; AZA, azathioprine; BCC, basal cell carcinoma; CD, Crohn disease; CI, confidence interval; Dx, diagnosis; HR, hazard ratio; IBD, inflammatory bowel disease; IRR, incidence rate ratio; NMSC, nonmelanoma skin cancer; OR, odds ratio; PRR, proportional reporting ratio; RR, relative risk; SCC, squamous cell carcinoma; SIR, standardized incidence ratio; TNF, tumor necrosis factor; TP, thiopurine; Tx, treatment; UC, ulcerative colitis.

Statistical risk assessments were very heterogeneous in the collection of reviewed studies. Seven studies (39%) reported hazard ratios (HRs) for NMSC risk associated with thiopurine treatment of IBD. These HRs ranged from 0.85 to 5.9 for recent or ongoing use of thiopurines and from 0.7 to 3.9 for past use of thiopurines (see Table 2 for specific HRs and confidence intervals). Most of the studies reporting HR indicated a ratio greater than 1 and 5 of the 7 reported confidence intervals that did not intercept 1 (n = 5 [of 7], 71% of studies reporting HR). A smaller set of studies (n = 4, 22%) reported odds ratios (ORs) for NMSC with thiopurine use in a range from 0.99 to 5.26, with 3 of 4 having significantly increased odds (Table 2).[11,14,25,28] Incidence rate ratios (IRRs)were reported by 3 studies (17%), with a range from 1.46 to 2.9, and all 3 showed confidence intervals that fell above the significance cutoff.[12,18,21] Relative risk calculation was provided by 1 study (4.9 [95% CI, 1.1–21.8])[13]; it was also calculated post hoc by the authors of this review for 1 study without statistical calculations provided specifically for NMSC risk (1.19 [95% CI, 0.42–3.40, p = .74]).[19] One study provided a proportional reporting ratio for NMSCs identified in an adverse event database,[23] and 1 study reported standardized incidence ratios (SIRs) for SCC in an IBD cohort with all treatment types (3.83 [95% CI, 1.83–7.04]) as well as a thiopurine-only IBD treatment group (3.88 [95% CI, 1.04–9.93]), both of which were statistically significant.[27]

Limitations and Bias

Study-specific limitations and potential for bias are reviewed in Table 2. Of note, 2 studies were set up in a manner that only analyzed patients with CD, but not other IBD subtypes.[17,24] Several studies were performed in databases that forced arbitrary age cutoffs.[12,18,26] Two studies only analyzed azathioprine users but not 6-mercaptopurine.[11,17] The potential impact of these limitations and biases are discussed below.

Discussion

Through the collaborative efforts of dermatologists and transplant surgeons, the authors now appreciate the degree to which immune suppression confers an

estimated 65- to 250-fold increase in NMSCs, as well as the significant morbidity and mortality associated with them.[30] This knowledge has translated into widespread aggressive, longitudinal screening programs and increased awareness at both the physician and patient level. By comparison, the dermatologic literature has directed much less attention to the potential risk of NMSC in other autoimmune disease states that require similar prolonged immune suppression using steroid-sparing agents. Skin cancer screening guidelines are lacking for these patients, as is consensus on the relative risk attributable to various therapeutic agents.

Risk in Inflammatory Bowel Disease Versus Noninflammatory Bowel Disease

The risk of NMSC in the IBD patient population compared with unaffected control patients was evaluated in a subset of health care database studies included in this review. Confirming what has been suggested in previous reports on the risk of general malignancies, the risk of NMSC within these populations was increased with an IRR of 1.46 to 1.64.[12,18] A large French cohort reported the SIR of NMSC in their patients with IBD at 2.71 (95% CI, 1.83–3.87; $p < .0001$), which includes those who have and have not received thiopurine therapy.[15] Data derived from a Canadian cohort suggested that increased risk of NMSC in patients with IBD as a whole was only present for those younger than 50 years of age, beyond which the risk returned to baseline.[14] These data are all consistent with reports of NMSC risk in patients with IBD predating the era of common use of immunosuppressants as treatment.[31]

Risk Attributable to Thiopurine Use

Large health care database cohorts have provided the most robust data on the NMSC risk attributable to thiopurine use. The VA health care system analysis showed an adjusted HR of 2.1 for development of NMSC while on thiopurine therapy.[21] Similarly, increased risk was noted in other large health care database cohorts[12,15,18,25] (Table 2). The largest collection of patient data is provided by a meta-analysis of 8 early studies, which indicated an adjusted NMSC HR of 2.28 (95% CI, 1.50–3.45) in patients with IBD using thiopurines.[20] Among the publications reviewed, studies with smaller case cohorts were more likely to report lack of statistical significance for reported risk.[11,16,19]

By asking whether thiopurine therapy (vs anti-TNF agents) increases the risk of a second incident NMSC, Scott and colleagues sought to address the danger of maintaining patients on these treatments (for short or longer courses) once they have identified themselves as sensitized individuals by virtue of a primary, incident NMSC. Their analysis, however, indicated that short-term thiopurine therapy (HR 1.53; 95% CI, 0.87–2.70) and 1 year or more of thiopurine therapy (HR 1.49; 95% CI, 0.98–2.27) was not statistically associated with increased risk of a second incident NMSC, although a trend toward increased risk was noted.[26] This conclusion may have been influenced by exclusion criteria that removed patients with new NMSCs during the first 6 months after the primary incident NMSC. The authors' experience (authors J.W.H. and M.A.P.-M.) in treating patients with IBD using thiopurine therapy would suggest that there is a subset of patients with rapid and frequent development of nonpreexisting NMSC that might be missed by application of this stringent exclusion criterion.

Dose and Duration Effect

From a theoretical and practical perspective, the degree to which the immune system is suppressed seems to correlate with frequency and severity of suppression-related sequelae. Solid organ transplant recipients who receive high levels of immune suppression present with an elevated risk profile for NMSC compared with the level of suppression typically seen in patients with IBD.[30] In so far as it was specifically addressed in a subset of the reviewed articles, however, azathioprine and 6-mercaptopurine did not show a daily dose-dependent risk at the doses that are typically used to treat patients with IBD.[21] This may indicate the presence of a threshold effect, wherein typical daily doses of thiopurine immunosuppression used in IBD supercede the dose required to observe sensitization but do not alter the order of magnitude of NMSC risk (as seen in transplant patients).

However, several studies suggested that overall duration of therapy (i.e. total cumulative dose) did affect risk profile, with longer use of thiopurines translating to escalating NMSC risk.[22] Incidence rate ratio rose from 1.6 ($p = .09$) to as high as 3.6 ($p < .0001$) by the fifth year and remained high (IRR 2.9, $p < .0001$) for treatment extending beyond Year 5.[21] Similarly, a 5-year treatment duration was identified as a threshold for further increasing NMSC risk in a Canadian cohort.[25] Comparing recent (≤90 days) versus persistent (>365 days) thiopurine use, Long and colleagues[12] demonstrate a similar trend toward increased risk with longer therapy (OR 3.56 vs 4.27, respectively). A Canadian cohort demonstrated that a cumulative dose of >5.7 g AZA/6-MP could be used as a threshold to stratify those with significantly increased odds of developing BCC or SCC.[14] In contrast to this, some authors find no significant risk from beginning to end of an extended therapeutic regimen.[16] Additional high-quality cohort analyses may help to better define the effect of therapy duration on NMSC risk, but current evidence weighs heavy on the side of cumulative dose influencing NMSC risk.

Impact of Age

Common knowledge supports that risk of NMSC increases with advancing age, a phenomenon that is echoed by the various studies included in this review. Of note, however, is the fact that studies specifically evaluating the risk of NMSC in IBD regarding patient age often identified exposure windows that more significantly impacted risk. Clowry and colleagues[28] suggest that thiopurine exposure between the ages of 30 to 50 and also those over 70 were age groups with greatest observed impact on NMSC risk. It is also interesting to note that population-based studies drawing from predominantly younger populations[12,15,18] produced more robustly increased NMSC risk than those studies cataloguing a decidedly older population.[21,26] This suggests that beyond a certain age, the impact of thiopurine use on NMSC risk is lessened due to accumulating age-related risk. It also highlights the importance of early preventative screening for young patients who are not otherwise thought of as high risk for NMSC.

Residual Risk

The question of whether NMSC risk is modifiable in affected patients with IBD by virtue of discontinuing thiopurine therapy has been addressed by a handful of studies. From a biochemical perspective, incorporation of modified purine analogues (6-thioguanine, peak absorbance 342 nm) into the DNA of replicating cells (e.g. basal keratinocytes) renders their DNA sensitive to UV-A–induced mutagenesis.[6,7] Although the authors traditionally recognize UV-B radiation as the primary driver of mutagenic events and counsel patients regarding UV-B protective habits, UV-A wavelengths pass through glass and constitute a more chronic, less-heralded source of mutagenesis in sensitized patients (e.g. thiopurine users). The process of cumulative UV-A–mediated mutagenesis during thiopurine use has been suggested to affect the tumor suppressor, patched, which has a well-established role in NMSC development.[32] A French, prospective observational cohort of patients with IBD showed potential evidence of a residual effect of past thiopurine exposure, with NMSC HR reported at 3.9 (95% CI, 1.3–12.1; $p = .02$). This risk is reduced, however, from the reported HR for ongoing thiopurine therapy (5.9, 95% CI, 2.1–16.4).[15] In comparison, a VA cohort indicated that relative risk of NMSC returned to baseline after stopping thiopurine use (adjusted HR 0.7, $p = .07$), even after up to 5 years of continual use.[21] Similar findings were reported in a Canadian cohort.[25] Although it seems clear that removing thiopurines from the therapeutic approach reduces NMSC risk, the degree of residual risk remains a question that requires additional study to further clarify the true benefit of therapeutic substitution/discontinuation.

Risk of Alternative Therapies

This analysis did not seek specifically to address a comparison of the NMSC risk between alternative therapeutic options for IBD. However, several of the individual studies that the authors evaluated did compare the relative risk of thiopurine therapy versus newer biologic therapies. In a study that failed to show a statistical increase in second incident NMSC on thiopurine therapy, anti-TNF therapy (i.e., infliximab,

adalimumab, certolizumab, golimumab, or etanercept) showed a HR of 1.36 (95% CI, 0.76–2.44) and slightly lower (but statistically insignificant) decreased incidence of a second NMSC while on therapy.[26] The authors argued that anti-TNF therapy does not demonstrate a clear benefit regarding NMSC risk because HR significantly overlap. In a larger health care database population, patients with IBD treated with recent anti-TNF agents did not show an increased risk of NMSC (adjusted OR 1.14; 95% CI, 0.95–1.36) but persistent use of biologic therapy alone increased NMSC OR to 1.63 (95% CI, 1.12–2.36).[18] This was still below the risk level of persistent thiopurine use or persistent thiopurine use combined with a biologic agent (OR, 2.72 and 3.89, respectively).[18] Osterman and colleagues[24] showed that adalimumab therapy alone did not increase NMSC risk (SIR 1.20; 95% CI, 0.39–2.80), whereas addition of a thiopurine to this regimen did increase NMSC risk significantly. As more data accumulate on the use of various biologic agents in IBD treatment, the authors will be able to make more confident assessments on risk profiles of alternative therapies. However, sufficient data exist to suggest a trend for decreased overall risk of NMSC with single-agent biologic treatments.

Limitations

The publications included in this review represent a range of study designs that introduce significant heterogeneity at the level of population selection (e.g., age, nationality, and care setting), definition of thiopurine exposure, duration of follow-up, and approach to statistical analysis of attributable risk. All studies, excluding one, were retrospective in nature and are therefore subject to selection and misclassification bias. Some, but not all, of the studies made attempts to address these potential biases. Several of the studies described comparably small IBD patient populations and their conclusions are often as odds with the consensus provided by meta-analysis and larger independent studies. Larger, nationwide health care database inquiries have provided robust statistical power but the data are sometimes limited to specific patient populations that individually limit their generalizability (e.g., age group limitations). Several of the large health care database studies provided shorter mean follow-up duration, which limits interpretation of long-term risk estimates. Studies that only evaluated azathioprine as an exposure cannot be reliably used to assess risk on 6-mercaptopurine users. The 2 studies which examined only patients with CD limit the ability to extend risk assessment to patients with UC, who have slightly different malignancy risk profiles. Additional limitations specific to each study reviewed are noted in Table 2.

Conclusion

Nonmelanoma skin cancer risk seems to be moderately increased in patients with IBD undergoing thiopurine therapy. This increased NMSC risk does not seem to be daily dose-dependent but some studies show a duration-dependent (cumulative dose) trend for increasing risk. Although there is a relative paucity of data directly addressing NMSC risk profile after discontinuing therapy, there is evidence to suggest that residual NMSC risk decreases and/or returns to baseline after stopping thiopurine therapy. There seems to be disproportionately increased risk in younger patients who, by virtue of their age, are not commonly targeted for routine skin screening. Dermatologists should educate patients with IBD using thiopurines on their increased NMSC risk, the importance of daily sun protective measures, and benefits of regular skin cancer screening starting at a younger age.

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