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Thiopurines and myeloid disorders: is more caution needed when treating inflammatory bowel disease patients?

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Thiopurines remain the backbone therapy of inflammatory bowel diseases (IBD). However, these drugs have potential mutagenic and carcinogenic effects, especially when prescribed for a long time. In addition to the increased risk of lymphoma and non-melanoma skin cancer, recent data suggest that risk of myeloid disorder is increased in IBD patients with past exposure to thiopurines. Even if individual risk is low, practitioners who take care of IBD patients should be aware of this potential complication of thiopurines treatment.

Inflammatory bowel diseases (IBDs) are chronic disabling conditions affecting approximately 6 million people worldwide. Immunosuppressive drugs remain the backbone therapy of IBD. Among them, thiopurines, represented by azathioprine (AZA) and 6-mercaptopurine, are recommended by the American College of Gastroenterology and European Crohn's and Colitis Organisation for inducing and maintaining remission in both Crohn's disease (CD) [1,2] and ulcerative colitis (UC) [3,4]. In a French referral center, the cumulative probabilities of receiving AZA 5 years after diagnosis were 71% among CD patients and 49% among UC patients [5,6].

Thiopurines were first used for the treatment of leukemias in the 1950s, and thereafter for organ transplantation [7]. First UC patients treated with 6-mercaptopurine were reported in 1962 [8]. Thiopurines are purine analogs that compete with endogenous purines, essential components of DNA and RNA [7]. They are prodrugs, metabolized by hypoxanthine-guanine phosphoribosyl transferase in 6-thioguanosine 5′-monophosphate, then in deoxy-6-thioguanosine 5′-triphosphate and in 6-thioguanine nucleotide (6-TGN), thanks to kinases and reductases. Incorporation of 6-TGN in DNA results in cell cycle arrest and lymphocyte apoptosis by a process involving the mismatch repair pathway. Efficacy of thiopurines in IBD may be related to an increase in T-cell apoptosis in the lamina propria of intestinal mucosa. Thiopurines have a mutagenic effect that is associated with total dose and duration of treatment, especially among IBD patients.

While the protective effect on colorectal cancer risk is debated [9], data from the CESAME cohort study indicate that thiopurines are associated with an increased risk of malignancy, including lymphoma and non-melanoma skin cancer [10]. Two previous reports outside IBD suggested an increased risk of myeloid disorders (MD) among patients treated with thiopurines [11,12]. A recent report from the CESAME cohort study found that the risk of MD was not increased among the overall IBD population compared to the general population, but past exposure to purine analogs increased this risk sevenfold (standardized incidence ratio [SIR]: 6.98; 95% CI: 1.44–20.36) [13]. Five incident MD cases were diagnosed and four of them were exposed to thiopurines.

MDs are a heterogeneous group of malignant diseases affecting myeloid cell lineage. Among them, most frequent are

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Table 1. Association between myeloid disorders and thiopurines.

Study (year)	Country	Disease type	Study type	Study period	Patients (n)	Number of cases	MD type	Calculated risk	95% CI	Ref.
Lopez *et al.* (2014)	France	IBD	Prospective observational study	2004–2007	19.486	5	MDS (n = 3) and AML (n = 2)	SIR: 6.98	1.44–20.36	[13]
Asten *et al.* (1999)	15 European countries	Rheumatoid arthritis	Prospective observational study	1979–2000	1.773	NA	NA	IRR: 3.74	1.48–9.47	[11]
Morton *et al.* (2014)	USA	Solid-organ transplantation	Population-based study	1987–2009	207.859	319	AML (n = 125) MDS (n = 101)	SIR: 6.6 SIR: 8.4	NA NA	[12]

AML: Acute myeloid leukemias; CI: Confidence interval; IBD: Inflammatory bowel diseases; IRR: Incidence rate ratio; MDS: Myelodysplastic syndromes; NA: Not available; SIR: Standardized incidence ratio.

acute myeloid leukemias (AMLs) and myelodysplastic syndromes (MDSs). AML is a clonal disorder of hemopoietic progenitor cells that lose the ability to differentiate normally and respond to normal regulators of proliferation, leading to fatal infection, bleeding or organ infiltration. In Europe, annual incidence was 3.7/100,000 during the 1995–2002 period, with a 5-year overall survival of 19%. A retrospective cohort study showed an association between IBD and hematological malignancies, with a SIR of 1.9 (95% CI: 1.5–2.3) [14]. First cases of AML among IBD patients were reported in 1980, with five cases in a cohort of 400 UC patients [15]. Several cohort studies subsequently assessed the over risk of AML in case of IBD, with odds ratios (OR) ranging from 1.7 to 7.0 [16–19]. Among reported cases of AML, some IBD patients were treated with thiopurines, but very few studies evaluated the association between drug and MD. In 1999, a population-based study with 550 IBD patients treated with 6-mercaptopurine between 1969 and 1997 found one case of leukemia, corresponding to an incidence of 11 per 100,000 patient-years. No statistical analysis was performed in order to quantify risk of AML among thiopurines-treated IBD patients [20].

MDSs are characterized by cytopenias and dysplasias ≥10% of at least one myeloid lineage, with a leukemic transformation risk. In Europe, annual incidence of MDS was 1.5/100,000 during the 1995–2002 period, with a 5-year overall survival of 29%. First descriptions of MDS among IBD patients were published in 1992, then 25 incident cases were reported in a 15,000 subjects IBD cohort [21]. Two of them had received purine analogs in the past [21]. In two population-based studies, no statistical association was found between MDS and CD (OR: 1.60; 95% CI: 0.91–2.78 and OR: 1.5; 95% CI: 0.4–5.7; respectively) or between MDS and UC (OR: 1.33; 95% CI: 0.86–2.07 and OR: 1.5; 95% CI: 0.6–3.7) [19,22].

The link between IBD, thiopurines and MD is complex, associating chronic inflammation and drug toxicity. Similar pathways are involved in the development of IBD and AML, such as the phosphatidylinositol 3-kinase/Akt (protein kinase B)/mammalian target of rapamycin-signaling pathway.

Outside IBD, a multicentric prospective cohort study of 1773 rheumatoid arthritis patients found an increased risk of neoplasms of the immune system in case of thiopurine exposure, with an incidence rate ratio of 3.74 (95% CI: 1.48–9.47) (Table 1) [11]. Recently, Morton *et al.* showed in a population-based study among 207,859 solid-organ transplant recipients an increased risk of AML (SIR: 6.6) and MDS (SIR: 8.4) when AZA was given for initial maintenance of immunosuppression (Table 1) [12].

In conclusion, several studies showed convergent results about the increased risk of MD among patients who received thiopurines, with a SIR ranging from 3.7 to 8.4 [11–13]. This must be balanced against the modest but well-known benefits of thiopurines in CD and UC. We have to identify risk factors for developing MD in order to decrease this risk among thiopurine-treated patients. In theory, high level of 6-TGN are more likely to result in immunosuppression-related side effects such as infection and neoplasias. Monitoring 6-TGN levels might identify patients 'at

risk', with a threshold of 550 pmol/8×10^8 erythrocytes [23]. In the CESAME cohort, mean duration of thiopurines treatment was 8 years [13], and among pediatric patients on 6MP/methotrexate maintenance therapy for an acute lymphoblastic leukemia, longer duration of treatment was related to an increased risk of MD ($p = 0.02$) [24]. American College of Gastroenterology and European Crohn's and Colitis Organisation recommend stopping thiopurines after at least 4 years with a quiescent CD [1,2]. Hence, we could consider stopping thiopurines once deep remission (clinical and endoscopic remission) is achieved in clinical practice.

Along with recent findings showing that the efficacy profile of thiopurines has been overestimated [25], the increased risk of malignancies, which had been underestimated, makes questionable the risk–benefit ratio of this drug class in IBD. However, safety profile of thiopurines must be balanced with risk of no treatment and risk of other medications such as TNF antagonists. Also, absolute risk of myeloid disorder with thiopurines among IBD patients remains low.

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