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Increased risk of thiopurine-related adverse events in elderly patients with IBD

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Summary

Background: Thiopurines are the most widely used immunosuppressants in IBD although drug-related adverse events (AE) occur in 20%-30% of cases.

Aim: To evaluate the safety of thiopurines in elderly IBD patients

Methods: Cohort study including all adult patients in the ENEIDA registry who received thiopurines. Patients were grouped in terms of age at the beginning of thiopurine treatment, specifically in those who started thiopurines over 60 years or between 18 and 50 years of age. Thiopurine-related AEs registered in the ENEIDA database were compared.

Results: Out of 48 752 patients, 1888 started thiopurines when over 60 years of age and 15 477 under 50 years of age. Median treatment duration was significantly shorter for those who started thiopurines >60 years (13 [IQR 2-55] vs 32 [IQR 5-82] months; $P < .001$). Patients starting >60 years had higher rates of all types of myelotoxicity, digestive intolerance and hepatotoxicity. Thiopurines were discontinued due to AEs (excluding malignancies and infections) in more patients starting >60 years (67.2% vs 63.1%; $P < .001$). Elderly age and female sex were independent risk factors for most AEs.

Conclusion: In elderly IBD patients, thiopurines are associated with an increased risk of non-infectious, non-neoplastic, AEs.

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*List of investigators of GETECCU-ENEIDA are listed in Appendix 2.

1 | INTRODUCTION

Thiopurines (azathioprine and mercaptopurine) are the most widely used immunosuppressants in IBD. These drugs are effective in maintaining remission in both ulcerative colitis and Crohn's disease.[1,2] However, their use is hampered by the high rate of adverse events (AEs) reported to occur to between 10% and 28% of IBD patients,[3,4] 31% of which require treatment discontinuation. The most common thiopurine-related AEs are leukopenia, nausea, hepatotoxicity and acute pancreatitis.

Recently, the elderly population with IBD is increasing due to the worldwide increased incidence of IBD and ageing.[5,6] In addition, a prevalence of up to 10%-23% of elderly onset IBD in patients has been reported.[7,8]

Starting immunosuppressants or biological therapies in elderly IBD patients is often a challenge for physicians due to comorbidities and polypharmacy. Polypharmacy, reported in 44% of these patients in some cohorts, increases the risk of developing AEs due to drug interactions and errors in medication intake.[9-11] Moreover, physiological changes in the elderly patients (pancreatic hypofunction, intestinal dysmotility, decreased hepatic mass and blood flow and decreased renal blood flow, and glomerular filtration rate) may impact the pharmacokinetics of orally administered drugs.[12]

In a recently published study, we evaluated the phenotypic characteristics and the use of therapeutic resources in patients with elderly onset IBD as compared to younger adult patients.[13] In addition to a lower use of immunosuppressants, in this study we found a different safety profile of thiopurines between the groups. It is known that elderly patients undergoing thiopurine treatment are at a higher risk of nonmelanoma skin cancer, urinary tract cancer and lymphoma.[14-17] It has also been shown that the risk of opportunistic or serious infections is higher in elderly patients under immunosuppressive therapy.[18,19] Although some studies have reported an increasing rate of thiopurine-related AEs with age among female patients with Crohn's disease,[20] no studies have specifically assessed the safety profile of thiopurines in elderly patients. Our aim was to evaluate the prevalence of non-infectious, non-neoplastic, thiopurine-related AEs in those IBD patients who started on these drugs when over 60 years of age.

2 | PATIENTS AND METHODS

This was an observational, retrospective, multicenter, nationwide study promoted by the Spanish Working Group in IBD (GETECCU).

2.1 | ENEIDA registry

Patients were identified in the ENEIDA registry of GETECCU, which includes patients with IBD. The database is prospectively maintained with continuous external monitoring for the completeness and consistency of the data entered. After registration, physicians from IBD centres can voluntarily include their patients' data in the registry. At the time of data extraction, the registry included more than 48 000 patients from 60 centres. The study was approved by the GETECCU Research Board and the local Ethics Committees of the participating centres. Written informed consent to participate in the ENEIDA registry was obtained from all patients. Clinical data, use, effectiveness and the AEs associated with immunosuppressive drugs, together with comorbidities are prospectively recorded in the database.

2.2 | Patients

All adult IBD patients who had received thiopurine treatment at any time during the course of the disease were identified in the ENEIDA registry. Only the first thiopurine compound was assessed in terms of safety and treatment discontinuation. In Spain, thiopurine dosing is not usually driven by erythrocyte thiopurine-methyltransferase activity (TPMTe) or gender, but only by body weight (2-2.5 mg/kg for azathioprine; and 1-1.5 mg/kg for mercaptopurine). Patients were grouped according to age at the beginning of thiopurine treatment. The elderly group included those patients who started thiopurines over 60 years of age, and they were compared with those adult patients who started thiopurines between 18 and 50 years of age. To avoid overlapping between study groups, follow-up was limited to 10 years and patients who started thiopurines between 51 and 59 years of age were excluded. Figure 1 shows the study flow chart.

2.3 | Variables and definitions

Data collection included age at the beginning of thiopurine treatment, gender, IBD type (ulcerative colitis, Crohn's disease or IBD unclassified), familial history of IBD, extraintestinal manifestations, perianal disease and patient comorbidities (cardiovascular risk factors and hyperuricaemia). Regarding thiopurine treatment, we recorded the type of thiopurine (azathioprine or mercaptopurine), TPMTe when available, and the type of AEs as recorded in the ENEIDA registry. Thiopurine-related AEs included dose-dependent AEs (hepatotoxicity and myelotoxicity—anaemia, leukopenia, lymphopenia thrombocytopenia and bone marrow suppression (suppression of the bone marrow activity leading to anaemia, leukopenia and thrombocytopenia)—) and idiosyncratic AEs (acute pancreatitis, digestive intolerance, flu-like syndrome, regenerative nodular hyperplasia, and arthralgia). Given that elderly IBD immunosuppressed patients are at a higher risk of developing malignancies and infections,[21] neoplastic and infectious thiopurine-related AEs were globally registered (not detailing their type) but excluded from the analysis of the treatment discontinuation because of AEs. Treatment discontinuation due to AEs and date were also recorded. The follow-up period was defined as the time on thiopurine treatment from the beginning of treatment until its discontinuation or the last follow-up visit.

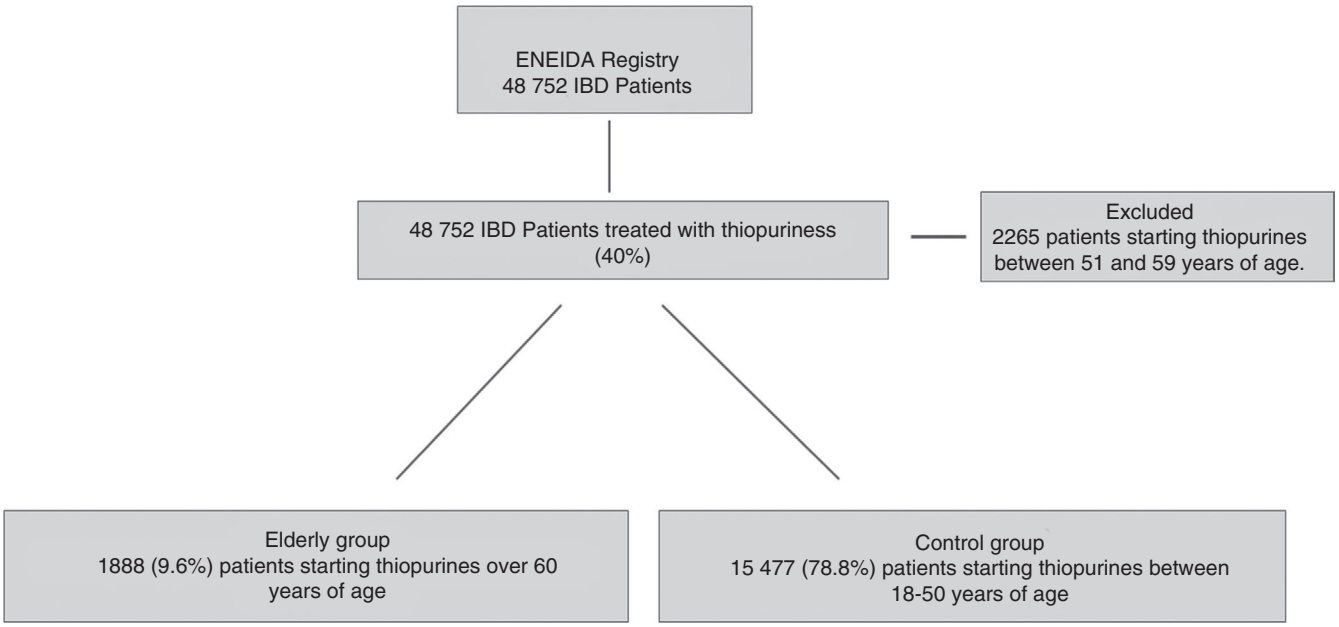

FIGURE 1 Study flow chart

2.4 | Statistical analysis

Continuous variables are expressed as mean with standard deviation or median and interquartile range (IQR) as needed and are compared using the Student's *t* test. Categorical variables are expressed as proportions with a 95% CI and compared by means of the chi-squared test. Kaplan-Meier curves were used to evaluate the cumulative probability of treatment discontinuation due to AEs and were compared between study groups by the log-rank test. We performed multivariable Cox regression to analyse the effect of age on AE-free survival with adjustment for potential confounding factors including cardiovascular risk factors, hyperuricaemia, type of IBD, type of thiopurine, gender, perianal disease, extraintestinal manifestations, familial history of IBD, and elderly or young adulthood onset of IBD.

3 | RESULTS

A total of 19 630 (40.0%) of the 48 752 IBD patients included in the ENEIDA registry had been treated at some time with thiopurines. Among them, 1888 patients (9.6%) started thiopurines when over 60 years of age and they were compared with 15 477 adult patients (78.8%) who started thiopurines between 18 and 50 years of age.

3.1 | Baseline characteristics of the cohort

The baseline characteristics of both study groups are shown in Table 1. A significantly higher proportion of the patients in the elderly group were males and had ulcerative colitis (as opposed to Crohn's disease) and comorbidities, and they also had a longer disease duration before thiopurine treatment compared to the control group. On the other hand, they had a lower rate of perianal disease, extraintestinal manifestations and familial history of IBD. In the elderly group, 1178 patients (62.4%) had elderly onset IBD (patients who were diagnosed IBD over 60 years of age) whereas the remaining patients in this group had IBD diagnosed prior to this age.

Regarding thiopurine therapy, azathioprine was the most frequent drug prescribed as the first choice (as opposed to mercaptopurine) with no differences between the study groups. TPMTe was available for 6350 patients in the whole cohort (32.0%), with more than 99.0% of them showing TPMTe higher than 5 U/mL RBCs, without differences between study groups. Median treatment duration was significantly shorter in those patients who started thiopurines over 60 years of age (13 [IQR 2-55] vs 32 [IQR 5-82] months; $P < .001$).

3.2 | Thiopurine-related adverse events

Eight hundred and twenty patients (43.4%, [95% CI; 41.2%-45.7%]) in the elderly group developed some kind of thiopurine-related AEs (a total of 951 AEs leading to a cumulative incidence rate of 205 per 1000 patients-year). This was significantly higher than the 4596 patients (29.7% [95% CI; 28.9%-30.4%]) in the control group (a total of 4982 AEs leading to a cumulative incidence rate of 99 per 1000 patients per year; $P < .001$). Although it was not the aim of our study, we observed that the elderly group presented a higher proportion of infections (3.6% vs 2.0%; $P < .001$) and neoplasms (1.5% vs 0.2%; $P < .001$) than the control group. Among patients who presented malignancies, this was the cause of thiopurine discontinuation in 88.5% (92.9% in the elderly vs 84.8% in

TABLE 1 Baseline clinical and demographic characteristics

	Elderly group	Control group	*P* value
n	1888	15 477	
Male, n (%)	1025 (54.3)	7999 (51.7)	.032
Median age at the beginning of thiopurine treatment, y (IQR)	66 (62-71)	33 (26-40)	<.001
IBD type: n (%)			
Crohn's disease	1102 (58.4)	11 073 (71.5)	
Ulcerative colitis	757 (40.1)	4286 (27.7)	<.001
IBD unclassified	29 (1.5)	118 (0.8)	
Extraintestinal manifestations, n (%)	354 (18.8)	3838 (24.8)	<.001
Perianal disease n (%)	275 (14.6)	3780 (24.4)	<.001
Median disease duration at the beginning of thiopurine treatment, months (IQR)	33 (7-117)	24 (5-85)	<.001
Familial history of IBD, n (%)	180 (9.5)	2,067 (13.4)	<.001
Hyperuricaemia, n (%)	37 (2.0)	37 (0.2)	<.001
Cardiovascular risk factors, n (%)	577 (30.6)	825 (5.3)	<.001
TPMTe > 5 U/mL RBCs, n (%)	707 (99.7)	5604 (99.3)	ns
TPMTe > 15 U/mL RBCs	596 (84.1)	4699 (83.3)	ns
Type of first choice thiopurine, n (%)			
Azathioprine	1796 (95.1)	14 627 (94.5)	
Mercaptopurine	92 (4.9)	850 (5.5)	ns

Abbreviations: IBD, inflammatory bowel disease; IQR, interquartile range; NS, nonsignificant; RBCs, red blood cells; TPMTe, erythrocyte thiopurine-methyltransferase activity.

the control group; $P = .43$), whereas this was only 61.6% in case of infections (67.6% in the elderly group vs 60.3% in the control group; $P = .27$).

When infectious and neoplastic AEs were excluded from the analysis, the incidence rate of AEs was still higher in the elderly group (40.4% [95% CI; 38.2%-42.6%] vs 28.3% [95% CI; 27.6%-29.0%] in the control group; $P < .001$), with a cumulative incidence of non-infectious and non-neoplastic AEs of 184 and 92 per 1000 patients-years in the elderly and control groups respectively. Moreover, the rate of treatment discontinuation due to non-infectious and non-neoplastic AEs was also significantly higher in the elderly group than in the control group (72.0%, [95% CI; 69.0%-75.2%] vs 66.2%, [95% CI; 64.8%-67.6%] respectively; $P < .001$), with a cumulative probability of thiopurine discontinuation of 31.0%, 34.9% and 37.6% at 1, 3 and 5 years in the elderly group, and 18.3%, 21.3% and 23.0% in the control group ($P < .001$) (Figure 2).

Thiopurine-related AEs are shown in Table 2. Regarding thiopurine-related dose-dependent AEs, the elderly group presented a significantly higher proportion of most types of myelotoxicity (anaemia, leukopenia, thrombocytopenia and bone marrow suppression) ($P < .001$) and hepatotoxicity ($P < .001$) than the control group. In relation to idiosyncratic AEs, the elderly group presented a significantly higher rate of digestive intolerance ($P = .002$), although there were no differences regarding other side effects such as acute pancreatitis, arthralgia, flu-like syndrome, hypersensitivity and regenerative nodular hyperplasia.

3.3 | Independent predictors for developing thiopurine-related adverse events

Table 3 summarises the risk factors found in the Cox regression analysis for developing any thiopurine-related AE, as well as for the most frequent AEs. Of note, starting thiopurines in old age, hyperuricaemia and using mercaptopurine as the initial thiopurine were independent risk factors for several AEs.

4 | DISCUSSION

The clinical management of IBD in the elderly patients may differ from standard practice for adult patients because of the less aggressive course of the disease in elderly onset patients[13,22] and a more cautious therapeutic approach due to comorbidities and polypharmacy and their potential causality of AEs and dosage mistakes. Beyond the known risk for some malignancies and infections,[17] there are few data about the safety profile of thiopurines in elderly IBD patients. Despite the introduction of several biological agents in recent years and the disappointing results of thiopurines in two recent clinical trials,[23,24] thiopurines still have a role in treatment algorithms and are commonly used in IBD.[25,26] Moreover, anti-TNF agents are also associated with a higher risk of serious infections and mycobacterial and bacterial infections than thiopurine monotherapy[27] and elderly IBD patients under anti-TNF treatment in particular are considered to be at a higher risk of severe infections.[18,19] Finally, older

age in itself is a risk factor for developing neoplasms. Therefore, starting thiopurines or anti-TNF agents in the elderly patients is a challenge for physicians and more evidence is necessary about the global safety profile of thiopurines in this subset of patients.

In the present study, which is, to our knowledge, the first to date to evaluate the safety profile of thiopurines in elderly IBD patients, we have shown that elderly IBD patients present a higher rate of thiopurine-related AEs than younger ones (even when only considering non-infectious and non-neoplastic AEs). In fact, the observed AEs rate among patients starting thiopurine therapy beyond 60 years was also greater than the rate previously reported in unselected cohort studies.[3,4,28] Moreover, when present, AEs more often resulted in discontinuation of treatment in the elderly group than in the younger patient group. However, we cannot be sure that treatment discontinuation rate is a direct consequence of the severity of AEs as it cannot be ruled out that physicians tend to be more cautious when faced with AEs in the elderly patients.

There are some factors that might explain the higher rate of AEs in the elderly group.

Firstly, the fact that dose-related AEs were more frequent in the elderly group but dose-independent AEs were not (with the only exception of digestive AEs, which are highly likely to be a mix of dose-related and dose-unrelated events) and that AEs were more frequent in females, points out that renal clearance might be the critical factor for this higher prevalence of AEs.[12] Both renal and hepatic clearance are reduced with age, and in females compared with males, leading to higher blood concentrations of drugs and their metabolites. Interestingly, Moran et al[20] in a small, retrospective, Canadian cohort already described that females over 40 years of age presented a higher risk of thiopurine-related AEs. Similarly, in one of the early ENEIDA studies with the largest cohort addressing thiopurine safety profile,[4] female gender was also a risk factor for developing nausea and myelotoxicity. Disappointingly, we cannot confirm this hypothesis definitively as thiopurine metabolite concentrations are not usually available in Spanish centres.

Moreover, the role of comorbidities and potential drug interactions may account for an increased risk of toxicity in this population. This was evident for patients with hyperuricaemia (potential users of allopurinol), in whom all types of AEs, and myelotoxicity was more common, probably because of the known inhibition of xanthine-oxidase activity by allopurinol as well as a direct TPMT inhibition affecting thiopurine metabolism.[29,30] Low TPMTe activity can be the cause of dose-dependent AEs, particularly myelotoxicity,[31] although a number of other genetic, pharmacological and infectious factors may also play a role in some cases.[32,33] In our study, low TPMTe (<5 U/mL RBCs) was not a risk factor for myelotoxicity. However, we cannot reach strong conclusions in this regard as in our cohort TPMTe was only available in 32% of patients, thiopurine metabolite determination is not available in most centres in Spain, and median dose at the time of developing AEs was not available.

In contrast, there were no differences between groups in the incidence of all types of idiosyncratic AEs except for digestive intolerance. Although we do not have a clear explanation for this, changes in immune responses in the elderly patients (which have been called immunosenescence) may play a role in this kind of side effects. In fact, although some authors state that elderly patients present a chronic pro-inflammatory status and an increased reactivity to endogenous signals, others suggest that the dysregulation of the immune system may also explain different immune responses in the

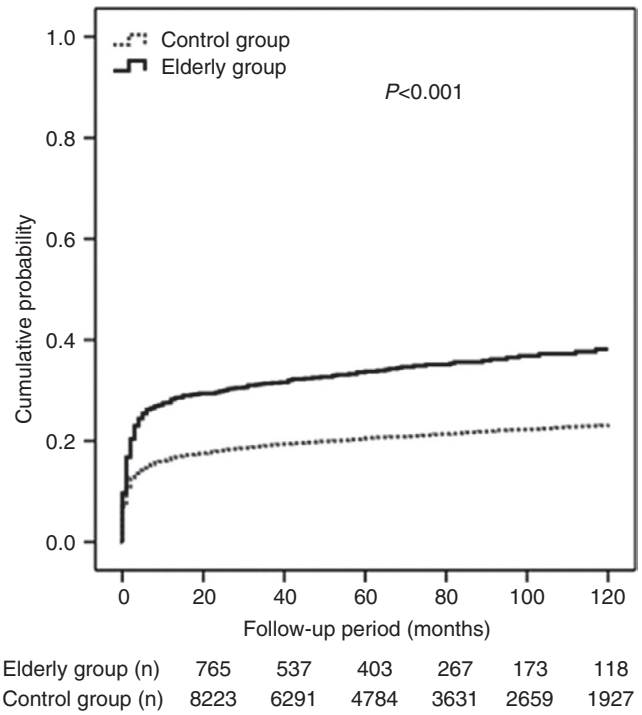

FIGURE 2 Cumulative probability of treatment discontinuation due to adverse events

TABLE 2 Thiopurine-related adverse events

Adverse event	Elderly group, n (%)	Control group, n (%)	*P* value
Myelotoxicity	264 (14.0)	1174 (7.6)	<.001
Anaemia	80 (4.3)	187 (1.2)	<.001
Leukopenia	197 (10.4)	937 (6.1)	<.001
Bone marrow suppression	37 (2.0)	142 (0.9)	<.001
Lymphopenia	6 (0.3)	34 (0.2)	ns
Thrombocytopenia	8 (0.4)	26 (0.2)	.026
Hepatotoxicity	169 (9.0)	721 (4.7)	<.001
Digestive intolerance	232 (12.3)	1550 (10.0)	.002
Acute pancreatitis	77 (4.1)	645 (4.2)	ns
Arthralgia	26 (1.4)	227 (1.5)	ns
Flu-like syndrome	1 (0.1)	7 (0)	ns
Regenerative nodular hyperplasia	0 (0.0)	2 (0.0)	ns
Hypersensitivity	9 (0.5)	69 (0.4)	ns
Other	13 (0.7)	95 (0.6)	ns

TABLE 3 Independent predictors for developing thiopurine-related adverse events

Adverse event	Risk factor	Hazard ratios (95% CI)	*P* value
Any adverse event	Elderly age	1.703 (1.568-1.849)	<.001
	Mercaptopurine	1.208 (1.078-1.355)	.024
	Hyperuricaemia	1.651 (1.194-2.284)	.002
	Female gender	1.140 (1.078-1.207)	.039
Myelotoxicity	Mercaptopurine	1.860 (1.546-2.238)	<.001
	Elderly age	2.215 (1.907-2.572)	<.001
	Female gender	1.202 (1.078-1.341)	<.001
	Hyperuricaemia	2.393 (1.444-3.968)	.002
	Cardiovascular risk factors	1.196 (1.008-1.419)	.040
	Crohn's disease	0.829 (0.736-0.933)	.002
Digestive intolerance	Elderly age	1.289 (1.105-1.504)	<.001
	Female gender	1.411 (1.202-1.656)	<.001
Hepatotoxicity	Mercaptopurine	1.705 (1.339-2.171)	<.001
	Female gender	0.846 (0.736-0.973)	.015
	Elderly age	2.073 (1.721-2.497)	<.001
	Extraintestinal manifestations	1.223 (1.048-1.429)	.010
	Crohn's disease	0.656 (0.567-0.760)	<.001
	Cardiovascular risk factors	1.412 (1.150-1.734)	<.001
Acute pancreatitis	Crohn's disease	3.996 (2.587-6.172)	<.001
	Female gender	1.250 (1.070-1.461)	.002

elderly, such as reduced hypersensitivity reactions,[34,35] which might balance the incidence of idiosyncratic AEs with that of the younger patients.

In addition to advanced age, we observed that the use of mercaptopurine instead of azathioprine was a risk factor for the development of thiopurine-related AEs. In Spain, azathioprine is the most often used thiopurine compound, whereas mercaptopurine is usually limited to paediatric patients and those patients who presented early AEs with azathioprine (mostly digestive intolerance, but also in some patients developing hepatotoxicity or myelotoxicity). Interestingly, we observed that mercaptopurine was associated with a higher risk of developing myelotoxicity and digestive intolerance. Although no prospective studies comparing both thiopurine compounds are available, several series reported a higher incidence of myelotoxicity with mercaptopurine.[4] In contrast, a systematic review concluded that the cumulative incidence of myelotoxicity was similar with azathioprine and mercaptopurine (9% and 7%, respectively).[33] However, we do not know how many patients included in that review were switched from azathioprine to mercaptopurine after developing AEs.[36,37] In our study, we only assessed the safety of the first thiopurine compound that was introduced, thus avoiding the bias of switched patients.

The main limitations of the present study are a consequence of the specific design of the ENEIDA database. Firstly, drug interactions were not suitably assessed because concomitant non-IBD drugs are not recorded and comorbidities are suboptimally collected in an open field. Furthermore, although biological therapies are recorded in detail, a number of other concomitant IBD drugs (namely, 5-ASA compounds and budesonide) are also poorly recorded in the registry; this may be particularly important for co-treatment with thiopurines and 5-ASA compounds. Although its clinical impact has not been definitively demonstrated, there is some evidence suggesting that 5-ASA might inhibit TPMT activity.[38-40] Secondly, the causality relationship between thiopurines and AEs relied on the physician's discretion, and a selection bias against mild AEs is likely to exist (although that would be so for both groups). As previously mentioned, the lack of genotype/phenotype of TPMT, and the detailed initial dose of thiopurines are additional limitations of our study. Finally, the lack of a pre-established protocol for the management of thiopurine-related AEs might have led to a more conservative approach in the elderly patients, perhaps leading to a higher rate of treatment discontinuation in this population. Despite these limitations, this is the first study that specifically evaluates the safety profile of thiopurines in a huge cohort of elderly IBD patients and should contribute to improving our knowledge on this issue in this particular population.

In conclusion, in this large, retrospective study, we observed that the initiation of thiopurine therapy at an advanced age is associated with a higher risk of thiopurine-related AEs, and specifically of all types of myelotoxicity, hepatotoxicity and digestive intolerance. Our findings very likely reflect reduced drug clearance in elderly patients and in females, and suggest that dosing guidelines should

recommend consideration of lower starting doses or close monitoring of drug metabolites in these populations.

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AUTHORSHIP

Guarantor of the article: MM is acting as the submission's guarantor.

Author contributions: MC, MM, FC and ED designed the study, performed the statistical analysis, evaluated the results and drafted the article. The remaining authors collected data, critically reviewed the manuscript and approved the article.

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APPENDIX 1

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