Thiopurine monotherapy has a limited place in treatment of patients with mild-to-moderate Crohn's disease

We read with interest the multicentre UK study by Stournaras *et al* on the long-term effectiveness of thiopurine monotherapy for the treatment of patients with IBD.¹ Through a similar retrospective, single-centre design at the tertiary IBD referral centre of the University Hospitals Leuven (Leuven, Belgium), we evaluated the outcome of patients with active Crohn's disease (CD) who initiated thiopurine monotherapy between 1988 and 2016. Response was defined as continuation of thiopurine monotherapy for at least 1 year,² with minimal corticosteroids use (<2 corticosteroids courses/year) and without additional treatment (surgery, biological agents). Patients had to be exposed to thiopurines for at least 4 months before response could be evaluated, as thiopurines are not recommended for induction of response.³ In total, 823 CD patients (99.9% azathioprine) with a median follow-up of 13.0 (IQR 7.7–18.0) years were screened (figure 1).

Similar to the discontinuation rates linked to intolerance reported in the UK study,¹ 229 patients (29.4%) discontinued thiopurine therapy after a median of 31.0 (IQR 13.0–74.7) days, mainly because of leucopenia (n=13), liver function abnormalities (n=26), pancreatitis (n=62) or GI intolerance (n=59). On the long term, three patients were diagnosed with a lymphoma and one with a chronic myeloid leukaemia.

Meta-analyses suggested a place for thiopurines in CD maintenance after steroid-induced clinical remission.^{4,5} However, SONIC demonstrated that infliximab–azathioprine combination and infliximab monotherapy are superior to azathioprine monotherapy.⁶ In the current cohort, we observed a thiopurine response rate of 34.5% after 1 year. Nevertheless, in case patients would have been evaluated endoscopically in the current treat-to-target era, endoscopic response and remission rates would presumably have been lower. Intriguingly, responders had a significant longer disease duration as compared with non-responders (table 1), which might reflect a more moderate disease course in thiopurine responders. Univariate analysis further identified older age at treatment initiation, absence of perianal disease and ileal disease involvement as baseline predictors of response. In line with the

Figure 1 Flowchart summarising the main findings of the current observational study on thiopurine monotherapy in Crohn's disease.

UK data,¹ multivariate analysis identified the absence of perianal disease (OR 0.08 (0.05–0.14)) as baseline predictor of thiopurine response. Similar to recent European Crohn's and Colitis Organisation (ECCO) guidelines,³ we would therefore not recommend thiopurine monotherapy in patients with perianal involvement.

Among the initial responders, 78.1% discontinued thiopurine monotherapy after a median of 4.9 (2.5–8.3) years because of adverse events (15.2%), loss-of-response (41.0%), pregnancy (5.7%), concomitant disease requiring other immunomodulators (1.4%) or sustained remission (36.7%). Among the 77 responders

Table 1 Comparison in baseline features between thiopurine responders and non-responders

	Responders n=269	Non-responders n=273	P value
Age at diagnosis, years, median (IQR)	23.4 (18.4–29.5)	21.6 (17.4–28.8)	N.S.
Age at thiopurine initiation, years, median (IQR)	31.6 (24.6–42.0)	27.8 (20.2–36.8)	p<0.001
Disease duration, years, median (IQR)	5.7 (1.0–14.0)	3.0 (0.4–9.3)	p<0.001
Female sex, n (%)	159 (59.1)	170 (62.1)	N.S.
Disease location			
L1, n (%)	56 (20.8)	30 (11.0)	
L2, n (%)	25 (9.3)	38 (13.8)	p<0.001
L3, n (%)	188 (69.9)	205 (75.2)	
Upper GI modifier, n (%)	20 (7.4)	24 (8.9)	N.S.
Disease behaviour			
B1, n (%)	97 (36.1)	112 (41.1)	
B2, n (%)	103 (38.3)	95 (34.8)	
B3, n (%)	69 (25.7)	66 (24.1)	N.S.
Perianal disease involvement, n (%)*	24 (8.9)	132 (48.2)	p<0.001
Median thiopurine dosage	150 mg/day	150 mg/day	N.S.

*Only baseline predictor for thiopurine (non-)response in multivariate analysis. IQR, interquartile range; n, number of patients; N.S., not significant.

who discontinued therapy because of sustained remission, 45 (58.4%) experienced disease recurrence requiring treatment after 2.7 (0.6–3.3) years (figure 1). Risk factors for disease recurrence after treatment discontinuation included presence of perianal disease ($p=0.01$), shorter time on thiopurines before treatment discontinuation ($p<0.0001$) and younger age at initial thiopurine initiation ($p=0.01$). Considering patients who continued thiopurine monotherapy till final follow-up ($n=59$) or who did not experience loss-of-response later beyond year 1 ($n=124$), 33.2% of all patients benefited from thiopurine monotherapy on the long term (figure 1). However, only 7.6% of all included patients continued monotherapy till final follow-up (median follow-up 6.7 years) and 4.1% discontinued therapy due to sustained remission and never relapsed (median follow-up 2.3 years) (figure 1).

This retrospective series has its inherent limitations, including the lack of objective disease markers or endoscopic assessment at predefined time-points. Furthermore, no thiopurine drug monitoring was applied. Nevertheless, the big sample size and long-term, single-centre data still provide relevant insights on the effect of thiopurine maintenance therapy in CD.

In conclusion, given the increasing availability of biological agents,⁷ which are well tolerated, becoming more affordable (biosimilars), generally considered safe and linked to higher endoscopic remission rates as compared with thiopurines, one can question if there is still a place for thiopurine monotherapy in the treatment algorithm of CD.¹ Despite primary and secondary loss-of-response to biological agents, long-term outcome of anti-tumour necrosis factor and vedolizumab series suggest a more sustained effect,^{8,9} as compared with the limited results observed with thiopurine monotherapy in the current study. Nevertheless, in case alternative therapies are failing or where drug cost is a key issue, thiopurines could still

be considered as maintenance monotherapy in CD, although the long-term efficacy and safety should be discussed with the patient. Furthermore, thiopurines still have a place in combination with anti-TNF therapy, especially in the first 6 months after induction to reduce the risk of immunogenicity.

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Contributors BV contributed to study design, data acquisition and interpretation, statistical analysis and drafting of the manuscript. LB contributed to data acquisition. JS contributed to critical revision of the manuscript. SV and MF contributed to study design, data interpretation, supervision and critical revision of the manuscript. All authors agreed with the final version of the manuscript prior to submission.

Funding SV and MF are senior clinical investigators of the research foundation Flanders (FWO), Belgium.

Competing interests BV reports financial support for research from Pfizer; lecture fees from Abbvie, Ferring, Takeda Pharmaceuticals, Janssen and R Biopharm; consultancy fees from Janssen and Sandoz. JS reports lecture fees from Abbvie, Takeda, Janssen and Nestle Health Sciences. SV reports financial support for research: MSD, AbbVie, Takeda, Pfizer, J&J; Lecture fee(s): MSD, AbbVie, Takeda, Ferring, Centocor, Hospira, Pfizer, J&J, Genentech/Roche; Consultancy: MSD, AbbVie, Takeda, Ferring, Centocor, Hospira, Pfizer, J&J, Genentech/Roche, Celgene, Mundipharma, Celltrion, SecondGenome, Prometheus, Shire, Prodigest, Gilead, Galapagos. MF reports financial support for research: Amgen, Biogen, Janssen, Pfizer, Takeda, Consultancy: Abbvie, Boehringer-Ingelheim, MSD, Pfizer, Sandoz, Takeda and Thermo Fisher; Speakers fee: Abbvie, Amgen, Biogen, Boehringer-Ingelheim, Falk, Ferring, Janssen, Lampro, MSD, Mylan, Pfizer, Sandoz, and Takeda.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Ethics approval All patients included in the analysis had given written consent to participate in the Institutional Review Board approved IBD Biobank (B322201213950/553684).

Provenance and peer review Not commissioned; externally peer reviewed.

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These data have been presented as an oral presentation at the 13th European Crohn's and Colitis Organization congress 2018 (Vienna, Austria) and the 30th Belgian Week of Gastroenterology (Antwerp, Belgium).

To cite Verstockt B, Boets L, Sabino J, *et al.* *Gut* Epub ahead of print: [please include Day Month Year]. doi:10.1136/gutjnl-2020-322646

Received 27 July 2020

Revised 17 August 2020

Accepted 24 August 2020

Gut 2020;0:1–2. doi:10.1136/gutjnl-2020-322646

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