ORIGINAL RESEARCH

Thiopurine monotherapy is effective in ulcerative colitis but significantly less so in Crohn’s disease: long-term outcomes for 11 928 patients in the UK inflammatory bowel disease bioresource

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ABSTRACT

Objective Thiopurines are widely used as maintenance therapy in inflammatory bowel disease (IBD) but the evidence base for their use is sparse and their role increasingly questioned. Using the largest series reported to date, we assessed the long-term effectiveness of thiopurines in ulcerative colitis (UC) and Crohn’s disease (CD), including their impact on need for surgery.

Design Outcomes were assessed in 11 928 patients (4968 UC, 6960 CD) in the UK IBD BioResource initiated on thiopurine monotherapy with the intention of maintaining medically induced remission. Effectiveness was assessed retrospectively using patient-level data and a definition that required avoidance of escalation to biological therapy or surgery while on thiopurines. Analyses included overall effectiveness, time-to-event analysis for treatment escalation and comparison of surgery rates in patients tolerant or intolerant of thiopurines.

Results Using 68 132 patient-years of exposure, thiopurine monotherapy appeared effective for the duration of treatment in 2617/4968 (52.7%) patients with UC compared with 2378/6960 (34.2%) patients with CD (p<0.0001). This difference was corroborated in a multivariable analysis: after adjusting for variables including treatment era, thiopurine monotherapy was less effective in CD than UC (OR 0.47, 95% CI 0.43 to 0.51, p<0.0001). Thiopurine intolerance was associated with increased risk of surgery in UC (HR 2.44, p<0.0001); with a more modest impact on need for surgery in CD (HR=1.23, p=0.0015).

Conclusion Thiopurine monotherapy is an effective long-term treatment for UC but significantly less effective in CD.

BACKGROUND

The thiopurine analogues azathioprine (AZA) and 6-mercaptopurine (6MP) have held a long-standing place in the management of inflammatory bowel disease (IBD). In both ulcerative colitis (UC) and Crohn’s disease (CD) they are used for maintaining remission in steroid-dependent or steroid-refractory disease.1–3 However, in recent years increasing emphasis has been placed on the known toxicity profile of thiopurines and, with increasing numbers of biological therapies including cheaper biosimilars available, some authorities are questioning their role.

Randomised controlled trials (RCTs) of thiopurines in IBD from the 1970s to the 90s suggested efficacy in both UC and CD but, as was typical for RCTs of this era, the number of patients included was small and follow-up limited.4–10 More recently, the AZathioprine for Treatment or Early Crohn’s disease in adults (AZTEC) and Résultat de

Significance of this study

What is already known on this subject?

► Thiopurines are commonly used for maintenance of remission in steroid-dependent and steroid-refractory inflammatory bowel disease (IBD).

► Despite their widespread use, real-life data demonstrating durable effectiveness of thiopurines are sparse and are mostly derived from cohorts with modest numbers of patients and limited follow-up.

► In the era of cheaper biosimilar antitumour necrosis factor therapy, other biologics and newer small molecule therapies, the role of thiopurines in IBD management is increasingly being questioned.

What are the new findings?

► Using data from 11 928 patients with IBD treated with thiopurine monotherapy, we compared long-term effectiveness in ulcerative colitis (UC) and Crohn’s disease (CD) and their impact on need for surgery.

► Thiopurine monotherapy was effective for the duration of treatment in 52.7% of patients with UC but only 34.2% of patients with CD. On Kaplan-Meier analysis median duration on thiopurines in those in whom they were effective was 16 years for CD and 17 years for UC. Thiopurine monotherapy was more effective in UC than in CD in both prebiological and postbiological eras.

► Inability to tolerate thiopurines correlated with increased risk of surgery in UC (HR=2.44), with a more modest effect in CD (HR=1.23).
Inflammatory bowel disease

**Significance of this study**

*How might it impact on clinical practice in the foreseeable future?*

- In re-evaluating their current role in inflammatory bowel disease management, our study suggests that thiopurine monotherapy is effective in maintaining long-term clinical remission in ulcerative colitis. In Crohn’s disease, however, thiopurines are less effective as monotherapy particularly where there is perianal involvement. Here, there should be a lower threshold for biological therapy from outset in combination with thiopurine.

l’Adjonction Précoce d’ImmunoDépresseurs (RAPID) strategy trials assessed the efficacy of azathioprine in maintaining remission when used very soon after diagnosis in CD. Neither demonstrated benefit of very early vs conventional use of thiopurines.11–12

To gain further insight, single-centre retrospective studies in population-based cohorts have investigated the real-world outcomes of AZA and 6MP treatment in IBD and suggested 40%–60% effectiveness.13–18 Again, however, the numbers involved have been relatively modest and/or the follow-up relatively short, and few studies have compared effectiveness in UC versus CD.13–18

The effect of thiopurines in reducing surgery has also been studied. Early need for thiopurine clearly defines patients at increased risk for colectomy in UC,19 and the inability to tolerate thiopurine has also been associated with increased colectomy risk.20 21 In CD results have been more mixed. One French study suggested that thiopurines reduced need for surgery while another did not.22 23 In two UK studies reduced need for surgery correlated with increased thiopurine use—within a national cohort study showing 44% less surgery in patients on thiopurine for at least 6 months.24 25

There is little consensus regarding how long thiopurine treatment should be continued. One retrospective series suggested 4 years,26 but relapse following thiopurine cessation is common and response cannot always be recaptured.13

With more biologic and newer small molecule therapies now available some question the role of thiopurine monotherapy in IBD, asserting that the newer agents are more effective and safer. Biological therapies are, however, not without their own problems including non-response and particularly loss of response over time,27–30 and the Janus-kinase inhibitor tofacitinib has also been associated with safety signals.31–32 Additionally, costs of biologic and JAK inhibitor therapies remain a bar in many healthcare settings.

Here, we present the outcomes of thiopurine use in the UK IBD BioResource—launched in 2016 as part of the UK National Institute for Health Research BioResource and encompassing a large cohort of ‘recallable’ patients on whom clinical details were ascertained at enrolment.33 We designed the study to investigate the long-term effectiveness of thiopurine monotherapy in UC and CD and explore the impact of thiopurine tolerance on the need for surgery.

**METHODS**

We undertook a retrospective analysis of the outcomes of thiopurine treatment (AZA or 6MP) for patients with CD or UC in the IBD BioResource. Those with IBD-unclassified (IBDU) were included with UC. Patients were involved in the study design. All participants provided signed consent. The IBD BioResource is currently recruiting in 104 hospitals UK-wide. At a data lock taken on 14 January 2020, 31 481 patients had been enrolled.

Structured IBD phenotype data, including drug therapy outcomes and surgeries, were ascertained at IBD BioResource enrolment by research nurses and clinicians using a combination of case note review, patient interview and patient questionnaire. Periodic data validation exercises are undertaken with independent reassessment of phenotype data. Most sites recruited unselected consecutive patients with IBD attending clinic, the overall numbers recruited at each site varying according to duration of study setup and resources available.

For each subject in the current study, the outcome of historic or current AZA or 6MP treatment was assessed by the question ‘Was the treatment effective?’, with responses being empirically classified into one of the following seven categories:

1. Yes.
2. No (on therapeutic dose >4 months—did not work).
3. Unable to assess (on therapeutic dose <4 months).
4. Unable to assess (unable to tolerate).
5. Worked for <12 months then lost response.
6. Worked for >12 months then lost response.
7. Response not known (eg, started antitumour necrosis factor (TNF) at same time, partial response only etc).

Our primary aim was to identify the proportion of patients treated with thiopurine monotherapy in whom this was deemed effective, satisfying both (A) response of ‘yes’ (option 1) to the question ‘Was the treatment effective?’ and (B) patient had not needed escalation to biological therapy or IBD surgery for the duration of thiopurine therapy. Patients were excluded if the treatment response data were missing; and those started on anti-TNF therapy at thiopurine initiation or undergoing surgery in the year of thiopurine initiation (where the drug may have been used as postsurgical prophylaxis) were excluded since we could not assess effectiveness of thiopurine monotherapy in these groups. UC patients who had undergone colectomy prior to thiopurine initiation were also excluded; as were cases where missing dates did not allow us to confirm whether biological therapy/surgery overlapped the indicated period of thiopurine monotherapy.

The effectiveness of thiopurine monotherapy was also investigated in terms of time from initiating thiopurine to requirement for treatment escalation with biological therapy or surgery, whichever occurred first.

To investigate whether thiopurine therapy has an impact on need for surgery in UC and CD, the time from treatment initiation to surgery was compared between patients able to tolerate thiopurine versus those unable to tolerate thiopurine. Only patients who were deemed unable to tolerate any thiopurine at any dose were labelled as ‘intolerant’ in this analysis (eg, this group did not include people unable to tolerate AZA but able to tolerate 6MP; or those able to tolerate thiopurine following dose reduction±concomitant allopurinol).

Descriptive statistics of the clinical characteristics were calculated, with continuous variables presented as medians (25th–75th percentile); and categorical variables as frequencies and percentages. Duration of thiopurine monotherapy was calculated from start to end of treatment or censored for participants who were still on thiopurine monotherapy at the time of data lock, and summarised using Kaplan-Meier estimates. Adverse event incidence was compared between UC and CD by $X^2$ testing. The Cochrane-Mantel-Haenszel (CMH) test was applied to compare the effectiveness of thiopurine monotherapy between UC and CD, using stratified treatment initiation time periods grouped 5 yearly. Comparison of the effectiveness of thiopurine between
UC and CD was also assessed using a multivariable logistic regression with covariates of age at diagnosis, gender, smoking history, treatment era and time from diagnosis to thiopurine initiation. Kaplan-Meier methods were applied for the time to treatment escalation with biological therapy or surgery. The differences of distributions between UC and CD were compared using the log-rank test. Logistical regression models were applied to explore the correlation between the thiopurine monotherapy effectiveness and the clinical characteristics within UC and CD using the same covariates as above but also including disease location. Similar analyses were performed using the Cox regression models for the time to surgery outcome. Due to the large size of the dataset, a conservative prespecified p value threshold of less than 0.005 was considered statistically significant. Statistical analyses were performed using the SAS V.9.4.

RESULTS

Patient population

Of the 31481 participants in the IBD BioResource at the data lock, 17921 (56.9%) had been treated with a thiopurine for IBD (71.9% with CD; 43.8% with UC), either as monotherapy or combined with anti-TNF therapy. A total of 11928 met the criteria for assessment of the effectiveness of thiopurine monotherapy (6960 CD and 4968 UC including 251 IBDU). Hereafter all analyses refer to this cohort of 11928 subjects (figure 1).

Patient characteristics are presented in table 1. Median age at CD/UC diagnosis was 26/33 years. Median time from diagnosis to data capture was 12 years (total follow-up 99555 patient-years/total thiopurine exposure 40807 patient-years) for CD and 10 years (total follow-up 60413 patient-years/thiopurine exposure 27325 patient-years) for UC.

Thiopurine treatment and tolerability

Of the 11928 subjects treated with thiopurine 11239 (94.2%) received AZA and 2698 (22.6%) 6MP; this included 2009 (16.8%) who received both at different time points. A total of 2984 (26.6%) subjects treated with AZA were unable to tolerate it and had to stop. Of those exposed only to 6MP, 138/689 (20.0%) experienced an adverse effect and consequently stopped. Of 11928, 2482 (20.8%) could not tolerate either thiopurine at any dose. A total of 1327 patients were exposed to both AZA and 6MP after intolerance of their first thiopurine, of whom 640/1327 (48.2%) were able to tolerate the second thiopurine.

Median overall duration of thiopurine treatment was 8 (1–25) years for CD and 9 (1–24) years for UC. Median time from diagnosis to thiopurine initiation was 2 years for both CD and UC, with 46.7% starting thiopurine within 2 years of diagnosis (figure 2). A total of 2905 (41.7%) of those with CD and 1377 (27.7%) with UC received biological therapies after attempted treatment with thiopurine monotherapy.

Adverse events were consistent with those reported previously (table 1). Nausea/vomiting and deranged liver function tests were the most common. Permanent thiopurine discontinuation due to pancreatitis was more common in CD than UC (2.7% vs 1.2%, X^2 p<0.0001), whereas treatment-limiting hepatotoxicity was more common in UC (3.2% vs 2.1% in CD, p=0.0003).

Effectiveness of thiopurine monotherapy

Of 11928 subjects with IBD treated with thiopurine monotherapy, it was reported to have been effective, without the need for escalation to biologic therapy or need for surgery for the duration of thiopurine treatment, in 4995 (41.9%). It was effective for UC in 2617/4968 (52.7%) of patients; and a lower proportion of patients with CD: 2378/6960 (34.2%).

Using the CMH test to stratify by treatment initiation era, thiopurine monotherapy appeared more effective in UC than CD for all 5-year chronological periods (RR 1.40, 95% CI 1.35 to 1.45, p<0.0001) (online supplementary figure 1). The absolute effectiveness of thiopurine monotherapy appeared to decrease in UC and increase in CD in more recent cohorts (online supplementary figures 2 and 3). We incorporated treatment era along with other possible confounding factors in a multivariable logistic regression analysis. This again demonstrated that thiopurine monotherapy was less effective in CD than UC (OR 0.47, 95% CI 0.43 to 0.51, p<0.0001), after adjusting for era of starting thiopurines, time from diagnosis to thiopurine initiation, age at diagnosis and smoking history (table 2).

Clinical characteristics and response to thiopurine monotherapy

For CD, in a multivariable analysis after controlling for confounding factors, thiopurine therapy appeared more effective in patients with colonic as opposed to ileocolonic involvement (OR 1.60, 95% CI 1.38 to 1.86, p=0.002) and older patients (1.01 per year, 95% CI 1.01 to 1.02, p<0.0001). By contrast, treatment initiation ≤1 year after IBD diagnosis (OR 0.69, 95% CI 0.60 to 0.78, p<0.0001) and perianal disease (OR 0.70, 95% CI 0.61 to 0.80, p<0.0001) were associated with lower thiopurine effectiveness (table 3). No correlation was found with gender or smoking history.

For UC, proctitis was associated with higher effectiveness (OR=1.56 vs extensive disease, 95% CI 1.23 to 1.98, p=0.0002) (table 3).

Duration of effect

For participants in whom thiopurine monotherapy was deemed effective, over 70% were still on this treatment at the time of our data lock. Median treatment duration on Kaplan-Meier analysis...
of this group was 16 (95% CI 15 to 19) years for CD and 17 (95% CI 15 to 20) years for UC (online supplementary figure 4).

We performed a time-to-event analysis for patients on thiopurine monotherapy assessing time to escalation to biological therapy or surgery. A total of 11,189 (4,464 CD, 4,725 UC) participants were included with 739 excluded due to missing data. Of patients continuing thiopurine 4,907 (44%) required treatment escalation after a median time of 4 (95% CI 4 to 5) years in CD and 12 (95% CI 11 to 13) years in UC (p<0.0001 for log-rank test) (figure 3). This remained significant after adjusting for treatment period and clinical characteristics using the Cox regression model (p<0.0001).

Table 1  Demographic and clinical characteristics and adverse reactions in the 11,928 patients in the IBD BioResource treated with thiopurine monotherapy

|            | CD | UC |
|------------|----|----|
| Age at diagnosis | 26(19–39) | 33 (24–45) |
| Gender | | |
| Male | 3181 (45.8%) | 2615 (52.7%) |
| Female | 3768 (54.2%) | 2347 (47.3%) |
| Smoking status at diagnosis | | |
| Never smoked | 3387 (51.9%) | 2538 (54.5%) |
| Smoking at diagnosis | 2236 (34.2%) | 673 (14.5%) |
| Ex-smoker | 909 (13.9%) | 1443 (31.0%) |
| Disease location | | |
| CD | | |
| Ileal | 2487 (37.0%) | |
| Colon | 1747 (26.0%) | |
| Ileo-colonic | 2413 (35.9%) | |
| Exclusive upper GI Crohn’s | 75 (1.1%) | |
| Perianal involvement | 1989 (30.2%) | |
| UC | | |
| Proctitis (E1) | 379 (8.5%) | |
| Left sided (E2) | 2143 (48.3%) | |
| Extensive (E3) | 1917 (43.2%) | |
| Tolerated thiopurine | 5382 (77.3%) | 4064 (81.8%) |
| Adverse reactions (X<sup>2</sup> test between groups unable to tolerate thiopurine) | Whole cohort | Intolerant group (had to discontinue thiopurines) |
| N (%) | N (%) | N (%) | N (%) |
| Abdominal pain (p=0.04) | 216 (3.2) | 134 (2.0) | 115 (2.3) | 71 (1.5) |
| Deranged LFT (p=0.0003) | 326 (4.8) | 146 (2.1) | 369 (7.5) | 158 (3.2) |
| Flu-like symptoms (p=0.01) | 177 (2.6) | 99 (1.5) | 119 (2.4) | 70 (1.4) |
| Leucopenia (p=0.45) | 145 (2.1) | 38 (0.6) | 123 (2.5) | 32 (1.4) |
| Nausea/vomiting (p=1.32) | 793 (11.6) | 424 (6.4) | 563 (11.5) | 286 (5.8) |
| Pancreatitis (p<0.0001) | 235 (3.4) | 182 (2.7) | 78 (1.6) | 57 (1.2) |
| Other (p=0.53) | 1490 (21.4) | 712 (10.2) | 1056 (21.6) | 488 (10) |

CD, Crohn’s disease; IBD, inflammatory bowel disease; LFT, liver function tests; UC, ulcerative colitis.

Table 2  Multivariable analysis of factors affecting thiopurine monotherapy effectiveness

|            | OR   | 95% CI          | P value |
|------------|------|-----------------|---------|
| Diagnosis  |      |                 |         |
| CD         | 0.47 | 0.43 to 0.51    | <0.0001 |
| UC         | 1 Referent | | |
| Treatment period | 1.06 | 1.02 to 1.09 | 0.0008 |
| Time from diagnosis to thiopurine initiation | 1.02 | 1.01 to 1.02 | <0.0001 |
| Age at diagnosis | 1.01 | 1.01 to 1.02 | <0.0001 |
| Gender | | |
| Female | 1.06 | 0.97 to 1.14 | 0.19 |
| Male | 1 Referent | | |
| Smoking history | | |
| No | 1.12 | 1.03 to 1.22 | 0.007 |
| Yes | 1 Referent | | |

Significant p values shown in bold.
CD, Crohn’s disease; UC, ulcerative colitis.

Figure 2  Time (years) from IBD diagnosis to thiopurine initiation in the 11,928 subjects. IBD, inflammatory bowel disease.
Inflammatory bowel disease

Of patients initiated on thiopurine monotherapy, at 1 and 3 years 69% and 54% of those with CD, and 76% and 69% with UC, respectively, remained on thiopurine and had not required treatment escalation to biological therapy or surgery (online supplementary table 1).

Effect of thiopurine therapy on surgery in UC

Of the 4968 patients with UC in whom thiopurine mono-therapy was assessed, 219 (4.4%) had required colec-tomy—92 for acute severe colitis, 92 for medically refractory disease, 12 for cancer/dysplasia and 23 with reasons not documented. We analysed the proportion of patients requiring colectomy according to tolerance of thiopurine treatment: 63/904 (7.0%) of patients intolerant of thiopurine required colectomy compared with 156/4064 (3.8%) of those able to tolerate thiopurines. Time to colectomy was shorter in individuals unable to tolerate vs able to tolerate thiopurine (figure 4, log-rank <0.0001). In a Cox proportional hazards model, the HR for colectomy was 2.44, 95% CI 1.71 to 3.50 (p<0.0001) in individuals unable to tolerate thiopurine.

Table 3 Regression analysis of factors influencing thiopurine effectives in CD and UC patients

|               | CD Univariable | CD Multivariable | UC Univariable | UC Multivariable |
|---------------|----------------|------------------|----------------|------------------|
| Age at diagnosis | 1.02 (1.01 to 1.02) | <0.0001 | 1.01 (1.01 to 1.02) | <0.0001 | 1 (1.00 to 1.01) | 0.49 |
| Gender        |              |                  |               |                  | 1.02 (0.91 to 1.14) | 0.72 |
| Male          | 1.09 (0.99 to 1.20) | 0.08 | Referent        |                  | Referent          |     |
| Female        | Referent      |                  | 1.02 (0.91 to 1.14) | 0.72 |
| Smoking history |              |                  |               |                  | 0.34 | 0.12 |
| No            | 0.95 (0.86 to 1.05) | <0.0001 | 1.01 (0.98 to 1.23) | <0.0001 | 1 (1.00 to 1.01) | 0.49 |
| Yes           | Referent      |                  | Referent      |                  |
| Treatment era | 1.2 (1.14 to 1.25) | <0.0001 | 0.88 (0.83 to 0.93) | <0.0001 | 1 (1.00 to 1.01) | 0.49 |
| Time from diagnosis to thiopurine initiation |              |                  |               |                  | 0.72 (0.64 to 0.82) | <0.0001 |
| <1 year       | 0.72 (0.64 to 0.82) | <0.0001 | 0.69 (0.60 to 0.78) | <0.0001 | 0.87 (0.76 to 1.0) | 0.36 |
| ≥1 and <2 years | 0.92 (0.80 to 1.06) | 0.24 | 0.81 (0.70 to 0.95) | <0.0001 | 0.86 (0.74 to 1.0) | 0.27 |
| ≥2 years      | Referent      |                  | Referent      |                  |
| Disease location (CD) | 1.28 (1.14 to 1.45) | 0.57 |                  |                  | 1.61 (1.42 to 1.84) | 0.008 |
| Left sided    | 1.53 (0.96 to 2.48) | 0.44 |                  |                  | Referent          |     |
| Perianal involve |              |                  |               |                  | 0.67 (0.59 to 0.75) | <0.0001 |
| Yes           | 0.67 (0.59 to 0.75) | <0.0001 | 0.7 (0.61 to 0.80) | <0.0001 | 1 (1.00 to 1.01) | 0.49 |
| No            | Referent      |                  | Referent      |                  |
| Disease location (UC) |              |                  |               |                  |                  |     |
| Proctitis (E1) | 1.47 (1.17 to 1.84) | 0.0006 | 1.56 (1.23 to 1.98) | 0.0002 | Referent          |     |
| Left sided (E2) | 1.01 (0.89 to 1.14) | 0.01 |                  |                  | Referent          |     |
| Extensive (E3) |              |                  |               |                  |                  |     |

Significant p values shown in bold.
CD, Crohn’s disease; UC, ulcerative colitis.
Effect of thiopurine therapy on surgery in CD

Unlike with UC, patients with CD with a surgical procedure prior to thiopurine initiation were included in this analysis, because reoperation is common in the natural history of CD. In total, 3077/6960 patients (44.2%) treated with thiopurine because reoperation is common in the natural history of CD.

A total of 1578 patients with CD could not tolerate thiopurine treatment. Their time to surgery was modestly shorter compared with the 5382 patients with CD able to tolerate thiopurines in the Kaplan-Meier analysis (log-rank=0.002 - figure 5). Inability to tolerate thiopurine was associated with risk of surgery in a Cox proportional hazards model (HR 1.23, 95% CI 1.08 to 1.40, p=0.0015). The latter also identified reduced risk of surgery in patients with CD where only the colon was involved (table 5), as previously reported.

Use of biological therapy again differed between the two groups, 782/1578 (49.6%) patients with CD unable to tolerate thiopurines were escalated to biological therapy, compared with 2123/5382 (39.4%) of patients able to tolerate these drugs (p<0.0001).

DISCUSSION

Thiopurines are commonly used in the treatment of IBD, but their role is increasingly questioned given the ever-expanding range of biologic therapy options, the introduction of modestly priced biosimilar anti-TNF, increasing concerns about the tolerability and safety of thiopurines and a lack of data regarding efficacy.11 12

We report the first large-scale study in the biological era assessing clinical practice and patient-level outcomes of IBD treatment with thiopurines. Long-term outcome data remain sparse for all IBD treatments, but durability is key in therapy planning for CD and UC given their chronic nature. The most striking finding from our study was the evidence that thiopurines provided an effective long-term treatment for 32.7% of patients with UC, without need for escalating to biological therapy or surgery; but that durable effectiveness in CD was lower at 34.2%. These results include all individuals in whom AZA and 6MP were initiated and do not exclude those intolerant of thiopurines.

Our finding of increased effectiveness for thiopurine monotherapy in UC compared with CD was consistent when we performed a multivariable logistic regression correcting for

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**Table 4** Cox regression analysis of factors affecting time to colectomy in UC patients

| Able to tolerate thiopurines | P value | HR   | 95% CI |
|-----------------------------|---------|------|--------|
| No                          | <0.0001 | 2.44 | 1.71 to 3.50 |
| Yes                         |         | 1 Referent |

**Table 5** Cox regression analysis of factors affecting time to surgery in CD patients

| Able to tolerate thiopurines | P value | HR   | 95% CI |
|-----------------------------|---------|------|--------|
| No                          | 0.0015  | 1.23 | 1.08 to 1.40 |
| Yes                         |         | 1 Referent |

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UC, ulcerative colitis.
recruits in over 100 hospitals covering the spectrum from small district hospitals to large university centres. In this cohort, broadly representative of UK hospital practice, it is clear that thiopurines have been and continue to be widely used—in 43.8% of patients with UC and 71.9% with CD. Interestingly, the proportion on thiopurines does not appear to have reduced significantly with increasing biological therapy availability (data not shown). National Institute for Health and Care Excellence recommendations may be relevant to this, as in UK practice all patients escalated to biologics should have first trialled immunomodulators.

A key question with any drug in IBD is when and whether to stop treatment in those achieving remission. Previous small studies considered thioupirne cessation appropriate after 4 years but relapse following cessation is common.13 26 Strikingly, in the current study, most patients in whom treatment was deemed effective were still on thiopurines at the data lock, with a median treatment duration of 16 (CD) and 17 (UC) years on Kaplan-Meier analysis (online supplementary figure 4). It seems that thiopurines are continued for prolonged periods where they are proving effective despite well-documented concerns about increased risk of skin cancers and lymphoma long term.34

Early RCTs of thiopurines in IBD included only modest numbers of patients and short follow-up—and one or both of these limitations also apply to subsequent ‘real-world’ studies.4-10 13-15 17 18 A recent meta-analysis of 489 CD subjects showed remission rates of 73% on AZA, but also 62% in the placebo group (RR 1.19, 95%CI 1.05 to 1.34) with limited follow-up of 6–18 months.5 Jharap et al reported thiopurine effectiveness of 48% for CD and 38% for UC in two 8 years intercept cohorts totaling 366 patients.32 However, effectiveness was defined as clinical remission in patients still on thiopurine at 5 years, regardless of surgery or anti-TNF commencement. Another ‘real-world’ study from Oxford undertook retrospective case note reviews on 622 thiopurine-experienced IBD patients.13 Relapse was defined as need for steroids or surgery, and the assessment of effectiveness required at least 6 months on azathioprine, therefore, patients unable to tolerate the medication were excluded from this analysis. Thiopurines appeared effective in 45% of patients with CD and 58% with UC but average treatment duration was less than 2 years.

RCTs of thiopurine in UC are even more limited. A meta-analysis of six studies included only 124 patients and suggested 60% remission on thiopurine vs 37% on placebo or 5 aminosalicylates.35 Observational studies have typically included 100–250 patients and reported benefit in 40%–60%.13 15 36–38

With 11928 participants contributing 68132 years of thiopurine exposure data, the large size of our study should underscore confidence in our findings. Nevertheless, our study clearly also has limitations. Necessarily for a large-scale retrospective study we used a pragmatic, but non-validated definition of effectiveness which may not always equal remission. This required a clinical judgement regarding effectiveness and also persistence on thiopurine without need for biological escalation or surgery. Studies frequently now use persistence on drug as a marker of continued effectiveness, so in this regard our definition was more rigorous than many.19 40

Other limitations include the lack of assessment of mucosal healing for example by calprotectin assay or endoscopy data. The IBD BioResource is a hospital-based programme, and hence may be skewed towards individuals with more severe disease. This will have inflated the proportion of patients with IBD who have been treated with thiopurines and indeed biologics compared with population cohorts. In addition, all patients on thiopurines,
regardless of dose, were included. We have not captured data on thiopurine dosing or metabolite monitoring to identify patients in whom thiopurines were ineffective due to underdosing. Nor have full data on concomitant use of 5-ASA, or the need for corticosteroids or hospitalisation been captured. However, we feel it unlikely that 5-ASA use alone would explain the differences we observed, and in UK practice recurrent need for either corticosteroids or hospitalisation in patients established on thiopurine would conventionally mandate escalation to biologic therapy or surgery—data which we did capture to signal lack of thiopurine effectiveness.

In UC, we observed a colectomy rate of 4.4% in individuals in whom thiopurine monotherapy was tried (and 5.1% in all patients with UC in the IBD BioResource). Although lower than many historic series, we recently British cohorts have reported similar rates. Chhaya et al reported that in a population cohort of 8673 incident UC patients (1766 receiving thiopurines) 5.5% underwent colectomy,

20 while Alexakis et al reported a 4.9% crude colectomy rate.

21 In common with the former study, we sought evidence that thiopurines reduced UC colectomy risk. By comparing patients able to tolerate the medication with those who had been treated with thiopurine but were unable to tolerate it we controlled for the impact of disease severity on colectomy risk (selection bias). Our regression analysis showed a significantly later need for surgery in thiopurine-intolerant patients (figure 4), with an HR of 2.44 for risk of earlier colectomy (table 4). Consistent with other studies our data also showed higher colectomy risk in extensive versus distal UC. Chhaya et al identified a 71% reduction colectomy risk in 1766 individuals with UC treated with thiopurine for at least 12 months compared those on it for less than 12 months. Similar conclusions were drawn from a population-based study from Manitoba and a recent Scandinavian hospital cohort (reduction in absolute colectomy risk from 29% to 19.5%) (20, 21, 22).

Evidence in our study for the benefits of thiopurine therapy on the need for surgery in CD was more modest than in UC (figure 5 and table 5). We observed a lower risk of abdominal surgery in older patients and in those with colonic disease without small bowel involvement, as previously reported.

In two recent studies, one a Danish CD population cohort of 13 185 patients, thiopurine use did not appear to affect surgical rates; but others suggest that thiopurines do reduce surgery in CD—for example, a UK population cohort study by Chatu et al and data from Hungary.

22–24 Our data revealed the same direction of effect as the earlier UK study but more modest benefit in reducing surgery. Substantial differences in study design may account for this difference, such as patient selection (population vs hospital-based cohorts), capturing of surgery (unlike Chatu et al we included all IBD-related surgery including perianal CD surgery) and era examined (we included patients diagnosed pre-1989 and post-2005). In a 2014 meta-analysis, thiopurine use correlated with a 40% reduced risk of resectional surgery in CD. However, asymmetry was observed in the funnel plot, with studies showing no benefit of thiopurines in surgery being under-represented. Additionally, this meta-analysis did not include the large, negative Danish study published shortly after.

CONCLUSION

The current study provides robust real-world evidence from the large UK IBD BioResource dataset that thiopurine monotherapy is an effective long-term treatment for UC. However, it appears less effective in CD (OR=0.47) particularly where there is perianal involvement. Previous studies showed no benefit of thiopurines initiated very soon after CD diagnosis (with consistent data in our study). and there is clear evidence from trials such as SONIC for improved efficacy when thiopurines are combined with infliximab for the treatment of CD.

Given recent substantial reductions in the cost of biosimilar anti-TNF therapy, and the evidence presented regarding the relative lack of durable effectiveness of thiopurine monotherapy in CD, there is perhaps a need to re-evaluate treatment strategies. For patients with anything more than mild to moderate CD thiopurines should perhaps be viewed primarily as an adjunct to anti-TNF therapy.

Acknowledgements The IBD BioResource is part of the National Institute for Health Research (NIHR) BioResource. We would like to acknowledge our IBD BioResource coordinators Rachel Simpkins, Deepthi Francis, Cathy Thorbinson and Laetitia Pele and the work of the admin team. Also, the support of all staff in the NIHR BioResource including Sofie Ashford, Nathalie Kingston and John Bradley. We thank the many Clinical Research Network nurses, IBD nurse specialists and clinicians who have helped with recruitment, and all the patients who are participating in the IBD BioResource programme. We thank the National Institute for Health Research, NHS Blood and Transplant, and Health Data Research UK as part of the Digital Innovation Hub Programme.

Collaborators UK IBD BioResource Investigators: Dr Tarig Ahmad (Royal Devon and Exeter NHS Foundation Trust, Exeter, UK), Dr Nick Kennedy (Royal Devon and Exeter NHS Foundation Trust, Exeter, UK), Dr Peter Irving (Guy’s and St Thomas’ NHS Foundation Trust, London, UK), Dr Natalie Prescott (Guy’s and St Thomas’ NHS Foundation Trust, London, UK), Dr Charlie Lees (Ward 7, Central Middlesex, London), Dr David Campbell (Royal In-Patient Hospital, Lothian, Edinburgh, UK), Dr John Mansfield (Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle, UK), Dr Chris Lamb (Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle, UK), Professor Jack Satsangi (Oxford University Hospitals NHS Foundation Trust, Oxford, UK), Professor Alison Hart (London North West University Healthcare NHS Trust, St Mark’s Hospital, Harrow, Middlesex, UK), Dr Sreedhar Subramanian (Royal Liverpool and Broadgreen University Hospitals NHS Trust, Liverpool, UK), Chris Probert (Royal Liverpool and Broadgreen University Hospitals NHS Trust, Liverpool, UK), Richard Shenderey (Airedale NHS Foundation Trust, West Yorkshire, UK), Dr Anton Gunasekera (Ashford and St. Peter’s Hospitals NHS Foundation Trust, Surrey, UK), Dr Klaartje Bel Kol (Barts Health NHS Trust, London, UK), Dr Babur Javid (Belfast Hospital South Wing, Belfast, UK), Dr Leena Sinha (Queen’s Hospital, Barking Havering and Romford University Hospitals NHS Trust, London, UK), Dr Salil Singh (Royal Bolton Hospital, Bolton, UK), Dr Cathryn Preston (Bradford Teaching Hospitals NHS Foundation Trust, Bradford, UK), Dr Mark Jarvis (Basildon and Thurrock University Hospitals NHS Foundation Trust, Basildon, UK), Ruth Penn (Buckinghamshire Healthcare NHS Trust, UK), Dr Anjana Dhar (County Durham and Darlington NHS Foundation Trust, Darlington, UK), Dr Achuth Shenoy (East Suffolk and North Essex Foundation Trust, Colchester, UK), Dr Carole Stiles (Chesterfield Royal Hospital NHS Foundation Trust, Chesterfield, UK), Arqis Oglesby (Dorset County Hospital NHS Foundation Trust Dorchester, Dorset, United Kingdom), Jude Tilbury (East Sussex Healthcare NHS Trust, Eastbourne, UK), Cyril Scott (East Kent Hospitals University NHS Foundation Trust, Canterbury, UK), Dr Joseph Collum (East Lancashire Hospitals NHS Trust, Blackburn, UK), Dr Martyn Carter (East and North Hertfordshire NHS Trust, Stevenage, UK), Dr Jamie Barbour (Gateshead Health NHS Trust, Gateshead, UK), Dr John Gordon (Hampshire Hospitals NHS Foundation Trust, Basingstoke, UK), Dr John Ramage (Hampshire Hospitals NHS Foundation Trust, Basingstoke, UK), Dr Ganesh Sivagi (Harrogate and District NHS Foundation Trust, Harrogate, UK), Dr Phil Roberts (North West Anglia NHS Foundation Trust, Hinchingbrooke Hospital, Hinchingbrooke, UK), Dr Monica Bose (Princess Alexandra Hospital NHS Trust, Harlow, UK), Dr Shaji Sebastian (Hull and East Yorkshire Hospitals NHS Trust, Hull, UK), Dr William Elizabeth (Hull and East Yorkshire Hospitals NHS Trust, Hull, UK), Dr Paul Banim (James Paget University Hospitals NHS Foundation Trust, Great Yarmouth, UK), Dr Alexandra Kent (King’s College Hospital NHS Foundation Trust, London, UK), Dr Ajay Verma (Kettering General Hospital NHS Foundation Trust, Kettering, UK), Dr Dawn Warren (Kingston Hospital NHS Foundation Trust, Kingston upon Thames, UK), Dr Alan Wiles (Queen Elizabeth Hospital NHS Foundation Trust, Kings Lynn, UK), Dr Matthew Johnson (Luton and Dunstable University Hospital NHS Foundation Trust, Luton, UK), Dr Konrad Koss (East Cheshire NHS Trust, Macclesfield District General Hospital, Macclesfield, UK), Dr Chirag Oza (Mid Essex Hospital Services NHS Trust, Broomfield, UK), Dr Khalid Elamin (Milton Keynes University Hospital NHS Foundation Trust, Milton Keynes, UK), Annette Woods (Medway Maritime Hospital, Gillingham, UK), Dr Bilal Babar (Maidstone and Tunbridge Wells NHS Trust, Maidstone, UK), Dr Chris MacDonald (Northumbria University Hospitals NHS Trust, Gateshead, UK), Dr Byron Thomson (Northern Devon Healthcare NHS Trust, UK), Dr Mark Tremrell (Norfolk and Norwich University Hospitals NHS Foundation Trust, Norwich, UK), Dr Udi Shmueli (Northampton General Hospital NHS Trust, Northampton, UK), Dr Roisin Bevan (North Tees and Hartlepool Hospitals NHS Trust).
Funding
Drafting of the manuscript: ES, WQ, AP, YYH, TR and MP. Critical revision of the data: ES, WQ, AP, YYH, RS and MP. Analysis and interpretation of data: all authors.

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Study design and concept: ES, AP, YYH, TR, MP. Acquisition of data: ES, WQ, AP, YYH, RS and MP. Analysis and interpretation of data: all authors. Manuscript drafting: ES, WQ, AP, YYH, TR and MP. Critical revision of the manuscript: ES, WQ, AP, YYH, RS and MP. Statistical analysis: WQ, AP, YYH, RS and MP. All authors have approved the final version of the manuscript.

Funding
The IBD BioResource is co-funded by the Medical Research Council (Grant number MR/M00533X/1), the Wellcome Sanger Institute, Open Targets, Crohn’s and Colitis UK (Grant number M14/1), National Institute for Health Research (NIHR, Grant/Portfolio number 20664) and the Cambridge Biomedical Research Centre (BRC). The Cambridge BRC is a partnership between Cambridge University Hospitals NHS Foundation Trust and the University of Cambridge, and is funded by the NIHR.

Competing interests
MP is in receipt of grant funding from Pfizer, Gilead and Roche, and has received speaker fees from Takeda. TR has received research/educational grants and/or speaker/consultation fees from Abbvie, BMS, Celgene, Ferring, Gilead, GSK, Mylan, LabGenius, Janssen, MSD, Novartis, Pfizer, Sandoz, Takeda and UCB.

Patient and public involvement
Patients and/or the public were involved in the design, or conducting, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication
Not required.

Ethics approval
Cambridge Central Research Ethics Committee gave approval (ref 15/EE/0286).

Provenance and peer review
Not commissioned; externally peer reviewed.

Data availability statement
Data are available on reasonable request. The deidentified data are available to bona fide researchers with ethics approved projects by applying to the NIHR IBD BioResource at https://www.ibdbioresource.nihr.ac.uk/index.php/resources/applying-for-access-to-the-ibd-bioresource-panel/

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REFERENCES
1. Chande N, Patton PH, Tsolis D, et al. Azathioprine or 6-mercaptopurine for maintenance of remission in Crohn’s disease. Cochrane Database Syst Rev 2015:C000067.
2. Timmer A, Patton PH, Chande N, et al. Azathioprine and 6-mercaptopurine for maintenance of remission in ulcerative colitis. Cochrane Database Syst Rev 2016:C000478.
3. Lamb CA, Kennedy NA, Raine T, et al. British Society of gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. Gut 2019;68:81–106.
4. Rhodes J, Bainton D, Beck P, et al. Controlled trial of azathioprine in Crohn’s disease. Lancet 1971;2:1273–4.
5. Jewell DP, Truelove SC. Azathioprine in ulcerative colitis: final report on controlled therapeutic trial. Br Med J 1974;4:627–30.
6. Present OH, Korelitz BJ, Wishn E, et al. Treatment of Crohn’s disease with 6-mercaptopurine. A long-term, randomized, double-blind study. N Engl J Med 1980;302:981–7.
7. Candy S, Wright I, Gerber M, et al. A controlled double blind study of azathioprine in the management of Crohn’s disease. Gut 1995;37:674–8.
8. Kirk AP, Lennard-Jones JE. Controlled trial of azathioprine in chronic ulcerative colitis. Br Med J 1982;284:1291–2.
9. Rosenberg JI, Wall AJ, Levin B, et al. A controlled trial of azathioprine in the management of chronic ulcerative colitis. Gastroenterology 1975;69:96–9.
10. Hawthorne AB, Logan RE, Hawkey CJ, et al. Randomised controlled trial of azathioprine withdrawal in ulcerative colitis. BMJ 1992;305:20–2.
11. Cosnes J, Bourrier A, Lahanie D, et al. Early administration of azathioprine vs conventional management of Crohn’s disease: a randomized controlled trial. Gastroenterology 2013;145:766–74.
12. Panés J, López-Sanromán A, Bermejo F, et al. Early azathioprine therapy is no more effective than placebo for newly diagnosed Crohn’s disease. Gastroenterology 2013;145:676–74.
13. Fraser AG, Orchard TR, Jewell DP. The efficacy of azathioprine for the treatment of inflammatory bowel disease: a 30 year review. Gut 2002;50:485–9.
14. Pugliese D, Arastu A, Festa S, et al. Sustained clinical efficacy and mucosal healing of thiopurine maintenance treatment in ulcerative colitis: a real-life study. Gastroenterol Res Pract 2018;2018:1–7.
15. Jarhap B, Seinen ML, de Boer NKh, et al. Thiopurine therapy in inflammatory bowel disease patients: analyses of two 8-year interpect cohorts. Inflamm Bowel Dis 2010;16:1451–9.
16. Holt et al. Methotrexate: a systematic review and meta-analysis of the published literature. Inflamm Bowel Dis 2006;12:1252–64.
17. Saibeni S, Virgilio T, D’Inca R, et al. Use of thiopurines for the treatment of inflammatory bowel diseases in clinical practice. Dig Liver Dis 2008;40:814–20.
Inflammatory bowel disease

18 Glazier KD, Palance AL, Griffel LH, et al. The ten-year single-center experience with 6-mercaptopurine in the treatment of inflammatory bowel disease. J Clin Gastroenterol 2005;39:21–6.
19 Cañas-Ventura A, Márquez L, Ricart E, et al. Risk of colectomy in patients with ulcerative colitis under thiopurine treatment. J Crohns Colitis 2014;8:1287–93.
20 Chihaya Y, Saxena S, Cecil E, et al. The impact of timing and duration of thiopurine treatment on colectomy in ulcerative colitis: a national population-based study of incidence cases between 1989-2009. Alliment Pharmacol Ther 2015;41:87–98.
21 Eriksson C, Rundquist S, Cao Y, et al. Impact of thiopurines on the natural history and surgical outcome of ulcerative colitis: a cohort study. Gut 2019;68:623–32.
22 Peyrin-Biroulet L, Oussalah A, Williet N, et al. Impact of azathioprine and tumour necrosis factor antagonists on the need for surgery in newly diagnosed Crohn’s disease. Gut 2011;60:930–6.
23 Cosnes J, Nion-Larmurier I, Beaugerie L, et al. Impact of the increasing use of immunosuppressants in Crohn’s disease on the need for intestinal surgery. Gut 2005;54:237–41.
24 Ramadas AV, Gunesh S, Thomas GA, et al. Natural history of Crohn’s disease in a population-based cohort from Cardiff (1986–2003): a study of changes in medical treatment and surgical resection rates. Gut 2010;59:1200–6.
25 Chatu S, Saxena S, Subramanian V, et al. The impact of timing and duration of thiopurine treatment on first intestinal resection in Crohn’s disease: national UK population-based study 1989-2010. Am J Gastroenterol 2014;109:409–16.
26 Bouthnik Y, Lémann M, Mary JF, Scemama G, Tai R, et al. Long-term follow-up of patients with Crohn’s disease treated with azathioprine or 6-mercaptopurine. Lancet 1996;347:215–9.
27 Kennedy NA, Heap GA, Green HD, et al. Predictors of anti-TNF treatment failure in anti-TNF-naive patients with active luminal Crohn’s disease: a prospective, multicentre, cohort study. Lancet Gastroenterol Hepatol 2019;4:341–53.
28 Murthy SK, Begum J, Benchimol EI, et al. Introduction of anti-TNF therapy has not yielded expected declines in hospitalisation and intestinal resection rates in inflammatory bowel diseases: a population-based interrupted time series study. Gut 2020;69:274–82.
29 Roda G, Jharab B, Neeja N, et al. Loss of response to Anti-TNFs: definition, epidemiology, and management. Clin Transl Gastroenterol 2016;7:e135.
30 Peyrin-Biroulet L, Danese S, Argollo M, et al. Loss of response to Vedolizumab and ability of dose intensification to restore response in patients with Crohn’s disease or ulcerative colitis: a systematic review and meta-analysis. Clin Gastroenterol Hepatol 2019;17:838–46.
31 Sandborn WJ, Panés J, D’Haens GR, et al. Safety of tofacitinib for treatment of ulcerative colitis, based on 4.4 years of data from global clinical trials. Clin Gastroenterol Hepatol 2019;17:1541–50.
32 Food and Drug Administration. FDA approves boxed warning about increased risk of blood clots and death with higher dose of arthritis and ulcerative colitis medicine tofacitinib, 2019. Available: https://www.fda.gov/drugs/drug-safety-and-availability/fda-approves-boxed-warning-about-increased-risk-blood-clots-and-death-higher-dose-arthritis-and (Accessed 8 Jun 2020).
33 Parkes M, IBD BioResource Investigators. IBD BioResource: an open-access platform of 25,000 patients to accelerate research in Crohn’s and Colitis. Gut 2019;68:1537–40.
34 Lemaître M, Kirchgesner J, Rudnichi A, et al. Association between use of thiopurines or tumor necrosis factor antagonists alone or in combination and risk of lymphoma in patients with inflammatory bowel disease. JAMA 2017;318:1679.
35 Gisbert JP, Linares PM, McNicholl AG, et al. Meta-analysis: the efficacy of azathioprine and mercaptopurine in ulcerative colitis. Alliment Pharmacol Ther 2009;30:126–37.
36 Lobo AJ, Foster PN, Burke DA, et al. The role of azathioprine in the management of ulcerative colitis. Dis Colon Rectum 1990;33:374–7.
37 Sood R, Ansari S, Clark T, et al. Long-term efficacy and safety of azathioprine in ulcerative colitis. J Crohns Colitis 2015;9:191–7.
38 Ardizzone S, Molteni P, Imbei V, et al. Azathioprine in steroid-resistant and steroid-dependent ulcerative colitis. J Clin Gastroenterol 1997;25:330–6.
39 Wolfe F. The epidemiology of drug treatment failure in rheumatoid arthritis. Baillieres Clin Rheumatol 1995;9:619–32.
40 Kane SV. Systematic review: adherence issues in the treatment of ulcerative colitis. Aliment Pharmacol Ther 2006;23:577–85.
41 Targownik LE, Singh H, Nugent Z, et al. The epidemiology of colectomy in ulcerative colitis: results from a population-based cohort. Am J Gastroenterol 2012;107:1228–35.
42 Leijonmarck CE, Löberg R, Ost A, et al. Long-term results of ileorectal anastomosis in ulcerative colitis in Stockholm County. Dis Colon Rectum 1990;33:195–200.
43 Parragi L, Fournier N, Zeitz I, et al. Colectomy rates in ulcerative colitis are low and decreasing: 10-year follow-up data from the Swiss IBD cohort study. J Crohns Colitis 2018;12:811–8.
44 Fumery M, Singh S, Dalai PS, et al. Natural history of adult ulcerative colitis in population-based cohorts: a systematic review. Clin Gastroenterol Hepatol 2018;16:343–56.
45 Hoie O, Wolters FL, Røis L, et al. Low colectomy rates in ulcerative colitis in an unselected European cohort followed for 10 years. Gastroenterology 2007;132:507–15.
46 Alexakis C, Saxena S, Chhaya V, et al. Do thiopurines reduce the risk of surgery in elderly onset inflammatory bowel disease? A 20-year national population-based cohort study. Inflamm Bowel Dis 2017;23:672–80.
47 Rungoe C, Langholz E, Andersson M, et al. Changes in medical treatment and surgery rates in inflammatory bowel disease: a nationwide cohort study 1979-2011. Gut 2014;63:1607–16.
48 Lakatos PL, Golovics PA, David G, et al. Has there been a change in the natural history of Crohn’s disease? surgical rates and medical management in a population-based inception cohort from Western Hungary between 1977-2009. Am J Gastroenterol 2012;107:579–88.
49 Chatu S, Subramanian V, Saxena S, et al. The role of thiopurines in reducing the need for surgical resection in Crohn’s disease: a systematic review and meta-analysis. Am J Gastroenterol 2014;109:23–34.
50 Colombel JF, Sandborn WJ, Reinisch W, et al. Infliximab, azathioprine, or combination therapy for Crohn’s disease. N Engl J Med 2010;362:1383–95.