A randomised, double-blind, parallel-group trial to assess mercaptopurine versus placebo to prevent or delay recurrence of Crohn's disease following surgical resection (TOPPIC)

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Scientific summary

The TOPPIC RCT

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Scientific summary

Background

Crohn's disease (CD) is a debilitating condition of unknown cause in which there is inflammation of the wall of the gut. This may result in diarrhoea, abdominal pain, weight loss, tiredness and feeling generally unwell. The disease commonly affects young people, affecting education, employment and family life. Most patients are first treated medically, but over the first 10 years of the condition up to 65% of patients will need an operation to control the disease. Recurrence of CD following surgery is almost universal, most commonly occurring at the anastomosis (join) between the two sections of bowel. In excess of 40% of these individuals will need further surgery to again control the disease within 10 years. A number of medications have been tested previously to prevent or delay the recurrence of CD. The 5-aminosalicylates drugs are ineffective and nitroimidazole antibiotics have some effect but cannot be taken in the long term because of their side effects. Azathioprine and mercaptopurine (MP) (collectively termed thiopurines) are drugs that alter the way that the immune system responds. They are well established in the maintenance of steroid-induced remission in CD. They have been tested to prevent the postoperative recurrence, but the studies have been flawed and results mixed.

Objectives

The primary objective of this study was to determine definitively if MP could prevent or delay postoperative clinical recurrence of CD when compared with placebo. Secondary objectives included determining if MP could prevent or delay endoscopic recurrence of CD using the Rutgeerts scoring system, whether or not endoscopic recurrence could predict clinical recurrence, the relationship between faecal calprotectin or 6-thioguanine nucleotide levels and clinical efficacy, and changes in self-rated quality-of-life scores.

Methods

This was a multicentre, parallel-group, double-blind, randomised controlled trial conducted in the UK (29 sites). Patients were eligible for the trial if they were aged $\geq$ 16 years in Scotland and $\geq$ 18 years in England and Wales, had an ileocolic or small bowel resection $\leq$ 3 months before randomisation during which all observable disease was removed, and had a histologically confirmed diagnosis of CD (according to the Lennard-Jones criteria). Patients were excluded if they had a known intolerance or hypersensitivity to thiopurines, were known to require further surgery, underwent strictureplasty alone, had a stoma, had an active or untreated malignancy, or had absent thiopurine *S*-methyltransferase (TPMT) activity. Prior to randomisation, any postoperative infections were fully treated and existing treatments for CD were stopped.

Intervention

The intervention was randomisation to either a daily oral dose of MP or placebo, with dose adjustment according to body weight (kg) and TPMT status. Following informed signed consent, patients were allocated 1 : 1 to the trial intervention. All clinicians and the study staff involved in day-to-day trial management and outcome assessment were blinded to the study allocation. Blood samples for genetic and serological analysis were taken at randomisation with additional blood and stool samples collected at weeks 0, 13, 49, 103 and 157 for central analysis of drug metabolite and faecal calprotectin levels, with endoscopic assessment at weeks 49 and 157. All clinicians caring for patients and study staff involved in day-to-day trial management and outcome assessment were blinded to study allocation.

Main outcome measures

The primary end point was clinical recurrence of CD [Crohn's Disease Activity Index (CDAI) score of > 150 points plus 100-point rise] and the need for anti-inflammatory rescue therapy or primary surgical intervention. We also looked at the secondary outcome of clinical recurrence defined by a CDAI score of ≥ 150 points together with a 100-point rise in the CDAI score from baseline or anti-inflammatory rescue therapy, or primary surgical intervention. In addition, we looked at endoscopic recurrence using the Rutgeerts scoring system and Crohn's Disease Endoscopic Index of Severity (CDEIS) score, faecal calprotectin levels, thioguanine (TGN) levels and changes in self-rated quality-of-life scores using the Inflammatory Bowel Disease Questionnaire (IBDQ) and EuroQol-5 Dimensions (EQ-5D).

All analyses were intention to treat. The primary outcome variable was postoperative recurrence of CD and its timing if it recurred. Analysis was intention to treat and based on the application of the Cox proportional hazards model. The primary analysis included terms for treatment, the variables on which the randomisation was stratified (smoking status and recruitment site) and adjusted for baseline values of previous treatment with MP and previous treatment with azathioprine. The adjusted analysis was considered to be the primary analysis of the primary outcome. Adjusted Cox proportional hazard ratios (HRs) were presented as the comparison of MP versus placebo, with a HR of < 1 indicating a treatment effect in favour of MP.

The secondary outcome variable of clinical recurrence was analysed in the same manner as the primary outcome. For both primary and secondary outcomes, the adjusted analysis was considered the primary analysis. Endoscopic recurrence using both the Rutgeerts and CDEIS scoring systems were summarised by time and treatment group. Colonoscopy results at week 157 post randomisation (study visit 12) were compared between the treatment groups using a chi-squared test. CDEIS scores at week 157 post randomisation were compared between treatment groups using a *t*-test. Results of faecal calprotectin levels were summarised by time and treatment group, both as a continuous measure and categorically. Faecal calprotectin and TGN levels of the MP drug metabolite were incorporated separately into a Cox proportional hazards model as time-varying covariates. Quality of life, as measured by the IBDQ, was analysed using a change from baseline repeated measures analysis of covariance to evaluate the effect of treatment over time for the overall average IBDQ score and also the overall total IBDQ score. Quality of life, as measured by the EQ-5D, was summarised by treatment group across study visits. We also carried out prespecified subgroup analyses of the primary and secondary outcomes to assess for a treatment effect in terms of thiopurine naivety, previous treatment with infliximab or methotrexate, previous surgery, smoking status, duration of disease and age at diagnosis. The interaction between subgroup and treatment was included in the Cox regression model to determine if the treatment effect differed by subgroup. The same subgroups analysed for the primary and secondary outcomes were also analysed with respect to colonoscopy results and CDEIS scores.

Results

Between June 2008 and April 2012, 240 patients were enrolled and received at least one dose of study drug. A total of 128 (53%) participants were randomised to receive MP and 112 (47%) were randomised to receive placebo. A protocol violation was recorded involving a participant who was prescribed a study drug from the wrong treatment arm 6 weeks post randomisation; the error was reported and correct study drug issued. The study was completed as planned with an extension to the originally proposed recruitment period. No randomised patients were excluded from the analysis. More patients achieved the primary end point in the placebo ($n = 26$, 23.2%) group than in the MP group ($n = 16$, 12.5%), with an adjusted *p*-value of 0.073 [HR 0.535, 95% confidence interval (CI) 0.27 to 1.06]. Smokers were more likely to reach the primary end point than non-smokers (HR 0.127, 95% CI 0.04 to 0.46 among smokers; HR 0.898, 95% CI 0.42 to 1.94 among non-smokers; $p = 0.018$). The proportion of patients experiencing adverse events was similar in the treatment and placebo groups. Likewise, there was little difference in the per-patient number of adverse events between the groups.

At baseline prior to randomisation, 146 participants (60.8%) of the whole cohort were female and 55 (22.9%) participants of the whole cohort were smokers. There were no differences between participants at randomisation in terms of weight, faecal calprotectin levels, or CDAI or IBDQ scores.

A total of 128 (53%) participants received MP and 112 (47%) received the placebo. A total of 104 (43.3%) participants received trial medication for the full 3-year treatment period. Overall, the mean period of treatment was 22.6 months (maximum treatment time possible: 36 months). In the MP group, the mean treatment period was 23.4 months, compared with 21.8 months in the placebo group. Adherence to trial protocol resulted in a dose reduction over the course of the study in 39.1% of participants on MP versus 16.1% on placebo. Consequently, 61 out of 102 patients on MP who had TGN levels measured at week 49 post randomisation were on subtherapeutic drug doses (< 235 pmol/8 × 10^8 red blood cell count). Trial medication was stopped in 37.5% of participants on MP versus 42.9% of participants on placebo. The reasons for discontinuation of trial medication were adverse events (58.8%), regular safety blood monitoring results (13.2%), early withdrawal (15.4%), loss to follow-up (11.8%) and death (0.7%). Follow-up data were not available for all participants for the following reasons: early withdrawal [21 participants (8.7%)], loss to follow-up [16 participants (6.6%)] and death [one participant (0.4%)].

Clinical recurrence of CD occurred in 42 (17%) participants: 16 out of 128 (12.5%) on MP versus 26 out of 112 (23.2%) on placebo (HR 0.535, 95% CI 0.27 to 1.06; $p = 0.073$). Of the 42 who reached the primary end point, 37 participants (88%) met the CDAI score trigger and had rescue therapy initiated, whereas five (12%) met the CDAI score trigger and had both rescue therapy and primary surgical intervention.

In the entire study cohort, the incidence of clinical recurrence was higher in smokers than among non-smokers [15/55 (27.3%) vs. 27/185 (14.6%); $p = 0.018$]. Among the smokers, 3 out of 29 on MP (10.3%) experience clinical recurrence, compared with 12 out of 26 (46.2%) on placebo, demonstrating that MP was effective at preventing postoperative recurrence in smokers (HR 0.127, 95% CI 0.04 to 0.46) but not in non-smokers (HR 0.898, 95% CI 0.42 to 1.94). Other subgroup analyses assessing previous thiopurine exposure, prior methotrexate use, prior infliximab use, previous surgery and age at diagnosis did not identify any differences between the groups.

The overall number of clinical recurrence secondary outcomes (defined by a CDAI score rise, or rescue therapy or surgery) was 34 (26.6%) in the treatment arm and 40 (35.7%) in the placebo arm, with an adjusted *p*-value of 0.243 (HR 0.737, 95% CI 0.44 to 1.23). Subgroup analyses for the secondary outcomes demonstrated no statistically significant differences between subgroups, with the exception of smokers.

The overall number of patients with endoscopic recurrence [defined as a Rutgeerts score of ≥ i2 (≥ 5 aphthous lesions with normal mucosa between lesions, or skip areas of larger lesions or lesions confined to the ileocolonic anastomosis) at week 157 post randomisation] was 29 (32.6%) in the treatment arm and 28 (38.9%) in the placebo arm, with an adjusted *p*-value of 0.382 (odds ratio 0.66, 95% CI 0.26 to 1.67).

There were no significant differences in endoscopic recurrence, as defined by the Rutgeerts score, by treatment group on subgroup analyses except in the thiopurine-naive group. CDEIS scores at visits 6 and 12 were higher in the placebo group than in those allocated to MP, although this difference was not statistically significant.

Analysis of faecal calprotectin levels as a time-varying covariate indicated that, for every 100-µg/g increase in faecal calprotectin, the hazard of reaching the primary end point increased by 17.7% (HR 1.177, 95% CI 1.082 to 1.282; $p = 0.0002$).

There was no statistically significant association between TGN concentrations and the primary end point (HR 0.800, 95% CI 0.565 to 1.132; $p = 0.207$).

The statistical analysis of patient-reported outcome measures (as measured by IBDQ) showed no significant difference between treatment and placebo groups across all study visits, the overall average across the study as a whole, and for the total IBDQ score.

Of 1747 reported adverse events, 355 (20.3%) were infections, of which only seven (0.4%) necessitated hospitalisation. Higher rates of adverse event reporting were seen in the group of patients allocated to placebo. The majority of adverse events were classed as either mild or moderate in severity [868 (91.6%) in the MP group and 728 (91.1%) in the placebo group]. Adverse events caused discontinuation of treatment in 80 patients overall (33%): 39 of the 128 (30%) patients in the MP group versus 41 of the 112 (36.6%) patients in the placebo group. There were two cases of pancreatitis among the overall 1747 reported adverse events (0.1%: one in the MP group and one in the placebo group) and four malignancies (0.2%: three in the MP group and one in the placebo group): basal cell carcinoma, breast cancer and two cases of lentigo maligna. One participant in the placebo group died of coronary heart disease.

There were 14 pregnancies reported during the course of the trial, with 12 normal children and maternal outcomes. We observed one spontaneous abortion at approximately 21 weeks' gestation and one congenital anomaly (heart murmur, septal defect and hydrocephalus) in the infant of a patient in the placebo group.

Conclusions

The Trial Of Prevention of Post operative Crohn's disease (TOPPIC) is the largest double-blind trial assessing the use of thiopurines to prevent postoperative recurrence in CD. From the trial itself, MP was not effective in reducing the frequency of clinical postoperative recurrence of CD overall, but the data suggest that it has clinically meaningful effect among the subgroup of patients who continue to smoke after surgery.

Recommendations for research

The trial results raise the following questions:

1. What is the impact of smoking cessation in this population and what are the mechanisms of action of smoking on increasing disease recurrence?
2. Could faecal calprotectin levels be used as a surrogate for endoscopic assessment?
3. What would the impact on the overall results have been if dosage levels had been informed throughout the duration of the trial by the use of metabolite data, and could these data be used to deliver treatment more effectively?
4. What are the factors behind an apparent discrepancy between clinical and endoscopic recurrence?
5. What are the long-term effects of MP in this population?

Future work

Exploratory analyses of possible predictors of disease recurrence using collected data and samples should be undertaken. Biomarker discovery to stratify high-risk responders should also be researched in more detail.

Trial registration

This trial is registered as ISRCTN89489788 and EudraCT 2006-005800-15.

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