Do thiopurines reduce the risk of surgery in elderly-onset Inflammatory Bowel Disease? A twenty year national population-based cohort study

Christopher Alexakis MBBS BSc MRCP*

Sonia Saxena MBBS MSc MD FRCGP**

Vivek Chhaya MBBS BSc MRCP MD*

Elizabeth Cecil (MSc)**

Vasa Curcin PhD, MSc, BSc (I) Hons***

Richard Pollok FRCP PhD BSc DTM&H*

Affiliations:

*Department of Gastroenterology, St George’s Hospital NHS Trust, London, SW17 0QT

**Department of Primary Care and Public Health, Charing Cross Campus, Imperial College London, London W6 8RF

***King’s College London, Division of Health and Social Care Research

London, UK

Corresponding author:

Christopher Alexakis

Department of Gastroenterology, St George’s Hospital NHS Trust, London, SW17 0QT.

Telephone: 0208 7251206, Email: christopher.alexakis@googlemail.com
Conflicts of interest and sources of funding

SS and EC were funded by a National Institute for Health Research Career Development Fellowship (NIHR CDF-2011-04-048). This article presents independent research commissioned by the National Institute for Health Research (NIHR). The views expressed in this publication are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health. Access to the CPRD database was funded through the Medical Research Council’s license agreement with the Medicines and Healthcare products Regulatory Agency (MHRA). However, the interpretation and conclusions contained in this study are those of the authors alone. No conflicts of interest declared by other authors.
**Abstract**

**Background:** Evidence that thiopurines impact on the risk of surgery in elderly-onset Inflammatory bowel disease (EO-IBD) is lacking. We aimed to compare rates of surgery in EO-IBD (>60 years at diagnosis) with adult-onset IBD (AO-IBD, 18-59 yrs), and examine the impact of thiopurines on surgical risk in EO-IBD.

**Method:** Using a UK database between 1990-2010, we compared rates of surgery between AO-IBD and EO-IBD using survival analysis. Ulcerative colitis (UC) and Crohn's disease (CD) were analysed separately. Cox proportional hazard modelling was used to determine the adjusted relative risk of surgery. We further assessed the impact of duration of thiopurine treatment on risk of surgery.

**Results:** We identified 2758/9515 UC patients and 1349/6490 CD patients, with EO-IBD. Cumulative 1, 5 and 10 year risk of colectomy was similar in EO-UC (2.2%, 4.5%, 5.8%) and AO-UC (2.2%, 5.0%, 7.3%, p=0.15). Cumulative 1, 5 and 10 year risk of first intestinal surgery was lower in EO-CD (9.5%, 14.6%, 17.9%) than AO-CD (12.2%, 19.0%, 24.4%, p<0.001). Early steroid use, steroid dependency and thiopurine use was associated with higher risk of colectomy in EO-UC. Amongst EO-UC receiving thiopurines for > 12 months, there was a 70% reduction in risk of colectomy (HR 0.30, 95% CI 0.15-0.58). Thiopurines were not associated with a reduced risk of surgery in EO-CD.

**Conclusion:** Risk of colectomy in EO-UC does not differ from AO-UC, but the risk of surgery in EO-CD is significantly lower than in AO-CD. Sustained thiopurine use of 12 months or more duration in EO-UC reduces the risk colectomy, but does not impact on risk of surgery in EO-CD. These findings are important given the greater risk of thiopurine-associated lymphoma in the elderly.

**Key words:** inflammatory bowel disease, elderly-onset, colectomy, intestinal surgery, thiopurine,
**Introduction**

The prevalence of elderly-onset inflammatory bowel disease (EO-IBD), usually defined as disease diagnosed at or after the age of 60 years, is increasing in keeping with an ageing population and the steady rise in overall incidence of IBD.\(^1\)\(^2\) In Western populations, the proportion of IBD patients diagnosed with elderly-onset disease is approximately 10-15%.\(^3\)

Compared with paediatric and adult-onset disease, there is limited data on EO-IBD, particularly concerning long-term clinical outcomes and the impact of treatments in this population. It is particularly important that we have a firm understanding of the efficacy of medical therapy with regards to clinical outcomes in this age group since drug related side effects and poly-pharmacy are more common, and notably there is a much greater risk of thiopurine-related malignancies.\(^4\)\(^5\)

Although data are limited, people who have EO-IBD may have a less aggressive disease phenotype compared with younger groups. EO-IBD patients from a large European cohort presented with less stricturing and penetrating disease at diagnosis compared with younger age groups, and also had very low rates of phenotypic progression from Montreal class B1 to B2/B3 disease patterns.\(^6\)\(^7\)

Surgical resection in IBD may be considered an objective marker of disease progression and also represents a distinct measurable endpoint to assess the efficacy of IBD medications. However, the limited available data from previous registry based studies comparing surgical rates between patients with EO-IBD and younger populations are conflicting. A study of the French 'Epidémiologie des maladies inflammatoires chroniques de l'Intestin' registry (EPIMAD) found the 5 year risk of intestinal resection in patients diagnosed with elderly-onset Crohn's disease (EO-CD) was approximately a fifth lower than that of a paediatric cohort from the same region of France.\(^6\)\(^8\) Conversely, a number of retrospective studies have shown no differences in the 5 year risk of surgery in CD patients diagnosed after the age of 60 years, compared with younger age groups.\(^9\)\(^10\) Similar inconsistencies exist regarding surgery in elderly-onset ulcerative colitis (EO-UC). Findings from the EPIMAD registry indicate a lower colectomy risk at 5 years in the EO-UC group compared with the paediatric cohort (8% vs 15%).\(^5\)\(^8\)
However, other population based studies have found no difference in the colectomy rates between these age groups.\(^9,2\)

In addition to disease severity, the risk of requiring surgery may be altered by medical therapy. The use of thiopurines has been associated with a reduced risk of surgery in both UC\(^11,12\) and CD.\(^13,14\) Early use of thiopurines may be beneficial in reducing the risk of surgery in CD\(^15,16\), notably in younger patients who start these medications within the first year of diagnosis.\(^17\) It is unclear whether thiopurines reduce surgery in EO-IBD. In previous randomised controlled trials of thiopurines, older patients have had limited representation.\(^18,19,20\)

Prolonged treatment with thiopurines in an elderly population risks potential iatrogenic harms, interactions with medications prescribed for other co-morbid conditions and a significantly increased risk of thiopurine-associated cancers in this age group, notably lymphoma.\(^4\) It is therefore particularly important to establish the efficacy of such medications in this age group if they are to be used safely.\(^21\)

A better understanding of the impact of treatments is also essential given the cost of prescribing and monitoring maintenance therapies in patients with IBD.\(^22\)

Given these uncertainties, we aimed to determine the relative risk of surgery in EO-IBD compared to adult-onset disease, and secondly, characterise the impact of thiopurine use on surgical outcomes in patients with EO-IBD using a nationally representative population based database. We hypothesised that patients with EO-IBD have a more benign disease course with a reduced requirement for surgery, and that thiopurines have a differential efficacy in reducing the need for surgery compared with IBD with onset earlier in life.
Methods

Data Source

We have previously published detailed methodologies on data extraction for studies in IBD using the Clinical Practice Research Datalink (CPRD).\textsuperscript{17,12,23} The CPRD is one of the largest prospectively collected sources of observational health-related data and is funded by the National Institute for Health Research and the Medicines and Healthcare Products Regulatory Agency. Patient-level clinical data are derived from participating surgeries in primary care. Data are available from 674 practices broadly representative for age and sex, and includes information on approximately 8% of the British population. Practices that contribute to the CPRD are subject to regular audit to ensure data accuracy and completeness, and retain 'Up to standard' (UTS) status if this is achieved consistently. Validation studies have reported a high level of accuracy and coding completeness for IBD, recording data on surgical procedures and hospitalization against full electronic records.\textsuperscript{24,25,26,27} A comprehensive range of demographic, clinical and prescription data is available for analysis. We included data for the period 1990 to 2010 inclusively. The protocols for data extraction and analysis were reviewed and agreed by the Independent Scientific Advisory Committee (ISAC).

Case definition

To differentiate incident from prevalent cases, we defined an incident case as a patient with a first recorded diagnosis of IBD occurring at least 12 months after registration in practices deemed 'up-to standard'. Patients with UC or CD were identified using standardised Read and Oxford Medical Indexing System (OXMIS) coding criteria (see appendix, supplementary Table 1). We included patients with an age at IBD diagnosis of greater than or equal to 17 years.

We excluded patients with non-specific diagnostic codes, for example ‘proctitis NOS’ (not otherwise specified) and patients with codes for both UC and CD. We also excluded patients with co-morbid
inflammatory conditions including asthma, chronic obstructive pulmonary disease, rheumatoid arthritis, temporal arteritis and polymyalgia rheumatica as steroid exposure in these groups cannot be used as a surrogate marker for flares of inflammatory bowel disease. Similarly, patients who received solid organ transplants were excluded as they may have been exposed to thiopurine therapy.

Patients were categorised by age at IBD diagnosis into two groups: Adult-onset IBD (AO-IBD) included patients diagnosed between the ages 17 and 59 years. Elderly-onset IBD (EO-IBD) was defined as any patient diagnosed at 60 years or older. Patients were followed up from index date of diagnosis to death, outmigration or primary endpoint (Figure 1).

The 20 year period was sub-divided in to five equal 4-year time eras to allow assessment of temporal changes within the study group; Era 1 (1990-93), Era 2 (1994-97), Era 3 (1998-2001), Era 4 (2002-05) and Era 5 (2006-09).

Outcomes

The primary outcome was colectomy in patients with UC and first intestinal surgery in patients with CD, derived using standardised Read and OXMIS codes, as previously described (see appendix, supplementary Table 2 for complete list).24

Exposures

Patients with oral prescriptions issued for 5-aminosalicylic acid (5-ASA) therapy, corticosteroids or thiopurines during follow up were identified. Patients receiving 5-ASA treatment were labelled as ‘users’ or ‘non-users’ based on whether they had received a prescription for any oral 5-ASA drug. Patients were considered to have had exposure to corticosteroids if they had any prescriptions issued for oral corticosteroids after diagnosis with IBD. A sub-group of early corticosteroid users was defined as any patient with a prescription for oral corticosteroids within 3 months of the date of diagnosis. Early corticosteroid use has previously been shown to be associated with an increased risk of surgery
in both UC and CD and may be used a proxy indicator of a more severe disease state.\textsuperscript{16,28} A second proxy indicator for disease severity, corticosteroid dependency, was also generated using the prescription data available. Corticosteroid dependency has previously been shown to be associated with the need for surgery in both UC and CD.\textsuperscript{29,30} We defined this variable as any patient receiving corticosteroid courses for greater than 3 months in duration, or patients restarting corticosteroids within 3 months of ending the last corticosteroid prescription, as previously described.\textsuperscript{31} The definition was modelled on the European Crohn's and Colitis Organisation's own classification of corticosteroid dependency.\textsuperscript{32,33}

Categories for thiopurine use were also generated: 'thiopurine users' defined as one or more prescriptions for azathioprine or 6-mercaptopurine during follow-up; 'non-users' with no prescriptions. Time to treatment with thiopurine was defined as the difference between the index date of diagnosis and the date of the first prescription. Finally, we further sub-categorised thiopurine use by duration of treatment to determine effect of treatment length on outcomes; less than 12 months use and greater than 12 months use (sustained use). As it can take up to 8 weeks or longer for thiopurines to become efficacious, a thiopurine effective date was generated as follows: date of first thiopurine prescription plus 56 days. Subsequently, the duration of thiopurine treatment was calculated as the time between the thiopurine effective date and the last thiopurine prescription plus the duration of the last prescription, assumed to be 30 days.

**Statistical Analysis**

We used $t$-tests to determine differences between groups of continuous data, and Chi-squared or Fisher's exact test for comparisons of categorical data.

We used Kaplan-Meier survival analysis to generate survival curves for the time to endpoints in each cohort. For each of the groups undergoing surgery (colectomy in UC, first intestinal surgery in CD), cumulative surgical rates were calculated for the entire follow-up period. The rate of surgery was
determined as a function of time, by calculating the duration between diagnosis of IBD and surgery, or end of follow up as defined previously. The 1, 5 and 10 year risk of surgery in each group was subsequently calculated. We used the log rank test to assess for any significant differences between EO-IBD and AO-IBD, in both UC and CD populations.

In our main analysis, we investigated the use of thiopurines on the risk of colectomy/intestinal surgery. Thiopurine exposure was treated as a time-dependent variable to minimise the effect of immortal time bias that can exist in studies comparing outcomes in sub-populations exposed and not exposed to a treatment regime during follow up.\(^{34}\) The regression model was adjusted for potential confounders including: sex, whether patients were smoking at diagnosis, 5-ASA exposure, early corticosteroid exposure, steroid dependency and thiopurine exposure.

In a further analysis including patients with adult and elderly-onset disease, we added elderly-onset disease as a separate dichotomous variable into the Cox proportional hazards model to determine whether the status of elderly-onset disease had an impact on the risk of surgery. We adjusted this analysis for the same confounders discussed in the previous regression model above.

To address the impact of duration of thiopurine treatment on the risk of surgery in EO-IBD, we conducted a further analysis using a Cox proportional hazards model to calculate the risk of colectomy and first intestinal resection in thiopurine users. In this analysis, patients with CD that were prescribed thiopurines after the date of first surgery were excluded. This model was adjusted for sex, 5-aminosalicylic acid use, early steroid use and steroid dependency.

A p-value of less than or equal to 0.05 was considered statistically significant. All analyses were performed using STATA 12 (StataCorp LP, USA).

**Results**
Over the study period (1990-2010), we identified 9515 patients (aged >17 years) with UC, 2758 (28%) of whom were diagnosed aged 60 years or older. A total of 6490 patients had a diagnosis of CD, 1349 (21%) of whom were diagnosed aged 60 years or older. The proportion of elderly-onset patients with UC and CD diagnosed in Era 1 and Era 5 did not change significantly (UC: 31.3% in Era 1 versus 29.1% in Era 5, p=0.29, CD: 22.9% in Era 1 versus 20.0% in Era 5, p=0.17).

There were fewer smokers at diagnosis and more ex-smokers at diagnosis amongst both patients with EO-UC and EO-CD compared with adult-onset disease (table 1). In UC, oral steroid and 5-ASA exposure were equivalent between the adult and elderly groups, but EO-UC patients had a higher proportion of early steroid exposure (38.1% vs 34.1%). Thiopurine use in the EO-UC group was significantly lower than in the adult-onset population (12.8% vs 21.6%).

There were proportionally fewer women with EO-CD, and fewer smokers at diagnosis compared with patients with AO-CD. They also had significantly lower exposure to oral 5-ASA (63.7% vs 70.0%), corticosteroid use (52.5% vs 57.0%), early corticosteroid use (36.8% vs 41.5%) and thiopurine use (16.4% vs 33.8%) compared with the AO-CD group.

Colectomy in elderly-onset UC

The crude colectomy rates were 4.9% and 3.9% (p=0.04) in adult and elderly-onset UC respectively. The proportion of patients with EO-UC undergoing colectomy in Era 1 was not significantly different than for Era 5 (4.7% versus 3.6%, p=0.53). The 1, 5 and 10 year risk of colectomy was 2.2%, 4.5% and 5.8% in the elderly-onset group, and 2.2%, 5.0% and 7.3% in the adult-onset group respectively (Figure 2a). No significant differences between the groups was found (log rank test for trend, p=0.15). Early steroid use, steroid dependency and thiopurine use were all associated with an increased risk of colectomy in the EO-UC group (Table 2).

First intestinal surgery in elderly-onset CD
Crude intestinal surgery rates were 18.2% in AO-CD and 13.0% in EO-CD respectively (p<0.0001). There was no significant difference in the proportion of patients with EO-CD undergoing intestinal surgery in Era 1 compared with Era 5 (14.6% vs 9.0% p=0.1). The 1, 5 and 10 year risk of first intestinal surgery was 9.5%, 14.6% and 17.9% in the elderly-onset group, and 12.2%, 19.0% and 24.4% in the adult-onset group respectively (Figure 2b). There was a significant difference between the two groups (log rank test for trend, p=0.0002).

Cox regression analysis for risk of first intestinal surgery in EO-CD indicated no significant associations with the need for intestinal resection (Table 2). Exposure to thiopurines was not associated with an altered risk of intestinal surgery.

Elderly-onset disease as a risk factor for surgery in UC and CD

In the multi-variate regression model including patients with both elderly-onset and adult-onset IBD, having EO-UC was not associated with an altered risk of colectomy compared to adult-onset disease diagnosed aged less than 60 years (HR 0.94, 95%CI 0.75-1.18, not significant). However, having EO-CD was associated with a 20% reduction in risk of intestinal surgery compared to AO-CD (HR 0.8, 95%CI 0.68-0.94, p = 0.006).

Thiopurine exposure and impact of duration of treatment on risk of surgery

Thiopurine exposure was 12.8% and 16.4% in elderly-onset UC and CD respectively. In patients with EO-UC, mean time to treatment with thiopurines was 20.7 months, and mean duration of treatment was 29.4 months. In EO-CD, mean time to treatment was 18.2 months, and mean duration of treatment was 33.9 months. No significant differences in time to treatment or duration of treatment were found between elderly-onset UC or CD. Similarly, no significant differences were found in time to treatment or duration of treatment between elderly-onset and adult-onset disease (both UC and CD).
Amongst patients with elderly-onset disease receiving thiopurines, there was no difference in the time to thiopurine treatment between patients who had treatment for greater than 12 months duration compared to those with less than 12 months treatment (21.9 months vs 19.4 months in EOUC, \( p=0.41 \) and 18.7 months vs 17.6 months in EOCD, \( p=0.77 \)). Sustained treatment of greater than 12 months in EO-UC was associated with a 70% reduction in risk of colectomy (Table 3). In contrast, sustained thiopurine use was not significantly associated with a reduced risk of first intestinal surgery in EO-CD.
Discussion

Main findings

This is the largest national population-based study of therapies and outcomes in EO-IBD to date, encompassing 20 years. We found approximately 1 in 4 patients with UC and 1 in 5 diagnosed with CD was aged over 60 years at diagnosis. In UC, colectomy rates were similar between elderly and adult-onset disease. In CD, rates of first intestinal surgery were approximately a third lower in the elderly-onset group compared with adult-onset disease. Amongst patients with EO-UC treated with thiopurines, sustained use for longer than 12 months was associated with a 70% reduction in rate of colectomy. By contrast, in EO-CD sustained thiopurine exposure was not associated with a reduced risk of intestinal surgery. This has important implications for their use particularly given the increased risk of thiopurine-related cancers in this age group.

Findings in relation to other studies

In keeping with our findings, several cohort studies in Europe and Asia report similar colectomy rates between patients with EO-UC and younger age groups. For example, Shi et al published a 10 year risk of colectomy of 6.1% in a cohort of 157 patients with EO-UC, very similar to our estimation of 5.8%. In contrast, other studies from the US and Europe report a lower colectomy rate in elderly patients compared to younger patients although the heterogeneity of disease severity and varying definitions for older and elderly-onset disease make it hard to find valid comparisons. A recent meta-analysis of older-onset IBD (>50 years) suggested an increased rate of colectomy in older-onset UC (OR 1.36, 95% CI 1.18-1.57) although there was substantial heterogeneity in the studies and largest study, accounting for the majority of the effect, is reported in abstract only.

In our population, intestinal resection rates in EO-CD were found to be significantly lower than in adults aged less than 60. Elderly-onset disease was associated with 20% reduced risk of intestinal surgery. Sub-analyses of European and American cohorts also indicate a reduced rate of surgery in elderly-onset CD although study heterogeneity make comparison difficult.
Previous small retrospective studies report a wide variation in rates of surgery in EO-CD, ranging from 6%-83%.\textsuperscript{40,41} We report a 5 year risk of intestinal resection of 14.6%. This figure is lower than rates reported from other recent European cohorts, which estimate 5 year risk of approximately 27-29% in the same age category.\textsuperscript{6,9} Differences in the populations studied are most likely to account for this since our data are derived from primary care, and thus less prone to referral centre bias.

We found a marked difference in thiopurine exposure between adult and elderly-onset cohorts, with much lower use in both EO-UC and EO-CD. Similar trends have been reported in registry and single centre studies.\textsuperscript{9,10,42} More recent studies have reported similar levels of use between age groups.\textsuperscript{36} Whereas low thiopurine use may reflect a more benign disease process in older patients, it may also reflect a reluctance to prescribe thiopurines in this age group, given their increased association with malignancies including lymphoma and skin cancer.\textsuperscript{5} Inherent differences in national prescribing habits may also explain the relative low rates of thiopurine use in the elderly. In a prescribing trends study of IBD medications in the elderly, the UK consistently had the lowest prescribing rates of thiopurines compared to Canada, Denmark and the US.\textsuperscript{43}

The associated benefit of thiopurines in clinical outcomes (including surgery rates) in EO-IBD remains largely unexplored, since very limited data on the efficacy of these agents exists for this population. Theoretical outcomes based on Markov modelling to assess the gain in quality adjusted life years (QALY) for a patient starting azathioprine therapy, indicated that gain in QALYs diminished with increasing age to the point that the model predicted no benefit in starting treatment over the age of 65 years.\textsuperscript{44}

We demonstrated that thiopurine use (compared to no exposure) was associated with a fourfold increased risk of colectomy in patients with EOUC. Similar results have been demonstrated in younger UC populations.\textsuperscript{12} This association likely reflects a more severe disease course in those needing treatment with thiopurines. Like early steroid use, thiopurine use may be a proxy marker of a more aggressive disease sub-type. By contrast, no such association was observed in EO-CD. Charpentier et
al reported that immunomodulator use was not associated with an altered risk of surgery in either EO-CD or EO-UC. However, there were notable differences in steroid and immunomodulator exposure between the French cohort and this study making comparisons difficult.

Among EO-UC patients who were treated with thiopurines, sustained treatment of greater than 12 months was associated with a 70% reduction in risk of colectomy, compared to those with less than 12 months duration of treatment. There was no such associated reduction in risk of first intestinal surgery in patients with EO-CD on sustained thiopurine therapy. Our findings contrast with younger age groups in whom both early and sustained thiopurine use is associated with a reduced risk of surgery in CD, and may have a disease modifying effect. This may suggest a continuum of efficacy by age; most effective in young Crohn’s patients, least effective in the old, and this may be dependent on the balance of genetic and environmental factors across the age groups.

**Strengths and limitations**

This study is the largest population-based cohort of incident cases of EO-IBD. It includes 4107 patients with EO-IBD drawn from 13 million patients attending primary care practices, followed up for over two decades. CPRD is a well validated primary care research tool and results are generalizable to the whole population, and less susceptible to referral centre bias.

In keeping with other population based studies there a number of potential limitations. Inherent biases include loss to follow-up amongst patients with EO-IBD. We also excluded a small group of patients likely to be taking corticosteroids for other indications, which may have impacted on our findings. Details regarding parameters of disease severity, extent and endoscopic findings are not readily available in CPRD. However, we attempted to adjust for severity by including ‘early steroid use’ and ‘steroid dependency’ in our regression model which are established surrogate markers for a more severe disease phenotype in both UC and CD. Although we used a comprehensive list of codes to determine whether a patient has had intestinal surgery (see supplementary Table 2), it is not always
possible to ascertain the reasons for surgery. Particularly in older subjects, patients may have
testinal surgery for reasons other than inflammatory bowel disease, including colonic malignancies
and diverticular disease. This may mean we overestimated the true burden of IBD-related surgery in
the elderly-onset cohort. However, our calculated rates of surgery, particularly colectomy are in
keeping with other recent population based studies. It is also possible that the dataset did not capture all thiopurine prescriptions, as some of them may
have been initiated in secondary care. However, thiopurine exposure in our elderly cohort was similar
to other published data from the UK. Inaccuracies in coding may also influence the primary outcome;
although the dataset is maintained by regular audit and only “up to standard” practices may
contribute to the data. The lack of data on biologic therapy in CPRD may be a potential confounding factor in this study. However the use of anti-TNF agents is this cohort of IBD patients is likely to have been very limited
during the study period. Data from a UK prospective IBD database indicated that by 2006, less than
1% and 3% of all British patients with UC and CD respectively were being treated with biologic
agents. Inferentially, the use of anti-TNF agents in the elderly-onset group is in all probability
negligible over the study period and thus unlikely to impact on surgical outcomes. Additionally, the
efficacy of these medications in altering surgical risk in elderly patients is neither established nor well
studied. Furthermore, we performed a sensitivity analysis on the proportion of elderly-onset patients
undergoing surgery in the era before and after the availability of aTNFs in the UK. We found no
significant difference in either colectomy or intestinal resection in elderly-onset IBD patients between
the two era. This suggests that any potential aTNF exposure in this age group probably did not impact
significantly on our main outcome.

Implications and future research
Our findings indicate risk of surgery in EO-UC is equivalent to that of AO-UC but the risk of surgery in EO-CD is a quarter lower than in AO-CD. These observations underscore the accumulating evidence that EO-CD has a more benign pattern of disease than in younger age groups. We also found that sustained thiopurine use in EO-CD, in contrast to younger age groups with IBD and in EO-UC, was not associated with a reduction in long term risk of surgery. This calls into question the long-term efficacy of thiopurines in reducing the risk of surgery in EO-CD. This is a particularly important since thiopurine use in older age groups is strongly linked to an increased risk of thiopurine-associated lymphoma and other malignancies. Methotrexate may be considered as an alternative steroid sparing treatment to thiopurines even in this age group.

Further observational and prospective studies are needed to evaluate the impact of thiopurines and other treatments, including anti-TNFs, on surgical outcomes in EO-IBD. The age-specific impact of medical therapies in IBD has not been well studied and warrants further attention as flagged in a recent European Crohn's and Colitis Organisation review on the topic.

Conclusion

The risk of surgery in patients with elderly-onset UC is similar to those with adult-onset disease. Sustained thiopurine use is associated with a two-thirds lower risk of colectomy in patients with elderly-onset UC. By contrast, although the risk of intestinal surgery in elderly-onset CD is substantially lower compared with adult-onset disease, thiopurine use is not associated with a reduced risk of surgery. Although our findings need to be corroborated in other countries, they highlight that prescribers must carefully weigh the relative benefits of long-term use of thiopurines in older patients against the potential for iatrogenic harms associated with thiopurine use, notably lymphoma and other malignancies.
Authorship

RP SS and CA designed the study. CA, V Ch and VC extracted and analysed data with statistical support from EC. CA, SS, RP, and EC contributed to interpretation and critically review. All approved the final draft.
References


Table 1: Baseline characteristics of cohort

<table>
<thead>
<tr>
<th>Disease subgroup</th>
<th>Ulcerative Colitis</th>
<th>Crohn's Disease</th>
<th>p-value</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>6757</td>
<td>2758</td>
<td>-</td>
<td>5141</td>
</tr>
<tr>
<td>Mean follow up (yrs)</td>
<td>5.6</td>
<td>4.9</td>
<td>p&lt;0.0001</td>
<td>5.4</td>
</tr>
<tr>
<td>Male (%)</td>
<td>52.1</td>
<td>50.0</td>
<td>p=0.12</td>
<td>43.4</td>
</tr>
<tr>
<td>Mean age at diagnosis (yrs)</td>
<td>39.2</td>
<td>71.8</td>
<td>-</td>
<td>35.6</td>
</tr>
</tbody>
</table>

**Smoking status at diagnosis(%)**
- smoker: 17.1 | 9.8 | p<0.0001 | 35.6 | 22.4 | p<0.0001 |
- non-smoker: 57.1 | 50.1 | p<0.0001 | 46.0 | 46.5 | p=0.37 |
- ex-smoker: 22.7 | 35.7 | p<0.0001 | 15.7 | 27.4 | P<0.0001 |
- missing: 3.1 | 4.4 | -       | 2.7  | 3.7  | -     |

**IBD medication exposure**
- CS (%): 55.5 | 56.6 | p=0.33 | 57.0 | 52.5 | p=0.003 |
- 5-ASA (%): 82.3 | 80.9 | p=0.11 | 70.2 | 63.7 | p<0.0001 |
- Thiopurine (%): 21.6 | 12.8 | p<0.0001 | 33.8 | 16.4 | p<0.0001 |

**Severity Indeces**
- Early CS (%) | 34.1 | 38.1 | p<0.0001 | 41.5 | 36.8 | p=0.002 |
- CS dependency (%) | 21.4 | 24.5 | 0.004 | 26.3 | 21.6 | 0.005 |

*Adult-onset disease defined as age of IBD diagnosis ≥17 years and <60 years

*Elderly-onset disease defined as age of IBD diagnosis ≥ 60 years

*Medication use (CS, 5-ASA, thiopurine) indicates the presence of at least one prescription for the medication in the patient’s record

*CS - corticosteroid

*5-ASA - 5 aminosalicylic acid.

*Early oral steroid exposure defined as any prescription for oral corticosteroid therapy within 3 months of date of diagnosis.

*CS dependency - corticosteroid dependency indicates patients receiving steroid courses of greater than 3 months in duration or patients restarting steroids within 3 months of ending the last steroid prescription

Continuous variables compared using t-test; categorical variables compared using χ² test.
Table 2: Multivariate Cox proportional regression analysis for risk of colectomy in elderly-onset UC and risk of intestinal surgery in elderly-onset CD

<table>
<thead>
<tr>
<th></th>
<th>Elderly-onset Ulcerative Colitis</th>
<th></th>
<th>Elderly-onset Crohn's disease</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard Ratio</td>
<td>95% CI</td>
<td>p-value</td>
<td>Hazard Ratio</td>
</tr>
<tr>
<td>Sex (ref. to female)</td>
<td>1.41</td>
<td>0.91-2.19</td>
<td>0.12</td>
<td>0.94</td>
</tr>
<tr>
<td>Smoker at diagnosis (ref. to non smoker)</td>
<td>0.81</td>
<td>0.35-1.87</td>
<td>0.63</td>
<td>1.16</td>
</tr>
<tr>
<td>Early CS use(^b)</td>
<td>1.93</td>
<td>1.19-3.16</td>
<td>(0.008)</td>
<td>1.98</td>
</tr>
<tr>
<td>CS dependency (^c)</td>
<td>2.47</td>
<td>1.52-4.02</td>
<td>(&lt;0.0001)</td>
<td>0.64</td>
</tr>
<tr>
<td>TP use(^d)</td>
<td>4.60</td>
<td>1.11-9.10</td>
<td>(0.03)</td>
<td>0.98</td>
</tr>
</tbody>
</table>

\(^a\) CI - confidence intervals.

\(^b\) Early oral corticosteroid (CS) exposure defined as any prescription for oral corticosteroid therapy within 3 months of date of diagnosis

\(^c\) CS dependency - corticosteroid dependency indicates patients receiving steroid courses of greater than 3 months in duration or patients restarting steroids within 3 months of ending the last steroid prescription

\(^d\) Thiopurine (TP) use considered as a time dependent co-variate

Analysis also adjusted for 5-aminosalicylate acid exposure
Table 3: Cox proportional hazards model showing adjusted hazard ratios for colectomy and first intestinal resection amongst thiopurine users in elderly-onset ulcerative colitis and Crohn’s disease

<table>
<thead>
<tr>
<th></th>
<th>Elderly-onset ulcerative colitis</th>
<th>Elderly-onset Crohn’s disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR(^b) 95% CI(^c)  p-value</td>
<td>HR  95% CI  p-value</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td>1.49  0.75-2.94  0.25</td>
<td>1.13  0.58-2.21  0.71</td>
</tr>
<tr>
<td>(ref. to female)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Smoker at diagnosis</strong></td>
<td>0.62  0.15-2.61  0.90</td>
<td>1.80  0.89-3.60  0.10</td>
</tr>
<tr>
<td>(ref. to non-smoker)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Early CS use(^d)</strong></td>
<td>1.96  0.93-4.12  0.08</td>
<td>1.28  0.64-2.56  0.48</td>
</tr>
<tr>
<td><strong>CS dependency(^e)</strong></td>
<td>0.67  0.34-1.33  0.25</td>
<td>0.60  0.29-1.20  0.15</td>
</tr>
<tr>
<td><strong>Duration of TP</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤12 months</td>
<td>1  -  -</td>
<td>1  -  -</td>
</tr>
<tr>
<td>&gt; 12 months</td>
<td>0.30  0.15-0.58  (&lt;0.0001)</td>
<td>1.63  0.80-3.36  0.18</td>
</tr>
</tbody>
</table>

\(^a\)TP - thiopurine  
\(^b\)HR - Hazard ratio  
\(^c\)CI - confidence interval  
\(^d\)Early oral corticosteroid (CS) exposure defined as any prescription for oral corticosteroid therapy within 3 months of date of diagnosis  
\(^e\)CS dependency - corticosteroid dependency indicates patients receiving steroid courses of greater than 3 months in duration or patients restarting steroids within 3 months of ending the last steroid prescription  

Analysis also adjusted for 5-aminosalicylic acid use
Figure 1: Flow chart schematic showing cohort construction of patients with elderly and adult-onset inflammatory bowel disease from original Clinical Practice Research Datalink
Figure 2 A) Kaplan Meier graph showing probability of colectomy in patients with adult and elderly-onset ulcerative colitis. B) Kaplan Meier graph showing probability of first intestinal resection in patients with adult and elderly-onset Crohn’s disease
Figure and table legends

Table 1 legend:

- Adult-onset disease defined as age of IBD diagnosis ≥17 years and <60 years
- Elderly-onset disease defined as age of IBD diagnosis ≥ 60 years
- Medication use (CS, 5-ASA, thiopurine) indicates the presence of at least one prescription for the medication in the patient’s record
- CS - corticosteroid
- 5-ASA - 5 aminosalicylic acid.
- Early oral steroid exposure defined as any prescription for oral corticosteroid therapy within 3 months of date of diagnosis.
- CS dependency - corticosteroid dependency indicates patients receiving steroid courses of greater than 3 months in duration or patients restarting steroids within 3 months of ending the last steroid prescription

Continuous variables compared using t-test; categorical variables compared using χ² test.

Table 2 legend:

- CI - confidence intervals.
- Early oral corticosteroid (CS) exposure defined as any prescription for oral corticosteroid therapy within 3 months of date of diagnosis
- CS dependency - corticosteroid dependency indicates patients receiving steroid courses of greater than 3 months in duration or patients restarting steroids within 3 months of ending the last steroid prescription
- Thiopurine (TP) use considered as a time dependent co-variate

Analysis also adjusted for 5-aminosalicylate acid exposure

Table 3 legend:

- TP - thiopurine
- HR - Hazard ratio
- CI - confidence interval
Early oral corticosteroid (CS) exposure defined as any prescription for oral corticosteroid therapy within 3 months of date of diagnosis

CS dependency - corticosteroid dependency indicates patients receiving steroid courses of greater than 3 months in duration or patients restarting steroids within 3 months of ending the last steroid prescription

Analysis also adjusted for 5-aminosalicylic acid use

**Figure 2 legend:**

Figure 2 A) Kaplan Meier graph showing probability of colectomy in patients with adult and elderly-onset ulcerative colitis.

B) Kaplan Meier graph showing probability of first intestinal resection in patients with adult and elderly-onset Crohn’s disease